การพัฒนาเรซิเนตที่บรรจุยาคู่ของเด็กซ์โทรเมทอร์แฟนและไดเฟนไฮดรามีน

นาย ประเสริฐ อัครมงคลพร

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DEVELOPMENT OF DUAL-DRUG RESINATES OF DEXTROMETHORPHAN AND DIPHENHYDRAMINE

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ประเสริฐ อัครมงคลพร: การพัฒนาเรซิเนตที่บรรจุยาคู่ของเด็กซ์โทรเมทอร์แฟนและไดเฟนไฮดรามีน (DEVELOPMENT OF DUAL-DRUG RESINATES OF DEXTROMETHORPHAN AND DIPHENHYDRAMINE) อ. ที่ปรึกษา: รศ.ดร. พจน์ กุลวานิช อ. ที่ปรึกษาร่วม: ผศ.ดร. มิตร ปทีปวณิช 179 หน้า ISBN 974-53-2598-8

วัตถุประสงค์ของการวิจัยนี้เพื่อพัฒนาเรซิเนตที่บรรจุยาคู่ซึ่งมีปริมาณสมมูลของยาเด็กซ์โทรเมทอร์แฟนและไดเฟนไฮดรามีน ศึกษาการเตรียมเรซิเนตที่บรรจุยาคู่ในปริมาณสมมูล ด้วยการนำเรซินมาบรรจุยาในสารละลายที่มีสัดส่วนของยาทั้งสองชนิดต่างๆกัน แล้วสร้างกราฟความสัมพันธ์ระหว่างปริมาณของยาแต่ละชนิดที่บรรจุได้กับสัดส่วนของยาในสารละลาย จุดที่เส้นกราฟทั้งสองตัดกันจะแสดงปริมาณสมมูลของยาที่บรรจุในเรซิเนต (EQC) และสัดส่วนของยาทั้งสองในสารละลายสำหรับใช้บรรจุ (ELS) ทั้งนี้ได้ศึกษาอิทธิพลของปัจจัยต่างๆ ที่มีต่อพฤติกรรมการบรรจุยา ได้แก่ ระดับการเชื่อมขวางของเรซินที่ใช้เตรียมเรซิเนต ความเข้มข้นของยารวมในสารละลาย ปริมาณของเรซินที่ใช้ในการบรรจุยาแต่ละครั้ง อุณหภูมิระหว่างการบรรจุยา และขนาดอนุภาคของเรซิน ผลการศึกษาพบว่า เรซินที่มีระดับการเชื่อมขวาง 2 และ 4 % เมื่อความเข้มข้นของยารวมเพิ่มขึ้นจาก 0.25 ถึง 1.0 % w/v ค่า EQC เพิ่มขึ้นจาก 18 เป็น 35 % w/w และค่า ELS เปลี่ยนแปลงจาก 0.50 เป็น 0.48 ในขณะที่เรซินซึ่งมีระดับการเชื่อมขวาง 8 % การเพิ่มความเข้มข้นของยารวมในช่วงดังกล่าวจะทำให้ค่า EQC เพิ่มขึ้นจาก 18 เป็น 27 % w/w และทำให้ค่า ELS เปลี่ยนแปลงจาก 0.50 เป็น 0.55 การเพิ่มปริมาณเรซินในการเตรียมเรซิเนตจะส่งผลต่อค่า EQC และ ELS ในลักษณะตรงกันข้ามกับการเพิ่มความเข้มข้นของยารวมดังกล่าวข้างต้น ผลของอุณหภูมิต่อการบรรจุยาเข้าสู่เรซินที่มีระดับการเชื่อมขวางต่ำและสูงให้ผลต่างกัน การเพิ่มอุณหภูมิจาก 35 ถึง 55 องศาเซลเซียสในระหว่างการบรรจุยาทั้งสองเข้าสู่เรซินที่มีระดับการเชื่อมขวางต่ำ จะไม่ส่งผลต่อค่า EQC และ ELS แต่ในกรณีของเรซินที่มีระดับการเชื่อมขวาง 8 % การเพิ่มอุณหภูมิจาก จาก 35 ถึง 65 องศาเซลเซียส จะทำให้ค่า EQC เพิ่มขึ้นอย่างต่อเนื่องจาก 27 เป็น 32 % w/w และค่า ELS เปลี่ยนแปลงไปในลักษณะตรงกันข้ามจาก 0.55 เป็น 0.48 ความแตกต่างของขนาดอนุภาคของเรซินที่มีระดับการเชื่อมขวางเหมือนกัน (4 %) ไม่มีผลต่อค่า EQC และ ELS การประเมินการปลดปล่อยยาทั้งสองออกจากเรซิเนตที่เตรียมขึ้นในสารละลายโพแทสเซียมคลอไรด์ความเข้มข้น 0.05 ถึง 0.4 นอร์มอล และสารละลายเลียนแบบลำไส้เล็ก พบว่าเรซิเนตที่เตรียมจากเรซินที่มีระดับการเชื่อมขวางสูงจะปลดปล่อยยาทั้งสองออกมาช้ากว่าเรซิเนตที่เตรียมจากเรซินที่มีระดับการเชื่อมขวางต่ำ การปลดปล่อยยาทั้งสองออกจากเรซิเนตจะมากขึ้นเป็นสัดส่วนกับความเข้มข้นของไอออนบวกในตัวกลาง ยกเว้นในสารละลายโพแทสเซียมคลอไรด์ 0.4 นอร์มอล การปลดปล่อยยาออกจากเรซิเนตที่เตรียมจากเรซินที่มีระดับการเชื่อมขวางสูงจะลดลงเล็กน้อย จลนศาสตร์ของการปลดปล่อยยาออกจากเรซิเนตสามารถอธิบายได้ด้วยรูปแบบการแพร่ของอนุภาคยาผ่านเมตริกซ์ การวิเคราะห์ด้วยวิธีการเปลี่ยนแปลงทางด้านความร้อนและการเบนของรังสีเอกซ์โดยใช้เรซิเนตที่เตรียมจากเรซินที่มีระดับการเชื่อมขวางสูง แสดงว่ายาทั้งสองเปลี่ยนแปลงจากรูปแบบสัญฐานไปเป็นรูปแบบอสัญฐาน ผลอินฟราเรดสเปกตรัมแสดงให้เห็นว่าเกิดปฏิกิริยาต่อกันระหว่างประจุของยาทั้งสองและของเรซิน สรุปได้ว่าวิธีการที่ได้พัฒนาขึ้นนี้สามารถเตรียมเรซิเนตของยาเด็กซ์โทรเมทอร์แฟนและไดเฟนไฮดรามีนในปริมาณสมมูลกันได้ และเรซิเนตที่บรรจุยาคู่เมื่อเตรียมจากเรซินที่มีระดับการเชื่อมขวางที่เหมาะสมจะเป็นรูปแบบทางเลือกสำหรับใช้นำส่งร่วมกันของยาสองชนิดที่มีปริมาณสมมูลกันได้

สาขาวิชา	เภสัชกรรม	ลายมือชื่อนิสิต .....
ปีการศึกษา	2548	ลายมือชื่ออาจารย์ที่ปรึกษา.....
		ลายมือชื่ออาจารย์ที่ปรึกษาร่วม.....

4476956033: MAJOR PHARMACEUTICS
KEY WORD: ION EXCHANGE RESINS / DEXTROMETHORPHAN / DIPHENHYDRAMINE / CONCURRENT DELIVERY / DUAL-DRUG RESINATES

PRASERT AKKARAMONGKOLPORN: DEVELOPMENT OF DUAL-DRUG RESINATES OF DEXTROMETHORPHAN AND DIPHENHYDRAMINE. THESIS ADVISOR: ASSOC. PROF. POJ KULVANICH, Ph.D., THESIS CO-ADVISOR: ASST. PROF. MITR PATHIPVANICH, Ph.D., 179 pp. ISBN 974-53-2598-8

The aim of this work was to develop the dual-drug resinate containing equivalent content of dextromethorphan hydrobromide (DTM) and diphenhydramine hydrochloride (DPH). To obtain this specific resinate, a procedure of simultaneous dual-drug loading using loading solutions composed of different proportions of DTM and DPH was performed and a dual-drug loading diagram was constructed to determine the equivalent drug content (EQC) and also the equivalent drug loading solution (ELS). The effects including degree of resin crosslinkage, overall drug concentration of loading solutions, resin quantity, temperature during drug loading and resin size on the values of ELS and EQC were assessed and discussed. It was found that increasing overall drug concentration from 0.25 to 1.0 % w/v elevated the EQC values from 18 to 35 % w/w for 2 and 4 % crosslinked resins, and from 18 to 27 % w/w for 8 % crosslinked resin. It also changed the values of ELS from 0.50 to 0.48 for 2 and 4 % crosslinked resins, while from 0.50 to 0.55 for 8 % crosslinked resin. Increasing resin quantity during drug loading exerted opposite effects on the values of EQC and ELS when compared with an effect of increasing overall drug concentration. For 8 % crosslinked resin, an increase of loading temperatures from 35 to 65°C caused further increase of EQC values from 27 to 32 % w/w but changed the values of ELS in the reverse direction from 0.55 to 0.48. The change of loading temperatures (35 to 55°C) did not have significant effect on the values of EQC and ELS for 2 and 4 % crosslinked resins. Different particle size of 4 % crosslinked resins had no effect on the values of EQC and ELS. The drug release from the resinates was performed in 0.05 to 0.4 N of KCl solutions and a simulated intestinal fluid. The resinates using 2 and 4 % crosslinked resins provided rapid drug release; while, the resinate using 8 % crosslinked resin gave considerably extended drug release. An increase in the total cation concentration generally accelerated the release of both drugs, except for 0.4 N KCl solution in which the drug release from the resinate of 8 % crosslinked resin was slightly decreased. The release kinetic of both drugs from the resinates could be described by the particle diffusion controlled process. DSC and XRD analysis revealed that DTM and DPH were transformed from the crystalline to amorphous state. It indicated that both drugs mono-molecularly dispersed in the resinate. IR results confirmed ionic interaction occurring between the opposite charges of loaded drugs and resin. In conclusion, the above finding demonstrated that the proposed method could be used to produce the equivalent content dual-drug resinate. The dual-drug resinate using a suitable crosslinked resin could be applied for the concurrent delivery of two combined drugs which have the same therapeutic dose.

Field of Study	Pharmaceutics	Student's signature .....
Academic year	2005	Advisor's signature.....
		Co-advisor's signature.....

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LIST OF ABBREVIATIONS

Å	Angstrom
°C	Degree Celsius
cm	Centimeter
DSC	Differential scanning calorimetry
DPH	Diphenhydramine hydrochloride
DTM	Dextromethorphan hydrobromide
ELS	Equivalent drug loading solution
EQC	Equivalent drug content
g	Gram
h	Hour
HPLC	High performance liquid chromatography
i.e.	That is
IR	Infrared spectroscopy
m	Meter
mA	Milliampere
mg	Milligram
ml	Milliliter
kV	Kilovolt
N	Normal
nm	Nanometer
rpm	Revolution per minute
R^2	Coefficient of determination
S.D.	Standard deviation
USP	United state pharmacopeia
UV	Ultraviolet
w/w	Weight by weight
w/v	Weight by volume
XRD	X-ray diffraction
μg	Microgram

μm	Micrometer
%	Percent

CHAPTER I

INTRODUCTION

Ion exchange resins have been used as an effective carrier for oral drug delivery systems (Borodkin, 1993). In contact with a drug solution, the resins will reversibly interchange its counter ion versus the like-charge drug until the establishment of equilibrium, forming the drug resin complex commonly referred as “resinate”. In digestive system, the loaded drug, which electrically binds with the binding site of resins, will liberate by exchanging with like-charge ions present in the gastrointestinal tract. By selecting suitable resin’s crosslinkage, the resins can provide gradual drug dissolution, and offer the resinate achievable to make extended-release formulations. The resins have been considered an ideal carrier for formulating the extended-release suspension since there is no considerable drug leached out from the resinate suspending in an ion-free vehicle during a storage period (Amsel et al., 1984; Sriwongjanya and Bodmeier, 1997). The resinate can protect the loaded drug from the burst exposure to surrounding vehicle and mouth, hence avoiding its instability and unwanted taste before swallow (Borodkin and Sundberg, 1971). Moreover, the use of resins in the development of controlled or sustained release systems has less risk in dose dumping because of their better drug-retaining property (Anand et al., 2001).

The resinate can be further coated with polymeric membrane to make drug release more controllable. Numerous polymers such as waxes (Motycka and Nairn, 1978), ethylcellulose (Motycka et al., 1985; Zhang et al., 2000), cellulose acetate butyrate (Sprockel and Price, 1989; Prapaitrakul and Whitworth, 1990), Eudragits (Cuna et al., 2000; Ichikawa et al., 2001) and so on have been used to coat the

resinate. Key factors influencing the coating (film) character and hence the release behavior of a drug are not only the polymers used but equally critical also the coating formulations, processes and conditions (Motycka and Nairn, 1979; Motycka et al., 1985; Moldenhauer and Nairn, 1992 and 1994; Akkaramongkolporn, 1995; Cuna et al., 2000). Partial coat of the resinate with some such polymers, which is termed "micro-particle", may also achieve adequate control of drug release from the resinate (Sriwongjanya and Bodmeier, 1997; Cuna et al., 2001).

Generally, the resinate is prepared by loading only single drug onto a resin. Therefore, a product of combined drugs is produced by blending the resinates of each drug (Amsel et al., 1984; Ogger et al., 1991). Recently, an alternative resinate, so called "dual-drug resinate", was introduced for the concurrent delivery of two combined drugs (Akkaramongkolporn and Ngawhirunpat, 2003). It was found that the dual-drug resinate could provide closer drug release characteristics to the individual of single drug loaded resinates as compared with the blended resinates. Since both drugs were simultaneously loaded to form the resinate, the preparation required only a single batch process to produce a combined drug product. In comparison with the blending approach, the delivery of two combined drugs in form of the dual-drug resinate practically reduces the step and cost of production.

In the previous investigation, two drugs were loaded onto resinates in different amounts (Akkaramongkolporn and Ngawhirunpat, 2003). Therefore, it is of interest to develop dual-drug resinates in case where the loaded drugs have the same therapeutic dose and require the same loading amount. In this present work, a new approach was developed and demonstrated as a method of preparation for this specific formulation. Dextromethorphan hydrobromide (DTM) and diphenhydramine hydrochloride (DPH)

were chosen as the model drugs. They have similar ranges of dose with short half-life, and can potentially be formulated in combined preparations for allergy and cough suppression (Jack, 1992; McEvoy, 2001). The objectives of this work were therefore as follows.

1. To develop and demonstrate the method for preparing equivalent content dual-drug resinates of DTM and DPH.

2. To investigate the effects of loading variables, including the degree of resin crosslinkage, overall drug concentration of loading solutions, resin quantity, temperature during drug loading and resin size, on the equivalent dual-drug loading prepared by the developed method.

3. To study drug release kinetic of the produced resinates and the factors that affect their drug release property, e.g. resin crosslinkage, ionic strength of release media and drug loading levels.

4. To characterize the molecular properties of loaded drugs in the produced dual-drug resinates.

Strategy to Prepare Equivalent Content Dual-Drug Resinates

Loading process of a cationic drug onto a cation exchange resin follows ion-exchange reaction below (Borodkin, 1993).

$$RNa + A^{+} \rightleftharpoons RA + Na^{+}$$

Where

RNa = resin in Na form

A^{+} = ionized drug A in loading solution

RA = resin containing drug A, called “resinate”

Na^+ = Na^+ in loading solution

The extent of drug loading onto the resin is governed mainly upon the inherent affinity of the drug with the resin and the concentration of the drug in the loading solution.

Likewise, the ion exchange reaction for dual-drug loading onto the resin is as follows.

$$R2Na + A^+ + B^+ \rightleftharpoons RAB + 2Na^+$$

Where

B^+ = ionized drug B in loading solution

RAB = resin containing drug A and B, called “dual-drug resinate”

In this situation, both drug A and B are simultaneously loaded onto the resin. Which drug species will prevail in binding with the resin mainly depends on domination of two parameters, the inherent affinity of each drug with the resin and the proportion of each drug in the loading solution. A drug with higher affinity with the resin will exhibit a greater extent of drug loading than the other drug with lower affinity. However, the latter drug can have the same, or even greater, drug loading if the proportion of this drug in the loading solution is increased until it outweighs the effect contributed by the superior affinity of the former drug. For any pair of drugs to be loaded, the inherent affinity of each drug with the resin is constant. Indeed, this parameter engages with the drug structure, it can not be modified without risk in changes of the drug properties, for example the physicochemical and the pharmacological properties. Therefore, the required equivalent dual-drug loading will be achieved by mean of modulating the proportion of each drug in the loading solution.

Based on the above concept, the equivalent drug loading solution is obtained by the following procedures. Firstly, a series of loading solutions (under a fixed overall drug concentration) containing various proportions of drug A to B is prepared. Then, each loading solution is agitated with a certain quantity of resins till the equilibrium is reached. Having known the content of drug loading from each loading solution, a dual-drug loading diagram is constructed as depicted in Figure 1.

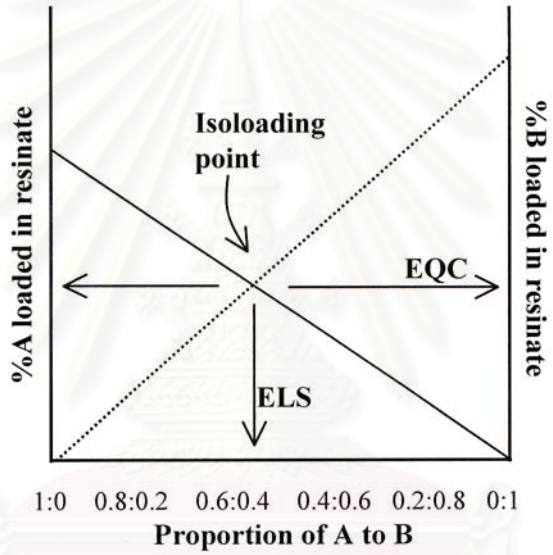


Figure 1 A typical dual-drug loading diagram;
% A loaded (——), % B loaded (·····)

The left and right y-axis represent the content (calculated as % w/w of drugs in the resinate) of drug A and B loaded, respectively. The x-axis represents the proportions of drug A to B in the loading solution. The left and right ends of the x-axis locate the loading solution containing only drug A and B, respectively. Then, across from the left to right end on the x-axis indicates declining proportions of drug

A to B in the loading solution, and vice versa toward the opposite direction. In this regard, the content of drug A loaded (solid line) is highest at the left end and then will decrease as the proportion of drug A in the loading solution is decreased. On the other hand, the content of drug B loaded (dash line) increases from the left end and will be highest at the right end of the x-axis, corresponding to the increased proportion of drug B in the loading solution. These two crossing lines, no matter they are linear or not, yield the intersecting point where drug A and B are equally loaded in the resinate. From this point, the equivalent drug loading solution (ELS), which is used to prepare the equivalent content dual-drug resinate, as well as the estimated equivalent content (EQC) of both drugs loaded can be determined by solving two equations of the crossing lines.

CHAPTER II

LITERATURE REVIEW

1. Ion Exchange Resins

1.1 Matrix structure

Ion exchange resins are water-insoluble high molecular weight crosslinked copolymer matrix containing ionic exchangeable groups (Figure 2) (Salmon and Hale, 1959; Russel, 1970; Borodkin, 1991, and 1993; Harland, 1994). The crosslinked matrix is generally textured from co-polymerization of methacrylic acid and divinylbenzene (Figure 3) or styrene and divinylbenzene (Figure 4 and 5). Commercial resins are produced in the range of 2-16% crosslinked matrix which is directly expressed from the percent of divinylbenzene used in the polymerization process. The degree of crosslinkage within the resins affects the physical properties including swelling or hydration, shrinking, porosity, density and mechanical resistance of resins. An increase in the degree of crosslinkage decreases the hydration and porosity, but increases the density and mechanical resistance of resins. Changes of these properties consequently affect the rate of ion and drug movement inward and outward the resins.

The swelling of resins is in close relation with the resin crosslinkage and the attached counter ions. When the resins imbibe water, the attached counter ions will dissociate and form concentrated electrolyte solution within the resins. The osmotic activity (or force) of the internal gel electrolyte causes further amounts of water to enter the resin phase which therefore continues to swell. The swelling of resins is meanwhile accompanied by stretching of the crosslinked hydrocarbon matrix, which

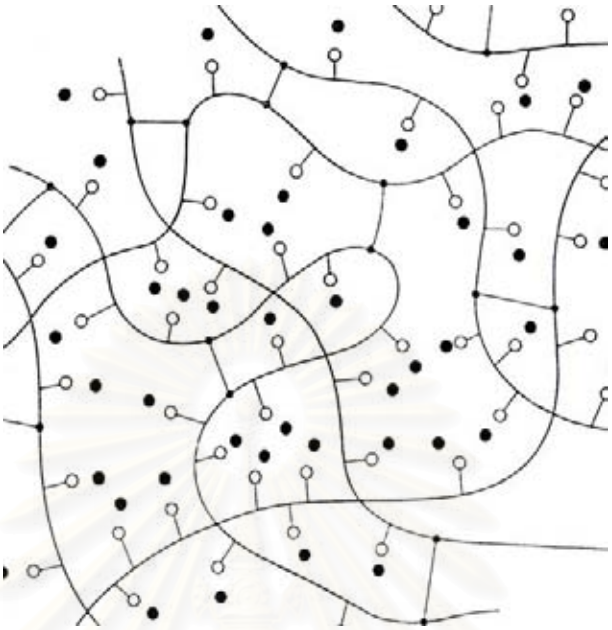


Figure 2 Schematic structure of ion exchange resins

Linear polymer

Cross-linking bond between chains

Counter ion

Fixed exchangeable group

(Reproduced from Russel, 1970)

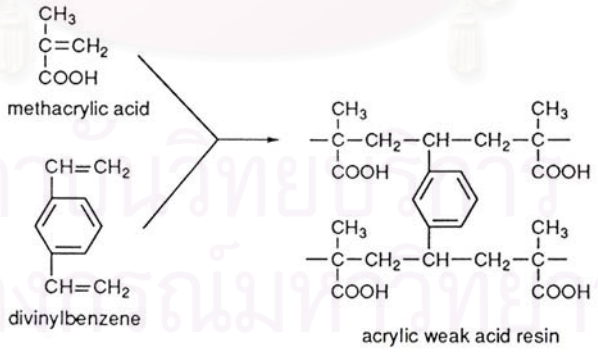


Figure 3 A co-polymerization process of a carboxylic cation exchange resin
(Reproduced from Harland, 1994)

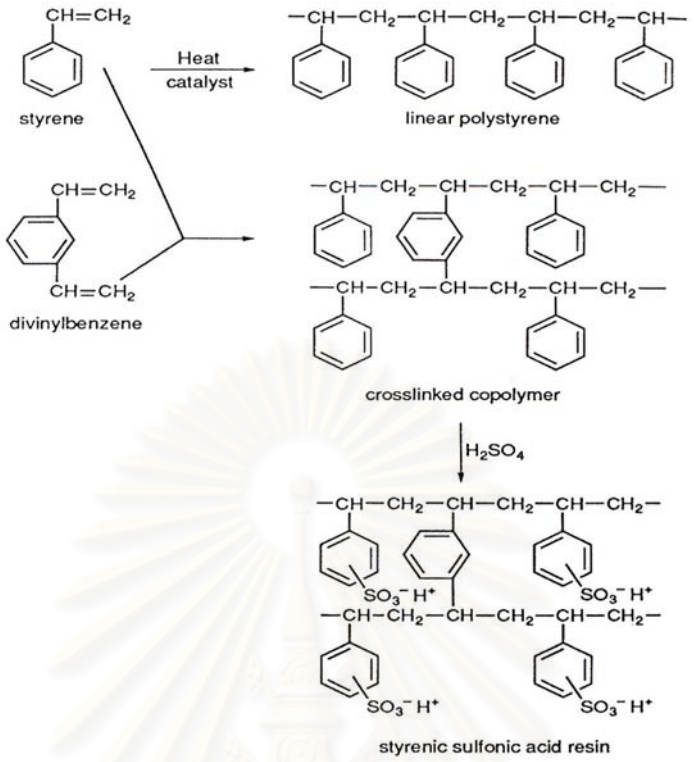


Figure 4 A co-polymerization process of a styrenic cation exchange resin (Reproduced from Harland, 1994)

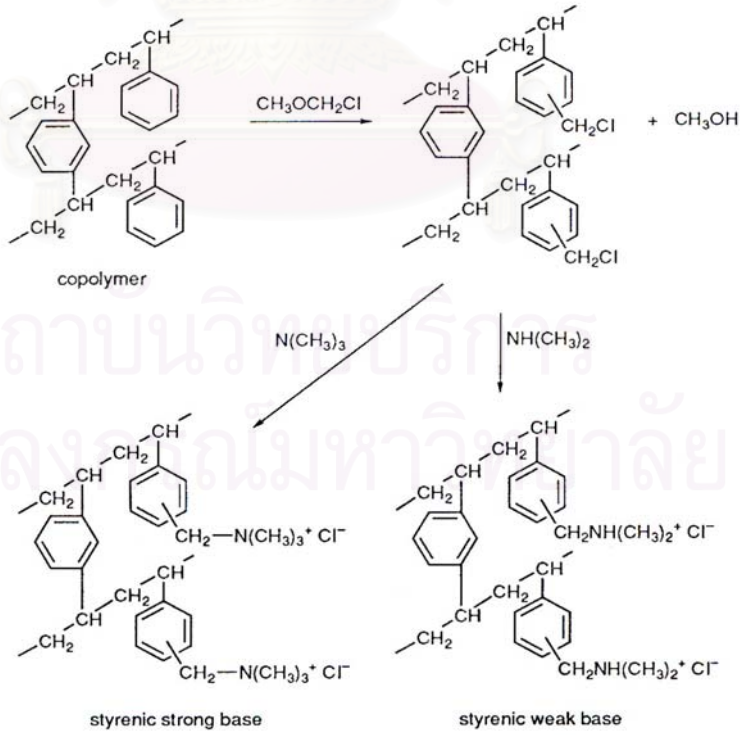


Figure 5 A co-polymerization process of a styrenic anion exchange resin (Reproduced from Harland, 1994)

behaves like an extension of the elastic springs (Simon, 1991; Harland, 1994). The restoring spring force that is dependent on the degree of resin crosslinkage exerts oppositely the above osmotic force to retain the matrix structure (Figure 6). Therefore, the swelling equilibrium results when the restoring spring force counterbalances the osmotic force, which consequently determines the pore volume and size within the resin matrix. From this viewpoint, it can be generalized that the swelling and hence the pore size of resins will decrease as a function of an increase in the degree of resin crosslinkage.

Owing to difference in reaction rate between the initial and the later stage of the polymerization during resin production, the copolymer first formed is greatly crosslinked (entangled), but as the reaction proceeds and the crosslinking agent (divinylbenzene) is consumed, the copolymer becomes less crosslinked. This behavior gives rise to a resin extremely heterogeneous in the matrix structure within which is very entangled in the inner but more opened in the outer region (Figure 7). However, this heterogeneous matrix is without discernible porosity, otherwise has no actual internal macroscopic structural pores (regular holes or channels), as presented in Figure 8. Instead, it is viewed likely as a knotted tangle of wool, which is once hydrated and ionized, can be linked to a dense electrolyte-gel within which dissociated counter ions (or drugs) are able to diffuse. The resins are therefore termed “gel-heteroporous or gel-microporous resin”, which their pore size has been established roughly less than 30 Å. Nevertheless, the resin pore size indeed does not denote the magnitude of interstices, but represents the average distance of the separation of copolymer chains (Russel, 1970; Simon, 1991; Harland, 1994).

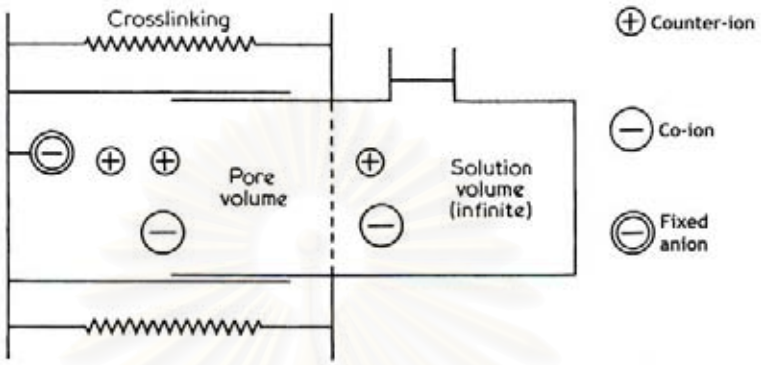


Figure 6 The elastic spring model of resin swelling
(Reproduced from Harland, 1994)

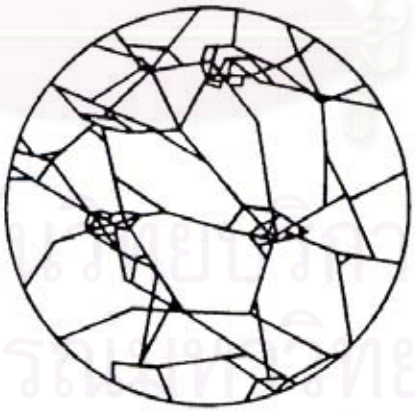


Figure 7 Heterogeniety of resin matrix
(Reproduced from Harland, 1994)

Figure 8 Surface of resin matrix (SEM 7500 magnification)
(Reproduced from Harland, 1994)

The non-uniform distribution of resin crosslinkage and exchangeable groups gives rise to different characters and non-symmetrical strains within the resin matrix. Upon hydration, such non-uniform crosslinked regions will swell differently, thereby creating further strains and leading to a collapsed matrix structure. The existence of the non-uniform strains can be evident by viewing the swollen resins under a transmitted polarized light microscope, which will reveal a transient birefringence as shown in Figure 9 (Harland, 1994).

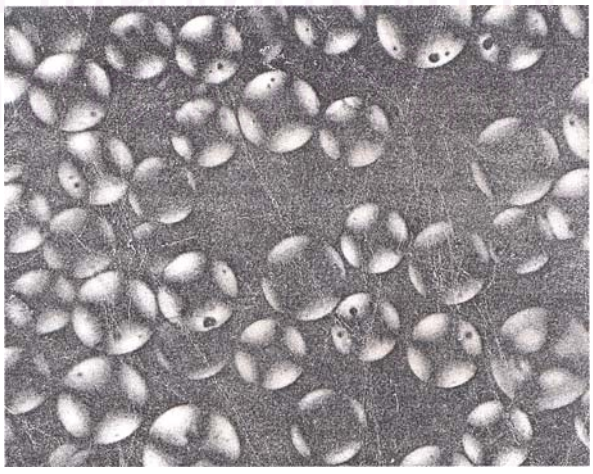


Figure 9 Birefringence of 12% crosslinked resins
(Reproduced from Harland, 1994)

1.2 Exchangeable groups

The resins can be divided into two categories based on exchangeable groups. One with negative ionized groups can exchange for cations in a solution so that it is termed “cation-exchange resin”. The other with positive ionized groups is “anion exchange resin”, which can exchange for anions in a solution. Within each category, they can be sub-classified as strong and weak ion exchange resins depending on the ionization of exchangeable groups (Table 1). The strong cation and anion exchange resins behave like strong acids and strong bases, which absolutely ionize at pH above 1 and below 13, respectively. In contrast, the weak cation and anion exchange resins will ionize within limited pH regions. The weak cation exchange resin substantially ionizes as pH above 4-6, while the weak anion exchange resin substantially ionizes when pH below 7-9 (Deasy, 1984; Kim, 2000).

Table 1 Exchangeable groups of resins and their pK_a values

Type	Exchangeable group	pK_a
Cation exchange resins		
Strong	$-SO_3H$	<1
Weak	-COOH	4-6
Anion exchange resins		
Strong	$-N^+(CH_3)_3$	>13
Weak	$-NH^+(CH_3)_2$	7-9

1.3 Ion-exchange properties

In contact with ions in a solution, the resins will exchange with incoming counter ions, undergoing toward the equilibrium of exchange reaction as follows (Russel, 1970; Borodkin, 1991, and 1993).

For strong and weak cation exchange resins, respectively

$$R\text{-}SO_3H + A^+ \rightleftharpoons R\text{-}SO_3A + H^+ \qquad \text{Eq.1}$$

$$R\text{-}COOH + A^+ \rightleftharpoons R\text{-}COOA + H^+ \qquad \text{Eq. 2}$$

Where H^+ is a counter ion and A^+ is an incoming counter ion

For strong and weak anion exchange resins, respectively

$$R\text{-}N^+(CH_3)_3\,Cl^- + X^- \rightleftharpoons R\text{-}N^+(CH_3)_3\,X^- + Cl^- \qquad \text{Eq.3}$$

$$R\text{-}NR_1R_2\,Cl^- + X^- \rightleftharpoons R\text{-}N\,R_1R_2X^- + Cl^- \qquad \text{Eq.4}$$

Where Cl^- is a counter ion and X^- is an incoming counter ion

According to the fundamental law of mass action, the equilibrium of exchange reaction (only Eq.1 is illustrated) can be defined as follows.

$$K_{H^+}^{A^+} = \frac{[A^+]_r[H^+]_s}{[A^+]_s[H^+]_r} \qquad \text{Eq.5}$$

Where, $[A^+]_r$ and $[H^+]_r$ are concentrations of A^+ and H^+ in the resin phase, respectively. $[A^+]_s$ and $[H^+]_s$ are concentrations of A^+ and H^+ in the solution phase,

respectively. $K_{H^+}^{A^+}$ is generally expressed as “selectivity coefficient”, which displays the relative affinity of the resin for the exchanging ions. If the selectivity coefficient is greater than 1, implying that the resin will bind preferentially with the incoming counter ion (A^+).

2. Benefits of Drugs Prepared as Resinates

2.1 Extended and controlled release

Ion exchange resins have been used as a drug carrier for the development of orally extended-release systems. A drug which ionizes into either a positively or negatively charged molecule can act as an incoming counter ion, replaces the counter ion, and electrically interacts with the oppositely charged binding site of resins. This drug and resin combination is generally referred to “absorbates”, “drug resin complex” or “resinate”. These terms are used interchangeably (Borodkin, 1993). The loaded drug will substantially release from the resinate on exposure to like-charge ions present in the gastrointestinal tract. The drug release can be tuned to a desired rate by selection of suitable crosslinked resins (Irwin et al., 1987, and 1990), entrapment (Sriwongjanya and Bodmeier, 1997) or encapsulation of the resinate (Garcia-Encina et al., 1993; Zhang et al., 2000) with suitable polymers.

Drug delivery based on ion exchange resins has several advantages (Deasy, 1984; Madan, 1990; Chang, 1992; Borodkin, 1993; Anand et al., 2001). The resins are potentially usable drug carriers for achieving a ready to use extended-release suspension which is an ideal dosage form for pediatric and geriatric patients owning to ease of swallow and flexibility in dosing adjustment. The resinate (drug resin complex) suspending in an ion-free vehicle has no obvious drug leaching occurring

during storage periods until it is orally administered. Owing to better drug-retaining property of resins, the resinate preparation has less risk in toxicity from dose dumping. Moreover, the tiny multiple-unit of resins is considered to be more uniform distribution and adsorption, and less local irritation on the gastrointestinal tract as compared with non-disintegrating single-unit dosage forms (Halder et al., 2005).

Recently, the resin carrier has been applied for the development of special or targeting drug delivery systems. For example, an ophthalmic formulation comprising microparticles of betaxolol-resin complex is developed for the treatment of glaucoma (Anand et al., 2001). This approach regulates release of the loaded drug in a controlled manner. Attempts have been made to employ the resins to deliver nicotine as well as insulin via nasal route (Takenaga et al., 1998; Chen et al., 2002). The results suggest that some resins may be potential carriers for nasal delivery of synthetic and bio-molecules. Interestingly, the resins can be effectively developed to a floating extended-release formulation (Atyabi et al., 1996a, and 1996b; Umamaheshwari et al., 2003). The intended drug and bicarbonate are simultaneously loaded into the resins. The system floats in the stomach because of carbon dioxide originated from exchange and consequent reaction between the GI acid and bicarbonate counterparts. Few researchers have tried to apply the resins for transdermal nicotine delivery. The utility of resins for this field however needs further experiments (Conaghey et al., 1998a, and 1998b).

2.2 Stability improvement

The drug loaded in the resinate is frequently more stable than the unloaded drug. This is exemplified by the stabilization of vitamin B_{12}. Vitamin B_{12} has a shelf

life of only a few months, but its resinate is stable more than 2 years. Another example is nicotine. Nicotine discolors quickly on exposure to air and light but the nicotine resinate (used in nicotine chewing gums and lozenges) is much more stable (Hughes, 2005). Even in topical formulations, the drug resinate system is successful in stabilizing the loaded neomycin with different gel forming agents that are sensitive to interact with the unloaded neomycin (Heyd, 1971).

2.3 Taste improvement

Because the resins are insoluble in water they have no taste. The rate of drug release from the resinate on contact with saliva is sufficiently slow, preventing the burst exposure of the released drug to mouth. This makes the resinate an excellent candidate for masking foul tasting drugs. Numerous studies have elucidated the success of the drug resinate system for masking the bitter taste of various drugs, e.g. bromhexine hydrochloride (Sayed and Bajaj, 2000), chloroquine phosphate (Agarwal et al., 2000), cinchona alkaloids (Kanhere et al., 1968), ciprofloxacin hydrochloride (Pisal et al., 2004a), codeine sulfate and chlorpheniramine maleate (Weintraub and Moscucci, 1986), dextromethorphan hydrochloride and so on (Borodkin and Sundberg, 1971; Manek and Kamat, 1981; Nanda, et al., 2002). This technology is equally applicable to liquid formulations (suspensions), dissolve-in-mouth tablets, chewing tablets and gums (Hughes, 2005).

2.4 Physical solid state improvement

The resinate can improve the physical properties of loaded drugs. For example, sodium valpoate is a highly deliquescent drug which quickly dissolves in the

water it absorbs. However, the resinates of varying amounts from 11 to 26 % of sodium valpoate are not deliquescent (at 40°C, 75 % relative humidity) and remain free flowing, permitting their formulations into typical dosage forms by standard equipment (Hughes, 2005).

Some drugs have several forms or polymorphs. Huge sums of money are spent for identifying polymorphs and trying to make stable, suitable water-soluble forms of such drugs. Formulation of unsuitable polymorphs can result in severe stability problems to the final products. Lansoprazole has at lest three polymorphs each of which dissolves differently in water based media. The resinates of different forms of lansoprasole are all amorphous solids that do absolutely not change their crystallinity. Accordingly, the release of the drugs from the resinates is comparable and independent of the crystal forms. (Hughes, 2005).

The resinate of all loaded drugs is solid no matter how state (solid or liquid) the loaded drugs originally are. This is an additional benefit in formulating a liquid or difficult-to-handle solid drug as the resinate. The obtained resinate is stable and free flowing, and thus can be easier formulated into required dosage forms by using existing standard equipment. A very well established example is the nicotine resinate formulated in nicotine chewing gums and lozenges. Nicotine is a liquid drug, but the nicotine resinate is stable and a free-flowing solid (Hughes, 2005).

2.5 Dissolution improvement

Generally, the loaded drug released or dissolved from the resinate is slower than the unloaded drug due to the crosslinked matrix structure of resins. However, it is exceptional to some drugs particularly having very low water solubilization.

Indomethacin lasts for 3 days for dissolving up to about 1 ppm in the simulated gastric fluid. Whereas, the indomethacin resinate achieves a saturated solution (6 ppm) of indomethacin in the same fluid within 30 minutes (Hughes, 2005).

2.6 Other applications of resins

The resins swell significantly on exposure to water, which lead to their use as effective tablet disintegrants. A few percent of resins in tablets can get complete disintegration within several minutes (Khan and Rhodes, 1975; Peppas, and Colombo, 1989; Hughes, 2005). Incorporation of resins in matrix tablets (Sriwongjanya and Bodmeier, 1998), pellets or beads (Albertini et al., 2004; Polsinger et al., 2004; Halder et al., 2005), and even topical ointments (Fiedler and Sperandio, 1957a, and 1957b) makes these dosage forms to have more controllable drug release and drug entrapment. Some resins themselves can be used for the clinical treatment of various disorders. Cholestyramine is a strong anion exchange resin which can bind bile salt, reducing cholesterol and lipid absorption. Therefore it is used for the treatment of hyperlipidemia. The sodium polysulfonate resin in the trademark of Kayexalate which preferentially binds with potassium ion is clinically prescribed for the treatment of hyperkalemia (Deasy, 1984).

3. Preparation of Resinates

Prior to preparation, a received resin is usually washed several times with deionized water or water-miscible solvents, e.g. alcohol and acetone. Unless deionized water is used, rinsing with deionized water is required before subsequent steps. The resin may need converting to a desired form by equilibrating it with a concentrated solution of the desired ion. Finally, the resin in the desired form is washed with deionized water, dried, and is now ready for preparation (Irwin et al., 1987; Harland, 1994; Cuna et al., 2000).

Resinate preparation can be carried out by either batch or column methods (Deasy, 1984; Borodkin, 1993). The batch method involves equilibrating a resin with a drug solution. The other method forms a resinate by cycling a drug solution through a resin packed in a column until the effluent has the same concentration as the eluent. The drug loading reactions are analogous to the ion exchange reactions earlier described (Eq. 1-4). Thereafter, the resinate is washed thoroughly with deionized water, and is dried. As compared to each other, the batch method is simpler, quicker to carry out, and more suitable for fine particle resins, although the column method is likely to offer greater loading capacity (Irwin et al., 1987; Jones, et al., 1989; Rhom and Haas company, 2005). Nevertheless, better loading capacity to the batch method can be achieved by repeated equilibration, or called "multiple batch method" (Rhom and Hass company, 2005; Akkaramongkolporn, 1997b).

The extent of drug loading is influenced by several factors including the drug characters, concentration of drug loading solution, resin quantity, pH of drug loading solution, competitive ions and temperature during drug loading. The resins seem to prefer binding with multivalent charged ions or drugs (Russel, 1970; Rhom and Hass

company, 2005). High drug loading is favored by hydrophobic drugs owning to additional Van der Waal force between the hydrophobic portion of drugs and the aromatic structure of resins (Kril and Fung, 1990; Harland, 1994). Large size and branch structure drugs have a tendency of low drug loading because of their bulky and steric effects (Kanhere et al., 1968; Irwin et al., 1987; Farrago and Nairn, 1988).

The drug loading in resinates is increased as a function of the increased drug quantity in loading solutions which, in practice, can be done by an increase in either the concentration or the volume of loading solutions (Sriwongjanya and Bodmeier, 1997; Akkaramongkolporn, 1997b). The increase in the drug quantity to be loaded will elevate the drug loading of resinates as long as the binding sites of resins are available. When all binding sites are used, such increase will not elevate any more drug loading.

The increased resin quantity exerts opposite effects upon drug loading to the increased drug quantity described above. The loaded drug interacting with the binding sites behaves like a dynamic electrolyte solution (Russel, 1970). At a constant amount of the loaded drug, an increase in the binding sites, by increasing the resin quantity, will dilute the loaded drug, and then decreases the drug loading in resinates. In contrast, a decrease in the binding sites will concentrate the loaded drug, increasing the drug loading. Nevertheless, the drug loading will not more rise with decreasing the resin quantity if all binding sites of resins are exhausted.

The pH of loading solutions influences the drug loading in resinates. This pH effect is complicate and more or less depends on types of resins and loaded drugs. Strong ion-exchange resins have pK_a around 1-2, fully dissociating in pH range of 1-14 (Deasy, 1984; Kim, 2000). Therefore, the pH affects only the dissociation or

solubility of loaded drugs. The drug loading onto strong ion-exchange resins will increase in the pH ranges that promote the dissociation or the solubility of loaded drugs. The weak ion exchange resins have pK_a around 6-7; the dissociation of resins will depend upon the pH of loading solutions. The pH therefore effects not only on the dissociation of drugs but also the dissociation of resins. For these weak ion-exchange resins, the pH effects complicatedly on the drug loading which may be optimal within narrow pH ranges (Borodkin and Yunker, 1970; Pisal et al., 2004).

Other ions presenting in loading solutions may interfere in drug loading. Competitive counter ions, ions having the same charge as loaded drugs, can compete with a loaded drug for exchange onto a resin, which subsequently decreases the drug loading in resinates (Borodkin and Yunker, 1970; Akkaramongkolporn, 1997a). The degree of this effect is dependent on the concentration and the ionic size of competitive counter ions. The extent of drug loading decreases with increasing the concentration of competitive counter ions. The smaller concurrent counter ions provide more effective competition against the loaded drug than the larger ions. The effect of co-ions, ions having the opposite charge to loaded drugs, has not been evidently reported yet. Nevertheless, it has been believed that the co-ions exert negligible interference in the drug loading (Russel, 1970).

Loading temperature can affect drug loading. It is found that the drug loading onto resins will increase with increasing the loading temperature (Irwin et al., 1988, and 1990). The applied heat can cause the expansion of resin particles, promoting the accessibility of a loaded drug into centered deep binding sites of resins. However, the increased loading temperature will not elevate any more drug loading if the binding sites of resins are already fully occupied (Agarwal et al., 2000).

Produced resinates are persistent in shape and crosslinked structure as unloaded resins. As characterized by DSC and XRD, the molecular state of loaded drugs in the resinates changes from crystalline to completely amorphous (Akkaramongkolporn et al., 2000, and 2001; Pisal et al., 2004). The IR study can elucidate the ionic interaction between the oppositely charged groups of loaded drugs and resins. Moreover, the drug-resin ionic interaction may be supplemented by van der Waals force generated from the hydrophobic portions of loaded drugs and resins (Kril and Fung, 1990; Harland, 1994).

All resinates mentioned above are classified as "single drug loaded resinate" which is prepared from loading only single drug onto a resin. Therefore, a product of combined drugs is produced by blending the resinates of each drug (Amsel et al., 1984; Ogger et al., 1991). Recently, an alternative resinate, so called "dual-drug resinate", was introduced for the concurrent delivery of two combined drugs (Akkaramongkolporn and Ngawhirunpat, 2003). For this novel resinate, both drugs are simultaneously loaded to form the resinate as a basic reaction written below.

$$R2H + A^+ + B^+ \rightleftharpoons RAB + 2H^+ \qquad \text{Eq.6}$$

Where

R2H = resin in H form

A^+, B^+ = ionized drug A and B in loading solution

RAB = resin containing drug A and B, called "dual drug resinate"

H^+ = H^+ in loading solution

Owing to simultaneous loading of both drugs, the preparation of this novel resinate required only a single batch process to produce a combined drug product. In comparison with the blending approach, the delivery of two combined drugs in the

form of the dual-drug resinate will practically reduce the step and cost of production. Moreover, it is found that the dual-drug resinate can provide similar drug release characteristics to the individual of single drug loaded resinates.

4. Drug Release from Resinates

4.1 Gastrointestinal transit of ion-exchange resins and resinates

After swallow, the intake resins rapidly move through oesophagus into the stomach with transit time within 1 minute. The oesophagus transit is independent of the particle size (20 and 90 μm) of resins (Burton et al., 1995). In the stomach, the resins fairly well distribute throughout all regions, i.e. fundus, body and antrum (Washington et al., 1989; Wilding et al., 1994; Burton et al., 1995; Thairs et al., 1998). They are found to display prolonged gastric residence; about 20 to 25 % resins persists in the stomach for the entire 6 h of the study. The distribution and the gastric transit (gastric emptying time) are much or less dependent on the dosage form and the particle size, but are not influenced by the dose size and the surface coating (with ethylcellulose) of formulated resins. These advantages make the resins to be a potentially useful carrier for the target treatment of Helicobacter pylori infection on the gastric mucosa (Burton et al., 1995; Cuna et al., 2001).

4.2 Release mechanism and kinetic

On exposure to electrolyte solutions, a like-charge counter ion will diffuse through the boundary layer and the resin matrix to the binding site from which it can replace the bound drug. Then, the free drug will diffuse outwardly from the binding site to the external phase. The drug liberation can be written as the reverse process of

drug loading, as the following reactions (Deasy, 1984; Borodkin, 1991; Kim, 2000). Drug-depleted resins are not absorbed but entirely excreted in feces.

For resinates of cation exchange resins

$$R\text{-}SO_3D + Na^+ \rightleftharpoons R\text{-}SO_3Na + D^+ \qquad \text{Eq.7}$$

$$R\text{-}COOD + Na^+ \rightleftharpoons R\text{-}COONa + D^+ \qquad \text{Eq.8}$$

For resinates of anion exchange resins

$$R\text{-}N^+(CH_3)_3\ D^- + Cl^- \rightleftharpoons R\text{-}N^+(CH_3)_3\ Cl^- + D^- \qquad \text{Eq.9}$$

$$R\text{-}NR_1R_2\ D^- + Cl^- \rightleftharpoons R\text{-}N\ R_1R_2Cl^- + D^- \qquad \text{Eq.10}$$

$Na^+$and Cl^- are common counter cations in the gastrointestinal fluid.

From the above release mechanism, the possible kinetics of the drug release from resinates can be identified into three distinct processes as follows (Boyd et al., 1947; Russel, 1970; Harland, 1994).

- Diffusion of the free drug through the matrix within the resin (referred as "particle diffusion controlled process").
- Diffusion of the free drug across the boundary layer surrounding the resin (referred as "film diffusion controlled process").
- Chemical reaction process at the binding site within the resin (referred as "chemical reaction controlled process").

The mathematical models for determining which process (rate controlling steps) governs the drug release from resinates are as follows.

Particle diffusion controlled model

The original expression of release kinetic regarding the particle diffusion controlled process is obtained by solving the basic partial differential equation, and the basic equations are as follows (Boyd et al., 1947).

$$F = 1 - \frac{6}{\pi^2}\sum_{n=1}^{\infty}\frac{e^{-n^2Bt}}{n^2} \qquad \text{Eq.11}$$

$$B = \frac{4\pi^2 D}{d^2} \qquad \text{Eq.12}$$

Where F = fractional drug release

B = exchange rate constant

n = summation variable

D = diffusion coefficient

d = diameter of resin particle

t = time

Above expression is very cumbersome to find out the release parameters (B and D); thus, they are transformed into simpler equations and procedures (Reichenberg, 1953).

$$Bt = 6.28318 - 3.2899F - 6.28318(1 - 1.0470F)^{1/2} \text{ ; when } F \leq 0.85 \qquad \text{Eq.13}$$

$$Bt = -2.30258\log(1 - F) - 0.49770 \text{ ; when } F > 0.85 \qquad \text{Eq.14}$$

When the Bt value corresponding to the F value is plotted against time, a straight line will be obtained if drug release from resinates is governed via the particle diffusion controlled process. The slope of the line is defined as the exchange rate constant (B), which is used to determine the diffusion coefficient of drug release (D) by using Eq. 12.

Even though the above kinetic model has recognition for determining the release kinetic of resinates (Schacht et al., 1982; Burke et al., 1986; Irwin et al., 1987 and 1990; Ichikawa et al., 2001), it is somewhat a tedious method and lack of elegance. An alternative kinetic model is therefore developed to test for the particle diffusion controlled process of the drug release from resinates. The equation of this model can be expressed as follows (Bhaskar et al., 1986).

$$-\ln(1-F) = 1.59\left(\frac{6}{d}\right)^{1.3} D^{0.65} t^{0.65} \qquad \text{Eq.15}$$

It suggests the particle diffusion controlled process if the plot between –ln(1-F) and $t^{0.65}$ is linear. The slope of the line is used to find out the diffusion coefficient of drug release (D) using the following equation.

$$D = \frac{d^2}{36}\left(\frac{slope}{1.59}\right)^{\frac{1}{0.65}} \qquad \text{Eq.16}$$

The resultant release parameters from above two kinetic models are analogous, but the alternate is easier to practice. The constant values of 1.59 and 0.65 in Eq. 15-16 are applicable for all drug resinate systems and need not be re-estimated. Several studies employed this kinetic model for determining the release kinetic of resinates (Garcia-Encina et al., 1993; Pongjanyakul et al., 2005a, and 2005b).

Film diffusion controlled model

Assuming that the thickness of the boundary layer is constant, the mathematical model used to test the drug release from resinates whether described by the film diffusion controlled process is the following expression (Boyd et al., 1947; Pongjanyakul et al., 2005a).

$$-\ln(1-F) = \frac{3Pt}{d} \qquad \text{Eq.17}$$

Where P = apparent permeability of the boundary layer

If the drug diffusion across the boundary layer is the rate controlling step, the plot between –ln(1-F) and time will provide a linear line with a constant slope, which is used to determine the permeability value (P).

Chemical reaction controlled model

For the exchange of two monovalent counter ions (the counter ion and the bound drug) of which the concentrations are maintained constant, the mathematical model to describe this process is displayed below.

$$-\ln(1-F) = St \qquad \text{Eq.18}$$

Where S = chemical reaction rate constant

The drug release from resinates can be described by the chemical reaction controlled process if the plot between -ln(1-F) and time provides a linear line. The chemical reaction rate constant can be calculated from the slope (Boyd et al., 1947; Plaizier-Vercammen, 1992b).

Even though there are three possible distinct processes governing the drug release from resinates, the diffusion of organic drug molecules through the resin matrix (the particle diffusion controlled process) is always found to be the rate controlling (slowest) step. Thus, the treatment of drug release using only the particle diffusion controlled models, either Reichenberg or Bhaskar' model, is usually sufficient to predict the determinant release kinetic of most resinates (Russel, 1970; Bhaskar et al., 1986; Irwin et al., 1987; Pongjanyakul et al., 2005b).

Other kinetic models

The drug release from resinates can be described using the matrix diffusion-controlled model of which the simple exponential expression can be written in the

following form (Moldenhauer and Nairn, 1990; Halder et al., 2005; Pongjanyakul et al., 2005a).

$$\frac{M_t}{M_\infty} = F = kt^n \qquad \text{Eq.19}$$

Where M_t = drug release at any time

M_∞ = total drug release or drug content

k = release constant

n = diffusion exponent

When the matrix diffusion-controlled model mainly controls the drug release from resinates, n could be defined as 0.5, or the drug transport is Fickian diffusion. This model can be expressed by determining the linearity of the plot between the fractional drug release and the square root of time ($t^{0.5}$). The slope of the linear line is a release constant.

4.3 Factors affecting drug release from resinates

Several factors influence the drug release from resinates. These include the concentration and nature of replacing counter ions, pH of release media, affinity or preference of loaded drugs for resins, degree of resin crosslinkage, particle size of resins, release condition and level of drug loading. Higher counter concentrations in the release media promote drug release owing to greater influx of the replacing ions (Irwin et al., 1987; Sprockel and Prapaitrakul, 1988; Pisal et al., 2004; Pongjanyakul et al., 2005a). Nevertheless, the ionic strength of the release media does not always generate higher drug release as reported in a previous work (Ogger et al., 1991). High rate and extent of the drug release is favored with the counter ion having preferred

affinity for the resin (Sprockel and Prapaitrakul, 1988). Also, the drug release from resinates is found to vary with the co-ions, ions having opposite charge to loaded drugs, in the release media (Ogger et al., 1991). The concurrent resinate administration of the same charge drugs may provide the release pattern of each drug differed from these resinates as administered individually (Akkaramongkolporn and Ngawhirunpat, 1998, and 2003).

The pH effect on the drug release from resinates mirrors that on drug loading as described earlier. In regard to the dissociation of resins, varying pH essentially alters the behavior of drug release for weak ion-exchange resins, but may little change that for strong ion-exchange resins. However, this pH effect on drug release may violate the above rule if the pH dramatically changes the solubility of drugs in release media (Atyabi and Kouchak, 2000). For this case, the release of drug loaded even in strong ion-exchange resins can be dramatically changed in accordance with its solubility in the encountered pH of release media. However, physiological pH variation in the range from 1.2 to 7.3 is considered having a slight effect on the drug release from resinates (Sensenbach and Hays, 1960).

The electrostatic (or ionic) and hydrophobic interactions are the key forces binding loaded drugs with resins. A drug with higher charge density and hydrophobicity exert stronger interactions so that it will release in a lower rate and extent than that with lower charge density and hydrophobicity. Small molecular size and weight drugs will release from resinates in a faster rate and greater extent than large size drugs (Irwin et al., 1987; Farag and Nairn, 1988; Kril and Fung, 1990; Rhom and Hass company, 2005).

Resin characters have significant influences on the drug release from resinates. A low crosslinked resin swells markedly upon hydration and has wide pores inside so that it can allow drug molecules to move rapidly out from the resin (Irwin et al., 1987, and 1990; Schacht et al., 1982; Burke et al., 1986). In contrast, a high crosslinked resin provides a slower rate of drug release because of its lower swelling and narrower pores. The degree of crosslinkage also contributes to the completeness of drug release. There is an incident that the drug molecules loaded particularly in very high crosslinked resins may not entirely release, which has dubbed this phenomenon as “irreversible exchange” (Burke et al., 1986; Farag and Nairn, 1988; Kril and Fung, 1990; Harland, 1994). Smaller resin particles provide faster rates of drug release owing to a reduction in the diffusive path length together with an increase in the surface area (Irwin et al., 1987, and 1990).

The drug release from resinates is normally evaluated using the USP dissolution methods (Amsel et al., 1984; Graves, et al., 1985; Burke et al., 1986; Irwin et al., 1987, and 1990; Ogger et al., 1991; Akkaramongkolporn and Ngawhirunpat, 2003; Pisal et al., 2004a, and 2004b; Pongjanyakul et al., 2005a, and 2005b). However, few works use own specific method to evaluate the drug release of resinate products (Schacht et al., 1982). The method and condition of release evaluation play an important role on the drug release from resinates. Different release evaluating methods, i.e. closed tubes, replacement closed tubes and definite bath vessels can provide distinct release behavior (Chaudhry and Saunders, 1956). Higher stirring speed provides more reduction in the diffusive or stagnant layer surrounding resinates, which subsequently results in faster drug release (Irwin et al., 1987). However, this effect may gradually level off at extreme stirring speeds.

The drug release is also significantly affected by the level of drug loading in resinates. There are coincident results that the drug release increases as increasing the drug loading in resinates. However, different explanations for this finding have been proposed. One explanation is described to be due to high drug loading resulting in a burst release of loaded drugs which weakly attach to resins via mechanisms other than ionic binding (Chen et al., 1992). Another explanation for such finding is proposed in relation with the equilibrium treatment of ion-exchange phenomenon (Akkaramongkolporn et al., 2000, and 2001).

5. Modification of Resinates for More Controllable Drug Release

In some situations, available crosslinked resins can not make resinates to have required release patterns. Microencapsulation or entrapment of resinates with polymers can tune their drug release more controllable. Desired release patterns from these modified resinates can be obtained by selecting suitable polymers together with optimizing the thickness and character of coating (film). Table 2 summarizes the modified resinates developed in previous works, which are categorized according to polymers used.

Several resinate and modified resinate formulations have been produced for sale on the markets (Table 3). It demonstrates the achievement of resins to be used as a drug carrier.

6. Loaded Drugs

Table 2 Examples of modified resinates

Polymer	Formed as*	Technique used	Drug loaded	Reference
Cellulose acetate butyrate	Coated resinate	Emulsion solvent evaporation	Diphenhydramine HCl, pseudoephedrine HCl and chlorpheniramine maleate	Sprockel and Price, 1989
	Coated resinate	Emulsion solvent evaporation	Phenylpropranolamine HCl	Prapaitrakul and Whitworth, 1990
	Coated resinate	Emulsion solvent evaporation	Sulfadiazine sodium	Kondo et al., 1996
	Coated resinate	Emulsion solvent evaporation	Terbutaline sulphate	Torres et al., 1998
	Coated resinate	Emulsion solvent evaporation	Acetohydroxyamic acid	Umamaheshwari et al., 2003
Ethylcellulose	Coated resinate	Polymer-polymer interaction and temperature change	Benzoic acid	Motycka and Nairn, 1979
	Coated resinate	wurster process	Phenylpropanolamine HCl and dextromethorphan HBr	Raghunathan et al., 1981
	Coated resinate	Polymer-polymer interaction and temperature change	Theophylline	Motycka et al., 1985.
	Coated resinate	Solvent evaporation	Theophylline	Moldenhauer and Nairn, 1990; 1992; 1994
	Coated resinate	Solvent alteration and temperature change	Salbutamal sulphate	Akkaramongkolporn, 1995
	Coated resinate	Solvent evaporation	Bromhexine HCl	Sayed and Bajaj, 2000
	Coated resinate	Spay drying	Tramadol HCl	Zhang et al., 2000
Ethylcellulose-hydroxypropyl methylcellulose	Coated resinate	Wurster process	Dextromethorphan HBr, ephedrine and pseudoephedrine HCl	Borodkin and Sundberg, 1971
Eudragit RS/RL	Coated resinate	Emulsion solvent evaporation	Terbutaline sulphate	Cuna et al., 2000

Table 2 Examples of modified resinates (continued)

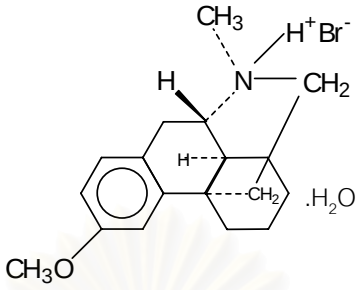
Polymer	Formed as*	Technique used	Drug loaded	Reference
Eudragit RS30D	Coated resinate	Wurster process	Diclofenac sodium	Ichikawa et al., 2001
Eudragit RS 100	Micro-sphere	Emulsion solvent evaporation	Chlorpheniramine maleate, Pseudoephedrine HCl and propranolol HCl	Sriwongjanya and Bodmeier, 1997
Gelatin-acacia	Coated resinate	Coacervation	Propranolol HCl	Irwin et al., 1988
Hydroxypropyl methylcellulose phthalate	Coated resinate	Non-aqueous emulsion solvent evaporation	Diclofenac sodium	Torres et al., 1995
Nylon	Coated resinate	Interfacial polycondensation	Diclofenac sodium	Torres et al., 1990
Polycarbophil and carbopol	Micro-sphere	Emulsion solvent evaporation	Amoxycillin trihydrate	Cuna et al., 2001
Polymethyl methacrylate	Coated resinate	Emulsion solvent evaporation	Chlorpheniramine maleate	Sprockel and Price,1990
Polyurea plus diisocyanates	Coated resinate	Interfacial water promoted reaction	Codeine	Lukaszczyk and Urbas, 1997
Waxes	Coated resinate	Melting	Benzoic acid	Motycka and Nairn, 1978

** Classified from the title or elsewhere in the cited papers.*

Table 3 Commercial products containing resinates and modified resinates

Trade name	Composition	Dosage form	Indication	Reference
Biphetamine	Amphetamine resinate	Capsule	CNS stimulant	Hinsvark et al.,1973
Bronchopront	Ambroxol resinate	Capsule	Mucolytic	NIMS Annual, 2000
Codipront	Codeine resinate and phenyltotoxamine resinate	Capsule and suspension	Cough suppressant and antihistamine	NIMS Annual, 2000
Delsym	Dextromethorphan resinate	Suspension	Cough suppressant	Ogger et al.,1991; Lilienfield and Zapolski, 1983
Ionamine	Phentermine resinate	Capsule	Anti-obesity	Hinsvark et al.,1973
Liquifer	Ferrous (Fe^{2+}) resinate	Suspension	Ferrous supplement	Borodkin, 1991, and 1993
Nicorette	Nicotine resinate	Chewing gum	Smoking cessation	Borodkin, 1991, and 1993
Penntuss	Codeine resinate and chlorpheniramine resinate	Suspension	Cough suppressant and antihistamine	Weintraub and Moscucci, 1986; Ogger et al.,1991
Rhinopront	Carbinoxamine resinate and phenlyephrine resinate	Suspension	Antihistamine and decongestant	NIMS Annual, 2000
Rhinotussal	Carbinoxamine resinate, phenlyephrine resinate and dextromethorphan resinate	Suspension	Antihistamine, decongestant and cough suppressant	NIMS Annual, 2000
Rondec	Pseudoephedrine resinate	Chewing tablet	Decongestant	Borodkin, 1991, and 1993
Tussionex	Hydrocodone resinate and chlorpheniramine resinate	Suspension	Cough suppressant and antihistamine	Borodkin, 1991, and 1993

6.1 Dextromethorphan hydrobromide



Formula : $C_{18}H_{25}NO.HBr.\ H_2O$

Molecular weight : 370.3 (anhydrous)

Melting point : 125°C

Dissociation constant (pK_a) : 8.3

Partition coefficient (LogP) : 4

(Holcomb and Fusari, 1974; Moffat, 1986; Jack, 1992)

Solubility:

Sparingly soluble or soluble 1 g in 65 ml of water, freely soluble in alcohol and chloroform, practically insoluble in ether (Martindale, 1996).

Stability:

Fairly stable as stored in airtight container and protected from light (rare data)

Pharmacology and indication:

DTM has antitussive activity with no expectorant action. DTM is about equal to codeine in depressing cough reflex, but is non-addictive and rarely produces drowsiness as well as gastrointestinal disturbances. It is used for the temporary relief of coughs caused by minor throat and bronchial irritation occurring with common colds and with inhaled irritants. It is recognized as an antitussive agent with well-

documented safety and efficacy (Woodworth et al., 1987a, and 1987b; Martindale, 1996; McEvoy, 2001).

Pharmacokinetics:

DTM is rapidly absorbed from the gastrointestinal tract with first pass metabolism in liver primarily by CYP2D6. The metabolism has greatly genetic variation (93 % is extensive metabolizers and 7 % is poor metabolizers). The major metabolite is dextrophan which has cough suppressant activity. The onset of antitussive action is about 15 min to 2 h. The plasma concentrations are found to be 1-8 ng/ml for extensive metabolizers and 8 to >30 ng/ml for poor metabolizers. The elimination half-life of DTM appears to be <4 to about 9. The apparent distribution volume of DTM reportedly is 2 L/kg. Usual dose of conventional DTM products is in the range of 15-30 mg taken every 4-8 h, and that of extended-release DTM products is 60 mg taken twice daily (Woodworth et al., 1987a, and 1987b; Jack, 1992; Martindale, 1996; McEvoy, 2001; Anderson et al., 2002).

6.2 Past researches of DTM manipulated as resinates

Borodkin and Yunker (1970) studied the interaction of DTM, and other amine drugs, with a polycaroboxylic acid ion-exchange resin (Amberlite IRP 88). The time for complete adsorption (equilibrating time) was within 24 h. The amount of DTM loaded was dependent on the pH of drug loading solution, having the optimal drug loading at pH 5-6. The presence of sodium ion in the drug loading solution reduced DTM loading.

Borodkin and Sundberg (1971) prepared DTM resinate (with Amberlite IRP 88), and coated the DTM resinate with ethycellulose-hydroxypropylmethycellulose

mixture for taste coverage of chewing tablets. Oral administration of the chewing tablets containing uncoated DTM resinate had less bitter taste than that of pure DTM. The coating of DTM resinate further reduced the bitter taste and provided more sustained release of DTM from the chewing tablets.

Raghunathan et al. (1981) coated DTM resinate (Amberlite IR 120) with ethylcellulose using an air suspension coating apparatus (Wurster process) for the purpose of sustaining drug release. It was found that direct application of an atomized polymer to the fluidized DTM resinate was ineffective in controlling drug release since the coating (film) would rupture in the dissolution medium due to resin swelling. Pretreatment of the resinate with an agent such as polyethylene glycol 4000 was essential for retaining the geometry of the resinate and hence the coating during dissolution.

Lilienfield and Zapolski (1983) and Woodworth et al. (1987) evaluated the clinical efficacy of a controlled release oral suspension containing DTM resinate (Delsym) in comparison with a traditional DTM dosage forms. Both works concluded that the controlled release DTM product equaled in efficacy (bioavailability) and safety to the tested traditional DTM dosage forms, while the former product produced a prolonged release of DTM over 12 h interval.

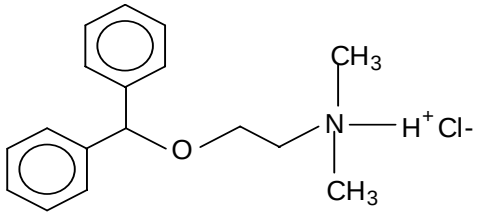
Pongpaibul et al. (1990) prepared long acting liquid antitussive products containing microparticles of DTM resinate made by using a modified emulsion solvent evaporation method. Unfortunately, the resin and the polymer used were not specified in this work. Some products were found to be stable and did not release the drug in suspending media. Furthermore, there was a little change in the drug release

from the microparticles of the products after storage at room temperature up to 40 days.

Ogger et al. (1991) tested drug release, in a variety of release media, of over-the -counter oral suspension containing DTM resinate (Delsym). The HPLC method was developed for analysis of DTM in the filtered release media. The higher DTM release was generally obtained in higher ion strength of the release media. Additionally, the release of DTM was affected by the type of counter ions as well as of anions (co-ions) present in the release media.

Pongjanyakul et al. (2005a) prepared DTM resinates using two polysulfonate resins, namely Amberlite IRP 69 and Dowex 50W. The equilibrating time used for DTM loading onto these resins was within 1-3 h. The properties of each resin including particle size and degree of crosslinkage affected DTM release from the resinates. The same authors (Pongjanyakul et al. 2005b) later compressed the resinates with different direct compression fillers such as microcrystalline cellulose, dicalcium phosphate dihydrate and spray dried rice starch to form compressed sustained release DTM tablets. The properties of resins such as particle shape and degree of crosslinkage, and the deformation under compression of the direct compression fillers dramatically influenced the physical properties (thickness, hardness, resin fracture) as well as the drug release from the resinate tablets.

6.3 Diphenhydramine hydrochloride (DPH)



Formula : $C_{17}H_{21}NO.HCl$

Molecular weight : 291.82

Melting point : 167-172 °C

Dissociation constant (pK_a) : 9.0-9.12 (25°C)

Partition coefficient (LogP) : 3.3

(Holcomb and Fusari, 1974; Moffat, 1986; Jack, 1992)

Solubility:

Very soluble or soluble 1 g in 1 ml of water, freely soluble or soluble 1 g in 2 ml of ethanol and chloroform, practically insoluble or very slightly soluble in ether (1 g in >10,000 ml of ether) (Martindale, 1996).

Stability:

DPH degrades in acidic media, whereas it is fairly stable in alkaline media. The decomposition is due to ether linkage hydrolysis through which the rate is first order and catalyzed by hydrogen ion. The major degradation products are benzhydrol and 2-(dimethylamino) ethanol (Holcomb and Fusari, 1974).

Pharmacology and indication:

DPH is an antihistamine agent that is mainly used for the symptomatic relief of hypersensitivity reactions (allergy). It is also prescribed as an antitussive for the temporary relief of cough caused by minor throat and bronchial irritation occurring with common colds or inhaled irritants. Other indications of DPH are the prevention and treatment of nausea, vomiting, vertigo associated with motion sickness, and the sleep aid for short-term management of insomnia (Martindale, 1996; McEvoy, 2001).

Pharmacokinetics:

DPH is well absorbed from the gastrointestinal tract with about 50 % first pass metabolism in liver. Peak plasma concentration is achieved about 1 to 4 h. Following oral administration of DPH dosages of 25 mg every 4 h or 50 mg every 6 h, the plasma concentration of DPH is in the range of about 25-85 ng/ml. The sedative effect appears to correlate with the plasma drug concentration. The marked drowsiness and sedation occur at the plasma drug concentration of 70 ng/ml or greater. The elimination half-life of DPH appears in the range of 2-9 h in healthy adults. Following IV administration, the apparent distribution volume of DPH reportedly is about 4-8 L/kg. Approximately 80-85% of DPH is bound to plasma proteins. Usual dose is in the range of 10-50 mg taken three or four times daily (Carruthers et al., 1978; Spector et al., 1980; Jack, 1992; Martindale, 1996; McEvoy, 2001).

6.4 Past researches of DPH manipulated as resinates

Fewer works were found for DPH manipulated as resinates. Manek and Kamat (1981) formulated DPH resinates with various resins (Indion CRP 244, Indion CRP 254 and Amberlite IRP 69), and then evaluated taste masking ability and drug release of the resinates. It was found that Indion CRP 254 provided the best taste masking ability and sustained performance.

Sprockel and Price (1989) prepared sustained release aqueous suspensions containing DPH resinates (Amberlite CG 120) coated with cellulose acetate butyrate polymer. The coating could prolong the release of this highly water-soluble drug. Storage of the aqueous suspensions containing the coated DPH resinates at room temperature for 16 days resulted in unchanged drug release profiles.

CHAPTER III

MATERIALS AND METHODS

Materials

1. Acetronitrile HPLC (Lab Scan, Ireland)
2. Deionized water produced from a water purifier (Option 3, Elka, England)
3. Dextromethorphan hydrobromide USP/BP (Wockhardt Ltd., India)
4. Diphenhydramine hydrochloride USP/BP (Beijing Shuanglao Pharmaceutical Co., China)
5. Dowex 50W×2-200 (Sigma-Aldrich, USA)
6. Dowex 50W×4-100 (Sigma-Aldrich, USA)
7. Dowex 50W×4-200 (Sigma-Aldrich, USA)
8. Dowex 50W×4-400 (Sigma-Aldrich, USA)
9. Dowex 50W×8-200 (Sigma-Aldrich, USA)
10. Orthophosphoric acid (Ajax Finechem, Australia)
11. Methanol HPLC (Lab Scan, Ireland)
12. Potassium chloride (Ajax Finechem, Australia)
13. Potassium dihydrogen orthophosphate (Fisher Scientifics, Great Britain)
14. Potassium hydrogen phthalate (Farmitalia Carlo Erba, Italy)
15. Sodium chloride (Merck, Germany)
16. Sodium hydroxide (Ajax Finechem, Australia)
17. Triethylamine (Fluka Chemika, Switzerland)

Methods

1. Treatment of Resins

The received resins were treated by the procedure used in previous works (Torres et al., 1998; Cuna et al., 2000). About 20 g of resins was consecutively washed with 3×100 ml of deionized water, 100 ml of 95 % ethanol, 100 ml of 50 % ethanol and 100 ml of deionized water. Removal of the supernatant was made consecutively by sedimentation and decantation after agitation on a magnetic stirrer. The washed resin was converted to Na form by equilibrating with 2×120 ml of 2 N NaOH. The resin (in Na form) was collected by filtration, and then thoroughly washed with deionized water until the pH value of the filtrate was neutral (pH meter, model 210, Orion, USA). Finally, the final resin was dried overnight at 50°C in a hot air oven (Laboratory Thermal Equipment Ltd., UK), and kept in a closed vial. The moisture content of the final resins was determined using a moisture analyzer balance (Sartorious MA 30, Germany).

2. Characterization of Resin Properties

2.1 Total exchange capacity

The total exchange capacity of resins was determined by the salt splitting titration (Salmon and Hale, 1959; Harland, 1994). The received resins (in H form) were cleaned, dried and determined for moisture content as mentioned above. An accurate amount (0.2 g) of the resins was weighed and added into a 250 ml Erlenmeyer flask containing 50 ml of 1 N sodium chloride solution. The slurry was swirled gently and was left overnight to assure complete exchange reaction. Thereafter, the slurry was titrated slowly with 0.1 N sodium hydroxide solution

standardized with potassium hydrogen phthalate. Phenolphthalein was used as an indicator for the titration. The total exchange capacity of the resin in H form (MC_H, meq/g) was calculated from c×v×1000/w; where c is the actual concentration (N) of sodium hydroxide solution, v is the volume (ml) of sodium hydroxide solution at end point and w is the dry weight of resins (g). Based on the fundamental law of mass action, the total exchange capacity of the resin in H form could be transformed into that in Na form (MC_{Na}, meq/g) by the following equation.

$$MC_{Na} = \frac{MC_H}{\left(1 + 0.001 \times MC_H \times (AW_{Na} - AW_H)\right)} \qquad \text{Eq .20}$$

AW_H and AW_{Na} are the atomic weight of H and Na, which are 1 and 23, respectively. The total exchange capacity was determined in triplicates at ambient condition.

2.2 Particle size and appearance of resins

The particle size of resins was measured by using a particle size analyzer (Mastersizer 2000, Malvern, England). The final resins were suspended in deionized water for 6 h, and then were measured for particle size; $d_{10\%}$, $d_{50\%}$ and $d_{90\%}$, which are the volume-number diameters where the given percentage of the resin volume is under that size. The size distribution (polydispersity) was computed in the term of the SPAN factor expressed as follows.

$$SPAN = \frac{d_{90\%} - d_{10\%}}{d_{50\%}} \qquad \text{Eq.21}$$

The measurement of particle size was conducted in triplicates. The appearance of the resins was examined by using an optical microscope (Nikon Eclipse E2000, Japan) connected with a digital camera (Nikon Coolpix4500, Japan).

2.3 Pore properties and radius of dry resins

The pore properties of the final resins were characterized by a gas (nitrogen) adsorption analyzer (Autosorb-1, Quantachrome, USA). Prior to measurement, the resins were out-gassed at 110.0°C for 6 h. The pore volume and area were calculated from the desorption isotherm by BJH method (Barrett, et al., 1951; Lowell, 1979) using the instrument's program. The pore radius of dry resins was estimated and presented in three following forms.

- r which is mean pore radius calculated by the following relationship.

$$r = \frac{2V_{cum}}{A_{cum}} \qquad \text{Eq. 22}$$

Where V_{cum} and A_{cum} are cumulative pore volume (m^3) and area (m^2) respectively.

- $r_{V50\%}$ which is the volume-number radius where 50 % pore volume is under this radius
- $r_{A50\%}$ which is the area-number radius where 50 % pore area is under this radius

2.4 The swelling of resins

The swelling of resins was expressed as the swelling ratio by the following relation (Halder et al., 2005).

$$\text{Swelling ratio} = \frac{d_{swell} - d_{dry}}{d_{dry}} \times 100 \qquad \text{Eq .23}$$

d_{dry} is the resin diameter after dried at 105°C until constant weight; d_{swell} is the resin diameter after suspended in deionized water for 6 h. The resin diameters were

photographed with proper magnification by a digital camera under an optical microscope. Then, two hundred particles of resins on the images were measured with suitable magnified micrometers by using the image analysis program (Image-Pro plus version 4.5, Media Cybernetics, Inc., USA).

3. Study of Dual-Drug Loading

3.1 Effect of resins with different cross-linkage and overall concentrations

The dual-drug loading onto Dowex 50W×2-200, ×4-200 and ×4-200 was studied under varying overall loading solution concentrations of 0.25, 0.5, 0.75 and 1.0 % w/v. For an overall drug concentration, six loading solutions comprising various proportions of DTM and DPH in the weight ratio of 1:0, 0.8:0.2, 0.6:0.4, 0.4:0.6, 0.2:0.8 and 0:1 were prepared. Then, 100 ml of each loading solution was agitated with 0.5 g (dry weight) of each final resin. The drug loading was conducted in a temperature-controlled shaking bath (Hetotherm-Hetomix, Denmark) at 35±1°C for 24 h. It was proved that this equilibrating time was adequate to reach the equilibrium (see Appendix A). At equilibrium, the remainder of both drugs in the loading solution was assayed by HPLC. The amount of drug loading onto the resinate was the difference of the initial and the remainder of drugs in the loading solution at the equilibrium, and was calculated as % w/w of drugs in the resinate by using the following equations.

$$\%\,\text{DTM loaded} = \frac{\text{DTM loaded (mg)}}{\text{DTM loaded (mg)} + \text{DPH loaded (mg)} + \text{resin (mg)}} \times 100 \quad \text{Eq. 24}$$

and

$$\%\ \text{DPH loaded} = \frac{\text{DPH loaded (mg)}}{\text{DTM loaded (mg)} + \text{DPH loaded (mg)} + \text{resin (mg)}} \times 100 \qquad \text{Eq. 25}$$

Having known the amounts of drug loading at varying proportions of the loading solution, the dual-drug loading diagram was constructed, and then the values of EQC and ELS were determined. Each study was made in triplicates. A preliminary work showed no considerable degradation of both drugs occurring during the drug loading process (see Appendix A).

3.2 Effect of quantity of resins

The dual-drug loading onto 0.125, 0.5 and 0.8 g (dry weight) of Dowex 50W×2-200, ×4-200 and ×4-200 was determined at a fixed overall loading solution concentration of 0.50 % w/v at 35±1°C. The rest of drug loading processes and determination of EQC and ELS were performed by the procedures previously described.

3.3 Effect of temperature during drug loading

At a fixed overall drug concentration (1.00 % w/v) of the loading solution, the dual-drug loading was determined at varying temperatures from 35 to 55±1°C for Dowex 50W×2-200 and ×4-200, and extended to 65±1°C for Dowex 50W×8-200, respectively. The rest of drug loading processes and determination of EQC and ELS were performed as described above. No significant degradation of both drugs in the loading solution was observed at the temperatures employed (see Appendix A).

3.4 Effect of particle size

The dual-drug loading was preformed onto 0.5 g (dry weight) of 100, 200 and 400 mesh size 4% cross-linked resins (Dowex 50W×4). The loading condition was fixed to be 0.50 %w/v of overall loading solution concentration at 35±1°C. The rest of drug loading processes and determination of EQC and ELS were performed by the same procedures as described above.

4. Preparation of Equivalent Content Dual-Drug Resinates

Several batches of selected equivalent content dual-drug resinates were prepared by equilibrating the resins with the corresponding equivalent drug loading solutions obtained from the above study. After equilibrium, the resinates were collected by filtration, and washed thoroughly with deionized water. The remainder of both drugs in the filtrate was assayed using HPLC method. The amount of drug loading was determined by the subtraction method, and presented as % w/w of drugs in the resinate. The obtained resinates were dried overnight in a hot air oven at 50°C, and then were kept in closed vials. The moisture content of the resinates was determined by a moisture analyzer balance.

5. Release Evaluation

Drug release was evaluated by USP dissolution apparatus type II (model DT6R, Erweka, Germany). The rotating speed and maintained temperature were set at 50±1 rpm and 37±1°C, respectively. Each produced equivalent content dual-drug resinate was accurately weighed to have 60±1.5 mg of each drug, and was directly transferred into the release vessels (n=3). At predetermined time, the medium (3 ml) was

withdrawn through a filter and then was analyzed by HPLC. The fresh medium was equally returned into the vessels. The variables evaluated were as follows.

- The produced dual-drug resinates with EQC 28 % prepared from varying crosslinked resins
- The release evaluated in 900 ml of 0.05 to 0.4 N potassium chloride (KCl) solution and the USP simulated intestinal fluid without enzyme (USP24/NF19, 2000)
- Comparison of the release of drugs from the dual-drug resinates with EQC 28 and 18 % (only with the resinates of Dowex 50W×8-200)
- Comparison between the release of drugs from the dual-drug resinate and the blend of conventional (single drug loaded) resinates by referring to the conventional resinates of each drug (all resinates having comparable drug content (28 %) and prepared from Dowex 50W×8-200)

6. Molecular Characterization of Loaded Drugs

Molecular properties of loaded drugs in the resinates of Dowex-50W×8-200 were characterized by the following method.

6.1 Differential scanning calorimetry (DSC)

Thermal properties of samples were examined using a differential scanning calorimeter (DSC 822^e, Mettler Toledo, Switzerland). Each sample was weighed (4-8 mg) and placed in an aluminum pan (40 μl) and crimped with its cover (Mettler Toledo, Switzerland). The increment of heating was 10 °C/min. The measurement was conducted over 25-250 °C under a nitrogen purge.

6.2 X-ray powder diffraction (XRD)

X-ray powder diffraction patterns of samples were determined using a X-ray powder diffractometer (JDX 8030, Jeol, Japan). The measuring conditions were as follows; CuK radiation, Ni filtered, graphite monochromator, voltage 35 kV and current 10 mA. All samples were run at 1° (2θ) min^{-1} from 5 to 45° (2θ).

6.3 Infrared spectroscopy (IR)

IR spectra were determined using a Fourier transform infrared spectrometer (FTIR 1760X, Perkin Elmer, USA). Each sample was prepared in a KBr disk and the spectrum was recorded over 400 to 4000 cm^{-1}.

7. Molar Volume of Drugs

The molar volume (V_{molar}, ml/mole) of DTM and DPH was estimated using the following relationship (Tuckerman, 2003).

$$V_{molar} = \frac{MW}{\rho} \qquad \text{Eq. 26}$$

MW and ρ are the molecular weight and true density of drugs. The molecular weight of DTM and DPH is 370.3 and 291.8, respectively. The true density of drugs was determined by a helium pycnometer (Ultrapycnometer 1000, Quantachrome, USA). From five replicate measurements, the true density of DTM and DPH was 1.3548±0.0022 and 1.1634±0.0015 g/ml, and hence the calculated molar volumes being 273.3 and 250.8 ml/mole, respectively.

8. HPLC Conditions for Drug Analysis

Drug analysis of all experiments was done on HPLC with UV detector (Shimadzu 10AVP, Japan), using a 4×250 mm column containing 5 μm Betasil C8 (Thermo Electron Corporation, UK). The mobile phase was a 65:35:003 mixture of 75 mM potassium dihydrogen orthophosphate (adjusted to pH 3.5 with orthophosphoric acid), acetronitrile and triethylamine. The HPLC conditions were operated at a constant flow rate of 1.0 ml/min, injection volume of 20 μl and detection wavelength at 257 nm. For each assay, a daily calibration curve was generated and used within the assay. The validation of the HPLC method was examined in system suitability, linearity, accuracy and precision (see Appendix B).

Statistical Analysis

Significant effect of variables on determined parameters was tested with one-way analysis of variance (ANOVA) and the least significant difference (LSD) test for multiple comparisons. Difference was considered statistically significant when p-value < 0.05. The statistical test was run on SPSS program, version 11.5.

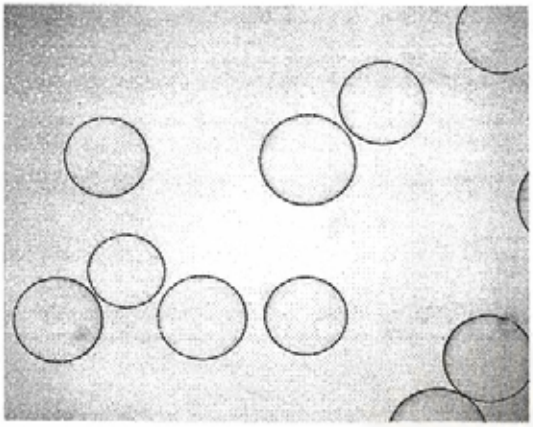
CHAPTER IV

RESULTS AND DISCUSSION

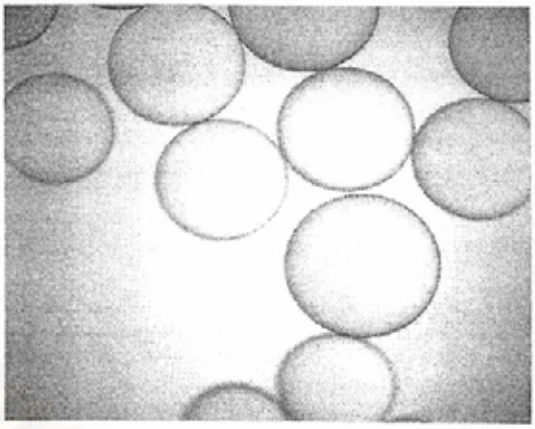
1. Properties of Resins

All resins were in spherical shape (Figure 10). The diameter and distribution of hydrated resins are shown in Table 4 and Figure 11. Dowex 50W×2-200 was found to be bigger than Dowex 50W×4-200 and ×8-200 even though they were specified in the same 200 mesh size. All resins had a comparable size distribution (SPAN). The total exchange capacity among the resins was similar, indicating that the crosslinkage and the particle size of resins did not affect the function of exchangeable groups.

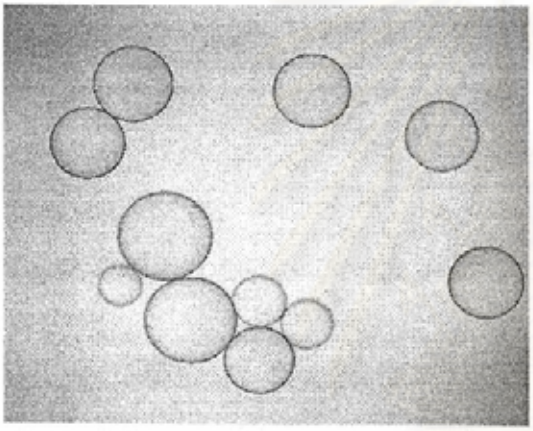
The pore character of dried resins was determined using the nitrogen adsorption technique. It was found that the obtained isotherms (Figure 12) could not match with any recognized isotherms, supporting that the resin pore was not like the regular internal structure of pores exhibiting on common drug solids or granules (Russel, 1970; Martin et al., 1983). The resins were chemically made up from inter-linked chains of copolymers. This rendered the internal pore structure of resins rather open, random in shape and in dimension, which resembled a knotted tangle of wool (Figure 1). The pore size obtained from the measurement therefore did not denote the magnitude of interstices, but was likely to represent the average distance of separation of copolymer chains (Harland, 1994). From the desorption isotherms, the cumulative pore volume (Figure 13) and area (Figure 14) as well as the distribution of pore volume (Figure 15) and area (Figure 16) could be obtained, and then the pore radius could be computed in the terms of r, $r_{V50\%}$ and $r_{A50\%}$ as presented in Table 5. It



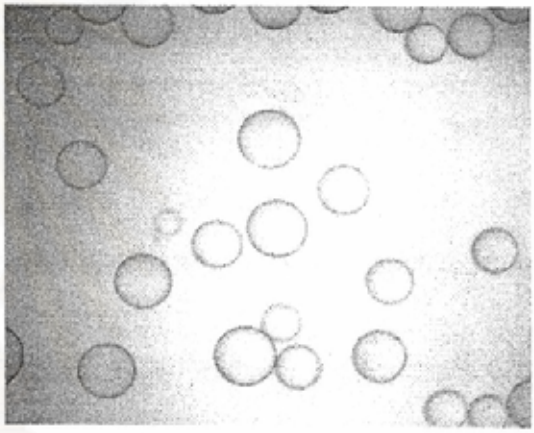
Dowex 50Wx2-200



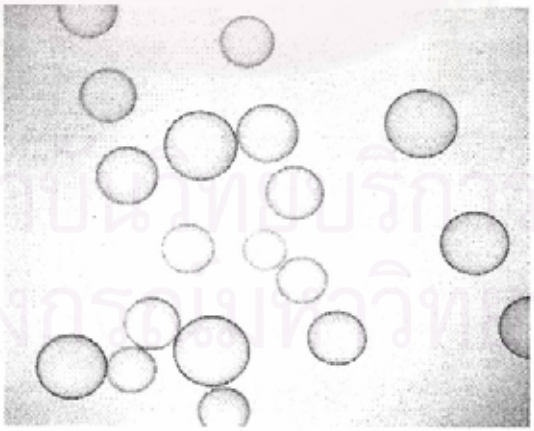
Dowex 50Wx4-100



Dowex 50Wx4-200



Dowex 50Wx4-400



Dowex 50Wx8-200

Figure 10 Photomicrograph of hydrated resins (10x10 magnification)

Table 4 Properties of resins used in the study

Resins	% Cross-linkage[b]	Total exchange capacity[a] (meq/g)		Hydrated particle size (μm)[a]				
		MC_H	MC_{Na}	Mesh size[b]	$d_{10\%}$	$d_{50\%}$	$d_{90\%}$	SPAN
Dowex 50W×2-200	2	5.27 (0.02)	4.72 (0.01)	200	137.588 (0.611)	188.446 (0.583)	257.590 (0.598)	0.637 (0.002)
Dowex 50W×4-100	4	4.99 (<0.01)	4.50 (<0.01)	100	235.000 (1.287)	320.951 (1.520)	435.503 (2.220)	0.625 (0.001)
Dowex 50W×4-200	4	5.34 (<0.01)	4.78 (<0.01)	200	108.444 (0.305)	149.294 (0.571)	204.700 (0.920)	0.645 (0.005)
Dowex 50W×4-400	4	5.25 (0.03)	4.70 (0.02)	400	76.768 (0.162)	107.964 (0.153)	151.203 (0.179)	0.690 (0.001)
Dowex 50W×8-200	8	5.18 (0.01)	4.65 (0.01)	200	107.628 (0.511)	148.119 (0.699)	202.570 (1.154)	0.641 (0.001)

[a] *Values are presented in mean (s.d.)*

[b] *Data from manufacturer*

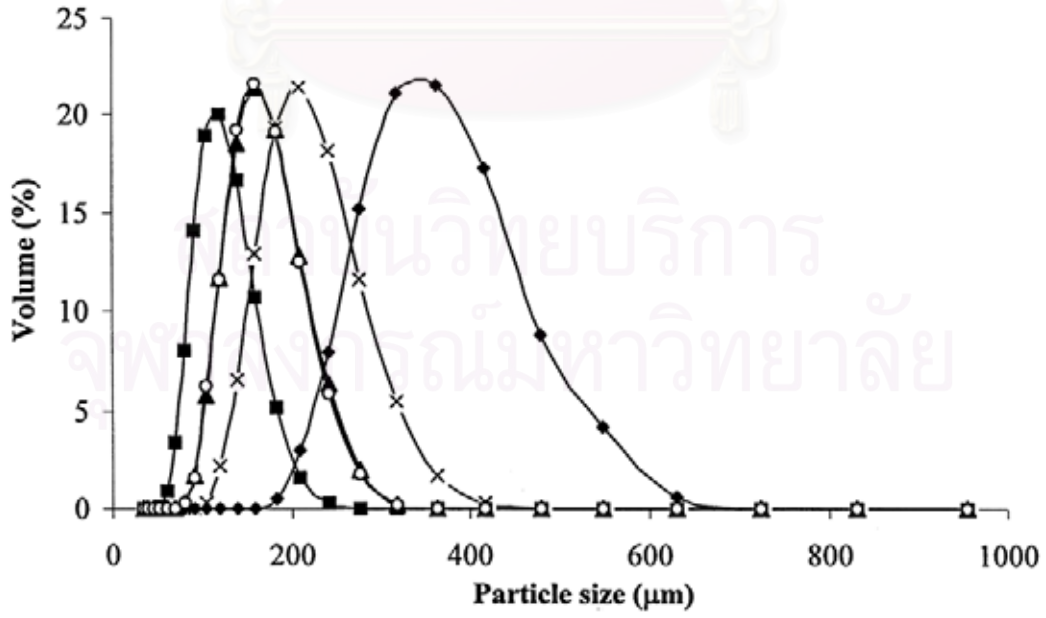


Figure 11 Particle distribution of various resins; Dowex 50W×2-200 (×), ×4-100 (◆), ×4-200 (▲), ×4-400 (■) and ×8-200 (O)

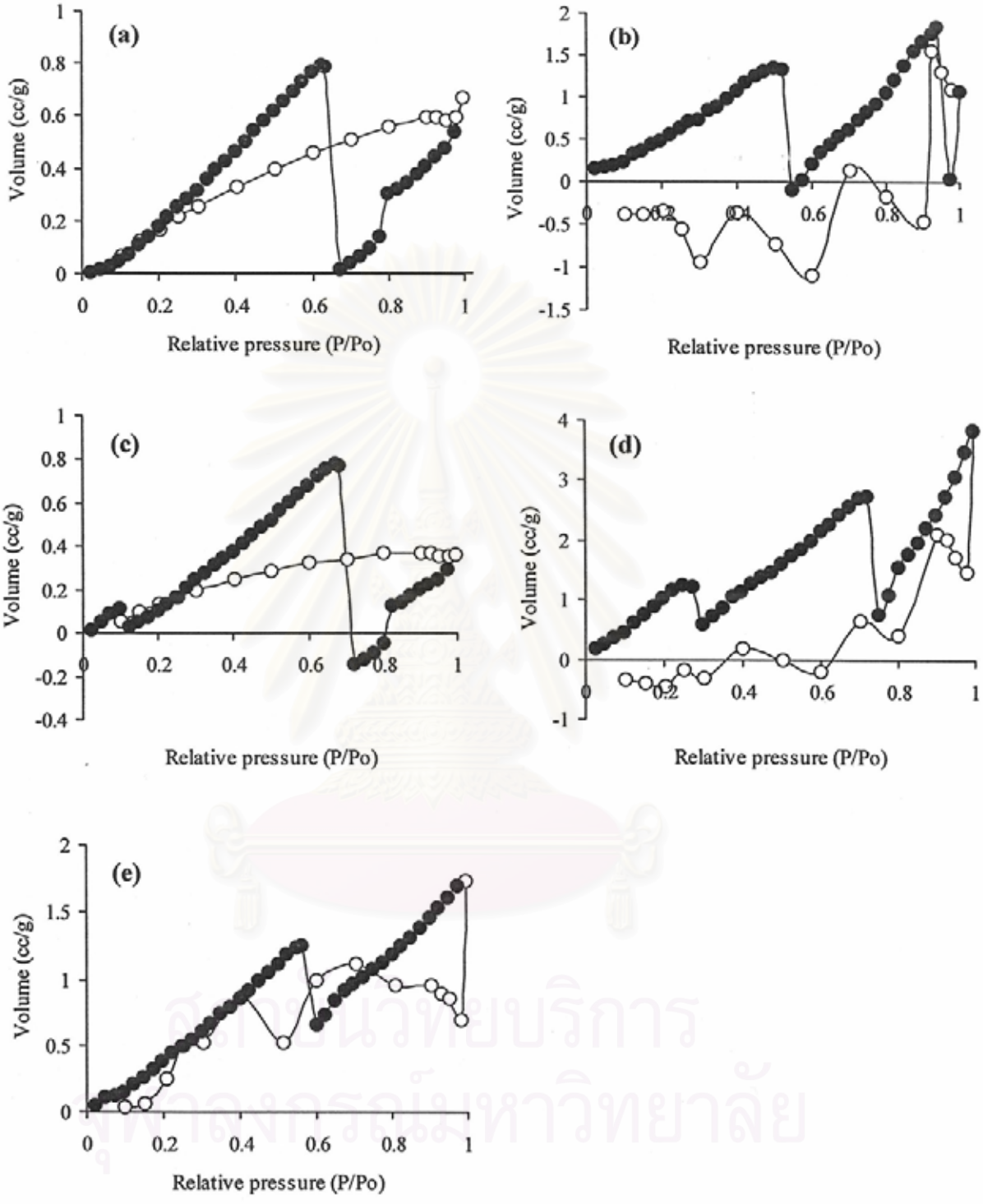


Figure 12 Adsorption (open symbol) and desorption (closed symbol) isotherms of resins; Dowex 50W×2-200 (a), ×4-100 (b), ×4-200 (c), ×4-400 (d) and ×8-200 (e)

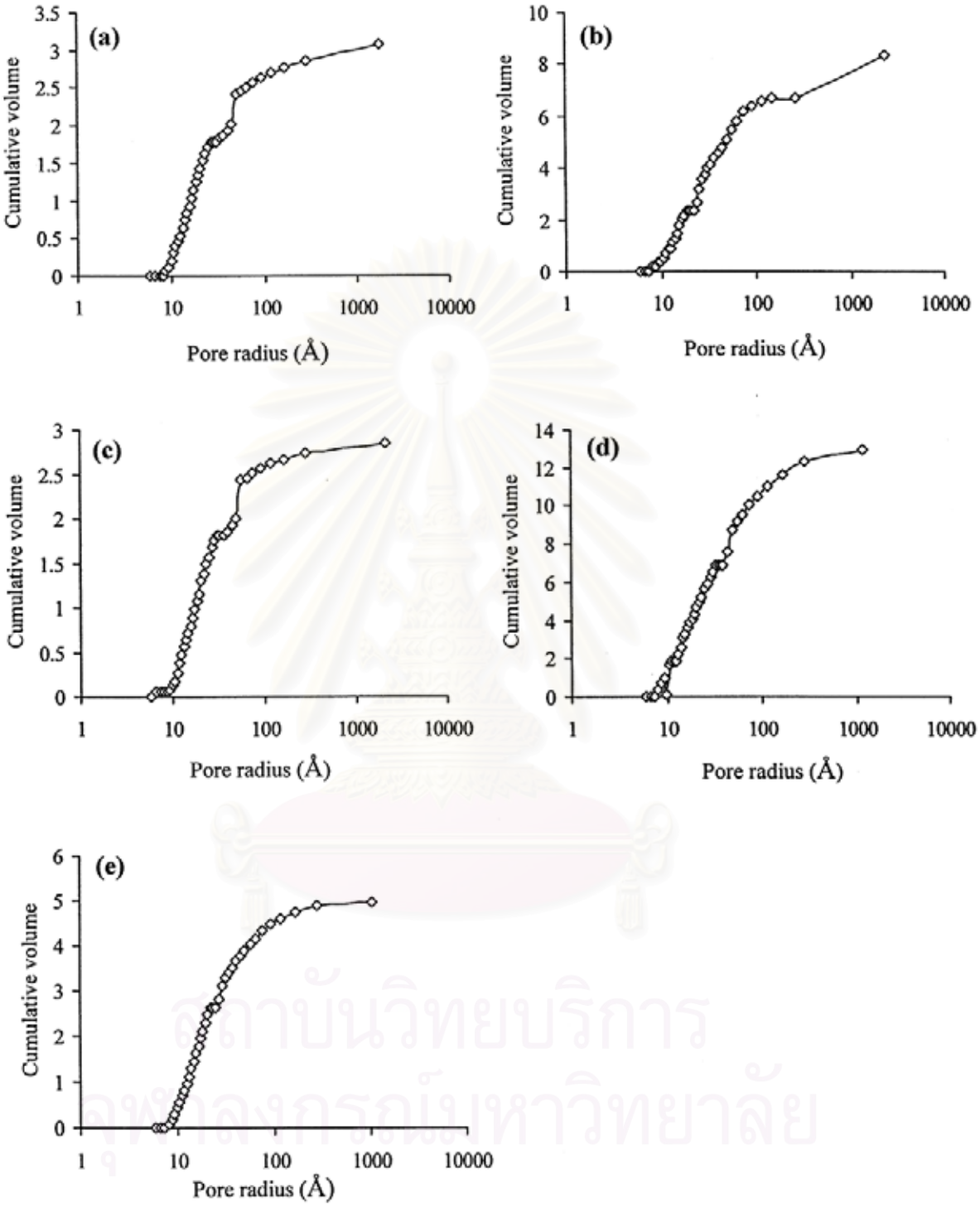


Figure 13 Cumulative pore volume of resins; Dowex 50W×2-200 (a), ×4-100 (b), ×4-200 (c), ×4-400 (d) and ×8-200 (e)

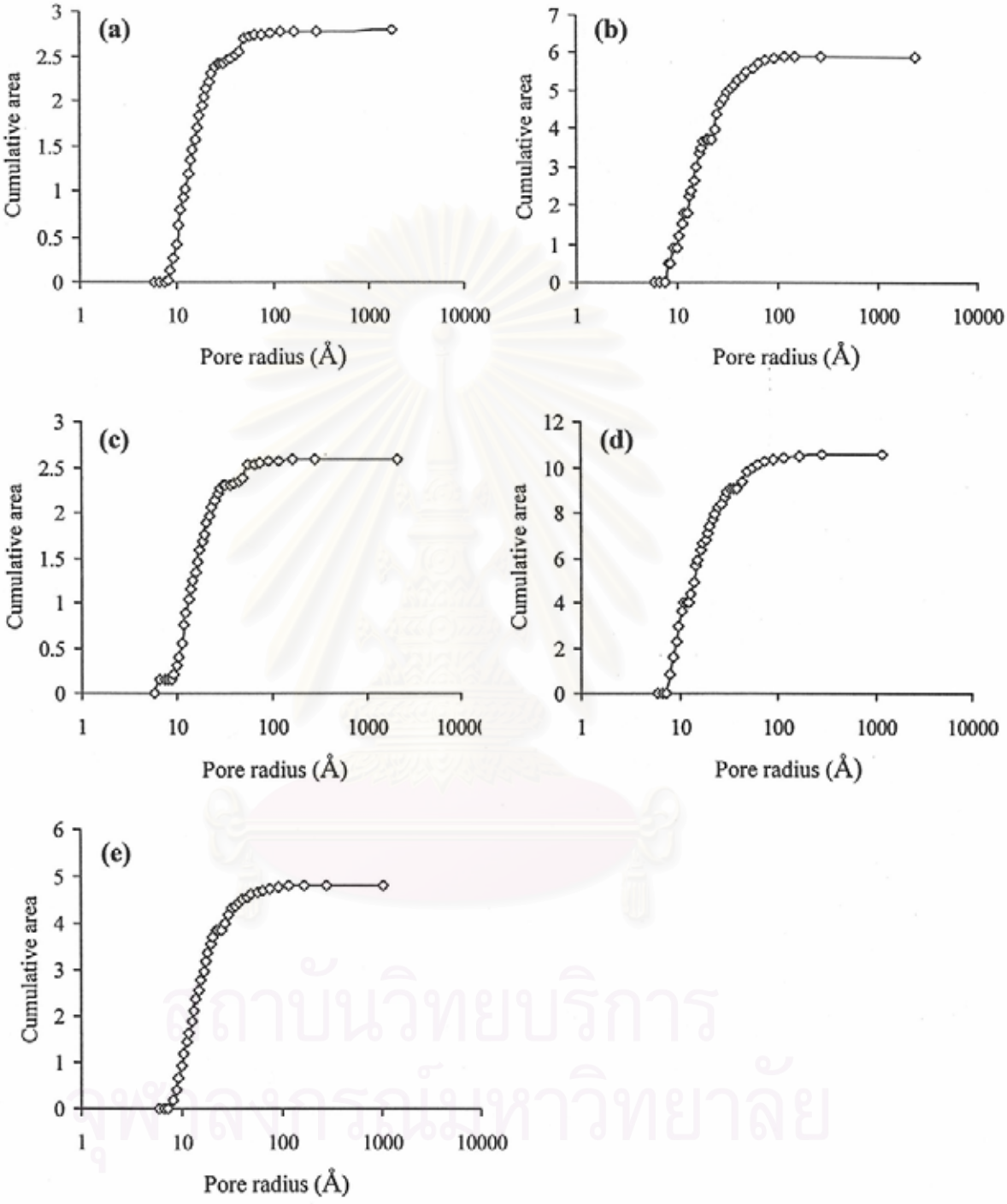


Figure 14 Cumulative pore area of resins; Dowex 50W×2-200 (a), ×4-100 (b), ×4-200 (c), ×4-400 (d) and ×8-200 (e)

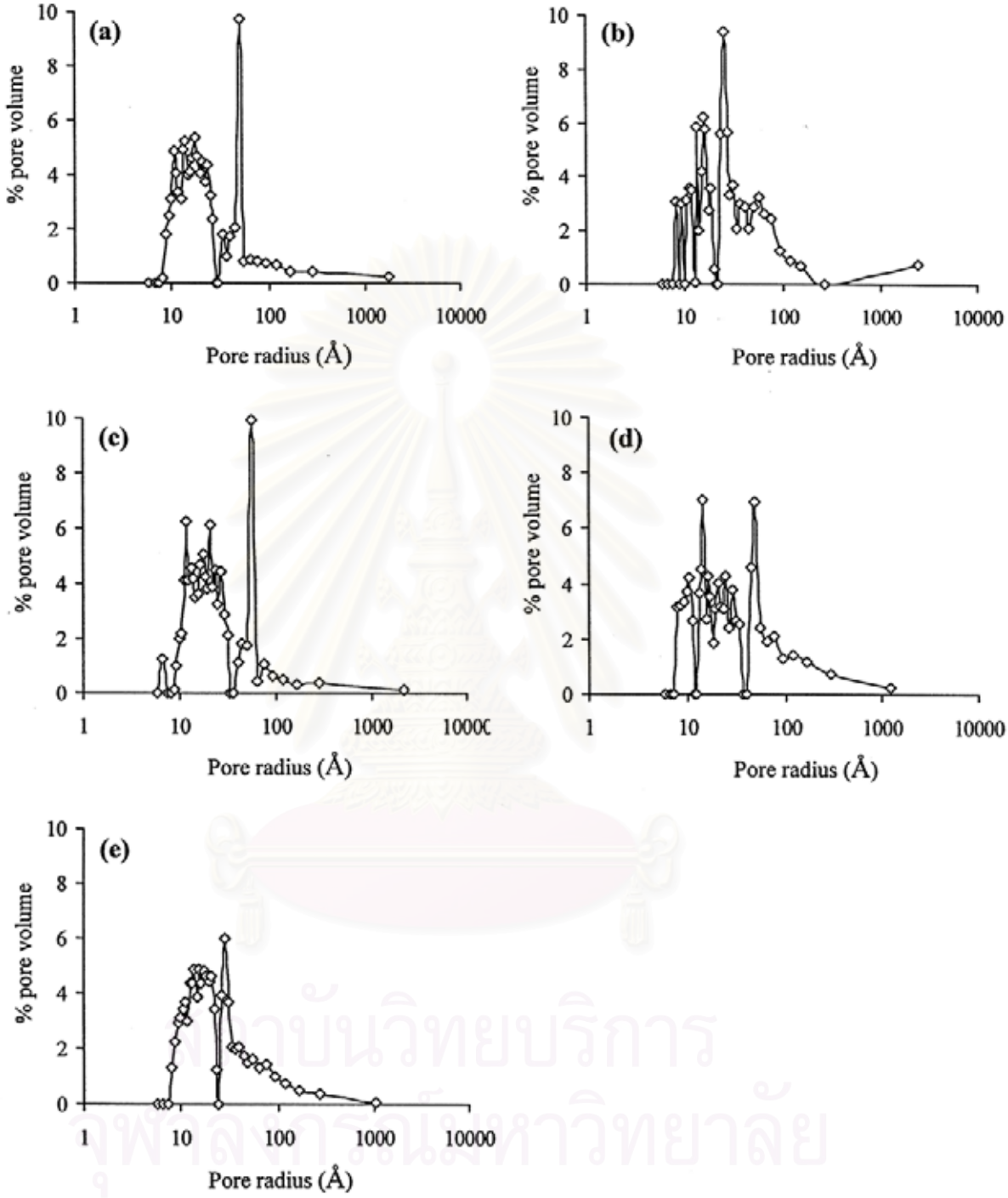


Figure 15 Pore volume distribution of resins; Dowex 50W×2-200 (a), ×4-100 (b), ×4-200 (c), ×4-400 (d) and ×8-200 (e)

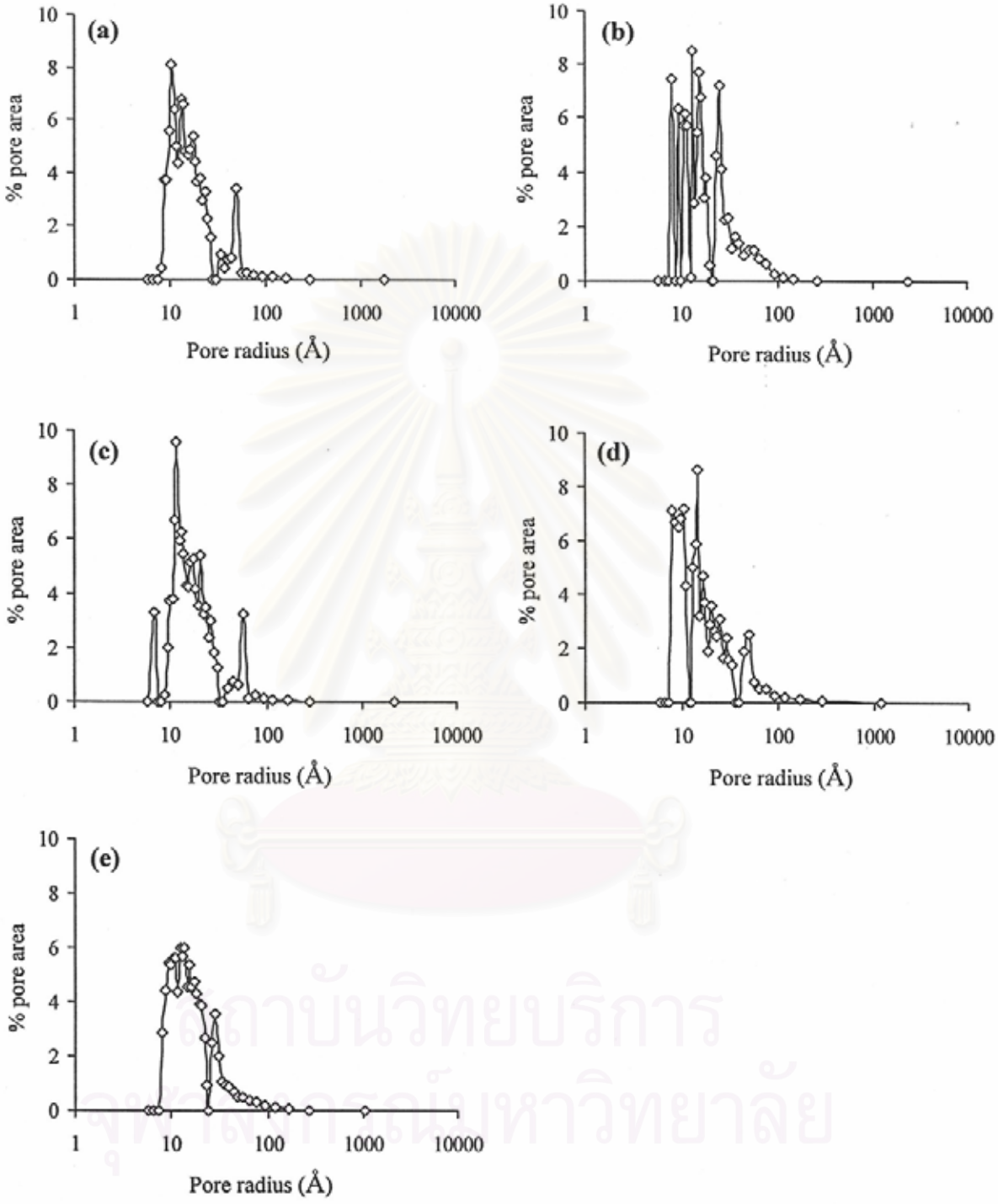


Figure 16 Pore area distribution of resins; Dowex 50W×2-200 (a), ×4-100 (b), ×4-200 (c), ×4-400 (d) and ×8-200 (e)

appeared that all resins were comparable in dry pore radius regardless of the degree of resin crosslinkage and the particle size.

The resins were viewed as if they contain elastic springs along crosslinked hydrocarbon chains (Figure 7) (Simon, 1991; Harland, 1994). In contact with water, the resins would swell driven by the swelling (osmotic) pressure. The swelling of resins meanwhile caused a stretching or an extension of the crosslinked hydrocarbon chains, subsequently resulting in the increment of resin size and internal pore radius (hydrated pore radius). The swollen size and hydrated pore radius of resins would amplify to the extent where the swelling pressure counterbalanced the restoring spring force of the crosslinked hydrocarbon chains that closely correlate with the resin crosslinkage. Lower crosslinked resins having weaker restoring force would swell in a greater extent than higher crosslinked resins having stronger restoring force, as shown in Figure 17 (Irwin et al., 1987; Simon, 1991). Using the obtained data of the resin swelling and the dry pore radius and assuming the direct proportion of the increased resin size and internal pore size from swelling, the hydrated pore radius of resins could be estimated as presented in Table 5. In contrast to the dry pore radius, the hydrated pore radius of resins was different, which evidently decreased with increasing the degree of crosslinkage within resins. While, the swelling of the different size resins with the same ×4 crosslinkage (Dowex 50W×4-100, ×4-200 and ×4-400) was similar (Figure 17), which was due to the equivalent restoring force of these resins. Accordingly, their hydrated pore radius estimated was comparable and insensitive to the particle size of resins (Table 5). From this result, it could clarify that the resin crosslinkage was the determining factor governing the swelling and the hydrated pore size of resins. Nevertheless, the resin crosslinkage did not practically

Table 5 Pore size analysis of dried and hydrated resins

Resins	r		$r_{V50\%}$		$r_{A50\%}$	
	dry	hydrated	dry	hydrated	dry	hydrated
Dowex 50W×2-200	22.10	40.05	22.15	40.14	14.31	25.93
Dowex 50W×4-100	28.20	41.70	34.03	50.32	15.53	22.96
	[22.78][a]	[33.68]	[25.95]	[38.37]		
Dowex 50W×4-200	21.98	32.75	22.56	33.62	15.15	22.58
Dowex 50W×4-400	24.50	36.39	30.45	45.23	14.38	21.36
Dowex 50W×8-200	20.58	25.48	20.79	25.74	14.18	17.56

[a] *Values estimated after excluding the last point*

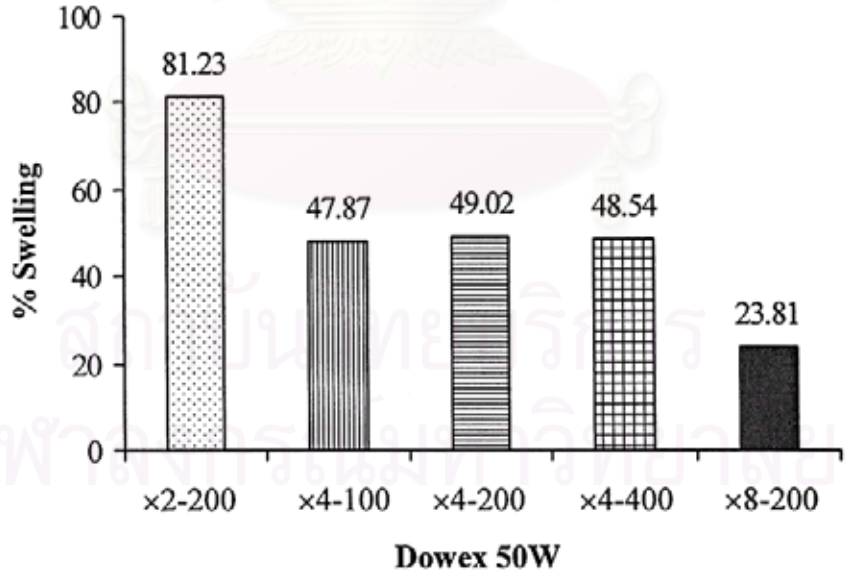


Figure 17 The swelling of resins

affect the swelling rate of resins which was very rapid. From our preliminary study, the complete swelling of all resins finished within 1-2 min, which agreed with the finding of a recent report (Pisal et al., 2004b).

2. Dual-Drug Loading

2.1 Effect of resins with different crosslinkage and overall concentrations

Figure 18 shows the dual-drug loading diagrams of Dowex 50W×2-200, ×4-200 and ×8-200 prepared under various overall drug concentrations of the loading solution. Interestingly, the percent of each drug loaded in the resinate linearly related to the proportion of that drug in the loading solution ($R^2 \geq 0.996$). From this standpoint, the EQC and ELS values were obtained by determining the crossing point of these two linear plots as follows.

$$X_{DTM} = M_{DTM}P_{DTM} + Y_{DTM} \qquad \text{Eq. 27}$$

$$X_{DPH} = M_{DPH}P_{DPH} + Y_{DPH} \qquad \text{Eq. 28}$$

Where X_{DTM} and X_{DPH} are the percent of DTM and DPH in the resinate, P_{DTM} and P_{DPH} are the proportion of DTM and DPH in the loading solution. The values of M_{DTM} and M_{DPH} are the slopes, and the values of Y_{DTM} and Y_{DPH} are the intercepts of the lines of DTM and DPH, respectively. Since $P_{DPH} = 1\text{-}P_{DTM}$, Eq.(28) will be transformed into the following equation.

$$X_{DPH} = -M_{DPH}P_{DTM} + (Y_{DPH} + M_{DPH}) \qquad \text{Eq. 29}$$

The equivalent content is the point where X_{DTM} in Eq.(27) equals X_{DPH} in Eq.(29). Having known the values of M_{DTM}, M_{DPH}, Y_{DTM} and Y_{DPH} from the regression analysis, equalizing Eq.(27) with Eq.(29) can thus estimate the value of P_{DTM}.

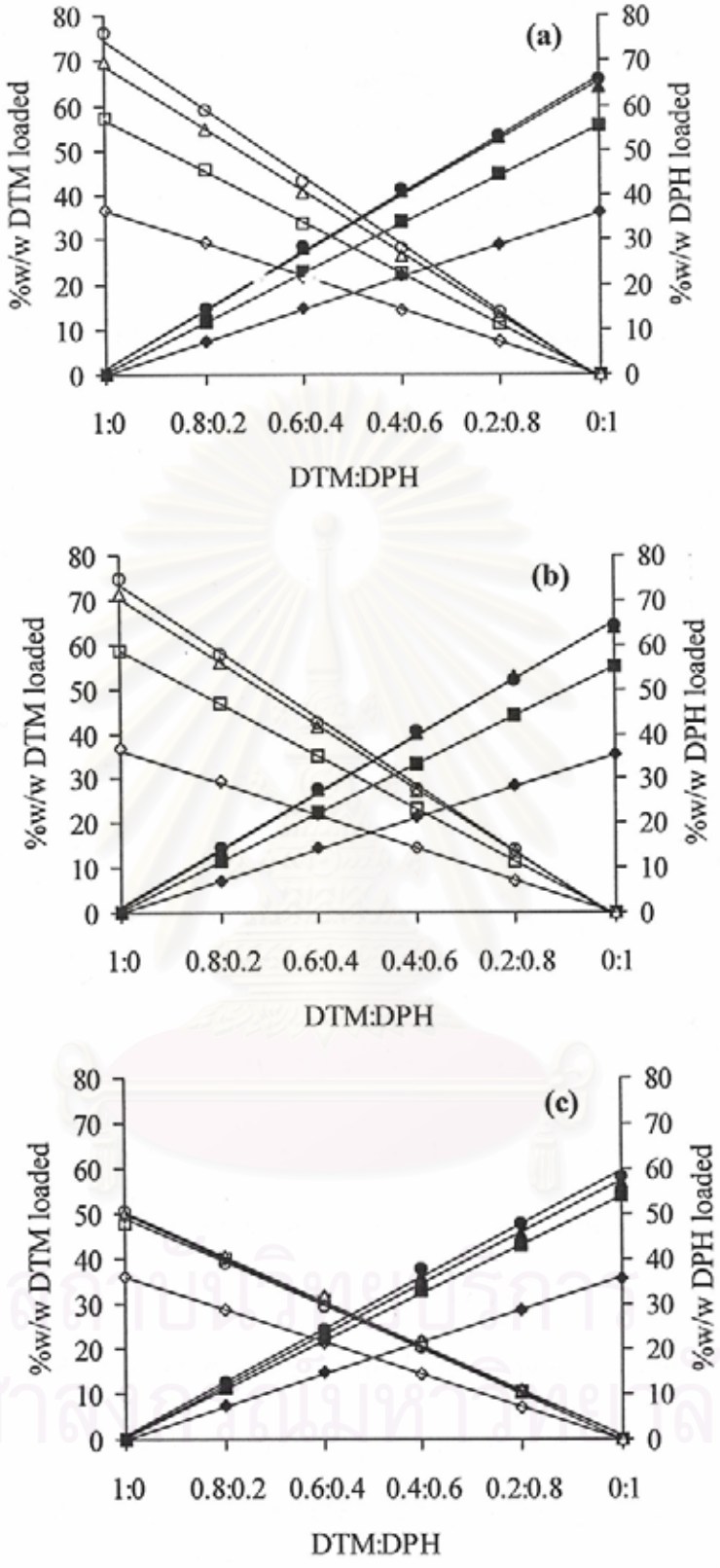


Figure 18 Dual-drug loading diagrams of Dowex 50W×2-200 (a), ×4-200 (b) and ×8-200 (c), obtained under varying overall drug concentrations; 0.25 (◇), 0.50 (□), 0.75 (Δ) and 1.00 %w/v (○), respectively. Where open symbols represent DTM and closed symbols represent DPH

$$P_{DTM} = ELS = \frac{(M_{DPH} + Y_{DPH} - Y_{DTM})}{(M_{DTM} + M_{DPH})} \qquad \text{Eq. 30}$$

ELS is defined to have the same value as P_{DTM}, but its meaning is exclusive. If the value of ELS is, for example, at any X, meaning that the proportions of DTM (P_{DTM}) and DPH (P_{DPH}) in the loading solution used to prepare the resinate are X and (1-X), respectively. Then, the value of EQC can be calculated by substituting either X in Eq.(27), or (1-X) in Eq.(28), which gives the same result.

The calculated EQC values at various overall drug concentrations of the loading solution are presented in Table 6 and depicted in Figure 19. For all resins, the values of EQC increased with increasing the overall drug concentrations ($p<0.05$), and then leveled off. However, the EQC values of Dowex 50W×8-200 reached the plateau earlier and were less than those of Dowex 50W×2-200 and ×4-200 ($p<0.05$). When the values of EQC on the plateau at 1 % w/v overall drug concentration were transformed into the term of exchanged capacity (Table 7), it demonstrated that almost binding sites of Dowex 50W×2-200 and ×4-200 were occupied with the loaded drugs. While, Dowex 50W×8-200 had nearly half of the total binding sites unoccupied. These vacant binding sites might locate in the deep and narrow pore region where the drugs could not access to the binding sites in the normal condition. Dowex 50W×8-200 had more tortuous structure of matrix so that it had greater extents of the inaccessible binding sites (Irwin et al., 1987).

ELS was the proportion of DTM and DPH in the drug loading solution employed to obtain an equivalent content dual-drug resinate. Moreover, it could be an indicative of competition between DTM and DPH in binding with resins. The calculated values of ELS are presented in Table 6. At the overall drug concentration

Table 6 Effect of overall drug concentrations (%w/v) on values of EQC and ELS[a].

Loading parameters of each resin	Overall drug concentrations (%w/v)			
	0.25	0.5	0.75	1.0
EQC				
Dowex 50W×2-200	18.130	28.154	33.586	35.122
	(0.001)	(0.002)	(0.024)	(0.029)
Dowex 50W×4-200	17.931	28.408	33.915	34.493
	(0.001)	(0.003)	(0.030)	(0.024)
Dowex 50W×8-200	18.016	26.031	27.295	27.347
	(0.003)	(0.184)	(0.264)	(0.042)
ELS				
Dowex 50W×2-200	0.500	0.498	0.494	0.480
	(<0.001)	(<0.001)	(0.002)	(0.001)
Dowex 50W×4-200	0.494	0.488	0.486	0.479
	(<0.001)	(<0.001)	(0.001)	(<0.001)
Dowex 50W×8-200	0.503	0.522	0.530	0.548
	(<0.001)	(0.003)	(0.002)	(0.006)

[a] *Values are presented in mean (s.d.).*

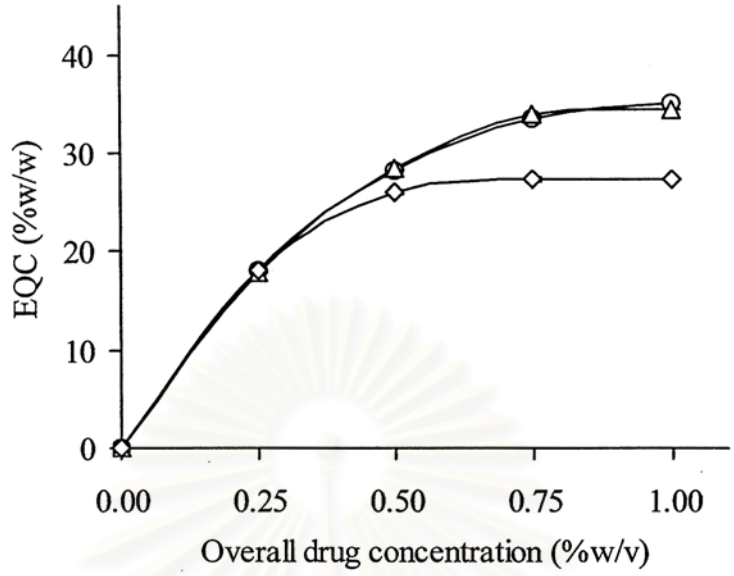


Figure 19 Effect of overall drug concentrations on EQC of Dowex 50W×2-200 (O), ×4-200 (Δ) and ×8-200 (◇)

Table 7 Exchanged capacity of resins prepared under varying overall drug concentrations (%w/v)

Resins	Overall drug concentration (%w/v)							
	0.25		0.50		0.75		1.0	
	meq/g	%[a]	meq/g	%	meq/g	%	meq/g	%
Dowex 50W×2-200	1.53	32.40	3.02	63.96	4.21	89.16	4.62	97.85
Dowex 50W×4-200	1.51	31.58	3.07	64.20	4.28	89.51	4.45	93.06
Dowex 50W×8-200	1.49	32.03	2.64	56.75	2.86	61.48	2.87	61.70

[a] *Values were calculated from* $100 \times (meq/g)/MC_{Na}$.

of 0.25 % w/v, it was found that the ELS values of all resins were around 0.50, indicating no considerable competition of the drugs in binding with the resins. It might be caused by the sufficiency of the accessible binding sites for most of the loaded drugs as the traces of unloaded drugs were found in the final loading solution. However, the values of ELS for Dowex 50W×2-200 and ×4-200 decreased when the overall drug concentration was increased ($p<0.05$). This behavior might indicate the competition occurring between DTM and DPH to share the binding sites in the resins, caused by the insufficiency of the binding sites. The decreased values of ELS far below 0.50 indicated that DTM was more competitive than DPH to bind with the resins. A reverse trend was observed in case of Dowex 50W×8-200, the values of ELS increased with increasing the overall drug concentration ($p<0.05$). An increase of the ELS values above 0.50 demonstrated that DPH was predominant in binding with this resin.

Probably, different mechanisms governing drug loading between low (Dowex 50W×2-200 and ×4-200) and high (Dowex 50W×8-200) crosslinked resins provided different effects of the overall drug concentration on ELS values. It is recognized that the drug loading is driven through electrostatic interaction between the opposite charges. Nevertheless, the magnitude of this interaction, and hence drug loading, is closely associated with the hydrophobicity and the molecular weight or size of loaded drugs (Hale and Packham, 1953; Farag and Nairn, 1988; Kril and Fung, 1990). For similar charged drug molecules, the drug loading will increase as the hydrophobicity of drugs increases owing to an additional van der Waals force generated from the hydrophobic portions between the loaded drug and resin. Moreover, high drug loading is preferable to a smaller molecular weight drug which is easier to introduce into the

binding sites, especially for the resin with high degree of crosslinkage. DTM is a sparingly water soluble drug while DPH is very soluble in water with the partition coefficient (Log P) of 4 and 3.3, respectively (Moffat, 1986; Jack, 1992). DTM is, therefore, likely to be more hydrophobic than DPH. DTM (MW = 370.3) has greater molecular weight than DPH (MW = 291.8). Additionally, the molar volumes of drugs emphasized that DTM (273.3 ml/mole) has relatively bigger size than DPH (250.8 ml/mole). In this work, DTM was found to be more competitive than DPH to bind with Dowex 50W×2-200 and ×4-200 (ELS<0.5, see Table 6). It was obvious that the hydrophobicity of drugs was the determining factor on drug loading onto the resins. As these resins have low crosslinked matrix, the drugs could be loaded to nearly reach the total exchange capacity (Table 7), revealing that the moieties of DTM and DPH were capable of filling most vicinity of the resins. With this regard, the difference in the molecular size of drugs therefore exhibited minor effect. In contrast, Dowex 50W×8-200 has high crosslinked matrix; therefore, the passage of drugs through the narrow pore matrix structure to interact with the binding sites should determine drug loading. DPH has smaller molecular size so that it has higher accessibility into the resin. This might outweigh its inferior hydrophobicity. Accordingly, DPH was more competitive than DTM to bind with the high crosslinked resin.

2.2 Effect of resin quantity

The dual-drug loading diagrams of Dowex 50W×2-200, ×4-200 and ×8-200 obtained from various resin quantities were depicted in Figure 20. The percent of each drug loaded linearly related against the proportion of that drug in the loading solution ($R^2 \geq 0.999$), and then the values of EQC and ELS (Table 8) were calculated using the

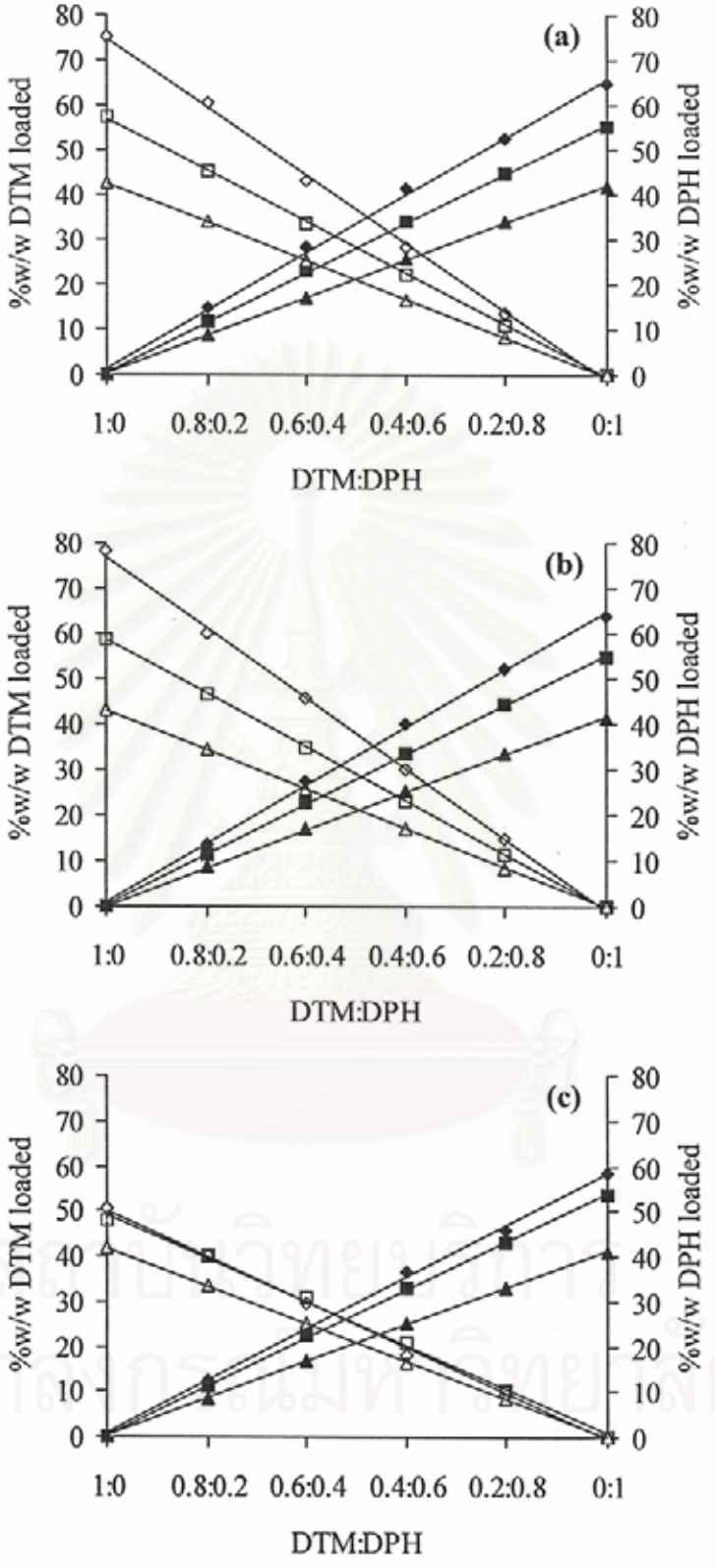


Figure 20 Dual-drug loading diagrams of Dowex 50W×2-200 (a), ×4-200 (b) and ×8-200 (c), obtained under varying quantity of resins; 0.125 (◇), 0.500 (□) and 0.800 g (Δ), respectively. Where open symbols represent DTM and closed symbols represent DPH

Table 8 Effect of resin quantity (g) on values of EQC and ELS[a]

Loading parameters of each resin	Resin quantity (g)		
	0.125	0.500	0.800
EQC			
Dowex 50W×2-200	35.093	28.154	21.137
	(0.138)	(0.002)	(0.001)
Dowex 50W×4-200	35.254	28.408	21.151
	(0.093)	(0.003)	(0.003)
Dowex 50W×8-200	26.990	26.031	20.767
	(0.364)	(0.185)	(0.030)
ELS			
Dowex 50W×2-200	0.478	0.498	0.500
	(0.002)	(<0.001)	(<0.001)
Dowex 50W×4-200	0.463	0.488	0.494
	(0.001)	(<0.001)	(<0.001)
Dowex 50W×8-200	0.543	0.522	0.500
	(0.009)	(0.003)	(0.001)

[a] *Values are presented in mean (s.d.).*

method as described earlier. It was found that the values of EQC decreased with increasing the quantity of resins ($p<0.05$). This was due to an increase in the available binding sites of resins, which thus exerted dilution on the extent of loaded drugs in the resinate. Using the values of EQC, the exchanged capacity was calculated as shown in Table 9. It demonstrated that the vacant binding sites (capacity) were more left as a function of the increased quantity of resins in drug loading.

Table 9 Exchanged capacity of resins prepared from varying resin quantity (g) in dual-drug loading

Resins	Resin quantity (g)					
	0.125		0.500		0.800	
	meq/g	%[a]	meq/g	%	meq/g	%
Dowex 50W×2-200	4.61	97.64	3.02	63.96	1.91	40.45
Dowex 50W×4-200	4.66	97.46	3.07	64.20	1.91	39.94
Dowex 50W×8-200	2.81	60.41	2.64	56.75	1.86	39.99

[a] *Values were calculated from* $100 \times (meq/g)/MC_{Na}$

A change in the quantities of resins (or binding sites) also led to alteration of the values of ELS ($p<0.05$, Table 8). At low quantity of resins (0.125 g resin), the ELS values for Dowex 50W×2-200 and ×4-200 were 0.478 and 0.463, respectively, indicating competition occurring between DTM and DPH to bind with the resins, which might be owing to insufficient binding sites. The above ELS values were less than 0.50, indicating that DTM preferentially bound with Dowex 50W×2-200 and ×4-200. While, the ELS values for Dowex 50W×8-200 was 0.543, implying that DPH was more competitive than DPM to bind with this high crosslinked resin. When the

quantity of resins was increased from 0.125 to 0.800 g, the ELS values of all resins approached to around 0.50. This demonstrated that the competition between DTM and DPH in binding with the resins decreased to a lesser extent. The compromise in drug loading might result from the excess in the binding sites of which the vacant extent was gradually more left when the quantity of resins in drug loading was increased (Table 9). In conclusion, increasing resin quantity provided the effects on equivalent dual-drug loading opposite to increasing overall drug loading concentrations as described above.

2.3 Effect of temperature

The effect of heat on dual-drug loading is shown in Figure 21. The plots of the percent of each drug loaded against the proportion of that drug in the loading solution were in good linearity ($R^2 \geq 0.994$). Therefore, the values of EQC as well as ELS were calculated by the same method as described previously (Table 10). It could be concluded that an increase in the loading temperatures from 35 to 55°C had no considerable effect on the equivalent dual-drug loading of Dowex 50W×2-200 and ×4-200. It might be attributed to the exhaust of the binding sites (Table 11) and the inherently large pores inside these resins. On the other hand, the heat significantly affected the equivalent dual-drug loading of Dowex 50W×8-200 ($p<0.05$). The values of EQC increased when more heat (35 to 65°C) was applied. This finding agreed well with the previous work which illustrated the promotion of heat on single drug loading onto this resin (Irwin et al., 1988). It was explained that the heat expanded the centered narrow pore region, affording the drugs accessible to deeper binding sites of the resin.

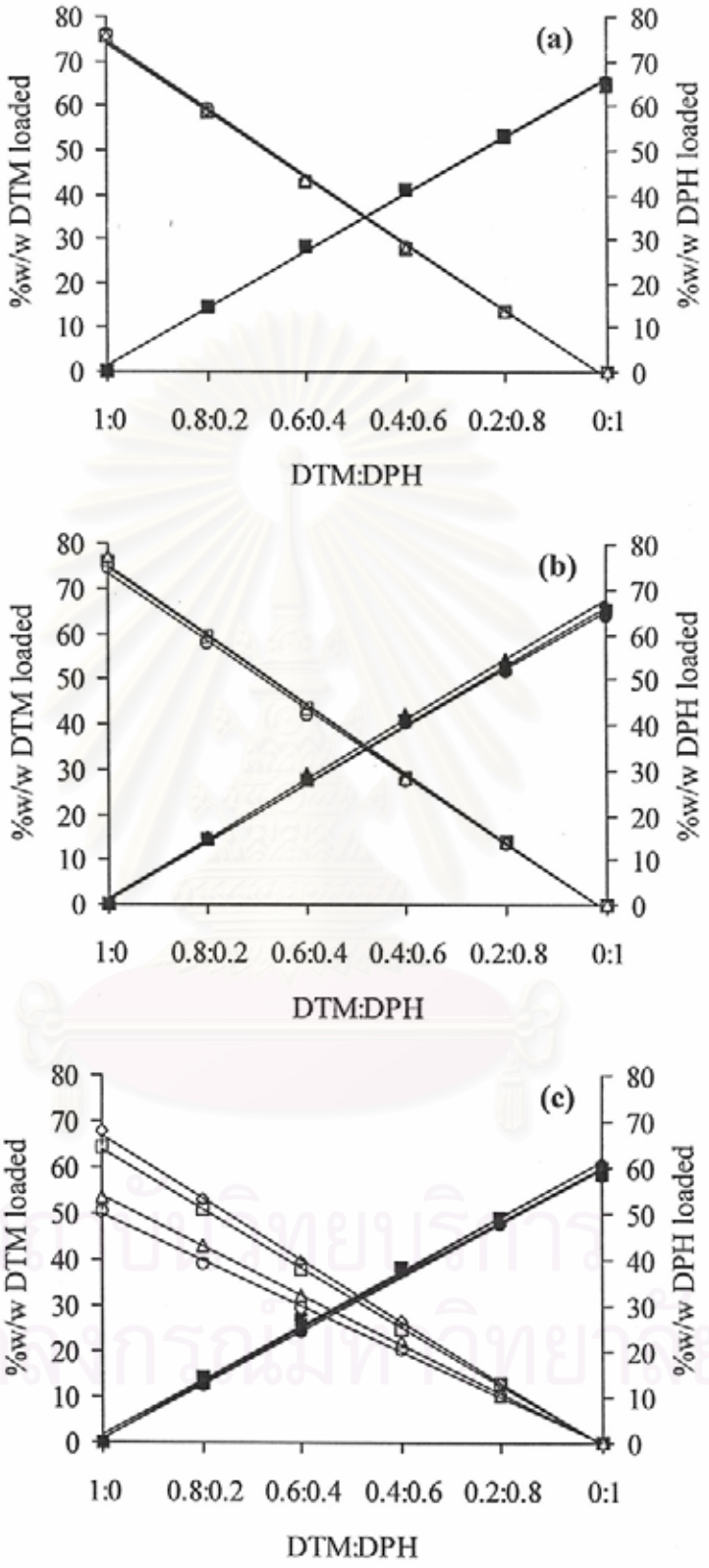


Figure 21 Dual-drug loading diagrams of Dowex 50W×2-200 (a), ×4-200 (b) and ×8-200 (c), obtained from varying temperatures; 35 (O), 45 (Δ), 55 (□), and 65°C (◇) respectively. Where open symbols represent DTM and closed symbols represent DPH

Table 10 Effect of temperatures on values of EQC and ELS[a]

Loading parameters of each resin	Loading temperatures			
	35°C	45°C	55°C	65°C
EQC				
Dowex 50W×2-200	35.122	34.958	34.941	-[b]
	(0.029)	(0.027)	(0.019)	
Dowex 50W×4-200	34.493	35.632	35.088	-[b]
	(0.024)	(0.017)	(0.036)	
Dowex 50W×8-200	27.347	28.814	31.650	32.174
	(0.042)	(0.033)	(0.059)	(0.057)
ELS				
Dowex 50W×2-200	0.480	0.479	0.482	-[b]
	(0.001)	(<0.001)	(<0.001)	
Dowex 50W×4-200	0.479	0.483	0.477	-[b]
	(<0.001)	(<0.001)	(0.001)	
Dowex 50W×8-200	0.548	0.535	0.498	0.483
	(0.006)	(0.002)	(0.001)	(0.001)

[a] *Values are presented in mean (s.d.).*

[b] *Did not perform.*

Table 11 Exchanged capacity of resins prepared under varying temperatures when using 1.00 % w/v overall drug concentration in drug loading

Resins	Loading temperatures							
	35°C		45°C		55°C		65°C	
	meq/g	%[a]	meq/g	%	meq/g	%	meq/g	%
Dowex 50W×2-200	4.62	97.85	4.58	97.00	4.57	96.79	-[b]	-[b]
Dowex 50W×4-200	4.45	93.06	4.77	99.76	4.61	96.47	-[b]	-[b]
Dowex 50W×8-200	2.87	61.70	3.14	67.59	3.74	80.42	3.86	82.98

[a] *Values were calculated from 100×(meq/g)/MC_{Na}.*

[b] *Did not perform.*

It was evident that the heat exhibited more enhancing effect on DTM adsorbed onto Dowex 50W×8-200 than on DPH (Figure 21(c)). The decrease in the values of ELS from 0.548 to 0.483 was observed ($p<0.05$, Table 10). This suggested that the preference of this resin to absorb DPH at low temperature (35°C) was gradually changed to bind preferentially with DTM at higher temperatures. This could be explained that the heat induced expansion of the narrow pore region of the resin where DTM was unable to enter at low temperature condition. Once without limited accessibility through the resin structure, DTM, which has superior hydrophobicity, then was more competitive than DPH to bind with this resin. In conclusion, the factor governing dual-drug loading onto Dowex 50W×8-200 at high temperature changed from the accessibility to the hydrophobicity of the loaded drugs.

2.4 Effect of particle size

The diagrams of dual-drug loading onto 100, 200 and 400 mesh size 4 % crosslinked resins (i.e. Dowex 50W×4-100, ×4-200 and ×4–400) were presented in Figure 22. All diagrams showed linear relationships of the percent of each drug loaded in the resinate against the proportion of that drug in the loading solution with the coefficient of determination greater than 0.996. The values of EQC, ELS and exchanged capacity were therefore obtained by the calculation described earlier. It seemed that three different size resins provided no obvious change in the values of EOC, ELS and hence the exchanged capacity (Table 12). The cause was due to the similarity in the total exchange capacity and the hydrated pore size among these resins (Table 4 and 5). Finally, it could be concluded that the particle size did not have considerable effect upon the equivalent dual-drug loading onto these 4 % crosslinked resins.

3. Preparation of Resinates for Release Studies

The resinates with similar values of EQC were employed for drug release study in order to avoid any confounding effects from different levels of drug loading (Chen et al., 1992; Akkaramongkolporn et al., 2000, and 2001). As presented in Table 6, the resinates of Dowex 50W×2-200 and ×4-200 prepared using 0.50 % w/v overall drug concentration (ELS = 0.498 and 0.488, respectively) and that of Dowex 50W×8-200 prepared using 1.00 % w/v overall drug concentration (ELS = 0.548) gave similar values of EQC (about 28%), then they were selected for release evaluation.

Several batches of each selected resinate were prepared using the same loading condition, and the resultant resinates are presented in Table 13. It was seen that all prepared resinates contained the similar contents of DTM and DPH. Moreover, the

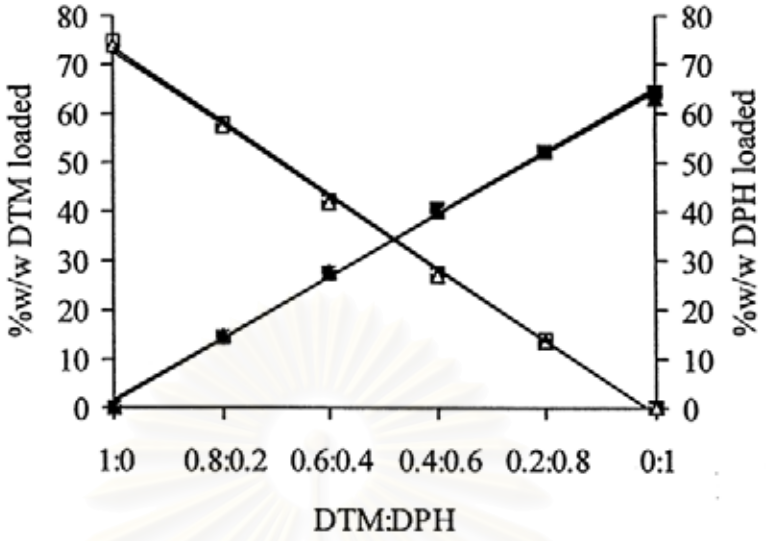


Figure 22 Dual-drug loading diagrams of various particle size of Dowex 50W×4; 100 mesh (Δ), 200 mesh (□) and 400 mesh (◇). Where open symbols represent DTM and closed symbols represent DPH

Table 12 Effect of particle size of Dowex 50W×4 on values of EQC, ELS and exchanged capacity

Mesh size	EQC	ELS	Exchanged capacity	
			meq/g	%
100	34.188[a]	0.481	4.37	97.11[b]
	(0.020)	(<0.001)		
200	34.493	0.479	4.45	93.06
	(0.024)	(<0.001)		
400	34.270	0.482	4.39	93.40
	(0.017)	(<0.001)		

[a] *Values are presented in mean (s.d.).*

[b] *Values were calculated from* $100 \times (meq/g)/MC_{Na}$

Table 13 % w/w of drugs in resinates from repeated preparations

Resins	Dowex 50W×2-200		Dowex 50W×4-200		Dowex 50W×8-200	
Batch no.	DTM	DPH	DTM	DPH	DTM	DPH
1	28.413	27.721	26.911	28.136	26.332	27.348
2	28.691	27.455	26.910	28.131	28.859	28.818
3	28.707	27.45	26.901	28.126	28.894	28.600
4	27.544	28.672	27.971	28.806	27.187	28.290
5	27.532	28.675	27.972	28.802	27.265	28.702
6	27.539	28.672	27.972	28.805	27.693	27.940
7	28.841	27.731	28.047	28.410	27.826	28.021
8	28.84	27.732	28.048	28.412	27.506	28.263
9	28.329	28.709	28.038	28.411	27.514	28.981
10	28.322	28.707			28.232	28.464
11	28.318	28.711			27.841	28.201
12					26.964	27.023
13					27.545	27.705
Mean	28.280	28.203	27.641	28.449	27.666	28.181
S.D.	0.515	0.569	0.551	0.293	0.709	0.573

obtained drug contents were very close to the estimated values of EQC (Table 6). The findings demonstrated the reproducibility and practicality of the proposed procedure in preparing the equivalent content dual-drug resinate.

4. In Vitro Release Characteristics

4.1 Release kinetic and rate

It has been recognized that drug release from resinates is governed by the pore diffusion resistance called “particle diffusion controlled process” (Reichenberg, 1953; Russel, 1970; Bhaskar et al., 1986; Irwin et al., 1987; Pongjanyakul et al., 2005b). Accordingly, the drug release of the resinates was tested for the kinetic of particle diffusion controlled process by using Reichenberg’ s model (Eq. 12-14). The relevant kinetic parameters of each drug, which were determined from linear portions of drug release (LRP), are summarized in Table 14 and 15, respectively. It was evident that the release kinetic of the resinates could be described by Reichenberg’s model of particle diffusion controlled process with the coefficient of determination (R^2) ≥ 0.97.

4.2 Effect of crosslinkage

As illustrated in Figure 23, the drug release from the resinates of Dowex 50W×2-200 and ×4-200 was rapid and reached plateaus within 2 h. At the same ionic strength, the resinates of Dowex 50W×4-200 showed slightly slower drug release ($p<0.05$, Table 14 and 15). The drug release from the resinates using Dowex 50W×8-200 was obviously slowest ($p<0.05$), and showed considerably more extended action up to 6 h. It was evident that the degree of crosslinkage markedly affected the swelling and the hydrated pore size of resins (Figure 17, Table 5). The higher

Table 14 Kinetic parameters of DTM released from the prepared dual-drug resinates

Resin	EQC	Ionic strength (N)	D ($\times 10^{-10}$ m^2/h)[a]	R^2	LPR (%)	% 12 h released[a]
Dowex 50W ×2-200	28	0.05	1.293 (0.055)	0.985	0-58	68.21 (0.33)
	28	0.1	2.380 (0.122)	0.981	0-72	81.86 (0.70)
	28	0.2	4.235 (0.074)	0.999	0-70	84.65 (2.08)
	28	0.4	7.216 (0.778)	0.994	0-82	91.76 (0.61)
Dowex 50W ×4-200	28	0.05	0.681 (0.042)	0.988	0-54	62.75 (0.38)
	28	0.1	1.175 (0.163)	0.995	0-66	77.72 (0.59)
	28	0.2	1.871 (0.184)	0.974	0-77	83.99 (0.79)
	28	0.4	2.374 (0.157)	0.983	0-83	92.40 (0.31)
Dowex 50W ×8-200	28	0.05	0.193 (0.001)	0.980	0-86	69.61 (0.26)
	28	0.1	0.259 (0.016)	0.978	0-73	79.34 (1.25)
	28	0.2	0.378 (0.023)	0.972	0-87	91.03 (0.42)
	28	0.4	0.316 (0.047)	0.998	0-92	92.00 (3.37)
	28	SIF	0.231 (0.003)	0.976	0-70	75.13 (0.13)
	18	0.4	0.257 (0.008)	0.989	0-79	80.00 (0.29)

[a] *Values are presented in mean (s.d.).*

Table 15 Kinetic parameters of DPH released from the prepared dual-drug resinates

Resin	EQC	Ionic strength (N)	D ($\times 10^{-10}$ m^2/h)[a]	R^2	LPR (%)	% 12 h released[a]
Dowex 50W ×2-200	28	0.05	1.662 (0.086)	0.985	0-63	74.52 (0.21)
	28	0.1	2.926 (0.129)	0.979	0-77	86.02 (1.08)
	28	0.2	5.792 (0.361)	0.977	0-92	96.65 (0.59)
	28	0.4	13.286 (2.089)	0.998	0-93	99.94 (1.04)
Dowex 50W ×4-200	28	0.05	1.069 (0.031)	0.986	0-64	73.34 (0.46)
	28	0.1	1.882 (0.285)	0.995	0-77	88.27 (0.41)
	28	0.2	2.976 (0.352)	0.972	0-88	93.09 (0.77)
	28	0.4	3.511 (0.176)	0.974	0-91	98.88 (0.26)
Dowex 50W ×8-200	28	0.05	0.238 (0.002)	0.975	0-77	77.82 (0.33)
	28	0.1	0.348 (0.022)	0.983	0-86	88.26 (0.26)
	28	0.2	0.407 (0.016)	0.972	0-92	93.02 (0.20)
	28	0.4	0.296 (0.034)	0.990	0-90	90.48 (1.49)
	28	SIF	0.306 (0.018)	0.965	0-82	84.06 (0.25)
	18	0.4	0.430 (0.029)	0.986	0-85	87.96 (0.43)

[a] *Values are presented in mean (s.d.).*

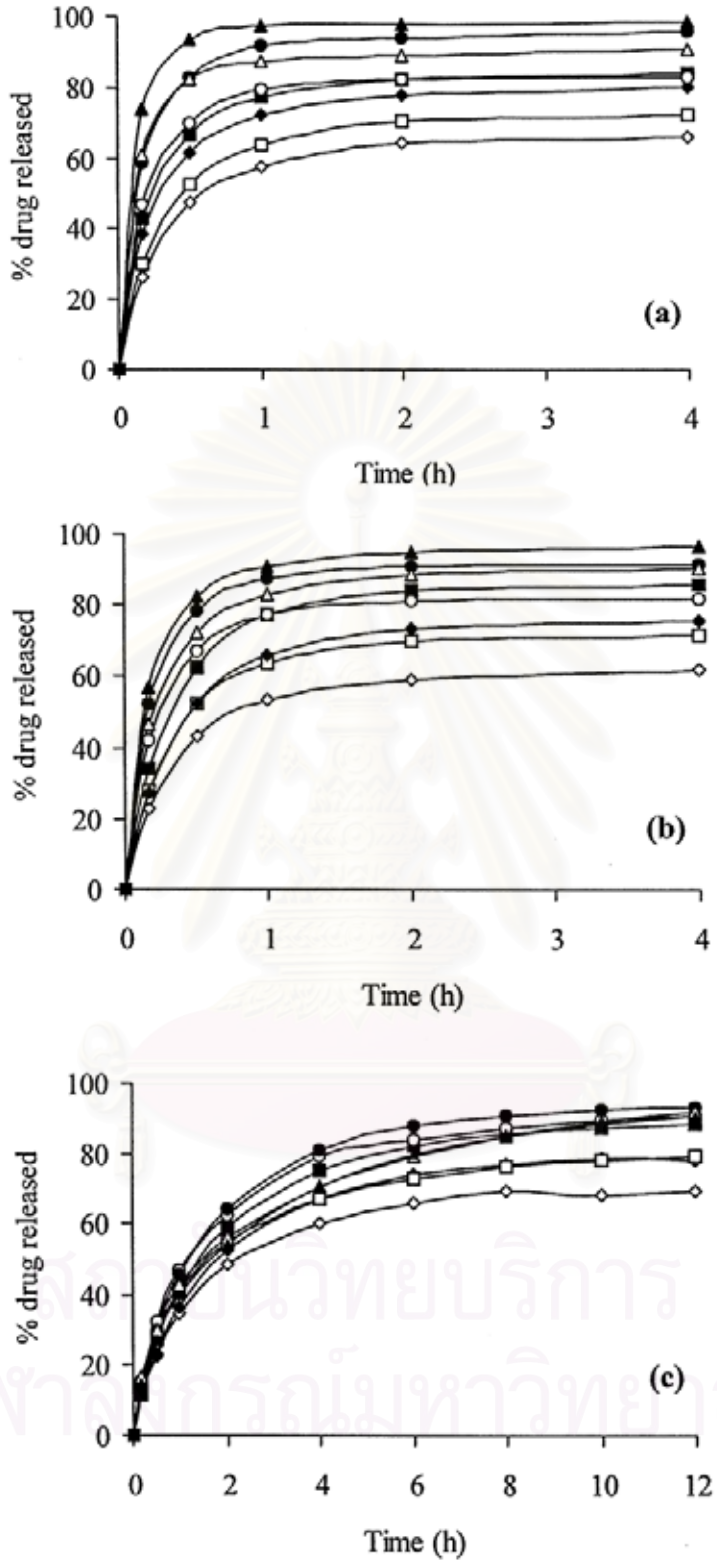


Figure 23 Profiles of DTM and DPH released from the resinates of Dowex 50W×2-200 (a), ×4-200 (b) and ×8-200 (c), performed in 0.05 (◇), 0.1 (□), 0.2 (○) and 0.4 N (Δ) KCl, respectively. Where open symbols represent DTM and closed symbols represent DPH

crosslinked resin provided the lower swelling and hence the narrower hydrated pore size, which thus exerted a greater resistance on the drug release from the resin particles. Therefore, the retardation of drug release from the resinates increased as a function of increasing degree of crosslinkage within the resins. This finding confirmed that the resin crosslinkage was clearly an important parameter in modifying the drug release of resinates (Schacht et al., 1982; Irwin et al., 1987).

4.3 Effect of ionic strength

With regard to the drug delivery based on ion exchange, the ionic strength plays an important role on drug release. An increase in the ionic strength enhances the influx of eluting ions, and will increase the liberation of the bound drug. This results in an increased concentration gradient of the liberated drug diffusing outwardly from the resin, and hence greater drug release (Irwin et al., 1987; Sprockel and Prapaitrakul, 1988; Ogger et al., 1991; Pisal et al., 2004a). In this work, the drug release from the resinates of Dowex 50W×2-200 and ×4-200 was found to be increasing with an increase in the ionic strength of release media ($p<0.05$) in accordance with the previous reports (Figure 23, Table 14 and 15). Interestingly, the increase of ionic strength might not produce faster drug release as it is always expected. In case of the resinates prepared using Dowex 50W×8-200, the ionic enhancing effect on drug release occurred only with increasing the ionic strength in the range from 0.05 to 0.2 N of KCl ($p<0.05$). While the drug release performed in 0.4 N KCl was considerably slower than that in the lower ionic strengths ($p<0.05$, Table 14 and 15). A similar result had been reported in a previous work (Ogger et al., 1991). The cause for this unexpected result might associate with the narrow pore matrix

structure of this resin. Potassium ion having very small size (atomic weight = 39), it was likely that further increasing the influx of eluting ions from 0.2 to 0.4 N extensively liberated the bound drugs. The burst extents of the free drugs whose molecular weights are about seven to eight times larger than the eluting ions probably exceeded the capacity of diffusive pathways within this resin. This might cause the congestion on the outward movement of drugs from the resin, which consequently resulted in the delay of drug release.

Also, drug release from the resinate of Dowex 50W×8-200 was evaluated in the USP simulated intestinal fluid without enzyme (SIF) which was a representative of physiological fluids. The release profile and the kinetic parameters are presented in Figure 24, Table 14 and 15, respectively. The percent release and release rate in SIF lay between that in 0.05 and 0.1 N KCl solutions, corresponding to the total cation in the release media. The total cation of K^+ plus Na^+ in SIF was about 87.0 mEq/l (Pongjanyakul et al., 2005) and that of K^+ in 0.05 and 0.1 N KCl solutions was 50 and 100 mEq/l, respectively. This finding confirmed the significance of ionic strength on the release of resinates.

4.4 Effects of loaded drugs

Most release of DPH was in faster rate and greater extent than that of DTM ($p<0.05$, Figure 23, Table 14 and 15), which might be explained by attribution of the hydrophobicity and the molecular size of the loaded drugs. DTM having greater hydrophobicity exerted stronger van der Waals force with the resins. Therefore, it was allowed less liberation than DPH. In addition, the larger molecular size might be responsible for the less release of DTM (Farag and Nairn, 1988; Kril and Fung, 1990).

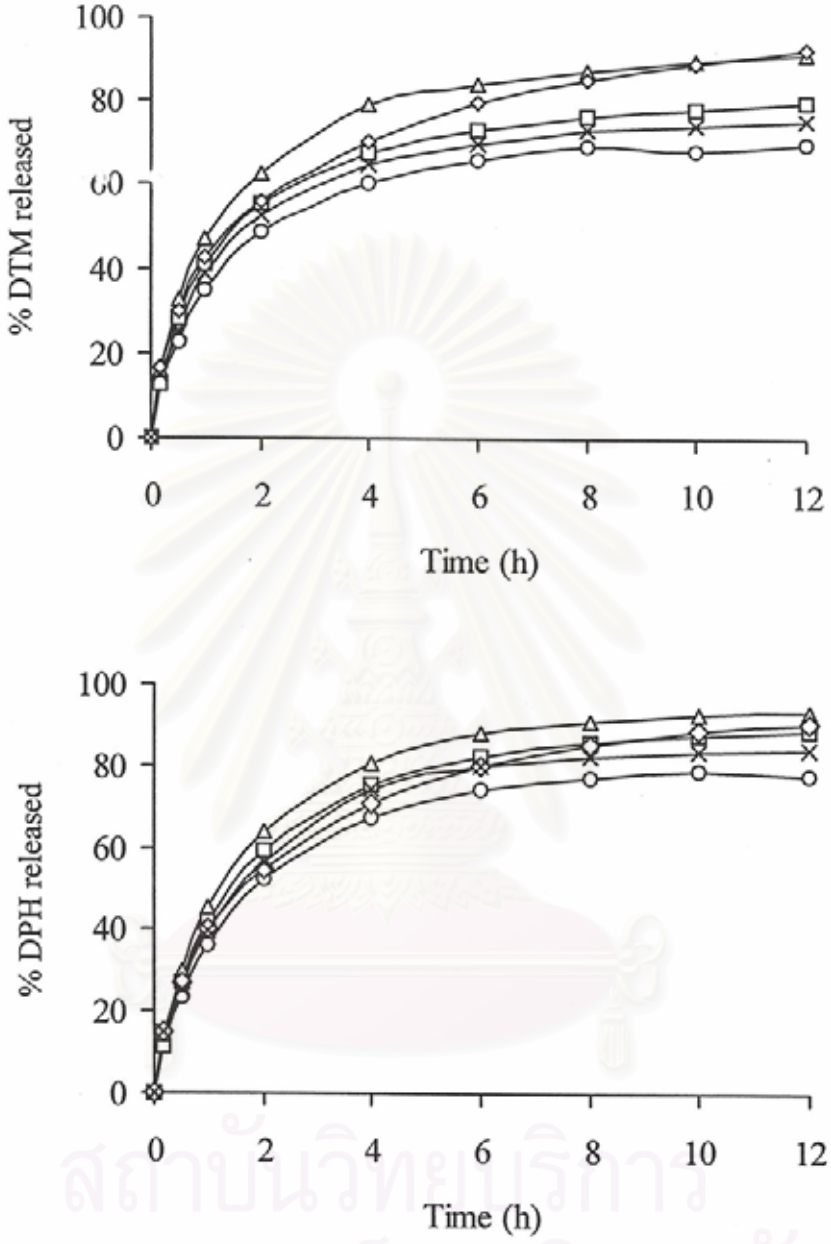


Figure 24 Profiles of DTM (upper) and DPH (lower) released from the resinates of Dowex 50W×8-200 performed in 0.05 (○), 0.1 (□), 0.2 (Δ), 0.4 N (◇) KCl and SIF (×), respectively

However, a unique character of drug release from the resinates of Dowex 50W×8-200 as a function of an increase in the ionic strength was found. The difference in the release between DTM and DPH tended to decrease when the ionic strength of KCl was increased ($p>0.05$ of the ionic strength at 0.4 N). Perhaps, it was a direct impact from the gradually increased congestion on the drug movement as just previously proposed, like the situation of traffic congestion slowing all running vehicles down to a certain speed.

4.5 Effect of drug loading levels

As illustrated in Figure 25, the 18 and 28 % EQC resinates prepared from the high crosslinked resin (Dowex 50W×8-200) gave different drug release patterns preformed in 0.4 N KCl solution. The 28% EQC resinate gave comparable release ($p>0.05$) of DTM and DPH of which the cause was due to the congested drug movement as previously mentioned. While, the lower (18 %) EQC resinate offered markedly greater release of DPH than DTM ($p<0.05$). The decrease in the level of drug loading led to a reduction of the sudden exchange of the free drugs from the binding sites, reliving the congestion of drug movement. Without this effect, the behavior of drug release depended on only the properties and the affinity of loaded drugs with the resin. DPH has greater hydrophilicity and smaller molecular weigh and size so that its release prevailed over DTM.

4.6 Comparison of drug release among different forms of resinates

The release profiles of DTM resinate, DPH resinate, the blend of DTM resinate and DPH resinate, and the dual-drug resinate of DTM and DPH are shown in

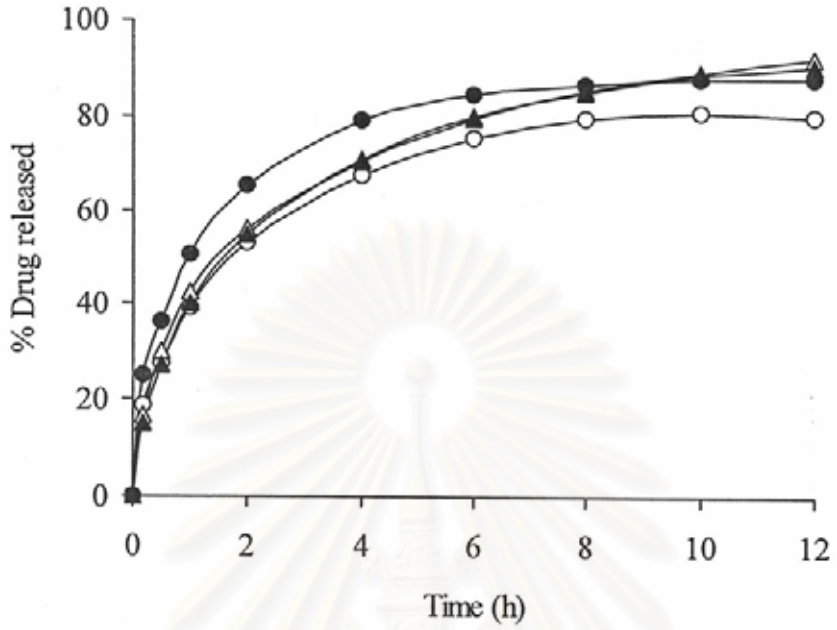


Figure 25 Release profiles of 18 (○) and 28 % (Δ) EQC resinates of Dowex 50W×8-200 performed in 0.4 N KCl. Where open symbols represent DTM and closed symbols represent DPH

Figure 26. By comparing the release profiles of the blended resinates and the dual-drug resinate with DTM resinate or DPH resinate, the difference and (f_1) the similarity factors (f_2) could be computed using Eq. 29 and 30, respectively (Costa and Lobo, 2001), which the values are presented in Table 16.

$$f_1 = \frac{\sum_{j=1}^{n} \left| R_j - T_j \right|}{\sum_{j=1}^{n} R_j} \times 100 \qquad \text{Eq. 29}$$

$$f_2 = 50 \times \log \left\{ \left[1 + \left(\frac{1}{n} \right) \sum_{j=1}^{n} \left| R_j - T_j \right|^2 \right]^{-0.5} \times 100 \right\} \qquad \text{Eq. 30}$$

Where n is the sampling number, T_j and R_j are the percent release of the test and the reference products at each time point j. Approaching the similar release profiles, the f_1 value should be close to 0 and the f_2 value should be close to 100. In general, the similarity of any compared release profiles can be declared if the f_1 value is lower than 15 (0-15) and the f_2 value is greater than 50 (50-100). From this standpoint, it demonstrated that the blended and the dual-drug resinate of which the f_1 and f_2 values of each drug fall within 0-15 and 50-100, respectively, provided the release of each drug comparable with their conventional resinates. However, the dual-drug resinate required only a single batch process to produce a combined drug product, practically reducing the step and cost of production. Accordingly, the dual-drug resinate would be more suitable and efficient as compared with the blended resinates for the concurrent delivery of two combined drugs.

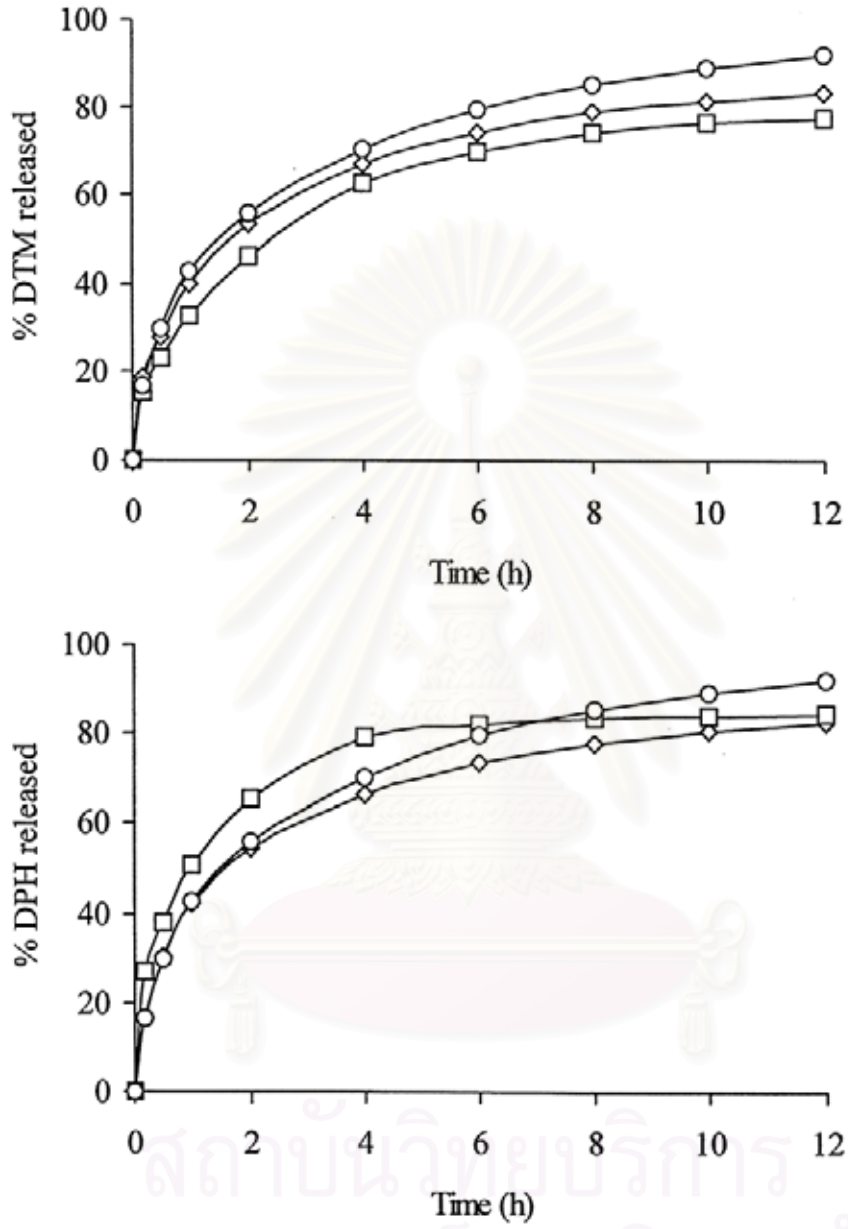


Figure 26 Profiles of DTM (upper) and DPH (lower) released from the resinates of Dowex 50W×8-200 prepared in forms of conventional resinates (◇), blended resinates (□) and dual-drug resinate (○), respectively

Table 16 The difference (f_1) and the similarity factors (f_2) of drug release from blended resinates and dual-drug resinate when using single-drug resinates as reference

Factors	DTM		DPH	
	Blended resinates	Dual-drug resinate	Blended resinates	Dual-drug resinate
f_1	8.9	8.0	13.4	7.5
f_2	63.3	62.1	53.4	62.1

5. Molecular Characteristics of Loaded Drugs

DSC curves are depicted in Figure 27. No peak was found in the DSC curve of the resin; while, the melting peaks of DTM and DPH were observed at 119.4 and 170.4 °C, respectively. The melting peaks of each drug persisted in the DSC curves of the binary mixtures of resin-DTM and resin-DPH, but they disappeared in the DSC curve of the dual-drug resinate. Similar findings were also seen in XRPD patterns of the samples (Figure 28). Each drug had own characteristic peaks; while, the resin provided a diffused curve. The binary mixtures of resin-DTM and resin-DPH displayed a combination of the characteristic peaks of each drug and the diffused curve of the resin. The dual-drug resinate provided merely the diffused curve as observed in the XRPD pattern of the resin. From these results, it demonstrated that the molecular state of the drugs was originally crystalline. The complexation of both drugs with the resin to form the dual-drug resinate transformed the molecular state of the drugs from crystalline to be amorphous. (Akkaramongkolporn et al., 2000, and 2001; Pisal et al., 2004a). The binary mixing of each drug with the resin showed no such crystalline transformation.

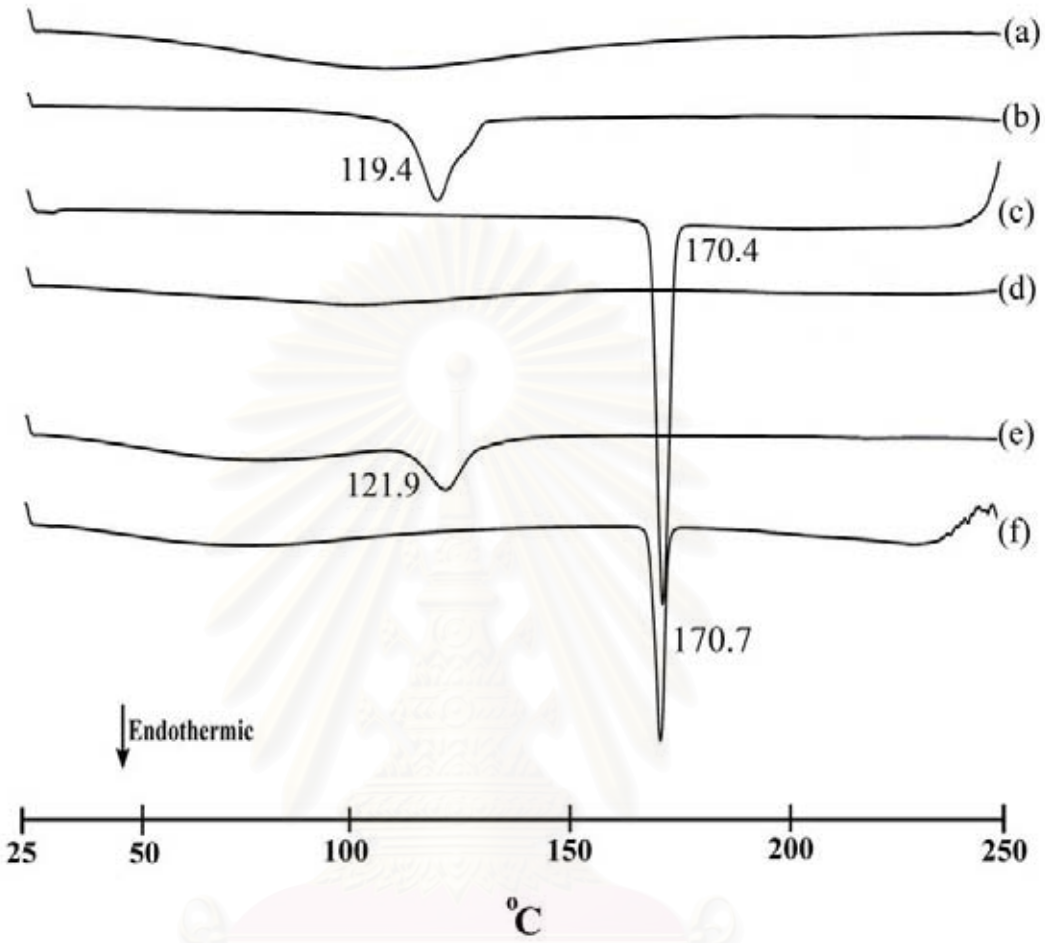


Figure 27 DSC curves of resin (Dowex 50W×8-200) (a), DTM (b), DPH (c), dual-drug resinate (d), binary mixtures of resin-DTM (e) and resin-DPH (f)

It is recognized that the drug resin complexation is formed by ionic interaction between the opposite charges (Borodkin, 1991, and 1993). To view this interaction in the resinate, IR spectra of various samples were investigated as illustrated in Figure 29. The multiple peaks around 2666-2594 cm^{-1} in the IR spectrum of DTM (Figure 29(b)) were defined to correlate the stretching of NH^+ interacting with bromide anion (or NH^+Br^-), and the peaks around 2568-2449 cm^{-1} in the IR spectrum of DPH (Figure 29(c)) were defined to correlate the stretching of NH^+ interacting with chloride anion

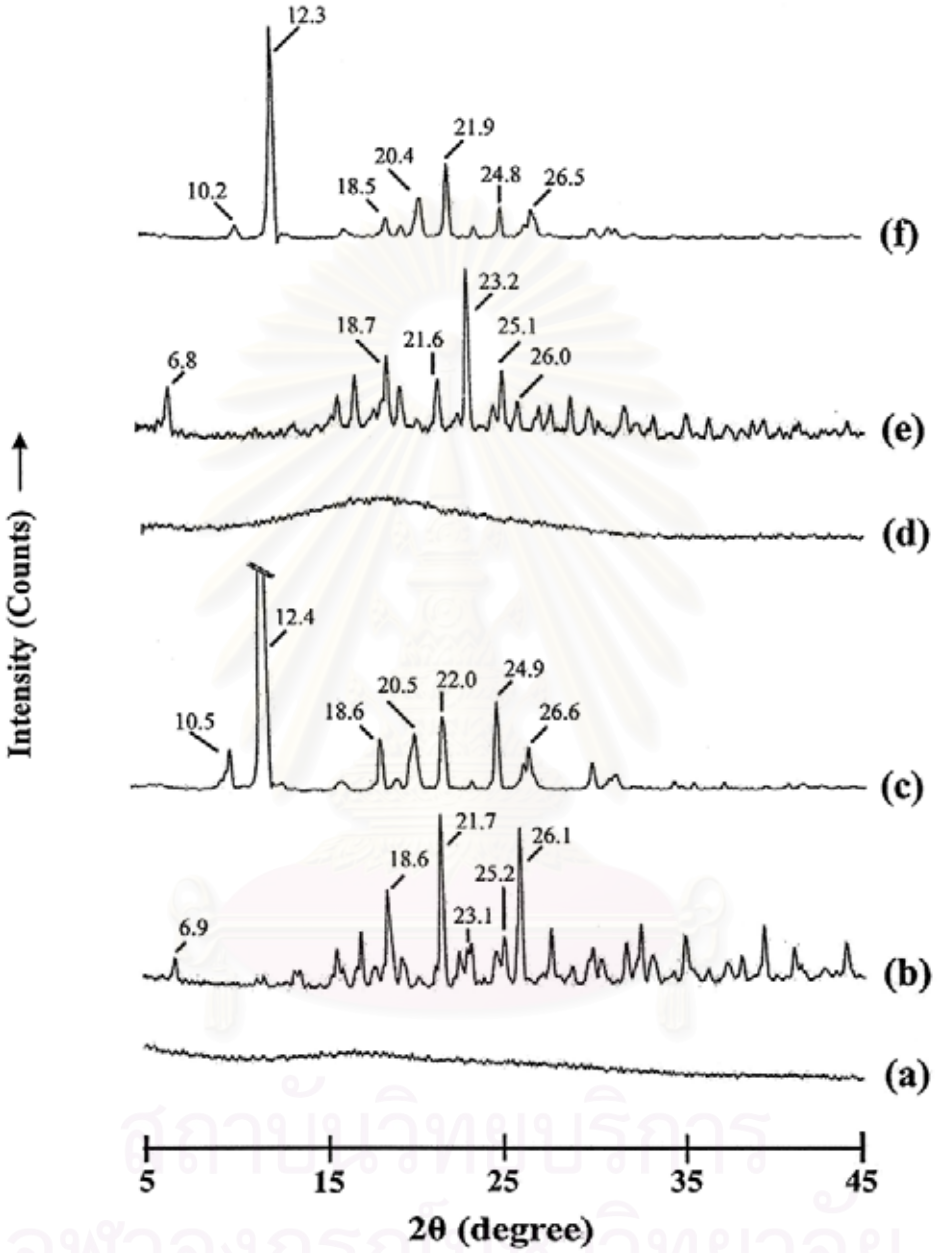


Figure 28 XRD patterns of resin (Dowex 50W×8-200) (a), DTM (b), DPH (c), dual-drug resinate (d), binary mixtures of resin-DTM (e) and resin-DPH (f)

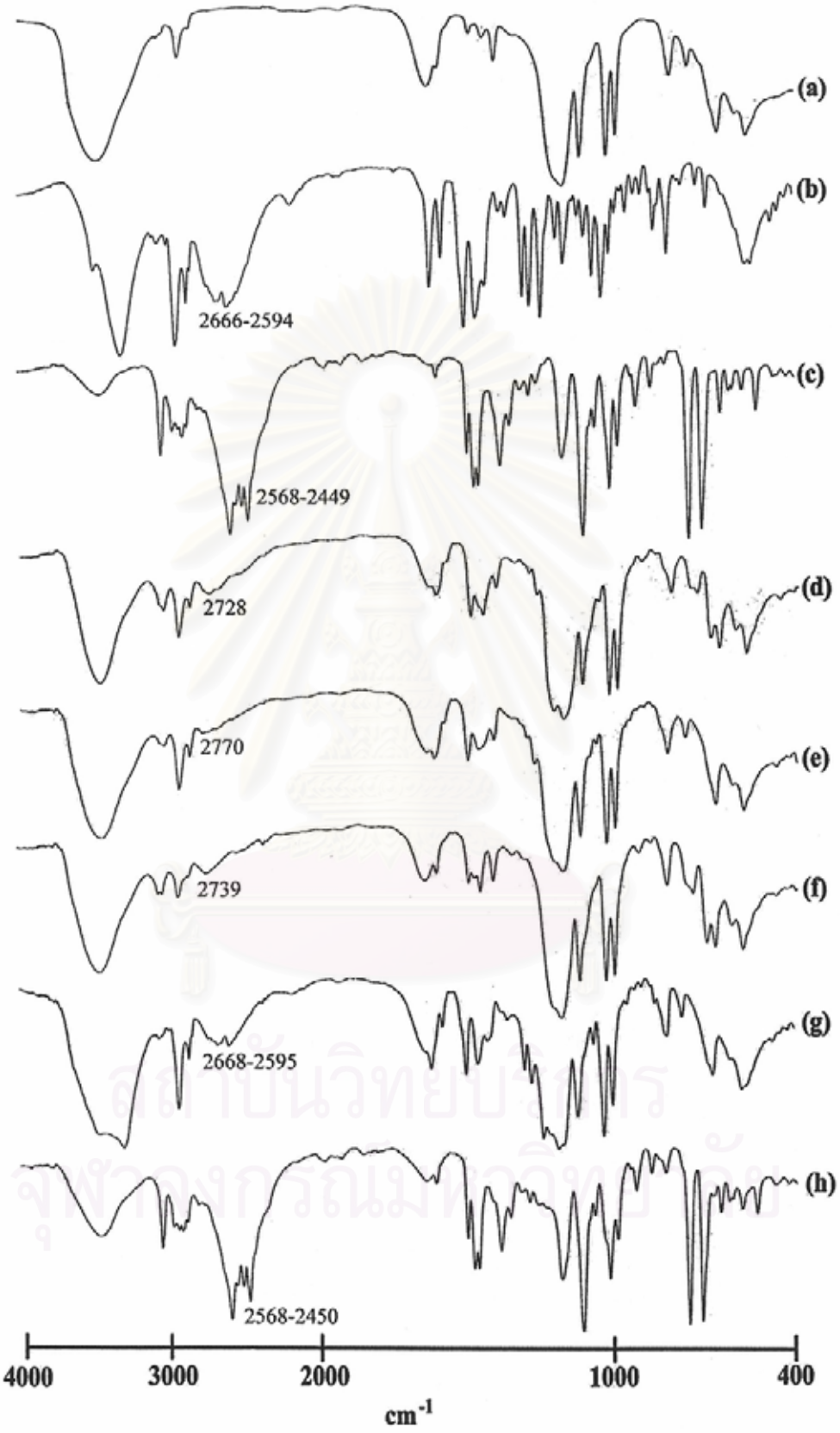


Figure 29 IR spectra of resin (Dowex 50W×8-200) (a), DTM (b), DPH (c), dual-drug resinate (d), DTM resinate (e), DPH resinate (f), binary mixtures of resin-DTM (g) and resin-DPH (h)

(or NH^+Cl^-) (Nakanishi, 1962). In the IR spectrum of the dual-drug resinate (Figure 5(d)), it was found that the stretching peaks of NH^+Br and NH^+Cl^- disappeared; instead, a new broad peak was found around 2728 cm^{-1}. To clarify this new peak, additional IR spectra of single drug loaded resinates (i.e. DTM resinate and DPH resinate prepared in the similar drug content) were determined. The stretching peaks of NH^+Br^- and NH^+Cl^- were absent, and a new peak was observed around 2770 and 2739 cm^{-1} in the IR spectra of DTM resinate and DPH resinate (Figure 29(e,f)), respectively, each of which was assigned to be the shifted stretching peak of NH^+ as interacting with the sulfonic anion of the resin (or $NH^+SO_3^-R$). The shift to higher wave number (from 2600 to 3100 cm^{-1}) of the NH^+ stretching peak of a mineral acid salt as the anion was changed from Cl^- to Br^- and ClO_4^- had been reported (Nakanishi, 1962). Besides, they were in good agreement with the $NH^+SO_3^-R$ stretching peak position of chlorpheniramine resinates previously recorded in the range of 2719-2753 cm^{-1} depending on the level of drug loading (Akkaramongkolporn et al., 2000). The similarity in peak position of the $NH^+SO_3^-R$ stretching peaks and the new peak at 2728 cm^{-1} of the dual-drug resinate suggested that the new peak at 2728 cm^{-1} corresponded to the combined $NH^+SO_3^-R$ stretching peaks of each drug. These evidences elucidated the ionic interaction occurring between the loaded drugs and the resin in the dual-drug resinate. In contrast, the IR spectra of the binary mixtures of resin-DTM and resin-DPH were a mere sum of the IR spectra of each component (Figure 29(g,h)), indicating no ionic interaction formed by physical mixing.

CHAPTER V

CONCLUSIONS

This work introduced a successful development of the method for preparing the dual-drug resinate containing the equivalent content of DTM and DPH. The behavior of equivalent dual-drug loading onto resins was affected by loading variables including the degree of resin crosslinkage, overall drug concentration of loading solutions, resin quantity and loading temperature. While, the particle size of resins showed insignificant effect on the equivalent dual-drug loading. Varying in the loading variables led to change not only in the equivalent dual-drug content (EQC) but also the condition of equivalent drug loading solution (ELS). Accordingly, formation of this novel resinate required a specific loading condition for a desired equivalent dual-drug content of each resin.

The release behavior of each drug from the resinates was influenced by the crosslinking degree of formulated resins, ionic strength (total cation) of release media, affinity of loaded drugs with resins and level of drug loading. Drug release from the resinates was retarded increasingly as a function of increasing degree of resin crosslinkage. The drug release from the resinates therefore could be tuned to a desired rate and extent by selecting a proper crosslinked resin. The increased ionic strength or total cation generally accelerated the release of both drugs. However, at too high ionic strength might not always produce greater drug release, especially from the resinates of high crosslinked resin. The congestion on the outward movement from the burst of free drugs through the high crosslinked matrix might cause the delay of drug release. The loaded drugs provided different drug release from the resinates. The drug with

more hydrophilicity and less molecular weight and size would prevail in drug release. However, the congested drug movement could alter the above release behavior, gradually equalizing the release of both drugs to a similar rate, like the situation of traffic congestion slowing all running vehicles down to a certain speed. The decrease in the level of drug loading could relive the congested drug movement, returning the drug release to be determined via the properties and the affinity of loaded drugs with the resin.

DSC and XRD studies showed that both loaded drugs in the dual-drug resinate prepared using Dowex 50W×8-200 were transformed from the crystalline to the amorphous state. IR spectra revealed significant shifts of the peaks corresponding to the stretching of positive amine group of loaded drugs, elucidating the ionic interaction between the loaded drugs and resin in the resinate. No crystalline transformation and ionic interaction were observed from the physical mixtures of each drug and the resin. Nevertheless, the amorphous properties of resinates to promote the drug solubility and release seemed to be minor and overshadowed by the determinant of resin crosslinkage which eventually delayed the drug release from the resinates.

Considering from the difference (f_1) and the similarity factors (f_2), the dual-drug resinate and the blended resinates provided the release of each drug comparable with their conventional (single drug loaded) resinates. The dual-drug resinate required only a single batch process to produce a combined drug product so that, in practice, reduced the step and cost of production. In conclusion, the dual-drug resinate would be more economically suitable and efficient as compared with the blended resinates for the concurrent delivery of two combined drugs.

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APPENDICES

Appendix A

Preliminary Studies

Study of drug stability

The stability of DTM and DPH in the conditions encountered during drug loading process was tested by incubating drug solutions (1 mg/ml in deionized water) at the temperatures ranged from 30 to 65°C for 24 h. Also, the stability of both drugs (90 μg/ml) in a variety of media, i.e. 0.1 N HCl, NaCl, KCl and 0.5 N NaCl and KCl, was evaluated at 37° C for 24 h. After the storage time was reached, the amount of drug remainder was assayed by HPLC method. The results are presented in Table A1.

Table A1 Stability of DMP and DPH in various conditions

Conditions	% Remaining drugs compared with initial amount[a]	
	DTM	DPH
Water, 1 mg/ml, 30°C	101.10	101.64
Water, 1 mg/ml, 37°C	99.70	99.37
Water, 1 mg/ml, 50°C	100.51	100.39
Water, 1 mg/ml, 55°C	101.13	100.77
Water, 1 mg/ml, 65°C	99.23	99.67
0.1 N HCl, 90 μg/ml, 37°C	98.78	72.30
0.1 N NaCl, 90 μg/ml, 37°C	99.42	99.32
0.5 N NaCl, 90 μg/ml, 37°C	99.12	99.02
0.1 N KCl, 90 μg/ml, 37°C	99.04	99.03
0.5 N KCl, 90 μg/ml, 37°C	99.19	99.44

[a] *Values averaged from duplicate studies*

It was evident that DTM and DPH were well stable in deionized water stored from 30 to 65°C, and in 0.1 and 0.5 N NaCl and KCl solutions incubated at 37°C.

DTM seemed to be stable whereas DPH showed obvious degradation in 0.1 N HCl. The decomposition of DPH in 0.1 N HCl might be due to the hydrolysis at ether linkage (Holcomb and Fusari, 1974). The resin in H form could liberate H^+ during drug loading step, and lower pH of the loading solution to around pH < 2 (Chen et. al., 1992). This pH caused serious degradation to DPH. For this reason, the resin in Na form was used throughout this work instead. From the stability study, it could speculate that the loading solution containing liberated Na^+ would not significantly destabilize both drugs.

Table A2 Pilot study showing the equilibrium of drug loading onto various resins preformed by different conditions

Resins	Quantity (g)	Loading solution[a]	Temp. (°C)	Drug	(% w/w) Drug loaded in resinates at various times (h)						
					24	25	26	27	28	29	30
Dowex 50W×2-200	0.500	DTM 1 % w/v	35	DTM	73.1	73.2	73.5	73.3	73.2	-	-
	0.500	DPH 1 % w/v	35	DPH	62.3	62.2	61.9	62.5	62.8	-	-
	0.500	Mix 1 % w/v	35	DTM	34.2	34.3	34.3	34.5	34.5	-	-
		DTM : DPH 50:50		DPH	33.3	33.3	33.3	33.7	33.6	-	-
Dowex 50W×4-100	0.500	Mix 1 % w/v	35	DTM	33.0	32.8	32.7	32.9	-	33.1	-
		DTM : DPH 50:50		DPH	32.9	32.9	33.0	32.8	-	32.9	-
Dowex 50W×4-200	0.250	Mix 1 % w/v	35	DTM	37.2	36.8	37.0	37.0	37.0	-	-
		DTM : DPH 50:50		DPH	31.0	30.5	31.1	30.4	30.8	-	-
	0.500	Mix 1 % w/v	30	DTM	33.6	34.3	33.7	33.7	33.6	-	-
		DTM : DPH 50:50		DPH	33.3	34.2	33.6	33.6	33.4	-	-
	0.500	Mix 1 % w/v	50	DTM	34.8	35.0	34.9	34.9	34.6	-	-
		DTM : DPH 50:50		DPH	33.8	34.0	33.9	33.5	33.7	-	-
	1.000	Mix 0.5 % w/v	35	DTM	28.8	28.8	28.8	28.8	28.8	-	-
		DTM : DPH 50:50		DPH	27.3	27.2	27.3	27.3	27.3	-	-
Dowex 50W×4-400	0.500	Mix 1 % w/v	35	DTM	32.6	33.0	33.1	33.1	-	33.1	-
		DTM : DPH 50:50		DPH	32.9	32.7	32.7	32.7	-	32.6	-
Dowex 50W×8-200	0.125	Mix 1 % w/v	35	DTM	14.8	15.0	15.1	15.1	-	14.9	-
		DTM : DPH 50:50		DPH	36.4	37.0	36.4	36.9	-	37.6	
	0.500	DTM 1 % w/v	35	DTM	44.6	-	45.3	-	44.8	-	46.2
	0.500	DPH 1 % w/v	35	DPH	57.1	-	57.5	-	57.4	-	57.4
	0.500	Mix 1 % w/v	35	DTM	23.6	23.9	23.6	24.3	23.8	-	-
		DTM : DPH 50:50		DPH	32.7	32.8	32.7	33.0	32.9	-	-
	0.800	Mix 1 % w/v	35	DTM	23.2	23.7	24.1	24.6	24.8		
		DTM : DPH 50:50		DPH	29.0	29.3	29.4	29.7	29.8		
	0.500	Mix 1 % w/v	65	DTM	32.0	32.2	31.8	31.7	32.1	-	-
		DTM : DPH 50:50		DPH	31.2	31.3	31.2	30.9	31.3	-	-

[a] *100 ml total loading solution*

Appendix B

HPLC Method and Validation

Validation of HPLC Method

The HPLC method was validated for system suitability (USP24/NF19, 2000), linearity, accuracy (recovery) and precision as follows.

System suitability

The resolution is the parameter to indicate whether the analyzed drugs are acceptably resolved from each other, which is calculated by the following equation.

$$R = \frac{2(t_2 - t_1)}{W_2 + W_1}$$

Where, t_1 and t_2 are the retention time of the analyzed drugs. W_1 and W_2 are the corresponding widths at the peak bases obtained by extrapolating the relatively straight sides of the peak to the base line as shown in Figure A1.

The tailing factor (T), a measure of peak symmetry, is calculated from the obtained peak from injection of drug solutions, using the following equation.

$$T = \frac{W_{0.05}}{2f}$$

Where, $W_{0.05}$ is the width of drug peak at 5 % height and f is the distance between the peak maximum and the leading peak side measured at 5 % height from the baseline (Figure A2).

Repeatability expresses the precision from five injections of varying known concentrations of drug solutions assayed under the same operating condition. The repeatability is displayed as the percent of relative standard deviation (% RSD).

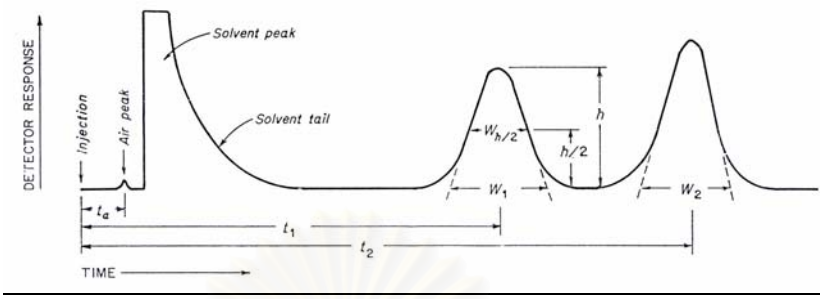

Figure A1 Chromatographic separation of two substances

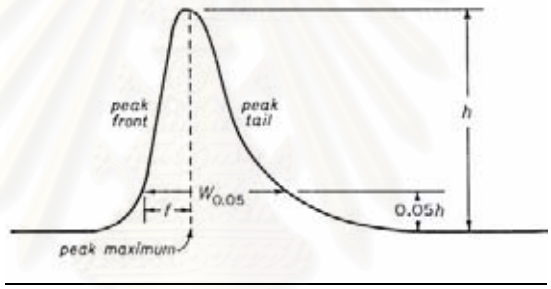

Figure A2 Asymmetrical chromatographic peak

Linearity

Linearity is determined by calculating a regression line using the least square method between the corresponding areas and the known concentrations of drug solutions. The coefficient of determination (R^2) of the regression line is presented to display the linearity; while, the slope and the intercept are determined to make the equation of the regression line.

Accuracy (recovery) and precision

The loading of 0.5 g resin (Dowex 50W×8-200) was performed at 35°C by using deionized water instead of drug solution. After the equilibrating time (24 h), the

supernatant was collected and diluted ten folds with deionized water. Then, the different known amounts of drugs were spiked into the final supernatant. The actual concentration of the spiked drug solutions was assayed by the HPLC method, and calculated from the calibration curve. The accuracy and precision were displayed as % recovery and RSD, respectively.

Validation Results

System suitability

The chromatograms of drugs are shown in Figure A3. The peaks of DTM and DPH were well resolved from each other with the resolution value about 5. This demonstrated that the HPLC method had adequate resolution for quantitative drug analysis.

The tailing factor was determined to measure peak symmetry. It is required to be less than 2.5 and 2 for HPLC analysis of DTM and DPH, respectively (USP24/NF19, 2000). The tailing factors of drug peaks obtained from injecting various determined concentrations of drug solutions are shown in Table A3 and A4. They were below 2.5 and 2 for DTM and DPH, respectively, signifying that the HPLC method provided suitable peak symmetry for quantitative drug analysis within the validated range.

The repeatability was determined from five replicate injections of each level of varying drug concentrations. It was expressed as % RSD which is required to be less than 2 % (USP24/NF19, 2000). The findings revealed that the % RSD values of all concentrations were less than 2 (Table A5 and A6). This indicated that the HPLC method had satisfactory repeatability for quantitative drug analysis within the validated range.

Linearity

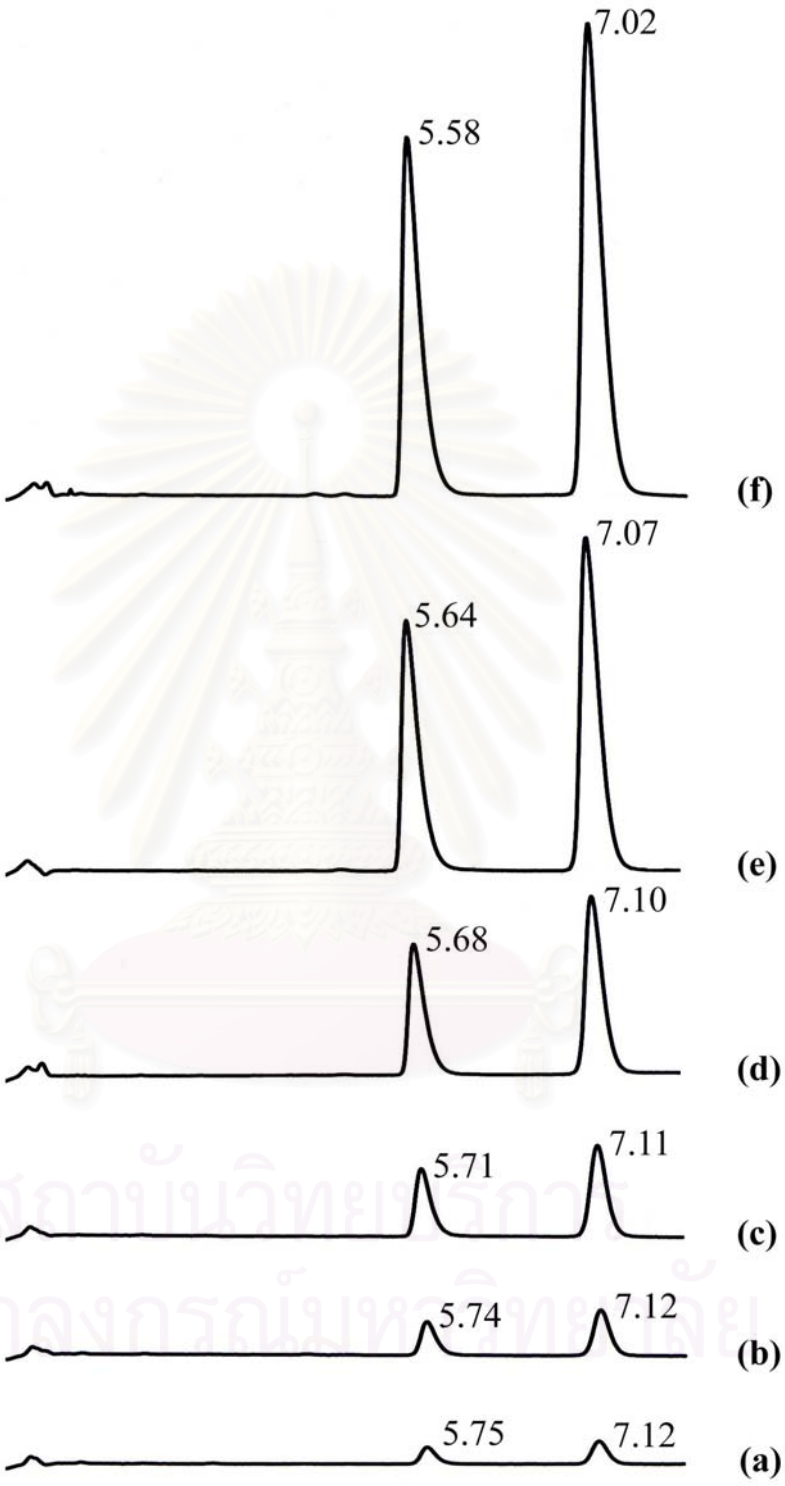

Figure A3 Chromatograms of DTM and DPH, respectively, at various drug concentrations; (a) 3.75, (b) 7.5, (c) 15, (d) 30, (e) 60 and (f) 90 μg/ml

Table A3 Tailing factor of DTM in HPLC analysis

Conc. (μg/ml)	Tailing factor					Mean	S.D.
	1	2	3	4	5		
0	0	0	0	0	0	0	0
3.75	1.37	1.33	1.37	1.40	1.40	1.37	0.03
7.5	1.47	1.46	1.46	1.51	1.52	1.48	0.03
15	1.64	1.62	1.62	1.64	1.65	1.63	0.01
30	1.83	1.82	1.80	1.82	1.84	1.82	0.01
60	2.12	2.08	2.06	2.07	2.12	2.09	0.03
90	2.30	2.27	2.26	2.27	2.29	2.28	0.02

Table A4 Tailing factor of DPH in HPLC analysis

Conc. (μg/ml)	Tailing factor					Mean	S.D.
	1	2	3	4	5		
0	0	0	0	0	0	0	0
3.75	1.19	1.21	1.19	1.20	1.19	1.20	0.01
7.5	1.24	1.24	1.24	1.24	1.24	1.24	0.00
15	1.30	1.30	1.30	1.31	1.30	1.30	0.00
30	1.43	1.43	1.43	1.44	1.45	1.44	0.01
60	1.68	1.68	1.68	1.68	1.71	1.69	0.01
90	1.91	1.90	1.90	1.90	1.93	1.91	0.01

Table A5 Repeatability of HPLC analysis for DTM

Conc. level	Calculated concentration (μg/ml)					Mean	S.D.	%RSD
	1	2	3	4	5			
0	0	0	0	0	0	0	0	0
3.75	3.760	3.823	3.866	3.814	3.889	3.830	0.050	1.31
7.5	7.406	7.399	7.455	7.449	7.542	7.450	0.057	0.76
15	15.000	15.034	15.088	14.957	15.088	15.033	0.057	0.38
30	29.616	30.016	29.774	29.710	29.696	29.763	0.152	0.51
60	59.784	59.376	59.415	59.466	59.831	59.574	0.216	0.36
90	89.563	90.704	91.089	91.173	89.710	90.448	0.764	0.84

Table A6 Repeatability of HPLC analysis for DPH

Conc. level	Calculated concentration (μg/ml)					Mean	S.D.	%RSD
	1	2	3	4	5			
0	0	0	0	0	0	0	0	0
3.75	3.774	3.836	3.855	3.860	3.802	3.826	0.037	0.96
7.5	7.476	7.413	7.515	7.460	7.485	7.470	0.037	0.50
15	14.927	14.940	14.987	14.966	15.066	14.977	0.055	0.36
30	29.739	29.642	29.817	29.806	29.885	29.778	0.092	0.31
60	59.377	59.367	59.705	59.609	59.573	59.526	0.149	0.25
90	89.941	90.278	90.494	90.590	90.165	90.294	0.259	0.29

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The response areas of each drug against various drug concentrations are presented in Table A7 and A8. The regression analysis of the average response areas against the determined concentrations was carried out by the method of least square, of which the plots are depicted in Figure A4 and A5. It was evident that the relationship between the response areas and drug concentrations was linear with the coefficient of determination (R^2) more than 0.9998, demonstrating that the HPLC method could be used for quantitative drug analysis within the validated range.

Accuracy (recovery) and precision

The accuracy and precision of the HPLC method are shown in Table A9 and A10. The lowest concentration used for drug analysis of the HPLC method was 3.75 μg/ml with 95 % recovery and 2.3 % RSD, respectively. This expressed that the HPLC method was effective for quantitative drug analysis within the validated range.

From above findings, it could be clarified that the HPLC method was acceptable for quantitative analysis of DTM and DPH within the validated range.

Table A7 Linearity of HPLC analysis for DTM[a]

Conc.	Area					Mean	S.D.
(μg/ml)	1	2	3	4	5		
0	0	0	0	0	0	0	0
3.75	4059	4133	4184	4123	4211	4142	58.86
7.5	8327	8319	8384	8378	8486	8379	66.67
15	17216	17255	17319	17165	17319	17255	66.73
30	34324	34792	34508	34434	34417	34495	178.48
60	69634	69157	69203	69262	69690	69389	252.57
90	104490	105826	106277	106375	104662	105526	893.67
R^2	1.0000	0.9999	0.9998	0.9998	1.0000	0.9999	0.0001
slope	1163	1172	1176	1178	1163	1170	6.95
intercept	-278	-351	-402	-472	-187	-338	110

[a] *In linear form of Y = slopeX + intercept; where Y is area and X is concentration*

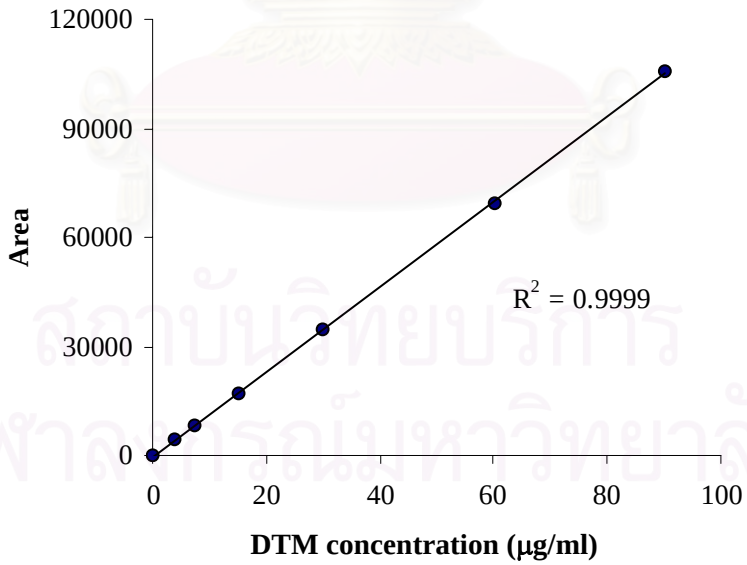

Figure A4 Linearity of HPLC analysis for DTM

Table A8 Linearity of HPLC analysis for DPH[a]

Conc.	Area					Mean	S.D.
(μg/ml)	1	2	3	4	5		
0	0	0	0	0	0	0	0
3.75	5993	6098	6130	6139	6039	6080	62.36
7.5	12276	12169	12341	12249	12291	12265	63.33
15	24922	24944	25023	24987	25157	25007	92.67
30	50061	49897	50194	50174	50308	50127	155.50
60	100364	100346	100921	100757	100696	100617	252.84
90	152238	152810	153177	153339	152618	152836	440.20
R^2	1.0000	0.9999	0.9999	0.9999	1.0000	0.9999	0.0000
slope	1691	1696	1701	1702	1695	1697	4.48
intercept	-388	-473	-403	-454	-331	-410	56

[a] *In linear form of Y = slopeX + intercept; where Y is area and X is concentration*

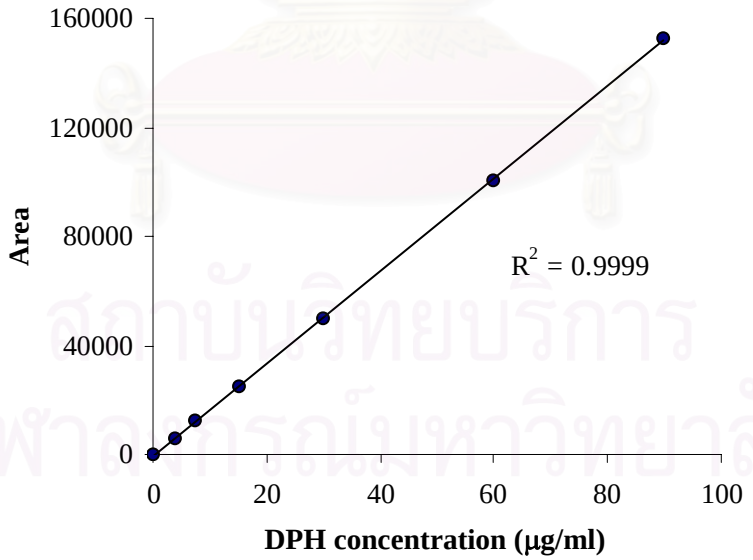

Figure A5 Linearity of HPLC analysis for DPH

Table A9 Accuracy and precision of HPLC analysis for DTM

Spiked conc.	Calculated concentration (μg/ml)					Mean	% Recovery	% RSD
	1	2	3	4	5			
3.735	3.599	3.477	3.568	3.454	3.651	3.550	95.0	2.34
29.880	30.381	30.174	30.418	30.330	30.359	30.332	101.5	0.31
89.640	88.889	89.304	88.245	89.086	88.917	88.888	99.2	0.45

Table A10 Accuracy and precision of HPLC analysis for DPH

Spiked conc.	Calculated concentration (μg/ml)					Mean	% Recovery	% RSD
	1	2	3	4	5			
3.735	3.494	3.582	3.479	3.540	3.625	3.544	94.9	1.72
29.880	30.403	30.154	30.275	30.241	30.332	30.281	101.3	0.31
89.640	89.039	89.276	88.304	89.026	89.045	88.938	99.2	0.41

Appendix C

Raw Data

Particle size, pore analysis and swelling of resins

Table A11 Particle size distribution of hydrated resins

Size (μm)	% Volume occupies at each size				
	Dowex 50W×2-200	Dowex 50W×4-100	Dowex 50W×4-200	Dowex 50W×4-400	Dowex 50W×8-200
30.2	0	0	0	0	0
34.7	0	0	0	0	0
39.8	0	0	0	0	0
45.7	0	0	0	0	0
52.5	0	0	0	0.12	0
60.3	0	0	0	0.93	0
69.2	0	0	0	3.41	0
79.4	0	0	0.25	8.05	0.26
91.2	0.02	0	1.67	14.07	1.61
104.7	0.35	0	5.73	18.91	6.26
120.2	2.15	0	11.68	20.03	11.60
138.0	6.59	0	18.51	16.68	19.21
158.5	12.90	0.02	21.47	10.72	21.65
182.0	19.30	0.47	19.29	5.13	19.10
208.9	21.39	2.95	12.81	1.64	12.46
239.9	18.20	7.94	6.34	0.27	5.89
275.4	11.63	15.15	2.02	0	1.79
316.2	5.47	21.09	0.23	0	0.16
363.1	1.72	21.55	0	0	0
416.9	0.27	17.24	0	0	0
478.6	0.01	8.84	0	0	0
549.5	0	4.16	0	0	0
631.0	0	0.57	0	0	0
724.4	0	0.02	0	0	0
831.8	0	0	0	0	0

955.0	0	0	0	0	0

Table A12 Isotherm and pore analysis of Dowex 50W×2-200

Isotherm		Pore radius	Cumulative	Cumulative	% Volume at	% Area at
P/P_0	Volume (cc/g)	(A)	pore volume ($\times 10^{-3}$ cc/g)	surface area (m^2/g)	each size (cc/g)	each size (m^2/g)
0.102	0.071	5.89	0	0	0	0
0.152	0.124	6.71	0	0	0	0
0.202	0.168	7.42	0	0	0	0
0.252	0.217	8.07	0.006	0.016	0.21	0.46
0.302	0.256	8.7	0.056	0.131	1.84	3.71
0.402	0.330	9.31	0.120	0.268	2.51	3.75
0.502	0.396	9.93	0.196	0.420	3.14	5.56
0.602	0.457	10.55	0.307	0.630	4.87	8.10
0.701	0.512	11.19	0.398	0.792	4.08	6.40
0.801	0.559	11.85	0.470	0.916	3.39	5.02
0.902	0.599	12.53	0.538	1.023	3.12	4.38
0.928	0.598	13.24	0.646	1.186	4.92	6.79
0.953	0.586	13.98	0.755	1.342	5.26	6.61
0.978	0.596	14.76	0.839	1.456	4.03	4.79
0.997	0.672	15.6	0.929	1.572	4.15	4.67
0.974	0.543	16.49	1.026	1.689	4.60	4.89
0.948	0.480	17.44	1.143	1.824	5.36	5.40
0.923	0.446	18.45	1.245	1.934	4.68	4.46
0.898	0.409	19.56	1.339	2.030	4.09	3.67
0.874	0.379	20.76	1.441	2.129	4.50	3.80
0.848	0.350	22.06	1.531	2.210	3.73	2.97
0.823	0.325	23.5	1.638	2.310	4.37	3.27
0.798	0.305	25.08	1.722	2.368	3.27	2.29
0.775	0.140	26.85	1.786	2.416	2.40	1.57
0.748	0.097	28.2	1.786	2.416	0.00	0.00
0.723	0.065	30.47	1.786	2.416	0.00	0.00
0.698	0.046	33.73	1.845	2.451	1.84	0.96
0.673	0.018	36.76	1.878	2.469	0.99	0.47
0.633	0.786	40.34	1.944	2.501	1.75	0.76
0.623	0.796	44.84	2.033	2.541	2.04	0.80
0.598	0.769	49.98	2.423	2.697	9.77	3.43
0.573	0.735	56.25	2.464	2.712	0.83	0.26
0.548	0.694	64.6	2.515	2.727	0.90	0.25
0.523	0.659	76.09	2.573	2.743	0.84	0.19
0.498	0.621	92.37	2.632	2.755	0.75	0.14
0.473	0.584	118	2.703	2.768	0.67	0.10
0.448	0.546	164.73	2.764	2.775	0.42	0.04
0.423	0.504	288.01	2.872	2.782	0.42	0.03
0.398	0.467	1770.14	3.076	2.785	0.25	0.00
0.372	0.432					
0.348	0.398					
0.323	0.358					
0.298	0.318					
0.272	0.288					
0.248	0.256					
0.223	0.220					
0.198	0.178					
0.172	0.143					
0.147	0.110					
0.122	0.077					
0.097	0.051					
0.072	0.033					
0.047	0.018					
0.024	0.005					

Table A13 Isotherm and pore analysis of Dowex 50W×4-100

Isotherm		Pore radius	Cumulative	Cumulative	% Volume at	% Area at
P/P_0	Volume (cc/g)	(A)	pore volume ($\times 10^{-3}$ cc/g)	surface area (m^2/g)	each size (cc/g)	each size (m^2/g)
0.103	-0.383	5.89	0.000	0.000	0.00	0.00
0.152	-0.388	6.72	0.000	0.000	0.00	0.00
0.202	-0.351	7.44	0.000	0.000	0.00	0.00
0.253	-0.560	8.08	0.207	0.512	3.10	7.45
0.304	-0.938	8.7	0.207	0.513	0.01	0.02
0.399	-0.373	9.31	0.379	0.882	3.03	6.31
0.502	-0.736	9.93	0.379	0.882	0.00	0.00
0.601	-1.098	10.56	0.540	1.186	3.13	5.74
0.701	0.142	11.19	0.714	1.498	3.56	6.16
0.801	-0.170	11.85	0.884	1.784	3.49	5.72
0.902	-0.466	12.53	0.888	1.791	0.08	0.13
0.926	1.556	13.24	1.165	2.209	5.82	8.52
0.952	1.317	13.99	1.261	2.346	2.04	2.83
0.978	1.102	14.78	1.456	2.610	4.19	5.49
0.998	1.068	15.61	1.752	2.990	6.22	7.72
0.973	0.036	16.50	2.026	3.322	5.78	6.80
0.938	1.838	17.45	2.159	3.475	2.76	3.07
0.923	1.771	18.46	2.333	3.663	3.59	3.77
0.899	1.671	19.56	2.360	3.691	0.54	0.53
0.874	1.559	20.63	2.360	3.691	0.00	0.00
0.848	1.377	21.95	2.360	3.691	0.00	0.00
0.824	1.221	23.54	2.671	3.955	5.61	4.62
0.799	1.052	25.12	3.195	4.372	9.36	7.22
0.774	0.920	26.91	3.543	4.631	5.68	4.09
0.748	0.830	28.92	3.750	4.774	3.32	2.23
0.723	0.722	31.16	3.995	4.931	3.71	2.31
0.698	0.619	33.77	4.145	5.020	2.10	1.20
0.673	0.547	36.81	4.377	5.146	3.05	1.61
0.648	0.443	40.37	4.615	5.264	2.90	1.39
0.624	0.353	44.65	4.804	5.348	2.09	0.91
0.598	0.215	49.9	5.090	5.463	2.88	1.12
0.574	0.022	56.47	5.459	5.594	3.29	1.13
0.548	-0.103	64.88	5.790	5.696	2.65	0.79
0.518	1.326	76.47	6.168	5.795	2.44	0.62
0.498	1.348	92.97	6.392	5.843	1.26	0.26
0.473	1.316	117.76	6.585	5.876	0.87	0.14
0.448	1.243	148.87	6.711	5.892	0.69	0.09
0.423	1.181	264.62	6.711	5.892	0.00	0.00
0.398	1.080	2396.62	8.330	5.906	0.76	0.01
0.373	0.973					
0.348	0.893					
0.323	0.838					
0.298	0.738					
0.273	0.704					
0.248	0.630					
0.223	0.555					
0.198	0.481					
0.173	0.451					
0.147	0.372					
0.122	0.325					
0.098	0.235					
0.073	0.193					
0.047	0.168					
0.024	0.159					

Table A14 Isotherm and pore analysis of Dowex 50W×4-200

Isotherm		Pore radius	Cumulative	Cumulative	% Volume at	% Area at
P/P_0	Volume (cc/g)	(A)	pore volume ($\times 10^{-3}$ cc/g)	surface area (m^2/g)	each size (cc/g)	each size (m^2/g)
0.102	0.056	5.91	0.000	0.000	0.00	0.00
0.152	0.101	6.71	0.049	0.147	1.22	3.31
0.202	0.136	7.40	0.049	0.147	0.00	0.00
0.252	0.170	8.05	0.049	0.147	0.00	0.00
0.303	0.197	8.70	0.052	0.154	0.12	0.24
0.402	0.248	9.31	0.077	0.206	1.01	1.97
0.502	0.289	9.93	0.123	0.299	2.02	3.70
0.602	0.323	10.55	0.171	0.391	2.21	3.81
0.702	0.345	11.19	0.258	0.547	4.12	6.70
0.802	0.369	11.85	0.387	0.763	6.25	9.60
0.902	0.373	12.53	0.470	0.896	4.10	5.95
0.928	0.370	13.24	0.562	1.035	4.58	6.30
0.953	0.359	13.98	0.646	1.155	4.20	5.47
0.978	0.356	14.76	0.715	1.249	3.47	4.28
0.998	0.364	15.60	0.789	1.343	3.63	4.23
0.973	0.299	16.49	0.883	1.458	4.69	5.18
0.948	0.253	17.43	0.989	1.579	5.08	5.31
0.922	0.230	18.46	1.078	1.676	4.25	4.19
0.898	0.204	19.56	1.160	1.760	3.84	3.57
0.873	0.179	20.75	1.295	1.889	6.13	5.37
0.847	0.145	22.06	1.384	1.970	3.90	3.22
0.823	0.133	23.50	1.488	2.059	4.48	3.47
0.801	-0.048	25.09	1.568	2.123	3.24	2.35
0.773	-0.089	26.86	1.681	2.207	4.41	2.99
0.748	-0.123	28.86	1.757	2.260	2.85	1.80
0.723	-0.144	31.07	1.816	2.298	2.14	1.26
0.684	0.774	32.86	1.816	2.298	0.00	0.00
0.672	0.782	35.91	1.816	2.298	0.00	0.00
0.648	0.756	40.27	1.856	2.317	1.14	0.51
0.623	0.724	44.51	1.925	2.348	1.82	0.74
0.598	0.680	50.04	2.009	2.382	1.76	0.64
0.573	0.648	56.49	2.425	2.529	9.94	3.20
0.548	0.607	64.45	2.447	2.536	0.41	0.12
0.523	0.572	75.85	2.517	2.554	1.08	0.26
0.498	0.523	92.23	2.566	2.565	0.64	0.13
0.473	0.490	116.61	2.616	2.574	0.53	0.08
0.448	0.455	163.55	2.657	2.579	0.29	0.03
0.423	0.415	280.20	2.737	2.584	0.35	0.02
0.398	0.379	2160.99	2.840	2.585	0.12	0.00
0.373	0.348					
0.348	0.318					
0.323	0.285					
0.298	0.249					
0.273	0.215					
0.248	0.171					
0.223	0.135					
0.198	0.107					
0.172	0.079					
0.147	0.054					
0.122	0.033					
0.096	0.112					
0.072	0.092					
0.047	0.053					
0.024	0.015					

Table A15 Isotherm and pore analysis of Dowex 50W×4-400

Isotherm		Pore radius	Cumulative	Cumulative	% Volume at	% Area at
P/P_0	Volume (cc/g)	(A)	pore volume ($\times 10^{-3}$ cc/g)	surface area (m^2/g)	each size (cc/g)	each size (m^2/g)
0.103	-0.351	5.94	0	0	0	0
0.152	-0.396	6.69	0	0	0	0
0.202	-0.464	7.41	0	0	0	0
0.251	-0.164	8.08	0.035	0.859	3.17	7.13
0.303	-0.303	8.71	0.067	1.607	3.22	6.72
0.400	0.184	9.32	0.098	2.269	3.34	6.51
0.501	-0.022	9.93	0.131	2.929	3.73	6.82
0.601	-0.191	10.56	0.167	3.604	4.19	7.22
0.701	0.648	11.19	0.188	3.982	2.64	4.29
0.800	0.400	11.81	0.188	3.982	0.00	0.00
0.901	2.102	12.5	0.188	3.982	0.00	0.00
0.928	2.009	13.25	0.216	4.410	3.65	5.01
0.951	1.728	13.99	0.251	4.913	4.55	5.91
0.978	1.473	14.78	0.305	5.647	7.00	8.61
0.995	3.848	15.61	0.327	5.917	2.73	3.18
0.975	3.479	16.5	0.361	6.333	4.27	4.71
0.949	3.065	17.46	0.389	6.652	3.52	3.67
0.925	2.728	18.47	0.404	6.816	1.88	1.85
0.899	2.427	19.57	0.430	7.086	3.12	2.90
0.874	2.219	20.78	0.465	7.419	4.06	3.55
0.849	1.968	22.09	0.493	7.672	3.18	2.62
0.824	1.767	23.53	0.521	7.911	3.13	2.42
0.799	1.558	25.13	0.562	8.239	4.26	3.08
0.775	1.081	26.91	0.586	8.414	2.44	1.65
0.749	0.757	28.91	0.626	8.695	3.80	2.39
0.717	2.728	31.17	0.655	8.879	2.70	1.57
0.699	2.714	33.77	0.686	9.060	2.55	1.37
0.673	2.573	36.39	0.686	9.060	0.00	0.00
0.649	2.442	39.95	0.686	9.060	0.00	0.00
0.623	2.270	44.8	0.758	9.384	4.62	1.87
0.599	2.159	50.06	0.868	9.821	6.95	2.52
0.573	1.990	56.47	0.912	9.977	2.42	0.78
0.548	1.866	65.04	0.953	10.100	1.90	0.53
0.523	1.743	76.58	1.004	10.240	2.08	0.49
0.498	1.601	93.11	1.044	10.320	1.32	0.26
0.473	1.485	120.04	1.101	10.420	1.41	0.21
0.448	1.403	168.42	1.162	10.490	1.15	0.12
0.423	1.285	293.73	1.233	10.540	0.76	0.05
0.398	1.149	1191.17	1.292	10.550	0.25	0.00
0.373	1.050					
0.348	0.864					
0.323	0.726					
0.298	0.605					
0.270	1.234					
0.247	1.262					
0.223	1.161					
0.198	1.025					
0.173	0.891					
0.148	0.758					
0.123	0.615					
0.098	0.460					
0.071	0.365					
0.047	0.272					
0.026	0.175					

Table A16 Isotherm and pore analysis of Dowex 50W×8-200

Isotherm		Pore radius	Cumulative	Cumulative	% Volume at	% Area at
P/P_0	Volume (cc/g)	(A)	pore volume ($\times 10^{-3}$ cc/g)	surface area (m^2/g)	each size (cc/g)	each size (m^2/g)
0.502	0.396	5.89	0	0	0	0
0.602	0.457	6.7	0	0	0	0
0.701	0.512	7.42	0	0	0	0
0.801	0.559	8.08	0.069	0.171	1.34	2.85
0.902	0.599	8.71	0.173	0.409	2.23	4.41
0.928	0.598	9.32	0.300	0.682	2.95	5.44
0.953	0.586	9.94	0.427	0.938	3.12	5.39
0.997	0.596	10.56	0.561	1.192	3.44	5.60
0.974	0.672	11.2	0.700	1.440	3.67	5.63
0.948	0.543	11.85	0.812	1.628	3.01	4.37
0.923	0.480	12.53	0.970	1.882	4.38	6.00
0.898	0.446	13.25	1.129	2.121	4.38	5.69
0.874	0.409	13.99	1.302	2.368	4.86	5.97
0.848	0.379	14.78	1.443	2.560	3.90	4.54
0.823	0.350	15.61	1.617	2.782	4.86	5.35
0.798	0.325	16.49	1.778	2.977	4.41	4.59
0.775	0.305	17.44	1.955	3.181	4.81	4.74
0.748	0.139	18.46	2.129	3.369	4.61	4.29
0.723	1.080	19.57	2.301	3.545	4.45	3.91
0.698	1.023	20.77	2.482	3.719	4.65	3.85
0.673	0.970	22.05	2.620	3.844	3.46	2.69
0.633	0.921	23.11	2.648	3.868	1.27	0.94
0.623	0.847	24.73	2.648	3.868	0.00	0.00
0.598	0.738	26.93	2.832	4.005	3.95	2.52
0.598	0.663	28.93	3.117	4.202	6.02	3.58
0.573	1.258	31.16	3.301	4.320	3.68	2.03
0.548	1.243	33.72	3.411	4.385	2.07	1.05
0.523	1.188	36.76	3.530	4.450	2.00	0.93
0.498	1.120	40.33	3.658	4.514	2.06	0.88
0.473	1.055	44.57	3.780	4.568	1.77	0.68
0.448	0.989	49.81	3.896	4.615	1.51	0.52
0.423	0.923	56.29	4.033	4.664	1.64	0.50
0.398	0.861	64.69	4.162	4.704	1.32	0.35
0.372	0.797	76.12	4.325	4.746	1.43	0.32
0.348	0.740	92.33	4.463	4.776	1.01	0.19
0.323	0.675	118.04	4.602	4.800	0.77	0.11
0.298	0.614	164.65	4.732	4.816	0.53	0.06
0.272	0.552	277.86	4.885	4.827	0.38	0.02
0.248	0.500	1060.93	4.969	4.828	0.08	0.00
0.223	0.442					
0.198	0.383					
0.172	0.325					
0.147	0.265					
0.122	0.207					
0.097	0.151					
0.072	0.121					
0.047	0.109					
0.024	0.050					

Table A17 Swelling of various resins

No.	Dowex 50W×2-200		Dowex 50W×4-100		Dowex 50W×4-200		Dowex 50W×4-400		Dowex 50W×8-200	
	Dry	Swell	Dry	Swell	Dry	Swell	Dry	Swell	Dry	Swell
1	123.3	212.2	205.7	307.5	127.6	181.4	35.4	134.4	142.1	203.1
2	121.3	205.1	193.4	317.0	123.4	142.1	76.8	99.6	75.8	120.5
3	111.9	189.3	169.0	311.3	136.1	168.0	58.6	77.7	139.8	133.5
4	120.7	177.0	241.0	280.2	136.8	165.1	70.1	145.6	143.9	140.3
5	122.3	202.2	213.6	322.4	144.0	180.9	83.5	54.6	113.6	151.5
6	123.8	143.6	167.0	319.7	104.9	184.2	76.9	114.0	150.5	193.6
7	126.8	202.9	277.0	256.5	117.0	185.6	77.6	94.0	142.6	163.1
8	84.1	237.4	223.4	300.8	110.6	157.4	37.8	132.5	138.0	120.6
9	132.4	180.6	225.5	267.3	143.8	168.0	64.0	108.4	148.7	127.1
10	123.3	190.5	221.6	314.8	103.9	206.8	29.9	140.3	101.0	143.3
11	61.5	160.5	195.7	270.4	108.5	181.0	55.6	117.9	157.3	147.5
12	131.3	210.2	217.8	285.9	149.8	120.3	84.0	135.4	133.7	118.0
13	96.6	228.7	247.7	322.0	143.9	224.2	61.8	117.3	199.0	129.1
14	123.5	203.9	282.8	266.5	115.9	182.7	75.4	81.0	104.8	175.7
15	97.4	227.9	182.1	324.8	106.0	205.8	77.0	111.5	81.6	122.1
16	130.4	217.5	211.2	279.8	111.2	197.8	82.6	133.1	118.6	128.3
17	121.4	224.4	206.3	332.2	150.3	180.4	68.9	134.9	130.3	140.0
18	121.9	151.3	243.1	273.1	101.6	216.6	83.5	112.6	106.8	126.5
19	122.3	202.0	229.3	219.9	138.7	164.9	44.0	122.4	126.4	107.8
20	107.8	159.3	193.8	250.4	111.4	186.8	83.5	118.0	134.0	123.2
21	113.7	244.7	195.6	280.1	125.3	170.9	86.4	117.8	116.7	130.1
22	121.3	185.6	220.4	223.6	154.5	166.2	75.8	87.4	122.3	83.9
23	126.1	171.5	252.2	258.8	152.0	172.4	78.1	113.2	131.1	66.9
24	121.9	146.8	223.5	314.9	121.0	189.6	66.1	98.2	105.8	162.5
25	119.4	150.7	134.2	300.0	107.5	154.5	91.4	48.2	116.5	139.0
26	125.9	214.5	196.1	238.4	120.6	193.7	94.3	122.3	120.4	139.0
27	125.4	227.4	240.4	243.9	97.4	202.2	70.5	127.4	127.2	118.0
28	73.5	218.5	257.2	241.4	120.4	145.6	84.2	62.3	123.3	146.1
29	126.2	173.8	158.8	311.3	113.6	189.5	70.9	124.3	137.9	139.9
30	132.1	210.8	189.8	299.6	124.8	161.3	13.9	118.9	114.6	129.7
31	103.8	240.4	163.0	255.1	128.4	193.1	63.5	98.0	110.7	132.7
32	91.3	206.2	188.6	300.4	98.4	213.8	68.6	67.5	134.0	139.5
33	97.9	223.0	223.3	288.8	117.0	172.0	60.8	90.1	127.5	160.2
34	126.4	208.8	250.2	286.3	110.3	140.0	71.3	69.0	121.4	125.8
35	121.5	214.7	210.8	241.0	87.6	218.7	85.3	110.3	122.3	124.4
36	78.0	230.8	177.5	252.5	126.3	214.3	90.5	118.0	85.5	126.4
37	124.1	167.3	187.8	255.8	133.8	146.7	54.7	133.3	109.7	125.5
38	130.2	247.7	187.9	270.4	127.2	139.8	34.3	110.5	134.0	136.8
39	99.4	126.9	196.1	258.8	137.2	194.4	59.3	135.2	112.6	151.2
40	109.2	233.4	177.0	222.3	117.4	186.6	96.2	118.5	119.4	116.9
41	43.1	216.2	149.4	244.8	97.1	184.5	35.6	97.5	130.1	93.3
42	109.2	213.4	161.2	243.8	129.0	173.9	55.3	122.3	135.9	151.5
43	57.5	216.8	145.6	290.0	115.1	172.0	82.4	103.3	128.2	122.8
44	108.7	198.7	140.5	241.6	142.8	154.2	97.5	104.2	125.2	116.4
45	126.0	141.2	163.9	235.6	121.9	225.3	39.0	116.7	124.3	122.5
46	133.9	214.8	203.5	283.9	100.4	215.5	88.8	108.9	118.9	122.7
47	102.5	219.4	185.4	271.4	130.0	147.1	52.3	60.3	122.3	121.3
48	102.5	234.9	155.4	258.8	99.0	193.7	49.5	65.2	132.0	139.4
49	126.9	215.6	167.9	237.8	115.8	179.6	46.1	91.5	120.4	139.2
50	128.5	234.0	172.7	290.6	69.0	202.9	83.8	115.2	116.5	152.6
51	90.3	221.0	167.2	246.2	88.9	148.5	75.9	107.8	122.3	121.7
52	94.5	233.7	225.2	267.9	120.1	139.3	21.6	129.0	104.8	137.4

Table A17 Swelling of various resins (Continued)

No.	Dowex 50W×2-200		Dowex 50W×4-100		Dowex 50W×4-200		Dowex 50W×4-400		Dowex 50W×8-200	
	Dry	Swell	Dry	Swell	Dry	Swell	Dry	Swell	Dry	Swell
53	65.9	209.7	174.8	335.6	127.2	86.8	27.8	138.5	125.3	145.7
54	121.8	187.8	171.5	228.5	98.9	210.1	84.6	99.9	112.2	126.5
55	116.9	214.0	215.9	284.9	135.9	195.4	52.5	117.8	88.4	113.2
56	112.3	180.6	252.4	206.6	96.2	172.4	67.0	85.3	108.8	127.0
57	96.8	134.5	140.0	223.1	124.0	206.8	31.3	116.6	118.4	145.1
58	71.2	200.0	183.2	309.9	111.2	204.4	43.6	86.7	129.2	170.5
59	73.5	212.6	166.7	322.0	129.8	185.6	48.5	83.6	101.0	126.7
60	84.6	232.1	171.0	275.2	133.1	160.6	47.8	81.3	129.1	133.4
61	84.0	204.5	156.9	263.2	109.7	187.9	46.6	91.3	116.4	144.7
62	106.1	109.5	170.3	231.6	134.4	166.1	27.2	79.7	89.4	123.8
63	116.9	235.6	178.9	256.5	113.3	184.6	85.3	118.6	118.5	111.7
64	77.4	189.9	230.4	355.0	93.3	147.2	69.0	113.3	109.7	178.0
65	112.5	176.2	171.8	308.7	115.4	123.0	20.7	90.4	88.5	138.1
66	119.9	148.1	212.5	407.9	102.4	171.7	92.2	102.9	107.8	149.5
67	114.6	165.0	257.5	311.5	95.6	157.2	84.7	60.4	137.9	141.2
68	135.2	218.7	227.2	373.9	118.9	143.8	63.7	125.0	143.7	169.2
69	106.3	222.5	144.5	326.4	143.1	192.7	82.2	50.9	99.0	125.9
70	118.4	225.9	202.0	307.2	67.3	171.2	86.4	49.6	128.2	133.7
71	120.1	149.5	171.6	273.9	86.4	176.3	92.6	97.5	100.0	177.7
72	119.6	162.4	169.5	281.9	109.9	165.8	22.2	107.0	102.9	149.1
73	69.5	220.6	206.0	320.4	147.6	177.1	89.1	99.6	111.9	152.6
74	112.6	191.6	182.1	267.0	111.3	170.4	69.9	135.0	111.9	141.0
75	89.9	142.8	175.0	336.8	103.1	159.4	100.0	110.7	96.9	135.2
76	116.8	207.1	194.2	250.7	114.8	173.2	73.0	109.1	106.8	186.5
77	95.3	194.3	161.3	217.7	152.4	186.4	70.9	134.7	99.1	135.6
78	98.9	229.3	140.1	268.6	137.2	175.5	63.5	116.4	105.0	89.8
79	90.3	200.0	171.8	297.2	96.7	163.2	83.5	91.3	116.7	101.2
80	113.4	109.9	172.6	361.5	124.6	213.1	31.6	116.6	122.9	115.6
81	125.8	124.7	186.7	239.6	106.6	173.4	56.5	58.6	109.7	147.9
82	80.8	214.6	141.7	403.8	107.8	170.0	91.4	87.5	125.2	117.0
83	66.0	212.2	227.0	307.2	141.5	169.4	54.8	100.9	116.5	149.0
84	108.7	237.0	184.6	218.4	120.0	162.8	57.3	110.7	108.7	122.5
85	89.9	227.1	209.8	243.9	122.7	184.9	26.2	115.7	97.1	105.0
86	101.1	128.0	188.5	249.0	102.5	164.2	48.9	131.8	102.9	129.8
87	45.5	225.3	189.5	91.0	129.2	211.4	85.9	102.5	131.1	117.1
88	118.8	194.2	204.8	238.4	107.5	182.5	79.5	129.6	113.6	154.5
89	122.7	243.5	143.8	240.1	109.7	228.1	73.8	112.6	116.5	140.1
90	126.3	148.6	218.7	320.9	120.4	138.9	84.0	126.2	136.5	138.5
91	120.4	217.6	204.0	277.0	104.2	139.2	51.6	121.7	116.5	121.0
92	98.2	230.4	167.0	339.5	93.0	95.3	51.9	99.1	134.3	149.8
93	103.9	151.4	223.0	261.9	97.0	140.5	48.5	39.9	118.8	90.3
94	124.8	172.8	189.3	254.5	99.0	179.9	82.6	64.8	115.0	115.9
95	100.0	226.2	164.1	257.5	81.3	188.3	77.0	77.1	96.6	121.0
96	125.2	198.6	224.1	274.9	157.9	196.3	21.0	95.1	130.1	134.0
97	85.4	190.6	155.8	299.9	136.3	189.7	48.0	107.9	131.1	133.1
98	80.8	231.3	167.5	286.0	111.4	172.1	72.8	73.8	129.1	126.5
99	92.4	234.9	190.1	256.0	104.7	173.8	80.6	123.4	111.0	143.7
100	101.1	201.5	249.0	259.5	103.2	186.9	56.8	118.8	121.4	159.4
101	33.0	192.9	227.9	246.2	102.9	165.5	32.6	130.8	149.5	132.2
102	95.3	193.2	227.2	275.2	124.5	191.4	78.6	98.2	131.1	184.1
103	65.5	214.8	182.5	190.0	157.8	172.5	31.6	108.8	118.4	145.9
104	93.3	244.8	180.7	344.3	50.5	180.6	61.5	140.8	112.6	123.3

Table A17 Swelling of various resins (Continued)

No.	Dowex 50W×2-200		Dowex 50W×4-100		Dowex 50W×4-200		Dowex 50W×4-400		Dowex 50W×8-200	
	Dry	Swell	Dry	Swell	Dry	Swell	Dry	Swell	Dry	Swell
105	128.3	195.4	198.5	331.5	137.9	183.8	67.1	122.3	117.9	113.7
106	103.4	199.0	117.3	230.4	103.9	160.2	45.6	126.2	101.9	144.3
107	61.4	172.1	185.1	226.9	128.1	184.5	54.7	54.7	98.1	134.9
108	131.4	205.3	238.8	296.4	136.9	205.4	59.7	93.8	128.4	150.3
109	78.9	229.2	227.9	334.5	135.9	210.7	89.7	121.4	93.2	141.8
110	129.1	228.6	249.8	276.3	156.3	200.9	68.2	89.9	107.8	156.4
111	130.7	207.8	170.5	237.8	129.1	150.5	48.5	133.5	134.9	131.3
112	80.5	218.7	161.2	231.9	107.8	196.4	16.6	122.7	109.7	129.3
113	129.5	209.6	231.2	290.8	127.5	213.9	31.1	67.6	109.7	123.5
114	53.2	243.7	161.7	282.8	146.8	154.5	57.5	96.1	113.6	199.0
115	125.5	230.6	147.6	244.4	116.5	152.5	40.9	55.8	80.6	158.1
116	91.6	216.8	173.7	334.9	102.0	191.2	79.7	56.3	70.9	151.8
117	112.2	159.2	173.8	267.0	155.3	137.8	62.9	97.5	105.0	142.7
118	122.2	220.3	158.7	256.5	109.8	177.8	99.3	115.9	129.1	136.9
119	98.6	113.4	243.0	308.3	151.9	194.2	70.4	113.5	98.0	146.6
120	96.9	144.6	159.2	297.3	109.8	194.2	70.1	133.2	104.8	136.3
121	100.4	122.8	182.7	327.1	102.0	214.7	18.6	136.9	101.0	176.1
122	122.6	231.4	183.5	198.4	120.6	159.8	70.1	43.8	90.3	145.4
123	97.1	173.5	161.3	300.4	149.9	202.4	90.1	111.5	138.8	169.3
124	124.3	137.1	131.0	295.4	140.0	212.5	59.1	30.2	129.1	123.3
125	114.0	234.4	145.7	262.7	107.0	233.2	90.7	30.2	114.6	132.5
126	71.9	223.2	172.4	257.5	125.4	159.3	37.2	125.0	84.5	169.4
127	113.5	232.3	150.4	276.8	122.6	152.6	79.5	98.1	90.3	163.8
128	83.5	204.5	171.8	293.5	132.1	164.2	72.2	120.8	112.6	144.9
129	80.2	241.0	186.4	347.5	146.2	183.4	85.2	37.9	120.4	124.7
130	98.9	189.8	216.1	427.6	146.4	170.3	76.7	101.9	103.8	128.2
131	126.9	226.5	178.5	276.3	114.4	160.2	86.9	126.4	106.8	129.1
132	123.6	221.7	258.2	260.5	105.8	147.6	26.2	131.4	115.5	145.7
133	121.6	146.7	182.5	360.9	120.8	157.9	43.9	116.8	112.6	142.1
134	127.4	234.2	220.3	284.7	129.3	191.8	85.3	102.2	112.8	133.1
135	79.1	199.6	236.9	286.3	126.7	193.8	88.3	125.5	112.6	106.8
136	73.9	219.8	200.0	260.6	129.9	221.3	90.1	135.5	95.1	171.6
137	118.7	206.7	168.1	283.4	91.4	169.9	92.1	98.4	105.8	144.7
138	134.5	208.5	155.1	351.4	139.0	231.7	36.7	131.1	104.9	140.2
139	116.6	245.5	182.5	340.5	70.7	168.1	91.5	102.4	98.4	177.5
140	118.5	152.8	195.9	284.8	132.0	140.0	58.3	104.8	121.5	183.6
141	128.9	131.2	164.1	315.3	123.6	97.4	82.9	87.1	100.5	148.6
142	117.5	171.9	182.6	223.1	120.2	158.6	93.7	66.9	82.5	171.8
143	120.6	170.3	243.3	262.4	122.5	208.2	75.8	102.0	84.7	127.5
144	124.4	238.5	187.9	275.9	85.5	157.3	87.0	63.8	105.9	143.9
145	124.7	211.6	243.7	312.1	129.4	182.0	90.7	58.4	95.2	133.4
146	117.0	211.5	201.8	258.2	104.0	170.4	93.2	42.6	102.9	126.3
147	104.8	230.1	170.7	259.4	99.8	153.2	76.6	110.1	100.2	114.6
148	129.5	223.4	272.4	226.4	101.3	210.7	80.5	93.4	127.2	152.1
149	129.7	210.0	194.5	271.1	113.8	201.1	60.3	99.5	120.4	108.7
150	136.6	226.2	198.3	239.8	105.0	210.3	89.1	96.3	118.4	128.4
151	108.7	226.2	223.8	233.0	119.6	118.0	60.4	128.2	120.4	165.0
152	130.3	160.5	169.2	258.5	88.4	183.8	49.0	129.1	107.8	102.8
153	111.9	212.0	236.5	241.8	144.2	186.2	68.8	86.0	84.5	146.7
154	91.4	147.8	216.8	238.5	105.0	196.0	102.5	101.5	124.3	150.2
155	116.7	186.5	243.8	273.5	149.3	140.8	91.8	123.8	98.2	144.4
156	121.3	201.1	204.3	327.9	101.3	189.9	99.2	56.5	102.2	180.2

Table A17 Swelling of various resins (Continued)

No.	Dowex 50W×2-200		Dowex 50W×4-100		Dowex 50W×4-200		Dowex 50W×4-400		Dowex 50W×8-200	
	Dry	Swell	Dry	Swell	Dry	Swell	Dry	Swell	Dry	Swell
157	129.9	228.5	195.4	338.2	109.8	172.6	95.6	114.0	113.6	170.3
158	109.2	205.8	172.7	328.4	125.6	210.8	89.7	34.1	117.5	133.2
159	92.1	205.8	159.2	350.4	105.5	227.6	57.0	75.7	89.3	121.3
160	62.7	211.4	292.5	333.0	91.4	191.4	57.2	94.6	126.2	154.4
161	132.9	235.0	270.1	210.3	139.5	212.7	83.6	116.6	115.5	123.3
162	130.3	237.8	175.8	276.8	98.2	230.2	83.8	91.6	128.1	119.4
163	128.6	204.6	226.4	368.4	107.8	172.7	61.7	130.5	88.4	142.7
164	124.4	232.2	242.3	257.2	127.6	215.1	50.6	102.8	68.0	139.2
165	110.4	160.6	200.2	299.8	103.0	174.4	90.8	128.5	134.0	135.1
166	128.1	229.6	187.8	322.2	126.9	209.8	90.5	115.5	112.7	155.3
167	123.8	224.4	187.9	275.2	105.8	195.2	80.8	129.1	111.7	136.2
168	130.9	147.9	196.1	272.9	146.6	168.5	97.4	104.3	93.1	157.2
169	27.5	244.5	177.0	318.3	118.8	167.7	29.8	89.5	100.1	123.9
170	114.2	184.3	149.4	344.1	116.5	188.4	96.5	91.5	121.4	117.7
171	105.7	211.2	161.2	221.4	114.4	176.6	85.5	108.1	79.6	147.6
172	127.6	224.3	145.6	289.8	149.1	154.4	49.5	105.8	75.0	145.0
173	117.9	160.1	140.5	302.6	112.7	136.0	29.5	88.4	105.0	154.4
174	124.7	216.5	163.9	361.8	113.6	191.3	71.7	102.8	117.6	128.4
175	125.5	211.5	203.5	336.0	120.9	142.1	71.4	128.7	91.2	138.7
176	128.7	244.7	185.4	313.7	97.1	192.3	84.3	86.2	125.2	126.3
177	130.2	196.3	155.4	350.6	165.8	230.2	93.0	80.3	89.8	167.0
178	140.8	175.2	167.9	386.6	131.4	208.8	47.6	124.6	101.1	191.4
179	123.9	237.4	172.7	393.9	111.8	172.3	92.2	80.8	110.7	154.4
180	131.2	208.2	167.2	265.5	115.3	192.2	90.3	119.7	119.4	147.0
181	134.1	189.8	225.2	322.0	154.3	174.4	75.0	105.2	118.6	118.5
182	118.9	231.1	174.8	307.8	149.9	218.6	88.4	103.6	126.2	171.9
183	130.9	116.9	171.5	355.2	147.6	205.8	59.2	115.8	88.7	175.3
184	132.7	214.1	215.9	211.4	66.6	225.7	67.4	55.6	126.2	181.6
185	126.1	235.0	252.4	309.0	93.2	151.2	85.6	60.2	96.2	129.8
186	121.9	202.3	140.0	330.0	118.1	183.8	98.9	102.1	115.5	118.3
187	130.8	120.4	203.9	312.3	137.0	152.9	31.4	52.1	98.1	178.6
188	132.2	131.4	182.9	368.8	163.0	155.9	97.3	121.8	106.9	182.7
189	131.5	215.5	241.9	318.3	105.6	148.1	89.0	98.5	136.0	177.3
190	131.9	185.3	158.7	245.9	127.3	88.6	66.2	71.3	68.9	160.9
191	129.5	211.7	188.4	346.8	112.0	134.9	70.7	62.3	86.4	145.8
192	119.8	157.9	157.3	266.6	142.1	210.3	98.0	123.4	130.1	126.8
193	121.9	205.9	172.8	307.0	147.7	194.2	86.4	125.9	102.9	185.4
194	118.6	224.3	190.4	297.8	107.5	171.9	56.5	112.6	97.1	174.0
195	109.9	194.7	155.4	255.8	101.0	147.6	57.2	111.7	115.5	159.4
196	118.5	124.3	209.9	376.1	114.5	175.4	98.4	101.7	108.8	145.6
197	122.8	170.0	189.5	201.3	126.2	121.8	99.6	49.7	107.8	145.4
198	114.4	156.5	269.9	297.5	116.7	148.7	90.7	136.6	104.2	176.6
199	105.0	205.0	139.0	341.7	114.4	152.4	60.3	98.4	100.1	139.0
200	118.2	212.7	196.3	318.6	121.4	75.7	65.2	104.0	104.9	126.8
Mean (d, μm)	109.8	199.0	193.0	285.4	119.0	177.3	68.2	101.4	113.5	140.5

Dual-Drug Loading

Table A18 Binary drug loading (overall concentration 0.25 %w/v) onto Dowex-50W×2-200 (0.5 g) at 35°C

Resinates	Ratio of DTM to DPH	% Drugs loaded onto resinates									
		DTM					DPH				
		1	1 2	3	Mean	S.D.	2	1 2	3	Mean	S.D.
DTM:DPH 1:0	1:0	36.591	36.590	36.586	36.589	0.003	0	0	0	0	0
DTM:DPH 8:2	8:2	29.075	29.074	29.073	29.074	0.001	7.380	7.380	7.381	7.380	0.000
DTM:DPH 6:4	6:4	21.664	21.661	21.661	21.662	0.002	14.664	14.660	14.662	14.662	0.002
DTM:DPH 4:6	4:6	14.346	14.345	14.346	14.346	0.000	21.848	21.849	21.844	21.847	0.003
DTM:DPH 2:8	2:8	7.123	7.126	7.127	7.125	0.002	28.938	28.940	28.939	28.939	0.001
DTM:DPH 0:1	0:1	0	0	0	0	0	35.941	35.941	35.939	35.940	0.001

Table A19 Regression analysis of binary drug loading (overall concentration 0.25 %w/v) onto Dowex-50W×2-200 (0.5 g) at 35°C

Regression parameters	DTM					DPH				
	Replicate number			Mean	S.D.	Replicate number			Mean	S.D.
	1	2	3			1	2	3		
Slope	36.589	36.587	36.584	36.587	0.003	35.937	35.939	35.936	35.938	0.002
Y-intercept	-0.162	-0.161	-0.160	-0.161	0.001	0.160	0.159	0.160	0.159	0.001
R^2	1.000	1.000	1.000	1.000	<0.001	1.000	1.000	1.000	1.000	<0.001
Isoloading parameters	Replicate number			Mean	S.D.					
	1	2	3							
EQC	18.131	18.131	18.130	18.130	<0.001					
ELS	0.500	0.500	0.500	0.500	<0.001					

Table A20 Binary drug loading (overall concentration 0.5 %w/v) onto Dowex-50W×2-200 (0.5 g) at 35°C

Resinates	Ratio of DTM to DPH	% Drugs loaded onto resinates									
		DTM					DPH				
		3 1	2	3	Mean	S.D.	4 1	2	3	Mean	S.D.
DTM:DPH 1:0	1:0	57.356	57.348	57.345	57.350	0.006	0	0	0	0	0
DTM:DPH 8:2	8:2	45.378	45.372	45.382	45.378	0.005	11.550	11.549	11.549	11.549	0.001
DTM:DPH 6:4	6:4	33.666	33.664	33.663	33.664	0.001	22.845	22.847	22.842	22.845	0.002
DTM:DPH 4:6	4:6	22.200	22.199	22.193	22.200	0.001	33.897	33.894	33.893	33.895	0.002
DTM:DPH 2:8	2:8	10.980	10.980	10.979	10.980	0.001	44.711	44.706	44.712	44.709	0.003
DTM:DPH 0:1	0:1	0	0	0	0	0	55.308	55.301	55.295	55.301	0.006

Table A21 Regression analysis of binary drug loading (overall concentration 0.5 %w/v) onto Dowex-50W×2-200 (0.5 g) at 35°C

Regression parameters	DTM					DPH				
	Replicate number			Mean	S.D.	Replicate number			Mean	S.D.
	1	2	3			1	2	3		
Slope	57.348	57.341	57.343	57.344	0.004	55.296	55.289	55.288	55.291	0.005
Y-intercept	-0.411	-0.410	-0.411	-0.411	0.001	0.404	0.405	0.405	0.404	0.001
R^2	1.000	1.000	1.000	1.000	<0.001	1.000	1.000	1.000	1.000	<0.001
Isoloading parameters	Replicate number			Mean	S.D.					
	1	2	3							
EQC	28.156	28.153	28.153	28.154	0.002					
ELS	0.498	0.498	0.498	0.498	<0.001					

Table A22 Binary drug loading (overall concentration 0.75 %w/v) onto Dowex-50W×2-200 (0.5 g) at 35°C

Resinates	Ratio of DTM to DPH	% Drugs loaded onto resinates									
		DTM					DPH				
		5 1	2	3	Mean	S.D	6 1	2	3	Mean	S.D.
DTM:DPH 1:0	1:0	69.607	69.631	69.639	69.626	0.017	0	0	0	0	0
DTM:DPH 8:2	8:2	54.792	54.745	54.749	54.762	0.026	14.169	14.163	14.166	14.166	0.003
DTM:DPH 6:4	6:4	40.287	40.262	40.288	40.279	0.015	27.764	27.748	27.759	27.757	0.008
DTM:DPH 4:6	4:6	26.224	26.235	26.248	26.230	0.008	40.693	40.677	40.644	40.685	0.012
DTM:DPH 2:8	2:8	12.803	12.839	12.851	12.831	0.025	52.649	52.836	52.802	52.762	0.100
DTM:DPH 0:1	0:1	0	0	0	0	0	64.135	64.371	64.166	64.224	0.128

Table A23 Regression analysis of binary drug loading (overall concentration 0.75%w/v) onto Dowex-50W×2-200 (0.5 g) at 35°C

Regression parameters	DTM					DPH				
	Replicate number			Mean	S.D.	Replicate number			Mean	S.D.
	1	2	3			1	2	3		
Slope	69.724	69.700	69.574	69.666	0.080	64.149	64.401	64.064	64.205	0.175
Y-intercept	-0.910	-0.898	-0.673	-0.827	0.133	1.160	1.099	1.028	1.096	0.066
R^2	0.999	0.999	0.999	0.999	<0.001	0.998	0.999	0.999	0.999	<0.001
Isoloading parameters	Replicate number			Mean	S.D.					
	1	2	3							
EQC	33.579	33.613	33.565	33.585	0.025					
ELS	0.495	0.495	0.492	0.494	0.002					

Table A24 Binary drug loading (overall concentration 1.0 %w/v) onto Dowex-50W×2-200 (0.5 g) at 35°C

Resinates	Ratio of DTM to DPH	% Drugs loaded onto resinates									
		DTM					DPH				
		7	1	2	3	Mean	S.D.	8	1	2	3	Mean	S.D.
DTM:DPH 1:0	1:0	75.978	75.842	76.321	76.047	0.247	0	0	0	0	0
DTM:DPH 8:2	8:2	59.041	59.222	59.146	59.136	0.091	14.665	14.660	14.310	14.545	0.203
DTM:DPH 6:4	6:4	42.904	42.899	42.941	42.915	0.023	28.446	28.199	28.423	28.356	0.136
DTM:DPH 4:6	4:6	28.023	28.154	28.167	28.115	0.080	41.201	40.951	41.220	41.124	0.150
DTM:DPH 2:8	2:8	13.761	13.600	13.723	13.695	0.084	53.179	53.256	53.156	53.197	0.052
DTM:DPH 0:1	0:1	0	0	0	0	0	65.802	65.595	65.450	65.616	0.177

Table A25 Regression analysis of binary drug loading (overall concentration 1.0 %w/v) onto Dowex-50W×2-200 (0.5 g) at 35°C

Regression parameters	DTM					DPH				
	Replicate number			Mean	S.D.	Replicate number			Mean	S.D.
	1	2	3			1	2	3		
Slope	75.802	75.832	76.092	75.909	0.160	65.330	65.216	65.226	65.258	0.063
Y-intercept	-1.283	-1.296	-1.330	-1.303	0.024	1.217	1.169	1.147	1.178	0.036
R^2	0.998	0.999	0.998	0.998	<0.001	0.999	0.999	0.998	0.999	<0.001
Isoloading parameters	Replicate number			Mean	S.D.					
	1	2	3							
EQC	35.148	35.091	35.125	35.121	0.029					
ELS	0.481	0.480	0.479	0.480	0.001					

Table A26 Binary drug loading (overall concentration 0.25 %w/v) onto Dowex-50W×4-200 (0.5 g) at 35°C

Resinates	Ratio of DTM to DPH	% Drugs loaded onto resinates									
		DTM					DPH				
		9 1	2	3	Mean	S.D.	10 1	2	3	Mean	S.D.
DTM:DPH 1:0	1:0	36.555	36.552	36.550	36.552	0.002	0	0	0	0	0
DTM:DPH 8:2	8:2	29.097	29.095	29.097	29.097	0.002	7.183	7.182	7.184	7.183	0.001
DTM:DPH 6:4	6:4	21.714	21.714	21.713	21.713	0.001	14.291	14.292	14.289	14.291	0.002
DTM:DPH 4:6	4:6	14.405	14.405	14.403	14.405	0.001	21.326	21.321	21.321	21.323	0.003
DTM:DPH 2:8	2:8	7.167	7.162	7.165	7.165	0.003	28.296	28.288	28.295	28.293	0.004
DTM:DPH 0:1	0:1	0	0	0	0	0	35.198	35.200	35.195	35.198	0.002

Table A27 Regression analysis of binary drug loading (overall concentration 0.25 %w/v) onto Dowex-50W×4-200 (0.5 g) at 35°C

Regression parameters	DTM					DPH				
	Replicate number			Mean	S.D.	Replicate number			Mean	S.D.
	1	2	3			1	2	3		
Slope	36.553	36.552	36.551	36.552	0.001	35.195	35.193	35.192	35.193	0.002
Y-intercept	-0.120	-0.122	-0.121	-0.121	0.001	0.118	0.118	0.118	0.118	0.000
R^2	1.000	1.000	1.000	1.000	<0.001	1.000	1.000	1.000	1.000	<0.001
Isoloading parameters	Replicate number			Mean	S.D.					
	1	2	3							
EQC	17.932	17.930	17.930	17.931	0.001					
ELS	0.494	0.494	0.494	0.494	<0.001					

Table A28 Binary drug loading (overall concentration 0.5 %w/v) onto Dowex-50W×4-200 (0.5 g) at 35°C

Resinates	Ratio of DTM to DPH	% Drugs loaded onto resinates									
		DTM					DPH				
		11 1	2	3	Mean	S.D.	12 1	2	3	Mean	S.D.
DTM:DPH 1:0	1:0	58.777	58.782	58.771	58.777	0.005	0	0	0	0	0
DTM:DPH 8:2	8:2	46.728	46.727	46.731	46.728	0.002	11.279	11.273	11.270	11.274	0.005
DTM:DPH 6:4	6:4	34.834	34.845	34.829	34.836	0.008	22.417	22.424	22.416	22.419	0.005
DTM:DPH 4:6	4:6	23.065	23.063	23.052	23.064	0.002	33.408	33.412	33.410	33.410	0.003
DTM:DPH 2:8	2:8	11.462	11.462	11.463	11.462	0.001	44.263	44.260	44.245	44.256	0.010
DTM:DPH 0:1	0:1	0	0	0	0	0	54.966	54.968	54.955	54.963	0.007

Table A29 Regression analysis of binary drug loading (overall concentration 0.5 %w/v) onto Dowex-50W×4-200 (0.5 g) at 35°C

Regression parameters	DTM					DPH				
	Replicate number			Mean	S.D.	Replicate number			Mean	S.D.
	1	2	3			1	2	3		
Slope	58.779	58.784	58.776	58.780	0.004	54.968	54.970	54.956	54.965	0.007
Y-intercept	-0.245	-0.246	-0.247	-0.246	0.001	0.238	0.238	0.238	0.238	<0.001
R^2	1.000	1.000	1.000	1.000	<0.001	1.000	1.000	1.000	1.000	<0.001
Isoloading parameters	Replicate number			Mean	S.D.					
	1	2	3							
EQC	28.409	28.411	28.405	28.408	0.003					
ELS	0.487	0.487	0.487	0.487	<0.001					

Table A30 Binary drug loading (overall concentration 0.75 %w/v) onto Dowex-50W×4-200 (0.5 g) at 35°C

Resinates	Ratio of DTM to DPH	% Drugs loaded onto resinates									
		DTM					DPH				
		13 1	2	3	Mean	S.D.	14 1	2	3	Mean	S.D.
DTM:DPH 1:0	1:0	71.179	71.134	71.137	71.150	0.025	0	0	0	0	0
DTM:DPH 8:2	8:2	56.112	56.119	56.151	56.127	0.021	13.901	13.884	13.895	13.893	0.009
DTM:DPH 6:4	6:4	41.594	41.511	41.379	41.495	0.108	27.500	27.429	27.307	27.412	0.098
DTM:DPH 4:6	4:6	27.166	27.097	-	27.132	0.049	40.337	40.226	-	40.282	0.079
DTM:DPH 2:8	2:8	13.378	13.341	13.357	13.359	0.019	52.778	52.669	52.815	52.754	0.076
DTM:DPH 0:1	0:1	0	0	0	0	0	64.008	63.988	64.117	64.038	0.069

Table A31 Regression analysis of binary drug loading (overall concentration 0.75 %w/v) onto Dowex-50W×4-200 (0.5 g) at 35°C

Regression parameters	DTM					DPH				
	Replicate number			Mean	S.D.	Replicate number			Mean	S.D.
	1	2	3			1	2	3		
Slope	71.218	71.202	71.082	71.167	0.075	64.216	64.156	64.195	64.189	0.030
Y-intercept	-0.704	-0.734	-0.558	-0.665	0.095	0.980	0.955	0.813	0.916	0.090
R^2	1.000	1.000	1.000	1.000	<0.001	0.999	0.999	0.999	0.999	<0.001
Isoloading parameters	Replicate number			Mean	S.D.					
	1	2	3							
EQC	33.949	33.902	33.894	33.915	0.030					
ELS	0.487	0.486	0.485	0.486	0.001					

Table A32 Binary drug loading (overall concentration 1.0 %w/v) onto Dowex-50W×4-200 (0.5 g) at 35°C

Resinates	Ratio of DTM to DPH	% Drugs loaded onto resinates									
		DTM					DPH				
		15 1	2	3	Mean	S.D.	16 1	2	3	Mean	S.D.
DTM:DPH 1:0	1:0	74.993	74.878	74.818	74.897	0.089	0	0	0	0	0
DTM:DPH 8:2	8:2	57.823	57.921	57.955	57.900	0.068	14.331	14.392	14.404	14.376	0.039
DTM:DPH 6:4	6:4	42.340	42.275	42.282	42.299	0.036	27.556	27.536	27.674	27.589	0.075
DTM:DPH 4:6	4:6	27.605	27.388	27.702	27.565	0.161	40.474	40.466	40.384	40.441	0.050
DTM:DPH 2:8	2:8	13.789	13.803	13.915	13.836	0.069	52.095	52.002	52.079	52.059	0.050
DTM:DPH 0:1	0:1	0	0	0	0	0	64.342	64.277	64.295	64.304	0.034

Table A33 Regression analysis of binary drug loading (overall concentration 1.0 %w/v) onto Dowex-50W×4-200 (0.5 g) at 35°C

Regression parameters	DTM					DPH				
	Replicate number			Mean	S.D.	Replicate number			Mean	S.D.
	1	2	3			1	2	3		
Slope	74.543	74.519	74.399	74.487	0.077	63.989	63.877	63.887	63.918	0.062
Y-intercept	-1.180	-1.215	-1.087	-1.161	0.066	1.139	1.173	1.196	1.169	0.029
R^2	0.998	0.998	0.998	0.998	<0.001	0.999	0.999	0.999	0.999	<0.001
Isoloading parameters	Replicate number			Mean	S.D.					
	1	2	3							
EQC	34.500	34.465	34.513	34.493	0.024					
ELS	0.479	0.479	0.479	0.479	<0.001					

Table A34 Binary drug loading (overall concentration 0.25 %w/v) onto Dowex-50W×8-200 (0.5 g) at 35°C

Resinates	Ratio of DTM to DPH	% Drugs loaded onto resinates									
		DTM					DPH				
		17 1	2	3	Mean	S.D.	18 1	2	3	Mean	S.D.
DTM:DPH 1:0	1:0	36.186	36.176	36.185	36.182	0.006	0	0	0	0	0
DTM:DPH 8:2	8:2	28.724	28.741	28.721	28.729	0.011	7.396	7.398	7.393	7.395	0.003
DTM:DPH 6:4	6:4	21.403	21.389	21.398	21.397	0.007	14.672	14.665	14.671	14.669	0.004
DTM:DPH 4:6	4:6	14.168	14.151	14.168	14.162	0.010	21.844	21.810	21.839	21.831	0.018
DTM:DPH 2:8	2:8	7.032	7.034	7.035	7.034	0.002	28.883	28.900	28.901	28.895	0.010
DTM:DPH 0:1	0:1	0	0	0	0	0	35.810	35.867	35.874	35.850	0.035

Table A35 Regression analysis of binary drug loading (overall concentration 0.25 %w/v) onto Dowex-50W×8-200 (0.5 g) at 35°C

Regression parameters	DTM					DPH				
	Replicate number			Mean	S.D.	Replicate number			Mean	S.D.
	1	2	3			1	2	3		
Slope	36.178	36.177	36.173	36.176	0.002	35.811	35.855	35.866	35.844	0.029
Y-intercept	-0.170	-0.173	-0.168	-0.170	0.002	0.195	0.179	0.180	0.185	0.009
R^2	1.000	1.000	1.000	1.000	<0.001	1.000	1.000	1.000	1.000	<0.001
Isoloading parameters	Replicate number			Mean	S.D.					
	1	2	3							
EQC	18.010	18.011	18.016	18.013	0.003					
ELS	0.503	0.503	0.503	0.503	<0.001					

Table A36 Binary drug loading (overall concentration 0.5 %w/v) onto Dowex-50W×8-200 (0.5 g) at 35°C

Resinates	Ratio of DTM to DPH	% Drugs loaded onto resinates									
		DTM					DPH				
		19 1	2	3	Mean	S.D.	20 1	2	3	Mean	S.D.
DTM:DPH 1:0	1:0	48.573	46.741	48.546	47.953	1.050	0	0	0	0	0
DTM:DPH 8:2	8:2	38.315	40.435	40.772	39.841	1.332	10.884	11.282	11.310	11.159	0.239
DTM:DPH 6:4	6:4	30.272	30.600	31.304	30.725	0.527	22.021	22.221	22.828	22.357	0.420
DTM:DPH 4:6	4:6	20.524	20.864	21.161	20.850	0.319	32.769	32.996	33.219	32.995	0.225
DTM:DPH 2:8	2:8	10.535	10.473	9.963	10.324	0.314	43.592	43.527	42.435	43.185	0.650
DTM:DPH 0:1	0:1	0	0	0	0	0	53.709	53.799	53.648	53.719	0.076

Table A37 Regression analysis of binary drug loading (overall concentration 0.5 %w/v) onto Dowex-50W×8-200 (0.5 g) at 35°C

Regression parameters	DTM					DPH				
	Replicate number			Mean	S.D.	Replicate number			Mean	S.D.
	1	2	3			1	2	3		
Slope	47.993	47.618	49.328	48.313	0.899	53.917	53.787	53.143	53.616	0.414
Y-intercept	0.707	1.043	0.627	0.792	0.221	0.204	0.411	0.668	0.428	0.233
R^2	0.999	0.995	0.997	0.997	0.002	1.000	1.000	0.999	0.999	0.001
Isoloading parameters	Replicate number			Mean	S.D.					
	1	2	3							
EQC	25.861	26.004	26.229	26.031	0.185					
ELS	0.524	0.524	0.519	0.522	0.003					

Table A38 Binary drug loading (overall concentration 0.75 %w/v) onto Dowex-50W×8-200 (0.5 g) at 35°C

Resinates	Ratio of DTM to DPH	% Drugs loaded onto resinates									
		DTM					DPH				
		21	1	2	3	Mean	S.D.	22	1	2	3	Mean	S.D.
DTM:DPH 1:0	1:0	50.709	49.441	49.275	49.808	0.785	0	0	0	0	0
DTM:DPH 8:2	8:2	40.799	40.883	39.818	40.500	0.592	11.769	12.060	11.551	11.794	0.255
DTM:DPH 6:4	6:4	31.498	31.676	31.873	31.683	0.188	23.358	23.472	23.863	23.564	0.265
DTM:DPH 4:6	4:6	21.904	21.684	21.976	21.855	0.152	36.041	35.827	35.984	35.951	0.111
DTM:DPH 2:8	2:8	11.031	11.213	10.653	10.966	0.286	46.258	46.919	43.749	45.642	1.672
DTM:DPH 0:1	0:1	0	0	0	0	0	57.414	57.713	56.273	57.133	0.760

Table A39 Regression analysis of binary drug loading (overall concentration 0.75 %w/v) onto Dowex-50W×8-200 (0.5 g) at 35°C

Regression parameters	DTM					DPH				
	Replicate number			Mean	S.D.	Replicate number			Mean	S.D.
	1	2	3			1	2	3		
Slope	50.350	49.458	49.109	49.639	0.640	57.602	57.929	55.725	57.085	1.189
Y-intercept	0.815	1.087	1.044	0.982	0.146	0.339	0.368	0.707	0.471	0.205
R^2	0.999	0.998	0.997	0.998	0.001	0.999	1.000	0.997	0.999	0.002
Isoloading parameters	Replicate number			Mean	S.D.					
	1	2	3							
EQC	27.459	27.435	26.991	27.295	0.264					
ELS	0.529	0.533	0.528	0.530	0.002					

Table A40 Binary drug loading (overall concentration 1.0 %w/v) onto Dowex-50W×8-200 (0.5 g) at 35°C

Resinates	Ratio of DTM to DPH	% Drugs loaded onto resinates									
		DTM					DPH				
		23	1 2 3	Mean	S.D.	24	1 2 3	Mean	S.D.		
DTM:DPH 1:0	1:0	50.905	49.687 50.378	50.323	0.611	0	0 0	0	0		
DTM:DPH 8:2	8:2	39.544	38.381 39.432	39.119	0.642	12.208	13.973 12.176	12.786	1.028		
DTM:DPH 6:4	6:4	29.758	29.761 29.743	29.754	0.010	24.300	24.726 24.172	24.399	0.290		
DTM:DPH 4:6	4:6	20.494	19.631 20.533	20.219	0.510	37.406	38.184 37.369	37.653	0.460		
DTM:DPH 2:8	2:8	10.235	10.181 10.418	10.278	0.124	47.617	47.879 47.865	47.787	0.147		
DTM:DPH 0:1	0:1	0	0 0	0	0	58.575	58.673 58.112	58.453	0.300		

Table A41 Regression analysis of binary drug loading (overall concentration 1.0 %w/v) onto Dowex-50W×8-200 (0.5 g) at 35°C

Regression parameters	DTM					DPH				
	Replicate number			Mean	S.D.	Replicate number			Mean	S.D.
	1	2	3			1	2	3		
Slope	50.245	49.023	49.735	49.668	0.614	58.886	58.3629	58.689	58.646	0.264
Y-intercept	0.033	0.095	0.217	0.115	0.093	0.5743	1.39092	0.60445	0.8566	0.4630
R^2	0.999	0.999	0.999	0.999	<0.001	0.9986	0.99702	0.99822	0.9980	0.0008
Isoloading parameters	Replicate number			Mean	S.D.					
	1	2	3							
EQC	27.394	27.330	27.316	27.347	0.042					
ELS	0.545	0.556	0.545	0.548	0.006					

Table A42 Binary drug loading (overall concentration 0.5 %w/v) onto Dowex-50W×2-200 (0.125 g) at 35°C

Resinates	Ratio of DTM to DPH	% Drugs loaded onto resinates									
		DTM					DPH				
		25 1	2	3	Mean	S.D.	26 1	2	3	Mean	S.D.
DTM:DPH 1:0	1:0	75.247	75.247	75.461	75.318	0.123	0	0	0	0	0
DTM:DPH 8:2	8:2	60.363	59.853	61.092	60.436	0.623	14.806	15.064	15.063	14.978	0.149
DTM:DPH 6:4	6:4	43.295	43.159	42.975	43.143	0.161	28.506	28.021	28.085	28.204	0.263
DTM:DPH 4:6	4:6	28.261	28.540	27.887	28.401	0.197	41.058	41.545	41.398	41.301	0.344
DTM:DPH 2:8	2:8	13.568	13.605	13.353	13.509	0.136	53.551	52.614	51.459	52.541	1.048
DTM:DPH 0:1	0:1	0	0	0	0	0	64.952	65.635	64.348	64.979	0.644

Table A43 Regression analysis of binary drug loading (overall concentration 0.5 %w/v) onto Dowex-50W×2-200 (0.125 g) at 35°C

Regression parameters	DTM					DPH				
	Replicate number			Mean	S.D.	Replicate number			Mean	S.D.
	1	2	3			1	2	3		
Slope	75.951	75.657	76.516	76.041	0.436	64.793	64.907	63.463	64.387	0.803
Y-intercept	-1.186	-1.095	-1.463	-1.248	0.192	1.416	1.360	1.661	1.479	0.160
R^2	0.999	0.999	0.998	0.999	0.001	0.998	0.998	0.997	0.998	0.001
Isoloading parameters	Replicate number			Mean	S.D.					
	1	2	3							
EQC	35.183	35.162	34.935	35.093	0.138					
ELS	0.479	0.479	0.476	0.478	0.002					

Table A44 Binary drug loading (overall concentration 0.5 %w/v) onto Dowex-50W×2-200 (0.8 g) at 35°C

Resinates	Ratio of DTM to DPH	% Drugs loaded onto resinates									
		DTM					DPH				
		27 1	2	3	Mean	S.D.	28 1	2	3	Mean	S.D.
DTM:DPH 1:0	1:0	42.743	42.741	42.741	42.742	0.001	0	0	0	0	0
DTM:DPH 8:2	8:2	33.917	33.916	33.916	33.916	0.001	8.634	8.634	8.635	8.634	0.001
DTM:DPH 6:4	6:4	25.234	25.235	25.234	25.234	0.001	17.130	17.129	17.127	17.128	0.001
DTM:DPH 4:6	4:6	16.690	16.691	16.691	16.691	0.001	25.487	25.487	25.486	25.487	0.000
DTM:DPH 2:8	2:8	8.281	8.281	8.281	8.281	0.000	33.715	33.714	33.706	33.712	0.004
DTM:DPH 0:1	0:1	0	0	0	0	0	41.817	41.815	41.814	41.816	0.002

Table A45 Regression analysis of binary drug loading (overall concentration 0.5 %w/v) onto Dowex-50W×2-200 (0.8 g) at 35°C

Regression parameters	DTM					DPH				
	Replicate number			Mean	S.D.	Replicate number			Mean	S.D.
	1	2	3			1	2	3		
Slope	42.738	42.736	42.736	42.737	0.001	41.812	41.810	41.806	41.810	0.003
Y-intercept	-0.225	-0.224	-0.224	-0.224	<0.001	0.224	0.225	0.225	0.225	<0.001
R^2	1.000	1.000	1.000	1.000	<0.001	1.000	1.000	1.000	1.000	<0.001
Isoloading parameters	Replicate number			Mean	S.D.					
	1	2	3							
EQC	21.137	21.137	21.136	21.137	0.001					
ELS	0.500	0.500	0.500	0.500	<0.001					

Table A46 Binary drug loading (overall concentration 0.5 %w/v) onto Dowex-50W×4-200 (0.125 g) at 35°C

Resinates	Ratio of DTM to DPH	% Drugs loaded onto resinates									
		DTM					DPH				
		29 1	2	3	Mean	S.D.	30 1	2	3	Mean	S.D.
DTM:DPH 1:0	1:0	78.217	78.352	78.479	78.349	0.131	0	0	0	0	0
DTM:DPH 8:2	8:2	60.473	59.108	60.539	60.040	0.808	13.711	13.265	13.816	13.598	0.293
DTM:DPH 6:4	6:4	45.231	45.835	46.371	45.812	0.570	26.748	27.774	28.055	27.526	0.688
DTM:DPH 4:6	4:6	29.891	29.901	29.933	29.896	0.007	39.826	40.157	39.840	39.992	0.234
DTM:DPH 2:8	2:8	14.810	14.914	14.668	14.797	0.124	52.453	52.456	52.111	52.340	0.198
DTM:DPH 0:1	0:1	0	0	0	0	0	63.661	64.085	63.657	63.801	0.246

Table A47 Regression analysis of binary drug loading (overall concentration 0.5 %w/v) onto Dowex-50W×4-200 (0.125 g) at 35°C

Regression parameters	DTM					DPH				
	Replicate number			Mean	S.D.	Replicate number			Mean	S.D.
	1	2	3			1	2	3		
Slope	77.631	77.182	78.064	77.626	0.441	63.944	64.340	63.565	63.950	0.388
Y-intercept	-0.712	-0.573	-0.700	-0.662	0.077	0.761	0.786	1.131	0.893	0.207
R^2	0.999	0.998	0.999	0.999	0.001	0.999	0.999	0.998	0.999	<0.001
Isoloading parameters	Replicate number			Mean	S.D.					
	1	2	3							
EQC	35.159	35.258	35.345	35.254	0.093					
ELS	0.462	0.464	0.462	0.463	0.001					

Table A48 Binary drug loading (overall concentration 0.5 %w/v) onto Dowex-50W×4-200 (0.8 g) at 35°C

Resinates	Ratio of DTM to DPH	% Drugs loaded onto resinates									
		DTM					DPH				
		31 1	2	3	Mean	S.D.	32 1	2	3	Mean	S.D.
DTM:DPH 1:0	1:0	43.162	43.166	43.163	43.164	0.002	0	0	0	0	0
DTM:DPH 8:2	8:2	34.311	34.316	34.315	34.314	0.002	8.505	8.506	8.504	8.505	0.001
DTM:DPH 6:4	6:4	25.574	25.577	25.577	25.576	0.002	16.898	16.902	16.901	16.900	0.002
DTM:DPH 4:6	4:6	16.943	16.944	16.944	16.943	0.001	25.194	25.198	25.198	25.196	0.003
DTM:DPH 2:8	2:8	8.422	8.423	8.422	8.422	0.001	33.386	33.387	33.387	33.386	0.001
DTM:DPH 0:1	0:1	0	0	0	0	0	41.478	41.486	41.435	41.467	0.028

Table A49 Regression analysis of binary drug loading (overall concentration 0.5 %w/v) onto Dowex-50W×4-200 (0.8 g) at 35°C

Regression parameters	DTM					DPH				
	Replicate number			Mean	S.D.	Replicate number			Mean	S.D.
	1	2	3			1	2	3		
Slope	43.159	43.163	43.161	43.161	0.002	41.476	41.482	41.446	41.468	0.019
Y-intercept	-0.177	-0.177	-0.177	-0.177	<0.001	0.172	0.172	0.181	0.175	0.005
R^2	1.000	1.000	1.000	1.000	<0.001	1.000	1.000	1.000	1.000	<0.001
Isoloading parameters	Replicate number			Mean	S.D.					
	1	2	3							
EQC	21.151	21.154	21.149	21.151	0.003					
ELS	0.494	0.494	0.494	0.494	<0.001					

Table A50 Binary drug loading (overall concentration 0.5 %w/v) onto Dowex-50W×8-200 (0.125 g) at 35°C

Resinates	Ratio of DTM to DPH	% Drugs loaded onto resinates									
		DTM					DPH				
		33 1	2	3	Mean	S.D.	34 1	2	3	Mean	S.D.
DTM:DPH 1:0	1:0	51.541	52.785	46.870	50.399	3.119	0	0	0	0	0
DTM:DPH 8:2	8:2	39.329	40.232	40.385	39.982	0.571	12.854	11.575	12.241	12.223	0.640
DTM:DPH 6:4	6:4	29.815	29.557	29.624	29.665	0.134	24.800	23.449	24.884	24.378	0.806
DTM:DPH 4:6	4:6	18.135	18.164	20.018	18.149	0.020	39.275	33.830	35.898	36.552	3.850
DTM:DPH 2:8	2:8	10.252	9.844	10.209	10.101	0.224	46.843	45.473	44.781	45.699	1.050
DTM:DPH 0:1	0:1	0	0	0	0	0	58.277	57.731	58.899	58.302	0.584

Table A51 Regression analysis of binary drug loading (overall concentration 0.5 %w/v) onto Dowex-50W×8-200 (0.125 g) at 35°C

Regression parameters	DTM					DPH				
	Replicate number			Mean	S.D.	Replicate number			Mean	S.D.
	1	2	3			1	2	3		
Slope	50.945	52.355	47.783	50.361	2.341	58.260	57.247	57.589	57.699	0.516
Y-intercept	-0.627	-1.081	0.626	-0.361	0.884	1.211	0.053	0.656	0.640	0.579
R^2	0.997	0.996	0.997	0.997	<0.001	0.994	1.000	0.997	0.997	0.003
Isoloading parameters	Replicate number			Mean	S.D.					
	1	2	3							
EQC	27.409	26.807	26.754	26.990	0.364					
ELS	0.550	0.533	0.547	0.543	0.009					

Table A52 Binary drug loading (overall concentration 0.5 %w/v) onto Dowex-50W×8-200 (0.8 g) at 35°C

Resinates	Ratio of DTM to DPH	% Drugs loaded onto resinates									
		DTM					DPH				
		35 1	2	3	Mean	S.D.	36 1	2	3	Mean	S.D.
DTM:DPH 1:0	1:0	41.962	41.901	41.306	41.723	0.362	0	0	0	0	0
DTM:DPH 8:2	8:2	33.415	33.404	33.413	33.411	0.006	8.487	8.485	8.483	8.485	0.002
DTM:DPH 6:4	6:4	24.890	24.898	24.873	24.887	0.013	16.820	16.822	16.826	16.823	0.003
DTM:DPH 4:6	4:6	16.473	16.477	16.472	16.475	0.003	25.034	25.026	25.023	25.030	0.005
DTM:DPH 2:8	2:8	8.181	8.179	8.177	8.179	0.002	33.111	33.129	33.110	33.117	0.011
DTM:DPH 0:1	0:1	0	0	0	0	0	41.062	41.072	41.094	41.076	0.017

Table A53 Regression analysis of binary drug loading (overall concentration 0.5 %w/v) onto Dowex-50W×8-200 (0.8 g) at 35°C

Regression parameters	DTM					DPH				
	Replicate number			Mean	S.D.	Replicate number			Mean	S.D.
	1	2	3			1	2	3		
Slope	41.990	41.943	41.520	41.817	0.259	41.056	41.071	41.079	41.069	0.011
Y-intercept	-0.175	-0.162	-0.053	-0.130	0.067	0.224	0.220	0.217	0.220	0.004
R^2	1.000	1.000	1.000	1.000	<0.001	1.000	1.000	1.000	1.000	<0.001
Isoloading parameters	Replicate number			Mean	S.D.					
	1	2	3							
EQC	20.786	20.782	20.732	20.767	0.030					
ELS	0.499	0.499	0.501	0.500	0.001					

Table A54 Binary drug loading (overall concentration 1.0 %w/v) onto Dowex-50W×2-200 (0.5 g) at 45°C

Resinates	Ratio of DTM to DPH	% Drugs loaded onto resinates									
		DTM					DPH				
		37	1	2	3	Mean	S.D.	38	1	2	3	Mean	S.D.
DTM:DPH 1:0	1:0	75.696		75.724	75.660	75.693	0.032	0		0	0	0	0
DTM:DPH 8:2	8:2	58.843		58.771	58.853	58.822	0.045	14.492		14.399	14.469	14.453	0.048
DTM:DPH 6:4	6:4	43.200		43.250	43.188	43.213	0.033	28.303		28.270	28.153	28.242	0.079
DTM:DPH 4:6	4:6	27.980		27.920	28.016	27.972	0.048	40.989		40.868	40.954	40.937	0.062
DTM:DPH 2:8	2:8	13.736		13.596	13.644	13.659	0.071	53.202		53.295	52.984	53.160	0.160
DTM:DPH 0:1	0:1	0		0	0	0	0	64.786		64.719	64.710	64.738	0.042

Table A55 Regression analysis of binary drug loading (overall concentration 1.0 %w/v) onto Dowex-50W×2-200 (0.5 g) at 45°C

Regression parameters	DTM					DPH				
	Replicate number			Mean	S.D.	Replicate number			Mean	S.D.
	1	2	3			1	2	3		
Slope	75.574	75.639	75.585	75.600	0.035	64.678	64.697	64.557	64.644	0.076
Y-intercept	-1.211	-1.276	-1.233	-1.240	0.033	1.290	1.243	1.267	1.267	0.023
R^2	0.999	0.999	0.999	0.999	<0.001	0.998	0.998	0.998	0.998	<0.001
Isoloading parameters	Replicate number			Mean	S.D.					
	1	2	3							
EQC	34.988	34.953	34.934	34.958	0.027					
ELS	0.479	0.479	0.478	0.479	<0.001					

Table A56 Binary drug loading (overall concentration 1.0 %w/v) onto Dowex-50W×2-200 (0.5 g) at 55°C

Resinates	Ratio of DTM to DPH	% Drugs loaded onto resinates									
		DTM					DPH				
		39 1	2	3	Mean	S.D.	40 1	2	3	Mean	S.D.
DTM:DPH 1:0	1:0	75.516	75.533	75.546	75.532	0.015	0	0	0	0	0
DTM:DPH 8:2	8:2	58.312	58.353	58.156	58.273	0.104	14.663	14.638	14.563	14.621	0.052
DTM:DPH 6:4	6:4	42.804	42.760	42.731	42.765	0.037	28.384	28.424	28.390	28.400	0.021
DTM:DPH 4:6	4:6	27.665	27.834	27.834	27.778	0.097	41.329	41.299	41.277	41.302	0.026
DTM:DPH 2:8	2:8	13.617	13.642	13.686	13.648	0.035	53.331	53.347	53.311	53.330	0.018
DTM:DPH 0:1	0:1	0	0	0	0	0	64.704	64.878	64.832	64.805	0.090

Table A57 Regression analysis of binary drug loading (overall concentration 1.0 %w/v) onto Dowex-50W×2-200 (0.5 g) at 55°C

Regression parameters	DTM					DPH				
	Replicate number			Mean	S.D.	Replicate number			Mean	S.D.
	1	2	3			1	2	3		
Slope	75.257	75.246	75.148	75.217	0.060	64.639	64.770	64.756	64.722	0.072
Y-intercept	-1.310	-1.270	-1.248	-1.276	0.031	1.416	1.379	1.351	1.382	0.032
R^2	0.998	0.998	0.998	0.998	<0.001	0.998	0.998	0.998	0.998	<0.001
Isoloading parameters	Replicate number			Mean	S.D.					
	1	2	3							
EQC	34.929	34.962	34.931	34.941	0.019					
ELS	0.482	0.482	0.481	0.481	<0.001					

Table A58 Binary drug loading (overall concentration 1.0 %w/v) onto Dowex-50W×4-200 (0.5 g) at 45°C

Resinates	Ratio of DTM to DPH	% Drugs loaded onto resinates									
		DTM					DPH				
		41	1	2	3	Mean	S.D.	42	1	2	3	Mean	S.D.
DTM:DPH 1:0	1:0	76.829	76.844	76.622	76.765	0.124	0	0	0	0	0
DTM:DPH 8:2	8:2	59.272	59.369	59.187	59.276	0.091	15.199	15.151	15.047	15.132	0.078
DTM:DPH 6:4	6:4	43.315	43.485	43.536	43.446	0.116	28.928	29.027	29.069	29.008	0.073
DTM:DPH 4:6	4:6	28.054	28.046	27.983	28.028	0.039	42.320	42.214	41.962	42.166	0.184
DTM:DPH 2:8	2:8	13.792	13.950	13.930	13.891	0.086	54.529	54.609	54.366	54.501	0.124
DTM:DPH 0:1	0:1	0	0	0	0	0	66.248	66.191	66.752	66.397	0.308

Table A59 Regression analysis of binary drug loading (overall concentration 1.0 %w/v) onto Dowex-50W×4-200 (0.5 g) at 45°C

Regression parameters	DTM					DPH				
	Replicate number			Mean	S.D.	Replicate number			Mean	S.D.
	1	2	3			1	2	3		
Slope	76.549	76.560	76.348	76.486	0.119	66.089	66.074	66.373	66.179	0.168
Y-intercept	-1.398	-1.331	-1.297	-1.342	0.051	1.493	1.495	1.346	1.445	0.085
R^2	0.998	0.998	0.998	0.998	<0.001	0.998	0.998	0.998	0.998	<0.001
Isoloading parameters	Replicate number			Mean	S.D.					
	1	2	3							
EQC	35.621	35.652	35.623	35.632	0.017					
ELS	0.484	0.483	0.484	0.483	<0.001					

Table A60 Binary drug loading (overall concentration 1.0 %w/v) onto Dowex-50W×4-200 (0.5 g) at 55°C

Resinates	Ratio of DTM to DPH	% Drugs loaded onto resinates									
		DTM					DPH				
		43 1	2	3	Mean	S.D.	44 1	2	3	Mean	S.D.
DTM:DPH 1:0	1:0	76.242	76.060	76.244	76.182	0.106	0	0	0	0	0
DTM:DPH 8:2	8:2	59.693	59.162	59.352	59.402	0.269	14.500	14.418	14.435	14.451	0.043
DTM:DPH 6:4	6:4	43.519	43.503	43.451	43.491	0.036	27.695	27.726	27.694	27.705	0.018
DTM:DPH 4:6	4:6	28.405	27.645	28.312	28.121	0.415	40.853	41.392	40.994	41.080	0.279
DTM:DPH 2:8	2:8	14.117	14.026	13.989	14.044	0.066	52.500	52.722	52.628	52.616	0.111
DTM:DPH 0:1	0:1	0	0	0	0	0	65.513	65.363	65.651	65.509	0.144

Table A61 Regression analysis of binary drug loading (overall concentration 1.0 %w/v) onto Dowex-50W×4-200 (0.5 g) at 55°C

Regression parameters	DTM					DPH				
	Replicate number			Mean	S.D.	Replicate number			Mean	S.D.
	1	2	3			1	2	3		
Slope	76.151	75.938	76.064	76.051	0.107	64.960	65.056	65.162	65.059	0.101
Y-intercept	-1.079	-1.236	-1.141	-1.152	0.079	1.030	1.075	0.986	1.030	0.045
R^2	0.999	0.998	0.999	0.999	<0.001	0.999	0.999	0.999	0.999	<0.001
Isoloading parameters	Replicate number			Mean	S.D.					
	1	2	3							
EQC	35.115	35.047	35.101	35.088	0.036					
ELS	0.475	0.478	0.476	0.477	0.001					

Table A62 Binary drug loading (overall concentration 1.0 %w/v) onto Dowex-50W×8-200 (0.5 g) at 45°C

Resinates	Ratio of DTM to DPH	% Drugs loaded onto resinates									
		DTM					DPH				
		45 1	2	3	Mean	S.D.	46 1	2	3	Mean	S.D.
DTM:DPH 1:0	1:0	53.932	53.712	53.388	53.677	0.274	0	0	0	0	0
DTM:DPH 8:2	8:2	42.984	43.405	43.342	43.244	0.227	13.320	13.277	13.088	13.228	0.124
DTM:DPH 6:4	6:4	31.699	32.765	32.037	32.167	0.544	27.145	26.036	27.182	26.788	0.651
DTM:DPH 4:6	4:6	22.330	22.013	22.385	22.243	0.201	37.973	37.817	38.091	37.960	0.137
DTM:DPH 2:8	2:8	10.390	10.146	10.327	10.288	0.127	48.607	48.422	48.646	48.558	0.120
DTM:DPH 0:1	0:1	0	0	0	0	0	58.834	58.651	58.310	58.598	0.266

Table A63 Regression analysis of binary drug loading (overall concentration 1.0 %w/v) onto Dowex-50W×8-200 (0.5 g) at 45°C

Regression parameters	DTM					DPH				
	Replicate number			Mean	S.D.	Replicate number			Mean	S.D.
	1	2	3			1	2	3		
Slope	53.830	54.155	53.662	53.883	0.251	58.694	58.639	58.448	58.593	0.129
Y-intercept	-0.026	-0.071	0.082	-0.005	0.079	1.633	1.381	1.662	1.559	0.155
R^2	0.999	1.000	0.999	0.999	<0.001	0.996	0.997	0.995	0.996	0.001
Isoloading parameters	Replicate number			Mean	S.D.					
	1	2	3							
EQC	28.846	28.780	28.815	28.814	0.033					
ELS	0.536	0.533	0.535	0.535	0.002					

Table A64 Binary drug loading (overall concentration 1.0 %w/v) onto Dowex-50W×8-200 (0.5 g) at 55°C

Resinates	Ratio of DTM to DPH	% Drugs loaded onto resinates									
		DTM					DPH				
		47 1	2	3	Mean	S.D.	48 1	2	3	Mean	S.D.
DTM:DPH 1:0	1:0	64.462	64.781	63.719	64.321	0.545	0	0	0	0	0
DTM:DPH 8:2	8:2	50.865	50.603	50.887	50.785	0.158	14.215	14.386	14.238	14.280	0.093
DTM:DPH 6:4	6:4	37.753	37.991	37.757	37.834	0.136	27.082	27.092	27.115	27.096	0.017
DTM:DPH 4:6	4:6	24.801	24.776	24.732	24.770	0.035	38.330	38.484	38.313	38.376	0.094
DTM:DPH 2:8	2:8	12.978	12.928	12.920	12.942	0.031	49.093	49.323	49.373	49.263	0.149
DTM:DPH 0:1	0:1	0	0	0	0	0	60.236	60.224	60.092	60.184	0.080

Table A65 Regression analysis of binary drug loading (overall concentration 1.0 %w/v) onto Dowex-50W×8-200 (0.5 g) at 55°C

Regression parameters	DTM					DPH				
	Replicate number			Mean	S.D.	Replicate number			Mean	S.D.
	1	2	3			1	2	3		
Slope	64.132	64.306	63.646	64.028	0.342	59.580	59.618	59.580	59.593	0.022
Y-intercept	-0.256	-0.306	-0.154	-0.239	0.078	1.703	1.776	1.732	1.737	0.037
R^2	1.000	0.999	1.000	1.000	<0.001	0.997	0.997	0.997	0.997	<0.001
Isoloading parameters	Replicate number			Mean	S.D.					
	1	2	3							
EQC	31.645	31.711	31.593	31.650	0.059					
ELS	0.497	0.498	0.499	0.498	0.001					

Table A66 Binary drug loading (overall concentration 1.0 %w/v) onto Dowex-50W×8-200 (0.5 g) at 65°C

Resinates	Ratio of DTM to DPH	% Drugs loaded onto resinates									
		DTM					DPH				
		49 1	2	3	Mean	S.D.	50 1	2	3	Mean	S.D.
DTM:DPH 1:0	1:0	67.860	67.724	67.404	67.662	0.234	0	0	0	0	0
DTM:DPH 8:2	8:2	52.949	53.380	53.291	53.207	0.228	13.746	13.617	13.573	13.645	0.090
DTM:DPH 6:4	6:4	39.479	39.628	39.332	39.480	0.148	25.526	25.620	25.601	25.582	0.050
DTM:DPH 4:6	4:6	26.682	26.530	26.333	26.515	0.175	37.881	37.822	37.671	37.791	0.109
DTM:DPH 2:8	2:8	13.155	13.147	13.039	13.114	0.065	49.258	49.248	48.915	49.140	0.195
DTM:DPH 0:1	0:1	0	0	0	0	0	60.934	60.168	60.940	60.680	0.444

Table A67 Regression analysis of binary drug loading (overall concentration 1.0 %w/v) onto Dowex-50W×8-200 (0.5 g) at 65°C

Regression parameters	DTM					DPH				
	Replicate number			Mean	S.D.	Replicate number			Mean	S.D.
	1	2	3			1	2	3		
Slope	67.354	67.488	67.253	67.365	0.118	60.509	59.990	60.399	60.299	0.273
Y-intercept	-0.323	-0.342	-0.394	-0.353	0.036	0.970	1.084	0.917	0.990	0.085
R^2	1.000	1.000	1.000	1.000	<0.001	0.999	0.999	0.999	0.999	<0.001
Isoloading parameters	Replicate number			Mean	S.D.					
	1	2	3							
EQC	32.232	32.172	32.118	32.174	0.057					
ELS	0.483	0.482	0.483	0.483	0.001					

Table A68 Binary drug loading (overall concentration 1.0 %w/v) onto Dowex-50W×4-100 (0.5 g) at 35°C

Resinates	Ratio of DTM to DPH	% Drugs loaded onto resinates									
		DTM					DPH				
		51 1	2	3	Mean	S.D.	52 1	2	3	Mean	S.D.
DTM:DPH 1:0	1:0	74.047	73.987	73.910	73.981	0.069	0	0	0	0	0
DTM:DPH 8:2	8:2	57.309	57.257	57.151	57.239	0.081	14.703	14.691	14.658	14.684	0.023
DTM:DPH 6:4	6:4	41.686	41.651	41.734	41.691	0.042	27.896	27.892	27.970	27.919	0.044
DTM:DPH 4:6	4:6	27.110	27.149	26.999	27.086	0.078	40.108	40.189	40.166	40.154	0.042
DTM:DPH 2:8	2:8	13.375	13.361	13.382	13.372	0.011	52.204	52.221	52.314	52.246	0.059
DTM:DPH 0:1	0:1	0	0	0	0	0	63.287	63.040	62.947	63.091	0.176

Table A69 Regression analysis of binary drug loading (overall concentration 1.0 %w/v) onto Dowex-50W×4-100 (0.5 g) at 35°C

Regression parameters	DTM					DPH				
	Replicate number			Mean	S.D.	Replicate number			Mean	S.D.
	1	2	3			1	2	3		
Slope	73.802	73.732	73.656	73.730	0.073	63.022	62.870	62.842	62.911	0.097
Y-intercept	-1.313	-1.299	-1.299	-1.304	0.008	1.522	1.570	1.588	1.560	0.034
R^2	0.998	0.998	0.998	0.998	<0.001	0.998	0.997	0.997	0.998	<0.001
Isoloading parameters	Replicate number			Mean	S.D.					
	1	2	3							
EQC	34.210	34.185	34.169	34.188	0.020					
ELS	0.481	0.481	0.482	0.481	<0.001					

Table A70 Binary drug loading (overall concentration 1.0 %w/v) onto Dowex-50W×4-400 (0.5 g) at 35°C

Resinates	Ratio of DTM to DPH	% Drugs loaded onto resinates									
		DTM					DPH				
		53 1	2	3	Mean	S.D.	54 1	2	3	Mean	S.D.
DTM:DPH 1:0	1:0	73.786	73.721	73.519	73.675	0.139	0	0	0	0	0
DTM:DPH 8:2	8:2	57.503	57.568	57.496	57.522	0.040	14.380	14.367	14.373	14.373	0.006
DTM:DPH 6:4	6:4	41.931	41.537	41.904	41.790	0.220	27.769	27.893	27.749	27.804	0.078
DTM:DPH 4:6	4:6	27.164	27.115	27.170	27.150	0.030	40.412	40.369	40.502	40.427	0.068
DTM:DPH 2:8	2:8	13.431	13.428	13.395	13.418	0.020	52.279	52.334	52.376	52.330	0.048
DTM:DPH 0:1	0:1	0	0	0	0	0	63.748	63.762	63.965	63.825	0.121

Table A71 Regression analysis of binary drug loading (overall concentration 1.0 %w/v) onto Dowex-50W×4-400 (0.5 g) at 35°C

Regression parameters	DTM					DPH				
	Replicate number			Mean	S.D.	Replicate number			Mean	S.D.
	1	2	3			1	2	3		
Slope	73.702	73.635	73.519	73.619	0.093	63.583	63.598	63.798	63.660	0.120
Y-intercept	-1.215	-1.256	-1.179	-1.217	0.039	1.306	1.322	1.262	1.297	0.031
R^2	0.999	0.998	0.999	0.999	<0.001	0.998	0.998	0.998	0.998	<0.001
Isoloading parameters	Replicate number			Mean	S.D.					
	1	2	3							
EQC	34.273	34.252	34.285	34.270	0.017					
ELS	0.482	0.482	0.482	0.482	<0.001					

In Vitro Release

Table A72 DTM and DPH released from the dual-drug resinate prepared from Dowex-50W×2-200 in 0.05 N KCl (EQC 28%)

Time	% DTM released						% DPH released					
(min)	1	2	3	Mean	S.D.	% CV	1	2	3	Mean	S.D.	% CV
0	0	0	0	0	0	0	0	0	0	0	0	0
15	26.181	24.677	28.397	26.418	1.871	7.082	30.056	28.217	32.313	30.195	2.052	6.795
30	46.738	46.227	48.941	47.302	1.443	3.050	52.150	51.271	54.220	52.547	1.514	2.881
60	57.278	56.943	58.894	57.705	1.043	1.808	62.861	62.585	64.951	63.466	1.294	2.039
120	64.339	63.336	64.286	63.987	0.565	0.882	70.614	69.597	70.412	70.208	0.538	0.767
240	66.048	65.828	65.797	65.891	0.137	0.207	72.437	72.145	71.995	72.192	0.225	0.311
360	68.305	67.808	66.991	67.701	0.664	0.980	73.774	73.331	72.861	73.322	0.457	0.623
480	68.524	68.100	67.483	68.036	0.523	0.769	73.968	74.074	73.742	73.928	0.170	0.230
600	67.699	67.784	68.051	67.845	0.183	0.270	73.959	73.914	74.263	74.045	0.190	0.257
720	67.940	68.109	68.571	68.207	0.326	0.479	74.374	74.435	74.762	74.524	0.208	0.280

Table A73 DTM and DPH released from the dual-drug resinate prepared from Dowex-50W×2-200 in 0.1 N KCl (EQC 28%)

Time	% DTM released						% DPH released					
(min)	1	2	3	Mean	S.D.	% CV	1	2	3	Mean	S.D.	% CV
0	0	0	0	0	0	0	0	0	0	0	0	0
15	40.457	33.623	40.915	38.332	4.084	10.655	45.621	37.954	45.652	43.076	4.435	10.297
30	62.476	57.981	63.457	61.305	2.920	4.762	67.614	63.215	68.838	66.556	2.957	4.443
60	73.539	70.674	72.464	72.226	1.447	2.003	78.405	75.852	77.428	77.228	1.288	1.668
120	78.362	77.285	77.498	77.715	0.571	0.734	82.794	82.035	82.198	82.343	0.399	0.485
240	80.065	79.646	79.837	79.849	0.210	0.263	84.355	83.435	84.438	84.076	0.557	0.662
360	80.141	80.314	80.672	80.375	0.271	0.337	84.116	84.182	84.863	84.387	0.414	0.490
480	80.661	80.472	81.233	80.788	0.396	0.491	84.313	84.585	85.198	84.699	0.453	0.535
600	80.774	80.566	82.077	81.139	0.819	1.009	84.608	84.598	86.623	85.276	1.166	1.368
720	81.582	81.344	82.665	81.864	0.704	0.860	85.404	85.394	87.274	86.024	1.083	1.258

Table A74 DTM and DPH released from the dual-drug resinate prepared from Dowex-50W×2-200 in 0.2 N KCl (EQC 28%)

Time	% DTM released						% DPH released					
(min)	1	2	3	Mean	S.D.	% CV	1	2	3	Mean	S.D.	% CV
0	0	0	0	0	0	0	0	0	0	0	0	0
15	60.437	59.453	62.859	60.916	1.753	2.877	72.554	72.100	75.825	73.493	2.032	2.765
30	82.101	80.036	84.678	82.272	2.326	2.827	93.045	91.313	95.726	93.361	2.223	2.382
60	87.401	85.842	88.337	87.193	1.260	1.445	96.898	96.108	98.777	97.261	1.371	1.410
120	88.394	87.287	90.801	88.827	1.797	2.023	97.443	97.102	99.279	97.941	1.171	1.196
240	90.153	89.319	91.245	90.239	0.966	1.070	98.069	97.377	99.560	98.335	1.116	1.135
360	89.730	89.106	91.712	90.183	1.361	1.509	98.240	98.206	100.433	98.960	1.276	1.289
480	90.311	88.910	92.607	90.609	1.867	2.060	98.657	98.347	101.278	99.427	1.610	1.620
600	90.330	90.357	92.753	91.147	1.391	1.527	98.488	98.412	100.616	99.172	1.251	1.262
720	92.991	91.788	92.583	92.454	0.612	0.662	99.329	99.343	101.134	99.935	1.038	1.039

Table A75 DTM and DPH released from the dual-drug resinate prepared from Dowex-50W×2-200 in 0.4 N KCl (EQC 28%)

Time	% DTM released						% DPH released					
(min)	1	2	3	Mean	S.D.	% CV	1	2	3	Mean	S.D.	% CV
0	0	0	0	0	0	0	0	0	0	0	0	0
15	60.437	59.453	62.859	60.916	1.753	2.877	72.554	72.100	75.825	73.493	2.032	2.765
30	82.101	80.036	84.678	82.272	2.326	2.827	93.045	91.313	95.726	93.361	2.223	2.382
60	87.401	85.842	88.337	87.193	1.260	1.445	96.898	96.108	98.777	97.261	1.371	1.410
120	88.394	87.287	90.801	88.827	1.797	2.023	97.443	97.102	99.279	97.941	1.171	1.196
240	90.153	89.319	91.245	90.239	0.966	1.070	98.069	97.377	99.560	98.335	1.116	1.135
360	89.730	89.106	91.712	90.183	1.361	1.509	98.240	98.206	100.433	98.960	1.276	1.289
480	90.311	88.910	92.607	90.609	1.867	2.060	98.657	98.347	101.278	99.427	1.610	1.620
600	89.634	89.662	92.058	90.451	1.391	1.538	98.488	98.412	100.616	99.172	1.251	1.262
720	92.293	91.090	91.885	91.756	0.611	0.666	99.329	99.343	101.134	99.935	1.038	1.039

Table A76 DTM and DPH released from the dual-drug resinate prepared from Dowex-50W×4-200 in 0.05 N KCl (EQC 28%)

Time	% DTM released						% DPH released					
(min)	1	2	3	Mean	S.D.	% CV	1	2	3	Mean	S.D.	% CV
0	0	0	0	0	0	0	0	0	0	0	0	0
15	19.581	24.445	23.660	22.562	2.611	11.573	24.063	30.481	29.802	28.116	3.526	12.540
30	40.696	44.649	44.039	43.128	2.128	4.935	49.909	54.368	52.866	52.381	2.269	4.331
60	52.468	55.284	53.320	53.690	1.444	2.690	63.240	64.714	63.608	63.854	0.767	1.202
120	58.992	59.421	59.350	59.254	0.230	0.389	70.127	70.143	69.846	70.038	0.167	0.239
240	61.886	61.114	62.058	61.686	0.503	0.815	71.751	71.530	72.075	71.785	0.274	0.382
360	61.666	62.142	62.477	62.095	0.407	0.656	72.831	72.846	72.956	72.878	0.068	0.094
480	62.424	63.026	62.217	62.555	0.420	0.672	73.045	73.301	73.361	73.235	0.168	0.229
600	63.191	63.014	62.039	62.748	0.620	0.989	73.915	73.279	72.153	73.116	0.893	1.221
720	63.151	62.388	62.725	62.755	0.383	0.610	73.760	73.409	72.841	73.337	0.464	0.633

Table A77 DTM and DPH released from the dual-drug resinate prepared from Dowex-50W×4-200 in 0.1 N KCl (EQC 28%)

Time	% DTM released						% DPH released					
(min)	1	2	3	Mean	S.D.	% CV	1	2	3	Mean	S.D.	% CV
0	0	0	0	0	0	0	0	0	0	0	0	0
15	23.980	27.504	30.862	27.449	3.441	12.538	29.759	34.559	38.603	34.307	4.428	12.906
30	47.741	53.445	55.295	52.160	3.938	7.550	57.372	64.414	66.131	62.639	4.642	7.410
60	61.942	67.570	68.256	65.923	3.464	5.255	72.678	78.787	79.693	77.053	3.815	4.952
120	71.956	74.377	74.373	73.569	1.396	1.898	82.311	85.007	84.943	84.087	1.538	1.830
240	75.160	75.967	75.576	75.567	0.403	0.534	85.247	86.204	85.898	85.783	0.489	0.570
360	76.154	76.706	76.334	76.398	0.281	0.368	86.205	87.039	86.658	86.634	0.417	0.481
480	76.743	77.156	76.778	76.892	0.229	0.298	86.520	87.402	86.961	86.961	0.441	0.507
600	77.176	77.481	77.515	77.391	0.187	0.242	87.264	87.737	87.608	87.536	0.244	0.279
720	77.761	77.651	77.744	77.718	0.059	0.076	87.959	88.116	88.728	88.268	0.406	0.460

Table A78 DTM and DPH released from the dual-drug resinate prepared from Dowex-50W×4-200 in 0.2 N KCl (EQC 28%)

Time	% DTM released						% DPH released					
(min)	1	2	3	Mean	S.D.	% CV	1	2	3	Mean	S.D.	% CV
0	0	0	0	0	0	0	0	0	0	0	0	0
15	41.230	35.371	49.130	41.911	6.905	16.474	51.364	44.335	60.695	52.131	8.207	15.743
30	67.432	61.343	72.956	67.243	5.809	8.639	78.850	72.575	84.116	78.513	5.778	7.359
60	77.573	74.738	79.859	77.390	2.565	3.315	87.725	85.075	90.215	87.672	2.571	2.932
120	80.715	80.563	81.908	81.062	0.737	0.909	90.294	90.259	91.770	90.775	0.862	0.950
240	81.455	81.559	82.423	81.812	0.531	0.650	90.725	90.774	92.240	91.247	0.861	0.943
360	82.391	82.533	83.560	82.828	0.638	0.770	90.757	91.434	92.884	91.691	1.087	1.185
480	80.724	83.021	83.996	82.580	1.680	2.034	92.049	91.830	92.764	92.214	0.488	0.530
600	83.022	83.302	84.405	83.576	0.731	0.875	91.831	92.142	93.428	92.467	0.846	0.915
720	83.612	83.456	84.891	83.986	0.788	0.938	92.611	92.693	93.980	93.094	0.768	0.825

Table A79 DTM and DPH released from the dual-drug resinate prepared from Dowex-50W×4-200 in 0.4 N KCl (EQC 28%)

Time	% DTM released						% DPH released					
(min)	1	2	3	Mean	S.D.	% CV	1	2	3	Mean	S.D.	% CV
0	0	0	0	0	0	0	0	0	0	0	0	0
15	45.998	48.124	46.167	46.763	1.182	2.528	55.391	58.970	56.453	56.938	1.838	3.228
30	70.123	74.109	71.548	71.927	2.020	2.808	81.250	84.304	81.680	82.411	1.653	2.006
60	81.946	84.562	82.481	82.996	1.382	1.665	90.573	92.004	90.506	91.028	0.846	0.930
120	88.956	88.225	88.754	88.645	0.377	0.426	95.530	94.542	95.521	95.198	0.568	0.597
240	90.695	89.957	90.791	90.481	0.456	0.504	96.755	96.433	97.080	96.756	0.324	0.335
360	91.504	91.196	91.483	91.394	0.172	0.188	97.932	97.634	97.807	97.791	0.150	0.153
480	91.429	91.352	91.874	91.552	0.282	0.308	97.936	97.953	98.234	98.041	0.167	0.171
600	92.156	91.336	92.206	91.899	0.489	0.532	98.618	98.196	98.884	98.566	0.347	0.352
720	92.109	92.350	92.730	92.396	0.313	0.339	98.719	98.743	99.172	98.878	0.255	0.258

Table A80 DTM and DPH released from the dual-drug resinate prepared from Dowex-50W×8-200 in 0.05 N KCl (EQC 28%)

Time	% DTM released						% DPH released					
(min)	1	2	3	Mean	S.D.	% CV	1	2	3	Mean	S.D.	% CV
0	0	0	0	0	0	0	0	0	0	0	0	0
15	8.831	9.556	9.370	9.252	0.376	4.069	8.327	8.659	8.554	8.514	0.170	1.993
30	22.752	22.796	23.356	22.968	0.337	1.466	20.791	21.234	21.792	21.272	0.502	2.358
60	35.685	35.607	36.030	35.774	0.225	0.629	34.103	34.236	34.998	34.446	0.483	1.401
120	50.203	50.788	50.945	50.645	0.391	0.772	50.028	51.887	51.718	51.211	1.028	2.007
240	63.363	64.768	65.129	64.420	0.933	1.448	68.441	69.097	69.809	69.116	0.684	0.989
360	70.640	70.839	72.330	71.270	0.924	1.296	76.746	76.202	78.352	77.100	1.118	1.450
480	74.158	74.201	75.396	74.585	0.703	0.943	79.955	80.162	81.509	80.542	0.844	1.048
600	74.897	75.974	77.244	76.038	1.175	1.545	80.139	81.989	81.990	81.373	1.069	1.313
720	76.590	77.390	77.811	77.264	0.620	0.803	82.788	82.405	82.926	82.706	0.270	0.327

Table A81 DTM and DPH released from the dual-drug resinate prepared from Dowex-50W×8-200 in 0.1 N KCl (EQC 28%)

Time	% DTM released						% DPH released					
(min)	1	2	3	Mean	S.D.	% CV	1	2	3	Mean	S.D.	% CV
0	0	0	0	0	0	0	0	0	0	0	0	0
15	12.285	12.098	13.540	12.641	0.784	6.201	11.402	11.336	12.466	11.735	0.634	5.405
30	27.177	26.954	29.917	28.016	1.650	5.889	26.301	26.140	28.513	26.985	1.326	4.913
60	39.339	40.600	43.353	41.097	2.053	4.995	40.014	41.279	43.792	41.695	1.923	4.613
120	53.461	54.404	57.067	54.977	1.870	3.401	57.568	57.839	61.330	58.912	2.098	3.561
240	65.844	66.604	68.979	67.142	1.636	2.436	73.820	74.273	77.562	75.218	2.042	2.715
360	71.684	72.081	74.368	72.711	1.449	1.993	81.258	81.217	83.924	82.133	1.551	1.889
480	74.977	75.555	77.613	76.048	1.385	1.822	84.544	85.167	87.014	85.575	1.285	1.501
600	77.311	77.488	79.104	77.968	0.988	1.267	86.441	87.082	88.496	87.339	1.051	1.204
720	78.360	78.916	80.757	79.344	1.255	1.581	87.436	87.892	89.441	88.256	1.051	1.191

Table A82 DTM and DPH released from the dual-drug resinate prepared from Dowex-50W×8-200 in 0.2 N KCl (EQC 28%)

Time	% DTM released						% DPH released					
(min)	1	2	3	Mean	S.D.	% CV	1	2	3	Mean	S.D.	% CV
0	0	0	0	0	0	0	0	0	0	0	0	0
15	13.761	15.986	17.684	15.810	1.967	12.443	12.391	14.390	15.554	14.112	1.600	11.337
30	28.437	33.398	35.996	32.610	3.840	11.776	26.186	30.863	32.844	29.964	3.419	11.410
60	40.386	49.441	51.379	47.069	5.868	12.467	38.874	47.876	49.728	45.493	5.806	12.763
120	56.258	65.102	66.339	62.566	5.498	8.787	57.428	66.740	67.921	64.030	5.748	8.977
240	79.823	78.868	78.860	79.183	0.554	0.699	74.979	83.421	83.681	80.694	4.951	6.135
360	80.739	85.431	85.244	83.805	2.656	3.169	84.709	89.388	89.319	87.805	2.682	3.054
480	85.817	88.424	88.352	87.531	1.485	1.696	89.725	91.176	91.678	90.859	1.014	1.117
600	88.958	90.171	89.959	89.696	0.648	0.722	91.824	92.481	92.576	92.294	0.409	0.443
720	90.650	91.478	90.966	91.031	0.418	0.459	93.014	93.037	92.998	93.016	0.019	0.021

Table A83 DTM and DPH released from the dual-drug resinate prepared from Dowex-50W×8-200 in 0.4 N KCl (EQC 28%)

Time	% DTM released						% DPH released					
(min)	1	2	3	Mean	S.D.	% CV	1	2	3	Mean	S.D.	% CV
0	0	0	0	0	0	0	0	0	0	0	0	0
15	16.281	17.825	15.961	16.689	0.997	5.972	14.720	16.888	14.707	15.438	1.255	8.131
30	28.111	31.788	29.896	29.931	1.839	6.143	25.825	29.627	27.804	27.752	1.901	6.851
60	40.193	44.036	44.029	42.753	2.217	5.185	38.035	42.000	41.838	40.625	2.244	5.523
120	52.211	58.138	57.451	55.934	3.242	5.796	51.109	57.037	57.090	55.079	3.438	6.242
240	66.443	73.807	70.851	70.367	3.706	5.266	66.868	74.088	72.683	71.213	3.828	5.375
360	75.711	82.818	79.780	79.437	3.566	4.489	76.284	83.652	81.557	80.498	3.797	4.716
480	82.072	88.293	85.269	85.211	3.111	3.650	82.064	88.135	86.565	85.588	3.151	3.682
600	86.149	92.503	88.775	89.142	3.193	3.582	85.917	91.594	89.438	88.983	2.866	3.220
720	93.480	94.383	88.142	92.002	3.373	3.666	90.046	92.675	90.167	90.963	1.484	1.631

Table A84 DTM and DPH released from the dual-drug resinate prepared from Dowex-50W×8-200 in SIF (EQC 28%)

Time	% DTM released						% DPH released					
(min)	1	2	3	Mean	S.D.	% CV	1	2	3	Mean	S.D.	% CV
0	0	0	0	0	0	0	0	0	0	0	0	0
15	14.349	15.013	15.643	15.002	0.647	4.316	14.807	15.364	15.256	15.143	0.295	1.950
30	23.795	25.633	25.894	25.108	1.144	4.556	24.980	25.410	25.603	25.331	0.319	1.260
60	37.987	39.035	39.060	38.694	0.612	1.582	38.765	39.813	39.782	39.453	0.596	1.512
120	51.975	52.841	52.923	52.580	0.526	1.000	56.044	56.451	56.465	56.320	0.239	0.424
240	64.543	64.854	65.020	64.806	0.242	0.373	71.800	78.695	72.353	74.283	3.831	5.158
360	69.576	69.855	70.183	69.871	0.304	0.435	78.534	81.626	79.278	79.813	1.614	2.022
480	72.204	72.603	73.727	72.845	0.790	1.084	81.390	82.778	82.270	82.146	0.702	0.855
600	74.295	73.950	74.156	74.134	0.173	0.234	82.732	83.736	83.285	83.251	0.503	0.604
720	75.002	75.265	75.132	75.133	0.131	0.175	83.835	84.010	84.331	84.059	0.251	0.299

Table A85 DTM and DPH released from the dual-drug resinate prepared from Dowex-50W×8-200 (EQC 18%)

Time	% DTM released						% DPH released					
(min)	1	2	3	Mean	S.D.	% CV	1	2	3	Mean	S.D.	% CV
0	0	0	0	0	0	0	0	0	0	0	0	0
15	16.518	17.839	21.679	18.679	2.681	14.353	22.368	24.249	29.023	25.214	3.431	13.606
30	25.057	26.123	31.077	27.419	3.212	11.715	33.223	35.542	40.978	36.581	3.981	10.881
60	35.537	38.182	44.009	39.243	4.335	11.045	45.706	49.215	56.425	50.449	5.465	10.833
120	48.609	52.397	58.276	53.094	4.871	9.174	59.502	64.920	71.387	65.270	5.950	9.116
240	64.088	68.115	70.456	67.553	3.221	4.768	74.615	80.249	82.262	79.042	3.964	5.015
360	74.391	74.967	76.304	75.221	0.981	1.304	83.615	84.844	85.589	84.683	0.997	1.177
480	78.718	79.085	80.485	79.429	0.932	1.174	86.571	86.758	86.645	86.658	0.094	0.109
600	80.556	81.030	80.989	80.858	0.263	0.325	87.971	88.197	87.857	88.008	0.173	0.197
720	79.935	80.313	79.740	79.996	0.292	0.365	87.995	88.374	87.522	87.964	0.427	0.485

Table A86 DTM released from DTM resinate prepared from Dowex-50W×8-200

Time	% DTM released					
(min)	1	2	3	Mean	S.D.	% CV
0	0	0	0	0	0	0
15	17.831	20.763	18.037	18.877	1.637	8.672
30	26.716	30.417	27.100	28.078	2.035	7.248
60	37.889	41.889	39.271	39.683	2.031	5.119
120	52.329	55.385	52.665	53.460	1.676	3.135
240	66.463	68.664	65.818	66.982	1.492	2.228
360	73.824	75.274	73.118	74.072	1.100	1.484
480	79.028	79.458	77.460	78.649	1.052	1.337
600	81.527	81.602	80.181	81.103	0.799	0.986
720	83.502	83.661	82.576	83.246	0.586	0.704

Table A87 DPH released from DPH resinate prepared from Dowex-50W×8-200

Time	% DPH released					
(min)	1	2	3	Mean	S.D.	% CV
0	0	0	0	0	0	0
15	17.075	16.346	16.303	16.575	0.434	2.618
30	29.925	31.413	30.224	30.521	0.787	2.578
60	41.546	43.507	41.516	42.190	1.141	2.704
120	53.136	54.812	55.503	54.484	1.217	2.234
240	65.590	64.984	68.133	66.236	1.671	2.523
360	73.700	70.697	75.315	73.237	2.344	3.200
480	79.278	74.000	79.253	77.510	3.040	3.922
600	82.755	76.361	82.008	80.374	3.496	4.350
720	84.948	78.477	83.798	82.408	3.452	4.189

Table A88 DTM and DPH released from the blend of DTM resinate and DPH resinate

Time	% DTM released						% DPH released					
(min)	1	2	3	Mean	S.D.	% CV	1	2	3	Mean	S.D.	% CV
0	0	0	0	0	0	0	0	0	0	0	0	0
15	14.732	15.720	16.412	15.621	0.844	5.406	24.493	26.113	29.861	26.822	2.754	10.266
30	22.187	22.746	23.915	22.949	0.882	3.842	34.865	36.585	41.806	37.752	3.615	9.574
60	31.852	32.118	34.266	32.746	1.324	4.042	47.015	48.866	55.800	50.560	4.631	9.160
120	46.156	44.952	47.710	46.273	1.382	2.988	63.015	63.311	70.492	65.606	4.234	6.454
240	63.032	61.947	62.226	62.402	0.563	0.903	77.291	77.737	82.073	79.034	2.642	3.343
360	70.182	69.391	69.133	69.569	0.547	0.786	80.482	81.008	85.070	82.187	2.511	3.055
480	74.639	73.813	73.017	73.823	0.811	1.099	82.139	82.178	86.166	83.494	2.314	2.771
600	77.532	76.791	74.664	76.329	1.489	1.951	82.509	83.198	86.377	84.028	2.063	2.455
720	78.765	78.132	75.851	77.583	1.532	1.975	83.027	83.406	86.830	84.421	2.095	2.481

VITA

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