CHAPTER III

RESULTS

1.Physical Properties Determinations of Active Raw Materials

1.1 Size and Shape from Scanning Electron Microscope

The particle morphology of various samples of active raw materials in this study were examined by scanning electron microscope. The microscopic appearance of Tetracycline Hydrochloride I-III, Cimetidine I-V and Mefenamic Acid I-III are shown in Figures 5-15 respectively.

Tetracycline Hydrochloride (Figures 5-7)

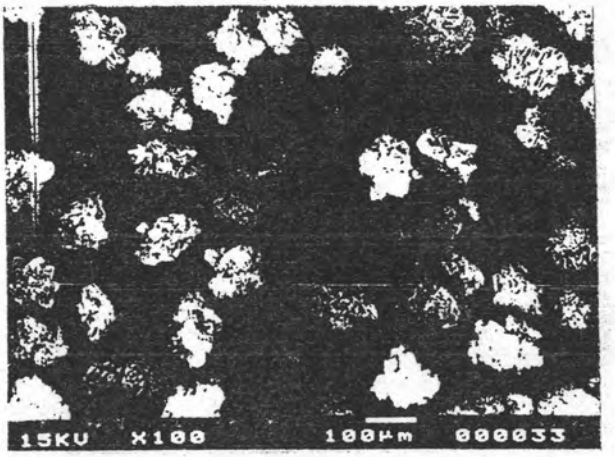
Tetracycline Hydrochloride powder composed of aggregates of thick rod-shaped particles. The powder characteristics for all samples were similar except Tetracycline II had thinner rod-shaped particle.

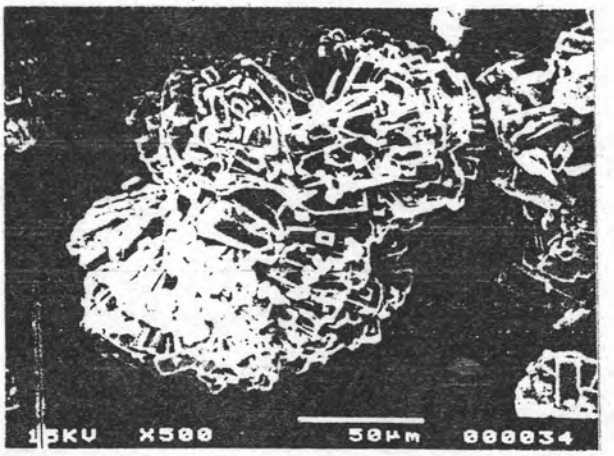
Cimetidine (Figures 8-12)

Cimetidine powder composed of irregular shape particles,most of them were rod-shaped microcrystals which were different in size. More aggregation and pin-liked microcrystals of Cimetidine I and V were observed.

Mefenamic Acid (Figures 13-15)

The scanning electron photomicrograph of Mefenamic Acid I, II and III were different. Mefenamic Acid I composed





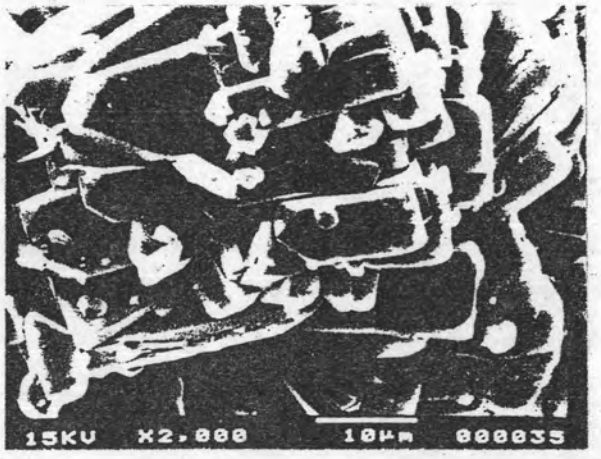
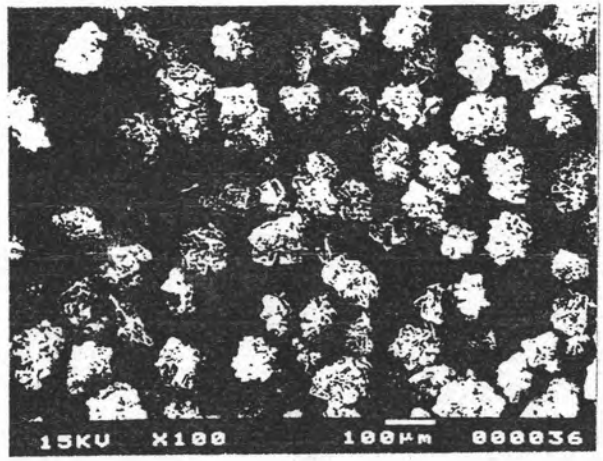


Figure 5 Photomicrographs of Raw Material Tetracycline I (Key : A x 100 , B x 500 , C x 2,000)



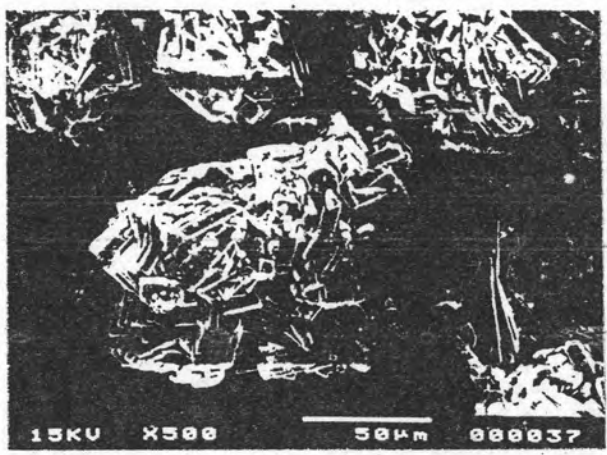
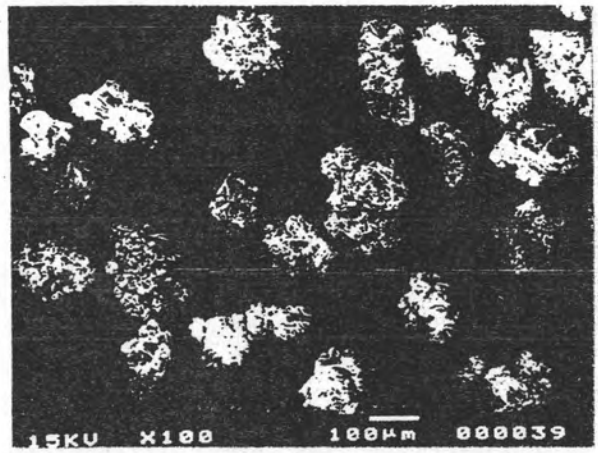
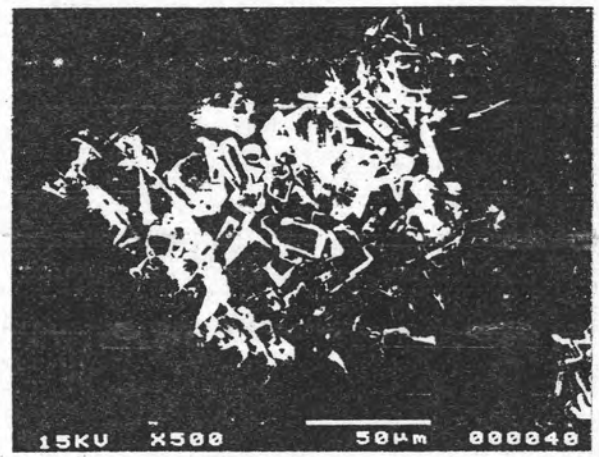


Figure 6 Photomicrographs of Raw Material Tetracycline II (Key : A x 100 , B x 500 , C x 2,000)





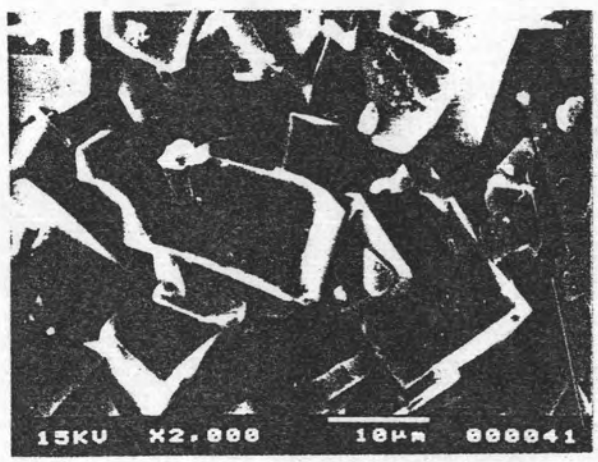
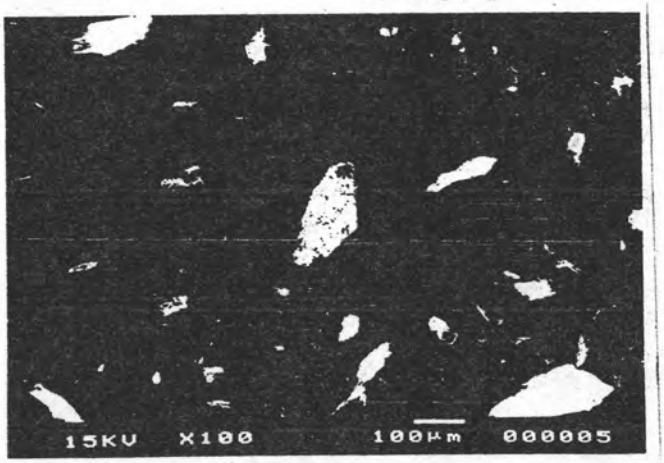
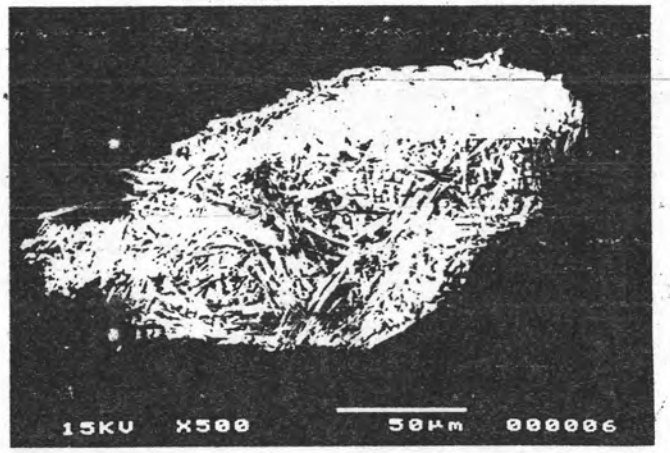


Figure 7 Photomicrographs of Raw Material Tetracycline III (Key : A x 100 , B x 500 , C x 2,000)





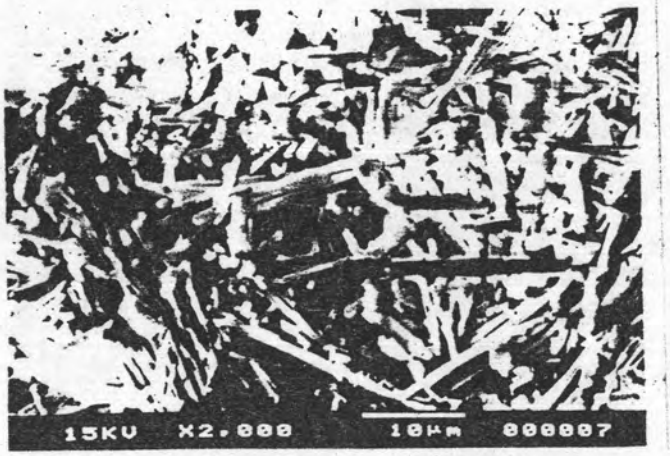
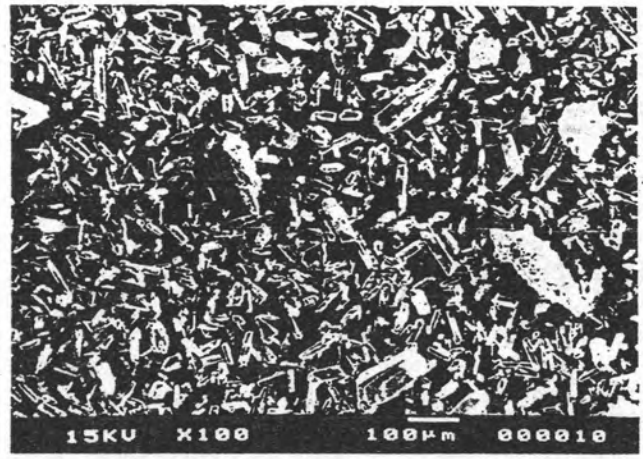
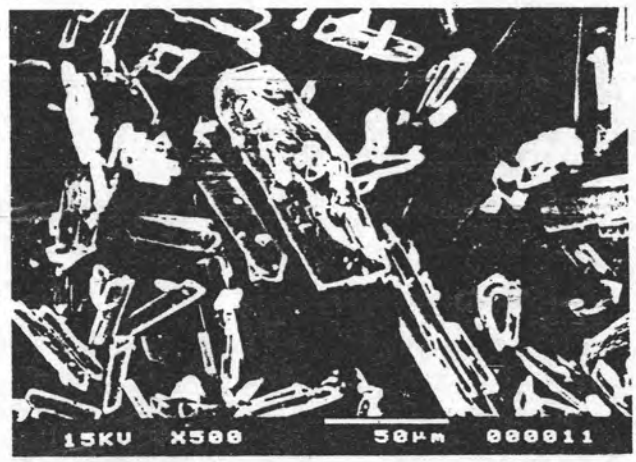


Figure 8 Photomicrographs of Raw Material Cimetidine I
(Key : A x 100 , B x 500 , C x 2,000)





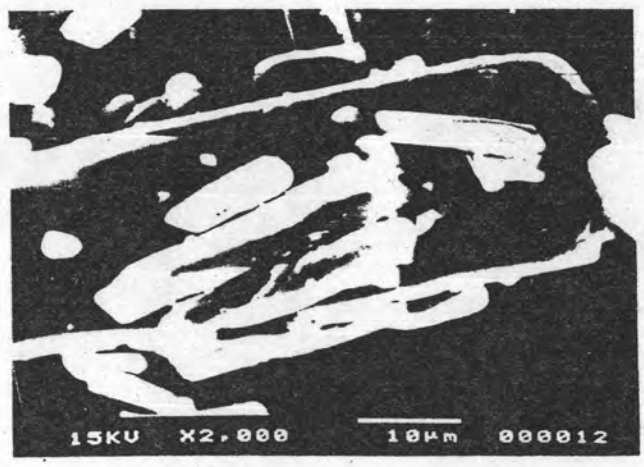
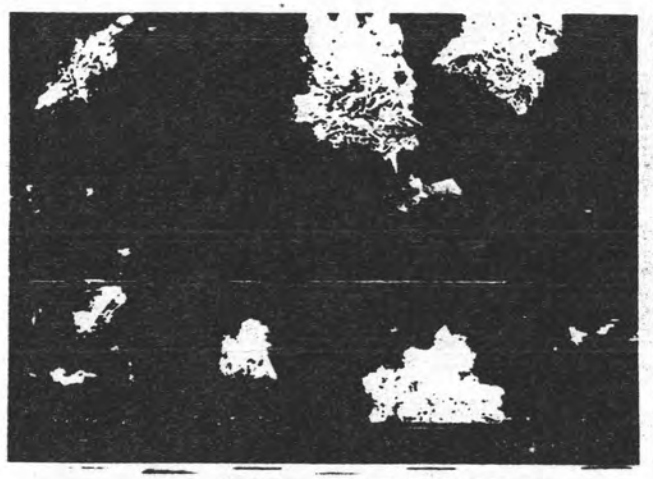
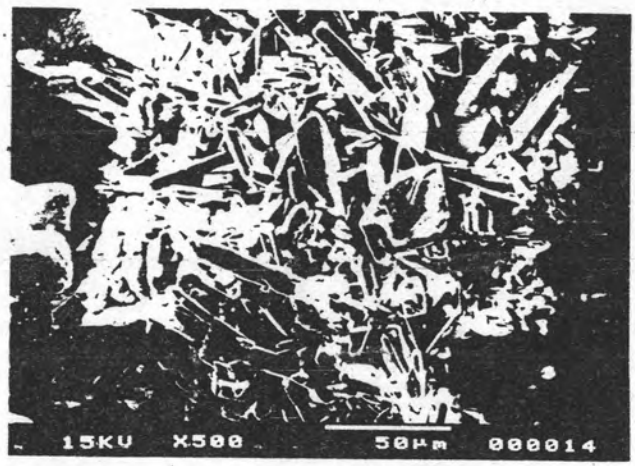


Figure 9 Photomicrographs of Raw Material Cimetidine II (Key : A x 100 , B x 500 , C x 2,000)





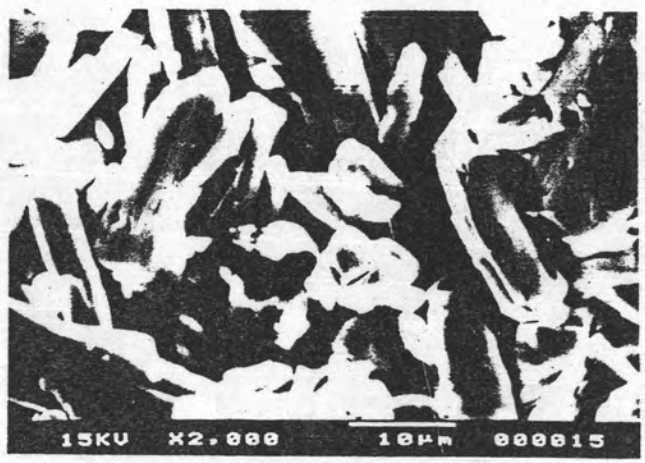
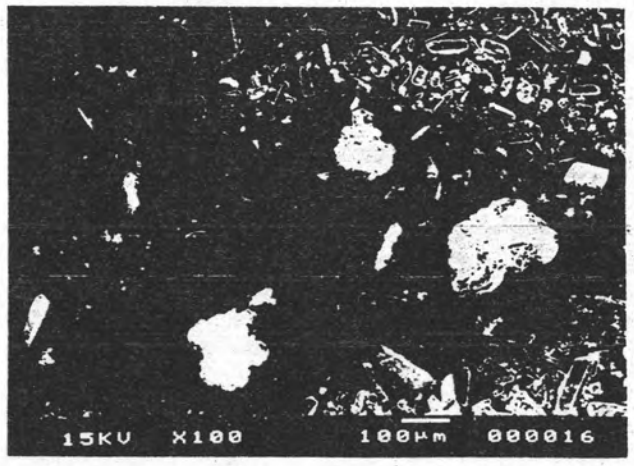
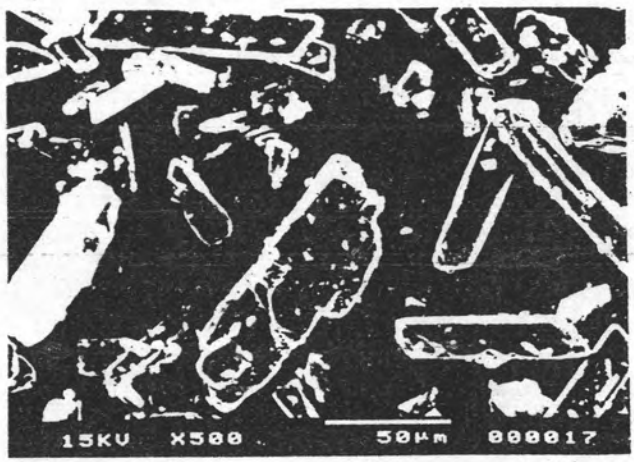


Figure 10 Photomicrographs of Raw Material Cimetidine III
(Key : A x 100 , B x 500 , C x 2,000)





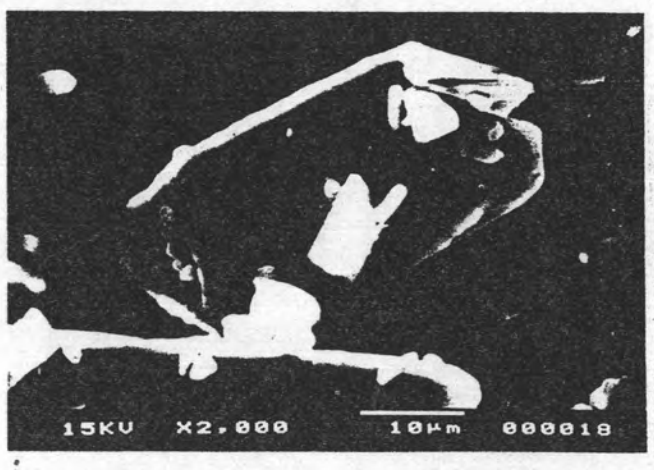
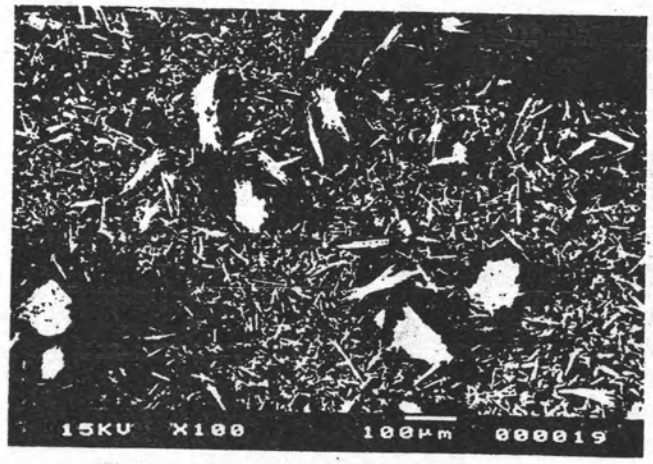
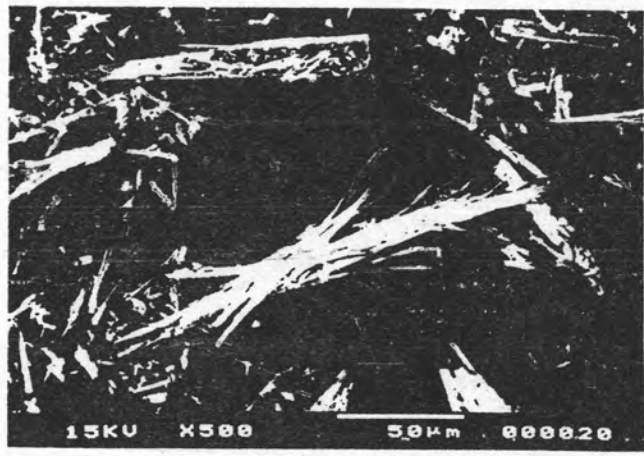


Figure 11 Photomicrographs of Raw Material Cimetidine IV
(Key : A x 100 , B x 500 , C x 2,000)





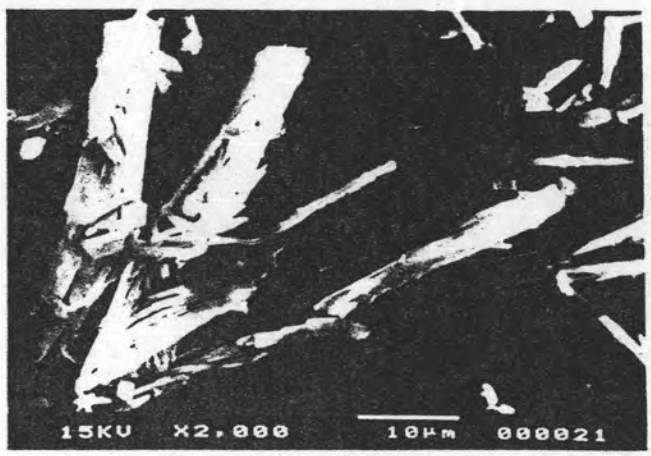
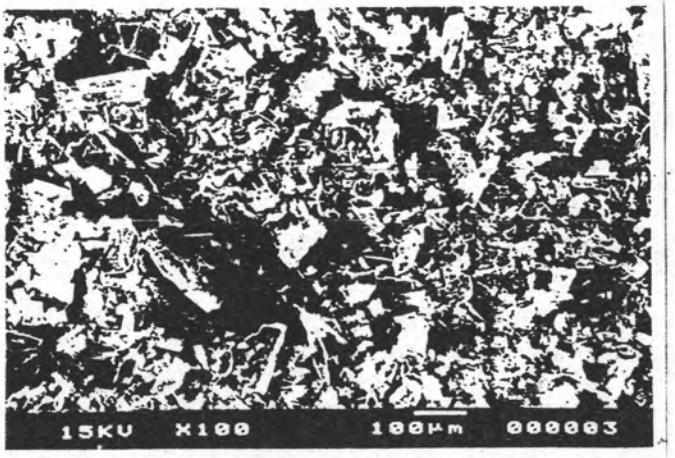
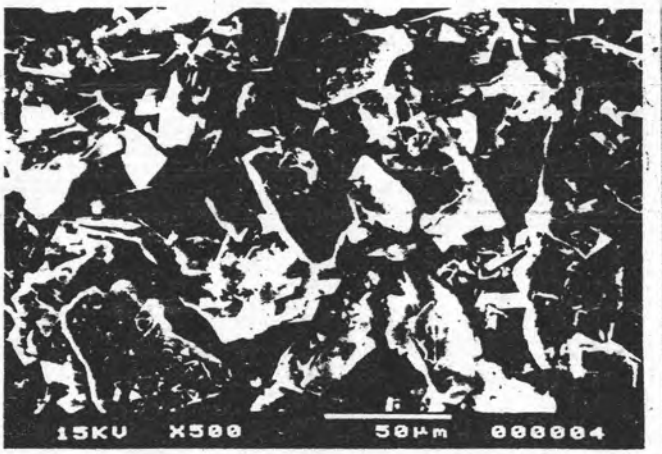


Figure 12 Photomicrographs of Raw Material Cimetidine V
(Key : A x 100 , B x 500 , C x 2,000)

Figure 13 Photomicrographs of Raw Material Mefenamic Acid I
(Key : A x 100 , B x 500 , C x 2,000)





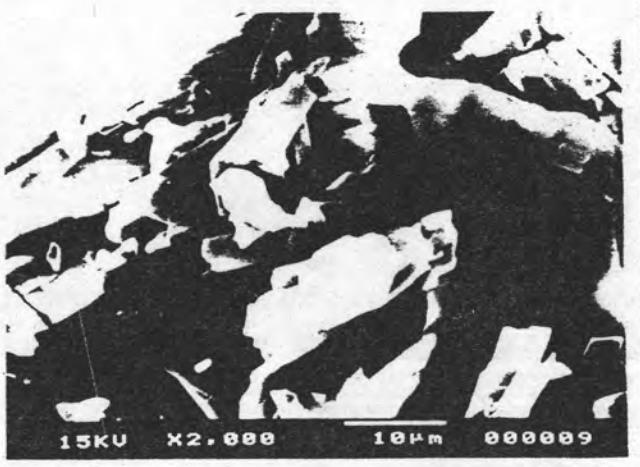
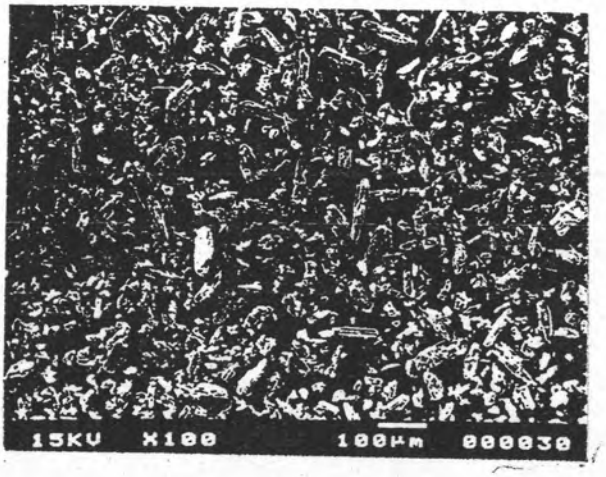
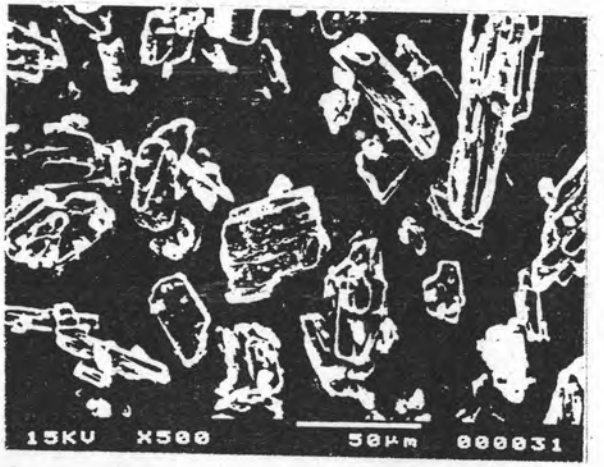


Figure 14 Photomicrographs of Raw Material Mefenamic Acid II (Key : A x 100 , B x 500 , C x 2,000)





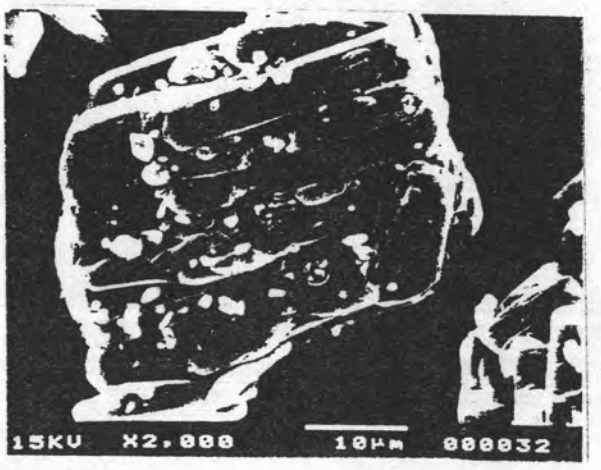


Figure 15 Photomicrographs of Raw Material Mefenamic Acid III (Key : A x 100 , B x 500 , C x 2,000)

of irregular shape particles. These particle occurred in a single microcrystal which were different in size. Mefenamic Acid II composed of compacted irregular shape particles held together, unlike Mefenamic Acid III which containing agglomerate of many short rod microcrystals.

1.2 Particle Size Distribution

Sieve analysis data of active raw materials from various sources are shown in Table 3.

Tetracycline Hydrochloride

Figures 16, 17, and 18 shows the particle size distribution of each Tetracycline Hydrochloride samples and Figure 15 shows the comparative particle size distribution of all samples. The particle size distribution of three sources were quite different. More than 60 % of Tetracycline Hydrochloride I and II passed through a 150 µm sieve, while less than 60 % of Tetracycline Hydrochloride III was bigger than 150 µm mesh.

Cimetidine

Figures 20, 21, 22, 23, and 24 shows the particle size distribution of each Cimetidine samples and Figure 25 shows the comparative particle size distribution of all samples. The particle size distribution of five sources were not very different. Cimetidine IV had a significant number of particles smaller than 180 µm mesh.

Mefenamic Acid

Figures 26, 27, and 28 shows the particle size

Table 3

Sieve Analysis of Active Raw Material from Various Sources

Active Raw Materials	% Weight Retained[a]					
	Sieve Size (μm)					
	850	425	250	180	150	Pan
Tetracycline I	0.00	0.00	0.00	1.20	37.28	61.52
Tetracycline II	0.00	0.00	0.00	0.00	1.10	98.90
TetracyclineIII	0.00	0.00	0.00	19.02	43.73	37.25
Cimetidine I	68.27	29.13	2.05	0.32	0.12	0.10
Cimetidine II	84.05	11.82	1.95	0.92	0.48	0.78
Cimetidine III	59.59	34.50	4.51	0.78	0.28	0.34
Cimetidine IV	77.70	13.09	0.62	2.63	3.72	2.23
Cimetidine V	88.78	9.06	1.80	0.28	0.08	0.00
Mefenamic I	63.13	26.59	3.07	1.60	4.37	1.24
Mefenamic II	93.68	6.10	0.22	0.00	0.00	0.00
Mefenamic III	88.55	8.97	1.70	0.58	0.14	0.06

(a) averaged from two determinations.

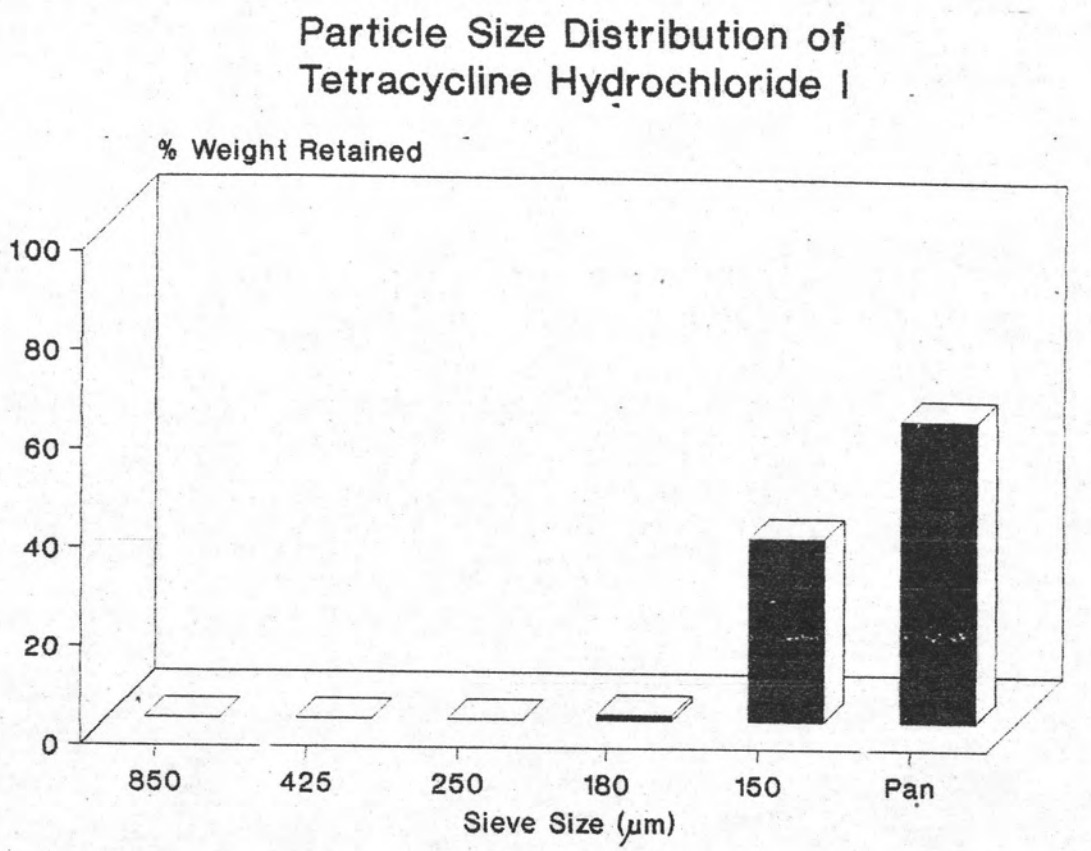


Figure 16 Particle Size Distribution of Tetracycline Hydrochloride I

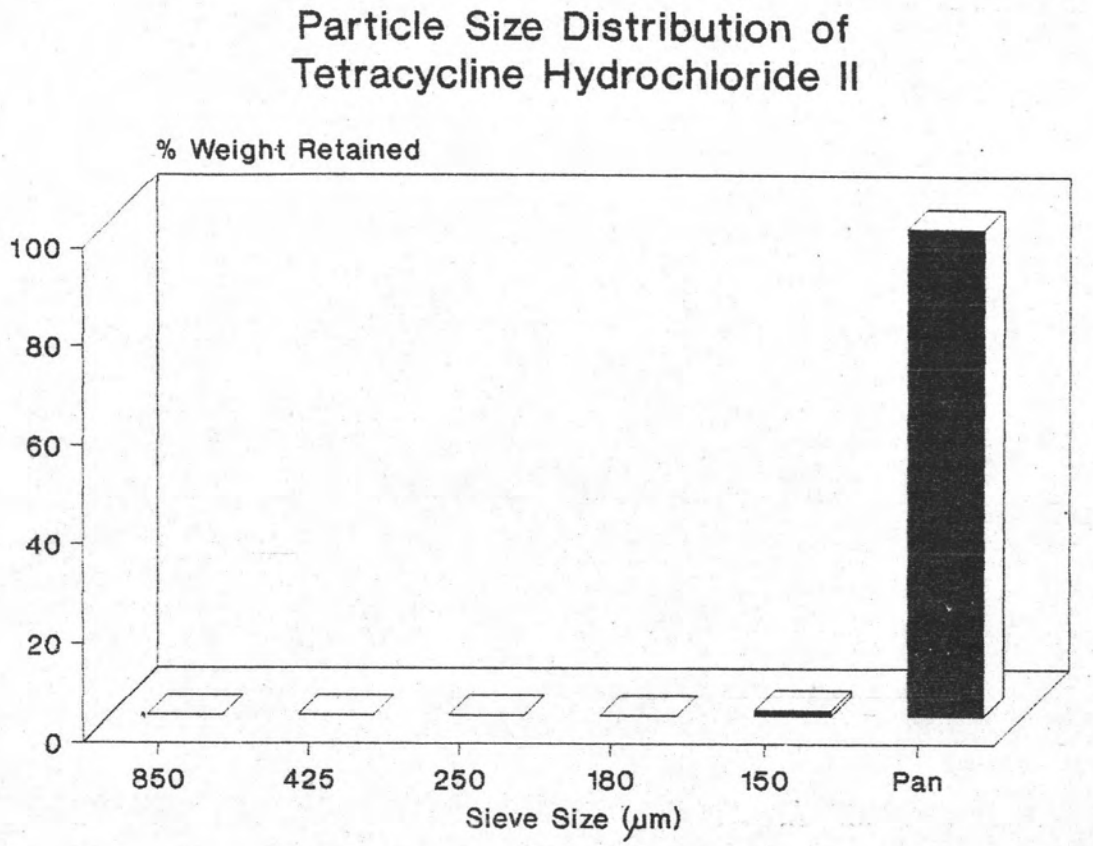


Figure 17 Particle Size Distribution of Tetracycline Hydrochloride II

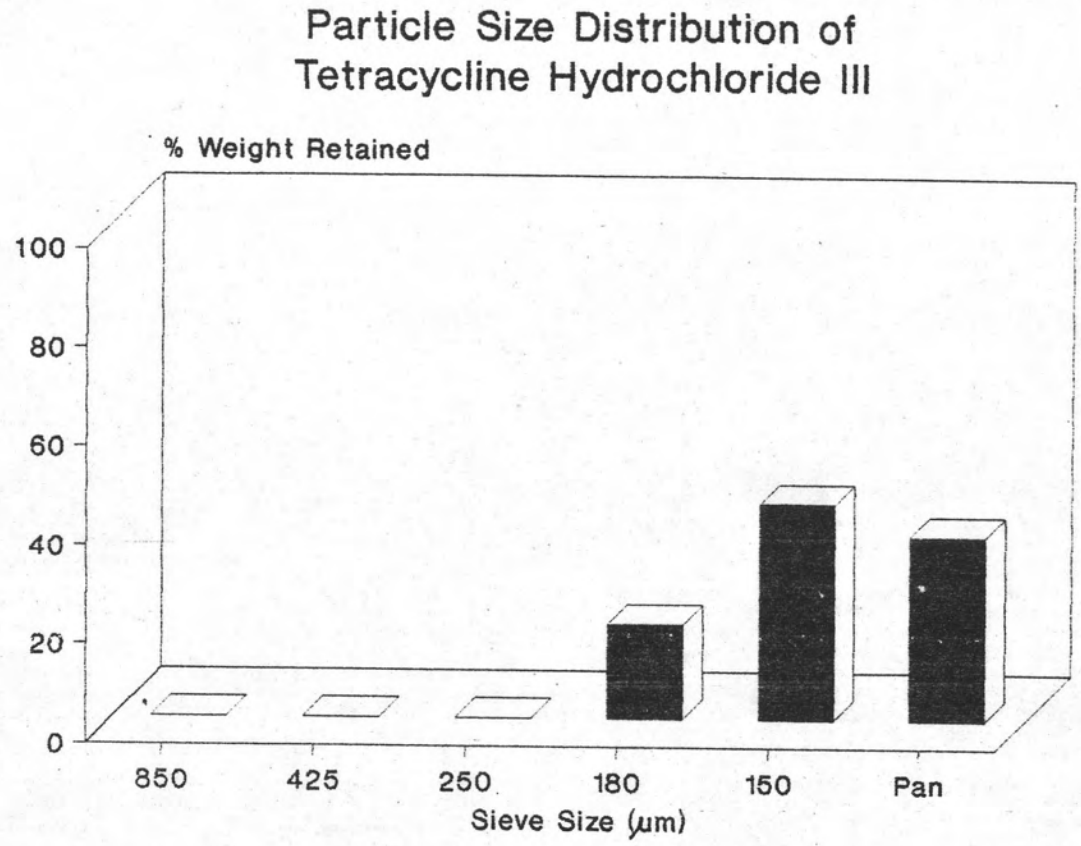


Figure 18 Particle Size Distribution of Tetracycline Hydrochloride III

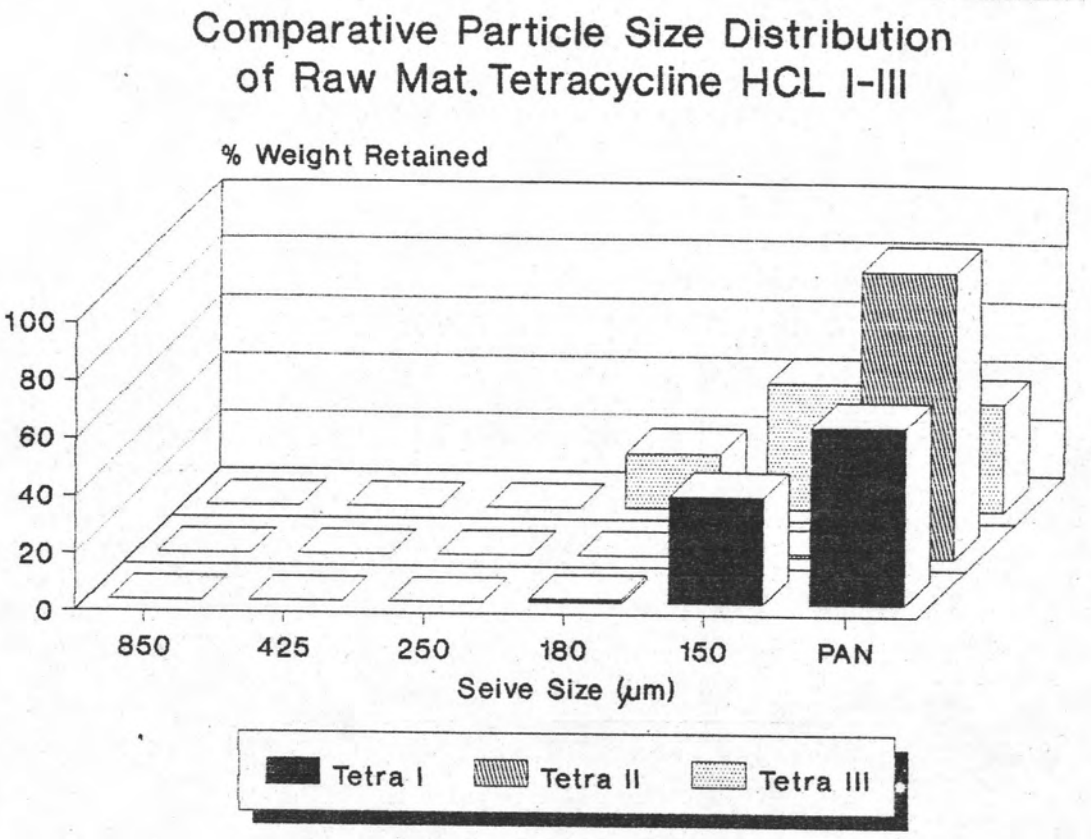


Figure 19 Comparative Particle Size Distribution of Raw Material Tetracycline Hydrochloride I, II and III

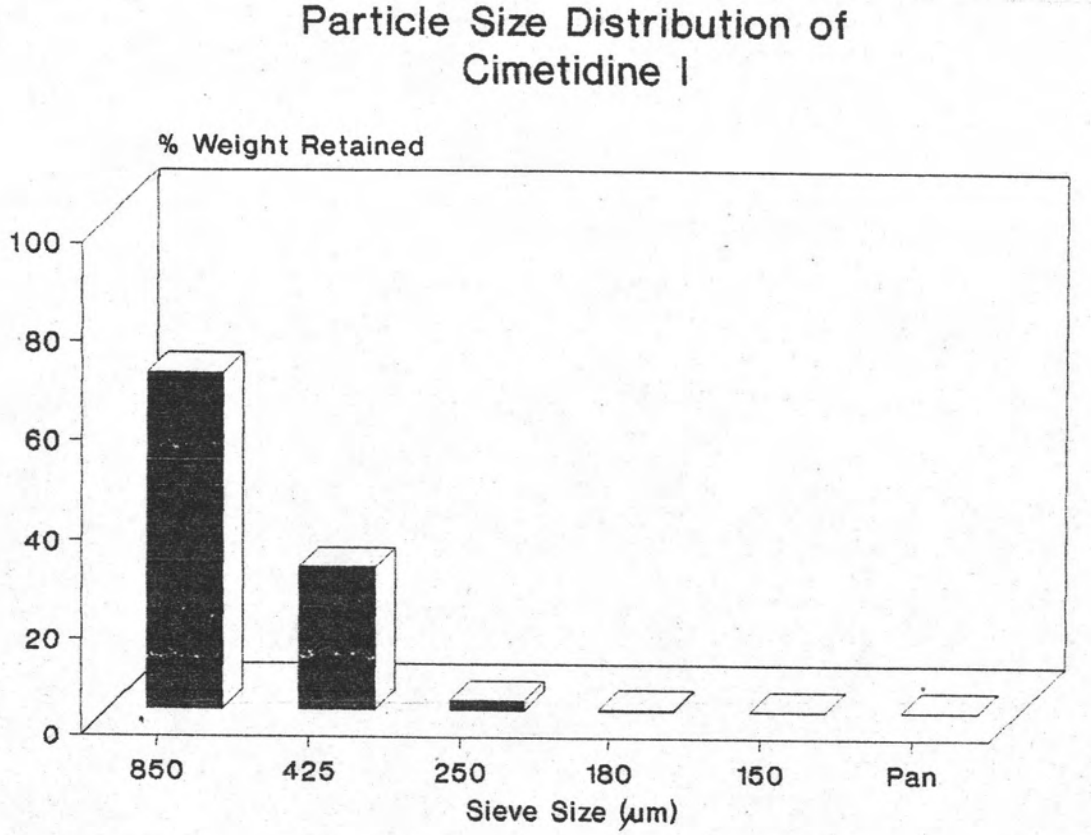


Figure 20 Particle Size Distribution of Cimetidine I

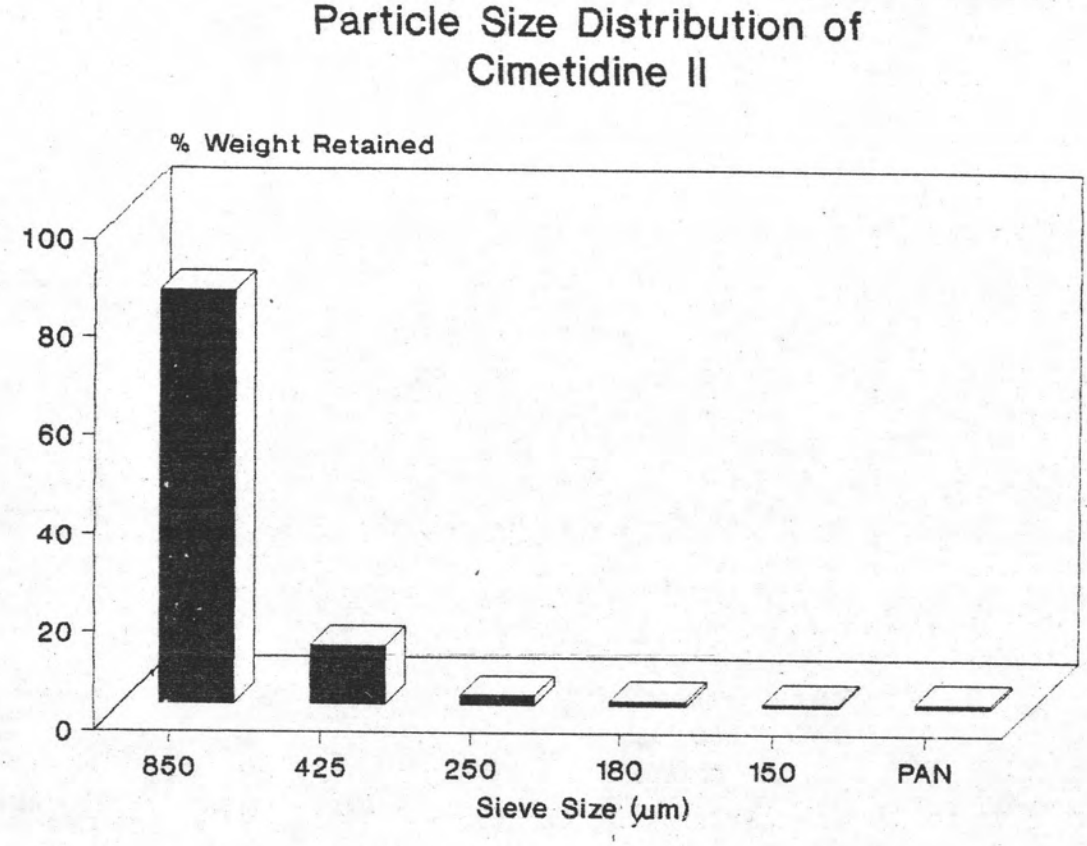


Figure 21 Particle Size Distribution of Cimetidine II

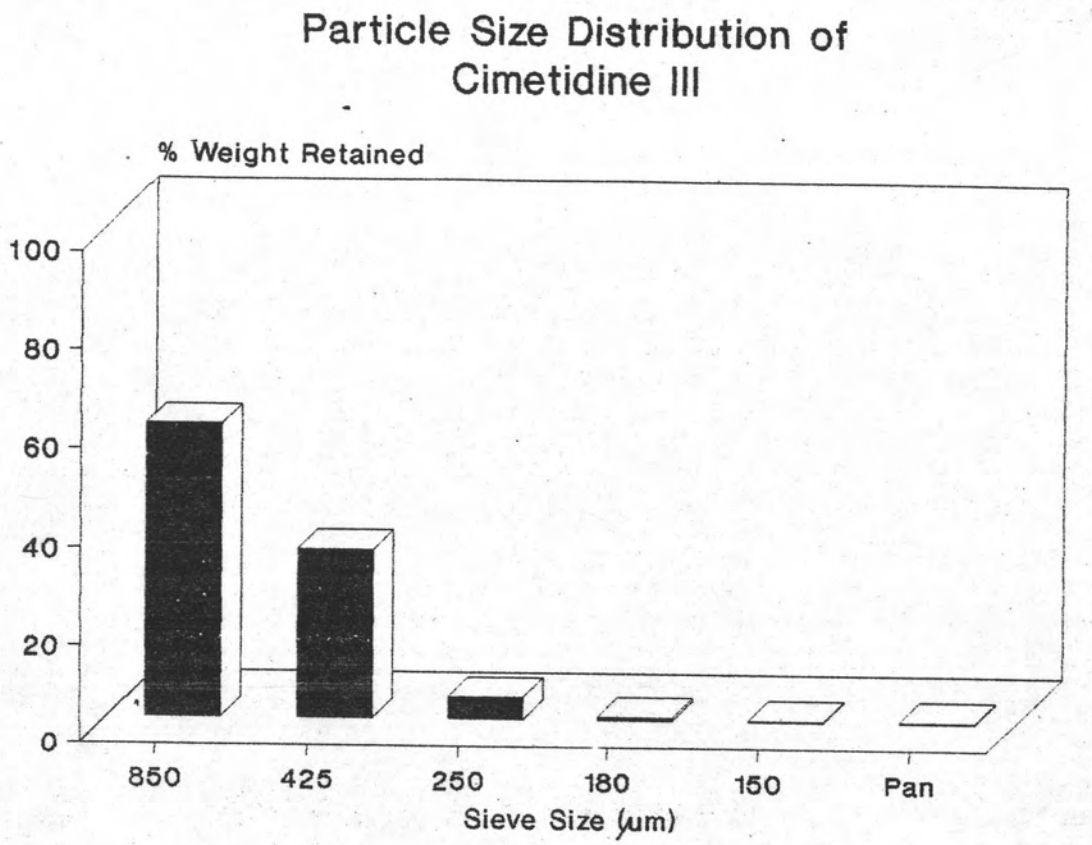


Figure 22 Particle Size Distribution of Cimetidine III

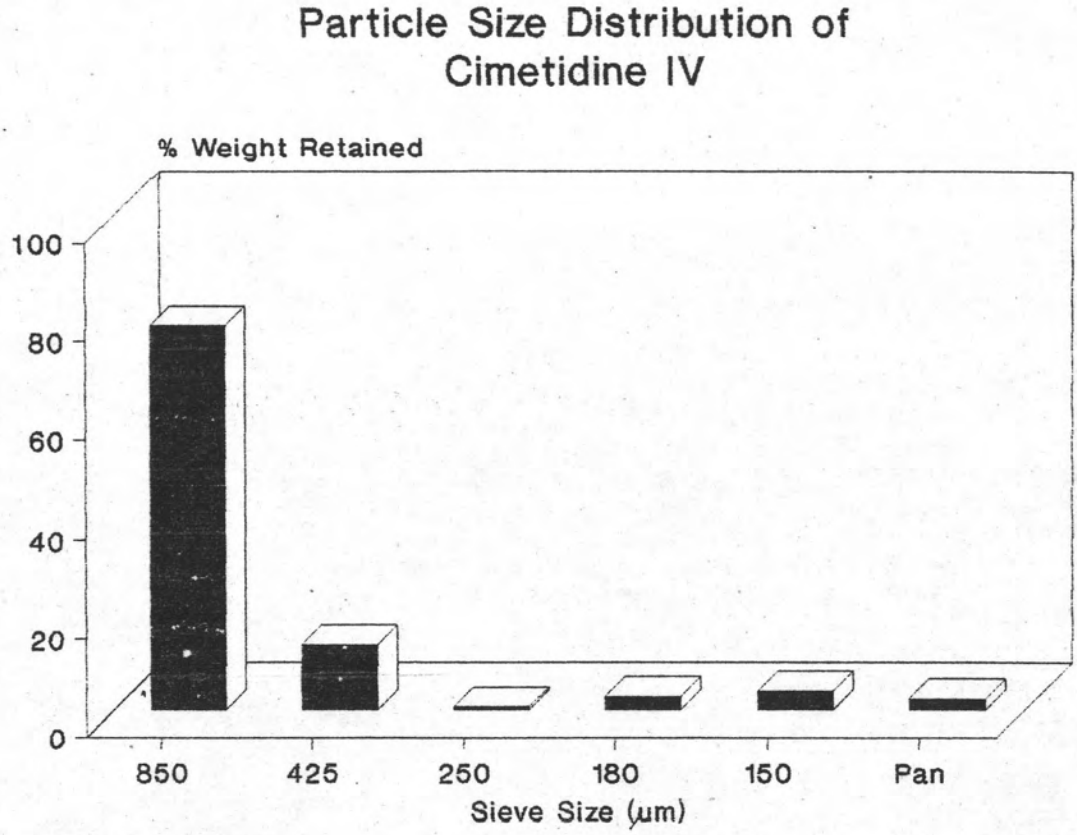


Figure 23 Particle Size Distribution of Cimetidine IV

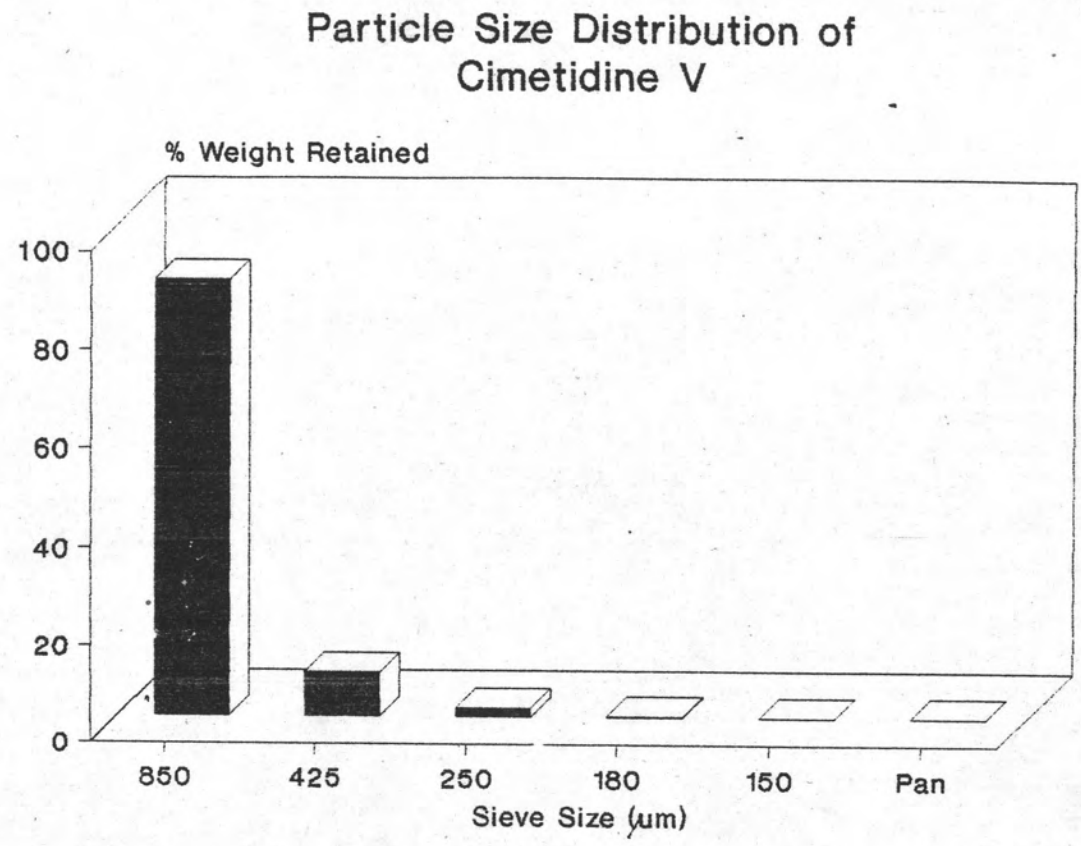


Figure 24 Particle Size Distribution of Cimetidine V

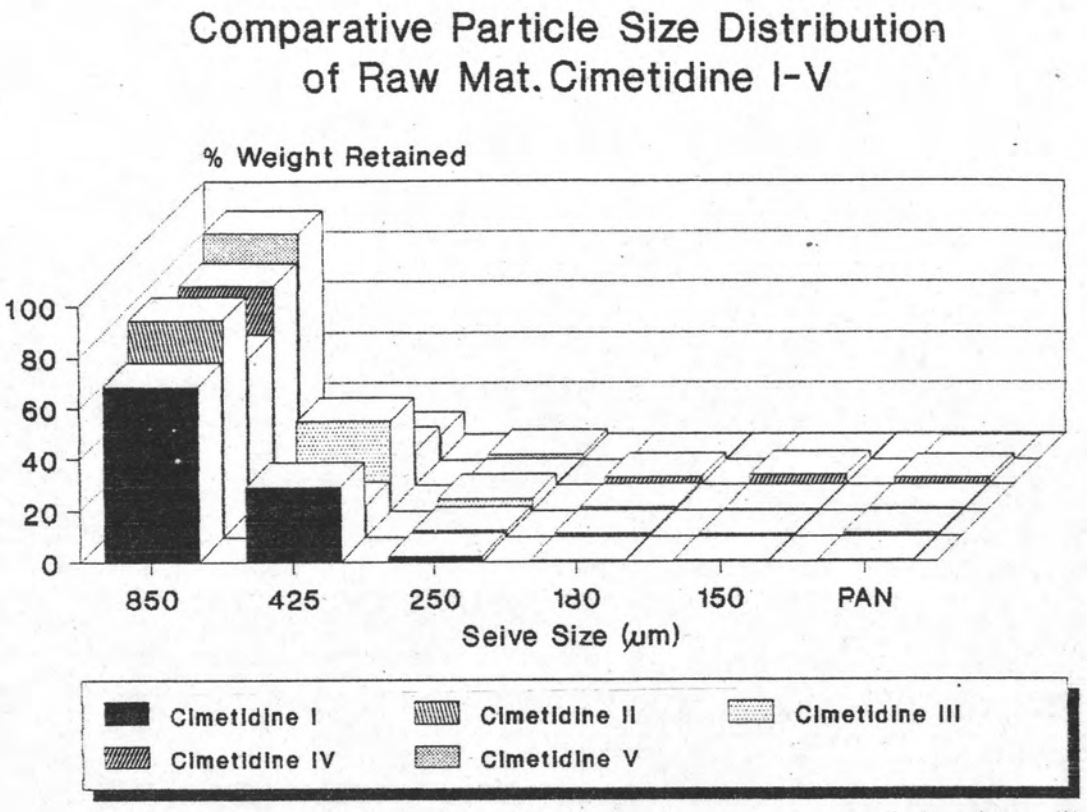


Figure 25 Comparative Particle Size Distribution of Raw Material Cimetidine I, II, III, IV and V

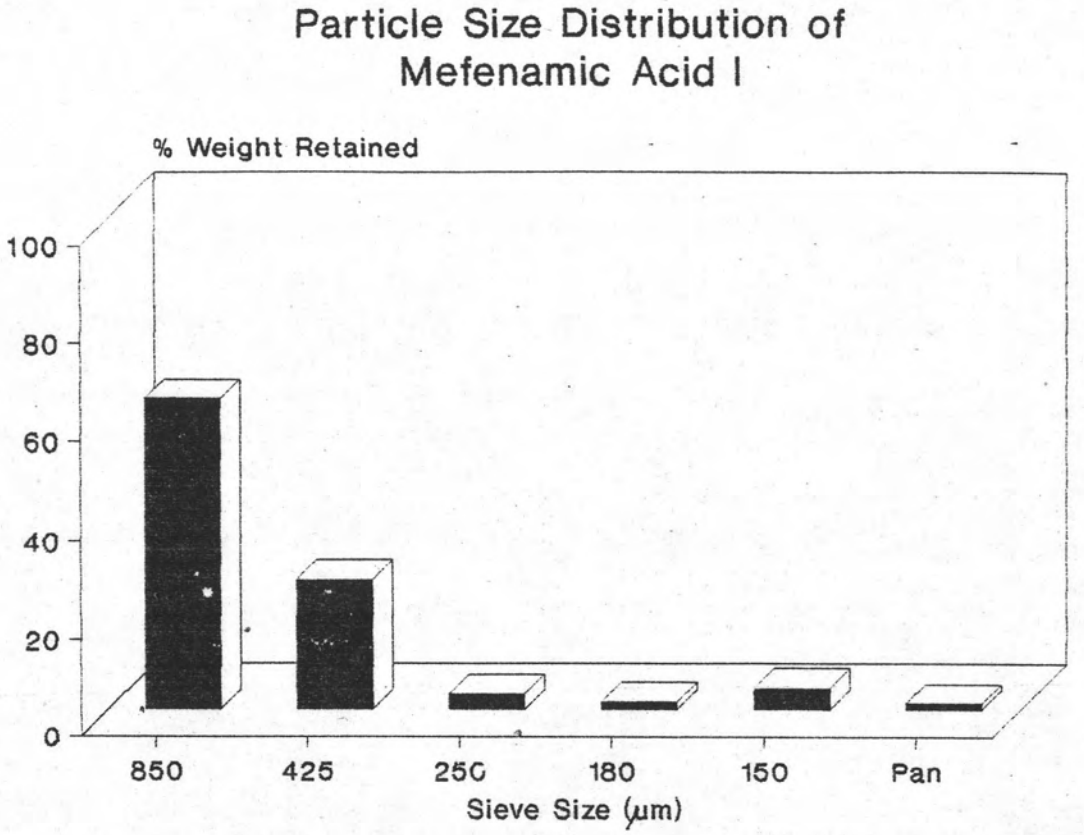


Figure 26 Particle Size Distribution of Mefenamic Acid I

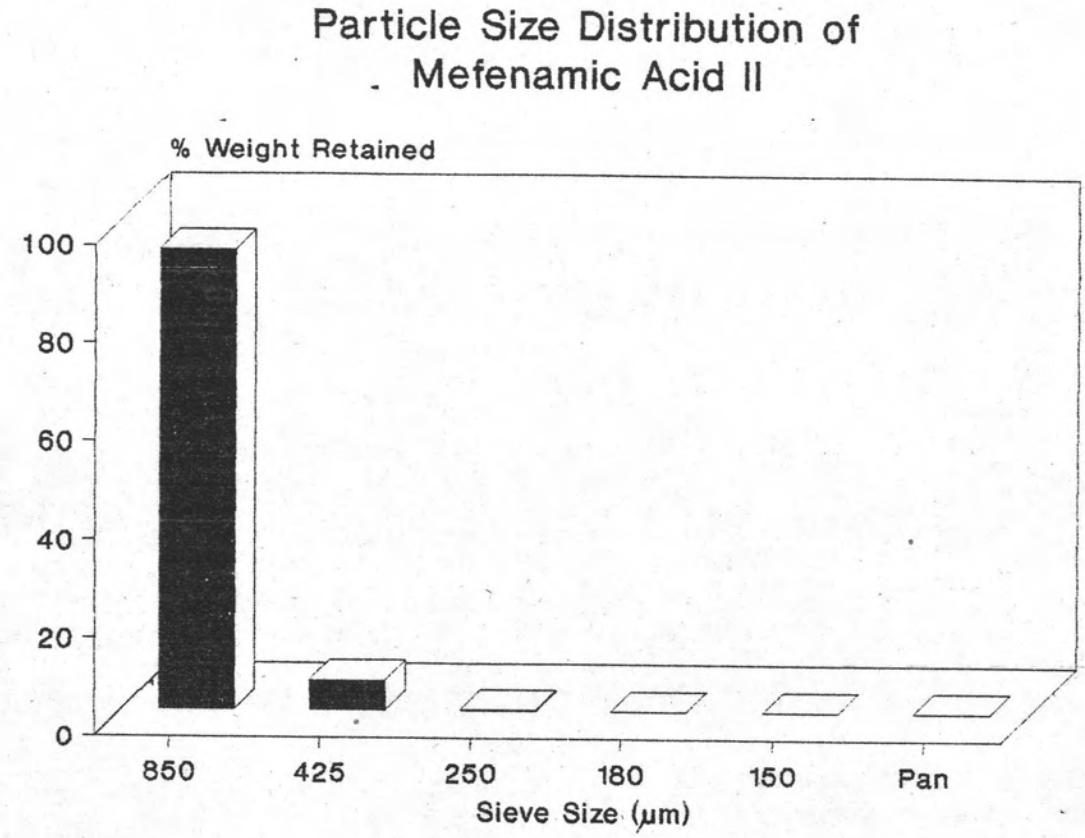


Figure 27 Particle Size Distribution of Mefenamic Acid II

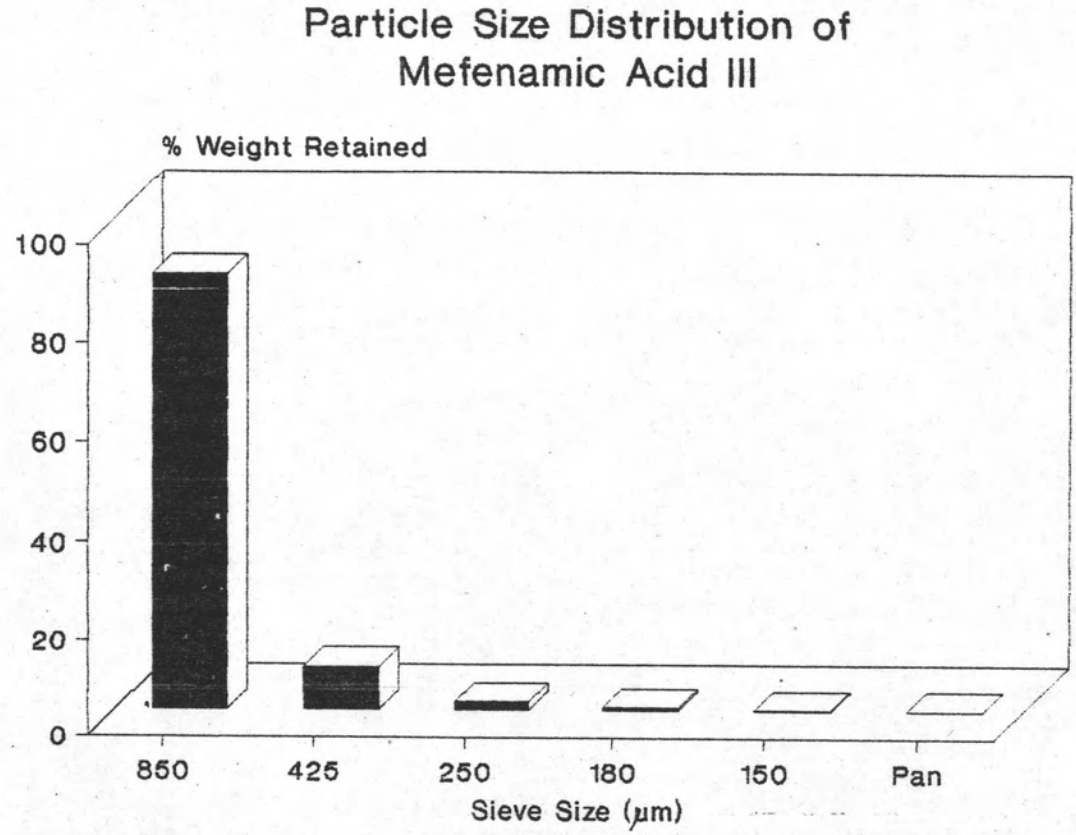


Figure 28 Particle Size Distribution of Mefenamic Acid III

distribution of each Mefenamic Acid samples and Figure 29 shows the comparative particle size distribution of all samples. The particle size distribution of three sources were quite different. Mefenamic Acid II and III had more than 85 % of particles bigger than 850 µm mesh while Mefenamic I had a wide range of particle size distribution.

1.3 Bulk Density, Tapped Density and Compressibility Determination

Bulk density, tapped density and percent compressibility of samples from various sources are shown in Table 4.

Tetracycline Hydrochloride

Bulk density and tapped density were ranging from 0.53 - 0.58 g/ml and 0.63 - 0.64 g/ml, respectively. The percent compressibility of Tetracycline Hydrochloride I and III were slightly lower than Tetracycline Hydrochloride II.

It was noticed that all of samples had percent compressibility less than 21% with indicated good flowability (Fonner et al.,1980).

Cimetidine

Bulk density, tapped density and percent compressibility of Cimetidine I - V were vary from 0.18 - 0.45 g/ml, 0.34 - 0.70 g/ml and 34.85 - 48.24 %, respectively. tI was noticed that Cimetidine I and V had higher percent compressibility.

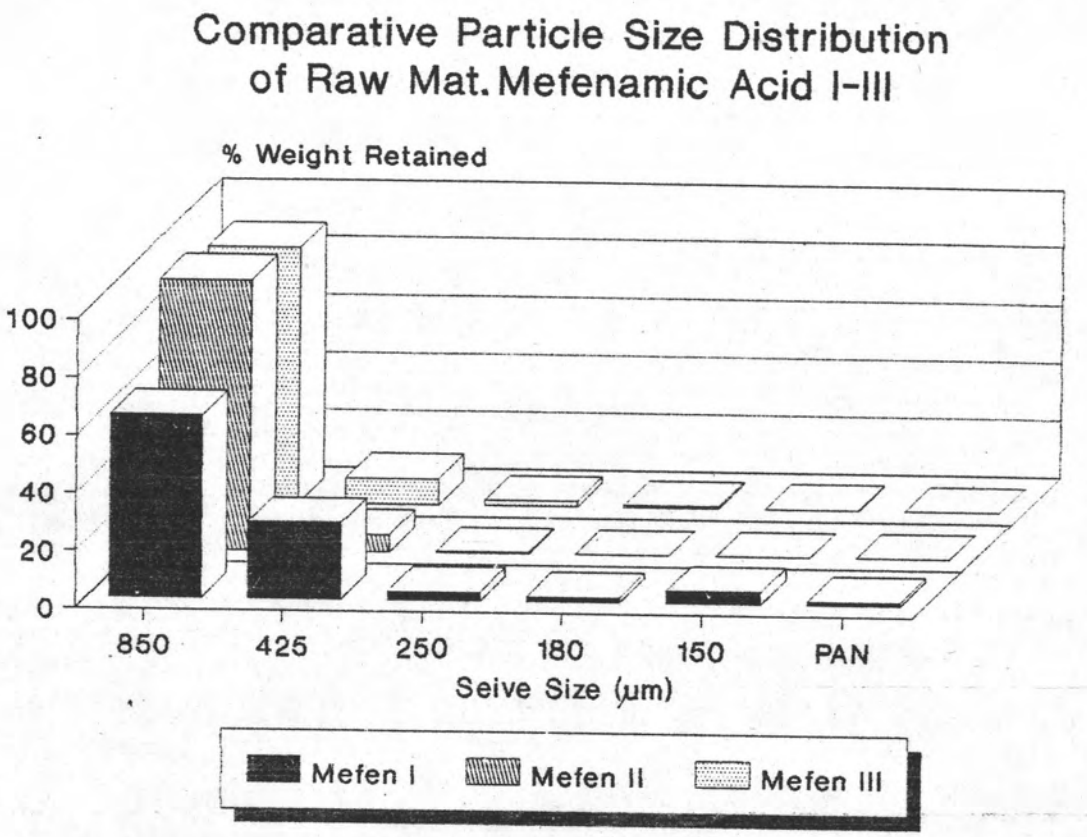


Figure 29 Comparative Particle Size Distribution of Raw Material Mefenamic Acid I, II and III

Table 4

Physical Characteristics of Active Raw Materials

Active Raw Materials	Density** (g/ml±SD) Bulk	Tapped	True	Compress** -ibility(%)	Flow Rate** (g/min) (±SD)	Angle** of Repose (°±SD)	Moisture Content* (%)	Melt. Range** (°C)
Tetra. I	0.58 (0.00)	0.64 (0.01)	1.41 (0.02)	9.62	499.80 (17.70)	32.03 (1.59)	0.57	dc.
Tetra.II	0.53 (0.00)	0.63 (0.00)	1.42 (0.02)	15.79	a	35.29 (1.45)	0.53	dc.
Tetra.III	0.57 (0.02)	0.63 (0.00)	1.43 (0.01)	9.43	495.15 (26.70)	32.17 (0.27)	0.80	dc.
Cimetidine I	0.24 (0.00)	0.39 (0.00)	1.32 (0.05)	40.16	b	45.38 (0.44)	0.13	141-142
Cimetidine II	0.40 (0.01)	0.64 (0.00)	1.27 (0.04)	37.33	b	45.84 (0.48)	0.17	140-141
CimetidineIII	0.39 (0.00)	0.61 (0.01)	1.35 (0.04)	36.36	b	48.29 (0.65)	0.17	139-140
Cimetidine IV	0.45 (0.00)	0.70 (0.00)	1.35 (0.04)	34.85	b	46.17 (0.51)	0.10	138-139
Cimetidine V	0.18 (0.02)	0.34 (0.00)	1.32 (0.03)	48.24	b	40.17 (0.52)	0.10	143-144
Mefenamic I	0.38 (0.00)	0.63 (0.00)	1.21 (0.05)	38.46	b	45.39 (0.17)	0.10	225-227
Mefenamic II	0.17 (0.02)	0.34 (0.00)	1.23 (0.01)	51.40	b	45.80 (0.18)	0.17	222-223
Mefenamic III	0.33 (0.00)	0.67 (0.00)	1.23 (0.00)	51.09	b	48.22 (0.31)	0.10	223-225

* averaged from two determinations
** averaged from three determinations
a flowed but could not be measured
b did not flow
dc decomposing occurred

Mefenamic Acid

Bulk density and tapped density were ranging from 0.17- 0.38 g/ml and 0.34 - 0.67 g/ml, respectively. The percent compressibility of Mefenamic Acid I was lower than Mefenamic Acid II and III.

1.4 True Density Determination

True density of each active raw material samples are compared in Table 4 (use acetone, ether and absolute ethanol as the solvent for tetracycline hydrochloride, cimetidine and mefenamic acid, respectively). The true density of each kind of samples were similar.

1.5 Moisture Determination

Moisture content of different active raw material samples are calculated as percent loss on drying and given in Table 4. The moisture content of each kind of samples were very small, not very different and within the compendial limit.

1.6 Angle of Repose Determination

The results are shown in Table 4. They could be ranked as follow : Tetracycline Hydrochloride II > Tetracycline Hydrochloride III > Tetracycline Hydrochloride I, Cimetidine III > Cimetidine IV > Cimetidine II > Cimetidine I > Cimetidine V and Mefenamic Acid III > Mefenamic Acid II > Mefenamic Acid I

It was noticed that all Tetracycline Hydrochloride samples had the values of lower than 40° which indicated good

1.7 Flowability Determination

Most of the samples have very poor flowability and are unable to be determined by the flowmeter except Tetracycline Hydrochloride I and III. On the other hand Tetracycline Hydrochloride II had tendency to block the orifice of the flowmeter during the test.

1.8 Melting Range Determination

Results on the melting ranges of all samples are summarized in Table 4. The melting points data of Cimetidine I-V ranged from 138°-144°C Mefenamic Acid I-III ranged from 222°-227°C and the melting points of Tetracycline I-III could not be observed because decomposition occurred.

1.9 Solubility Determination

Results on the solubility of all active raw materials are summarized in Table 5. The solubility of Tetracycline Hydrochloride I-III were ranging from 122.15 - 150.58 g/l in water and 8.95 - 11.54 g/l in ethanol. The results of Tetracycline Hydrochloride III showed the lowest solubility. The solubility of Cimetidine I-V were similar and ranging from 6.94 - 7.57 g/l in water and 38.47 - 41.91 in alcohol. The solubility of Mefenamic Acid I-III were also similar and ranging from 6.30 - 7.02 g/l in ethanol.

1.10 The IR Spectroscopy

Comparative infrared absorption spectrum of Tetracycline Hydrochloride I-III, Cimetidine I-V and Mefenamic Acid I-III are shown in Figures 30, 31 and 32 ,respectively.

Table 5

Solubility test of Active Raw Materials Used

Active Raw Materials	Source	Solubility* in water(g/l)	Solubility* in Ethanol(g/l)
Tetracycline I	China	150.58	11.54
Tetracycline II	Germany	139.04	9.23
TetracyclineIII	U.S.A.	122.15	8.95
Cimetidine I	Italy	6.94	40.86
Cimetidine II	Yugoslavia	6.98	38.48
Cimetidine III	Korea	7.42	41.91
Cimetidine IV	Hungary	7.58	40.59
Cimetidine V	Germany	7.09	40.46
Mefenamic I	Korea	insoluble	6.32
Mefenamic II	Taiwan	insoluble	7.02
Mefenamic III	U.S.A.	insoluble	6.31

* averaged from two determinations at room temperature (28°C)

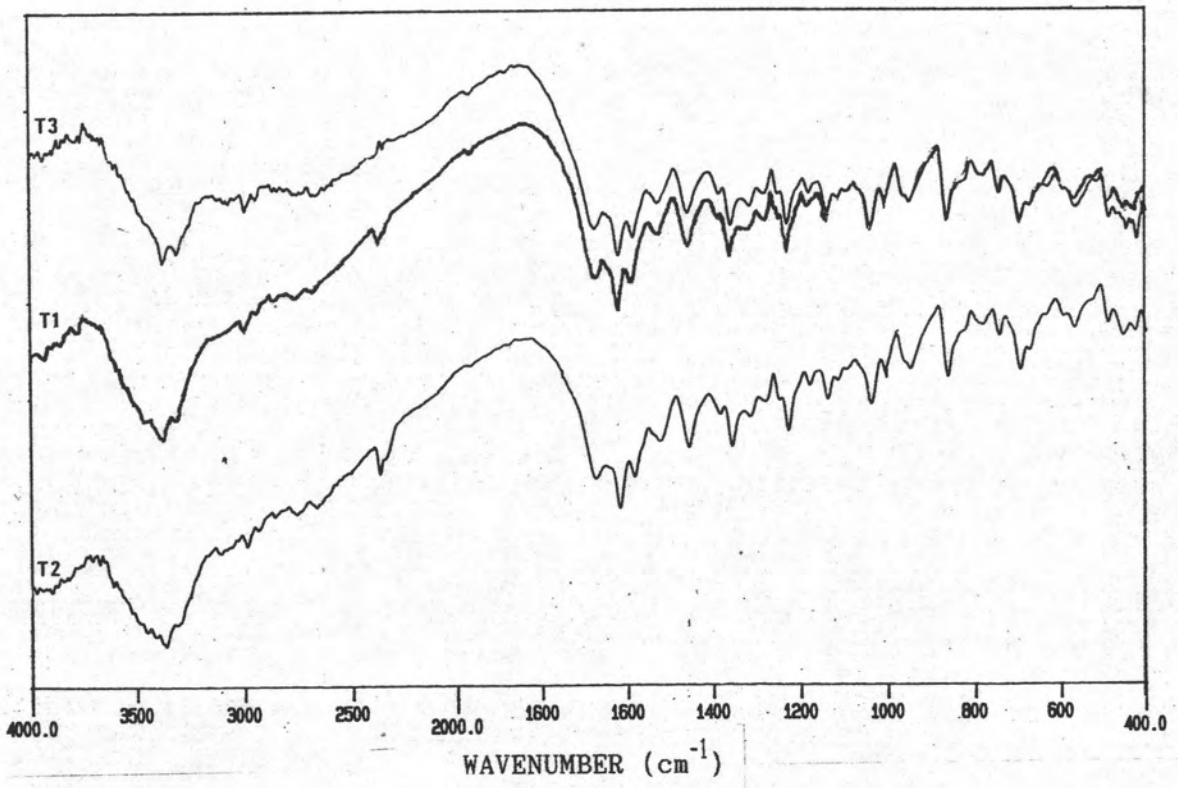


Figure 30 Comparative IR Spectra of Tetracycline Hydrochloride I, II and III
Key : T1 - Tetracycline Hydrochloride I
T2 - Tetracycline Hydrochloride II
T3 - Tetracycline Hydrochloride III

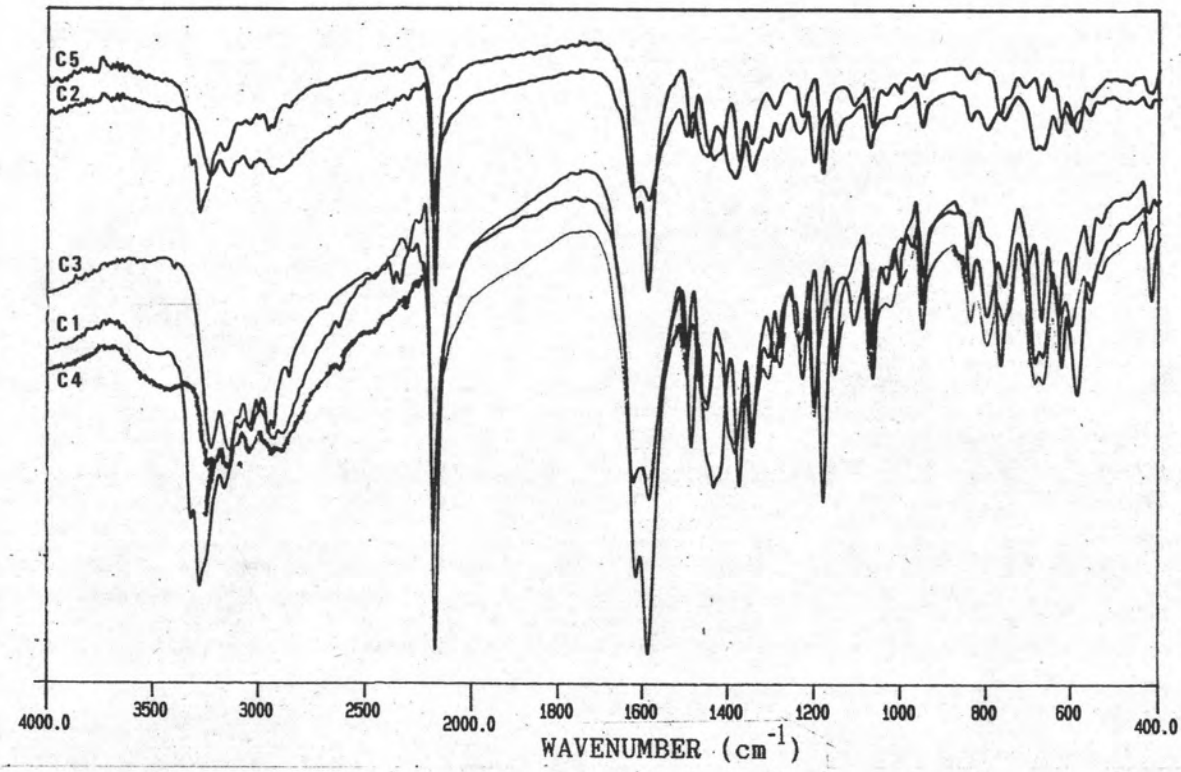


Figure 31 Comparative IR Spectra of Cimetidine I, II, III IV and V

Key : C1 - Cimetidine I
C2 - Cimetidine II
C3 - Cimetidine III
C4 - Cimetidine IV
C5 - Cimetidine V

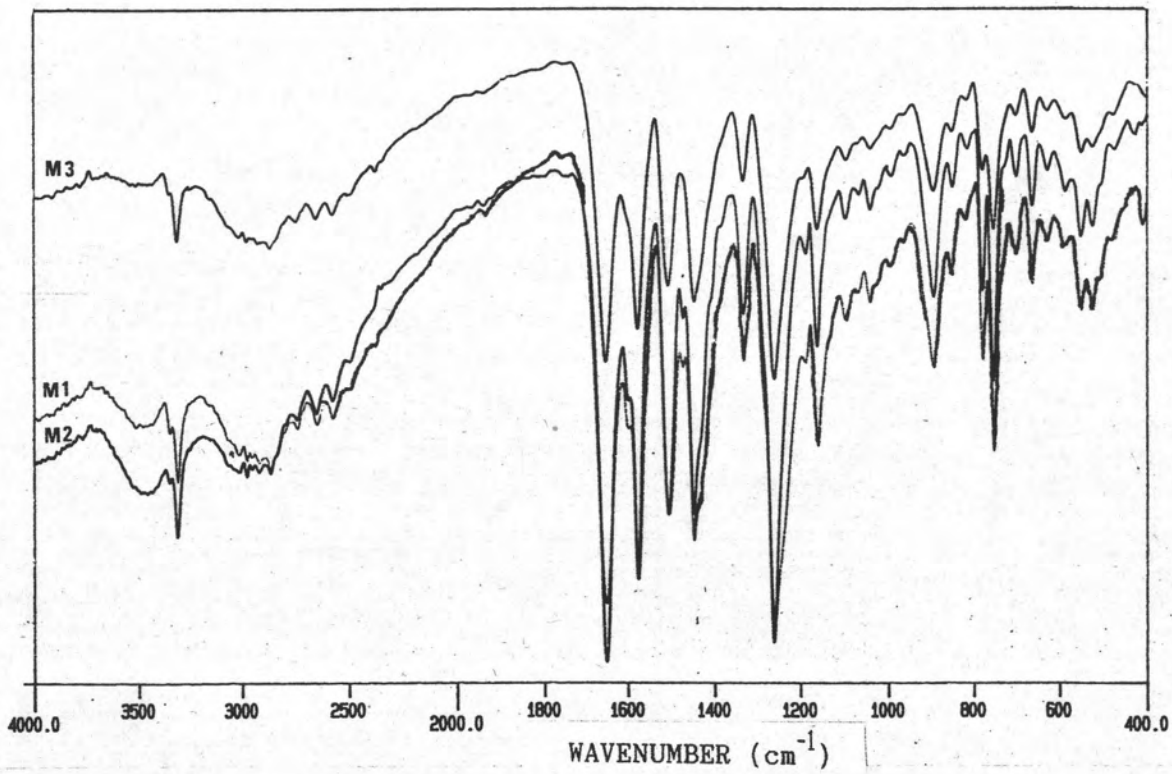


Figure 32 Comparative IR Spectra of Mefenamic Acid I, II and III
Key : M1 - Mefenamic Acid I
M2 - Mefenamic Acid II
M3 - Mefenamic Acid III

The results show that the position and relative intensity of the bands agreed in all respects, it indicates that all of the same drugs from various sources are identical.

2. Determination of % Content of Active Raw Materials

The percent content of all samples are listed in Table 6 and none of the samples failed the test.

2.1 Tetracycline Hydrochloride

The USP XXII states that all samples must contain not less than 90.0% Tetracycline Hydrochloride. Tetracycline Hydrochloride I-III contain over 95.0% tetracycline hydrochloride and conformed to this potency specification.

2.2 Cimetidine

The USP XXII claims that cimetidine must contain not less than 99.0% and not more than 101.5%. The cimetidine content of all samples were between 99.38% - 99.77%. All samples tested conformed to this specification.

2.3 Mefenamic Acid

The BP 1988 states that the samples must contain not less than 99.0% and not more than 100.5%.The mefenamic acid content of all samples ranged from 99.61% - 100.25% and conformed to this specification.

Table 6

% Assay of Active Raw Materials Used

Active Raw Materials	Source	% Assay*	% Official
Tetracycline I	China	95.31	not less than 90%[a]
Tetracycline II	Germany	95.89	not less than 90%
TetracyclineIII	U.S.A.	96.46	not less than 90%
Cimetidine I	Italy	99.50	99.00-100.50[a]
Cimetidine II	Yugoslavia	99.77	99.00-100.50
Cimetidine III	Korea	99.38	99.00-100.50
Cimetidine IV	Hungary	99.72	99.00-100.50
Cimetidine V	Germany	99.48	99.00-100.50
Mefenamic I	Korea	100.25	99.00-100.50[b]
Mefenamic II	Taiwan	100.07	99.00-100.50
Mefenamic III	U.S.A.	99.61	99.00-100.50

* averaged from two determinations.
(a) USP XXII
(b) BP 1988

3. Preparation of Tetracycline Hydrochloride, Cimetidine and Mefenamic Acid Capsules

The actual formulas in Table 7 were used in preparing tetracycline hydrochloride, cimetidine and mefenamic acid capsules. The actual formulas for fixed amount of diluent are showed in Table 8. The quantities were for one capsule.

4. Evaluation of Tetracycline Hydrochloride, Cimetidine, Mefenamic Acid Capsules and its Fixed-diluent Capsules

4.1 Weight variation of experimental capsules

4.1.1 Tetracycline Hydrochloride (I-III) Capsules, Cimetidine (I-V) Capsules and Mefenamic Acid (I-III) Capsules

The average weight, standard deviation and relative standard deviation of all capsules were shown in Table 9. All capsule formulations of Tetracycline Hydrochloride (I-III) and Cimetidine (I-V) capsules exhibited average weight variation and percent of relative standard deviation within the USP XX requirement (±10%) and all capsule formulations of Mefenamic Acid (I-III) capsules possessed the uniformity of weight in the limit of BP1988 requirement (±7.5% if average weight of capsule content is 300 mg or more and ±10% if average weight of capsule content is less than 300 mg).

4.1.2 The Fixed-diluent formulas of Tetracycline Hydrochloride (I,III) Capsules, Cimetidine (II-V) Capsule and Mefenamic Acid (I-II) Capsules

The average weight , standard deviation and relative

Table 7

The Actual Amount In The Formulas of Experimental Capsules

Active Raw Materials (mg/capsule)		Lactose	Magnesium Stearate
Tetracycline I	250.00	220.00	9.40
Tetracycline II	250.00	206.67	9.13
TetracyclineIII	250.00	213.33	9.27
Cimetidine I	200.00	80.00	5.60
Cimetidine II	200.00	193.33	7.87
Cimetidine III	200.00	186.67	7.73
Cimetidine IV	200.00	220.00	8.40
Cimetidine V	200.00	93.33	5.87
Mefenamic I	200.00	142.00	6.84
Mefenamic II	200.00	33.33	4.67
Mefenamic III	200.00	100.00	6.00

Table 8

The Fixed-Diluent Formulas of Experimental Capsules

Active Raw Materials (mg/capsule)		Lactose	Magnesium Stearate
Tetracycline I	250.00	206.67	9.13
TetracyclineII*	250.00	206.67	9.13
TetracyclineIII	250.00	206.67	9.13
Cimetidine I*	200.00	80.00	5.60
Cimetidine II	200.00	80.00	5.60
Cimetidine III	200.00	80.00	5.60
Cimetidine IV	200.00	80.00	5.60
Cimetidine V	200.00	80.00	5.60
Mefenamic I	200.00	100.00	6.00
Mefenamic II	200.00	100.00	6.00
Mefenamic III*	200.00	100.00	6.00

* used as working standard

Table 9

Physical Properties of Experimental Capsules

Experimen-tal Capsules	Weight Variation (mg±SD) n=20	% RSD*	Content Uniformity (%±SD) n=10	Disintegra-tion Time (min.±SD) n=6
Tetra I	472.33±10.51	2.23	95.99 ± 3.58	4.04 ± 0.51
Tetra II	459.19± 8.75	1.91	97.24 ± 1.91	3.50 ± 0.55
Tetra III	464.92±14.67	3.16	96.50 ± 3.22	3.83 ± 0.75
Cimet I	290.42± 8.64	2.98	101.26 ± 4.81	4.38 ± 0.14
Cimet II	410.96±11.05	2.69	99.27 ± 4.71	3.33 ± 0.26
Cimet III	386.18±11.05	2.86	96.97 ± 4.07	3.38 ± 0.38
Cimet IV	440.03±11.68	2.65	94.93 ± 4.04	4.25 ± 0.27
Cimet V	294.69±12.21	4.14	96.92 ± 4.11	4.33 ± 0.41
Mefen I	392.49±10.74	2.74	99.77 ± 2.83	4.75 ± 0.52
Mefen II	269.63±12.40	4.60	96.75 ± 1.81	18.83 ± 1.60
Mefen III	349.60±12.08	3.46	99.48 ± 3.56	10.66 ± 0.41

* Relative Standard Deviation

standard deviation of all capsules were shown in Table 10. The formulas of Fixed-diluent Tetracycline Hydrochloride (I, III) Capsules exhibited average weight variation and relative standard deviation within the USPXX requirement but the formulas of Fixed-diluent Cimetidine III exceeded the USP limit. The Fixed-diluent Cimetidine II, IV , V and the Fixed-diluent Mefenamic Acid (I, II) Capsules were still within the USP and the BP requirement, respectively.

4.2 Content Uniformity

The mean and standard deviation of content uniformity of all experimental capsules are illustrated in Tables 9 and 10. The results of Tetracycline Hydrochloride and Cimetidine Capsules were all within the range of USPXXII standard (90.0-125.0% for Tetracycline Hydrochloride Capsules and 90.0%-110.0% for Cimetidine Tablets) and the results of Mefenamic Acid Capsules were within the range of BP1988 standard (92.5-107.5%). The fixed-diluent capsule formulations of all source exceeded the range of standard except Tetracycline Hydrochloride I and II fixed-diluent formulas exhibited within the USP requirement.

4.3 Disintegration Time of Tetracycline Hydrochloride Capsules, Cimetidine Capsules Mefenamic Acid Capsules and their fixed-diluent formulas were shown in Table 9 and Table 10, respectively.

The disintegration Time of all experimental capsules were slightly different except for Mefenamic Acid II and

Table 10

Physical Properties of Experimental Capsules

Experimental Capsules	Weight Variation (mg±SD) n = 20	% RSD	Content Uniformity (%±SD) n = 10	Disintegration Time (min.±SD) n = 6
Tetra I Fix	460.02±10.09	2.19	95.05 ± 3.10	3.63 ± 0.80
Tetra III Fix	460.14±10.30	2.24	95.59 ± 2.79	4.17 ± 0.44
Cimet II Fix	273.80±26.54	9.69	103.28 ±13.66	4.58 ± 0.20
Cimet III Fix	271.83±31.74	11.68	94.32 ±14.90	3.75 ± 0.45
Cimet IV Fix	281.86±17.45	6.19	97.20 ± 9.81	4.00 ± 0.32
Cimet V Fix	291.36±13.75	4.72	97.00 ± 7.72	4.29 ± 0.56
Mefen I Fix	351.08±17.91	5.10	104.72 ± 9.96	10.63 ±0.38
Mefen II Fix	259.92±17.08	6.57	93.04 ± 9.43	19.83 ±0.41

fixed-diluent formulas of Mefenamic Acid II exceeded the BP limit (15 min.).

4.4 Dissolution Studies

4.4.1 Raw material of Tetracycline Hydrochloride and Tetracycline Hydrochloride Capsules

The dissolution behaviors of various raw material tetracycline capsules and experimental tetracycline capsules are shown in Figures 33 and 34 respectively. The dissolution profiles of raw material capsules are similar and exhibited 70% tetracycline hydrochloride released within 5 minutes, unlike Tetracycline Hydrochloride I and II capsules exhibited 70% release within 7 minutes and Tetracycline Hydrochloride III capsules exhibited 70% release within 50 minutes. All of the experimental capsules meet the USP specification (70% within 60 minutes). It was noticed that the dissolution of Tetracycline Hydrochloride III capsules took longer time to release the drug but still within the compendial limit.

Consideration through the data in Tables 11 and 12, it was found that there were no statistically significant differences in percent and time for drug to release from raw material Tetracycline Hydrochloride capsules unlike the data in Tables 13 and 14 show that there were statistically significant differences in percent and time for drug to release from the experimental Tetracycline Hydrochloride Capsules.

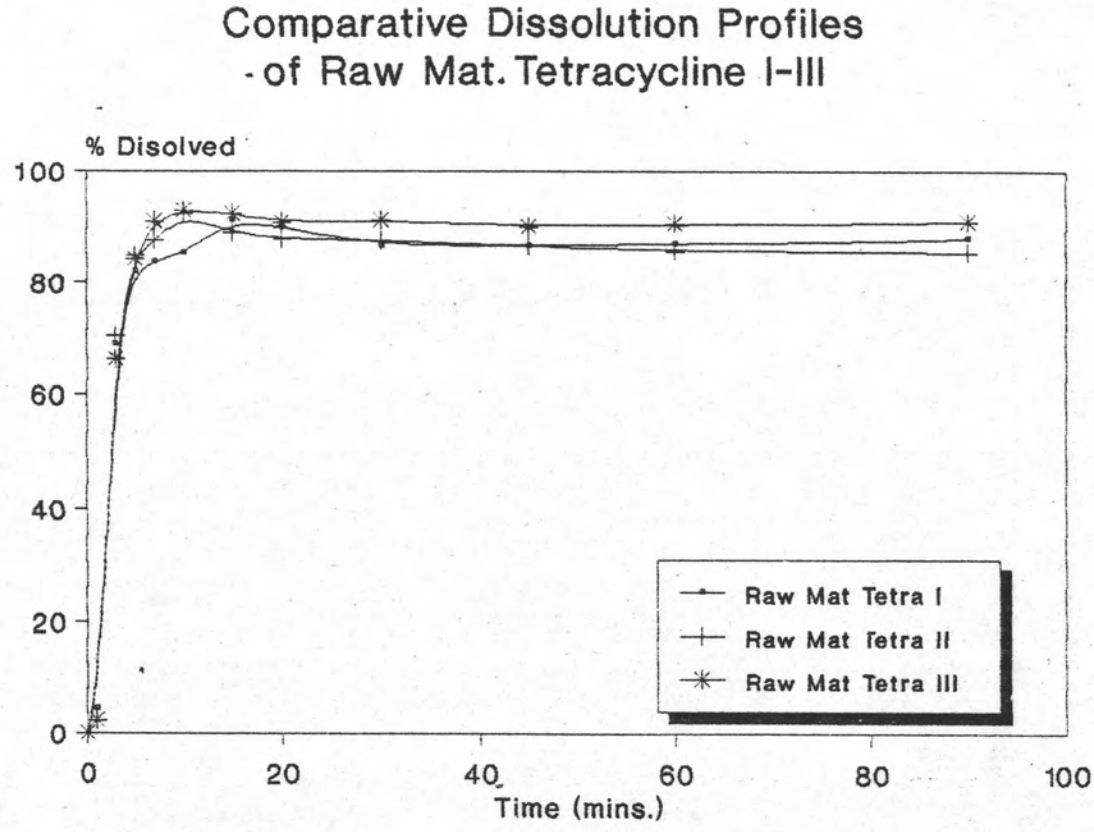


Figure 33 Comparative Dissolution Profiles of Raw Material Tetracycline Hydrochloride I, II and III

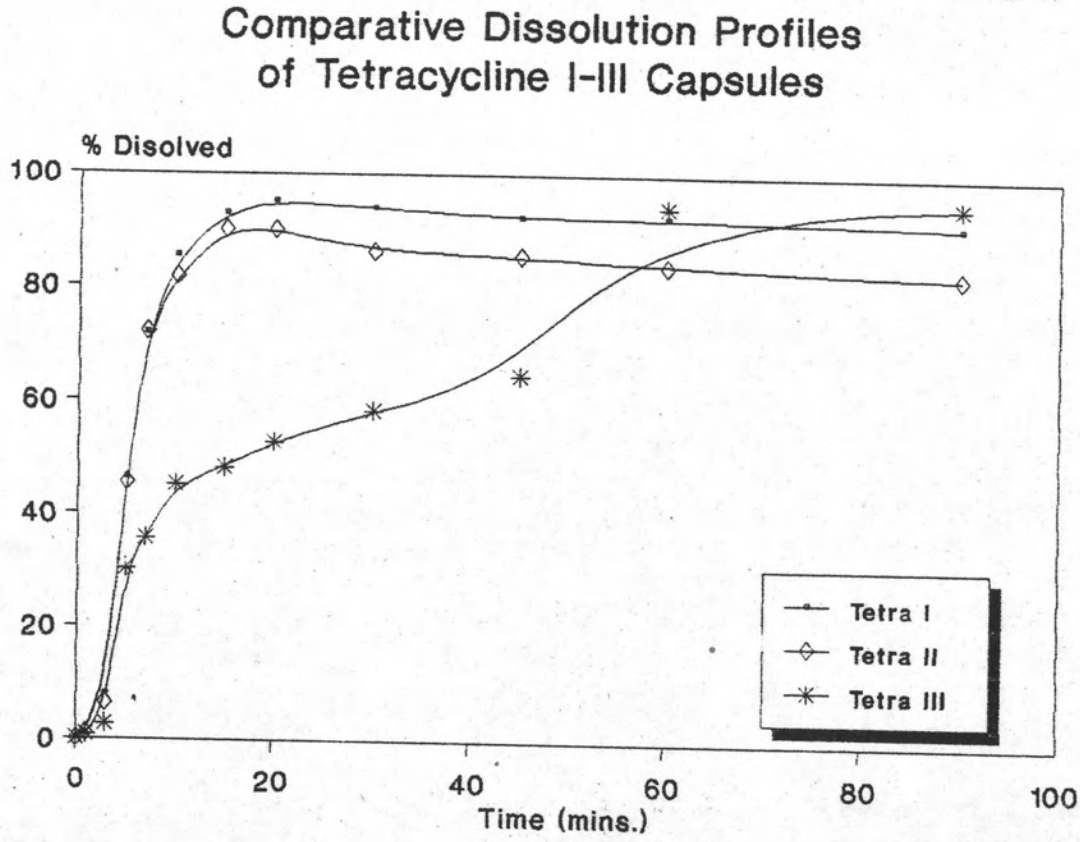


Figure 34 Comparative Dissolution Profiles of Tetracycline Hydrochloride I, II and III Capsules

Table 11

Analysis of Variance for percent drug released of various Raw Material Tetracycline Hydrochloride Capsules at 60 min.

Source of Variance	DF[a]	SS*	MS**	F***
Among Groups	2	36.160	18.080	1.803
Within Groups	6	60.159	10.026	1.803
Total	8	96.319	12.040	

[a] Degree of freedom
* Sum of squares
** Mean of squares
*** F ratio
Table $F_{0.05(2,6)} = 5.14$

Table 12

Analysis of Variance for time of various Raw Material Tetracycline Hydrochloride Capsules at 70% released.

Source of Variance	DF	SS	MS	F
Among Groups	2	0.086	0.043	0.375
Within Groups	6	0.690	0.115	0.375
Total	8	0.776	0.097	

$F_{0.05(2,6)} = 5.14$

Table 13

Analysis of Variance for percent drug released of Experimental Tetracycline Hydrochloride Capsule at 60 min.

Source of Variance	DF	SS	MS	F
Among Groups	2	153.929	76.965	6.590
Within Groups	6	70.078	11.680	6.590
Total	8	224.008	28.001	

$F_{0.05(2,6)} = 5.14$

Table 14

Analysis of Variance for time of Experimental Tetracycline Hydrochloride Capsule at 70% released.

Source of Variance	DF	SS	MS	F
Among Groups	2	2783.874	1391.937	225.398
Within Groups	6	37.053	6.175	225.398
Total	8	2820.927	352.616	

$F_{0.05(2,6)} = 5.14$

4.4.2 Raw material of Cimetidine and Cimetidine Capsules

The dissolution behaviors of various raw material cimetidine capsules and experimental capsules are shown in Figures 35 and 36 respectively. The dissolution profiles of raw material capsules are slightly different and exhibited 75% Cimetidine released within 10 minutes, unlike Cimetidine I-IV Capsules exhibited 75% release within 7 minutes and Cimetidine V Capsules exhibited 75% release within 15 minutes. All of the experimental capsules meet the USP specification (75% within 15 minutes). It was noticed that the dissolution of Cimetidine V Capsules took longer time to release the drug but still within the compendial limit.

Consideration through the data in Tables 15 and 16, it was found that there were statistically significant differences in percent and time for drug to release from raw material cimetidine capsules and the data in Tables 17 and 18 show that there were statistically significant differences in percent and time for the drug to release from the experimental Cimetidine capsules too.

4.4.3 Raw material of Mefenamic Acid and Mefenamic Acid Capsule

The dissolution behaviors of various raw material mefenamic acid capsules and experimental capsules are shown in Figures 37 and 38 respectively. The dissolution profiles of raw material capsules and experimental capsules

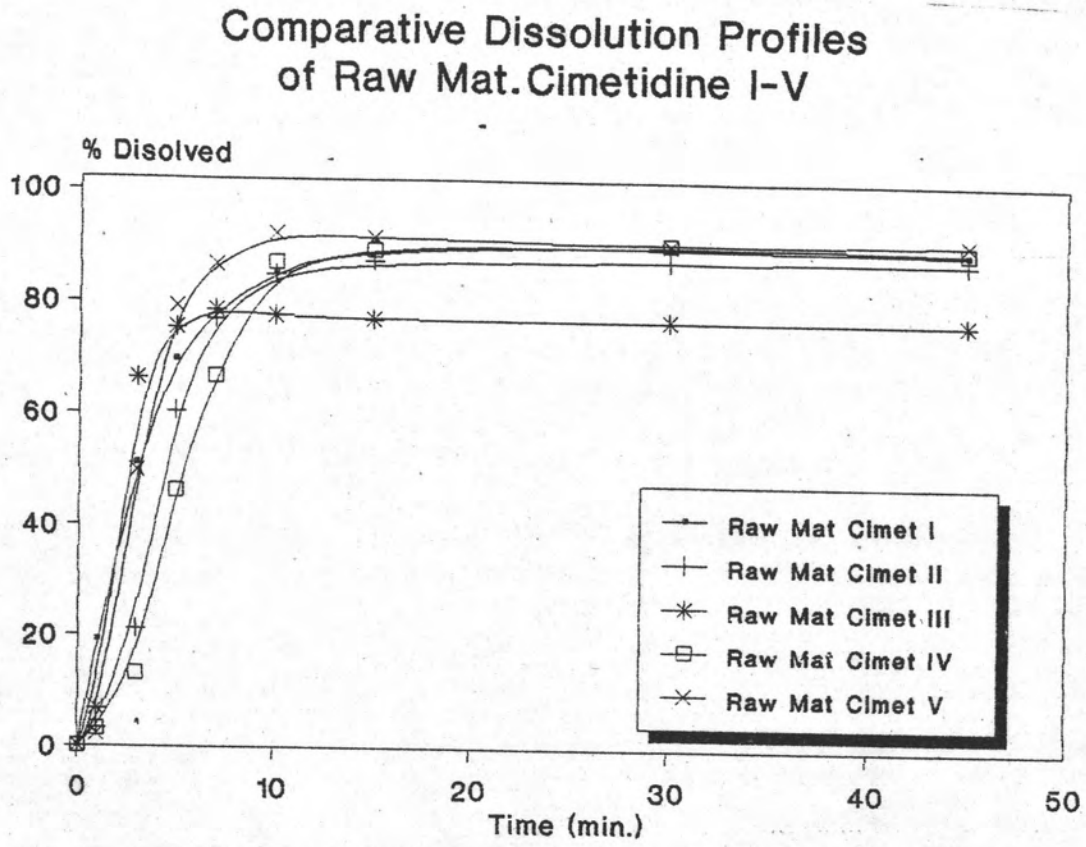


Figure 35 Comparative Dissolution Profiles of Raw Material Cimetidine I, II, III, IV and V

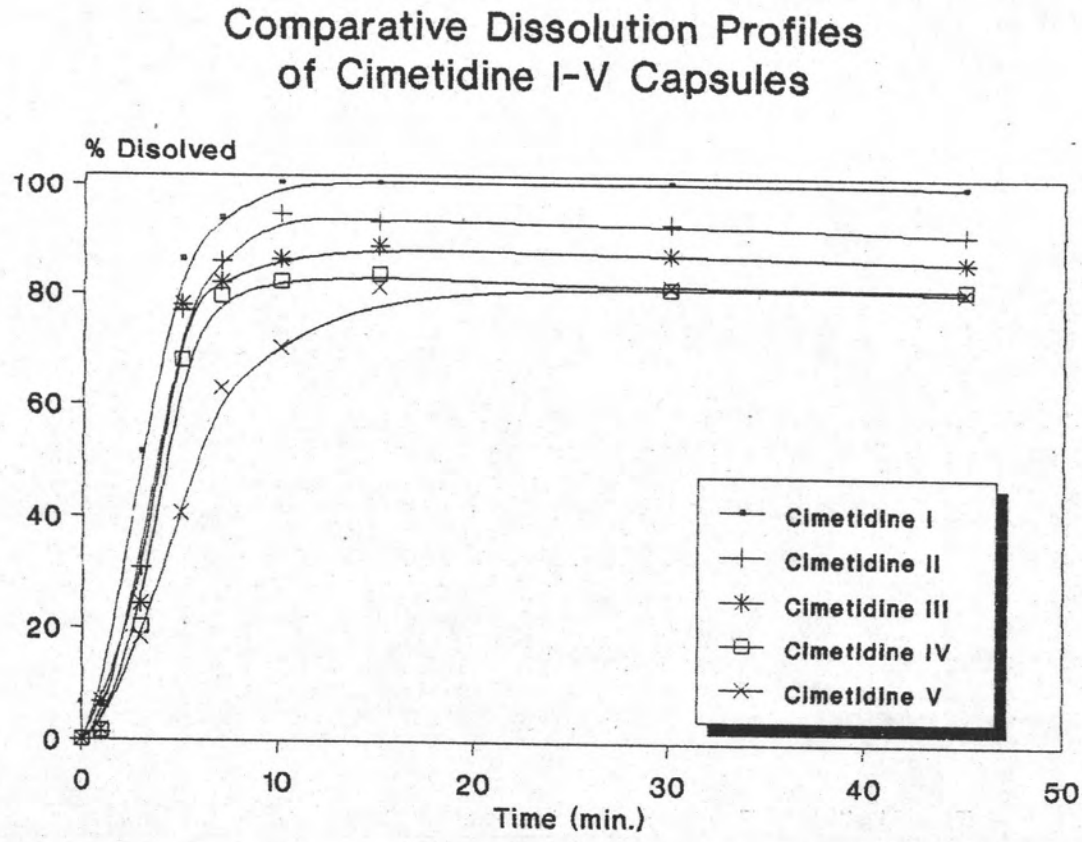


Figure 36 Comparative Dissolution Profiles of Cimetidine I, II, III, IV and V Capsules

Table 15

Analysis of Variance for percent drug released of various Raw Material Cimetidine Capsules at 15 min.

Source of Variance	DF	SS	MS	F
Among Groups	4	425.037	106.259	11.381
Within Groups	10	93.369	9.337	11.381
Total	14	518.406	37.029	

$F_{0.05(4,10)} = 3.48$

Table 16

Analysis of Variance for time of various Raw Material Cimetidine Capsules at 75% released.

Source of Variance	DF	SS	MS	F
Among Groups	4	19.084	4.771	6.870
Within Groups	10	6.945	0.694	6.870
Total	14	26.029	1.859	

$F_{0.05(4,10)} = 3.48$

Table 17

Analysis of Variance for percent drug released of Experimental Cimetidine Capsules at 15 min.

Source of Variance	DF	SS	MS	F
Among Groups	4	576.800	144.200	29.205
Within Groups	10	49.376	4.938	29.205
Total	14	626.176	44.727	

$F_{0.05(4,10)} = 3.48$

Table 18

Analysis of Variance for time of Experimental Cimetidine Capsules at 75% released.

Source of Variance	DF	SS	MS	F
Among Groups	4	116.200	29.050	81.477
Within Groups	10	3.565	0.357	81.477
Total	14	119.765	8.555	

$F_{0.05(4,10)} = 3.48$

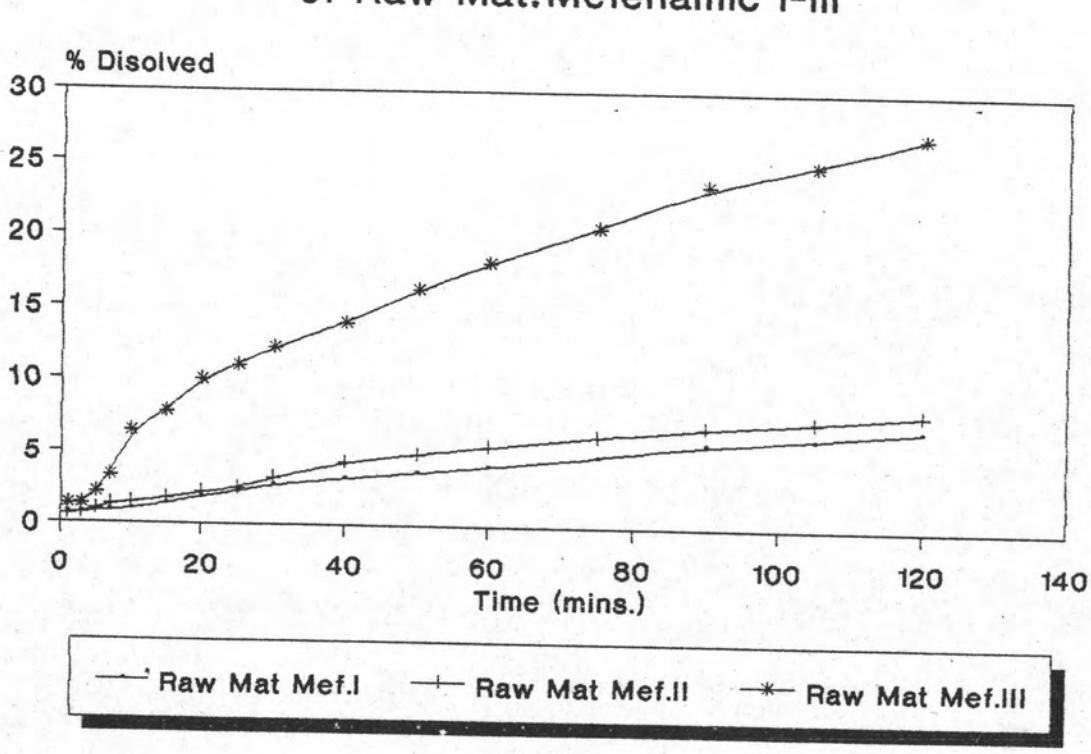


Figure 37 Comparative Dissolution Profiles of Raw Material Mefenamic Acid I, II and III

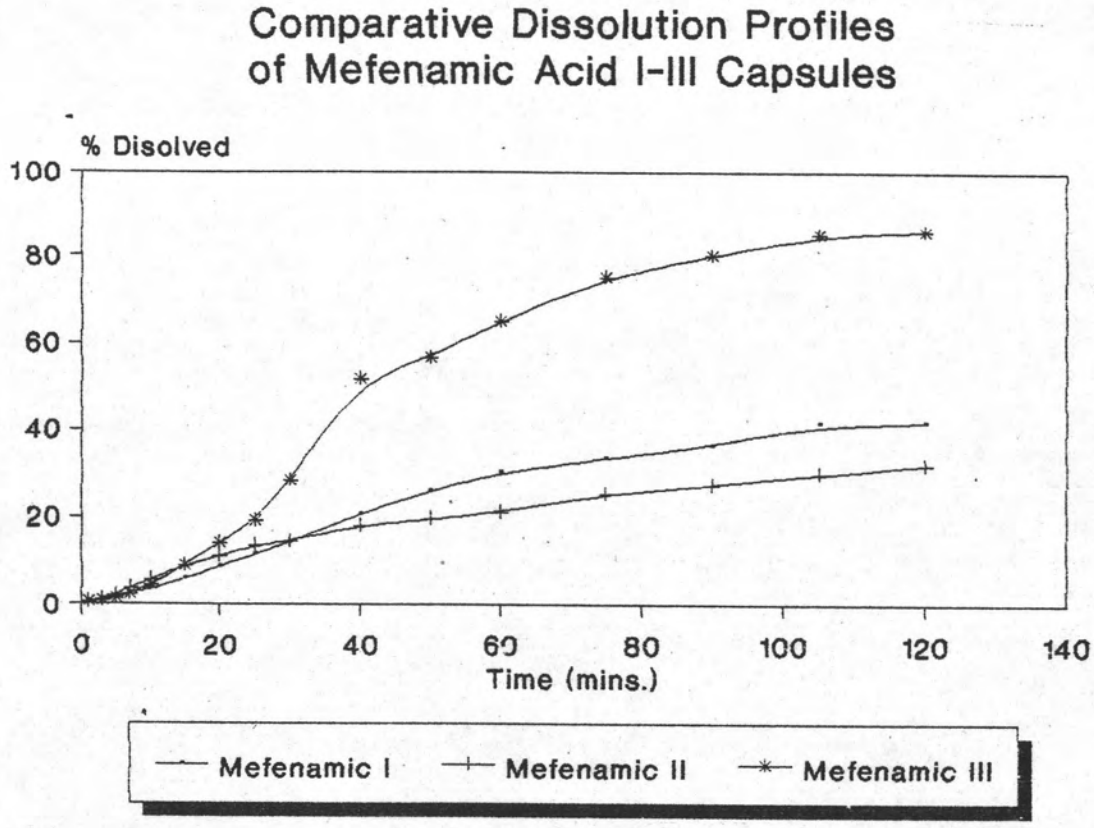


Figure 38 Comparative Dissolution Profiles of Mefenamic Acid I, II and III Capsules

are very different. There was no compendial limit for dissolution in BP monograph and the only formula of Mefenamic Acid III capsules that exhibited more than 50% mefenamic acid released within 40 minutes.

Consideration through the data in Tables 19 and 20, it was found that there were statistically significant differences in percent for drug to release from raw material capsules and the experimental capsules at 60 min.

4.4.4 Fixed-diluent Capsules

4.4.4.1 Tetracycline Hydrochloride

The dissolution behaviors of Fixed-diluent tetracycline capsule samples are shown in Figure 39. The dissolution profiles of Fixed-Diluent Tetracycline Hydrochloride Capsules and the Working formula of Tetracycline Hydrochloride II are not similar. The Fixed-Diluent Formula of Tetracycline Hydrochloride I exhibited 70% tetracycline hydrochloride released within 20 minutes, unlike the Fixed-Diluent Formula of Tetracycline Hydrochloride III Capsules exhibited 70% release within 60 minutes while the Working formula of Tetracycline Hydrochloride II Capsules exhibited 70% release within 10 minutes. All of the experimental capsules meet the USP specification (70% within 60 minutes). It was noticed that the dissolution of Fixed-Diluent Formula of Tetracycline Hydrochloride III Capsules took longer time to release the drug but still within the compendial limit.

Consideration through the data in Tables 21 and 22,

Table 19

Analysis of Variance for percent drug released of various Raw Material Mefenamic Acid Capsules at 60 min.

Source of Variance	DF	SS	MS	F
Among Groups	2	354.642	177.321	88.087
Within Groups	6	12.078	2.013	88.087
Total	8	366.720	45.840	

$F_{0.05(2,6)} = 5.14$

Table 20

Analysis of Variance for percent drug released of Experimental Mefenamic Acid Capsules at 60 min.

Source of Variance	DF	SS	MS	F
Among Groups	2	3230.360	1615.18	62.642
Within Groups	6	154.706	25.78	62.642
Total	8	3385.066	423.133	

$F_{0.05(2,6)} = 5.14$

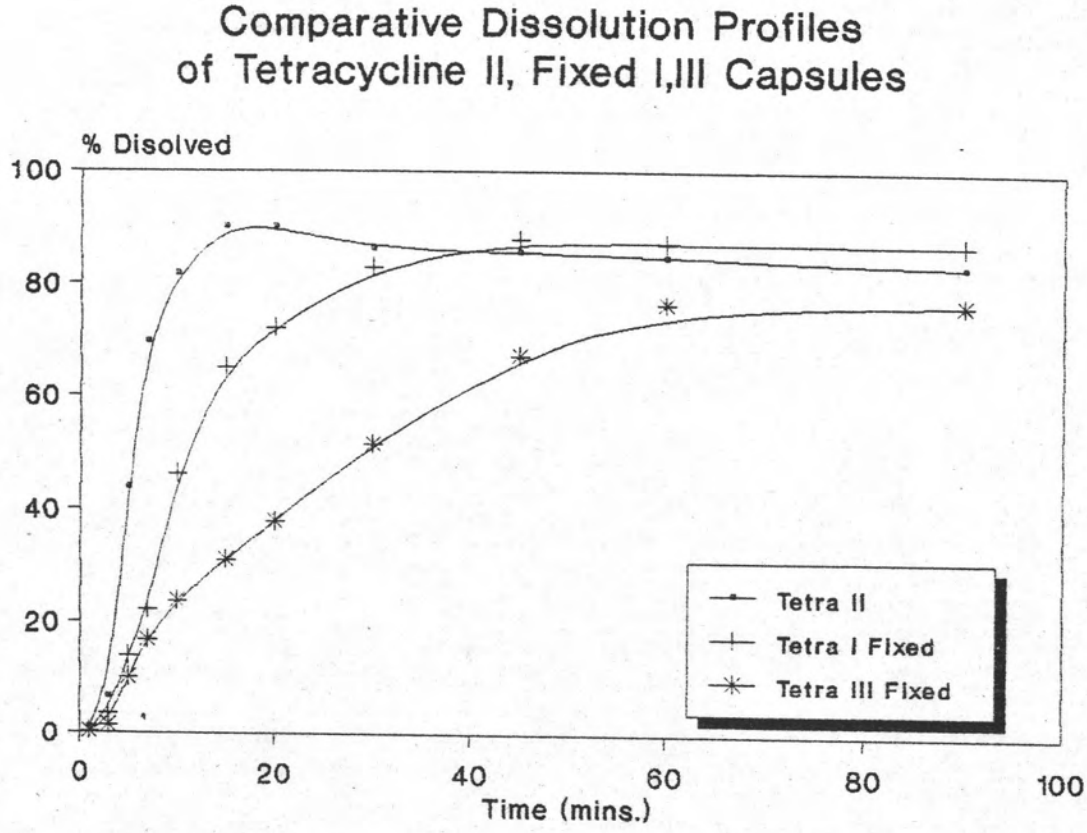


Figure 39 Comparative Dissolution Profiles of Tetracycline Hydrochloride II, Fixed-diluent I and Fixed-diluent III Capsules

Table 21

Analysis of Variance for percent drug released of Tetracycline II, Fixed-diluent Tetracycline (I and III) Capsules at 60 min.

Source of Variance	DF	SS	MS	F
Among Groups	2	188.516	94.258	8.625
Within Groups	6	65.574	10.929	8.625
Total	8	254.090	31.761	

$F_{0.05(2,6)} = 5.14$

Table 22

Analysis of Variance for time of Tetracycline II, Fixed-diluent Tetracycline (I and III) Capsules at 70% released.

Source of Variance	DF	SS	MS	F
Among Groups	2	2250.518	1125.259	74.275
Within Groups	6	90.899	15.150	74.275
Total	8	2341.417	292.677	

$F_{0.05(2,6)} = 5.14$

it was found that there were statistically significant differences in percent and time for drug to release from the experimental Fixed-Diluent Formulas and Working Formula of Tetracycline Hydrochloride capsules.

4.4.4.2 Cimetidine

The dissolution behaviors of Fixed-diluent Cimetidine capsule samples are shown in Figure 40. The dissolution profiles of Fixed-Diluent Formulas and the Working Formula of Cimetidine Capsules are slightly different and exhibited 75% Cimetidine released within 7 minutes. All of the experimental capsules meet the USP specification (75% within 15 minutes).

Consideration through the data in Tables 23 and 24, it was found that there was a statistically significant difference in time for drug to release from the experimental Fixed-diluent and Working Formula of Cimetidine capsules but there was no statistically significant difference in 75 percent drug released.

4.4.4.3 Mefenamic Acid

The dissolution behaviors of Fixed-diluent Mefenamic Acid capsule samples are shown in Figure 41. The dissolution profiles of Fixed-diluent Formulas and Working Formula of Mefenamic Acid Capsules were very different. There was no compendial limit for dissolution in BP monograph and the only formula of Mefenamic Acid III capsules that exhibited more than 50% mefenamic acid released within 40 minutes.

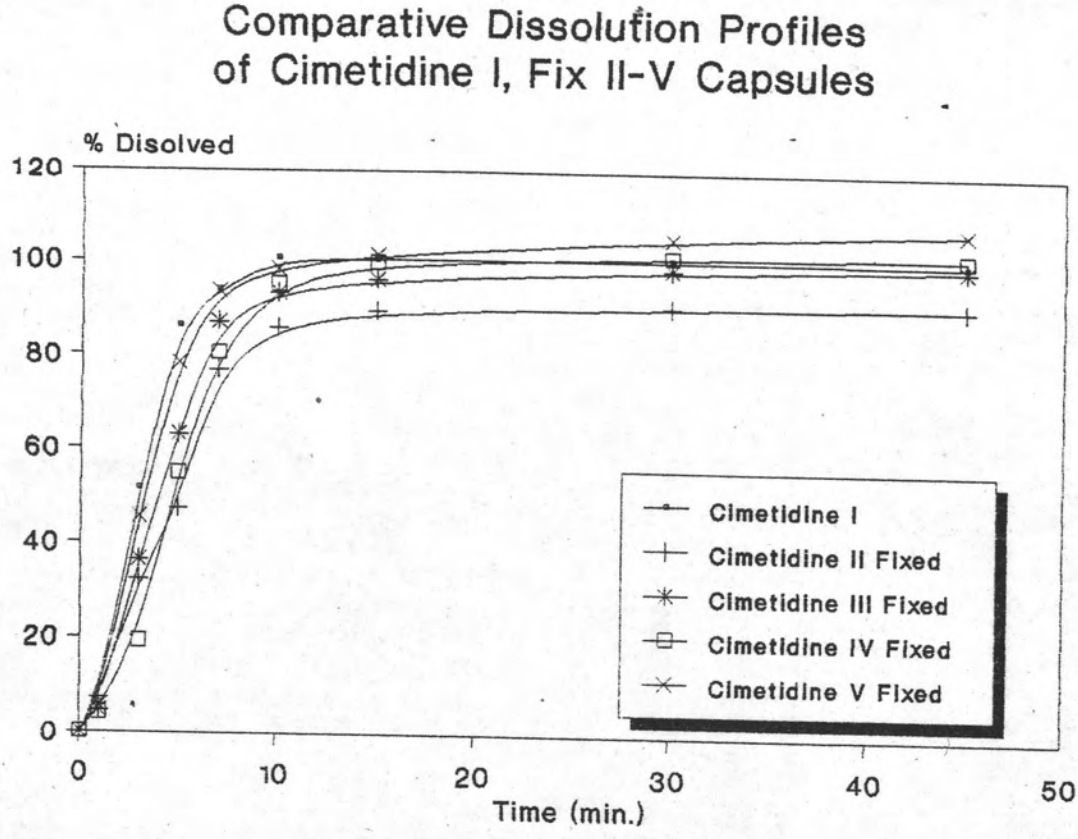


Figure 40 Comparative Dissolution Profiles of Cimetidine I, Fixed-diluent II,III,IV and V Capsules

Table 23

Analysis of Variance for percent drug released of Cimetidine I, Fixed-diluent Cimetidine (II,III,IV and V) Capsules at 15 min.

Source of Variance	DF	SS	MS	F
Among Groups	4	2.560	0.640	4.754
Within Groups	10	1.346	0.135	4.754
Total	14	3.907	0.279	

$F_{0.05(4,10)} = 3.48$

Table 24

Analysis of Variance for time of Cimetidine I, Fixed-diluent Cimetidine(II, III, IV and V) Capsules at 75% released.

Source of Variance	DF	SS	MS	F
Among Groups	4	16.181	4.045	3.424
Within Groups	10	11.814	1.181	3.424
Total	14	27.995	2.000	

$F_{0.05(4,10)} = 3.48$

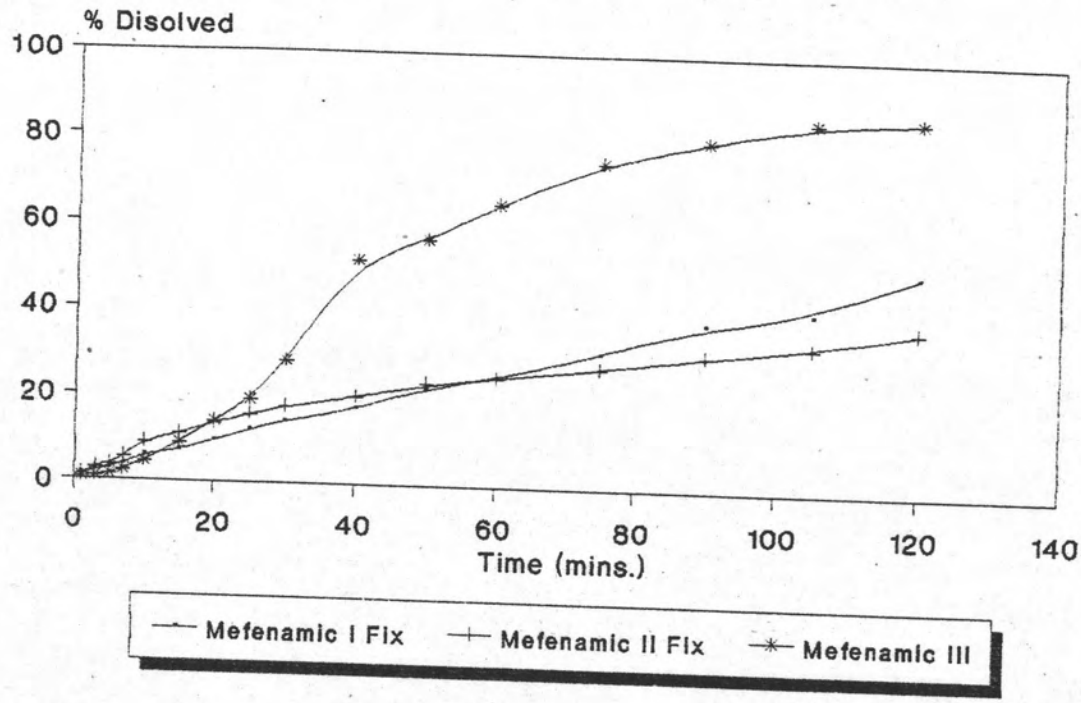


Figure 41 Comparative Dissolution Profiles of Mefenamic Acid III, Fixed-diluent I and Fixed-diluent III Capsules

Consideration through the data in Table 25, it was found that there were statistically significant differences in percent and time for drug to release from the experimental Fixed-diluent and Working Formula of Mefenamic Acid capsules.

Table 25

Analysis of Variance for percent drug released of Mefenamic Acid III , Fixed-diluent Mefenamic Acid (I and II) Capsules at 60 min.

Source of Variance	DF	SS	MS	F
Among Groups	2	3175.357	1587.67	26.652
Within Groups	6	357.427	59.57	26.652
Total	8	3532.784	441.598	

$F_{0.05(2,6)} = 5.14$