CHAPTER III

RESULTS

Typical standard curves for HCTZ data at 273 and 317 nm as determined using linear regression are shown in Figure 1 and 2 and Table 1 and 2, respectively. The correlation coefficient for each fit of a straight line was significant.

Preparation of Solid Dispersions

From the preliminary study, it was shown that the melting method could not be used for preparing solid dispersions of HCTZ and PVP. Furthermore, the solvent method could not be used for preparing solid dispersions of HCTZ and PEG of all ratios, since the products appeared to be sticky masses.

Solid dispersions of HCTZ and PVP K-17 or PVP K-90 could be readily prepared by solvent method, and the coprecipitates obtained were glass-like, transparent and brittle, easily pulverized, and free-flowing powder. When PVP K-90 was used as a carrier, the coprecipitates could be easily prepared at the HCTZ:PVP K-90 ratio not higher than 1:4. However, with the higher PVP K-90 weight fractions, the coprecipitate could not be achieved due to the difficulty in scraping off the evaporating flask.

Solid dispersions of HCTZ and PEG could be prepared only by

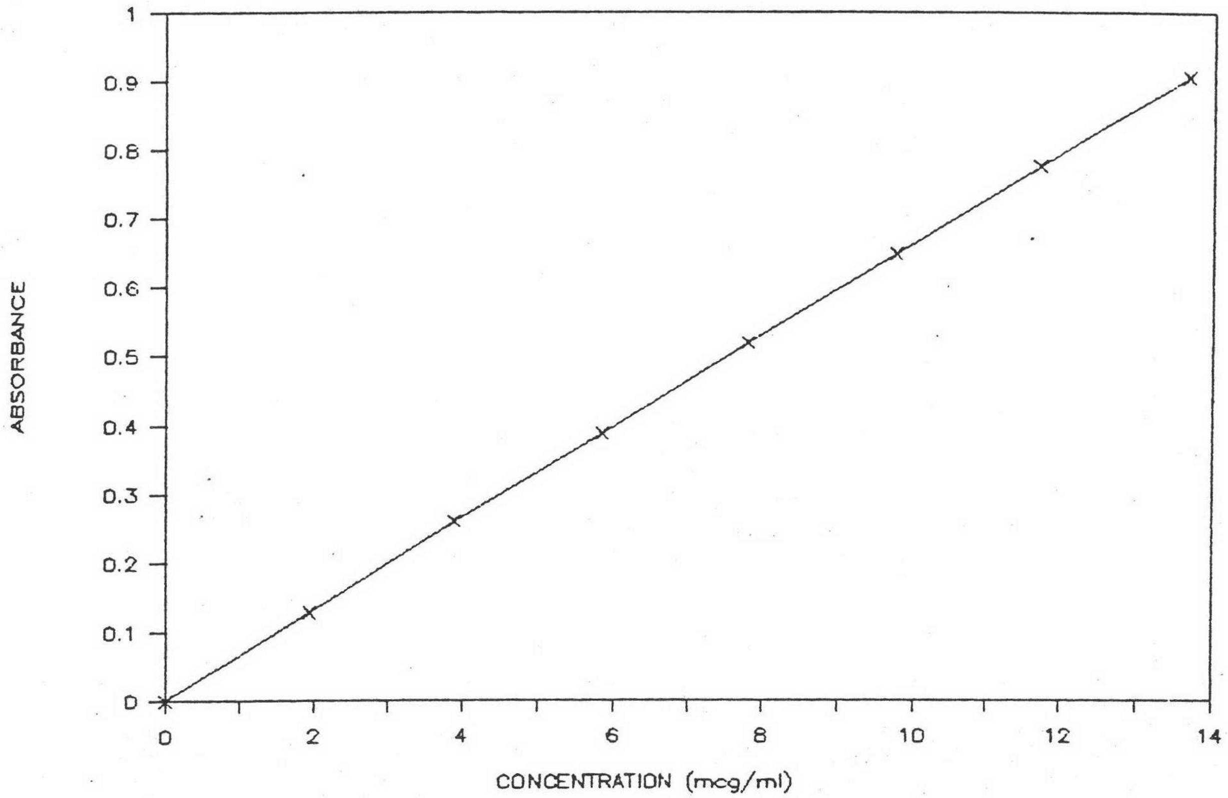

Figure 1 Typical standard curve for HCTZ concentration at 273 nm.

Table 1 Typical Standard Curve Data for HCTZ Concentration at 273 nm Estimated Using Linear Regression[a].

Std.No.	Conc. (mcg/ml)	Absorbance	Inv. Est. Conc.[b]	% Theory[c]
1	0	0	0	100.00
2	1.95	0.128	1.9420	99.59
3	3.91	0.259	3.9188	100.22
4	5.86	0.386	5.8352	99.58
5	7.82	0.518	7.8272	100.09
6	9.77	0.647	9.7738	100.04
7	11.72	0.776	11.7204	100.00
8	13.68	0.906	13.6822	100.02
Mean	-	-	-	99.94
S.D.	-	-	-	0.23
C.V.[d]	-	-	-	0.23

a R^2 = 0.9999

b Inversely estimated concentration = (Absorbance + 0.00069)/ 0.066268

c % Theory = (inversely estimated concentration / known concentration)100

d Coefficient of variation = (S.D./Mean)100

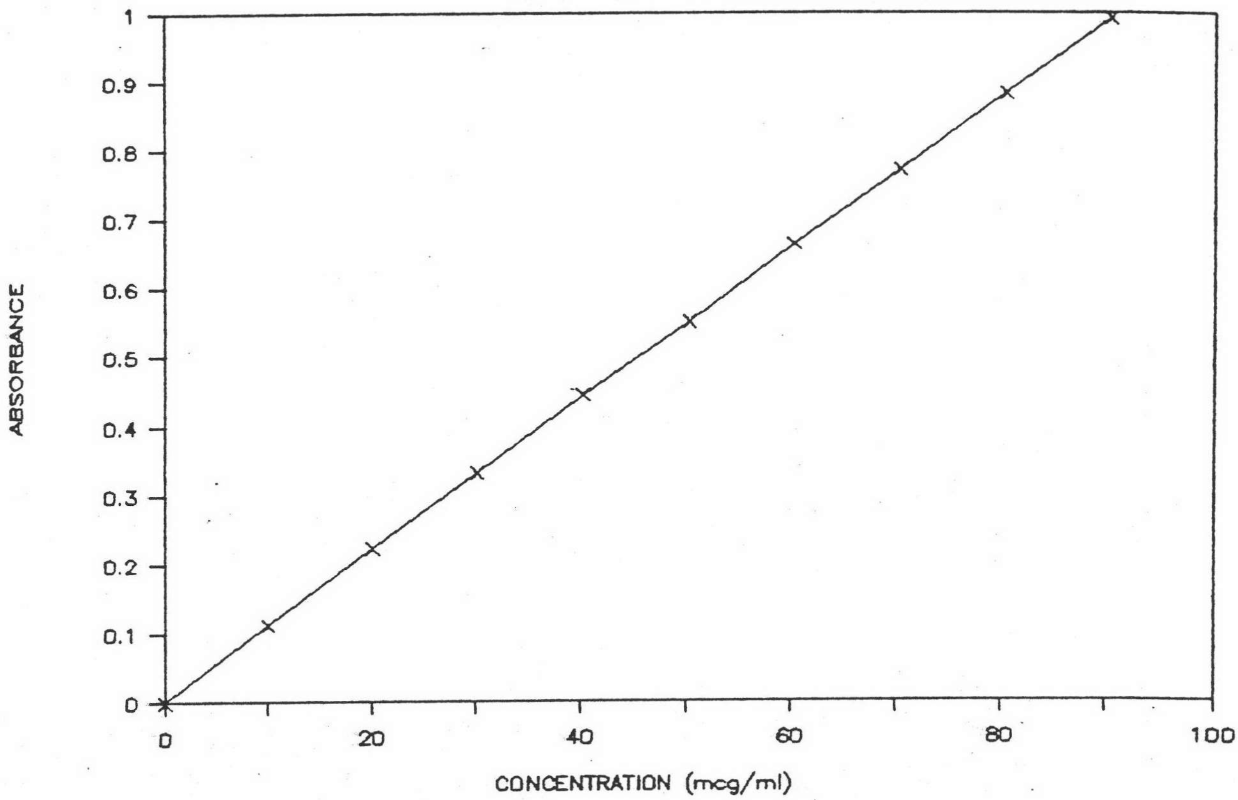

Figure 2 Typical standard curve for HCTZ concentration at 317 nm.

Table 2 Typical Standard Curve Data for HCTZ Concentration at 317 nm Estimated Using Linear Regression[a]

Std.No.	Conc. (mcg/ml)	Absorbance	Inv. Est. Conc.[b]	% Theory[c]
1	0	0	0	100.00
2	10.09	0.111	10.0275	99.38
3	20.18	0.222	20.2129	100.16
4	30.27	0.331	30.2147	99.82
5	40.36	0.444	40.5836	100.55
6	50.45	0.550	50.3101	99.72
7	60.54	0.662	60.5873	100.08
8	70.63	0.771	70.5891	99.94
9	80.72	0.882	80.7744	100.07
10	90.81	0.991	90.7763	99.96
Mean	-	-	-	99.97
S.D.	-	-	-	0.30
C.V.[d]	-	-	-	0.30

a $R^2 = 0.9999$

b Inversely estimated concentration = (Absorbance - 0.00172)/ 0.010898

c % Theory = (inversely estimated concentration / known concentration)100

d Coefficient of variation = (S.D./Mean)100 melting method. As low weight fractions of PEG, the mixtures were immiscible because HCTZ could not be melted. However, the melts could be achieved when the HCTZ-PEG ratios were 1:5 or at higher PEG weight fraction. Although the 1:5 HCTZ-PEG 4000 melt could not be pulverized due to the tendency to stick together, so it was not suitable for further studies. It was found that other melts with PEG appeared to be wax-like, easily pulverized, and free-flowing powder.

Solid dispersions of HCTZ and urea could be prepared by either melting or solvent method. The coprecipitates obtained from solvent method were easily pulverized, free-flowing powder. Using melting method, however, it appeared that 2:1 HCTZ-urea mixture could not be completely melted. The melts could be prepared when HCTZ-urea ratios were 1:1 or at higher urea weight fractions. The melts were solidified rapidly, yielding translucent and easy-to-pulverize solid masses except 2:1 and 1:1 melts which were not free-flowing powder.

The percentage contents of HCTZ in each solid dispersion obtained are shown in Table 3.

Dissolution Studies

Dissolution profiles of all solid dispersions of HCTZ followed first-order kinetics. Semilogarithmic plots of the percent drug undissolved versus time were linear.

Table 3 Percentage Labeled Amount and Dissolution of HCTZ from Pure HCTZ, Solid Dispersions, and Physical Mixtures.

Preparation	% Labeled Amount[a]	Dissolution Rate Constant (min^{-1})[b]	% HCTZ Dissolved at 5 Minutes[b,c]
Pure HCTZ	99.70 (0.01)	0.03460 (0.00217)	22.703 (1.699)
HCTZ-PVP K-17 Coprecipitates			
2:1	99.10 (0.23)	0.02087 (0.00394)	18.380 (5.495)
1:1	99.64 (0.82)	0.18025 (0.01062)	46.924 (2.343)
1:3	99.57 (0.36)	0.32617 (0.06310)	71.868 (4.089)
1:4	99.64 (0.17)	0.72507 (0.02462)	91.328 (1.925)
1:5	100.22 (0.10)	*	92.723 (0.238)
1:10	100.24 (0.20)	0.88255 (0.09373)	92.495 (0.155)
1:20	95.17 (0.10)	0.52956 (0.02559)	90.685 (0.580)
1:5 HCTZ-PVP K-17 Physical Mixture	95.07 (0.31)	0.02465 (0.00180)	49.587 (0.840)
HCTZ-PVP K-30 Coprecipitates			
2:1	98.60 (0.19)	0.02635 (0.00100)	31.180 (3.785)
1:1	96.39 (0.15)	0.05273 (0.00321)	27.402 (7.905)
1:3	98.74 (0.17)	0.32617 (0.06310)	71.868 (4.089)
1:4	97.43 (0.11)	0.63500 (0.00882)	89.895 (0.339)
1:5	98.73 (0.75)	0.96756 (0.00165)	92.727 (0.167)
1:10	99.38 (0.88)	0.56428 (0.04934)	90.012 (0.989)
1:20	95.17 (0.01)	0.36786 (0.04238)	65.409 (13.667)
1:5 HCTZ-PVP K-30 Physical Mixture	95.04 (0.95)	0.03080 (0.00691)	32.807 (0.255)
HCTZ-PVP K-90 Coprecipitates			
2:1	95.59 (0.04)	0.11155 (0.02906)	49.046 (2.140)
1:1	96.44 (0.21)	0.29936 (0.02329)	50.772 (6.684)
1:2	99.70 (0.08)	0.26458 (0.04142)	61.855 (2.963)
1:3	95.84 (0.24)	0.26319 (0.04725)	44.331 (4.337)

Table 3 (cont.)

Preparation	% Labeled Amount[a]	Dissolution Rate Constant (min^{-1})[b]	% HCTZ Dissolved at 5 Minutes[b,c]
1:4	96.31 (0.16)	0.23943 (0.07856)	44.865 (7.556)
1:1 HCTZ-PVP K-90 Physical Mixture	97.40 (0.07)	0.03043 (0.00177)	35.182 (3.001)
HCTZ-PEG 4000 Melts			
1:10	96.10 (0.12)	0.82907 (0.09235)	96.890 (1.553)
1:20	96.51 (0.76)	0.50430 (0.00838)	86.774 (0.228)
1:10 HCTZ-PEG 4000 Physical Mixture	97.27 (0.94)	0.02760 (0.00184)	49.439 (2.657)
HCTZ-PEG 6000 Melts			
1:5	95.39 (0.23)	0.73919 (0.07618)	96.075 (1.023)
1:10	96.46 (0.28)	1.00196 (0.07031)	91.468 (0.744)
1:20	102.54 (0.19)	0.42752 (0.07824)	81.996 (3.796)
1:10 HCTZ-PEG 6000 Physical Mixture	97.27 (0.06)	0.02760 (0.00184)	47.573 (4.454)
HCTZ-PEG 20000 Melts			
1:5	99.82 (0.83)	0.18213 (0.05231)	72.406 (4.249)
1:10	97.98 (0.09)	0.28495 (0.03342)	70.240 (5.282)
1:20	96.51 (0.76)	0.13407 (0.01586)	48.293 (6.880)
1:10 HCTZ-PEG 20000 Physical Mixture	94.46 (0.86)	0.02789 (0.00260)	50.370 (1.871)
HCTZ-Urea Melts			
1:1	98.17 (0.01)	0.04628 (0.00438)	67.963 (2.733)
1:2	101.72 (0.54)	*	98.432 (0.152)
1:3	99.94 (0.30)	*	99.162 (0.205)
1:5	97.90 (0.09)	*	99.127 (0.116)
1:10	96.12 (0.29)	*	99.115 (0.239)
1:20	97.30 (0.01)	*	98.880 (0.139)
1:3 HCTZ-Urea Physical Mixture	100.40 (0.13)	0.02796 (0.00052)	39.004 (1.183)

Table 3 (cont.)

Preparation	% Labeled Amount[a]	Dissolution Rate Constant (min^{-1})[b]	% HCTZ Dissolved at 5 Minutes[b,c]
HCTZ-Urea Coprecipitates			
1:1	99.18 (0.25)	0.02094 (0.00306)	34.137 (2.469)
1:3	99.05 (0.86)	0.08944 (0.00810)	73.540 (2.238)
1:5	100.12 (0.06)	0.16372 (0.00062)	74.082 (2.023)
1:10	99.35 (0.17)	0.26481 (0.02205)	85.699 (0.561)
1:20	96.85 (0.16)	*	92.165 (1.373)

a Mean (S.D.) of two determinations

b Mean (S.D.) of three determinations

* Dissolution rate was too fast to be calculated using regression analysis

c % HCTZ dissolved at 5 minutes was shown to represent dissolution behavior of each solid dispersion since dissolution rates of some solid dispersions were too fast to be calculated.

1. HCTZ-PVP Coprecipitates

Dissolution profiles of HCTZ from HCTZ-PVP coprecipitates with various HCTZ:PVP ratios are shown in Figure 3-12 and Table 4, 7, 9. Each point represents the average value obtained for three determinations at a given sampling time. All of HCTZ-PVP coprecipitates, except those with the ratio 2:1 of HCTZ and PVP K-17, PVP K-30 or PVP K-90 and 1:1 of HCTZ and PVP K-30, exhibited faster dissolution rate than HCTZ alone and the physical mixtures. At each time interval, marked differences existed between the amount of drug in solution from coprecipitates and pure HCTZ or the physical mixtures.

Increasing in the weight fraction of PVP resulted in a corresponding increase of the dissolution rate (Table 3,5-6,8,10). Coprecipitates of HCTZ-PVP K-17, HCTZ-PVP K-30 and HCTZ-PVP K-90 exhibited fastest dissolution rates at the HCTZ:PVP ratios of 1:5, 1:5 and 1:1, respectively. With the higher weight fractions of PVP, the dissolution rates were slower. Thus, maximum drug release was achieved after 5, 10, and 20 minutes from the dispersions of 1:5 HCTZ-PVP K-17, 1:5 HCTZ-PVP K-30, and 1:1 HCTZ-PVP K-90. Additionally, it was demonstrated that the fastest dissolution rate was achieved from the 1:5 HCTZ-PVP K-17 coprecipitate (Table 11).

2. HCTZ-PEG Melts

Dissolution profiles of HCTZ-PEG melts with various HCTZ: PEG ratios are shown in Figure 13-19 and Table 12, 14, 16. All of the melts exhibited faster dissolution rate than HCTZ alone or physical mixtures. Dissolution rates of HCTZ from the melts were maximum when PEG 4000, PEG 6000 or PEG 20000 were used with the 1:10 HCTZ:PEG ratio (Table 13, 15, 17). With the higher weight fraction of PEG, the dissolution rates of the melts became slower. The 1:10 HCTZ-PEG 4000 melt exhibited the higher amount of HCTZ released at 5 minutes than either 1:10 HCTZ-PEG 6000 or 1:10 HCTZ-PEG 20000 melts (Table 18). The peak of HCTZ released from 1:10 HCTZ-PEG 4000 melt obtained within 10 minutes of dissolution.

3. HCTZ-Urea Melts and Coprecipitates

Dissolution profiles of HCTZ-urea solid dispersions prepared by two methods, melting and solvent, with various HCTZ:urea ratios are shown in Figure 20-24 and Table 19, 21. The melts and coprecipitates of all HCTZ:urea ratios except 1:1, exhibited faster dissolution rates than HCTZ alone or physical mixtures (Table 20). The peaks of HCTZ dissolved from melts with 1:2 HCTZ:urea ratio or with higher urea weight fractions were achieved after 5 minutes of disolution. Increasing the weight fraction of urea markedly increased dissolution rates of the coprecipitates (Table 22). It should be noted that all of the melts exhibited faster dissolution rates than the coprecipitates with the same HCTZ:urea ratio (Table 23).

The comparison between percentage of HCTZ dissolved at 5 minutes of the 1:5 HCTZ-PVP K-17 coprecipitate, the 1:10 HCTZ-PEG 4000 melt, and the 1:3 HCTZ-urea melt is shown in Figure 25 and Table 24. The percentage amount of drug dissolved from the melts of HCTZ-PEG 4000 and HCTZ-urea were significantly higher than that from the HCTZ-PVP K-17 coprecipitate. However, the significant difference between the two melts was not found.

The physical mixtures of all carriers except 1:5 HCTZ-PVP K-17 physical mixture did not exhibit dissolution rate significantly different from pure HCTZ (Table 25).

Table 4 Dissolution of HCTZ from HCTZ-PVP K-17 Coprecipitates with Various HCTZ K-17 Ratios (1:0, 2:1, 1:1, 1:3, 1:4, 1:5, 1:10, 1:20) and Physical Mixture.

Time (min)	Percentage Amount of HCTZ Dissolved[a]								
	1:0	2:1	1:1	1:3	1:4	1:5	1:10	1:20	1:5 PM[b]
0	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)
2	8.005 (1.186)	6.713 (0.333)	9.831 (0.939)	19.684 (4.962)	47.586 (3.151)	59.506 (3.621)	52.968 (2.209)	35.030 (0.840)	23.313 (2.867)
5	22.703 (1.699)	18.380 (5.495)	46.924 (2.343)	71.868 (4.089)	91.328 (1.925)	92.723 (0.238)	92.495 (0.155)	90.685 (0.580)	49.587 (0.840)
10	41.403 (2.216)	28.713 (6.521)	79.804 (0.391)	94.397 (2.585)	94.086 (1.713)	92.502 (0.333)	93.868 (0.690)	98.239 (0.365)	51.439 (0.929)
15	53.151 (0.885)	34.158 (6.338)	86.158 (1.133)	98.555 (0.805)	93.975 (1.619)	92.282 (0.429)	93.209 (0.102)	98.011 (0.373)	52.596 (1.492)
20	60.722 (1.358)	37.269 (5.641)	90.640 (0.940)	99.652 (0.199)	93.699 (1.524)	91.732 (0.525)	92.769 (0.090)	97.500 (0.287)	53.522 (1.993)
25	64.834 (1.852)	40.213 (5.530)	92.244 (1.118)	99.247 (0.387)	93.369 (1.654)	91.182 (0.335)	92.220 (0.101)	96.932 (0.227)	54.390 (2.716)
30	67.356 (2.515)	42.713 (5.333)	92.907 (1.028)	98.612 (0.197)	92.762 (1.428)	90.742 (0.526)	91.726 (0.101)	96.364 (0.364)	55.084 (2.841)
45	71.798 (2.906)	50.102 (5.987)	93.404 (0.863)	98.034 (0.261)	92.265 (1.557)	90.467 (0.432)	91.232 (0.101)	95.967 (0.287)	57.283 (3.795)
60	74.265 (2.680)	55.491 (6.019)	92.963 (0.883)	97.687 (0.214)	91.989 (1.332)	90.467 (0.432)	91.122 (0.091)	95.456 (0.287)	59.656 (4.604)
90	78.542 (2.344)	64.213 (6.058)	92.632 (1.001)	97.456 (0.189)	91.658 (1.311)	89.697 (0.338)	90.628 (0.091)	94.888 (0.280)	64.227 (5.656)
120	81.998 (2.090)	74.325 (3.384)	92.190 (0.940)	96.820 (0.418)	91.327 (1.176)	89.367 (0.338)	90.079 (0.100)	94.547 (0.279)	67.931 (6.937)

a Mean (S.D.) of three determinations

b Physical Mixture

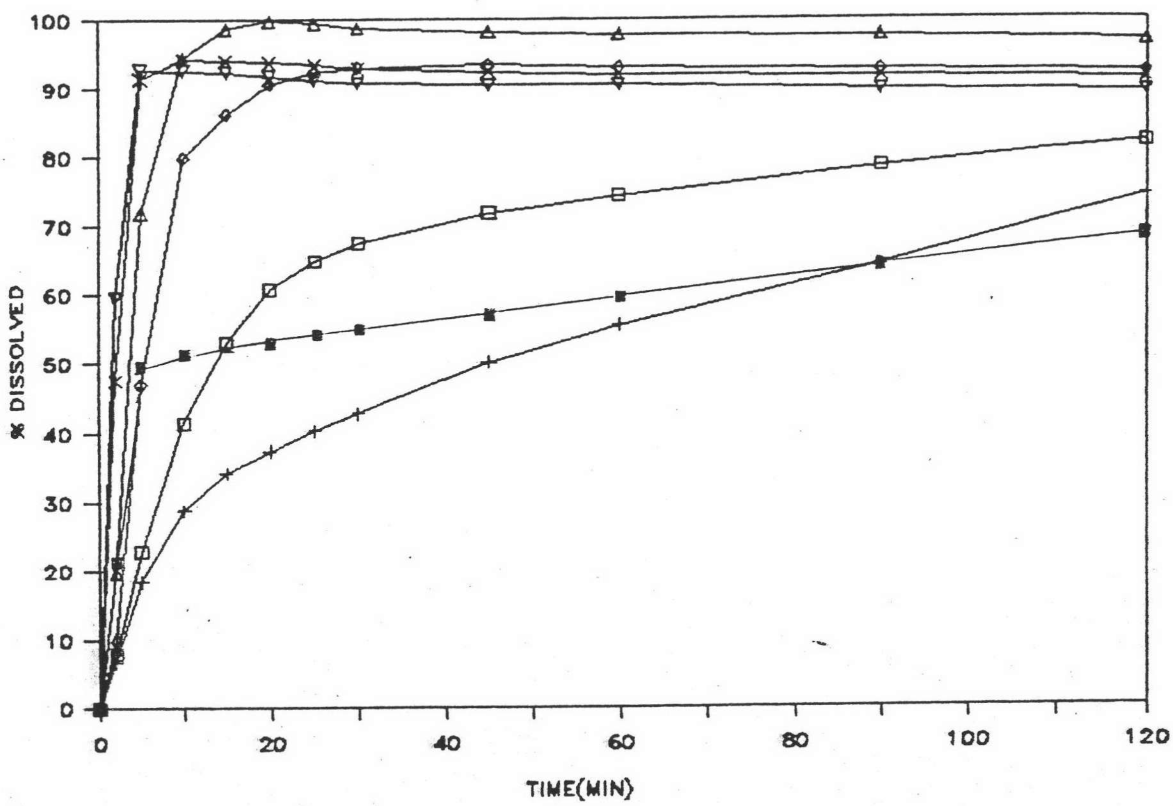

Figure 3 Dissolution profiles of HCTZ from HCTZ-PVP K-17 coprecipitates with various HCTZ:PVP K-17 ratios (□ 1:0, + 2:1, ◇ 1:1, △ 1:3, × 1:4, ▽ 1:5, ■ 1:5 physical mixture).

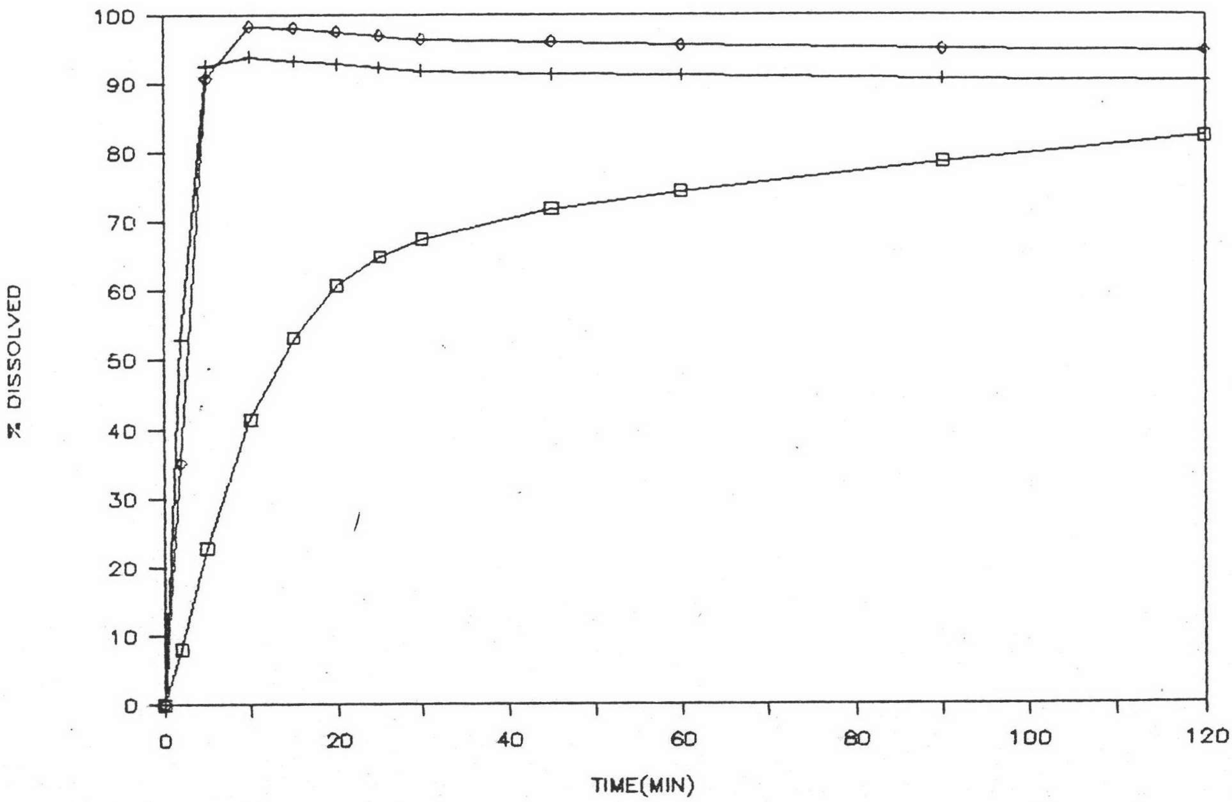

Figure 4 Dissolution profiles of HCTZ from HCTZ-PVP K-17 coprecipitates with various HCTZ-PVP K-17 ratios (□ 1:0, + 1:10, ◇ 1:20).

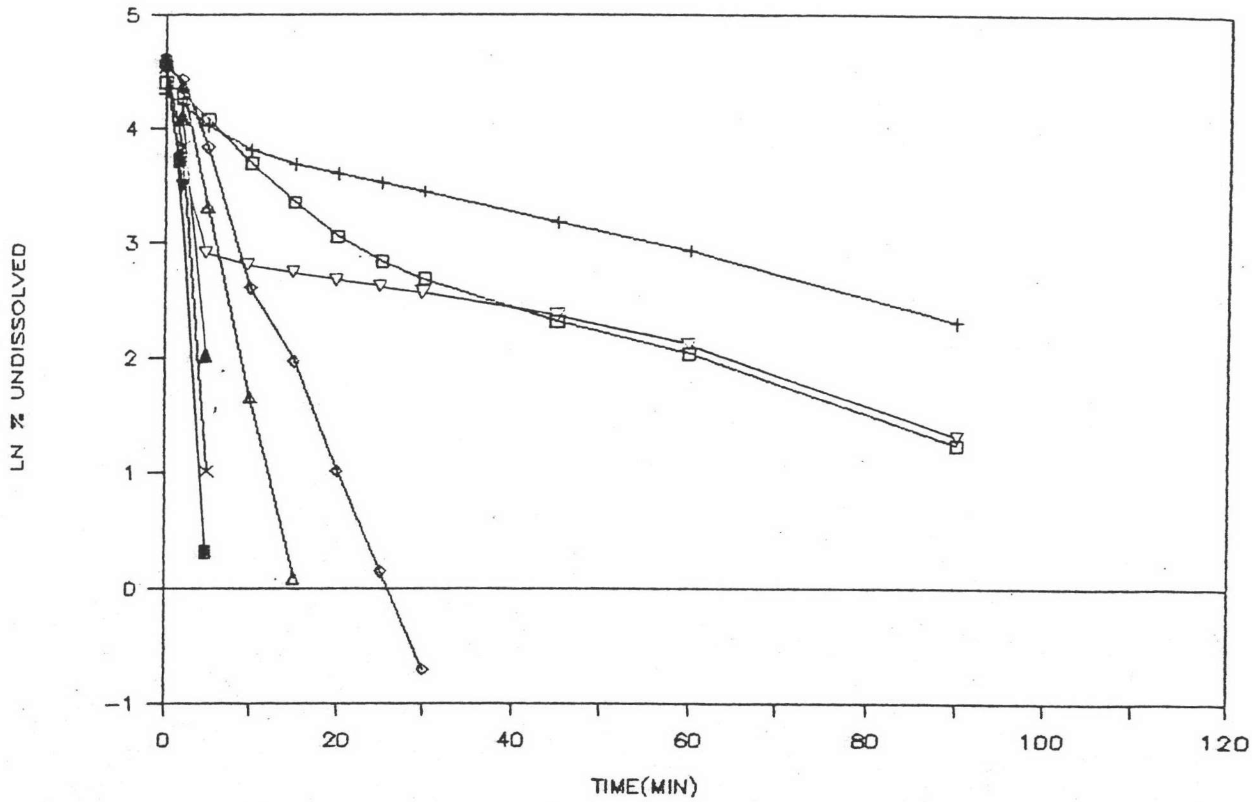

Figure 5 The first order plot between ln % HCTZ undissolved versus time for HCTZ-PVP K-17 coprecipitates with various HCTZ:PVP K-17 ratios (□ 1:0, + 2:1, ◇ 1:1, △ 1:3, × 1:4, ▼ 1:5, ■ 1:10, ▲ 1:20, ▽ 1:5 physical mixture).

Table 5 Multiple Comparison (HSD Test) for Dissolution Rate Constants of HCTZ-PVP K-17 Coprecipitates with Various HCTZ:PVP K-17 Ratios.

A \ B	1:0	2:1	1:1	1:3	1:4	1:10	1:20
1:0	-	NS	@	@	@	@	@
2:1	NS	-	@	@	@	@	@
1:1	*	*	-	@	@	@	@
1:3	*	*	*	-	@	@	@
1:4	*	*	*	*	-	@	*
1:10	*	*	*	*	*	-	*
1:20	*	*	*	*	@	@	-

$q_{0.05,7,14} = 4.83$, HSD = 0.1254

NS not significantly different, $\alpha = 0.05$

@ A is significantly less than B, $\alpha = 0.05$

* A is significantly more than B, $\alpha = 0.05$

Table 6 Multiple Comparison (HSD Test) for Percentage Amount of HCTZ Dissolved at 5 minutes of HCTZ-PVP K-17 Coprecipitates with Various HCTZ:PVP K-17 Ratios.

A \ B	1:0	2:1	1:1	1:3	1:4	1:5	1:10	1:20
1:0	-	NS	@	@	@	@	@	@
2:1	NS	-	@	@	@	@	@	@
1:1	*	*	-	@	@	@	@	@
1:3	*	*	*	-	@	@	@	@
1:4	*	*	*	*	-	NS	NS	NS
1:5	*	*	*	*	NS	-	NS	NS
1:10	*	*	*	*	NS	NS	-	NS
1:20	*	*	*	*	NS	NS	NS	-

$q_{0.05,8,16}$ = 4.9, HSD = 7.7473

NS not significantly different, $\alpha = 0.05$

@ A is significantly less than B, $\alpha = 0.05$

* A is significantly more than B, $\alpha = 0.05$

Table 7 Dissolution of HCTZ from HCTZ-PVP K-30 Coprecipitates with Various HCTZ-PVP K-30 Ratios (1:0, 2:1, 1:1, 1:3, 1:4, 1:5, 1:10, 1:20) and 1:5 Physical Mixture.

Time (min)	Percentage Amount of HCTZ Dissolved[a]								
	1:0	2:1	1:1	1:3	1:4	1:5	1:10	1:20	1:5 PM[b]
0	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)
2	8.005 (1.186)	8.568 (1.220)	8.481 (2.015)	19.684 (4.962)	41.411 (0.678)	58.041 (2.725)	11.250 (1.349)	10.402 (2.955)	3.347 (0.170)
5	22.703 (1.699)	31.180 (3.785)	27.402 (7.905)	71.868 (4.089)	89.895 (0.339)	92.727 (0.167)	90.012 (0.989)	65.409 (13.667)	32.807 (0.255)
10	41.403 (2.216)	43.703 (5.107)	61.575 (2.689)	94.397 (2.585)	94.190 (0.518)	93.563 (0.167)	96.657 (0.666)	94.216 (2.023)	44.326 (1.614)
15	53.151 (0.885)	48.878 (3.832)	74.902 (0.529)	98.555 (0.805)	94.077 (0.545)	93.173 (0.348)	96.273 (0.718)	96.877 (1.257)	47.393 (1.291)
20	60.722 (1.358)	51.885 (3.554)	82.137 (0.637)	99.652 (0.199)	93.625 (0.587)	92.559 (0.290)	95.669 (0.907)	97.224 (0.612)	50.228 (1.368)
25	64.834 (1.852)	53.723 (3.063)	85.612 (0.913)	99.247 (0.387)	93.060 (0.685)	92.113 (0.538)	95.174 (0.761)	96.819 (0.376)	52.079 (1.983)
30	67.356 (2.515)	55.672 (2.968)	87.150 (1.420)	98.612 (0.197)	92.721 (0.870)	91.444 (0.256)	94.570 (0.813)	96.357 (0.473)	53.699 (2.812)
45	71.798 (2.906)	60.628 (3.942)	91.138 (2.363)	98.034 (0.261)	92.382 (0.706)	90.998 (0.348)	94.570 (0.813)	96.125 (0.376)	56.824 (3.288)
60	74.265 (2.680)	66.192 (6.007)	94.272 (1.365)	97.687 (0.214)	91.986 (0.853)	90.496 (0.256)	94.296 (0.285)	95.431 (0.368)	59.660 (3.613)
90	78.542 (2.344)	72.537 (7.873)	96.435 (0.819)	97.456 (0.189)	91.590 (0.739)	91.165 (0.256)	93.362 (0.761)	94.968 (0.312)	63.538 (2.802)
120	81.998 (2.090)	78.106 (8.046)	97.233 (1.019)	96.820 (0.418)	91.308 (0.853)	91.109 (0.921)	93.197 (0.624)	94.506 (0.270)	66.954 (2.130)

a Mean (S.D.) of three determinations

b Physical mixture

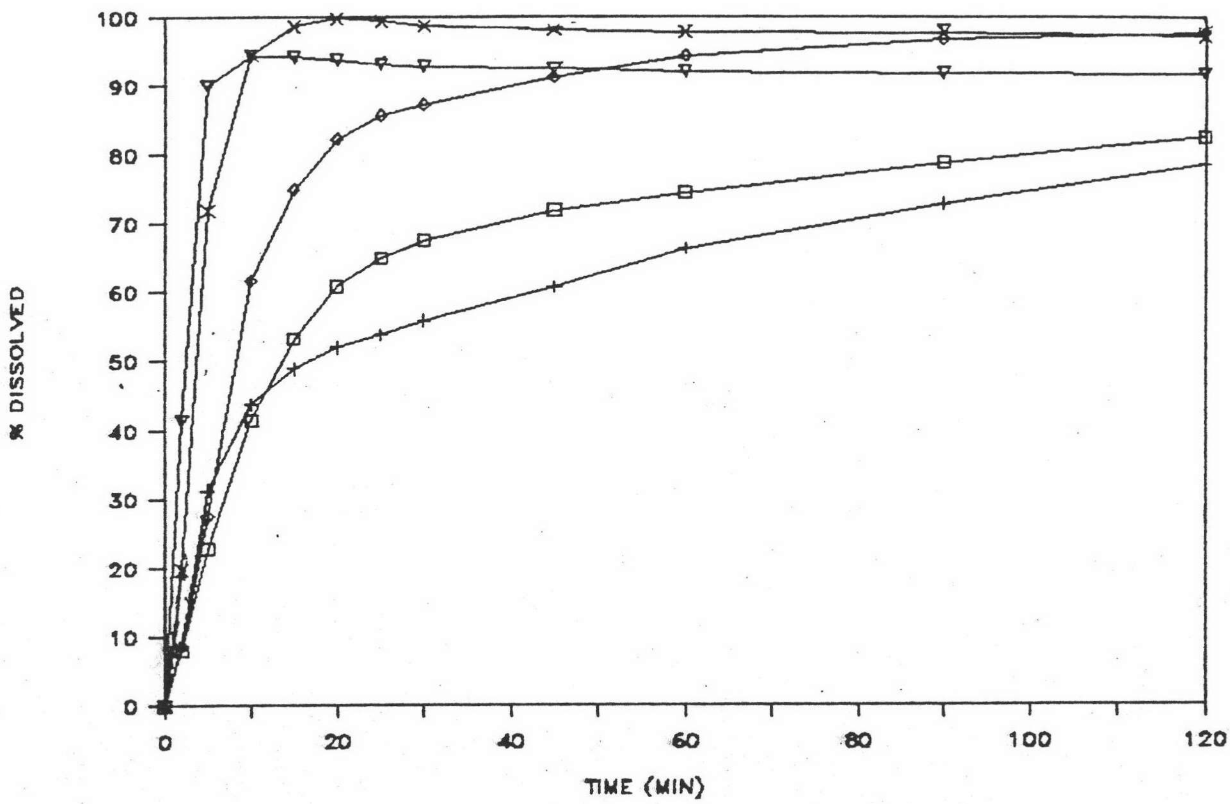

Figure 6 Dissolution profiles of HCTZ from HCTZ-PVP K-30 coprecipitates with various HCTZ:PVP K-30 ratios (□ 1:0, + 2:1, ◇ 1:1, × 1:3, ▽ 1:4).

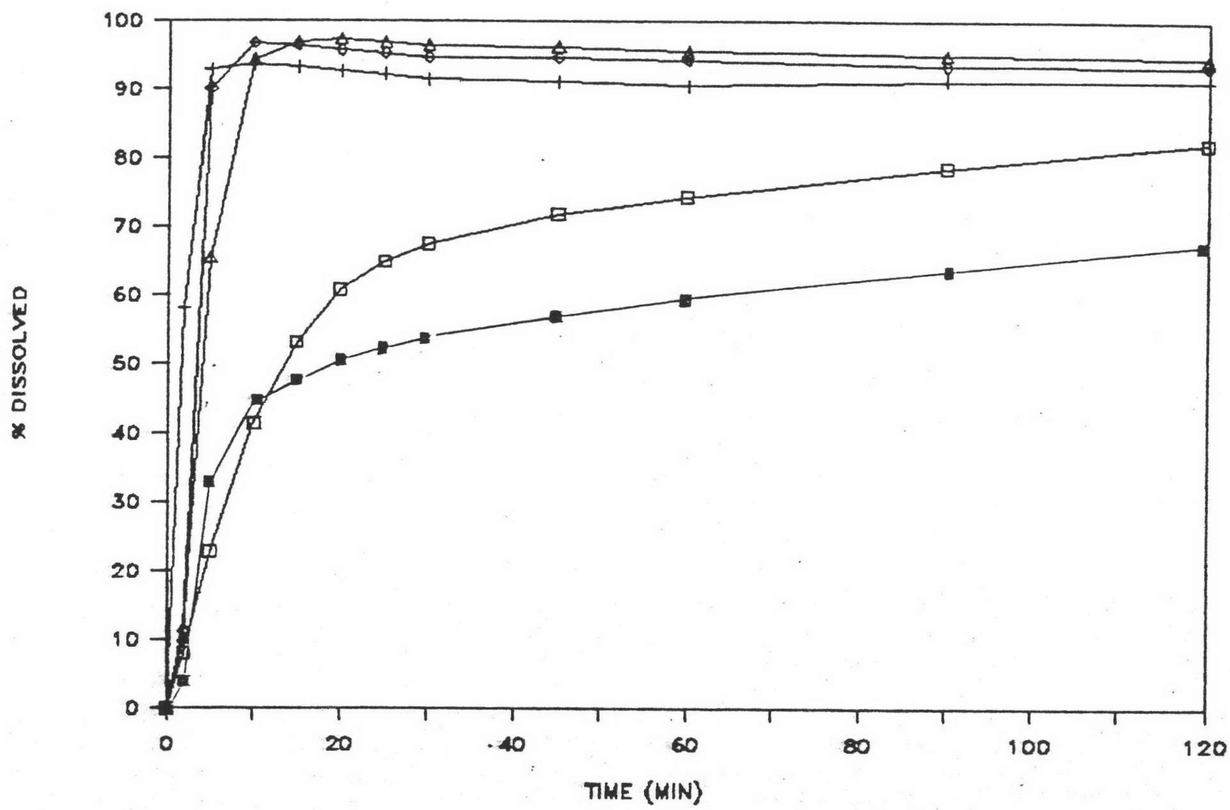

Figure 7 Dissolution profiles of HCTZ from HCTZ-PVP K-30 coprecipitates with various HCTZ:PVP K-30 ratios (□ 1:0, + 1:5, ◇ 1:10, △ 1:20, ■ 1:5 physical mixture).

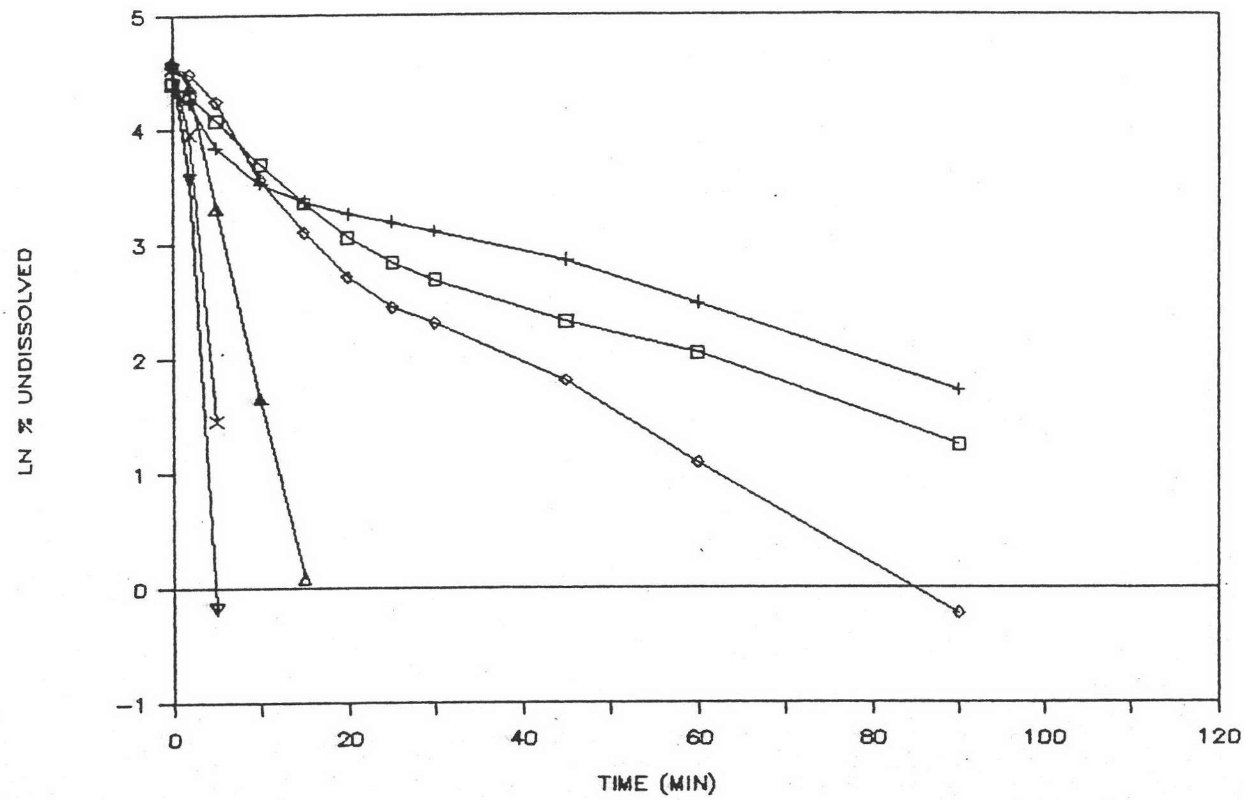

Figure 8 The first order plot between ln % HCTZ undissolved versus time for HCTZ-PVP K-30 coprecipitates with various HCTZ:PVP K-30 ratios (□ 1:0, + 2:1, ◇ 1:1, △ 1:3, × 1:4, ▽ 1:5).

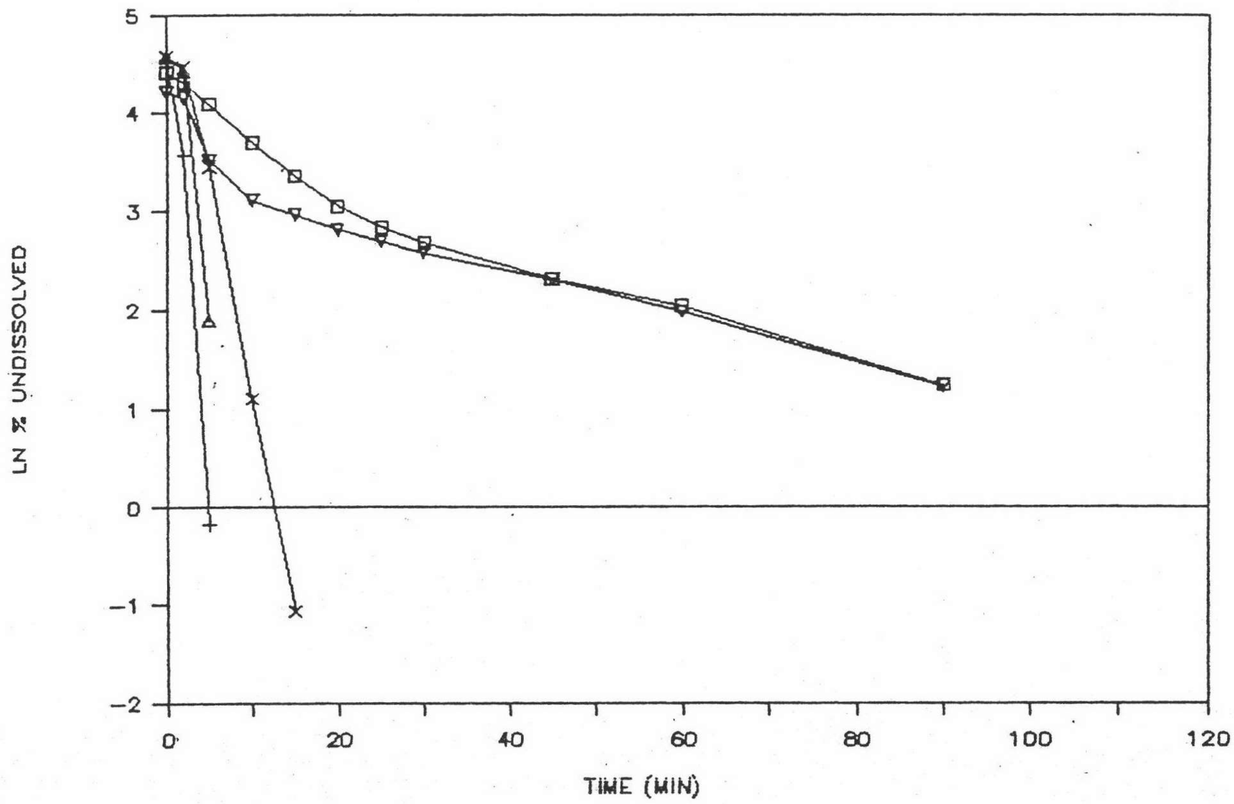

Figure 9 The first order plot between ln % HCTZ undissolved versus time for HCTZ-PVP K-30 coprecipitates with various HCTZ:PVP K-30 ratios (□ 1:0, + 1:5, △ 1:10, × 1:20, ▽ 1:5 physical mixture).

Table 8 Multiple Comparison (HSD Test) for Dissolution Rate Constants of HCTZ-PVP K-30 Coprecipitates with Various HCTZ:PVP K-30 Ratios.

A \ B	1:0	2:1	1:1	1:3	1:4	1:5	1:10	1:20
1:0	-	NS	NS	@	@	@	@	@
2:1	NS	-	NS	@	@	@	@	@
1:1	NS	NS	-	@	@	@	@	@
1:3	*	*	*	-	@	@	@	NS
1:4	*	*	*	*	-	@	NS	*
1:5	*	*	*	*	*	-	*	*
1:10	*	*	*	*	NS	@	-	*
1:20	*	*	*	NS	@	@	@	-

$q_{0.05,8,16}$ = 4.9, HCTZ = 0.09117

NS not significantly different, α = 0.05

@ A is significantly less than B, α = 0.05

* A is significantly more than B, α = 0.05

Table 9 Dissolution of HCTZ from HCTZ-PVP K-90 Coprecipitates with Various HCTZ:PVP K-90 Ratios (1:0, 2:1, 1:1, 1:2, 1:3, 1:4) and 1:1 Physical Mixture.

Time	Percentage Amount of HCTZ Dissolved[a]						
(min)	1:0	2:1	1:1	1:2	1:3	1:4	1:1 PM[b]
0	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)
2	8.005 (1.186)	21.248 (3.167)	13.161 (3.516)	22.527 (2.644)	7.268 (1.009)	9.880 (0.551)	12.291 (9.011)
5	22.703 (1.699)	49.046 (2.140)	50.772 (6.684)	61.855 (2.963)	44.331 (4.337)	44.865 (7.556)	35.182 (3.001)
10	41.403 (2.216)	67.220 (0.564)	84.227 (1.151)	80.526 (2.847)	72.902 (4.511)	73.848 (10.750)	49.306 (0.995)
15	53.151 (0.885)	76.910 (0.641)	93.574 (0.490)	84.226 (1.279)	83.056 (1.986)	84.481 (7.951)	54.011 (1.136)
20	60.722 (1.358)	81.727 (1.509)	94.714 (0.075)	86.491 (0.028)	87.531 (0.352)	89.511 (3.516)	56.736 (1.958)
25	64.834 (1.852)	84.137 (2.138)	94.201 (0.074)	86.270 (0.226)	88.449 (0.190)	92.313 (0.748)	59.056 (1.410)
30	67.356 (2.515)	85.341 (2.314)	93.745 (0.173)	86.160 (0.144)	87.990 (0.122)	93.056 (0.990)	60.815 (1.844)
45	71.798 (2.906)	86.829 (1.549)	93.346 (0.071)	85.939 (0.068)	87.646 (0.122)	93.056 (0.880)	63.992 (2.216)
60	74.265 (2.680)	87.800 (0.769)	92.719 (0.029)	85.773 (0.068)	87.302 (0.091)	92.999 (0.907)	67.895 (0.980)
90	78.542 (2.344)	87.629 (0.953)	92.491 (0.069)	85.442 (0.068)	86.958 (0.260)	92.827 (0.786)	70.856 (3.304)
120	81.998 (2.090)	86.940 (0.622)	92.149 (0.068)	85.331 (0.418)	86.728 (0.174)	92.770 (0.810)	74.770 (3.885)

a Mean (S.D.) of three determinations

b Physical mixture

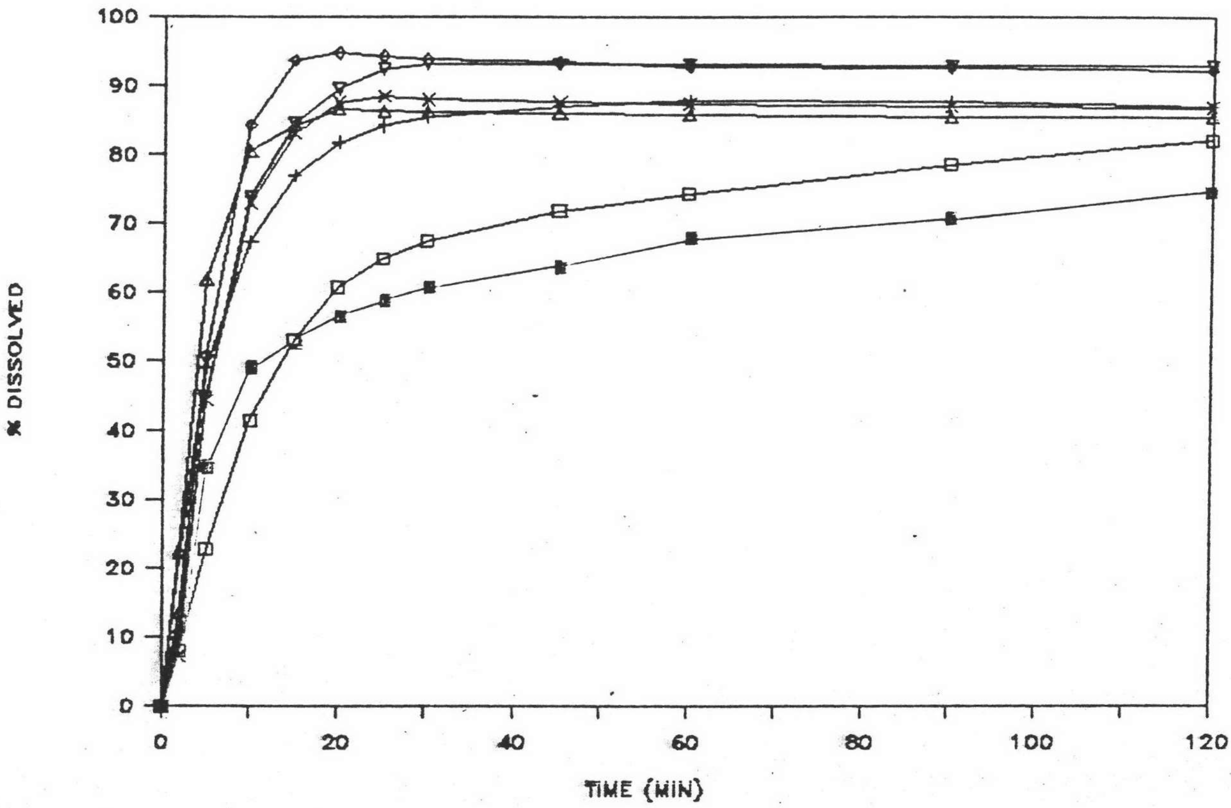

Figure 10 Dissolution profiles of HCTZ from HCTZ-PVP K-90 coprecipitates with various HCTZ:PVP K-90 ratios (□ 1:0, + 2:1, ◇ 1:1, △ 1:2, × 1:3, ▽ 1:4, ■ 1:1 physical mixture).

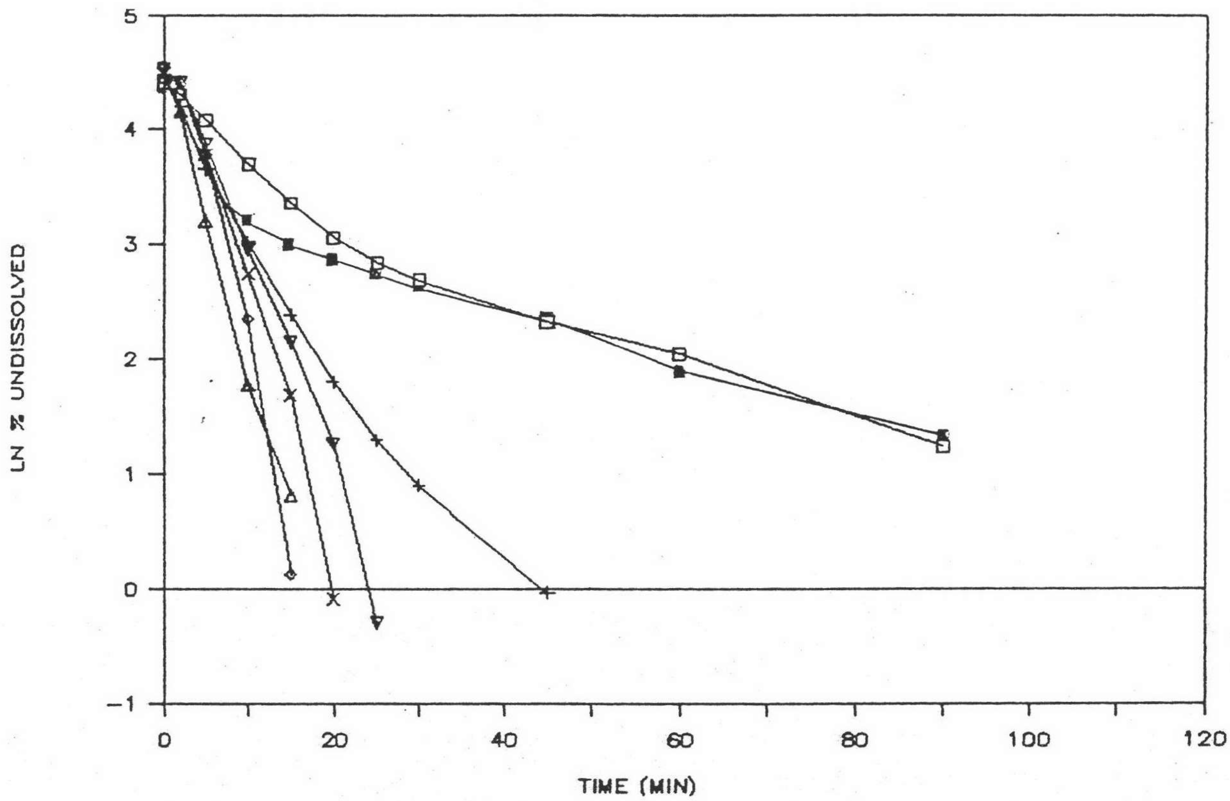

Figure 11 The first order plot between ln % HCTZ undissolved versus time for HCTZ-PVP K-90 coprecipitates with various HCTZ:PVP K-90 ratios (□ 1:0, + 2:1, ◇ 1:1, △ 1:2, × 1:3, ▽ 1:4, ■ 1:1 physical mixture).

Table 10 Multiple Comparison (HSD Test) for Dissolution Rate Constants of HCTZ-PVP K-90 Coprecipitates with Various HCTZ:PVP K-90 Ratios (1:0, 2:1, 1:1, 1:2, 1:3, 1:4).

A \ B	1:0	2:1	1:1	1:2	1:3	1:4
1:0	-	NS	@	@	@	@
2:1	NS	-	@	@	@	NS
1:1	*	*	-	NS	NS	NS
1:2	*	*	NS	-	NS	NS
1:3	*	*	NS	NS	-	NS
1:4	*	NS	NS	NS	NS	-

$q_{0.05,6,12} = 4.75$, HSD = 0.1085

NS not significantly different, $\alpha = 0.05$

@ A is significantly less than B, $\alpha = 0.05$

* A is significantly more than B, $\alpha = 0.05$

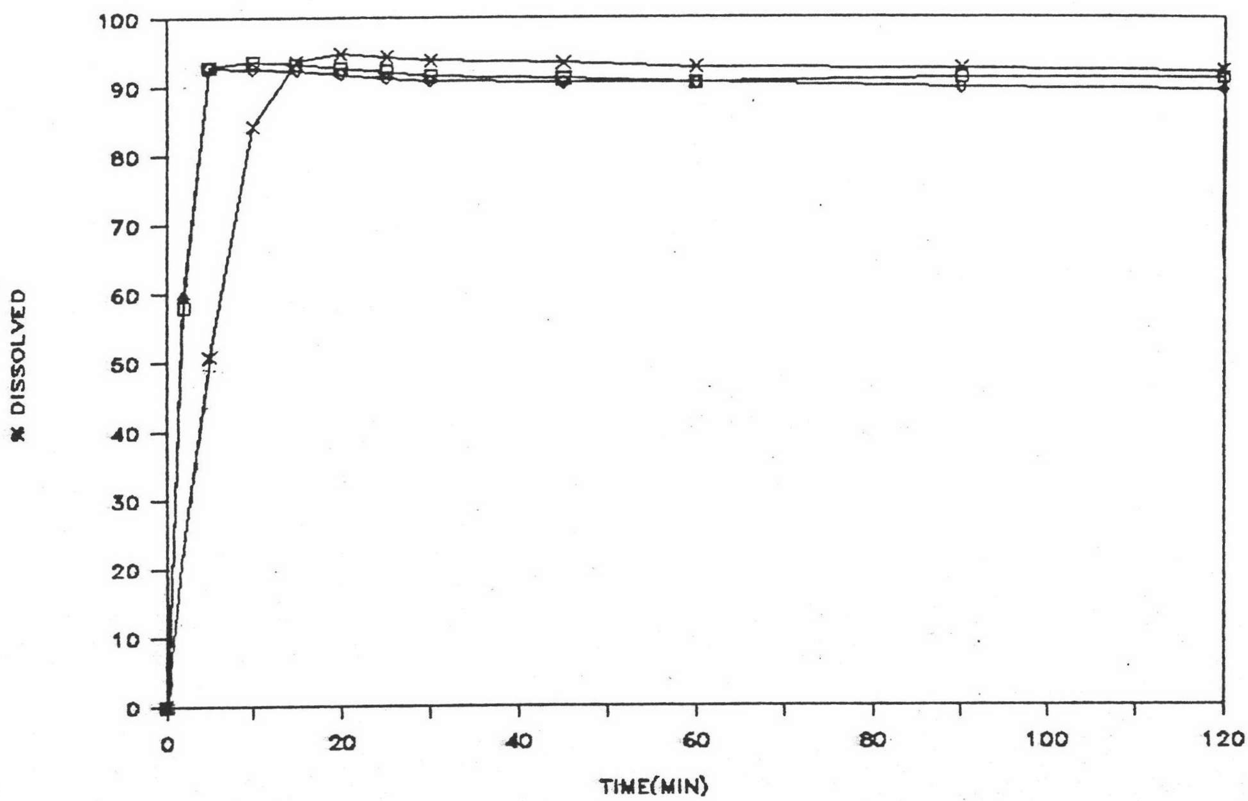

Figure 12 Dissolution profiles of HCTZ from HCTZ-PVP coprecipitates with optimum HCTZ:PVP ratio (◇ 1:5 HCTZ-PVP K-17, □ 1:5 HCTZ-PVP K-30, X 1:1 HCTZ-PVP K-90).

Table 11 Multiple Comparison (HSD Test) for Percentage Amount of HCTZ Dissolved at 5 Minutes of 1:5 HCTZ-PVP K-17 (a), 1:5 HCTZ-PVP K-30 (b) and 1:1 HCTZ-PVP K-90 (c) Coprecipitates.

A \ B	a	b	c
a	-	NS	*
b	NS	-	*
c	@	@	-

$q_{0.05,3,6} = 4.34$, HSD = 0.1342

NS not significantly different, $\alpha = 0.05$

@ A is significantly less than B, $\alpha = 0.05$

* A is significantly more than B, $\alpha = 0.05$

Table 12 Dissolution of HCTZ from HCTZ-PEG 4000 Melts with Various HCTZ:PEG 4000 Ratios (1:0, 1:10, 1:20) and 1:10 Physical Mixture.

Time (min)	Percentage Amount of HCTZ Dissolved[a]			
	1:0	1:10	1:20	1:10 PM[b]
0	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)
2	8.005 (1.186)	73.476 (6.241)	42.943 (0.801)	23.187 (0.974)
5	22.703 (1.699)	96.890 (1.553)	86.774 (0.228)	49.439 (2.657)
10	41.403 (2.216)	98.601 (1.235)	94.583 (0.466)	58.208 (1.926)
15	53.151 (0.885)	98.104 (1.234)	94.638 (0.123)	61.376 (2.118)
20	60.722 (1.358)	97.718 (1.200)	94.088 (0.314)	63.243 (2.228)
25	64.834 (1.852)	97.055 (1.178)	93.428 (0.030)	64.318 (2.229)
30	67.356 (2.515)	96.558 (1.178)	93.098 (0.193)	65.619 (2.209)
45	71.798 (2.906)	96.227 (1.357)	92.878 (0.221)	69.467 (2.300)
60	74.265 (2.680)	96.061 (1.177)	92.713 (0.479)	72.465 (2.506)
90	78.542 (2.344)	95.620 (1.425)	91.998 (0.083)	77.670 (2.822)
120	81.998 (2.090)	95.068 (1.176)	91.559 (0.063)	81.744 (2.805)

a Mean (S.D.) of three determinations

b Physical mixture

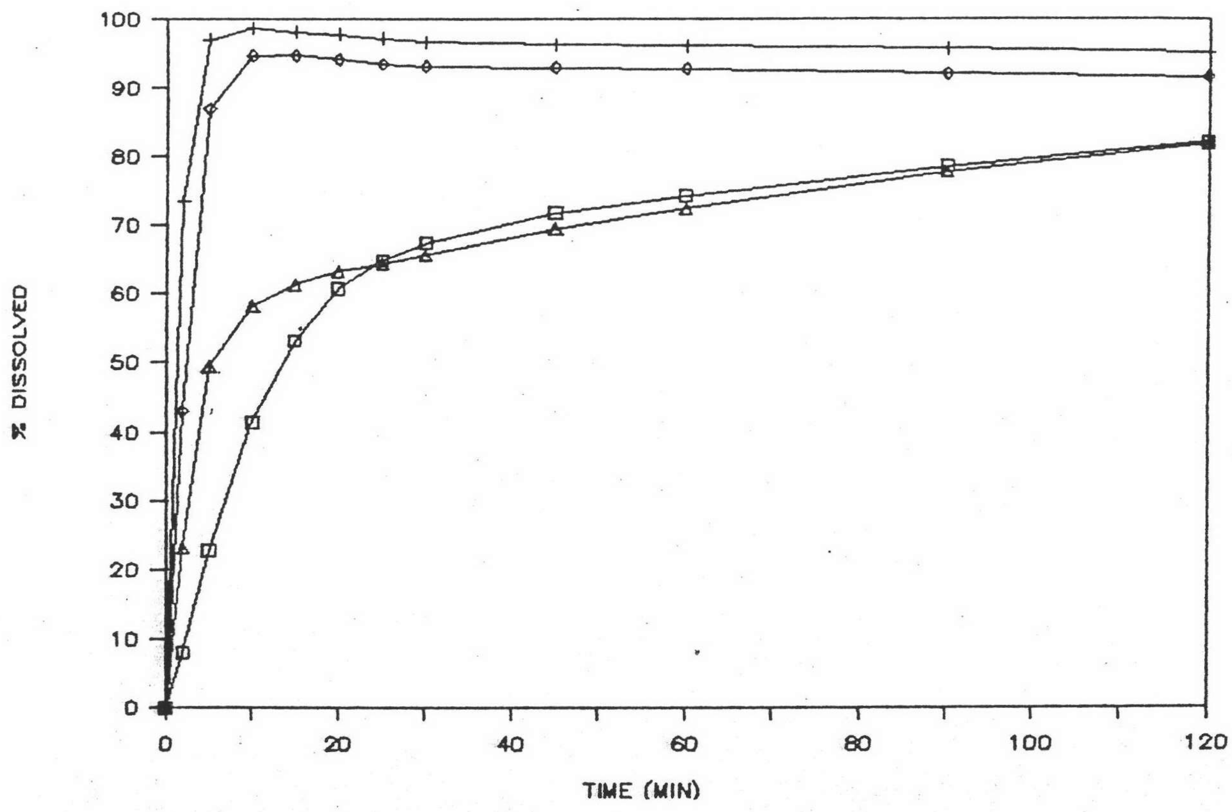

Figure 13 Dissolution profiles of HCTZ from HCTZ-PEG 4000 melts with various HCTZ:PEG 4000 ratios (□ 1:0, + 1:10, ◊ 1:20, △ 1:10 physical mixture).

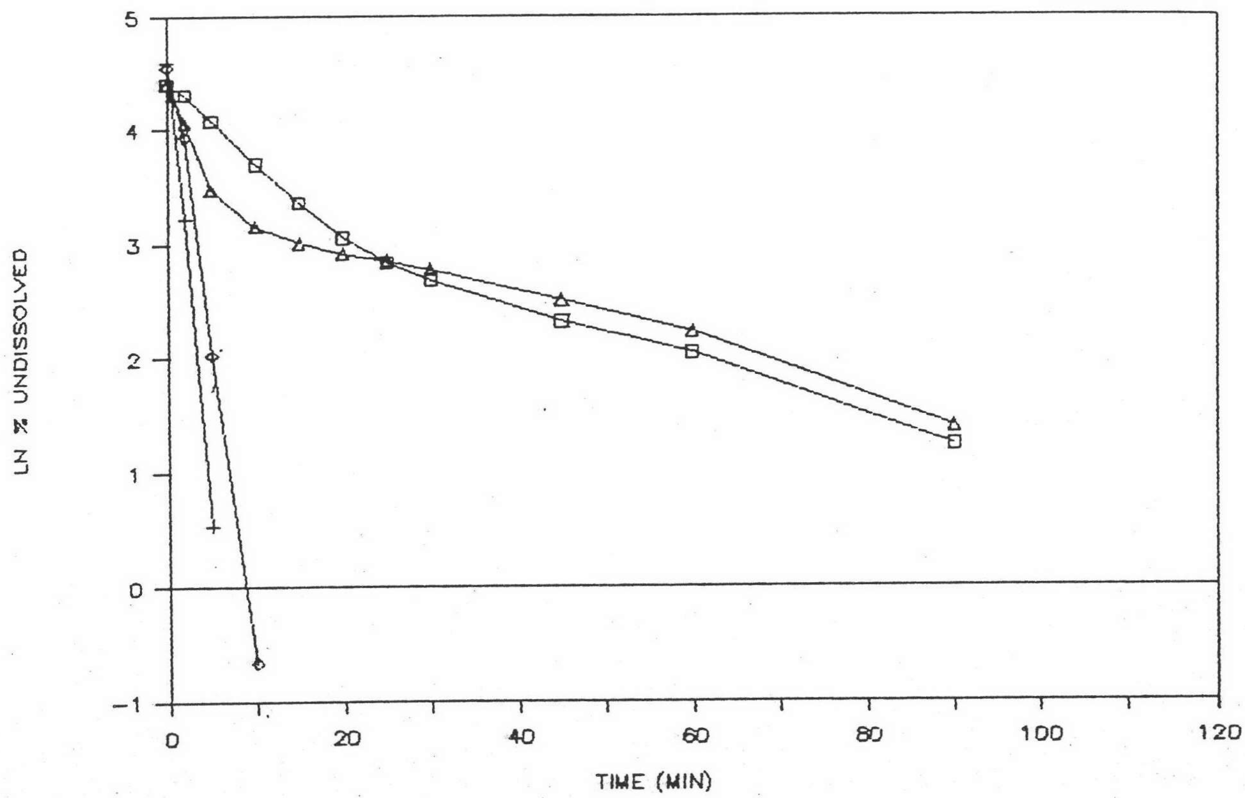

Figure 14 The first order plot between ln % HCTZ undissolved versus time for HCTZ-PEG 4000 melts with various HCTZ:PEG 4000 ratios (□ 1:0, + 1:10, ◊ 1:20, △ 1:10 physical mixture).

Table 13 Multiple Comparison (HSD Test) for Dissolution Rate Constants of HCTZ-PEG 4000 Melts with Various HCTZ:PEG 4000 Ratios (1:0, 1:10, 1:20).

A \ B	1:0	1:10	1:20
1:0	-	@	@
1:10	*	-	*
1:20	*	@	-

$q_{0.05,3,6}$ = 4.34, HSD = 0.1342

NS not significantly different, $\alpha = 0.05$

@ A is significantly less than B, $\alpha = 0.05$

* A is significantly more than B, $\alpha = 0.05$

Table 14 Dissolution of HCTZ from HCTZ-PEG 6000 Melts with Various HCTZ:PEG 6000 Ratios (1:0, 1:5, 1:10, 1:20) and 1:10 Physical Mixture.

Time	Percentage Amount of HCTZ Dissolved[a]				
(min)	1:0	1:5	1:10	1:20	1:10 PM[b]
0	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)
2	8.005 (1.187)	56.683 (5.264)	61.177 (8.218)	45.847 (2.059)	21.207 (0.844)
5	22.703 (1.699)	96.075 (1.023)	91.468 (0.744)	81.996 (3.796)	47.573 (4.454)
10	41.403 (2.216)	98.843 (0.121)	92.184 (0.512)	91.919 (0.865)	57.020 (2.537)
15	53.151 (0.885)	98.728 (0.315)	92.074 (0.577)	93.099 (0.313)	61.036 (5.534)
20	60.722 (1.358)	98.381 (0.337)	91.964 (0.606)	92.402 (0.479)	63.356 (5.946)
25	64.834 (1.852)	97.920 (0.248)	91.633 (0.458)	91.758 (0.682)	65.732 (5.811)
30	67.356 (2.515)	97.459 (0.266)	91.138 (0.458)	91.222 (0.198)	67.203 (6.021)
45	71.798 (2.906)	96.997 (0.168)	90.917 (0.314)	91.061 (0.120)	71.898 (6.677)
60	74.265 (2.680)	96.478 (0.168)	90.752 (0.418)	90.256 (0.079)	74.501 (6.193)
90	78.542 (2.344)	96.305 (0.601)	90.422 (0.267)	90.042 (0.106)	77.500 (5.338)
120	81.998 (2.090)	95.383 (0.059)	90.163 (0.455)	89.613 (0.308)	79.254 (4.305)

a Mean (S.D.) of three determinations

b Physical mixture

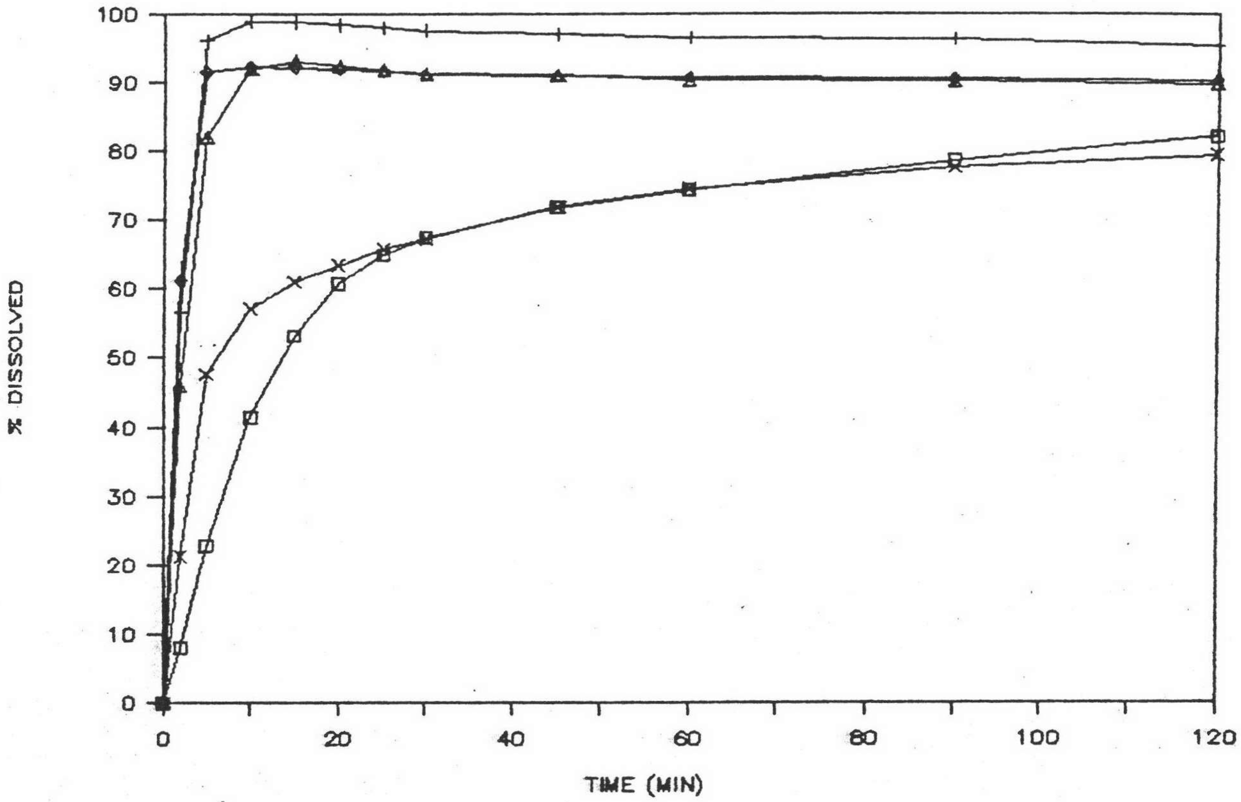

Figure 15 Dissolution profiles of HCTZ from HCTZ-PEG 6000 melts with various HCTZ:PEG 6000 ratios (□ 1:0, + 1:5, ◊ 1:10, △ 1:20, × 1:10 physical mixture).

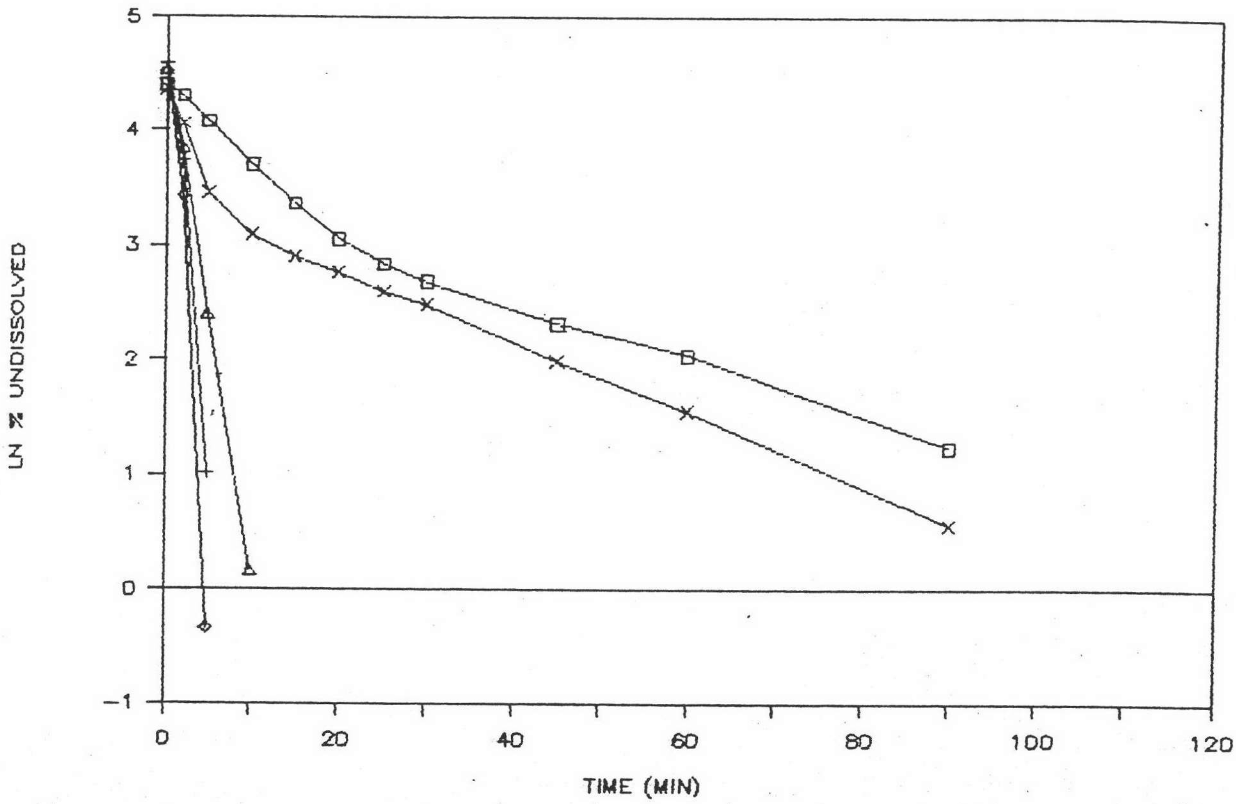

Figure 16 The first order plot between ln % HCTZ undissolved versus time for HCTZ-PEG 6000 melts with various HCTZ:PEG 6000 ratios (□ 1:0, + 1:5, ◇ 1:10, △ 1:20, × 1:10 physical mixture).

Table 15 Multiple Comparison (HSD Test) for Dissolution Rate Constants of HCTZ-PEG 6000 Melts with Various HCTZ:PEG 6000 Ratios (1:0, 1:5, 1:10, 1:20).

A \ B	1:0	1:5	1:10	1:20
1:0	-	@	@	@
1:5	*	-	@	*
1:10	*	*	-	*
1:20	*	@	@	-

$q_{0.05,4,8}$ = 4.53, HSD = 0.1699

NS not significantly different, $\alpha = 0.05$

@ A is significantly less than B, $\alpha = 0.05$

* A is significantly more than B, $\alpha = 0.05$

Table 16 Dissolution of HCTZ from HCTZ-PEG 20000 Melts with Various HCTZ:PEG 20000 Ratios (1:0, 1:5, 1:10, 1:20) and 1:10 Physical Mixture.

Time	Percentage Amount of HCTZ Dissolved[a]				
(min)	1:0	1:5	1:10	1:20	1:10 PM[b]
0	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)
2	8.005 (1.186)	31.436 (3.902)	28.769 (1.775)	21.643 (0.455)	13.925 (2.041)
5	22.703 (1.699)	72.406 (4.249)	70.240 (5.282)	48.293 (6.880)	50.370 (1.871)
10	41.403 (2.216)	83.531 (2.494)	85.340 (0.921)	61.097 (7.766)	61.040 (2.194)
15	53.151 (0.885)	86.779 (3.661)	91.554 (0.268)	74.287 (4.347)	64.481 (0.372)
20	60.722 (1.358)	90.359 (2.135)	92.916 (0.355)	84.565 (3.364)	66.347 (1.246)
25	64.834 (1.852)	93.940 (0.441)	92.644 (0.540)	90.170 (2.061)	67.688 (1.511)
30	67.356 (2.515)	93.830 (0.303)	92.262 (0.488)	92.588 (1.281)	68.913 (1.512)
45	71.798 (2.906)	93.609 (0.336)	91.826 (0.393)	93.248 (0.175)	72.645 (1.414)
60	74.265 (2.680)	93.004 0.357)	91.554 (0.298)	92.534 (0.253)	76.202 (1.657)
90	78.542 (2.344)	92.453 (0.533)	90.954 (0.356)	92.369 (0.089)	82.149 (1.970)
120	81.998 (2.090)	92.178 (0.624)	90.627 (0.353)	92.094 (0.196)	86.581 (2.091)

a Mean (S.D.) of three determinations

b Physical mixture

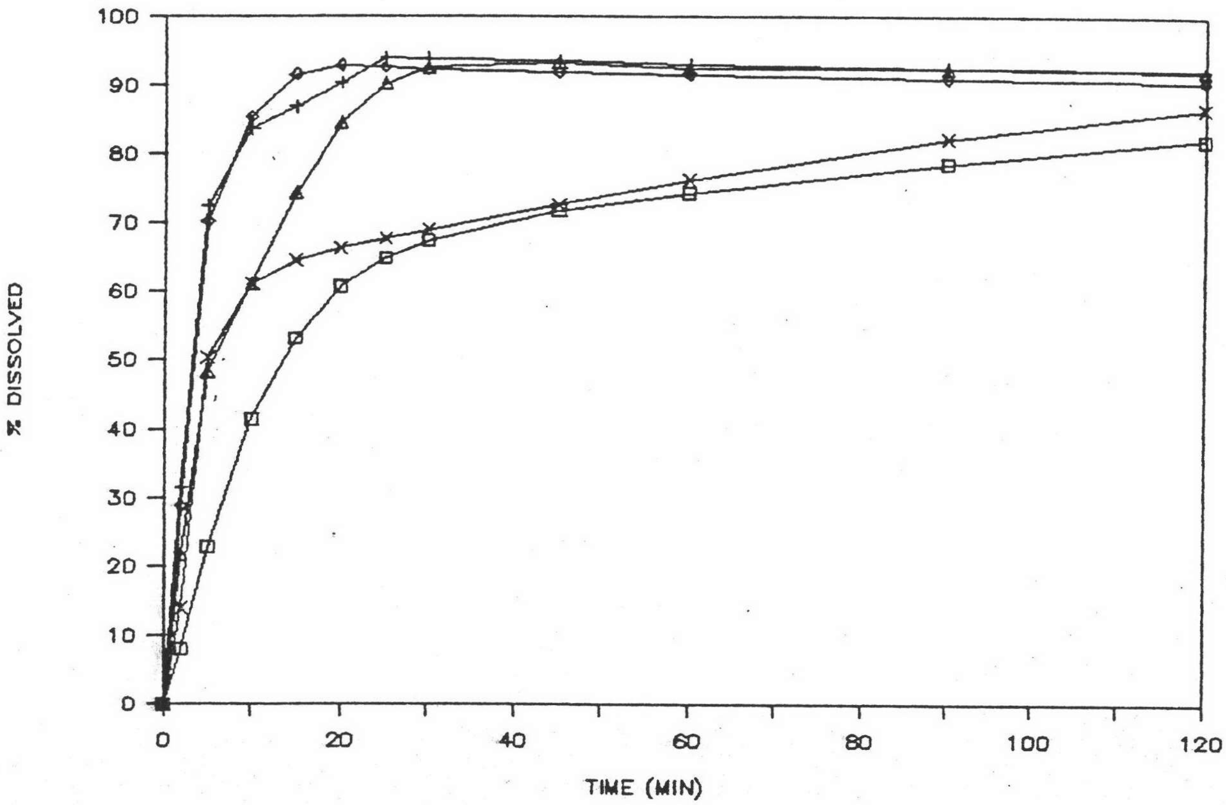

Figure 17 Dissolution profiles of HCTZ from HCTZ-PEG 20000 melts with various HCTZ:PEG 20000 ratios (□ 1:0, + 1:5, ◇ 1:10, △ 1:20, × 1:10 physical mixture).

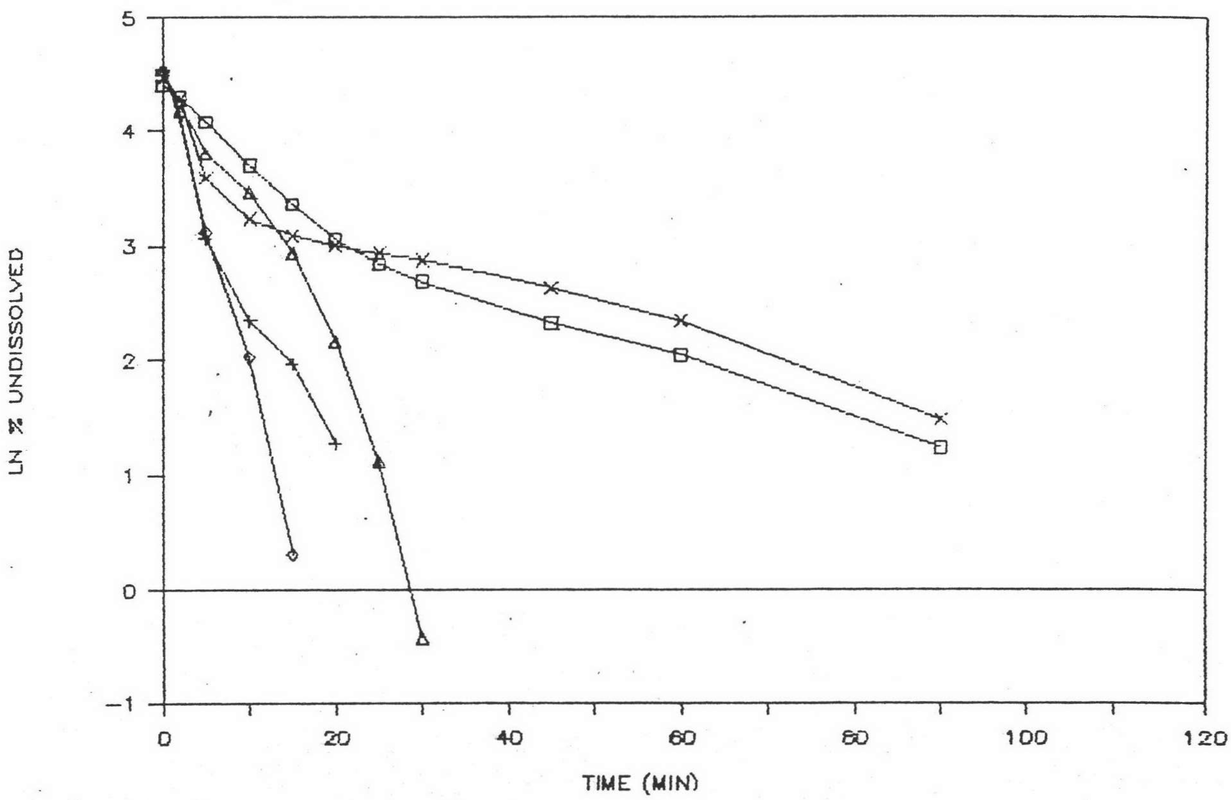

Figure 18 The first order plot between ln % HCTZ undissolved versus time for HCTZ-PEG 20000 melts with various HCTZ:PEG 20000 ratios (□ 1:0, + 1:5, ◇ 1:10, △ 1:20 × 1:10 physical mixture).

Table 17 Multiple Comparison (HSD Test) for Dissolution Rate Constants of HCTZ-PEG 20000 Melts with Various HCTZ: PEG 20000 Ratios (1:0, 1:5, 1:10, 1:20).

A \ B	1:0	1:5	1:10	1:20
1:0	-	@	@	@
1:5	*	-	@	NS
1:10	*	*	-	*
1:20	*	NS	@	-

$q_{0.05,4,8}$ =4.53, HSD = 0.0755

NS not significantly different, $\alpha = 0.05$

@ A is significantly less than B, $\alpha = 0.05$

* A is significantly more than B, $\alpha = 0.05$

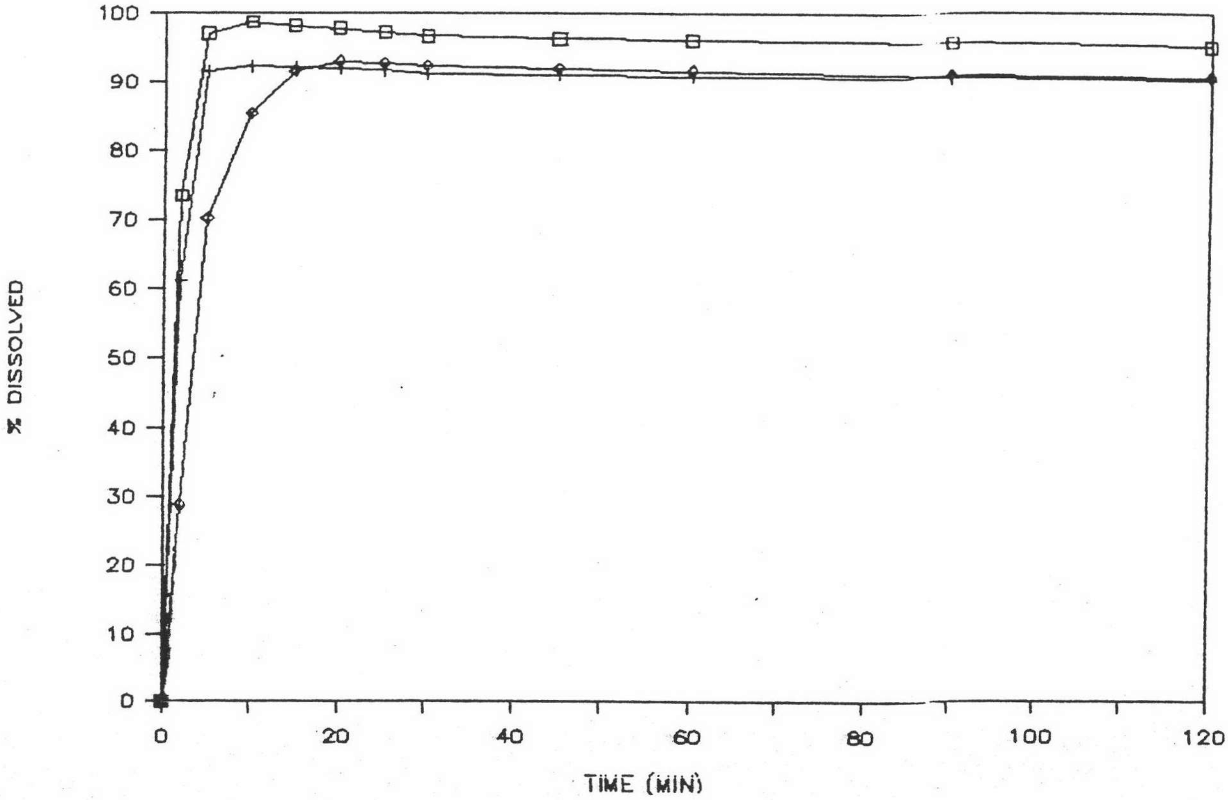

Figure 19 Dissolution profiles of HCTZ from HCTZ-PEG melts with optimum HCTZ:PEG ratio (□ 1:10 HCTZ-PEG 4000, + 1:10 HCTZ -PEG 6000, ◇ 1:10 HCTZ-PEG 20000).

Table 18 Multiple Comparison (HSD Test) for Dissolution Rate Constants of 1:10 HCTZ-PEG 4000 (a), 1:10 HCTZ-PEG 6000 (b), and 1:10 HCTZ-PEG 20000 (c) Melts.

A \ B	a	b	c
a	-	NS	*
b	NS	-	*
c	@	@	-

$q_{0.05,3,6}$ = 4.34, HSD = 0.1747

NS not significantly different, $\alpha = 0.05$

@ A is significantly less than B, $\alpha = 0.05$

* A is significantly more than B, $\alpha = 0.05$

Table 19 Dissolution of HCTZ from HCTZ-Urea Melts with Various HCTZ:Urea Ratios (1:0, 1:1, 1:2, 1:3, 1:5, 1:10, 1:20) and 1:3 Physical Mixture.

Time (min)	Percentage Amount of HCTZ Dissolved[a]							
	1:0	1:1	1:2	1:3	1:5	1:10	1:20	1:3 PM[b]
0	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)
2	8.005 (1.186)	40.374 (5.600)	89.673 (2.091)	97.843 (0.176)	98.508 (0.312)	96.080 (0.643)	95.374 (0.859)	19.253 (3.303)
5	22.703 (1.699)	67.963 (2.733)	98.432 (0.152)	99.162 (0.205)	99.127 (0.116)	99.115 (0.239)	98.880 (0.139)	39.004 (1.183)
10	41.403 (2.216)	73.469 (1.904)	97.942 (0.151)	98.668 (0.204)	98.846 (0.068)	98.715 (0.143)	98.202 (0.223)	46.471 (1.611)
15	53.151 (0.885)	77.177 (2.228)	97.290 (0.150)	98.119 (0.336)	98.227 (0.324)	98.314 (0.057)	97.693 (0.090)	51.827 (1.538)
20	60.722 (1.358)	80.378 (1.640)	96.909 (0.119)	97.789 (0.171)	97.890 (0.303)	97.855 (0.214)	96.901 (0.128)	55.614 (1.531)
25	64.834 (1.852)	82.625 (1.269)	96.528 (0.323)	97.129 (0.170)	97.778 (0.115)	97.512 (0.207)	96.505 (0.140)	59.077 (1.392)
30	67.356 (2.515)	84.198 (1.517)	96.310 (0.288)	96.800 (0.169)	97.047 (0.158)	97.168 (0.207)	95.940 (0.206)	62.269 (1.311)
45	71.798 (2.906)	88.241 (1.186)	95.821 (0.449)	96.195 (0.200)	96.654 (0.069)	96.767 (0.121)	95.035 (0.128)	70.332 (1.000)
60	74.265 (2.680)	90.825 (1.284)	95.440 (0.538)	96.030 (0.092)	96.148 (0.206)	96.367 (0.306)	94.753 (0.137)	75.366 (0.835)
90	78.542 (2.344)	92.793 (0.919)	94.950 (0.660)	95.426 (0.104)	95.811 (0.206)	95.851 (0.143)	94.131 (0.224)	83.917 (0.122)
120	81.998 (2.090)	93.747 (0.843)	94.569 (0.630)	94.877 (0.198)	95.361 (0.301)	95.279 (0.130)	93.452 (0.081)	89.166 (2.242)

a Mean (S.D.) of three determinations

b Physical mixture

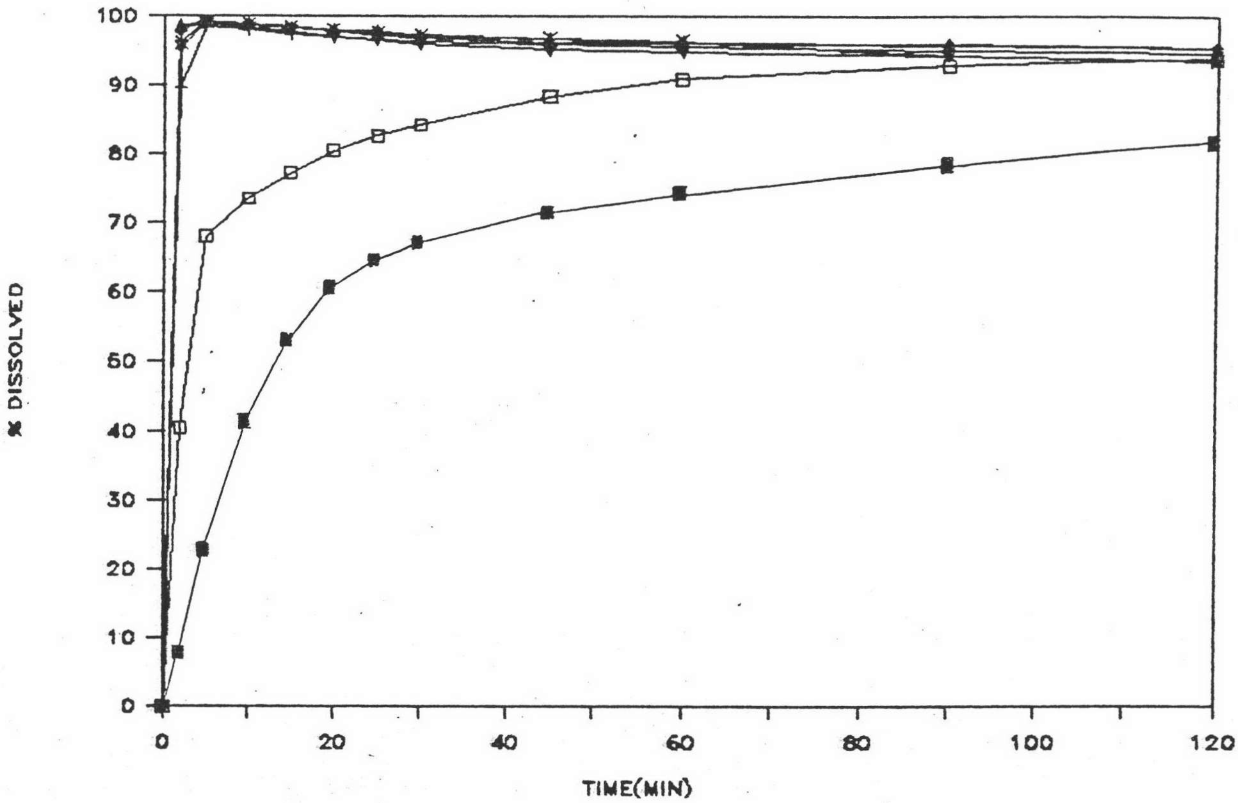

Figure 20 Dissolution profiles of HCTZ from HCTZ-urea melts with various HCTZ:urea ratios (■ 1:0, □ 1:1, + 1:2, ◇ 1:3, △ 1:5, × 1:10, ▽ 1:20).

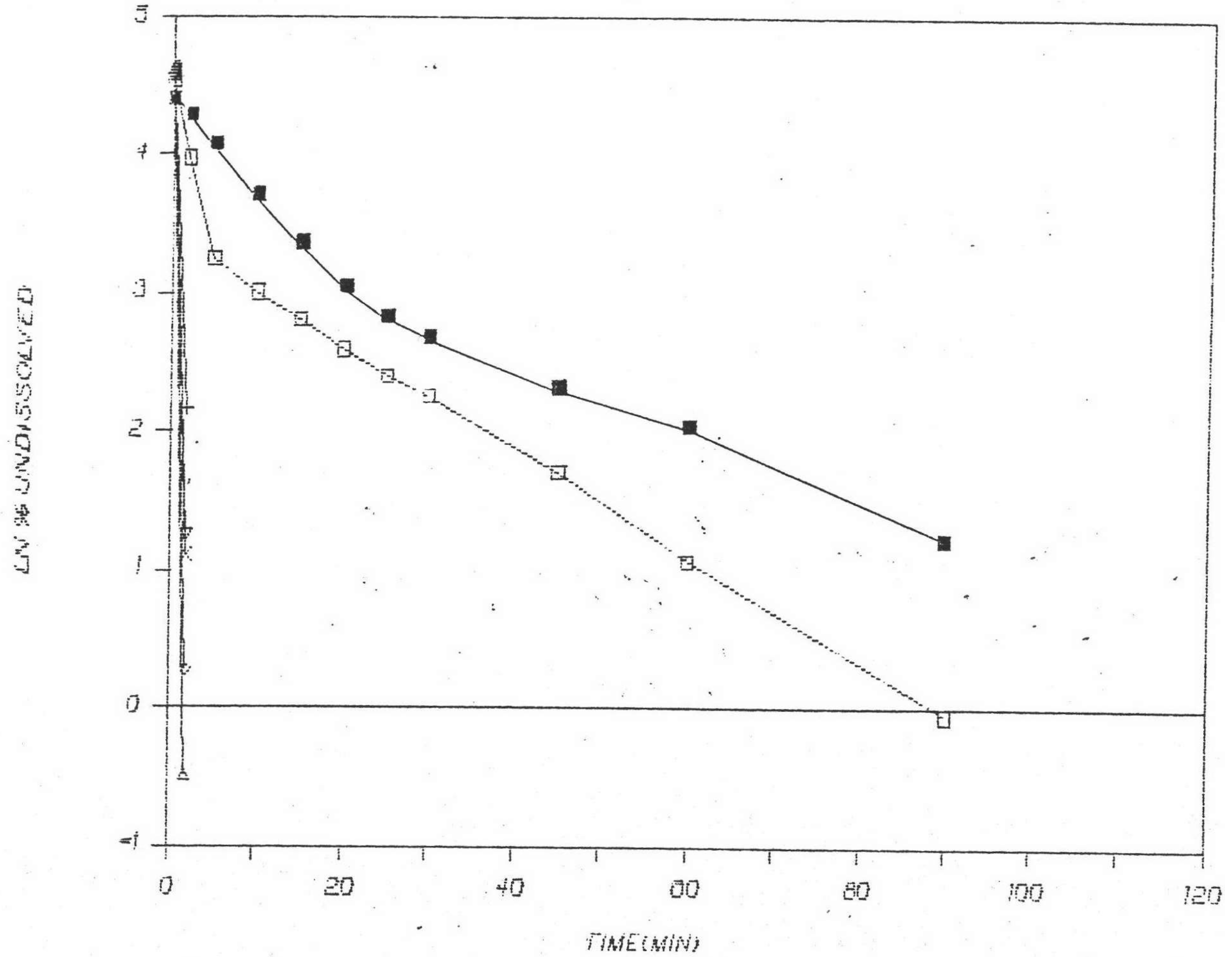

Figure 21 The first order plot between ln % HCTZ undissolved versus time for HCTZ-urea melts with various HCTZ:urea ratios (■ 1:0, □ 1:1, + 1:2, ◇ 1:3, △ 1:5, x 1:10, ▽ 1:20).

Table 20 Multiple Comparison (HSD Test) for Percentage Amount of HCTZ Dissolved at 5 Minutes of HCTZ-Urea Melts with Various HCTZ:Urea Ratios (1:0, 1:1, 1:2, 1:3, 1:5, 1:10, 1:20).

A \ B	1:0	1:1	1:2	1:3	1:5	1:10	1:20
1:0	-	@	@	@	@	@	@
1:1	*	-	@	@	@	@	@
1:2	*	*	-	NS	NS	NS	NS
1:3	*	*	NS	-	NS	NS	NS
1:5	*	*	NS	NS	-	NS	NS
1:10	*	*	NS	NS	NS	-	NS
1:20	*	*	NS	NS	NS	NS	-

$q_{0.05,7,14} = 4.83$, HSD = 3.5118

NS not significantly different, $\alpha = 0.05$

@ A is significantly less than B, $\alpha = 0.05$

* A is significantly more than B, $\alpha = 0.05$

Table 21 Dissolution of HCTZ from HCTZ-Urea Coprecipitates with Various HCTZ:Urea Ratios (1:0, 1:1, 1:3, 1:5, 1:10, 1:20).

Time (min)	Percentage Amount of HCTZ Dissolved[a]					
	1:0	1:1	1:3	1:5	1:10	1:20
0	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)
2	8.005 (1.186)	24.900 (0.688)	48.371 (5.677)	42.995 (1.203)	63.033 (8.266)	86.593 (1.482)
5	22.703 (1.699)	34.137 (2.469)	73.540 (2.238)	74.082 (2.023)	85.699 (0.561)	92.165 (1.373)
10	41.403 (2.216)	36.695 (2.254)	80.333 (3.059)	79.794 (0.589)	89.522 (0.143)	92.108 (0.750)
15	53.151 (0.885)	41.371 (3.446)	84.787 (2.421)	84.902 (1.062)	91.848 (1.112)	91.881 (0.499)
20	60.722 (1.358)	44.209 (4.218)	87.125 (1.753)	88.417 (0.240)	92.679 (0.806)	91.597 (0.348)
25	64.834 (1.852)	47.103 (4.964)	88.628 (1.350)	90.099 (0.210)	93.011 (0.671)	91.312 (0.156)
30	67.356 (2.515)	49.830 (5.477)	89.797 (0.629)	90.504 (0.210)	92.956 (0.614)	90.914 (0.239)
45	71 798 (2.906)	57.175 (6.873)	91.579 (0.106)	90.998 (0.209)	92.790 (0.759)	90.118 (0.034)
60	74.265 (2.680)	62.625 (6.842)	92.749 (0.355)	90.668 (0.210)	92.513 (0.806)	89.948 (0.034)
90	78.542 (2.344)	71.745 (6.148)	92.080 (0.107)	90.449 (0.366)	92.014 (1.243)	89.550 (0.104)
120	81.998 (2.090)	80.751 (4.602)	91.301 (0.101)	89.570 (0.997)	91.626 (1.339)	89.322 (0.071)

a Mean (S.D.) of three determinations

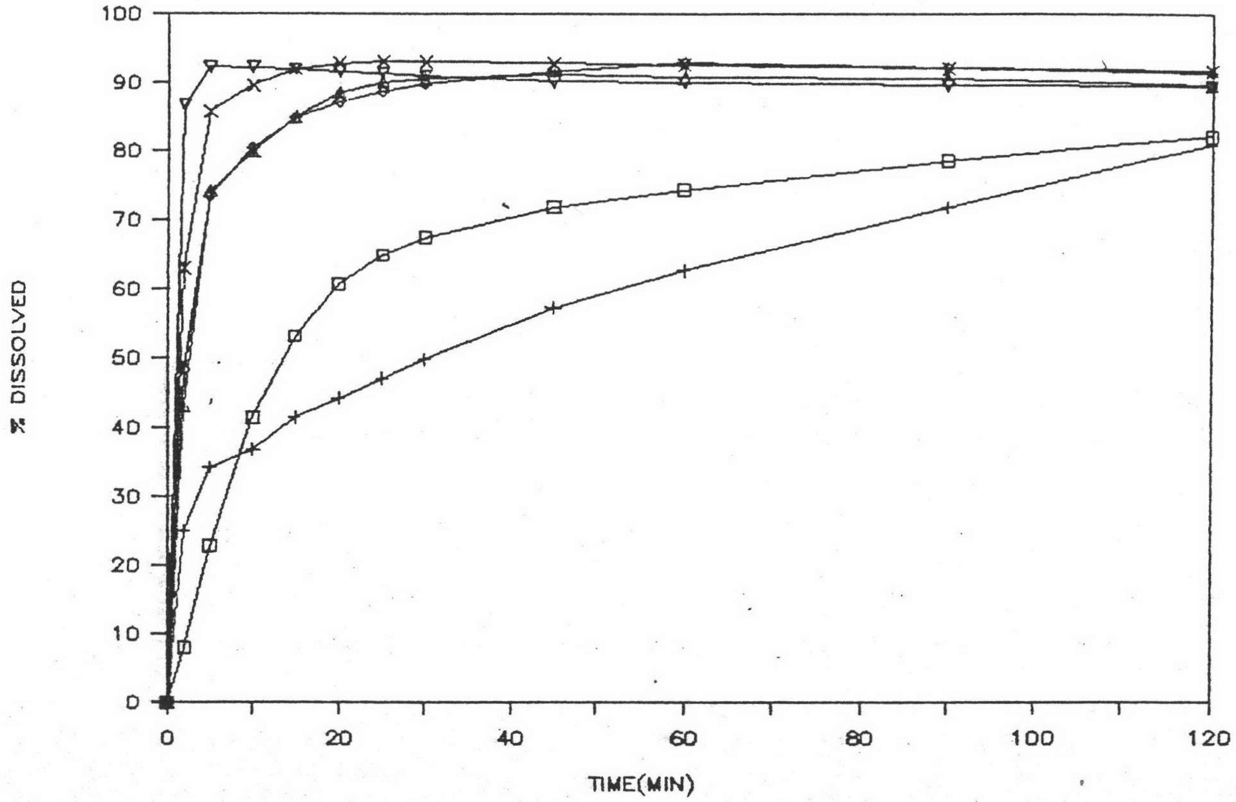

Figure 22 Dissolution profiles of HCTZ from HCTZ-urea coprecipitates with various HCTZ:urea ratios (□ 1:0, + 1:1, ◇ 1:3, △ 1:5, × 1:10, ▽ 1:20).

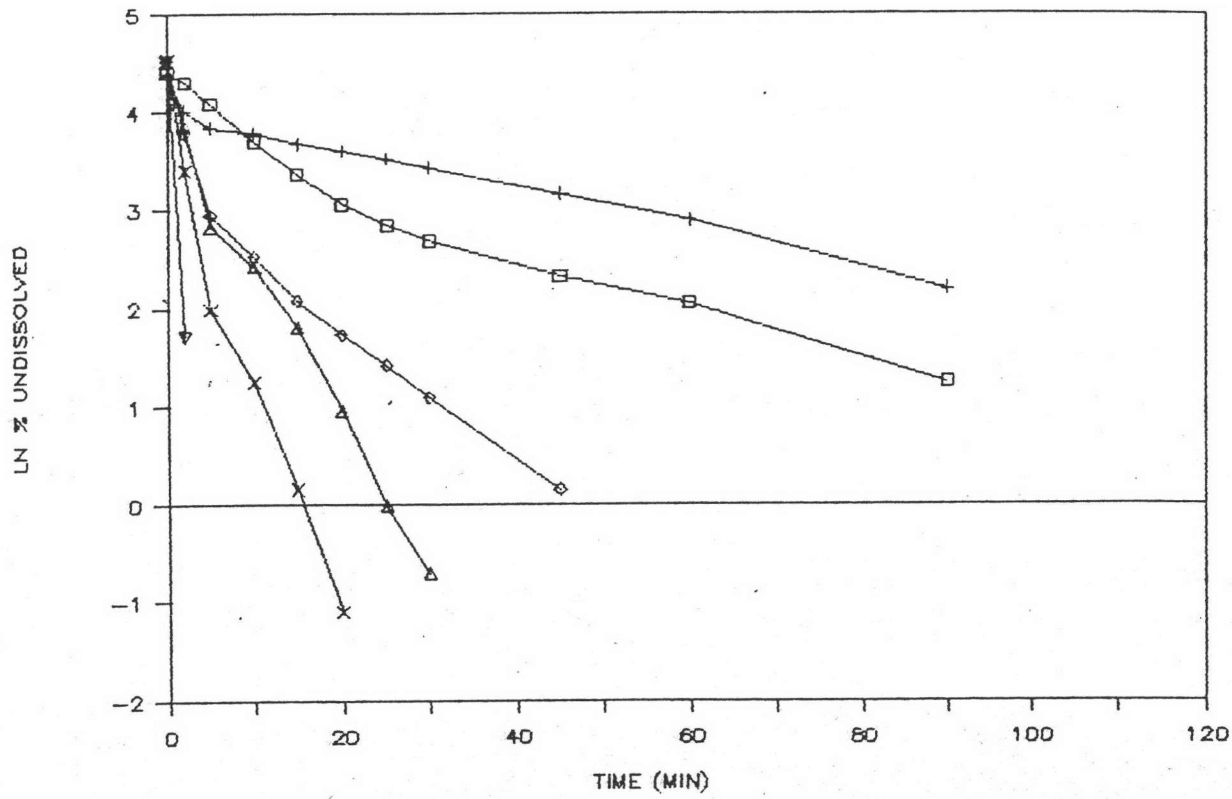

Figure 23 The first order plot between ln % HCTZ undissolved versus time for HCTZ-urea coprecipitates with various HCTZ:urea ratios (□ 1:0, + 1:1, ◇ 1:3, △ 1:5, × 1:10, ▽ 1:20).

Table 22 Multiple Comparison (HSD Test) for Dissolution Rate Constants of HCTZ-Urea Coprecipitates with Various HCTZ:Urea Ratios (1:0, 1:1, 1:3, 1:5, 1:10).

A \ B	1:0	1:1	1:3	1:5	1:10
1:0	-	NS	@	@	@
1:1	NS	-	@	@	@
1:3	*	*	-	@	@
1:5	*	*	*	-	@
1:10	*	*	*	*	-

$q_{0.05,5,10}$ = 4.65, HSD = 0.0286

NS not significantly different, $\alpha = 0.05$

@ A is significantly less than B, $\alpha = 0.05$

* A is significantly more than B, $\alpha = 0.05$

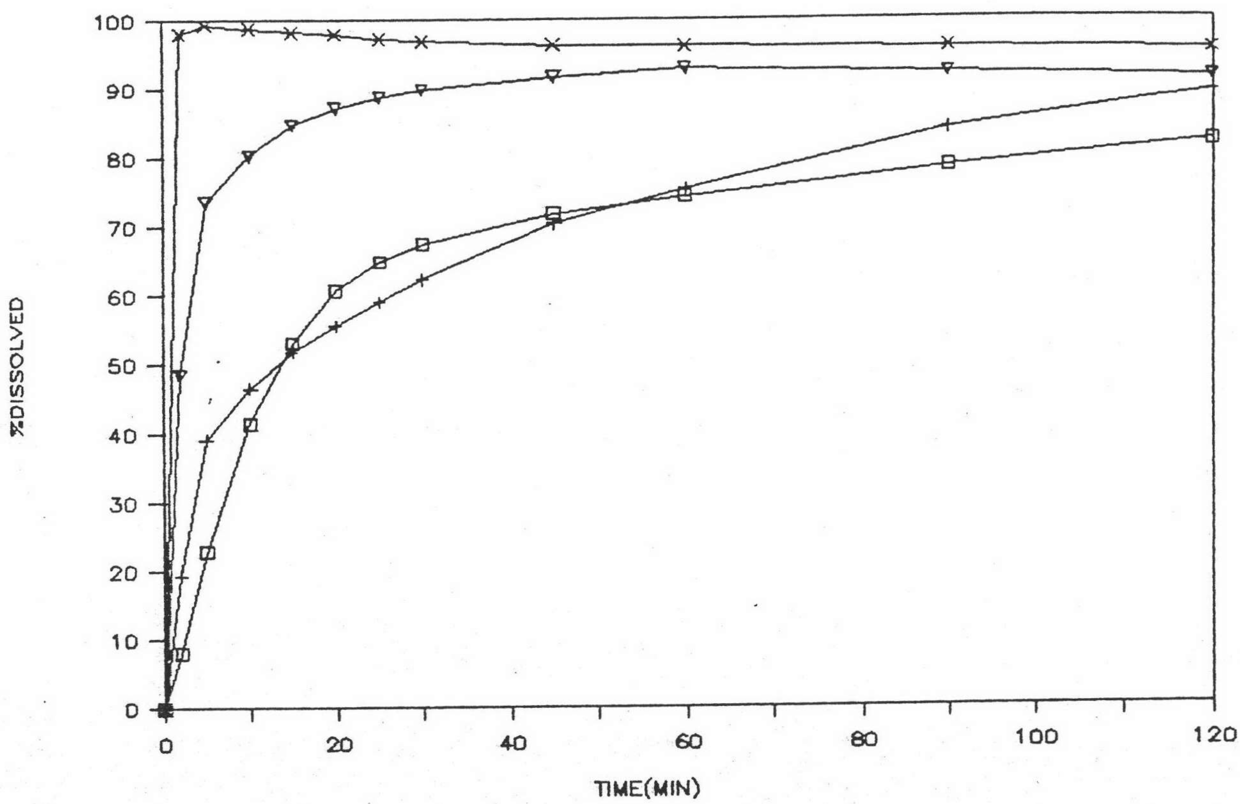

Figure 24 Dissolution profiles of HCTZ from 1:3 HCTZ-urea solid dispersions prepared by two methods (▽ coprecipitate, × melt) compare with 1:3 physical mixture (+) and pure drug (□).

Table 23 Multiple Comparison (HSD Test) for Percentage Amount of HCTZ Dissolved at 5 Minutes of 1:3 HCTZ-Urea Melt (a), 1:3 HCTZ-Urea Coprecipitate (b), and 1:20 HCTZ-Urea Coprecipitate (c).

A \ B	a	b	c
a	-	*	*
b	@	-	@
c	@	*	-

$q_{0.05,3,6} = 4.34$, HSD = 3.8104

NS not significantly different, $\alpha = 0.05$

@ A is significantly less than B, $\alpha = 0.05$

* A is significantly more than B, $\alpha = 0.05$

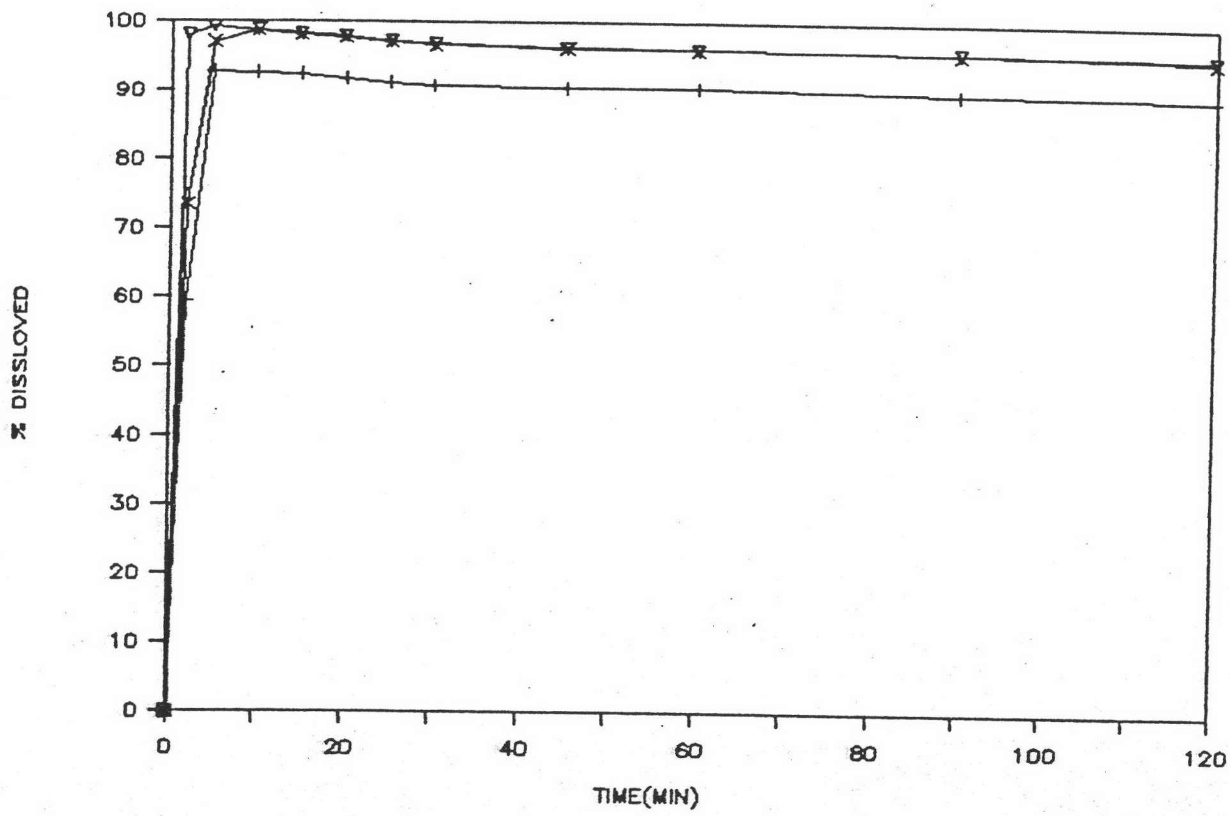

Figure 25 Dissolution profiles of HCTZ from HCTZ solid dispersions with the fastest dissolution rate of each carrier (+ 1:5 HCTZ-PVP K-17 coprecipitate, x 1:10 HCTZ 4000 melt, ∇ 1:3 HCTZ-urea melt).

Table 24 Multiple Comparison (HSD Test) for Percentage Amount of HCTZ Dissolved at 5 minutes of 1:5 HCTZ-PVP K-17 Coprecipitate (a), 1:10 HCTZ-PEG 4000 Melt (b), and 1:3 HCTZ-Urea Melt (c).

A \ B	a	b	c
a	-	@	@
b	*	-	NS
c	*	NS	-

$q_{0.05,3,6}$ = 4.34, HSD = 2.2927

NS not significantly different, $\alpha = 0.05$

@ A is significantly less than B, $\alpha = 0.05$

* A is significantly more than B, $\alpha = 0.05$

Table 25 Multiple Comparison (HSD Test) for Dissolution Rate Constants of Pure HCTZ (A), 1:5 HCTZ-PVP K-17 (b), 1:5 HCTZ-PVP K-30 (c), 1:1 HCTZ-PVP K-90 (d), 1:10 HCTZ-PEG 4000 (e), 1:10 HCTZ-PEG 6000 (f), 1:10 HCTZ-PEG 20000 (g), and 1:3 HCTZ-Urea (h) Physical Mixtures.

A \ B	a	b	c	d	e	f	g	h
a	-	*	NS	NS	NS	NS	NS	NS
b	@	-	NS	NS	NS	NS	NS	NS
c	NS	NS	-	NS	NS	NS	NS	NS
d	NS	NS	NS	-	NS	NS	NS	NS
e	NS	NS	NS	NS	-	NS	NS	NS
f	NS	NS	NS	NS	NS	-	NS	NS
g	NS	NS	NS	NS	NS	NS	-	NS
h	NS	NS	NS	NS	NS	NS	NS	-

$q_{0.05,8,16}$ = 4.90, HSD = 0.0085

NS not significantly different, $\alpha = 0.05$

@ A is significantly less than B, $\alpha = 0.05$

* A is significantly more than B, $\alpha = 0.05$

X-Ray Diffractograms

X-ray diffraction spectra of HCTZ, various carriers, physical mixtures and solid dispersions of HCTZ with various carriers of various ratios are shown in Figure 26-35. It revealed that, HCTZ, PEG, and urea were crystalline forms but PVP was amorphous form.

Major X-ray diffraction peaks of HCTZ, particularly at 19° and 29° were present in pure HCTZ and all physical mixtures of HCTZ and PVP or urea.

The X-ray diffraction spectra of HCTZ-PVP coprecipitates with various HCTZ:PVP ratios compared with HCTZ alone and the physical mixtures are shown in Figure 26-29. In the coprecipitates with the ratio 2:1 of HCTZ to PVP K-17, PVP K-30 or PVP K-90, diffraction peaks of HCTZ were still remained but the height was lower than that of HCTZ alone. The sharp diffraction peaks attributed to HCTZ crystals disappeared in 1:1 HCTZ-PVP coprecipitate or at higher weight fraction of PVP.

The X-ray diffraction spectra of HCTZ-PEG melts with various HCTZ:PEG ratios comparing with HCTZ alone, PEG alone, and the physical mixtures are shown in Figure 30-32. All of the X-ray diffraction patterns of the melts were similar to the patterns of PEG alone. The peaks of HCTZ did not occur when HCTZ was mixed with PEG of any ratios.

The X-ray diffraction spectra of HCTZ-urea melts and coprecipitates with various HCTZ:urea ratios and the physical mixture are shown in Figure 33-35. The sharp diffraction peaks attributed

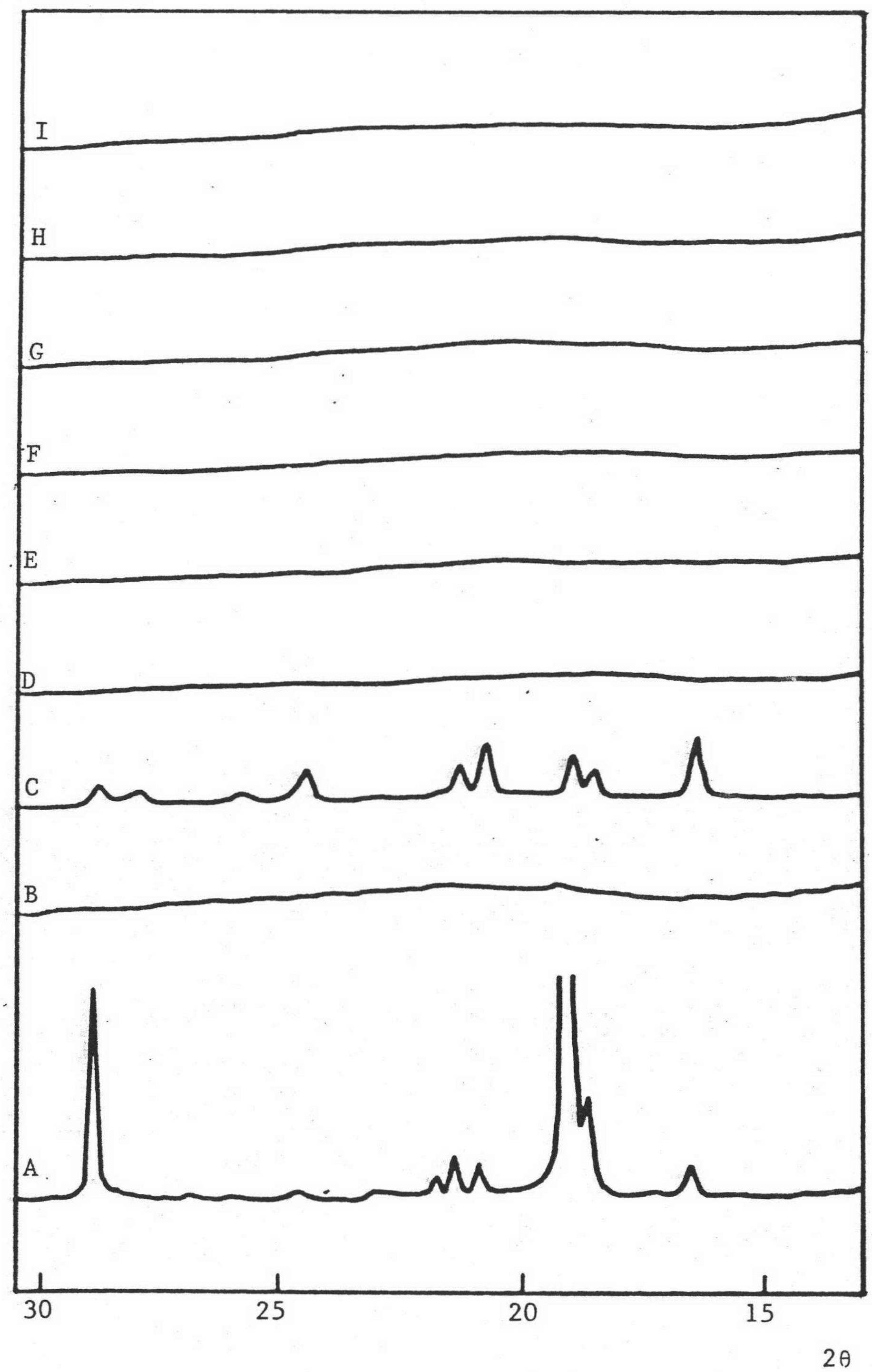

Figure 26 X-ray diffraction spectra of HCTZ-PVP K-17 systems with various HCTZ:PVP K-17 ratios

Key: A, HCTZ alone; B, PVP K-17 alone; C, 2:1; D,1:1; E, 1:3; F, 1:4; G, 1:5; H, 1:10; I, 1:20.

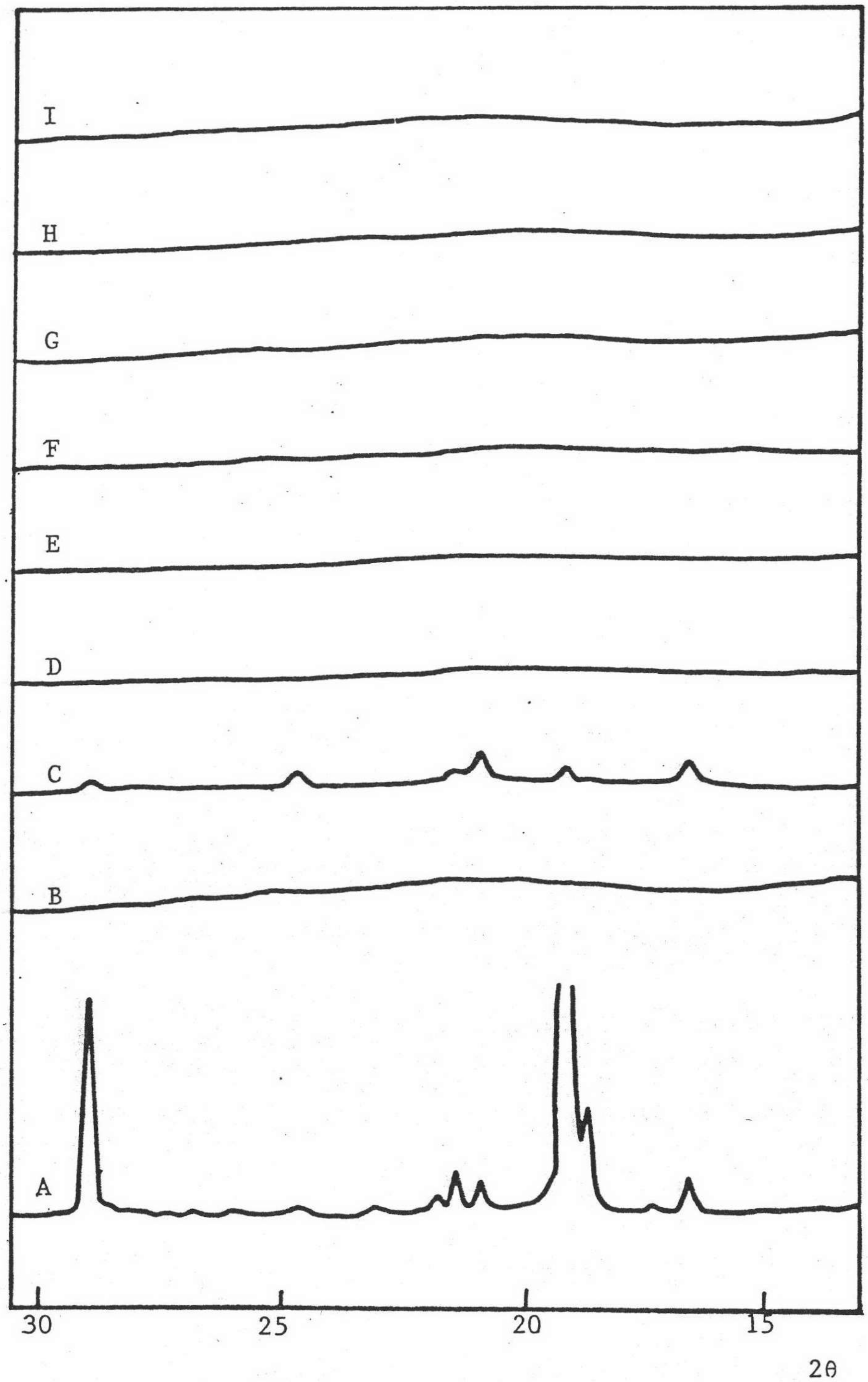

Figure 27 X-ray diffraction spectra of HCTZ-PVP K-30 systems with various HCTZ:PVP K-30 ratios

Key: A, HCTZ alone; B, PVP K-30 alone; C, 2:1; D,1:1; E,1:3; F, 1:4; G,1:5; H,1:10; I, 1:20.

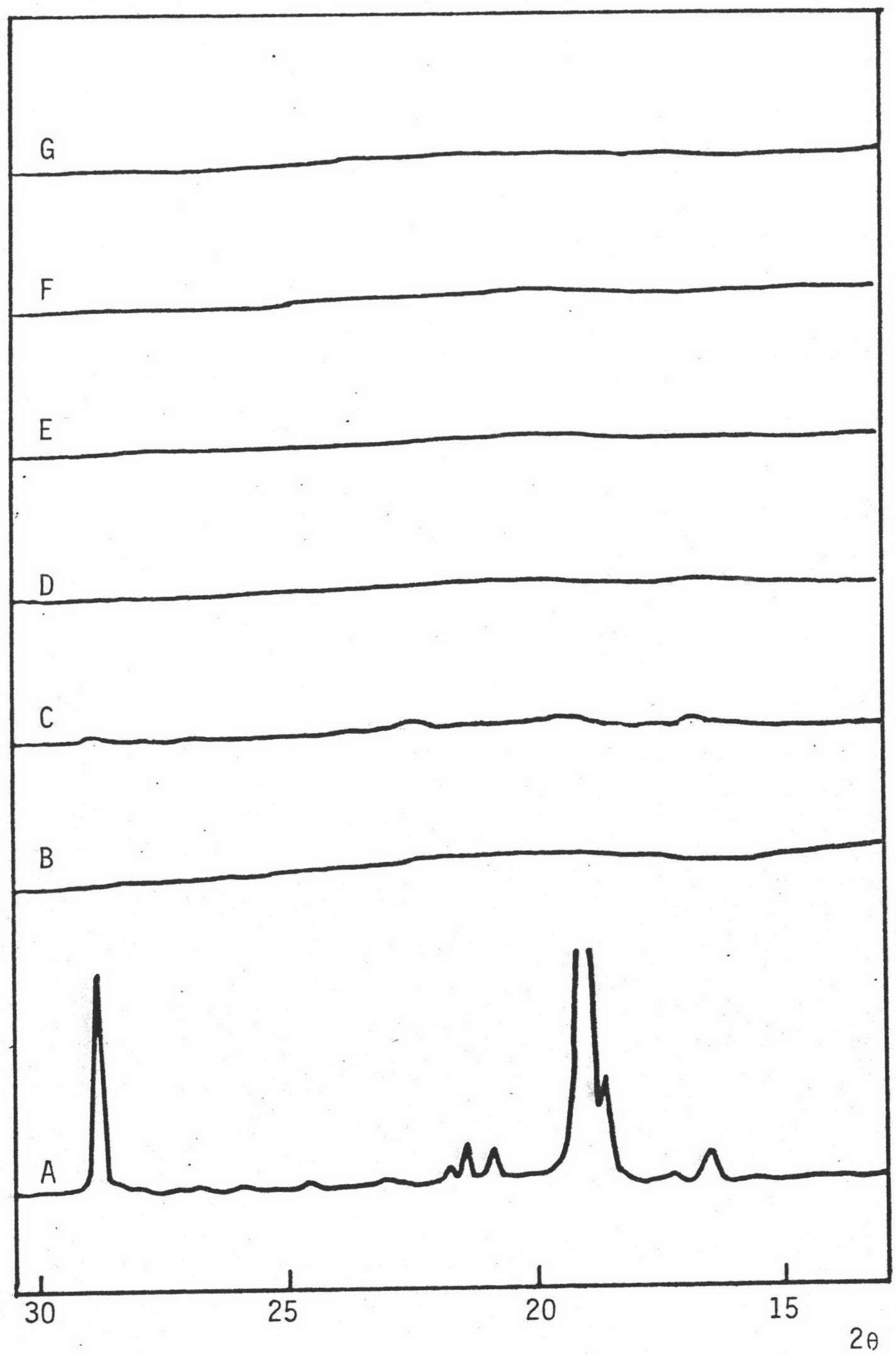

Figure 28 X-ray diffraction spectra of HCTZ-PVP K-90 systems with various HCTZ:PVP K-90 ratios

Key: A,HCTZ alone; b, PVP K-90 alone; C,2:1; D,1:1; E, 1:2; F,1:3; G,1:4.

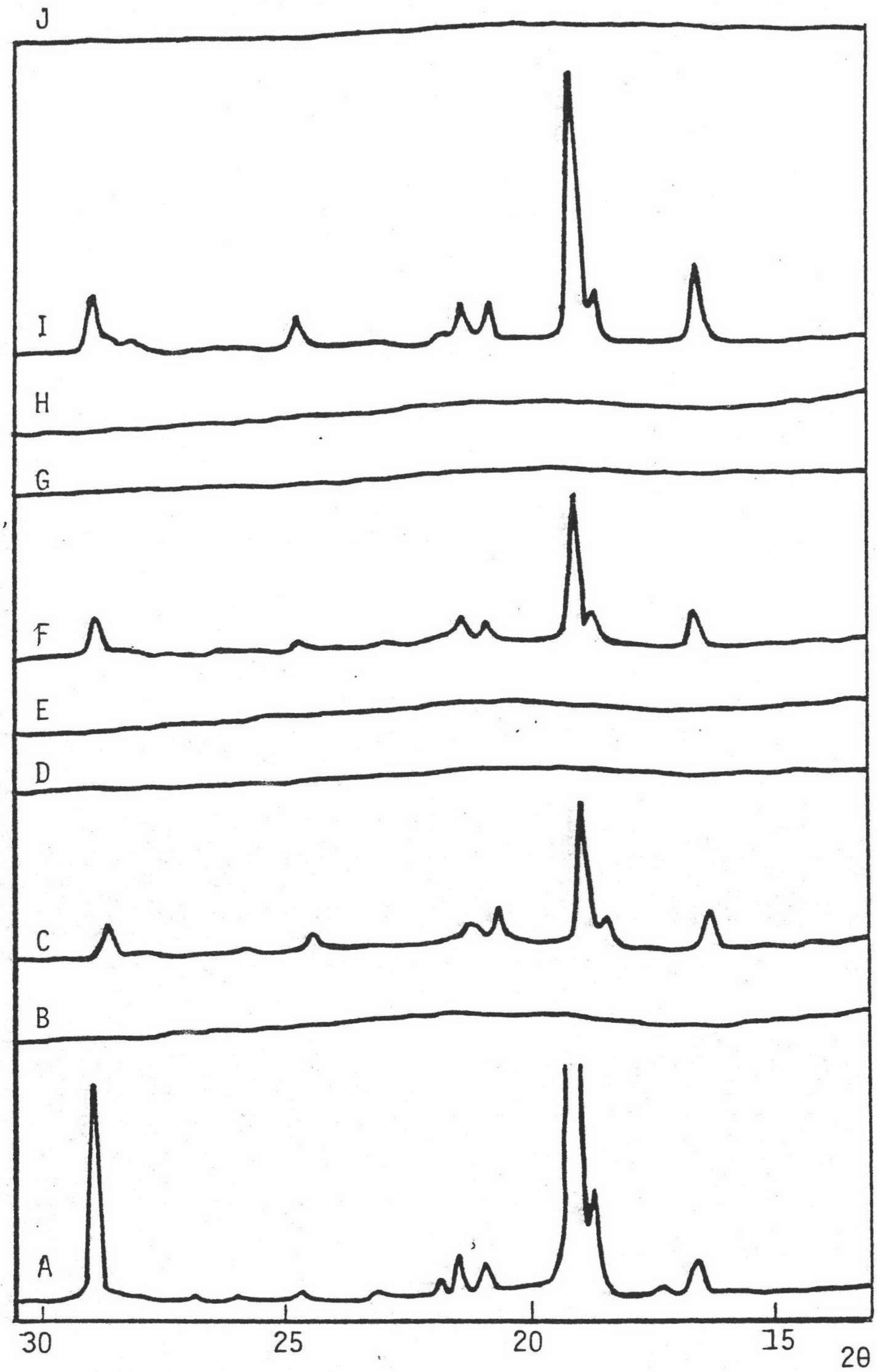

Figure 29 X-ray diffraction spectra of HCTZ-PVP systems

Key: A, HCTZ; B, PVP K-17; C, 1:5 HCTZ-PVP K-17 physical mixture; D, 1:5 HCTZ-PVP K-17 coprecipitate; E, PVP K-30; F, 1:5 HCTZ-PVP K-30 physical mixture; G, 1:5 HCTZ-PVP K-30 coprecipitates; H, PVP K-90; I, 1:1 HCTZ-PVP K-90 physical mixture; J, 1:1 HCTZ-PVP K-90 coprecipitate.

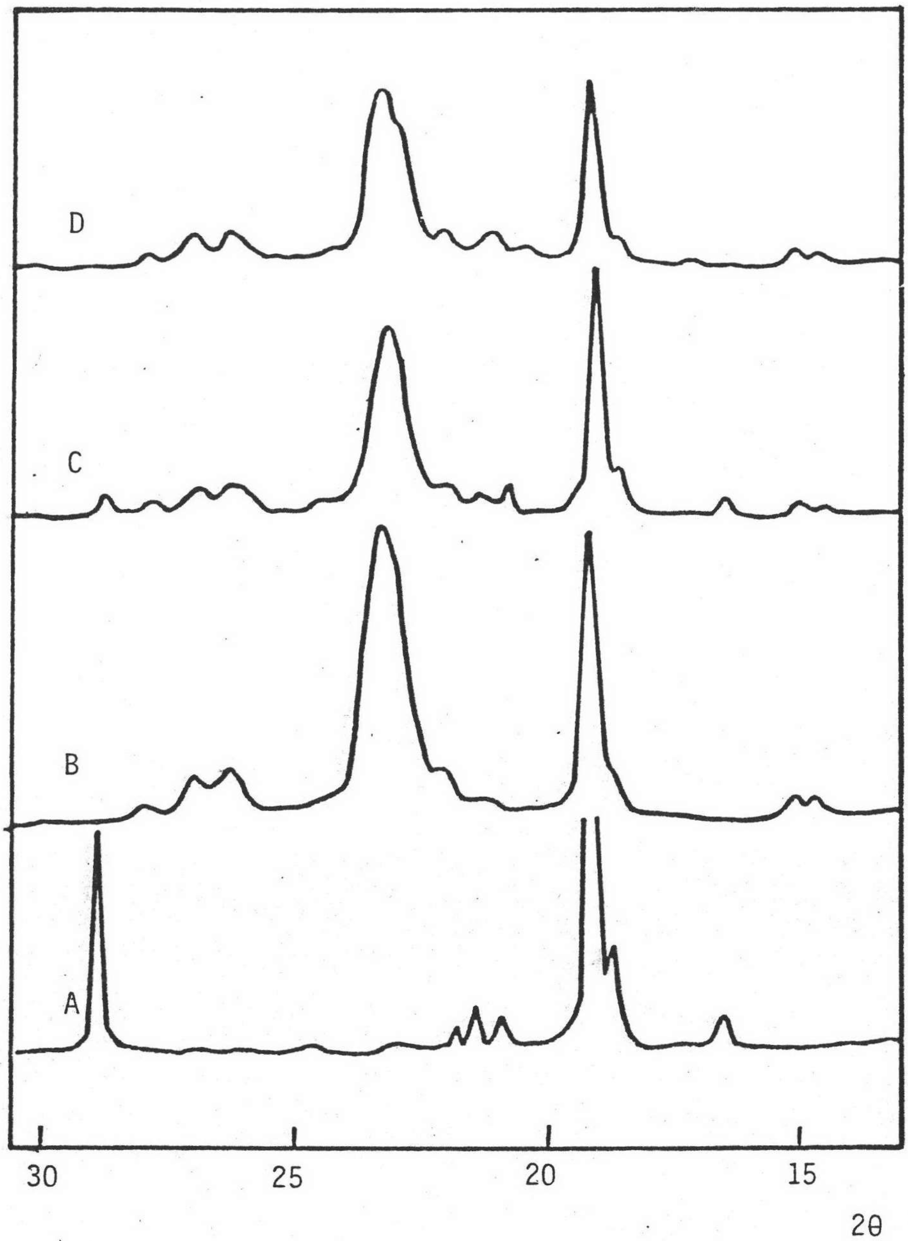

Figure 30 X-ray diffraction spectra of HCTZ-PEG 4000 systems
Key: A, HCTZ alone; B, PEG 4000 alone; C, 1:10 HCTZ-PEG 4000 physical mixture; D, 1:10 HCTZ-PEG 4000 melt.

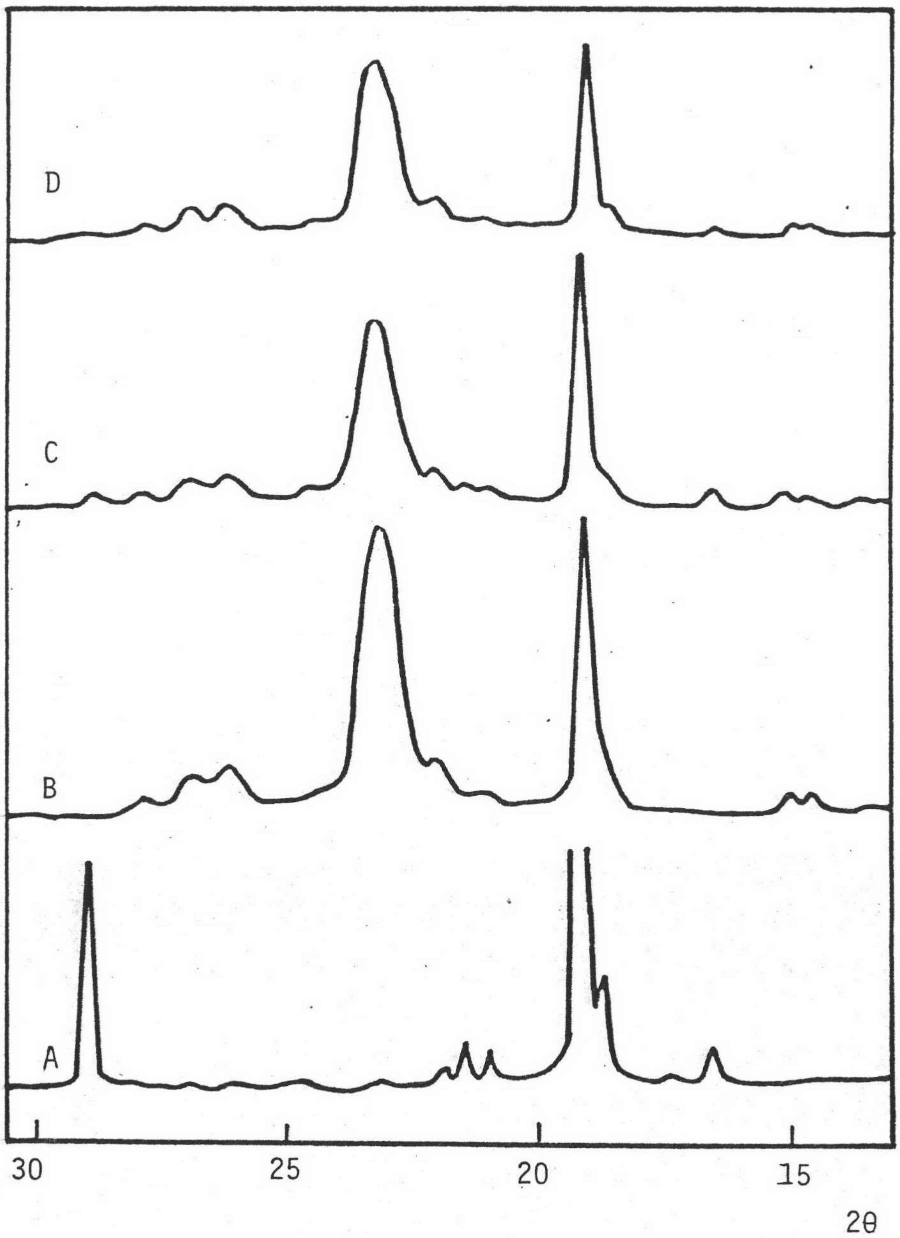

Figure 31 X-ray diffraction spectra of HCTZ-PEG 6000 systems
Key: A, HCTZ alone; B, PEG 6000 alone; C, 1:10 HCTZ-PEG 6000 physical mixture; D, 1:10 HCTZ-PEG 6000 melt.

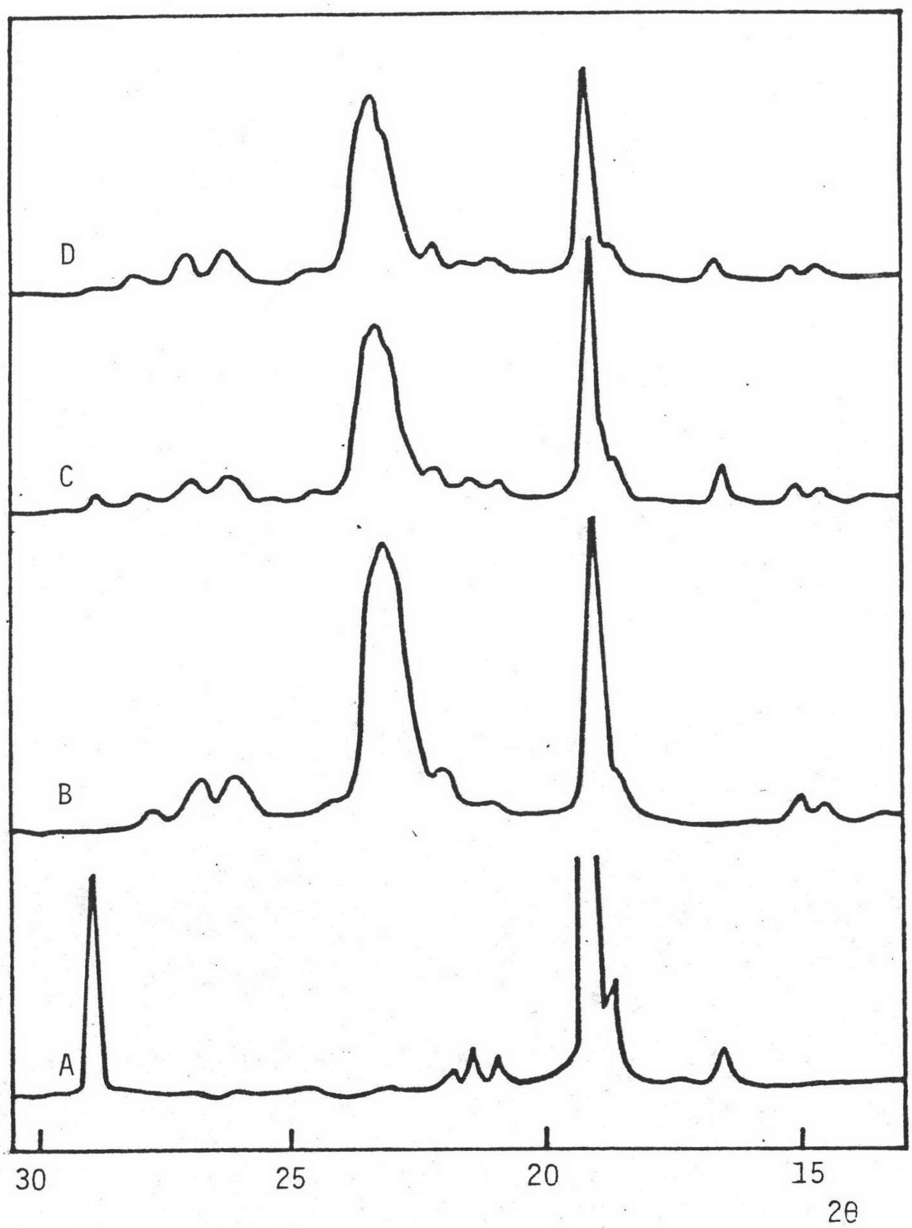

Figure 32 X-ray diffraction spectra of HCTZ-PEG 20000 systems

Key: A, HCTZ alone; B, PEG 20000 alone; C, 1:10 HCTZ-PEG 20000 physical mixture; D, 1:10 HCTZ-PEG 20000 melt.

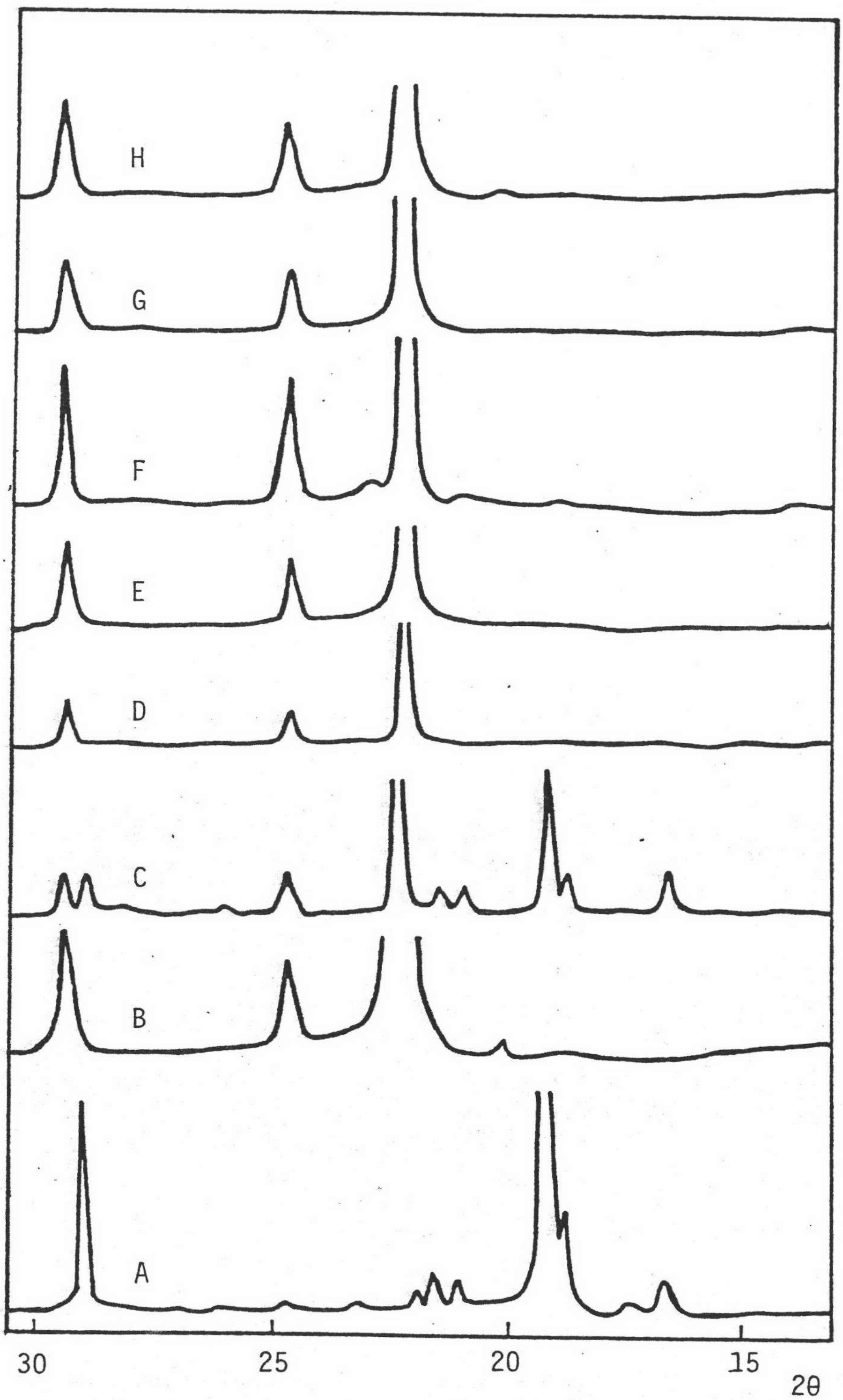

Figure 33 X-ray diffraction spectra of HCTZ-urea melts with various HCTZ-urea ratios

Key: A, HCTZ alone; B, urea alone; C, 1:1; D, 1:2 E, 1:3; F, 1:5; G, 1:10; H,1:20.

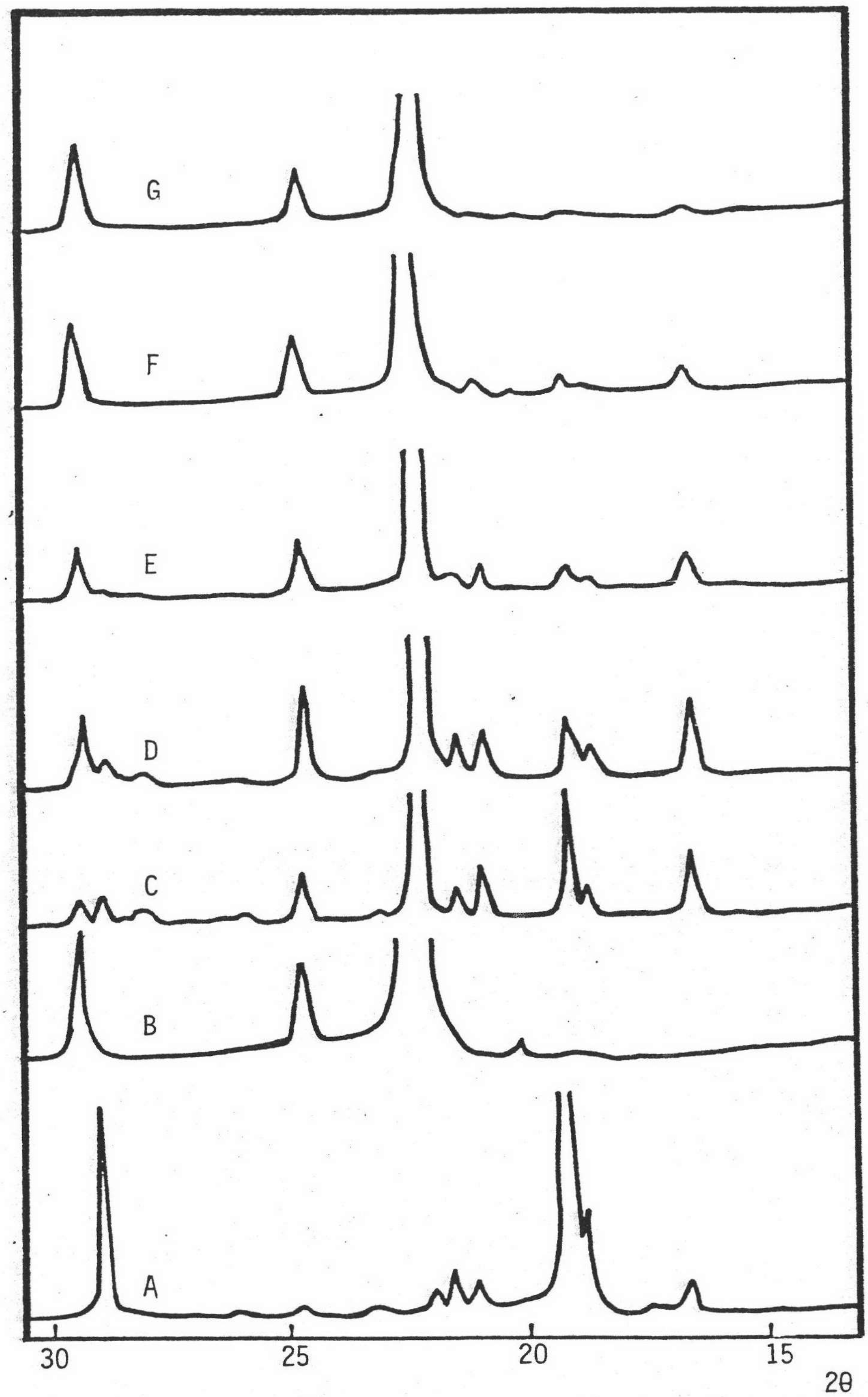

Figure 34 X-ray diffraction spectra of HCTZ-urea coprecipitates with various HCTZ:urea ratios

Key: A, HCTZ alone; B, urea alone; C, 1:1; D, 1:3; E, 1:5; F, 1:10; G, 1:20.

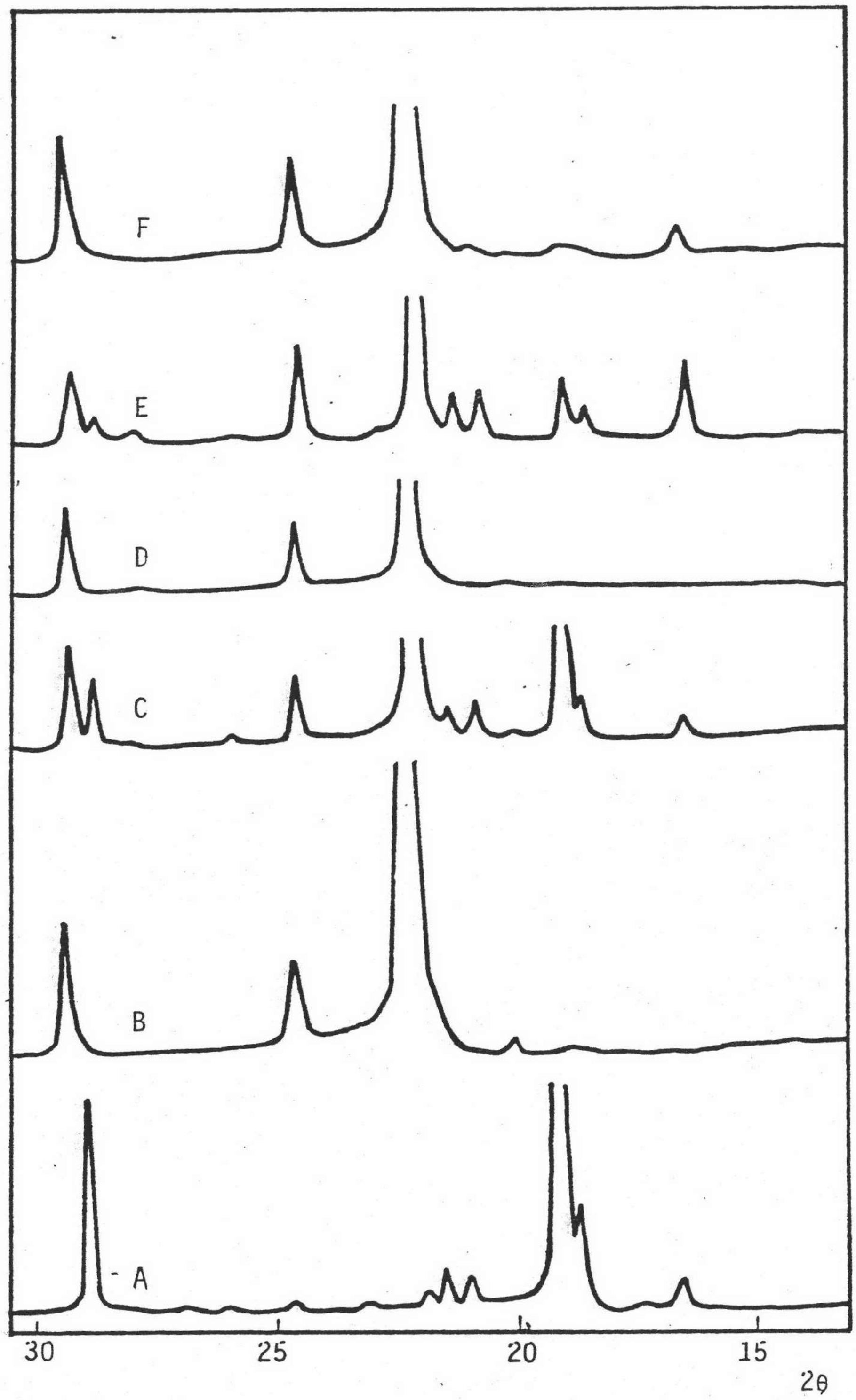

Figure 35 X-ray diffraction spectra of HCTZ-Urea Systems

Key: A, HCTZ alone; B, Urea alone; C, 1;3 HCTZ-Urea physical mixture; D, 1:3 HCTZ-Urea Melt; E, 1:3 HCTZ-Urea Coprecipitate; F, 1:20 HCTZ-Urea Coprecipitate.

to HCTZ crystals still remained in the physical mixture and the coprecipitates, increased weight fraction of urea, the height of the peaks became lower. The peaks did not occur in all of the melts, except that with 1:1 HCTZ-urea weight ratio which the height ofthe peaks was lower than that of pure drug.

Infrared Spectra (14,27,28)

The IR spectrum of HCTZ is shown in Figure 36. The coprecipitates of HCTZ and PVP K-17 or PVP K-30 (1:5 drug:PVP) showed the peak of PVP and HCTZ at 1660 and 1600 cm^{-1}, respectively. Their physical mixtures showed only the peak of PVP (Figure 37-38). The 1:1 HCTZ-PVP K-90 coprecipitate also showed the peak of PVP and HCTZ at 1660 and 1600 cm^{-1}, respectively while the physical mixture of the same ratio showed only the peak of HCTZ (Figure 39).

The melt of HCTZ and PEG 4000, PEG 6000 or PEG 20000 (1:10 HCTZ:PEG) and their physical mixtures of the same ratio gave the spectra of HCTZ and PEG at 1600 and 1470 cm^{-1} ,respectively. The intensity of the peak of HCTZ at 1600 cm^{-1} in the melts was stronger than that of their physical mixtures (Figure 40-42).

The 1:3 HCTZ-urea melt and its physical mixture showed the spectra of HCTZ and urea. The peaks of HCTZ at 1335 and 1320 cm^{-1} are doublet resulted from the stretching of cyclic secondary and primary sulfonamide respectively. The peak of urea at 1460 cm^{-1} occured in both the melt and physical mixture while the doublet peak of HCTZ occured only in the physical mixture but not in the melt (Figure 43).

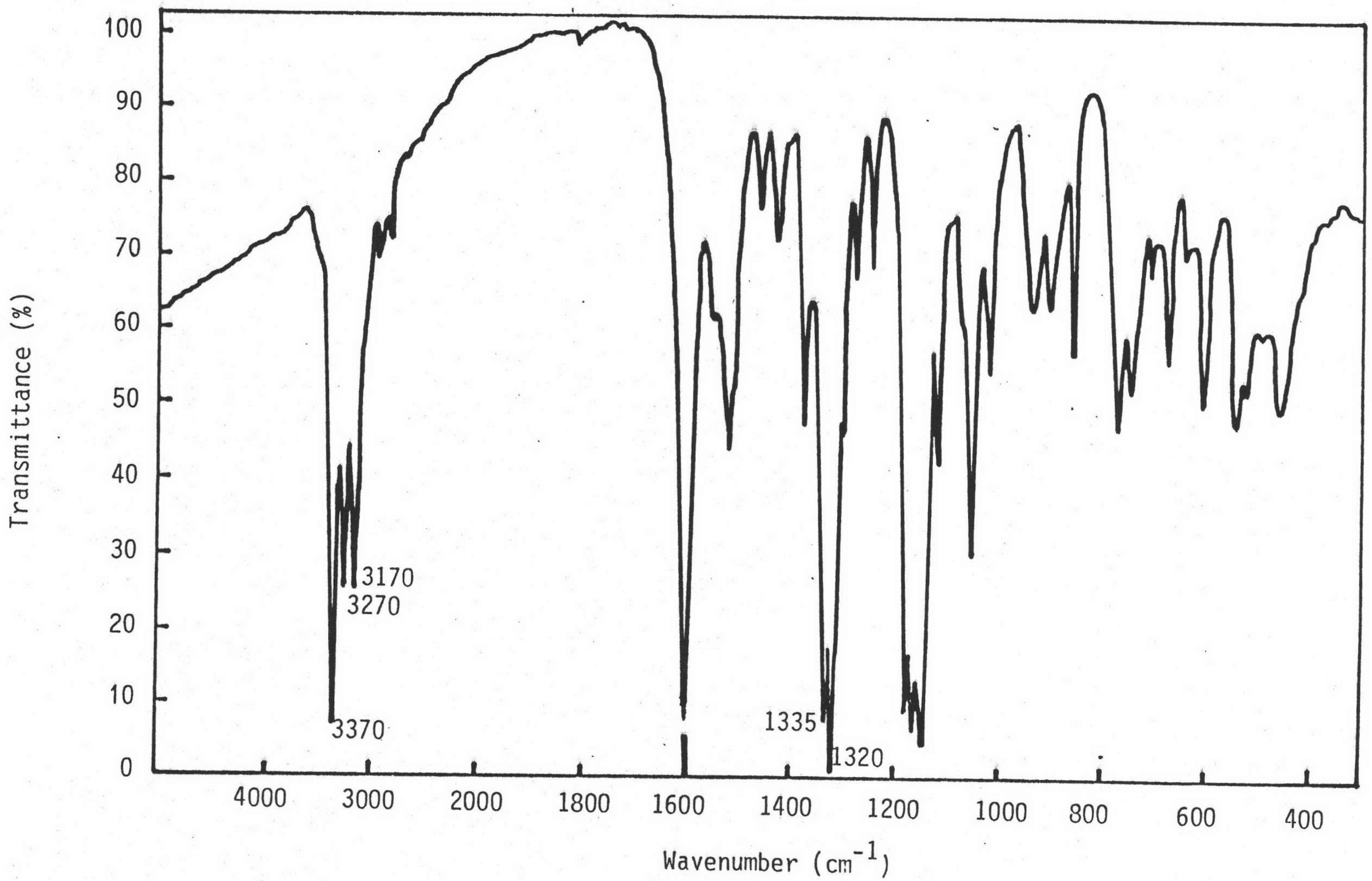

Figure 36 Infrared spectrum of hydrochlorothiazide.

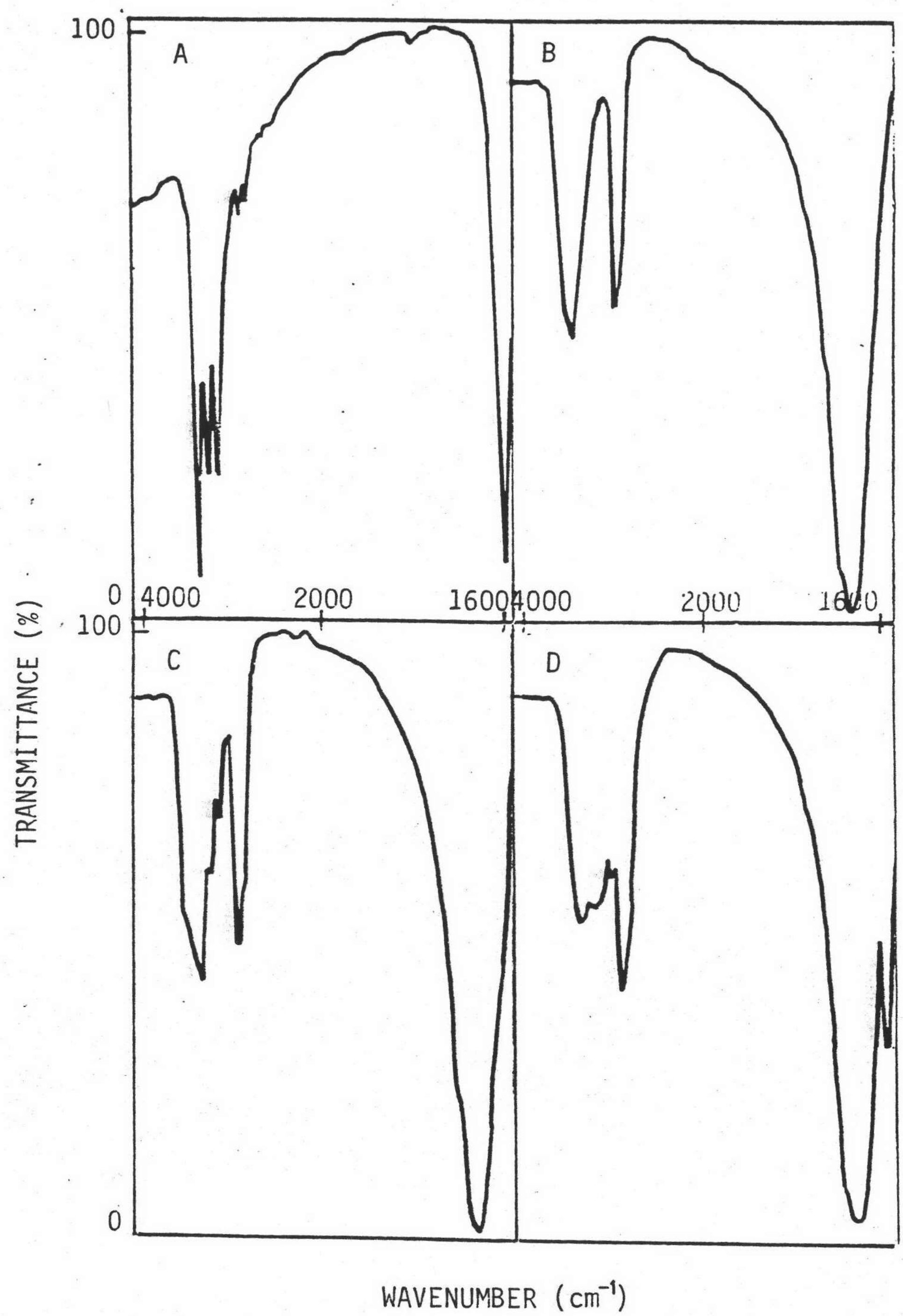

Figure 37 IR spectra of HCTZ-PVP K-17 systems

Key: A, HCTZ alone; B, PVP K-17 alone; C, 1:5 HCTZ-PVP K-17 physical mixture; D, 1:5 HCTZ-PVP K-17 coprecipitate.

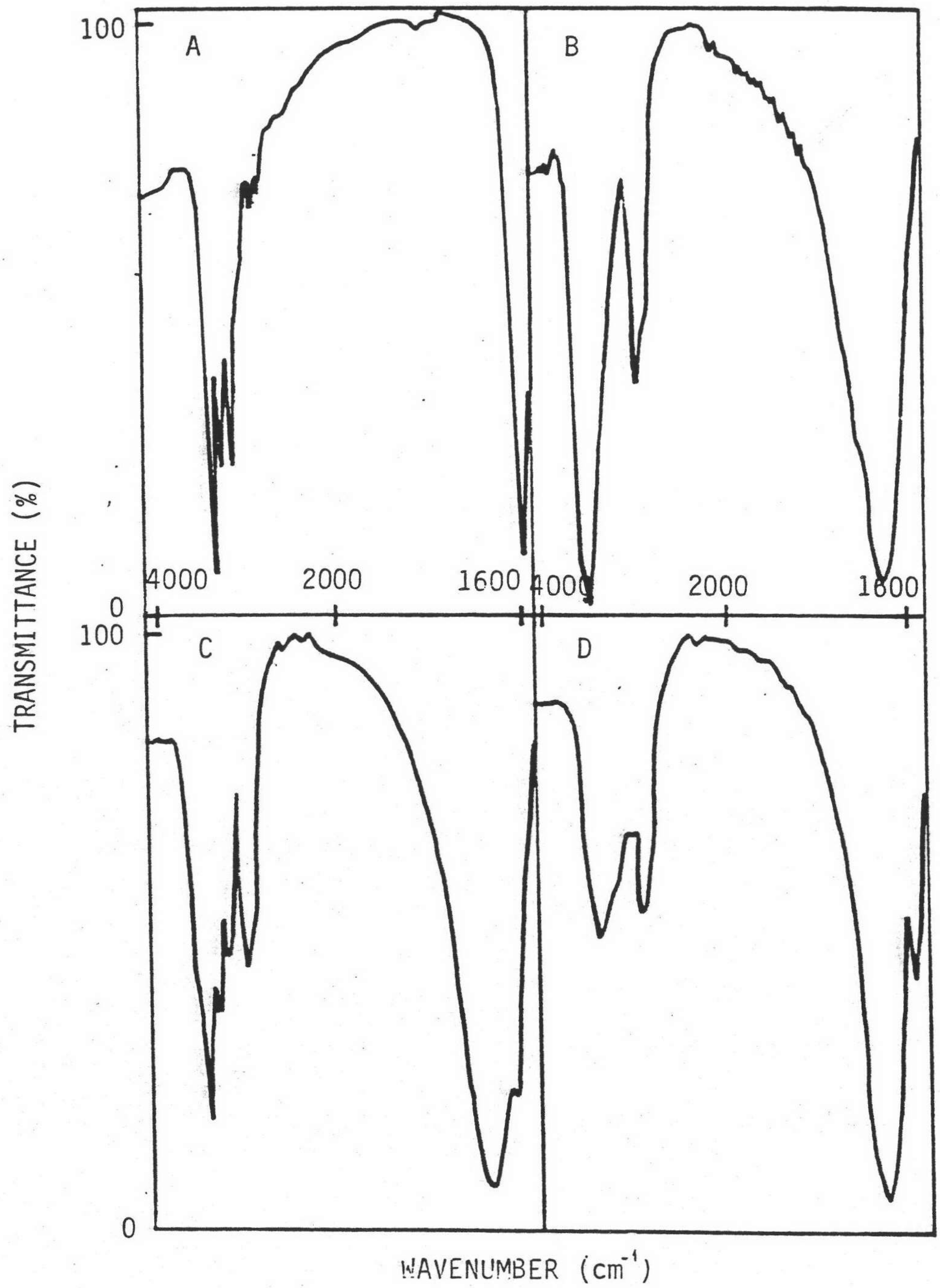

Figure 38 IR spectra of HCTZ-PVP K-30 systems

Key: a, HCTZ alone; B, PVP K-30 alone; C, 1:5 HCTZ-PVP K-30 physical mixture; D, HCTZ-PVP K-30 coprecipitate.

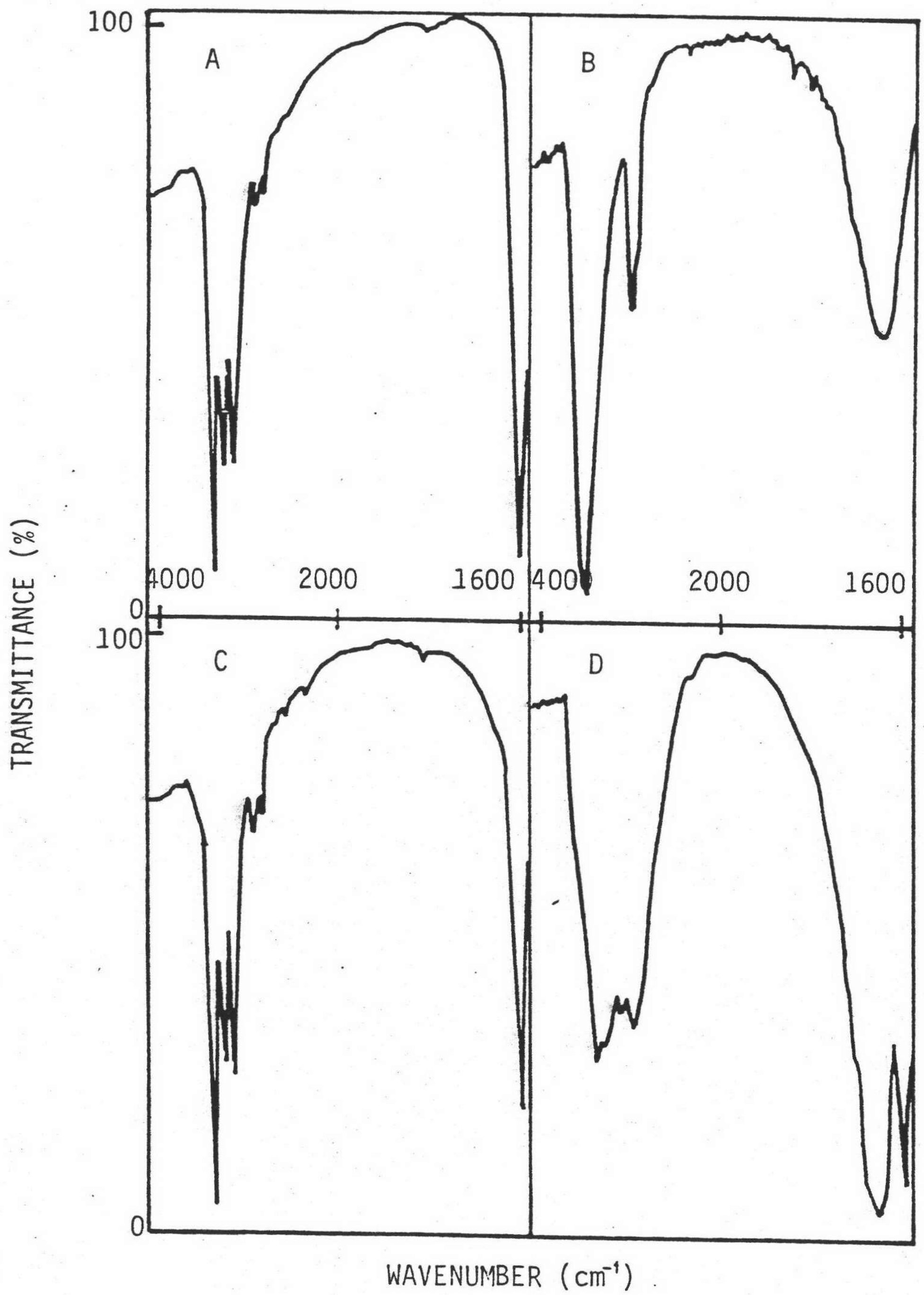

Figure 39 IR spectra of HCTZ-PVP K-90 systems

Key: A, HCTZ alone; B, PVP K-90 alone; C, 1:1 HCTZ-PVP K-90 physical mixture; D, 1:1 HCTZ-PVP K-90 coprecipitate.

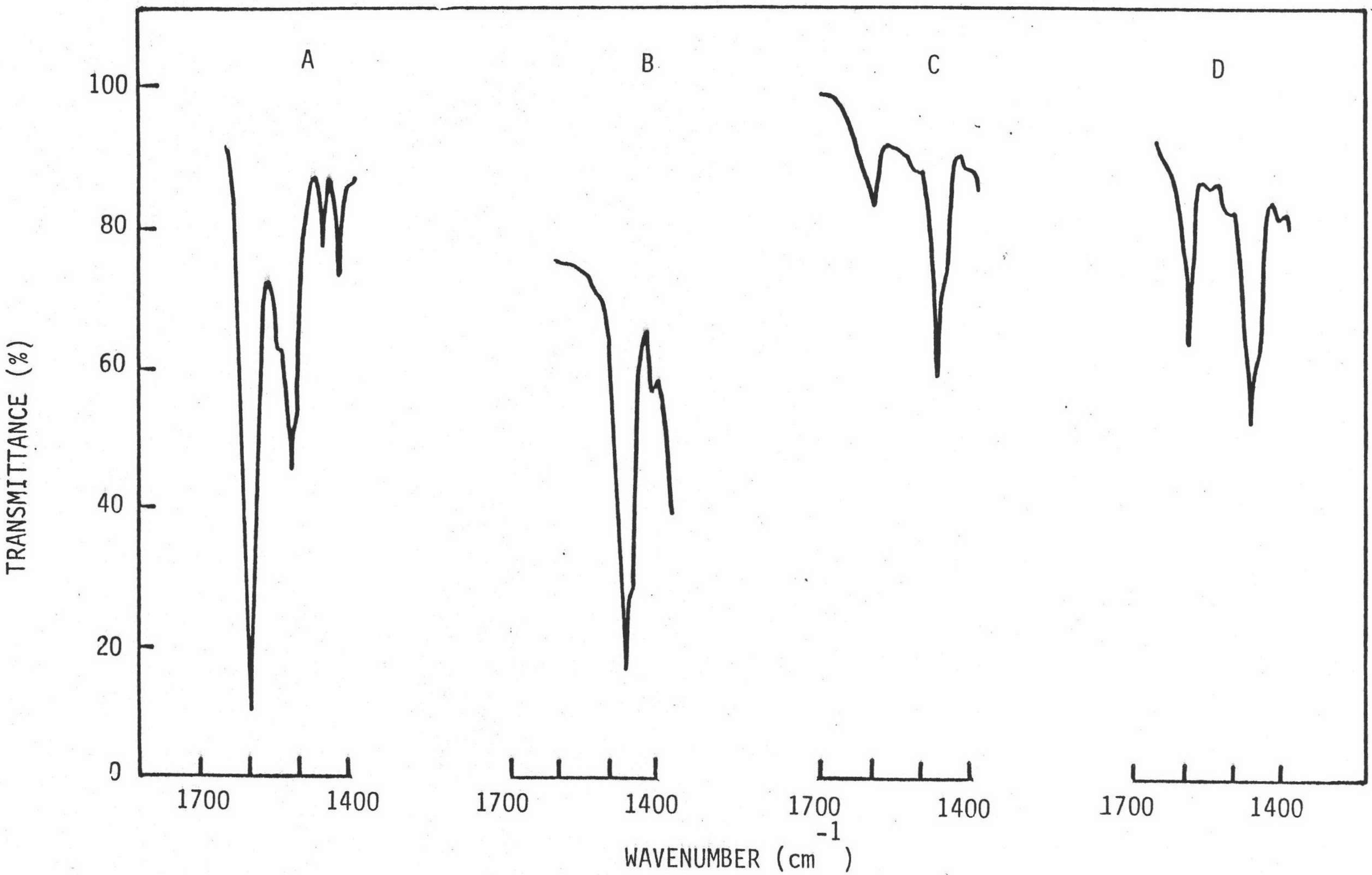

Figure 40 IR spectra of HCTZ-PEG 4000 systems

Key: A, HCTZ alone; B, PEG 4000 alone; C, 1:10 HCTZ-PEG 4000 physical mixture; D, 1:10 HCTZ -PEG 4000 coprecipitate.

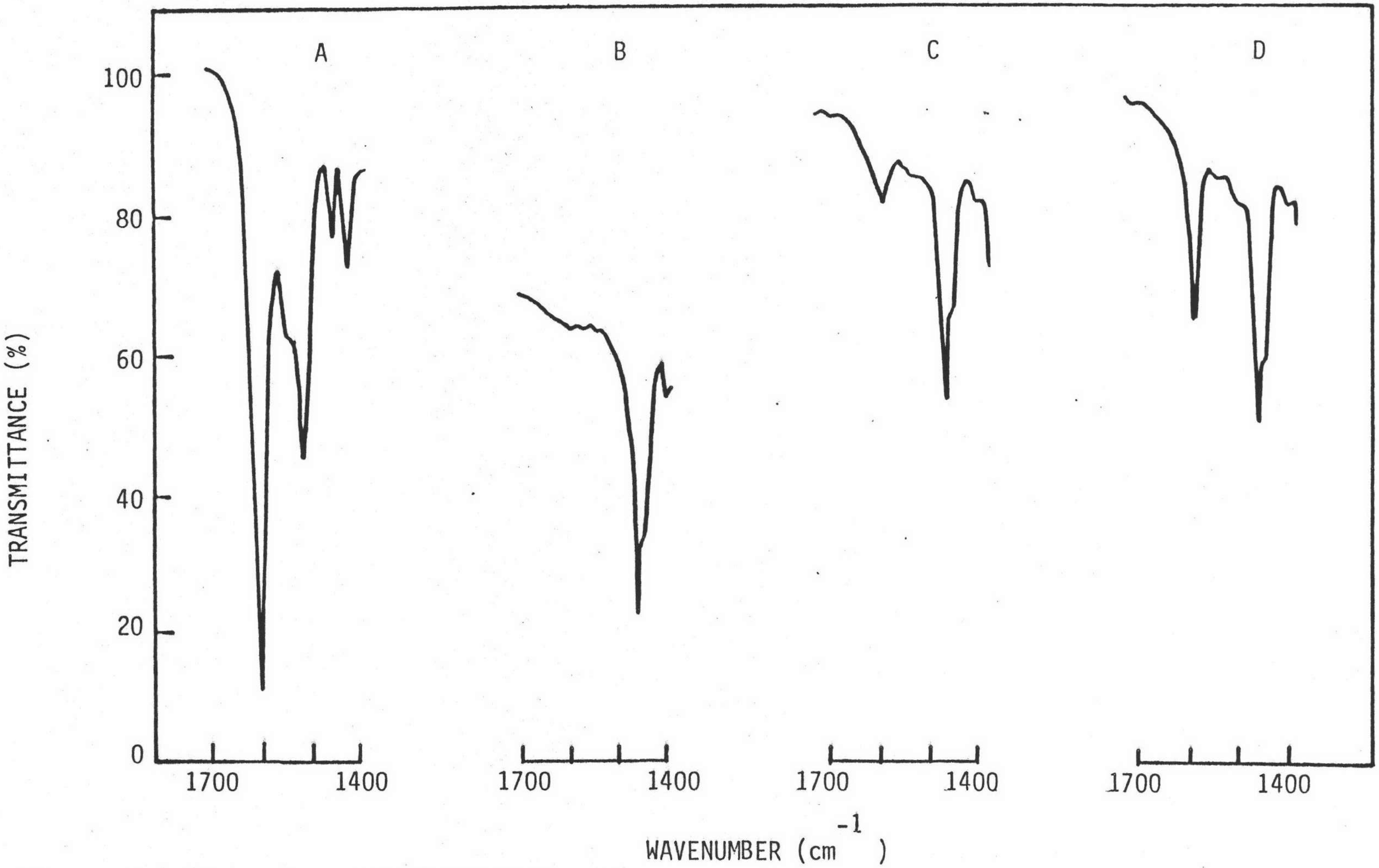

Figure 41 IR spectra of HCTZ-PEG 6000 systems
Key: A, HCTZ alone; B, PEG 6000 alone; C, 1:10 HCTZ-PEG 6000 physical mixture; D, 1:10 HCTZ-PEG 6000 coprecipitate.

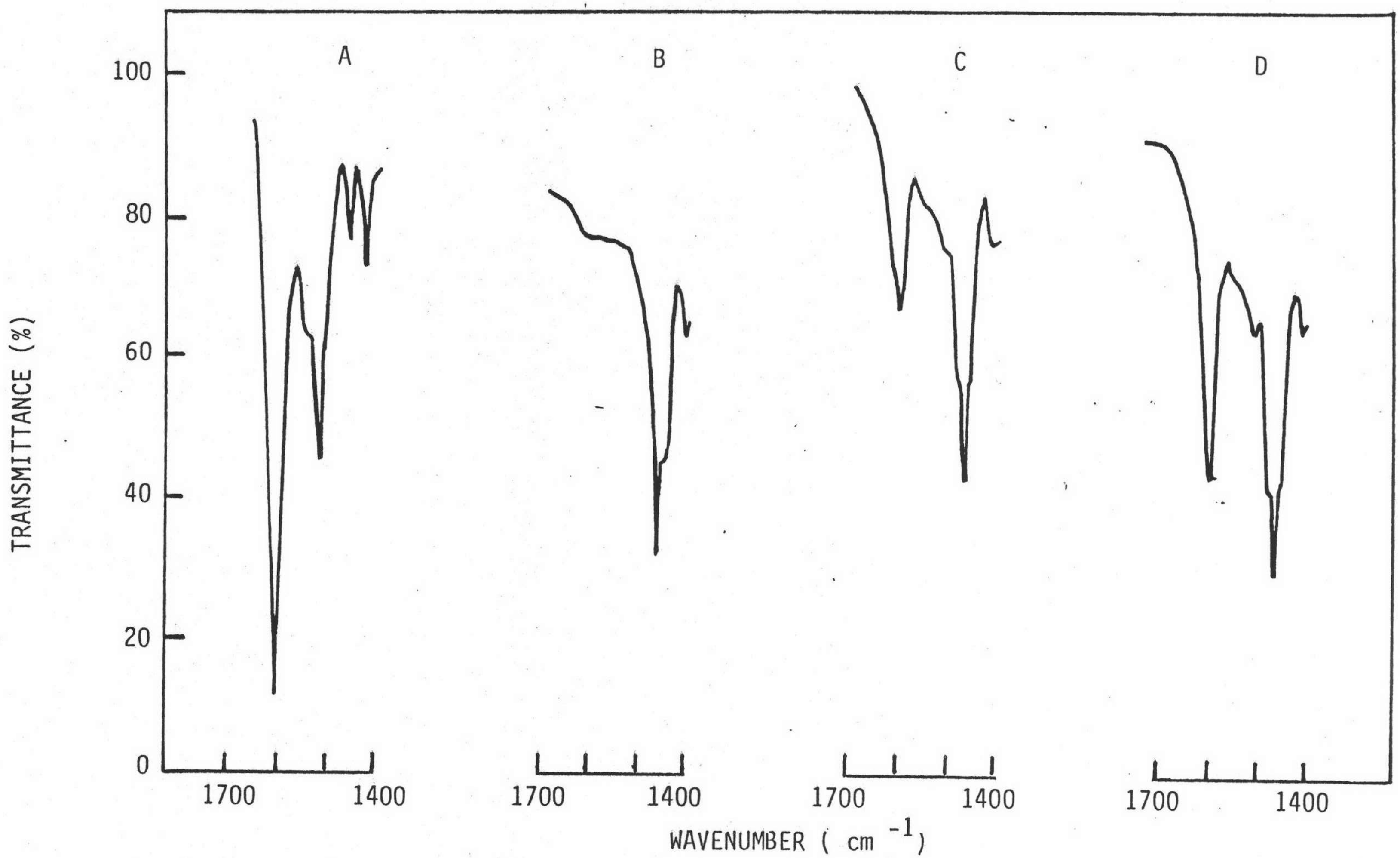

Figure 42 IR spectra of HCTZ-PEG 20000 systems Key: A, HCTZ alone; B, PEG 20000 alone; C, 1:10 HCTZ-PEG 20000 physical mixture; D, 1:10 HCTZ-PEG 20000 coprecipitate.

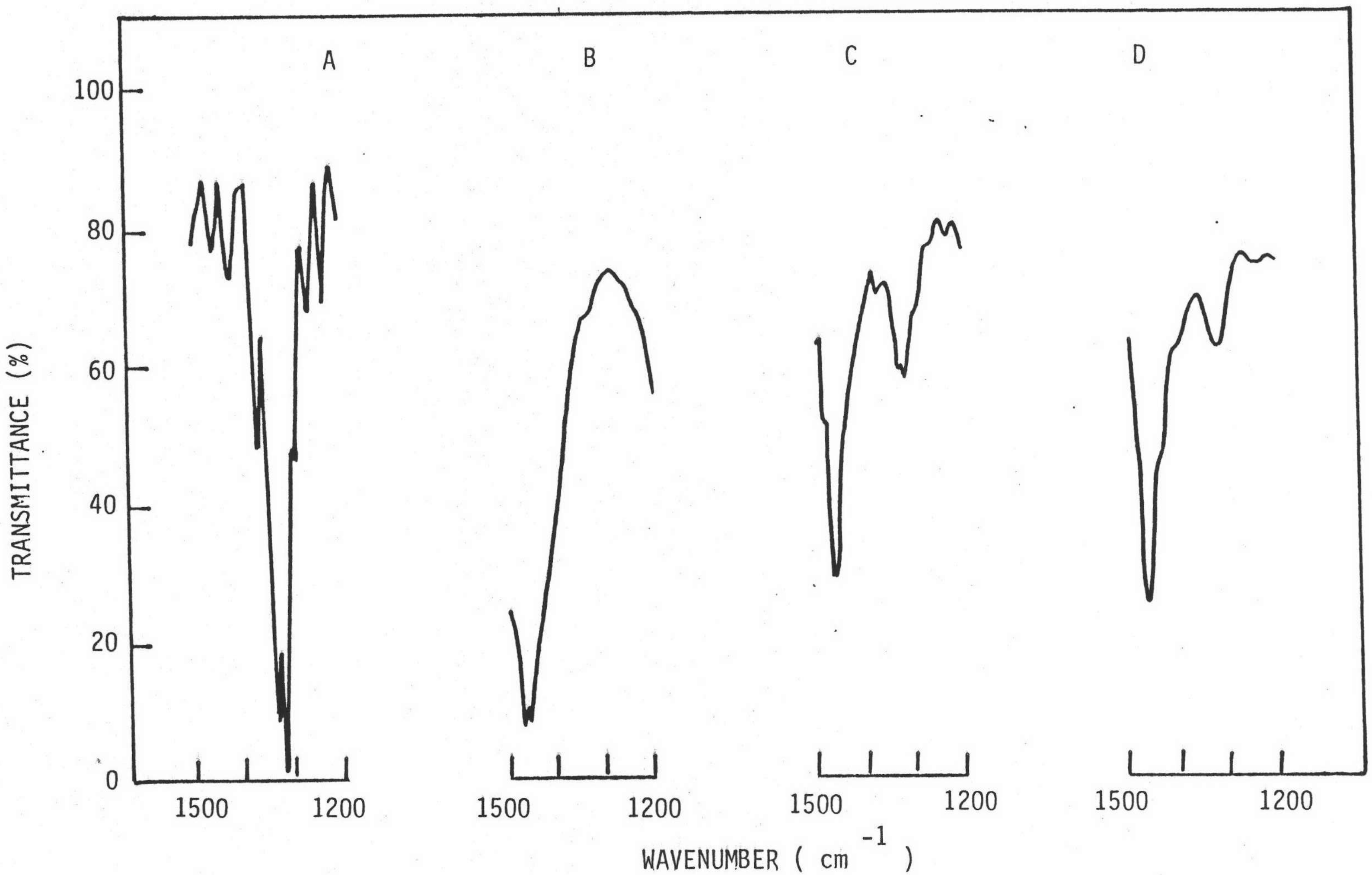

Figure 43 IR spectra Of HCTZ-urea systems Key: A, HCTZ alone; B, urea alone; C, 1:3 HCTZ-urea physical mixture; D, 1:3 HCTZ-urea melt.

DTA Thermograms

Thermograms of HCTZ alone, carriers, solid dispersions and physical mixtures of HCTZ and various carriers are shown 44-46. The thermogram of pure drug gave the characteristic melting endotherm at 268°C and the exotherm at 322°C while PVP and PEG showed the melting endotherm at 70 and 78 °C, respectively. Urea showed two melting endotherms at 125 and 240 °C, indicating different crystalline forms. HCTZ-PVP coprecipitates exhibited the characteristic melting endotherm of PVP but not that of HCTZ (Figure 44). Furthermore, HCTZ-PEG melts exhibit the characteristic melting endotherm of PEG but not that of HCTZ. The new endotherm did not occur (Figure 45). The HCTZ-urea melts showed two melting endotherms of urea which the endotherm at 240 °C was broad but did not show the melting endotherm of HCTZ (Figure 46).

Stability Studies

Percentage labeled amount of HCTZ in plained HCTZ portion and the 1:3 HCTZ-urea melts after storage under various conditions were shown in Table 26-27. At appropriate time intervals, HCTZ contents in the stored samples were determined. No significant decrease of HCTZ content in any systems after storage under these conditions was observed (Appendix B: Table 48-49).

The dissolution profiles, X-ray diffractograms, IR spectra, and DTA thermograms of pure drug and the melts after storage under various conditions were studied in order to investigate their physicochemical states.

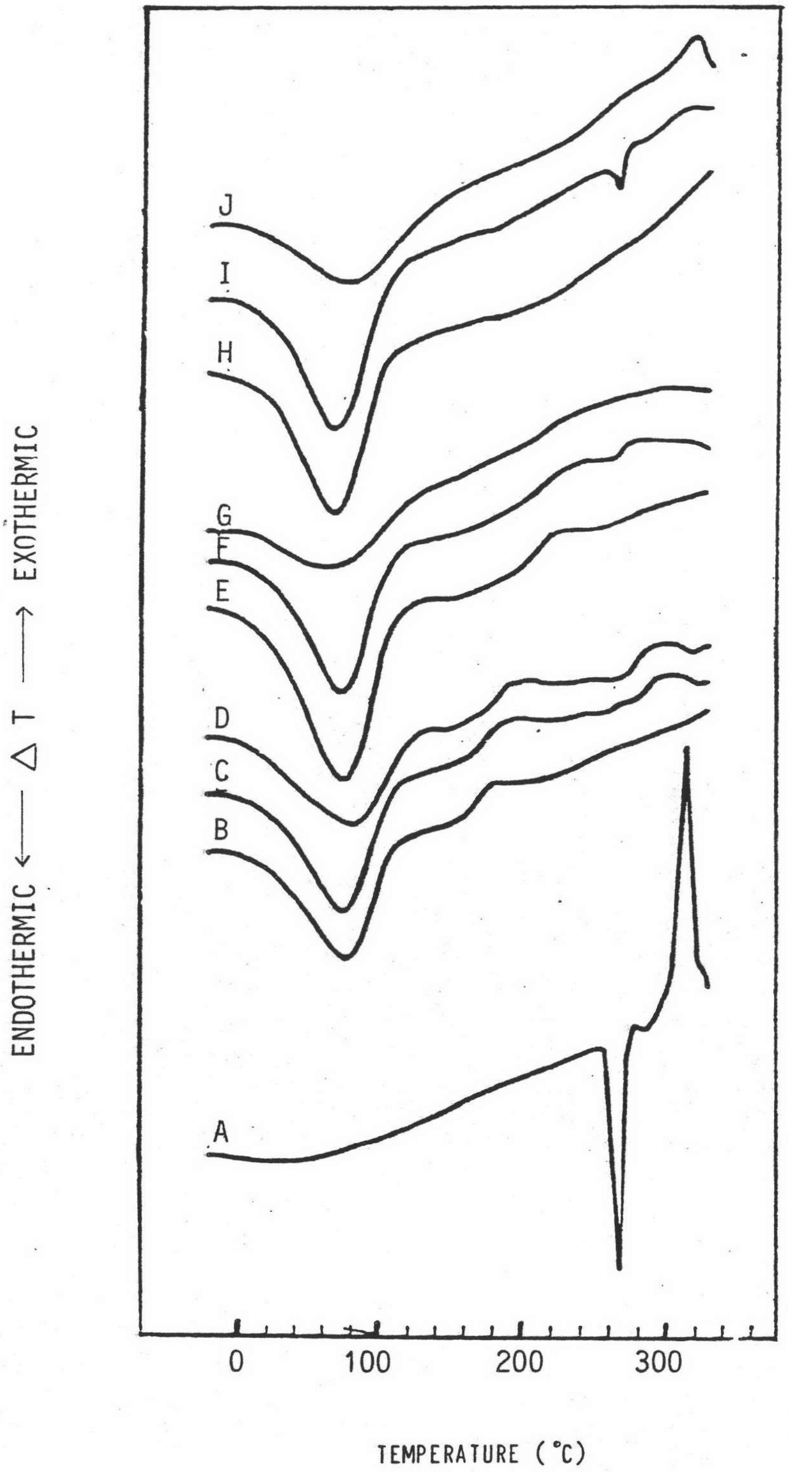

Figure 44 DTA Thermograms of HCTZ-PVP Systems Key: A, HCTZ alone; B, PVP K-17; C, 1:5 HCTZ-PVP K-17 Physical Mixture; D, 1:5 HCTZ-PVP K-17 Coprecipitate; E, PVP K-30; F, 1:5 HCTZ-PVP K-30 Physical Mixture; G, 1:5 HCTZ-PVP K-30 Coprecipitate; H, PVP K-90; I, 1:1 HCTZ-PVP K-90 Physical Mixture; J, 1:1 HCTZ-PVP K-90 Coprecipitate.

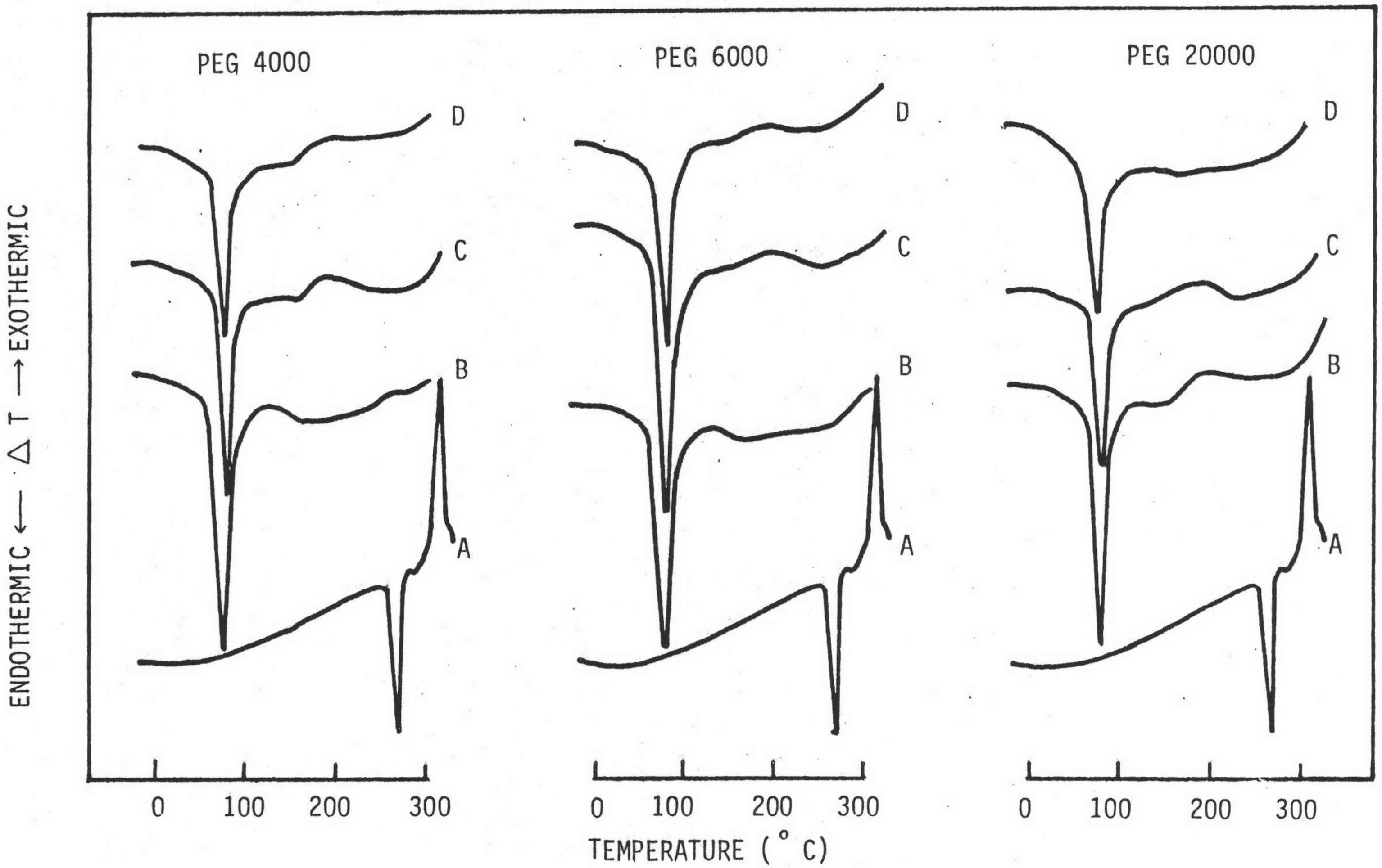

Figure 45 DTA thermograms of HCTZ-PEG systems Key; A, HCTZ alone; B, PEG alone; C, 1:10 HCTZ-PEG physical mixture; D, 1:10 HCTZ-PEG melt.

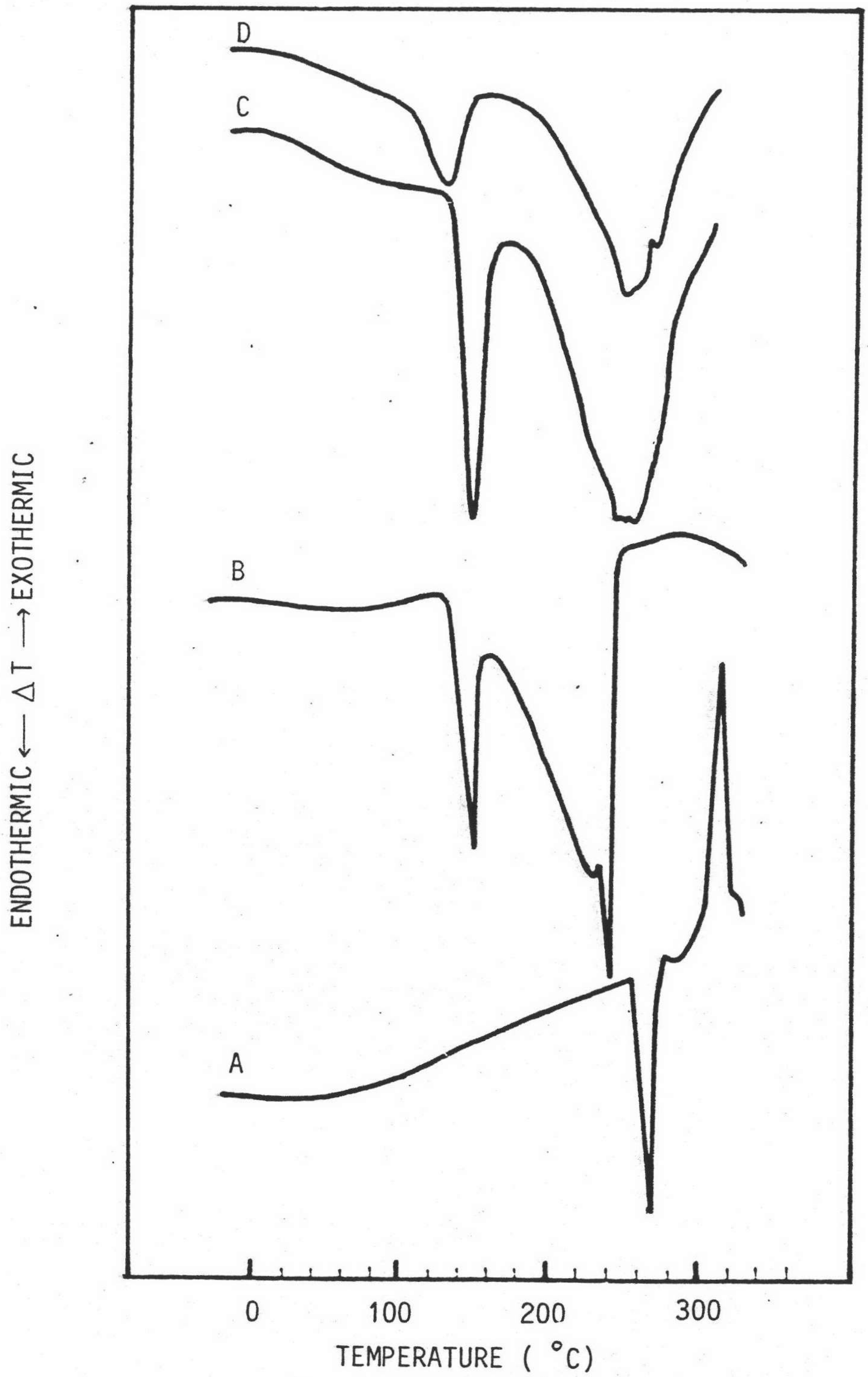

Figure 46 DTA thermograms of HCTZ-urea systems

Key: A, HCTZ alone; B, urea alone; C, 1:3 HCTZ-urea physical mixture; D, 1:3 HCTZ-urea melt.

Table 26 Percentage Labeled Amount and Dissolution of HCTZ from Pure HCTZ Storage under Various Conditions.

Storage Condition	% Labeled Amount[a]	Dissolution Rate Constant $\times 10^{-3}$ (min^{-1})	% HCTZ Dissolved at 5 Minutes[b]
0 day	99.70 (0.01)	34.60 (2.17)	22.703 (1.699)
Dry Storage			
10 days	99.74 (0.14)	29.88 (3.12)	28.032 (3.820)
30 days	99.64 (0.03)	34.69 (1.43)	29.165 (4.713)
Accelerated Storage (40°C)			
10 days	99.64 (0.17)	28.43 (3.32)	24.585 (2.358)
30 days	99.76 (0.17)	33.70 (9.08)	28.971 (2.291)
Moist Storage (75 ± 5 % R.H.)			
5 days	99.73 (0.85)	35.42 (3.75)	30.293 (3.896)
10 days	99.94 (0.14)	30.98 (0.78)	28.170 (2.052)
20 days	99.85 (0.01)	36.61 (5.12)	24.069 (1.401)
30 days	99.92 (0.14)	35.64 (4.35)	26.145 (2.008)

a Mean (S.D.) of two determinations

b Mean (S.D.) of three determinations

Table 27 Percentage Labeled Amount and Dissolution of HCTZ from 1:3 HCTZ-Urea Melt Storage under Various Conditions.

Storage Condition	% Labeled Amount[a]	% HCTZ Dissolved at 5 Minutes[b]
0 day	99.94 (0.30)	99.162 (0.205)
Dry Storage		
10 days	99.64 (0.16)	99.892 (0.096)
30 days	99.58 (0.40)	99.786 (0.096)
Accelerated Storage (40°C)		
10 days	99.68 (0.82)	99.465 (0.168)
30 days	99.86 (0.07)	99.628 (0.083)
Moist Storage (75 ± 5% R.H.)		
5 days	99.12 (0.37)	95.218 (0.204)
10 days	98.99 (0.84)	94.875 (0.172)
20 days	99.64 (0.16)	92.309 (0.490)
30 days	99.44 (0.35)	89.938 (1.143)

a Mean (S.D.) of two determinations

b Mean (S.D.) Of three determinations

1. Dissolution Behavior

Dissolution rates of pure HCTZ after storage under various conditions were not significantly different from those before storage (Figure 47-50, Table 26,28, Appendix B: Table 50).

Before storage, the melt dissolved rapidly, the peak of HCTZ dissolved from the melt was achieved within 5 minutes of dissolution. Storage at ambient or 40°C in dry place had no effect on the dissolution behavior of the melts, the peak of HCTZ dissolved from the melts was still achieved within 5 minutes (Figure 51, Table 29). The amount of HCTZ dissolved from the stored melts were not significantly different from before storage (Table 30). On the other hand, storage under humid condition (75% R.H. at ambient temperature) resulted in a marked change of dissolution behavior (Figure 52). The peak of HCTZ dissolved was not achieved within 5 minutes and the percentage amount of HCTZ dissolved were significantly decreased (Table 29-30). Thus the longer storage, the slower dissolution rate and the smaller percentage amount of HCTZ dissolved were shown.

2. X-ray Diffraction Patterns

X-ray diffraction patterns of the melts before and after storage under various conditions are shown in Figure 53. The diffraction pattern of the initial melt did not show any sharp peak attributable to that of HCTZ. After storage at 40°C for 30 days or 75% R.H. for 5, 10, 20, or 30 days, the melts showed a slightly change of the diffraction pattern. However, the diffraction peak attributable to HCTZ crystal was observed, but not sharp.

Table 28 The Effect of Storage on Dissolution of HCTZ from Pure HCTZ.

Time (min)	Percentage Amount of HCTZ Dissolved[a]								
	Freshly	**Dry Storage**		**Accelerated Storage**		**Moist Storage**			
	Prepared	10 days	30 days	10 days	30 days	5 days	10 days	20 days	30 days
0	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)
2	8.005 (1.186)	7.112 (1.243)	8.003 (1.160)	3.600 (0.639)	5.911 (1.434)	5.024 (1.378)	6.950 (0.951)	6.193 (0.537)	11.421 (1.462)
5	22.703 (1.699)	28.032 (3.820)	29.165 (4.713)	24.585 (2.358)	28.971 (2.291)	30.293 (3.896)	28.170 (2.052)	24.069 (1.401)	26.145 (2.008)
10	41.403 (2.216)	45.751 (0.287)	40.493 (4.357)	42.958 (1.327)	48.206 (2.798)	48.754 (3.980)	45.125 (1.548)	44.879 (2.326)	36.042 (1.231)
15	53.151 (0.885)	55.080 (1.817)	52.649 (1.495)	51.787 (2.380)	52.465 (2.113)	59.531 (4.509)	56.553 (1.381)	57.497 (3.319)	49.618 (1.463)
20	60.722 (1.358)	59.882 (0.970)	59.721 (1.591)	55.898 (4.243)	57.328 (3.452)	65.665 (6.073)	60.030 (1.875)	62.258 (3.372)	56.708 (3.063)
25	64.834 (1.852)	63.029 (2.248)	65.799 (3.151)	59.674 (4.780)	60.034 (4.785)	69.811 (5.369)	63.673 (2.052)	67.020 (2.926)	63.808 (4.856)
30	67.356 (2.515)	65.016 (3.161)	68.286 (1.935)	61.728 (5.338)	62.742 (5.699)	72.520 (5.395)	65.827 (2.015)	69.683 (2.726)	67.380 (5.500)
45	71.798 (2.906)	68.438 (2.650)	76.906 (0.999)	67.335 (6.203)	67.938 (6.783)	77.831 (5.305)	70.523 (1.775)	75.832 (2.429)	75.175 (4.613)
60	74.265 (2.680)	73.241 (2.873)	81.105 (1.035)	72.387 (7.394)	72.195 (7.242)	82.254 (3.525)	73.892 (1.793)	79.322 (1.904)	80.728 (4.352)
90	78.542 (2.344)	79.478 (4.445)	87.901 (2.037)	78.993 (7.819)	78.113 (6.550)	86.732 (3.264)	80.191 (1.593)	85.074 (1.317)	87.597 (3.250)
120	81.998 (2.090)	84.225 (4.223)	91.438 (1.635)	84.710 (6.569)	81.767 (5.733)	90.270 (3.519)	84.445 (1.743)	88.114 (2.183)	90.947 (2.531)

a Mean (S.D.) of three determinations

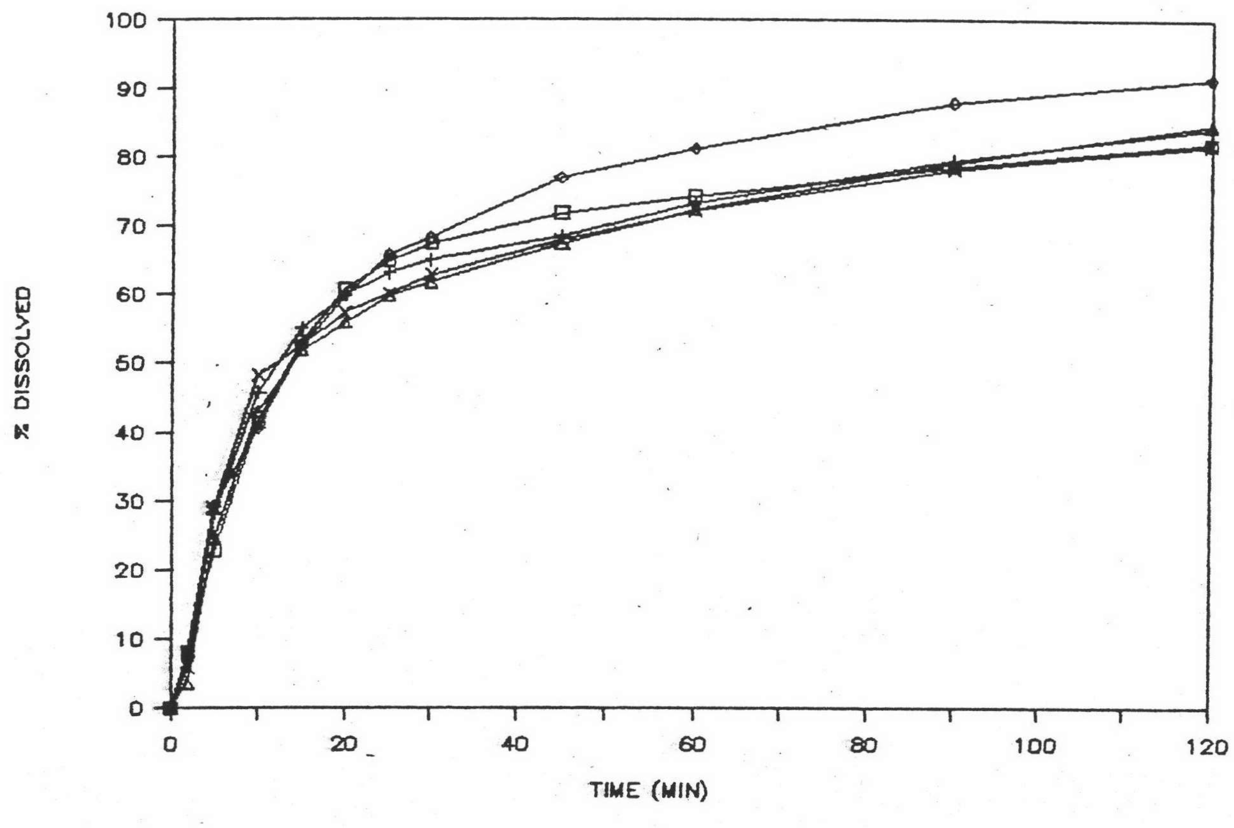

Figure 47 The effect of storage on dissolution profiles of HCTZ from pure HCTZ (□ 0 day, + dry storage 10 days, ◇ dry storage 30 days, △ accelerated storage 10 days, × accelerated storage 30 days).

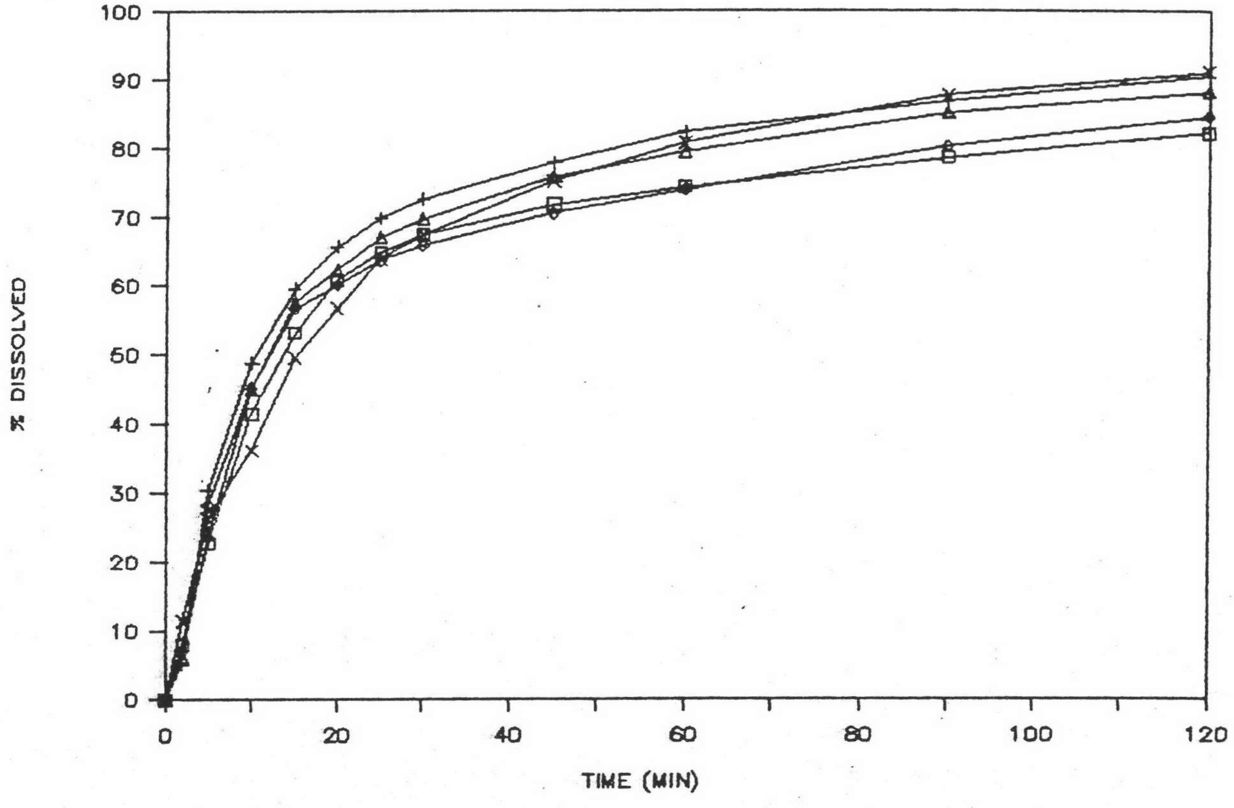

Figure 48 The effect of moist storage on dissolution profiles of HCTZ from pure HCTZ (□ 0 day, + 5 days, ◇ 10 days, △ 20 days, × 30 days).

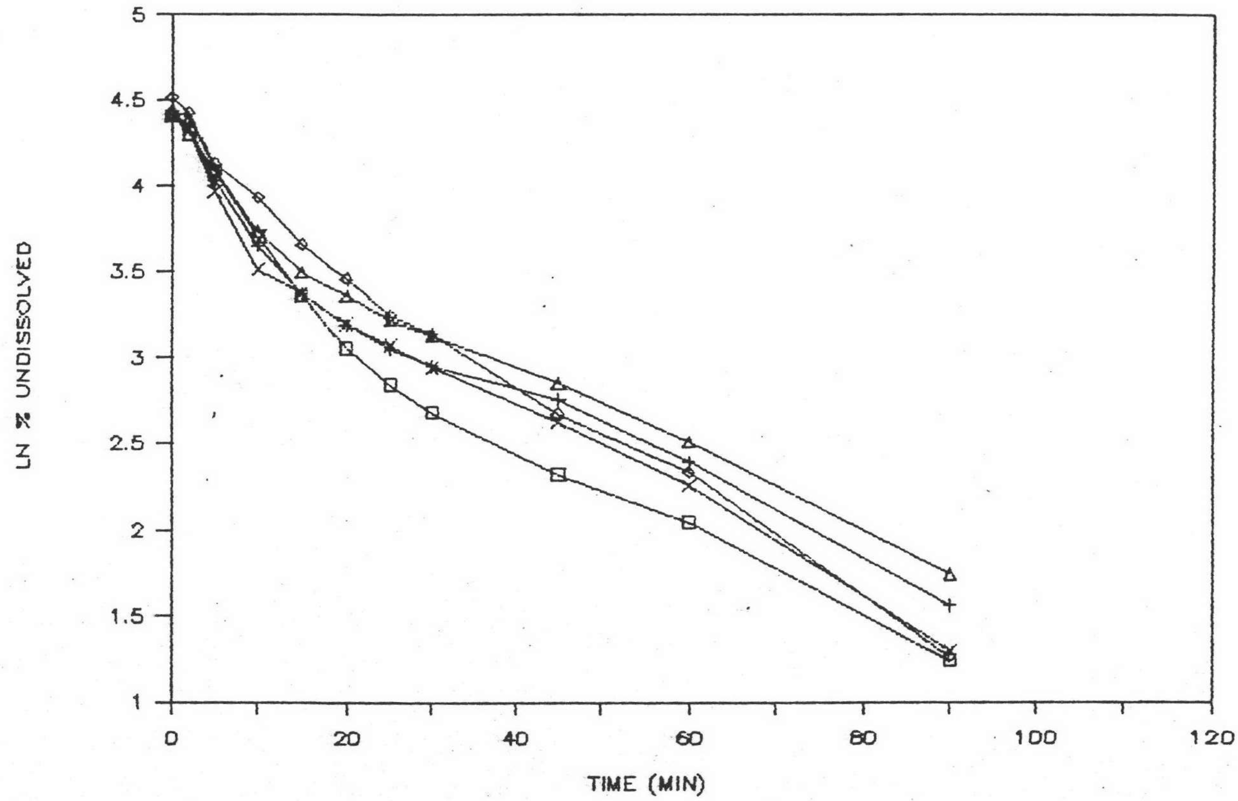

Figure 49 The first order plot between ln %HCTZ undissolved versus time for stored pure HCTZ (□ 0 day, + dry storage 10 days, ◊ dry storage 30 days, △ accelerated storage 10 days, × accelerated storage 30 days).

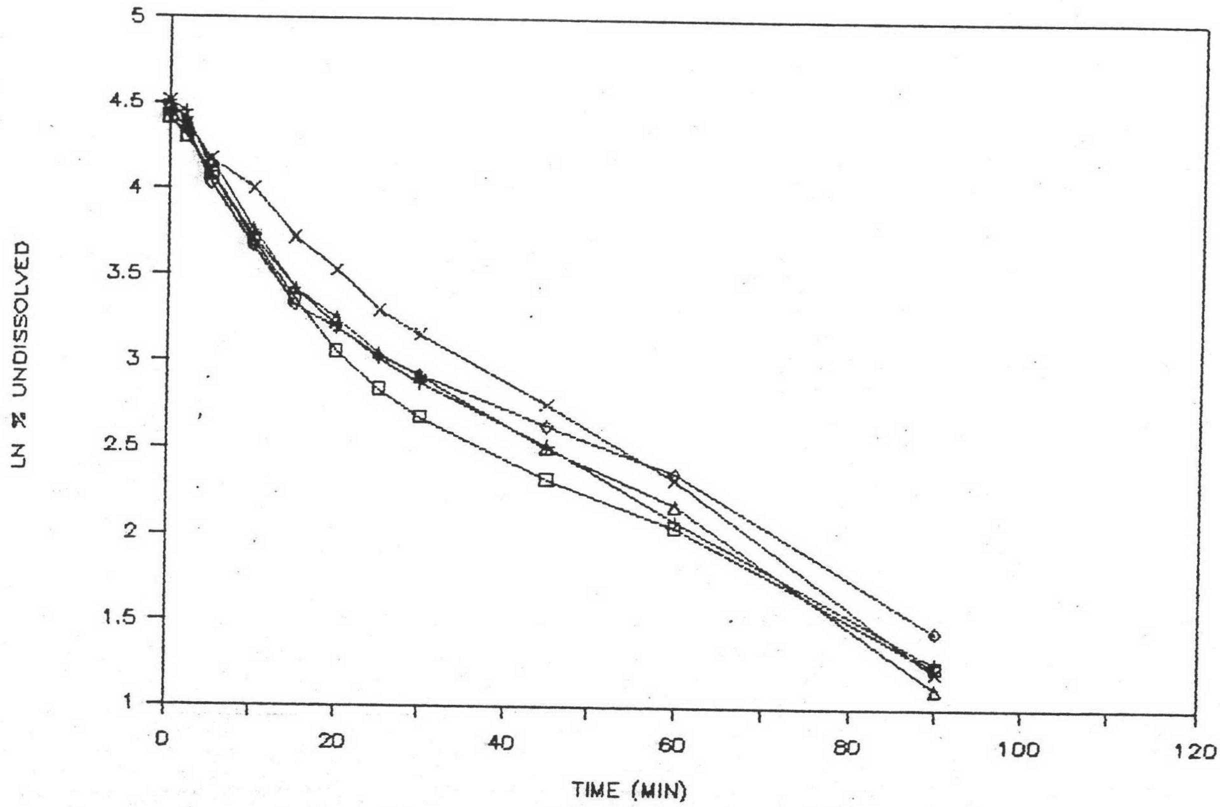

Figure 50 The first order plot between ln % HCTZ undissolved versus time for stored pure HCTZ (moist storage: □ 0 day, + 5 days, ◊ 10 days, △ 20 days, × 30 days).

Table 29 The Effect of Storage on Dissolution of HCTZ from 1:3 HCTZ-Urea Melt.

Time (min)	Percentage Amount of HCTZ Dissolved[a]								
	0	**Dry Storage**		**Accelerated Storage**		**Moist Storage**			
	day	10 days	30 days	10 days	30 days	5 days	10 days	20 days	30 days
0	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)
2	97.843 (0.176)	98.289 (0.345)	97.906 (0.598)	78.464 (10.573)	86.994 (0.045)	78.104 (5.244)	75.543 (0.123)	78.681 (1.666)	81.646 (0.961)
5	99.162 (0.205)	99.892 (0.096)	99.786 (0.096)	99.465 (0.168)	99.628 (0.083)	95.218 (0.204)	94.875 (0.172)	92.309 (0.490)	89.938 (1.143)
10	98.668 (0.204)	99.560 (0.096)	99.399 (0.166)	99.078 (0.250)	99.352 (0.057)	97.608 (0.246)	95.708 (0.100)	93.302 (0.125)	93.474 (0.361)
15	98.119 (0.336)	99.008 (0.166)	98.846 (0.096)	98.525 (0.505)	99.021 (0.057)	97.441 (0.515)	94.930 (0.826)	92.861 (0.220)	93.142 (0.503)
20	97.789 (0.171)	98.400 (0.253)	98.349 (0.192)	97.918 (0.419)	98.690 (0.057)	97.274 (0.515)	95.153 (0.180)	92.530 (0.133)	92.755 (0.471)
25	97.129 (0.170)	97.681 (0.166)	97.740 (0.166)	97.587 (0.357)	98.469 (0.083)	97.108 (0.516)	94.820 (0.024)	92.144 (0.125)	92.479 (0.504)
30	96.800 (0.169)	97.405 (0.096)	97.298 (0.192)	96.868 (0.346)	98.138 (0.225)	96.179 (0.500)	93.931 (0.116)	91.757 (0.203)	91.981 (0.505)
45	96.195 (0.200)	96.632 (0.096)	96.579 (0.166)	96.482 (0.505)	97.807 (0.225)	96.497 (0.263)	93.431 (0.101)	91.316 (0.125)	91.871 (0.457)
60	96.030 (0.092)	95.913 (0.096)	95.861 (0.096)	95.874 (0.512)	97.918 (0.891)	96.330 (0.425)	92.875 (0.079)	91.206 (0.075)	91.595 (0.315)
90	95.426 (0.104)	95.748 (0.096)	95.584 (0.166)	95.488 (0.286)	97.090 (0.269)	95.551 (0.502)	91.986 (0.182)	90.930 (0.203)	91.152 (0.464)
120	94.877 (0.198)	95.306 (0.096)	95.031 (0.096)	94.935 (0.383)	96.924 (0.170)	95.162 (0.427)	91.597 (0.103)	90.654 (0.182)	90.433 (0.490)

a Mean (S.D.) of three determinations

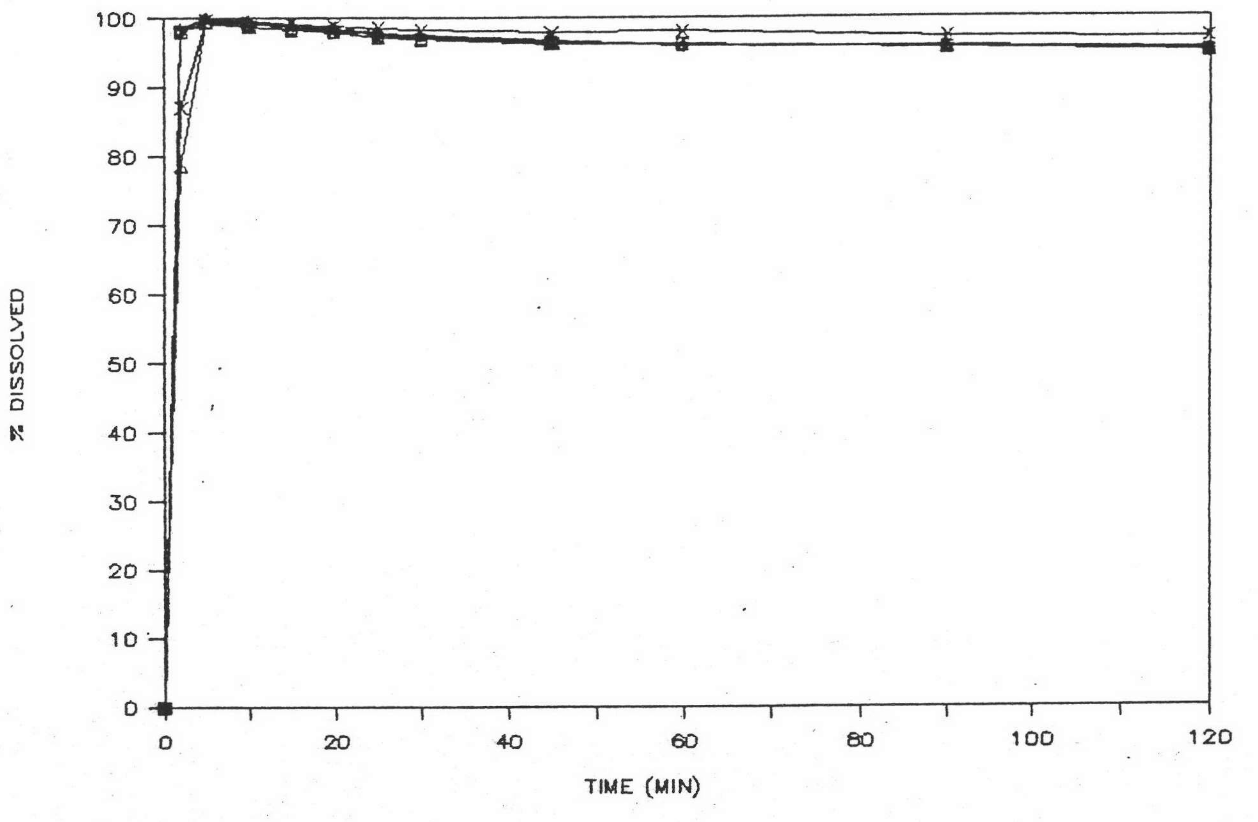

Figure 51 The effect of storage on dissolution profiles of HCTZ from 1:3 HCTZ-urea melt (□ 0 day, + dry storage 10 days, ◊ dry storage 30 days, △ accelerated storage 10 days, × accelerated storage 30 days).

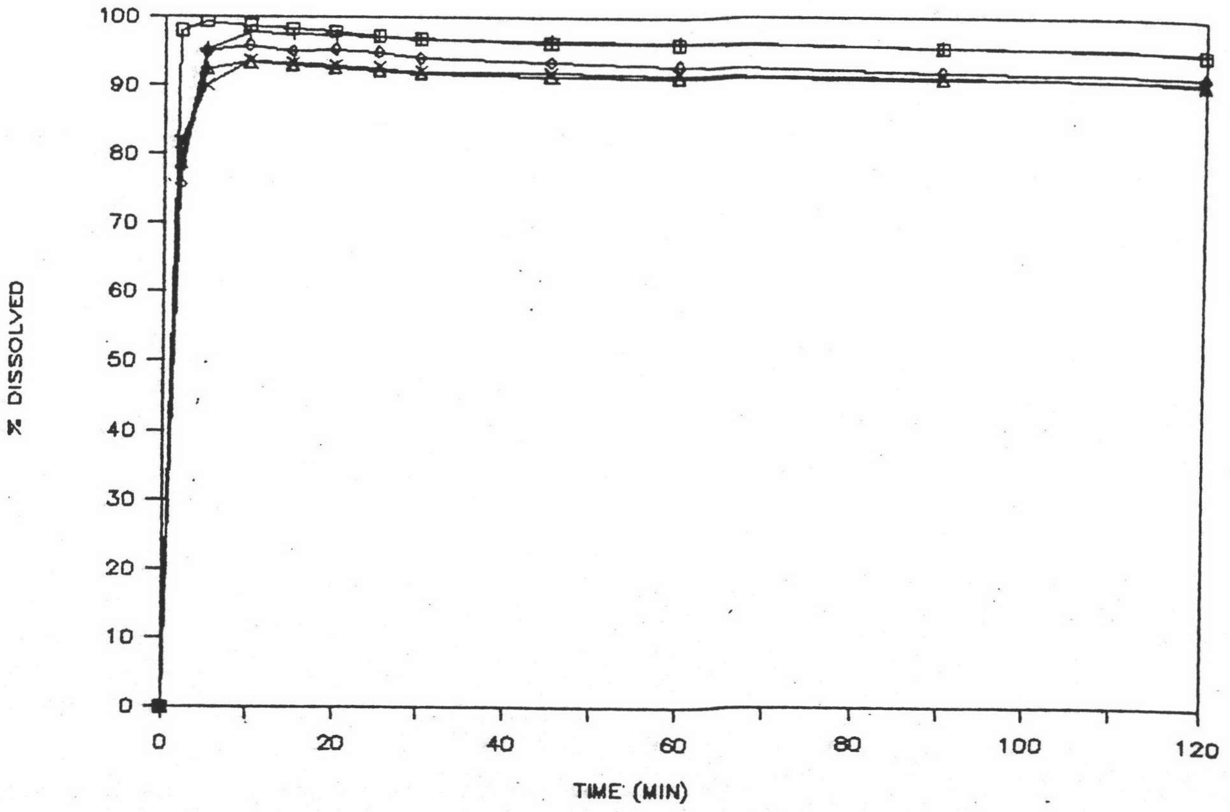

Figure 52 The effect of moist storage on dissolution profiles of HCTZ from HCTZ-urea melt (□ 0 day, + 5 days, ◇ 10 days, △ 20 days, × 30 days).

Table 30 Multiple Comparison (HSD Test) for Percentage Amount of HCTZ Dissolved at 5 Minutes of 1:3 HCTZ-Urea Melt with Various Storage Conditions [Dry Storage (a), Accelerated Storage (b) and Moist Storage (c)] and Pure Drug.

A \ B	Pure Drug		a		b		c			
		days 0	10	30	10	30	5	10	20	30
Pure Drug	-	@	@	@	@	@	@	@	@	@
0 day	*	-	NS	NS	NS	NS	*	*	*	*
a, 10 days	*	NS	-	NS	NS	NS	*	*	*	*
a, 30 days	*	NS	NS	-	NS	NS	*	*	*	*
b, 10 days	*	NS	NS	NS	-	NS	*	*	*	*
b, 30 days	*	NS	NS	NS	NS	-	*	*	*	*
c, 5 days	*	@	@	@	@	@	-	NS	*	*
c, 10 days	*	@	@	@	@	@	NS	-	*	*
c, 20 days	*	@	@	@	@	@	@	@	-	*
c, 30 days	*	@	@	@	@	@	@	@	@	-

$q_{0.05,10,20} = 5.01$, HSD = 2.0833

NS not significantly different, $\alpha = 0.05$

@ A is significantly less than B, $\alpha = 0.05$

* A is significantly more than B, $\alpha = 0.05$

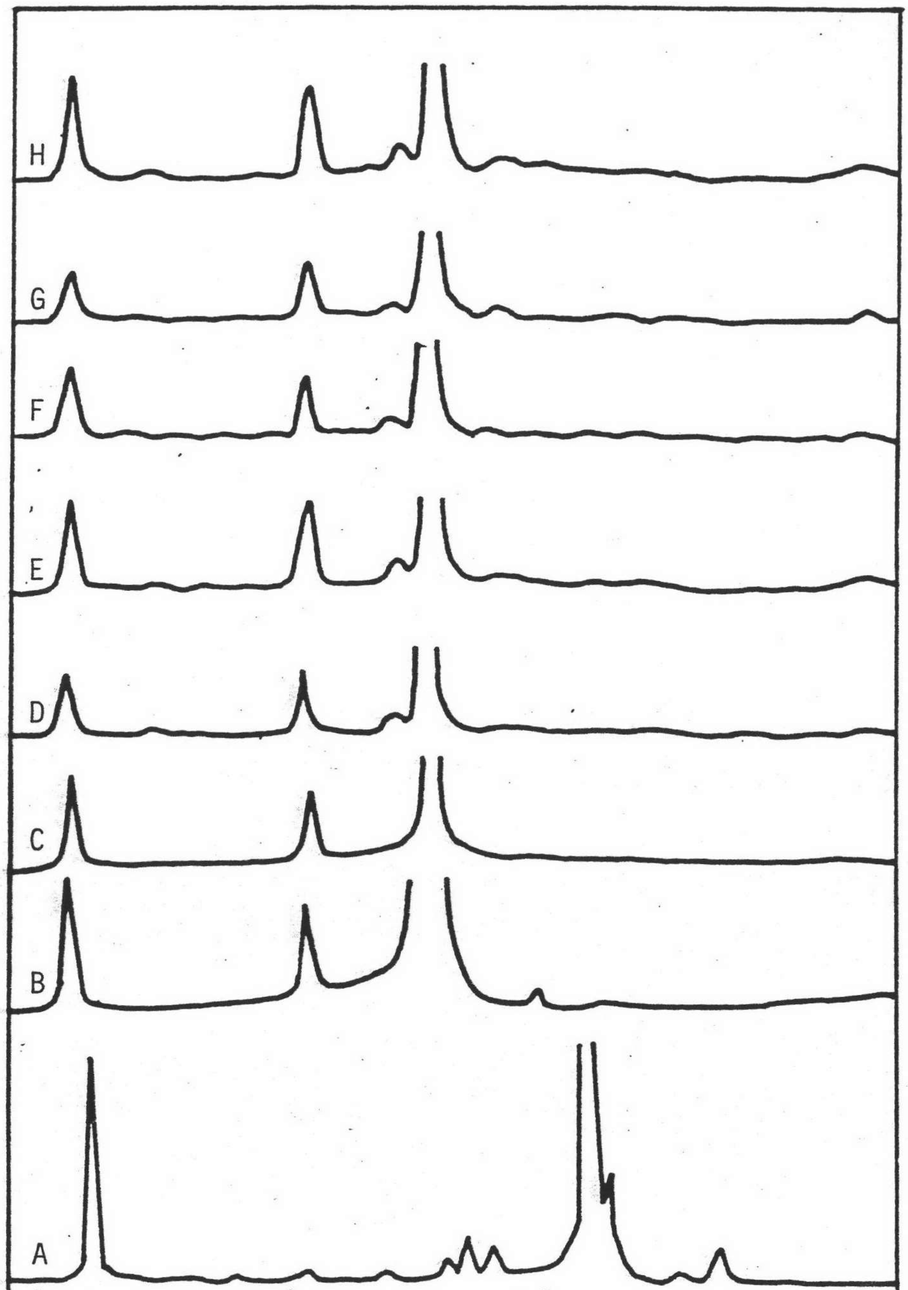

Figure 53 X-ray diffraction spectra of HCTZ, urea, and stored 1:3 HCTZ-urea melt (A, HCTZ, B, urea, C, 0 day, D, accelerated storage 30 days, E, F, G, and H, moist storage 5, 10, 20, and 30 days, respectively).

3. IR Spectra

After storage at 40 °C for 30 days or 75% R.H. for a short time, the melt showed the stronger intensity of doublet peak at 1335 and 1320 cm^{-1} . The longer storage, the stronger intensity of the peak was shown (Figure 54).

4. DTA Thermograms

The initial melt did not show the melting endotherm of HCTZ at 268 °C. But after storage at 40 °C for 30 days or 75% R.H. for 5 or 30 days, the melting endotherm of HCTZ was shown and became stronger with the longer storage (Figure 55).

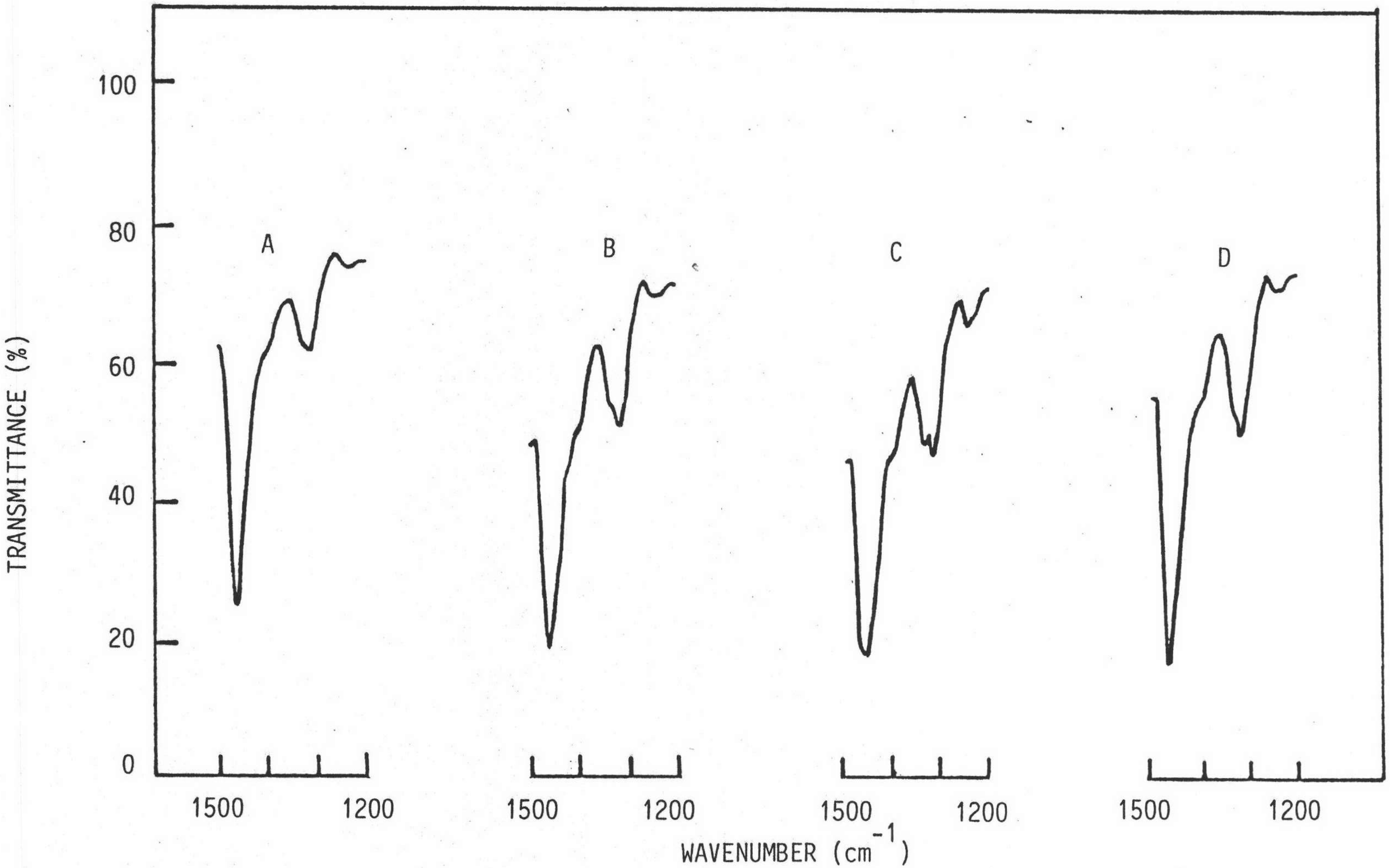

Figure 54 IR spectra of stored 1:3 HCTZ-urea melt (A, 0 day, B, moist storage 5 days, C, moist storage 30 days, D, accelerated storage 30 days).

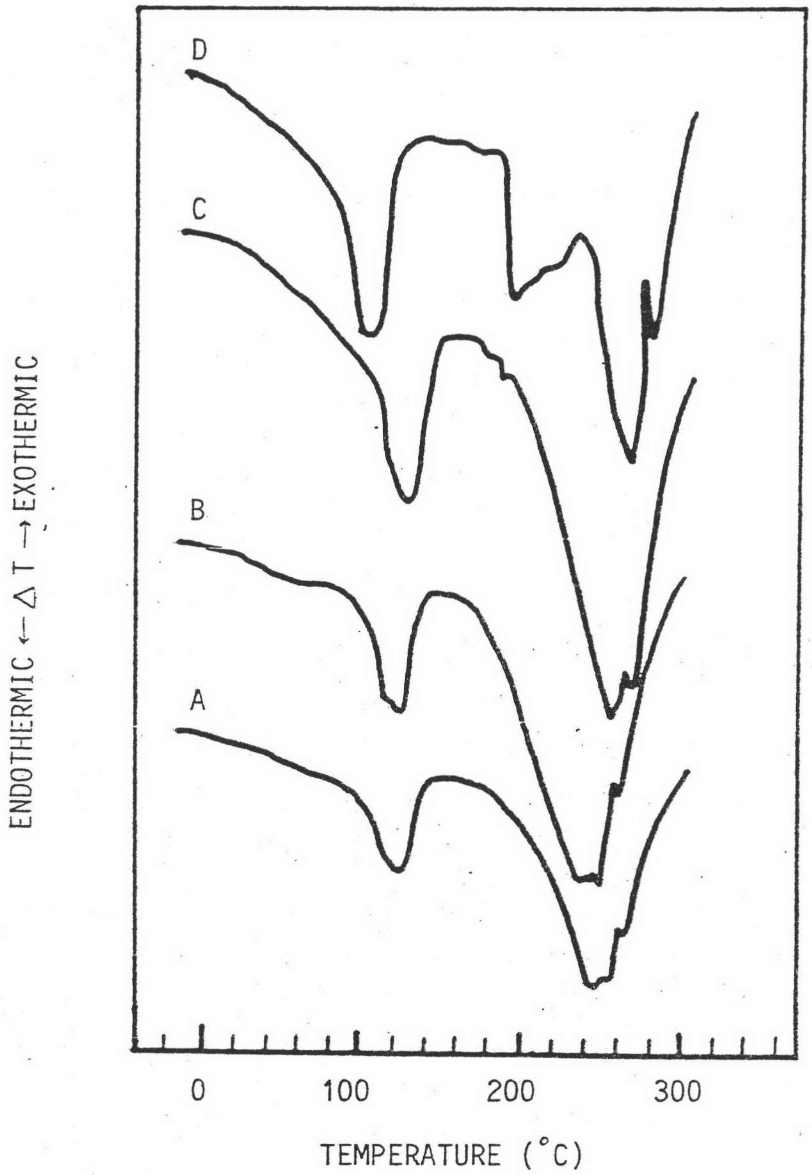

Figure 55 DTA thermograms of stored 1:3 HCTZ-urea melt (A, 0 day, B, accelerated storage 30 days, C, moist storage 5 days, D, moist storage 30 days).