DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY, 20(17), 2729-2740 (1994)

DISSOLUTION RATE STUDY OF FRESH AND AGING TRIAMTERENE-UREA SOLID DISPERSIONS

J.M. GINES, M.J. ARIAS, M.A. HOLGADO, M.F. AREVALO, A.M. RABASCO

Departamento de Farmacia y Tecnología Farmacéutica,
Cátedra de Farmacia Galénica, Facultad de Farmacia,
C/ Profesor García González, s/n, Universidad de Sevilla,
41012 Sevilla (Spain)

ABSTRACT

Triamterene-urea solid dispersions of varying weight fractions were elaborated by the melting carrier method and their dissolution profiles compared with the pure drug and physical mixtures. The dissolution rates of triamterene from solid dispersions were faster than the pure drug and physical mixtures.

Solubility studies revealed a linear increase in the solubility of the triamterene with the increase of urea concentration.

The intrinsic dissolution rates, determined by the rotating disc method, showed linear dissolution profiles in spite of that the scanning electron microscopy examination revealed that the surfaces do not maintain constant during the dissolution process.

Aging of the different preparations for one year at room temperature does not induced significant changes in their dissolution profiles.

INTRODUCTION

Triamterene is a pteridine derivative, potassium-sparing diuretic which is structurally related to folic acid. It is practically insoluble in water and very slightly soluble in alcohol (1). This limited aqueous solubility in gastrointestinal fluids may create variation in its dissolution rate and consequently in its bioavailability. It is reported that slow release from dosage forms results in incomplete, erratic and unpredictable absorption (2).

Triamterene is not a recent drug. In spite of this circumstance, there are only a few studies about solid dispersions containing this drug (3 - 5).

Urea has been extensively used for preparing solid dispersions (6 - 9); it has been shown to increase the dissolution rate of poorly soluble drugs and shows the best results when it is compared with other carriers (10 - 11).

As a continuing part of our studies on solid dispersions (4, 12 - 14), we want report the improving of solubility and dissolution rate of triamterene via solid dispersion technique using urea as a carrier. The effect of aging has also been investigated.

EXPERIMENTAL

Materials. Micronized triamterene was a gift from Laboratories Miquel S.A. (E-Barcelona) and was used without further purification. Commercial urea of pharmaceutical grade was supplied by Acofar (E-Barcelona).

Preparation of the samples. Triamterene-urea solid dispersions were prepared by melting the carrier and adding amounts of triamterene corresponding to 5, 10, 20 and 40 % w/w. The urea was gradually heated to 150 °C (this temperature is lightly higher than its melting point) in a small porcelain dish, with constant stirring, employing a magnetic stirrer heater *(Selecta Agimatic S-243)*. When the carrier was

completely melted, the drug was added. Once this melt was homogeneous, the melted mixture was cooled and solidified quickly by placing the dish in an ice-water bath. After cooling, the resulting solid was ground and sieved. The fraction under 270 mesh was selected.

Physical mixtures were prepared by simple mixing of the two components previously sieved (under 270 mesh) in 1:20, 1:10, 1:5 and 2:5 w/w ratios. These physical mixtures were used for comparison with solid dispersions.

Solubility studies. An excess of triamterene was placed in Erlenmeyer flasks containing 20 mL of purified water or aqueous solution of different urea concentrations. The solutions, in stoppered glass Erlenmeyer flasks, were continuously shaken in a water bath at 25 and 37 °C for 4 days. The solutions were filtered through a number of 4 sintered glass filters, and the filtrate was analyzed spectrophotometrically *(Hitachi U-2000)* (357 nm) to measure the amount of dissolved drug.

Dissolution rate (D.R.) study. The *in vitro* D.R. of untreated sample, solid dispersions and physical mixtures with urea were determined according to the USP rotating basket dissolution method (Turu Grau D-6) at a speed of 50 rpm and at a temperature of 37 ± 0.5 °C. Sampling interval was 5 minutes and sample volume was 3 mL each one. Dissolution runs for all samples were performed in triplicate. 20 mg of triamterene, contained in dry filled capsules, was introduced in 1000 mL artificial gastric medium without enzymes (15).

Constant surface area dissolution studies. The rotating disc method is frequently used for the determination of intrinsic dissolution rates (I.D.R.) for drugs in solid dispersions (8, 9, 16). The I.D.R. were determined using the above-cited USP dissolution apparatus at the same conditions of rotation speed, temperature and gastric medium. The discs were attached in their molds, on a round rotating support with the dissolving surface area (0.85 cm^2) facing downwards and immersed 10 cm in the dissolution medium. Samples of 3 mL were measured each 5 minutes spectrophotometrically (wavelength 357 nm). The D.R. (mg/min) were calculated by linear regression analysis from the amount drug dissolved versus time. I.D.R. (mg/min.cm^2) and relative intrinsic dissolution rates (R.I.D.R.) (mg/min.cm^2.%) refered to drug percentage, were also calculated.

Aging studies. Some solid dispersions were stored for 12 months at room temperature and ambiental moisture to study the effects of aging. These systems were maintained in darkness.

Statistical analysis. ANOVA has been applied to the release data to determine the influence of percentage of drug, type of preparation and aging effect.

Scanning electron microscopy study. Scanning electron microscopy *(Isi SS-40)* was used to study the triamterene-urea systems before and after dissolution. Samples, deposited on a Cu holder, were coated with a thin film of Au to make them conducting and examined in the scanning electron microscope at 20 Kv.

RESULTS AND DISCUSSION

Solubility. A linear relationship between the solubilizing effect and the carrier concentration was showed. The solubility of triamterene, in different urea concentrations, was increased significantly when the carrier concentration and the temperature were increased (Figure 1). Similar results were obtained by Bloch et al. (9) using chlorthalidone in urea.

Influence of drug concentration on dissolution rate of solid dispersions. Dissolution results of preparations containing solid dispersions of triamterene-urea and pure drug are presented in Figure 2. The lowest concentrations of drug (5 and 10 % w/w) in the solid dispersions showed the fastest D.R.. Similar results for other drugs are frequently reported in the literature. Mura et al., found that the dissolution of ibuprofen-urea solid dispersions is enhanced when the urea concentration is increased due to the solubilizing effect of urea (17). This enhancement can be due to the fact that each single particle of triamterene is very intimately encircled by the soluble carrier, which readily dissolves and makes the water contact and wet the drug particles. We can also have taken into account the possibility of the influence of the reduction of drug particle size found in solid dispersions when the preparations are elaborated with high proportions of vehicle, as we have found in diazepam solid dispersions (14).

In this paper, it can be found that solid dispersions containing 5 and 10 % w/w triamterene show the same highest D.R. profiles. There are not statistical differences

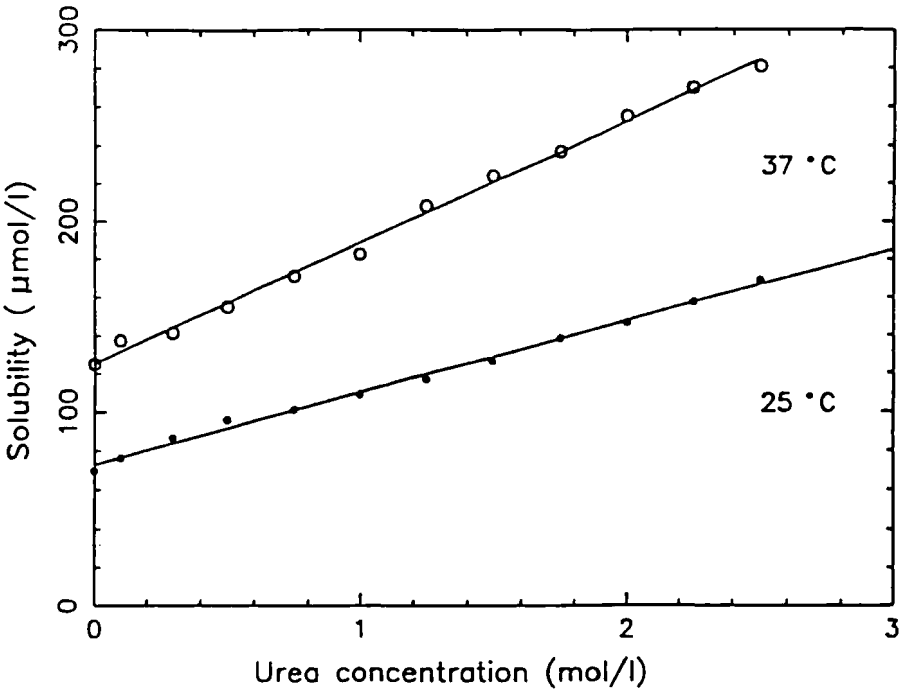


FIGURE 1

Solubility of triamterene in aqueous urea solutions at 27 °C and 37 °C.

in their behavior, as it is demonstrated by the ANOVA results (Table 1). When the amount of triamterene is increased (20 % w/w drug solid dispersion), a clear diminution in its D.R. is observed. Furthermore, the D.R. for 40 % w/w solid dispersion is markedly decreased, showing this last preparation and the pure drug similar dissolution profiles, situation according to the lowest wettability due to the hydrophobic nature of the drug. In this case, the amount of urea is not enough to prevent the aggregation between the particles of triamterene.

The dissolution profiles of physical mixtures (5, 10, 20 and 40 % w/w) of triamterene in urea are compared with those obtained from solid dispersions at the same triamterene concentrations (Figure 2). Solid dispersions with 5 and 10 % w/w drug show higher release rates than the physical mixtures at the same concentrations. On the other hand, preparations containing 20 and 40 % w/w drug do not exhibit

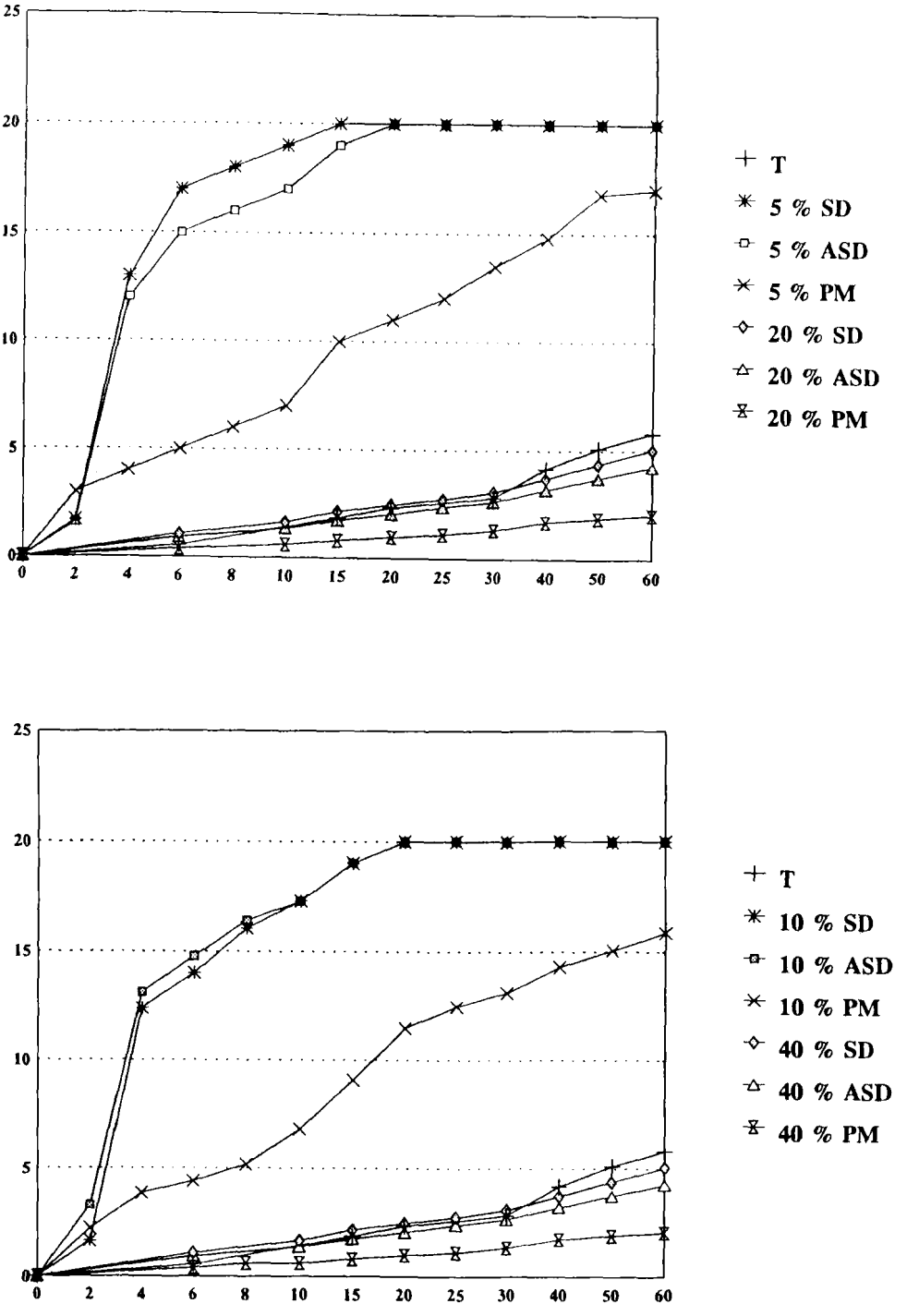


FIGURE 2

Dissolution profiles of triamterene from different preparations.
(SD) Solid dispersion recently prepared (ASD) Aging solid dispersion
(PM) Physical mixture (T) Pure drug

TABLE 1

ANOVA data obtained from the global comparative study of the different percentages.

Samples (%)	D.F.	F	Prob.
5 - 10 - 20 - 40	143	40.71	0.0000
5 - 10	71	0.04	0.8388
5 - 20	71	17.79	0.0000
5 - 40	71	110.44	0.0000
10 - 20	71	16.17	0.0001
10 - 40	71	106.70	0.0000
20 - 40	71	38.71	0.0000

TABLE 2

ANOVA data obtained from the comparative study of the indicated preparations.

%	Samples	D.F.	F	Prob.
5	SD - ASD - PM	35	7.46	0.0021
5	SD - ASD	23	0.09	0.7621
5	SD - PM	23	12.71	0.0017
5	ASD - PM	23	10.37	0.0039
10	SD - ASD - PM	35	8.43	0.0011
10	SD - ASD	23	0.02	0.8904
10	SD - PM	23	11.79	0.0024
10	ASD - PM	23	14.18	0.0011
20	SD - ASD - PM	35	2.22	0.1250
20	SD - ASD	23	2.31	0.1426
20	SD - PM	23	3.54	0.0733
20	ASD - PM	23	0.22	0.6421
40	SD - ASD - PM	35	1.01	0.3760
40	SD - ASD	23	0.49	0.4909
40	SD - PM	23	2.12	0.1599
40	ASD - PM	23	0.51	0.4847

SD ≡ Fresh solid dispersions ASD ≡ Aging solid dispersion PM ≡ Physical mixtures

TABLE 3

Dissolution rate (D.R.), intrinsic dissolution rate (I.D.R.) and relative intrinsic dissolution rate (R.I.D.R.) values of the different triamterene-urea preparations discs.

Product Type	% Drug	D.R. μg/min	I.D.R. μg/min.cm²	R.I.D.R. μg/min.cm².%	Correlation Coefficient (n = 9)
SD	5	50.1	58.9	1178	0.987
	10	53.1	62.4	624	0.998
	20	68.9	81.0	405	0.996
	40	47.5	55.8	139	0.995
ASD	5	42.0	49.4	988	0.997
	10	37.1	43.5	435	0.998
	20	59.3	69.4	347	0.996
	40	36.1	42.4	106	0.997
PM	5	27.6	32.4	648	0.986
	10	27.1	31.7	317	0.981
	20	30.7	36.4	182	0.988
	40	34.8	41.1	103	0.996
Drug	100	24.5	28.8	28.8	0.993

SD = Fresh solid dispersion
ASD = Aged solid dispersion
PM = Physical mixture
Drug = Triamterene

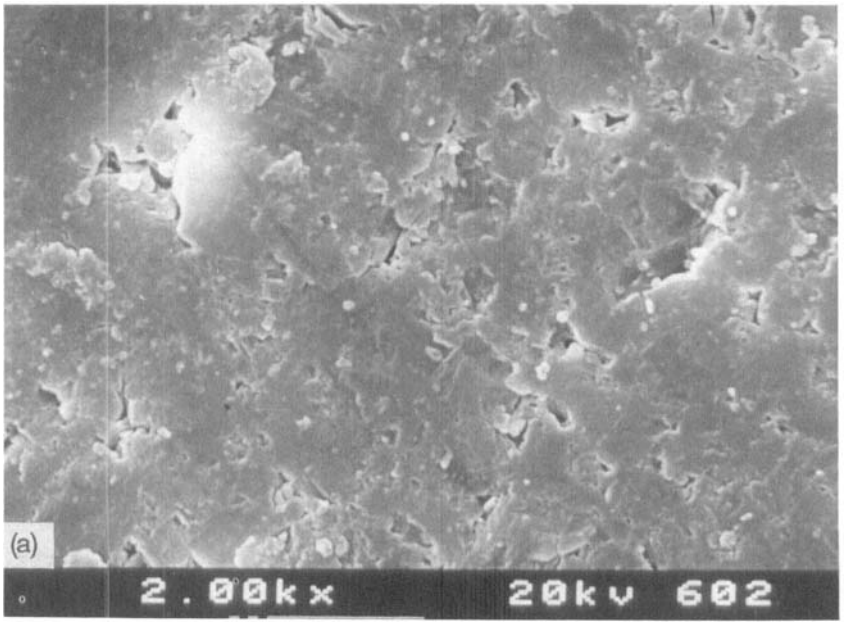
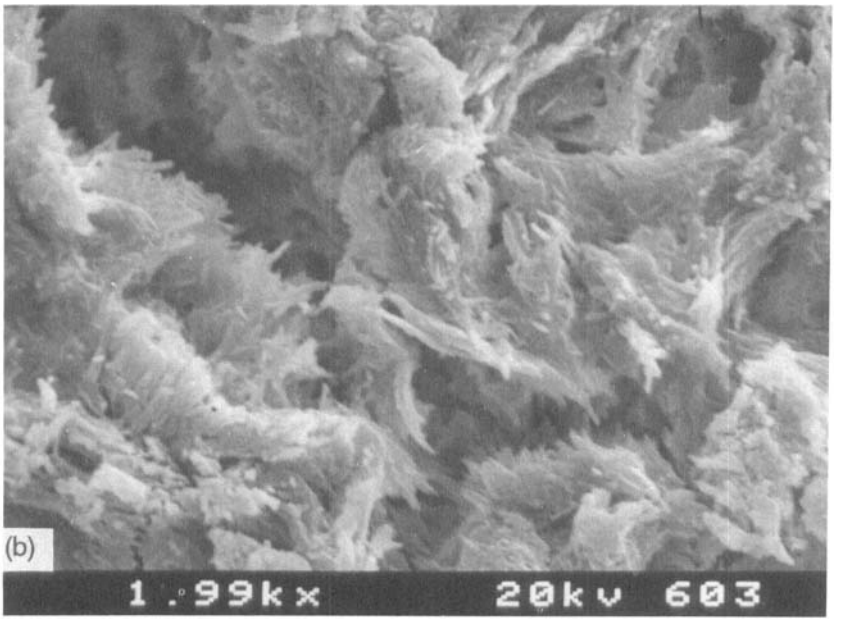


FIGURE 3

Scanning electron microphotographs of pure triamterene disc before (a), after (b) dissolution process and solid dispersion 20 % (c), original magnifications were 2000x.



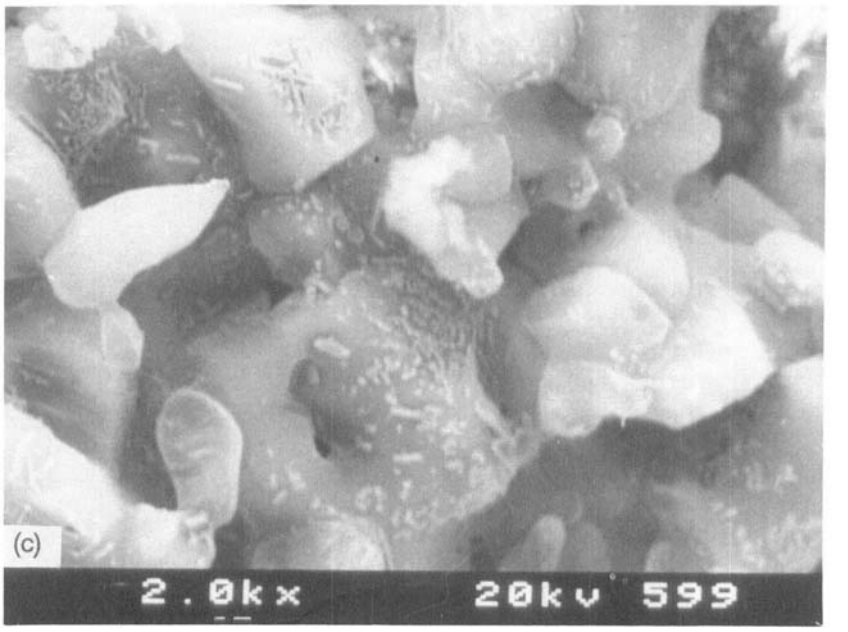


FIGURE 3 Continued

statistical differences in their release profiles, as it is shown in data presented in Table 2.

Influence of nature sample on dissolution rate. This difference between solid dispersions and physical mixtures can be explained on the basis that the components in the solid dispersions are more intimately associated than in the physical mixtures, always by using enough proportion of vehicle.

The D.R. of triamterene is enhanced in solid dispersions and physical mixtures systems in comparison with the pure drug. This is mainly due to the solubilizing effect of urea and the resultant better wetting of the drug in the dissolution medium because of the greater concentration of urea in the diffusion layer. The presence of urea increases the solubility of the drug (Figure 1) and thereby, it increases the D.R. of physical mixtures and solid dispersions.

Influence of storage over dissolution process of solid dispersions. The D.R. study determined after one year storage suggests that the effect of aging can be dependent of the drug percentage. Some authors find that the solid dispersions displayed an increased tendency to show age-induced changes as the drug content is increased (18).

In relation with this situation and comparing the release profiles of solid dispersions and aging solid dispersions (Figure 2), it is clear that preparations with low content of drug (5 and 10 % w/w) are not affected by the storage conditions. This situation is corroborated by the ANOVA results (Table 2).

Preparations with 20 % w/w triamterene suggest an apparent diminution of release rate due to the aging process, but ANOVA data presented in Table 2 indicate that there is no statistical significance in this difference.

Finally, 40 % w/w triamterene solid dispersions, which are affected to be more influenced by the storage conditions as a function of its higher level of drug, did not show statistical difference in their behaviours (Table 2). This situation can be explained by their slow initial D.R. (near that of pure drug) and so, the aging conditions have small influence over the dissolution profiles.

Constant surface area dissolution studies. Dissolution profiles of solid dispersions and physical mixtures showed a linear relationship, indicating an apparent zero order process. The maximum I.D.R. was obtained at 20 % w/w triamterene and the maximum R.I.D.R. at 5 % w/w triamterene. Lower I.D.R. were obtained from physical mixtures. In all cases, an I.D.R. diminution was found after 1 year storage at room temperature (Table 3); however, the dissolution profiles remained essentially linear.

Scanning electron microscopy. Figures 3a and 3b show the triamterene compacts surfaces before and after the dissolution assay, respectively. The disc surface after dissolution (Figure 3b) presents holes being constituted by fine and long particles of the drug. It is reasonable to conclude that these conglomerates of hydrophobic crystals decrease their wettability and diminue their dissolution.

Compact surfaces microscopical examination after dissolution assay of 20 % w/w triamterene solid dispersion (Figure 3c), shows the drug particles dispersed on the urea mass surface, decreasing aggregation and agglomeration of drug particles which can quickly dissolve due to a better wettability. Respecting to 20 % w/w triamterene physical mixture, we can observe the presence of drug agglomerates and large number of undispersed particles localized in small areas. This disposition decreases the surface area of drug particles available for dissolution and hence, reduces the dissolution efficiency.

The results demonstrate that the compacts surface during the dissolution assay, does not maintain constant. However, the dissolution profiles obtained were linear during the first 60 minutes. Similar results were obtained by Doherty et al. (19) with the frusemide. These authors suggest that the term "constant surface area" in the Noyes-Whitney equation appears to relate more to the diffusion layer area than the true solid surface area. We can conclude that it has been found a clear improvement in the triamterene dissolution behaviour by its processing into solid dispersions with a charge of 5 - 10 % w/w drug. The aging process does not affect the release profiles. On the other hand, it appears an apparent zero-order process in the I.D.R., corresponding to the greatest R.I.D.R. (5 % w/w triamterene solid dispersion) and the highest I.D.R. (20 % w/w drug solid dispersion).

REFERENCES

1. O. Dahl, K.H. Ziedrich, G.J. Marek, H.H. Paradies, J. Pharm. Sci., **78**, 598 (1989).

2. A.W. Pruit, J.S. Winkel, P.G. Dayton, Clin. Pharmac. Ther., **21**, 610 (1971).

3. S.E. Walker, J.A. Ganley, K. Bedford, T. Eaves, J. Pharm. Pharmacol., **32**, 389 (1979).

4. A.M. Rabasco, J.M. Ginés, M.F. Arévalo, M.T. Vela, Abstracts of 6th International Symposium on Biopharmaceutics and Pharmacokinetics, Bratislava, May 1990, p. 27.

5. S.K. Dordunoo, J.L. Ford, M.H. Rubinstein, Proceedings of 10th Pharmaceutical Technology Conference, Bologna, April 1991, vol. 3, pp. 13-46.

6. H.M. El-Banna, S.A. Khalil, M.W. Gouda, J. Pharm. Sci., **67**, 1112 (1978).

7. H.M. El-Banna, N.A. Daabis, S.A. El-Fattah, J. Pharm. Sci., **67**, 1631 (1978).

8. J.L. Ford, M.H. Rubinstein, Int. J. Pharm., **8**, 311 (1981).

9. D.W. Bloch, M.A. Elegakey, P.P. Speiser, Pharm. Acta Helv., **57**, 231 (1982).

10. N.A. El Gindy, A.A. Shalaby, M.M.A. El-Khalek, Drug Dev. Ind. Pharm., **9**, 1031 (1983).

11. M.R. Jafari, A.G. Danti, I. Ahmed, Int. J. Pharm., **48**, 207 (1988).

12. J.M. Ginés, M.F. Arévalo, A.M. Rabasco, Ind. Farm., **4**, 139 (1989).

13. P.J. Sánchez-Soto, J.M. Ginés, A.M. Rabasco, A. Justo, J.L. Pérez, Thermochim. Acta, **65**, 225 (1990).

14. A.M. Rabasco, J.M. Ginés, M.F. Arévalo, M.A. Holgado, Int. J. Pharm., **67**, 201 (1991).

15. The United States Pharmacopeia XXII, 22nd rev., 1990, p. 1242.

16. R. Kaur, D.J.W. Grant, T. Eaves, J. Pharm. Sci., **69**, 1321 (1980).

17. P. Mura, A. Liguori, G. Bramanti, Farmaco Ed. Sci., **41**, 377 (1986).

18. J.L. Dubois, J.C. Chaumeil, J.L. Ford, S.T.P. Pharma, **8**, 711 (1985).

19. C. Doherty, P. York, in "Pharmaceutical Technology: Controlled Drug Release", M.H. Rubinstein, Ed.; Ellis Horwood Ltd., Chichester, 1987, pp. 99-111.