ELSEVIER

International Journal of Pharmaceutics 164 (1998) 1–10

international journal of pharmaceutics

Sustained release theophylline tablets by direct compression Part 1: formulation and in vitro testing

S. Indiran Pather [1,a,b,*], Irina Russell [a], James A. Syce [a], Steven H. Neau [b]

[a] *School of Pharmacy, University of the Western Cape, Private Bag X 17, Bellville 7535, South Africa*
[b] *School of Pharmacy, University of Missouri, Kansas City, 5005 Rockhill Road, Kansas City, MO 64110, USA*

Received 4 November 1996; received in revised form 12 May 1997; accepted 6 October 1997

Abstract

In an effort to reduce production costs, a simple, direct compression sustained release formulation consisting, principally, of the drug (theophylline) and ethylcellulose was investigated. Ethylcellulose compacts well and also retards drug release. In addition, matrices of this polymer display slow surface erosion which can be enhanced by the incorporation of a swelling agent. This property was utilized in an attempt to decrease the attenuation of the release rate that is observed with matrix tablets that follow the Higuchi pattern of drug release. The release rate decreases because the external layers of the tablet become depleted and water must penetrate the deeper layers of the tablet to reach the remaining drug. The theophylline to ethylcellulose ratio and the tablet hardness were found to influence the rate of drug release. It was possible to sustain the release of a therapeutic dose of theophylline over a 12-h period. Mathematical modeling showed an equally good fit between the data and (a) the Higuchi model, or (b) a model that took into account diffusion, relaxation of the polymer, and erosion. However, the shape of the release curve was altered slightly in those tablets that eroded to a greater extent and residuals analysis illustrated a better fit with the latter model. The erosion mechanism can be used to lessen one of the major problems associated with hydrophobic and plastic matrix tablets, i.e. the continuous reduction in the terminal release rate with time.

Keywords: Theophylline; Ethylcellulose; Polymeric retardants; Sustained release; Matrix tablets; Mathematical modeling; Erosion

1. Introduction

For many drugs, the optimal therapeutic response is only observed when adequate blood

* Corresponding author. E-mail: ipather@cctr.umkc.edu
[1] Present address: University of Missouri, Kansas City, USA.

0378-5173/98/$19.00
PII S0378-5173(97)00348-7

levels are achieved and maintained with minimal fluctuations. Sustained release products have became popular for the oral administration of such drugs because they give more consistent blood levels. However, increasingly sophisticated products have become so expensive that they are beyond the reach of many people. Cost containment has, therefore, become important in the pharmaceutical manufacturing industry. This is evident not only in Third World Countries but also in affluent societies where the threat of alternative medicine (Anonymous, 1987) is real.

In the manufacture of tablets, in general, direct compression is a cost effective production method. When the technique is applied to sustained release medication, the savings in time and labour are very attractive. This paper describes the production and in vitro testing of directly compressed sustained release theophylline tablets, while the in vivo evaluation of these tablets is described in part 2. Theophylline was chosen as the model drug because around-the-clock therapy is required for effective treatment of chronic obstructive pulmonary disease (Hendeles et al., 1978).

2. Theory

In keeping with the concept of reducing production costs, a simple, directly compressed formulation consisting of two principal components was envisaged. These components are the drug and a material that retards drug release. With appropriate choice of the retardant, compaction of the mixture would lead to the formation of a matrix tablet. Drug release from matrix tablets becomes progressively slower with time (Higuchi, 1963). This is in contrast to the ideal situation in which the drug is released from the tablet at the same slow rate throughout the release period. The Higuchi profile is compared with the ideal release pattern (zero order profile) in Fig. 1.

For each plot, the initial release rate mentioned in the figure is the difference ($Q_{30\,\mathrm{min}} - Q_{0\,\mathrm{min}}$) and the final release rate is ($Q_{720\,\mathrm{min}} - Q_{690\,\mathrm{min}}$), where $Q_{30\,\mathrm{min}}$ refers to the amount of drug released after 30 min, etc. While complete drug release is achieved over essentially the same period in each case, the dissolution rates at various times during the dissolution process differ dramatically between the two profiles.

The reason for the attenuation of the drug release rate in the Higuchi profile is illustrated in Fig. 2. When a matrix tablet is placed in the dissolution medium, the initial drug release occurs from the tablet's superficial layers and, consequently, the release rate is relatively fast. As time passes, the external layers of the tablet become depleted of the drug and water molecules must travel through long, tortuous channels to reach the drug remaining in the deeper layers of the tablet. Similarly, the drug solution that is formed within the tablet must diffuse through long capillaries to reach the external dissolution medium. The primary reason for the continuously decreasing rate of drug release is the increasing distance that must be traversed by water and drug molecules into, and out of, the tablet, respectively. Therefore, any mechanism that lessens the time-dependent increase in the diffusion path length would reduce the attenuation of the dissolution rate.

Erosion[2] of the tablet will gradually reduce its diameter and, hence, the diffusion path length will be reduced. The classical concept of a plastic or a hydrophobic matrix was one that was inert. More recently, however, it has been recognised that the matrix may disintegrate or erode to some extent during the dissolution process (Brossard et al., 1983). While these authors used partially soluble polymers to form the erodible matrix, insoluble ethylcellulose was used in the present work. Ethylcellulose has a natural tendency to erode in water due to a separation of the surface particles of the matrix. Erosion occurs slowly but can be promoted by the addition of small quantities of silicon dioxide to the matrix. The silicon dioxide particles swell when in contact with aqueous media, promoting the loosening of the outer particles of the tablet. This effect causes layers of the tablet

[2] The term erosion refers to the slow removal of particles from the surface of the tablet. Erosion is similar to disintegration, except that the former process is slow and occurs only from the surface of the tablet.

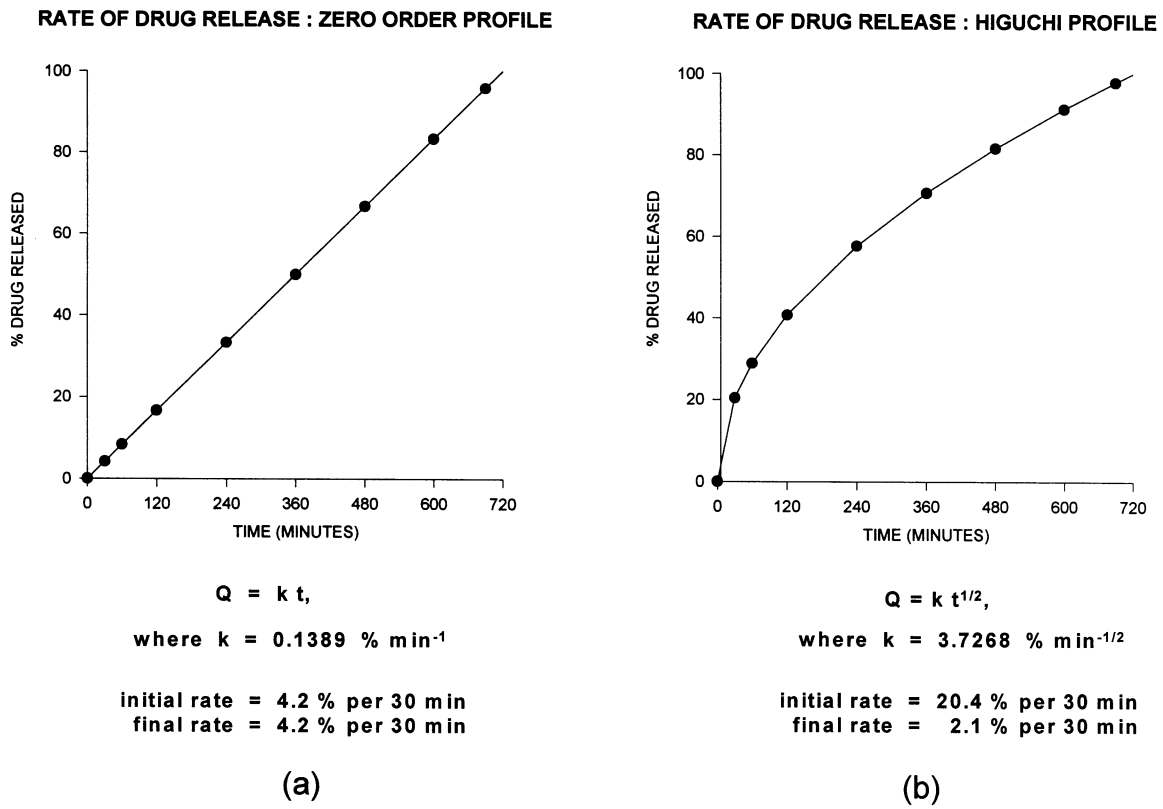

Fig. 1. Comparison of (a) Higuchi and (b) zero order release profiles. Note that in each case 100% of the drug is released in 12 h.

to separate sequentially and, thus, the drug-depleted zone or dead weight is removed. Obviously, the boundary of the drug-containing zone must recede into the tablet at a faster rate than that at which erosion occurs in order to retain the sustained release properties of the tablet. By incorporating an erosion-promoting substance within the matrix, an attempt was made, in this work, to alter the expected Higuchi release profile so that it would resemble zero order release.

3. Materials and methods

Theophylline was purchased from Fluka A.G. (Switzerland). Ethylcellulose (ethoxy content 47.5–49%, viscosity 14 cP) and magnesium stearate were purchased from B.D.H. Chemicals (Poole, England). Silicon dioxide (Aerosil® 200) was donated by Lennons, (South Africa). All materials were used as received.

3.1. Moisture content determination

The moisture content values of the major components of the tablets were determined using a moisture balance (Mettler PE 160) fitted with an infrared heating unit (Mettler LP 15). The balance was preheated to 80°C for 10 min and the sample (≈ 1 g) was heated for a further 30 min at this temperature.

3.2. Angle of repose test

The angles of repose of the major components of the tablet formulations, ethylcellulose and theophylline, were determined. Since a specially constructed device was used, it was appropriate to

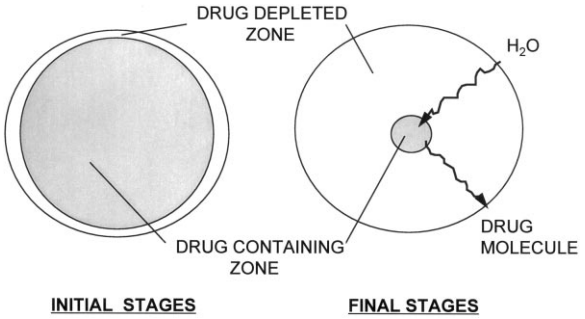

Fig. 2. Diagrammatic representation of drug release according to the Higuchi model.

also determine the angle of repose of a free-flowing substance. Starch 1500®, a direct compression filler, was chosen for such a comparison. This excipient was, however, not included in any formulation.

The device consisted of a glass cylinder (open at both ends) and an oil-filled hydraulic machine for lifting the cylinder smoothly. The cylinder (80 mm height and 23 mm internal diameter) was approximately half filled with the powder. The height of the powder cone, formed upon lifting the cylinder, was measured with a cathetometer and the diameter of the cone base was also determined.

Concentric graph paper embedded in the perspex base of the apparatus facilitated the latter measurement. The angle of repose (Φ) was calculated from:

$$\tan \Phi = \frac{h}{r} \quad (1)$$

The powder mixtures described in Table 1 were similarly evaluated.

3.3. Particle size analysis

Particle size analysis of theophylline, ethylcellulose, and Starch 1500® was done by a microscopic method (Nikon binocular microscope) with the aid of a stage micrometer and an eye piece micrometer (Graticules). Once again, Starch 1500® was included for comparative purposes only.

3.4. Tablet production

Based on the flowability of the mixed powders, selected formulations from Table 1 were tabletted. An angle of repose of 42° was regarded as evidence of good flow. For the manufacture of each batch, the appropriate quantities of ethylcellulose and theophylline were premixed for 10 min in a cube mixer (Erweka). Magnesium stearate was added and mixed for 15 min. Then, silicon dioxide was added and mixing continued for a further 3 min. Compression was accomplished using a single punch tabletting machine (Korsch EKO). Each formulation was produced at a range of compression force settings of the tablet machine, resulting in several batches (designated A, B, C, or D) which differed from each other by the mean tablet hardness.

3.5. Quality control tests

The BP uniformity of mass test was performed on each batch of tablets and the coefficient of mass variation was also calculated. Using an Erweka hardness tester, the breaking strength of the

Table 1
Composition[a] and flowability of tablet formulations

	Formula 6	Formula 7	Formula 8	Formula 9
Theophylline (T)	31.667	38.000	47.500	63.333
Ethylcellulose (EC)	63.333	57.000	47.500	31.667
Silicon dioxide	3.000	3.000	3.000	3.000
Magnesium stearate	2.000	2.000	2.000	2.000
Ratio of T:EC	1:2	1:1.5	1:1	1:0.5
Φ[b] ($n = 3$)	34.0 ($\pm$ 1.2)	37.8 ($\pm$ 0.7)	39.3 ($\pm$ 0.5)	42.6 ($\pm$ 0.4)

[a] Percent w/w.
[b] Values are given in degrees $\pm$ S.D.

Table 2
Some properties of tablet components

	Moisture content (%) ($n = 2$)	Particle size (μm) ($n = 100$)	Angle of repose (°) ($n = 2$)
Theophylline	0.24	60.4	—
Ethylcellulose	1.54	49.6	29.5
Starch 1500®[a]	10.93	47.3	31.6

[a] Data presented for comparison.

tablets was determined. This was done 24 h after production to allow for stress relaxation. The friability test was performed using 20 tablets in an Erweka friabilitator at 25 rpm for 4 min. The theophylline content of the tablets was measured using UV-spectrophotometry (Hitachi Model U 3200 spectrophotometer).

3.6. Dissolution tests

The dissolution tests were performed in pH 7.4 buffer and the USP method (apparatus 1) was used at 100 rpm. The UV absorbance of the dissolution samples was read at 272 nm.

4. Results and discussion

In Table 2, the moisture content values, particle sizes, and angles of repose of the major tablet components are compared to those for Starch 1500®, a well-known direct compression filler. Since the proposed tablet components had moisture content values of less than 2%, this property was not expected to adversely influence flowability. The moisture content of Starch 1500® was found to be high (10.93%) but this value is similar to literature values (10%, Banker and Anderson (1986); 12%, Sheth et al. (1980)). It is unlikely that the high moisture content of this excipient influences tabletting characteristics, since there is no evidence that the moisture is easily released (Sheth et al., 1980). The particle size of ethylcellulose was similar to that of Starch 1500®. Optical microscopy revealed that theophylline consisted of elongated crystals. Heywood's ratio for elongation was determined (Allen, 1968). The calculated value of 2.81 ($\pm$ 1.15) ($n = 100$) is consistent with needle crystals. Since needle crystals flow poorly, flowability problems were anticipated with formulations containing a high percentage of theophylline.

The lower the angle of repose, the better is the flowability. The lowest value, for most pharmaceutical powders, is 25° (Wadke and Jacobson, 1980). While it is generally agreed that higher angles of repose give poor flow, it is difficult to establish an exact figure above which flow will not be acceptable. According to Marshall (1986), angles above 50° result in poor flow, while Wadke and Jacobson (1980) regard 45° as the limit. In this work, however, 42° was regarded as the cut-off point for good flowability, based on experience in our laboratories. Theophylline did not flow to form a cone but retained the cylindrical form of its container. Therefore, the angle of repose of theophylline could not be determined. The results of the remaining tests showed that the flowability of ethylcellulose was comparable to that of Starch 1500®, a known direct compression filler. Anticipated flowability problems with the tabletting formulations were thus reduced to being able to combine the drug with sufficient ethylcellulose for the mixture to have adequate flow. The ethylcellulose content also had to be sufficient to produce hard compacts. In this way, ethylcellulose served as the direct compression filler and, simultaneously, as the retardant. This is in contrast to previous work with ethylcellulose, such as that of Fassihi (1986). This author combined ethylcellulose with additional fatty or waxy materials in the molten state. The powdered drug was mixed into this melt and, upon congealing, the mass was milled to form granules for compaction. In the present work, on the other hand, ethylcellulose was not melted (nor dissolved) but served as the direct compression vehicle.

Table 3
Results of tablet quality control tests

	7A	7B	7C	7D	8A	8B	8C
Coefficient of mass variation (%)	1.01	0.80	1.07	0.96	1.84	1.93	1.18
Friability (%)	0.29	0.35	0.47	0.60	0.56	0.25	0.36
Hardness ($\pm$S.D.) (kg) ($n=4$)	4.88 ($\pm$0.22)	7.25 ($\pm$0.29)	7.00 ($\pm$0.50)	2.90 ($\pm$0.26)	3.88 ($\pm$0.48)	6.63 ($\pm$0.25)	8.38 ($\pm$0.25)
Assay (%)	104.5	101.2	103.1	102.2	100.8	102.9	103.5

The composition of the tablet formulations shown in Table 1 differ only with respect to the ratio of drug to ethylcellulose. While higher proportions of ethylcellulose give better flowability, they also lead to larger tablets since the drug content must be kept constant. Formula 6 was omitted from further study because the large tablet may have been unacceptable to patients. Formulae 7 and 8 displayed good flowability while that of Formula 9 was regarded as being marginally acceptable.

The formulations contain 2% magnesium stearate which, generally, would be regarded as excessive. Magnesium stearate has a laminar structure and, with mixing, the layers slough off and coat the other particles of the mixture (Bolhuis et al., 1975). This creates a hydrophobic surface on the particles since magnesium stearate has a contact angle of 121° (Lerk et al., 1976). Upon compression of the powders into tablets, the magnesium stearate layer retards the entry of water into the tablet and, hence, decreases the rate of drug release. This mechanism improves the sustained release effect but its efficiency is limited by the tablet-softening action of magnesium stearate (Lerk and Bolhuis, 1977; Lerk et al., 1977; Ragnarsson et al., 1979; Jarosz and Parrott, 1984; Van der Watt, 1987). It is desirable to maintain dissolution at a constant rate throughout the dissolution process. Any further decrease in the rate (caused by the increasing diffusion path length, as previously described) was expected to be offset by erosion.

To obtain an intimate mix, magnesium stearate was added early in the mixing process and mixed for longer than usual (15 min). When mixing was continued for 40 min, tablets of approximately 3 kg hardness were produced at the maximum hardness setting of the tabletting machine. The mixing time was, therefore, reduced to obtain tablets of acceptable hardness. Silicon dioxide was added at the end and mixed briefly. If mixed too long, silicon dioxide can remove magnesium stearate from its substrate and spheres consisting of magnesium stearate and silicon dioxide are formed (Lerk and Bolhuis, 1977).

The results of the quality control tests (Table 3) indicate that tablets of good quality were produced. The tablets comply with the BP Uniformity of Mass Test and also show a low coefficient of mass variation, indicating that the tabletting mixtures were able to accommodate the poor flowability of theophylline.

The dissolution profiles of Formula 7 and Formula 8 tablets are shown, respectively, in Figs. 3 and 4. It can be seen that the softer tablets gave a faster dissolution rate within each series. Observation of the tablets during the dissolution process revealed that all formulations were eroding. This effect was, however, much more prominent with the softer tablets. In general, the tablets became smaller by the end of the dissolution study and their surfaces were rough.

The relationship between the time for 50% drug release and the tablet hardness is shown in Fig. 5. The curves have approximately the same slope, indicating that an increase in the hardness of the tablets slows down the dissolution rate in both cases. The effect of the concentration of ethylcellulose in the tablets on the drug release rate can

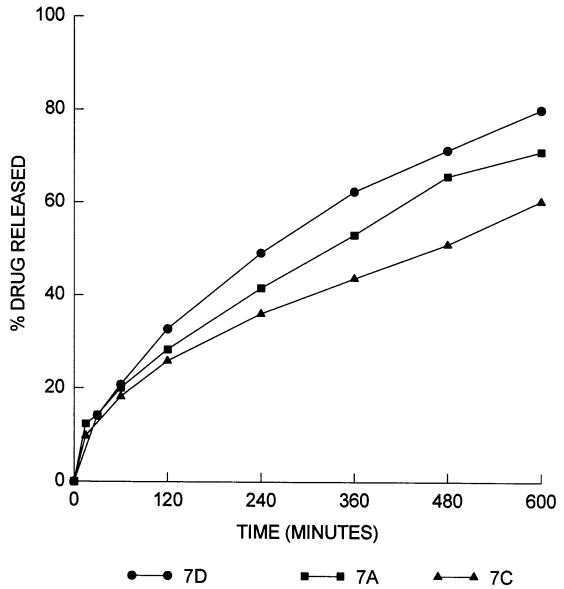

Fig. 3. Dissolution of Formula 7 tablets.

also be seen in Fig. 5. Formula 7 tablets, which contain approximately 9.5% more ethylcellulose than Formula 8 tablets, take about 85 min longer to release 50% of the drug, comparing tablets of similar hardness. The foregoing indicates that

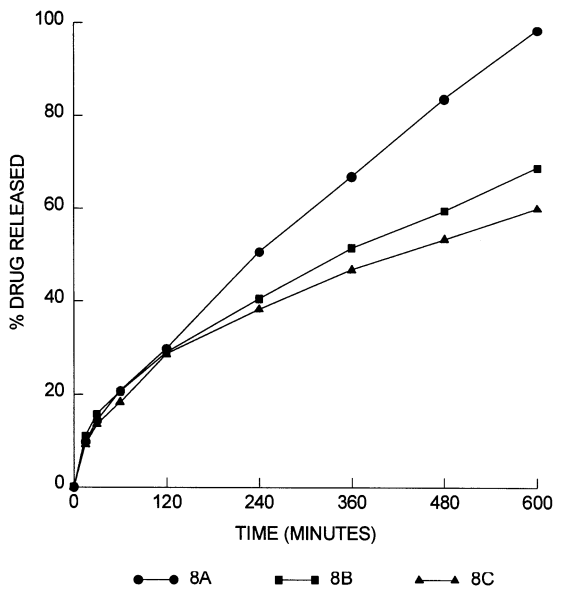

Fig. 4. Dissolution of Formula 8 tablets.

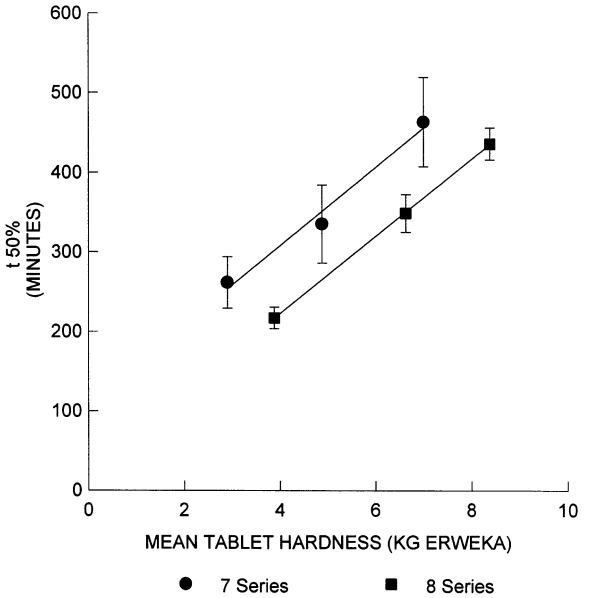

Fig. 5. Relationship between mean tablet hardness and time to 50% drug release.

tablet hardness and ethylcellulose content can be varied to control the drug release rate.

From 1 to 10 h, the curves were approximately linear with time (the linear regression coefficients were in the range 0.9835–0.9981). However, the entire curve showed a poor correlation with the zero order profile, probably due to the fast initial dissolution of the drug from the superficial layers of the tablet.

The dissolution results for the entire curve were fitted to the Higuchi model (Higuchi, 1963) as well as to the diffusion–relaxation–erosion (DRE) model (Upadrashta et al., 1993). The equations for these models are given below as Eqs. (2) and (3), respectively.

$$Q = kt^{1/2} \tag{2}$$

$$Q = k_4 t^{1/2} + Kt + k_2 t^2 + k_3 t^3 \tag{3}$$

where Q is the amount of drug released, t is the time, and the k-terms are constants.

If one considers the r^2 values (Table 4), both models describe the dissolution data reasonably well. Where there are competing models (with similar r^2 values), residuals analysis can be used to distinguish between the models (Draper and Smith, 1981).

Table 4
Statistical data for fit between dissolution results and models

	Higuchi model		DRE model	
	r^2	SSR	r^2	SSR
8A	0.9561	342.7826	0.9996	2.8270
8B	0.9973	8.6191	0.9996	1.2914
8C	0.9984	4.0067	0.9991	2.2921
7D	0.9932	39.8248	0.9999	0.7288
7A	0.9905	35.4264	0.9992	4.1855
7C	0.9973	8.2984	0.9999	0.4193

For the Higuchi model, the sum of the squared residuals (SSR) are large for the softer tablets and smaller for the harder tablets. On the other hand, the SSR values for the DRE model are uniformly small. Fig. 6 is the residuals plot for formula 8A. The residuals are greater for the Higuchi model which also shows systematic deviation: the model overpredicts initially and underpredicts at the later stages of the dissolution process. This indicates that the Higuchi model is not as good as the DRE model in describing the dissolution behaviour of these tablets.

The residuals plot for Formula 8C (Fig. 7) reveals small, randomly-distributed residuals for both models. The residuals for the Higuchi model are not as large, and they are also more random, than the corresponding residuals for Formula 8A. Formula 8C tablets are the hardest of the series and they were observed not to have eroded much. As a result, the Higuchi model fits the data well. The residuals for Formula 8B (plot not shown) are intermediate in size and distribution. The fit between the Higuchi model and the data (as reflected by the size and distribution of the residuals) appears to depend on the extent of erosion which, in turn, depends on tablet hardness. By contrast, the DRE model shows uniformly small residuals, irrespective of tablet hardness and the residuals are also more randomly dispersed. The 7 series revealed a similar pattern, with the Higuchi model fitting the dissolution profiles of the harder tablets better than those of the softer tablets, whereas the DRE model fit was equally good for soft or hard tablets.

Only diffusion is taken into account in the Higuchi equation, thus leading to the observed variable fit. A good fit was seen when erosion was limited and diffusion was the major mechanism of drug release; the fit was poor when erosion was

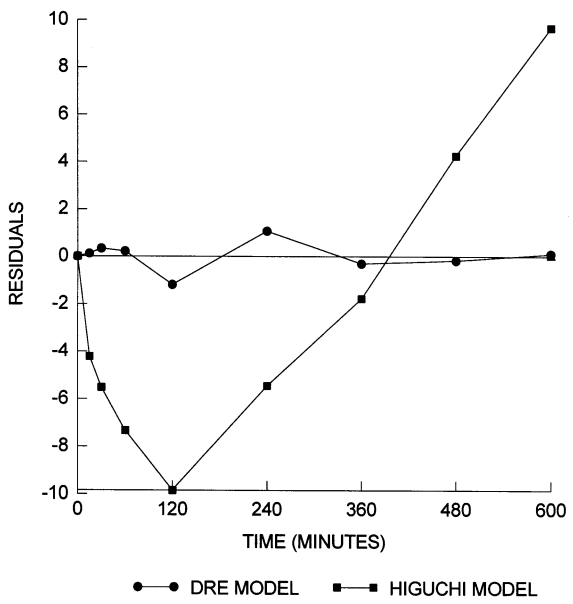

Fig. 6. Formula 8A residuals plot.

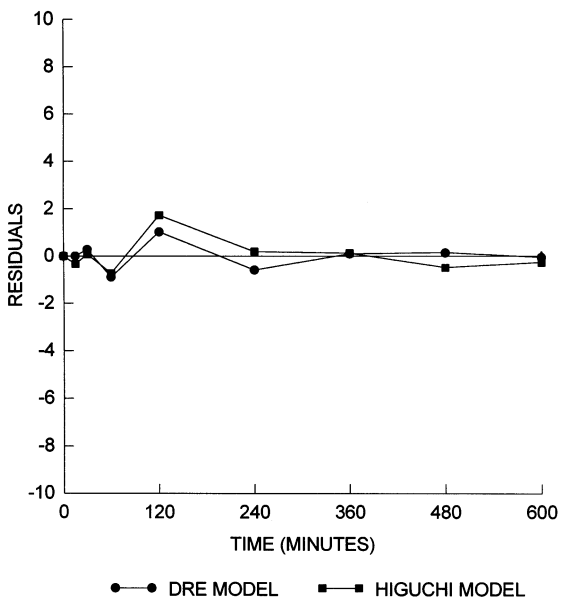

Fig. 7. Formula 8C residuals plot.

extensive. Since the DRE equation contains a mathematical term to represent erosion, the fit between the equation and the dissolution results was good irrespective of whether erosion was limited or extensive. The DRE model takes into account all the processes that are likely to have a major influence on the rate of drug release (diffusion, relaxation or swelling of the polymer, and erosion). It is, therefore, the more appropriate model for these formulations.

5. Conclusions

The very poor flowability of the asicular theophylline crystals was accommodated by ethylcellulose within the admixtures. Consequently, good tablets, with a low weight variation, were produced. In addition, the incorporation of ethylcellulose resulted in the production of tablets of sufficient hardness. It can, therefore, be concluded that ethylcellulose is a good direct compression filler. These tablets are simple to manufacture and should be economical to produce on an industrial scale.

The described erodible matrix tablets adequately sustain the release of theophylline. The rate of drug release can be altered by changing the ratio of theophylline to ethylcellulose and by adjusting the compression force used to prepare the tablets. As these variables are easily controlled, the desired rate of drug release can be obtained. Although the release data did not fit the zero order model, the release pattern differed from the Higuchi profile in those tablets that eroded to an appreciable extent, illustrating that the formulation objectives had been partially met. The effect of erosion is to decrease the attenuation of the release rate and, thus, one of the major problems associated with sustained release matrix tablets is tempered.

Acknowledgements

This paper is abstracted, in part, from a thesis submitted by S.I. Pather to the University of the Western Cape, South Africa (in 1989) in partial fulfilment of the requirements for the degree of Master of Pharmacy (Pharmaceutics). This work was presented at the 8th Annual Meeting and Exposition of the American Association of Pharmaceutical Scientists (Lake Buena Vista, Florida, November, 1993).

References

Allen, T., 1968. Particle Size Measurement. In: Williams, J.C. (Ed.), Powder Technology Series. Chapman and Hall, London.

Anonymous, 1987. Profitability in a changing market: the new realities of pharmaceutical manufacturing. Aerosol Age 32 (9), 28-29.

Banker, G.S., Anderson, N.R., 1986. Tablets. In: Lachman, L., Lieberman, H.A., Kanig, J.L. (Eds.), The Theory and Practice of Industrial Pharmacy. 3rd ed. Lea and Febiger, Philadelphia, PA.

Bolhuis, G.K., Lerk, C.F., Zijlstra, H.T., de Boer, A.H., 1975. Film formation by magnesium stearate during mixing and its effect on tabletting. Pharm. Weekbl. 110, 317–325.

Brossard, C., Lefort des Ylouses, D., Duchene, D., Puisieux, F., Carstensen, J.T., 1983. Dissolution of a soluble drug substance from vinyl polymer matrices. J. Pharm. Sci. 72, 162–169.

Draper, N., Smith, H., 1981. Applied Regression Analysis, 2nd ed. Wiley, New York.

Fassihi, A.R., 1986. Continuous matrix formation for controlled drug release: compression of isotropic polymeric system. Int. J. Pharm. 34, 169–172.

Hendeles, L., Weinberger, M., Johnson, G., 1978. Monitoring serum theophylline levels. Clin. Pharmacokinet. 3, 294–312.

Higuchi, T., 1963. Mechanism of sustained-action medication. Theoretical analysis of rate of release of solid drugs dispersed in solid matrices. J. Pharm. Sci. 52, 1145–1149.

Jarosz, P.J., Parrott, E.L., 1984. Effect of lubricants on tensile strengths of tablets. Drug Dev. Ind. Pharm. 10, 259–273.

Lerk, C.F., Bolhuis, G.K., 1977. Interaction of lubricants and colloidal silica during mixing with excipients II. Its effect on wettability and dissolution velocity. Pharm. Acta Helv. 52, 39–44.

Lerk, C.F., Schoonen, A.J.M., Fell, J.T., 1976. Contact angles and wetting of pharmaceutical powders. J. Pharm. Sci. 65, 843–847.

Lerk, C.F., Bolhuis, G.K., Smedema, S.S., 1977. Interaction of lubricants and colloidal silica during mixing with excipients. Pharm. Acta Helv. 52, 33–39.

Marshall, K., 1986. Compression and consolidation of powdered solids. In: Lachman, L., Lieberman, H.A., Kanig, J.L. (Eds.), The Theory and Practice of Industrial Pharmacy, 3rd ed. Lea and Febiger, Philadelphia, PA.

Ragnarsson, G., Holzer, A.W., Sjogren, J., 1979. The influence of mixing time and colloidal silica on the lubricating properties of magnesium stearate. Int. J. Pharm. 3, 127–131.

Sheth, B.B., Bandelin, F.J., Shangraw, R.F., 1980. Compressed tablets by direct compression. In: Lieberman, H.A., Lachman, L. (Eds.), Pharmaceutical Dosage Forms: Tablets, vol. 1. Marcel Dekker, New York.

Upadrashta, S.M., Katikaneni, P.R., Hileman, G.A., Keshary, P.R., 1993. Direct compression controlled release tablets using ethylcellulose matrices. Drug Dev. Ind. Pharm. 19, 449–460.

Van der Watt, J.G., 1987. The effect of the particle size of microcrystalline cellulose on tablet properties in mixtures with magnesium stearate. Int. J. Pharm. 36, 51–54.

Wadke, D.A., Jacobson, H., 1980. Preformulation testing. In: Lieberman, H.A., Lachman, L. (Eds.), Pharmaceutical Dosage Forms: Tablets, vol. 1. Marcel Dekker, New York.

.