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DEVELOPMENT AND IN-VITRO EVALUATION OF ETHYL CELLULOSE MICROPELLETS AS A CONTROLLED RELEASE DOSAGE FORM FOR THEOPHYLLINE

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ABSTRACT

A micropellet dosage form was developed using ethyl cellulose as a polymer with a view to achieve a controlled release oral drug delivery system for theophylline. Drug-polymer ratios and stirring speeds were found to influence the size-distribution of micropellets. Time required for 50% release of theophylline from micropellets was found to vary linearly with the drug content and reciprocal of diameter of micropellets. Invitro release of theophylline from micropellets, having different drug-polymer ratios and different sizes, was found apparently to follow both the First-order release and Diffusion controlled release processes. By differential rate treatment it was found that the overall release, in fact, followed diffusion controlled process.

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INTRODUCTION

Theophylline, a xanthene derivative, is still widely used as an effective bronchodilator in the management of asthmatic patients. It is used both as a prophylactic drug and to prevent acute exacerbations of asthma. During acute attack of asthma it becomes difficult for a patient to take oral medications repeatedly. On the other hand, a plasma theophylline concentration above 15 mg/l may produce moderate to serious toxic effects (1-4). Under the best of conditions, steady-state plateau theophylline concentration from 5-20 mg/l cause effective bronchodilation in acute asthma (5). Hence it is rational to administer theophylline in a sustained release dosage form which will minimise repeated administration of the drug and possibility of plasma theophylline concentration reaching a level which may produce toxicity.

Besides the sustained release tablet and capsule preparations, newer drug delivery systems, like microcapsules and micropellets, are under extensive investigation. Tanaka et. al. (6) first reported a gelatinised micropelleted dosage form for sulphanilamide and riboflavin in order to prolong the action of these drugs. Similar formulation for indomethacin (7) has also been reported.

The present investigation envisages the development of a new micropelleted dosage form for theophylline, using ethyl cellulose as a polymer, in order to maximise the therapeutic effects and minimise side effects.

EXPERIMENTAL

Materials

Anhydrous theophylline - Indian Pharmacopoeia, 1970 was generously supplied by Dey's Medical Stores (Mfg.) Ltd., Calcutta, India. Ethyl cellulose having a degree of substitution 2.42 to 2.53 and viscosity of 5% w/w solution in 80 : 20 toluene : ethanol by wt. at 25 ^{o}C approximately 14 cps

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(BDH Chemicals Ltd., Poole, England), acetone A.R., heavy liquid paraffin, light liquid paraffin, petroleum ether A. R. (B.R. 60-80° C), and chloroform A.R. (S.D. fine-chem. Pvt. Ltd. Bombay, India), hydrochloric acid AnalaR, potassium dihydrogen phosphate AnalaR (glaxo Laboratories India, Ltd. Bombay, India), and sodium hydroxide pellets purified (E. Merck, India, Pvt., Ltd. Bombay, India) were obtained commercially and used as received.

Preparation of Dosage Form

Ethyl cellulose micropellets were prepared at two stirring speed of 1175 r.p.m and 1375 r.p.m. Theophylline and ethyl cellulose were used in the proportion of 1 : 1, 1.5:1, and 2 : 1. Each batch was prepared in triplicate. 4 gms. of ethyl cellulose was sprinkled, small quantity at a time, in 20 ml of acetone, maintained at 15° C, which was being stirred with a magnetic stirrer. Stirring was continued untill a smooth polymer solution was formed. Required amount of theophylline was dispersed uniformly in the polymer solution. The resulting slurry was poured at a constant and steady stream in liquid paraffin, also maintained at 15 °C, which was being stirred at the specified speed with an electrical stirrer. The liquid paraffin had an absolute viscosity of 87.1 c.p., at 30°c, obtained by blending heavy liquid paraffin with light liquid paraffin in a ratio of 3:1. The slurry was converted into spherical micropellets. While continuing the stirring for sufficient time to flash off acetone, petroleum ether was added at a rate of 2 ml/min. to extract residual amount of acetone and to rigidize the resultant micropellets. The micropellets were recovered by filtering through a 100 mesh nylon cloth and washed with cold petroleum ether and dried at 40°c for 3 hours.

Particle Size Distribution

The different sizes of micropellets, present in each batch, were separated into different fractions by sieving for 15 minutes on a mechanical shaker using a nest of standard sieves.

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Determination of Micropellet Content

Approximately 100 mg of micropellets, accurately weighed, were dissolved in 5 ml of chloroform. 150 ml of 0.1 (N) Hcl was added and stirred for 30 minutes. The mixture was heated to remove chloroform completely. The mixture, after cooling to room temparature, was filtered and an aliquote, suitably diluted, was analysed spectrophotometrically at 271 nm using Hitachi double beam spectrophotometer model 200-20 (Hitachi Ltd., Tokyo, Japan). A blank was run to confirm non-interference of residual chloroform, if any. The overall reliability of this method was judged by conducting recovery experiments. The recovery averaged 98 $\pm$ 0.18%.

In-vitro Dissolution Study

In-vitro drug release was studied in 0.1 (N) Hcl and phosphate buffer of pH 7.4 (8) using U.S.P. - XX rotating basket dissolution apparatus. Accurately weighed micropellets, containing approximately 150 mg of theophylline, were placed into a basket covered with a 80 mesh nylon cloth. The basket was immersed in 500 ml of dissolution media maintained at 37 $\pm$ 1^{o}c and rotated at 100 r.p.m. 10 ml samples were withdrawn from dissolution media at specified time intervals and same volume of fresh media were replanished immediately. Withdrawn samples were filtered and the filtrates, after suitable dilution, were assayed spectrophotometrically for theophylline release at 271 nm and 272 nm for dissolution media 0.1 (N) Hcl and phosphate buffer of pH 7.4 respectively. Dissolution experiments were duplicated.

RESULTS AND DISCUSSION

Content Uniformity

Uniformity of the drug content in each fraction of each of the formulations (Table 1) indicated the reproducibility of the manufacturing process.

Particle Size - distribution

The size-distribution and its standard deviation of ethyl cellulose micropellets prepared at 1175 r.p.m. and 1375 r.p.m.

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TABLE 1

Reproducibility of the Manufacturing Process.

Theophylline: Ethyl cellulose	Yield (%)	Size Range (μm)	Mean Size d (μm)	Drug Content, mean percent	SD
1 : 1	83.5	991–854	922.5	50.3046	± 0.2715
		854–600	727	50.2621	± 0.2038
		600–500	550	50.5771	± 0.6027
1.5:1	87.6	991–854	922.5	60.2384	+ 0.1729
		854–600	727	60.1048	± 0.1398
		600–500	550	59.0854	± 0.3415
2 : 1	89.6	991–854	922.5	66.4734	± 0.2877
		854–600	727	65.7013	± 0.0324
		600–500	550	66.30	± 0.2513

Values are mean of triplicate batches.

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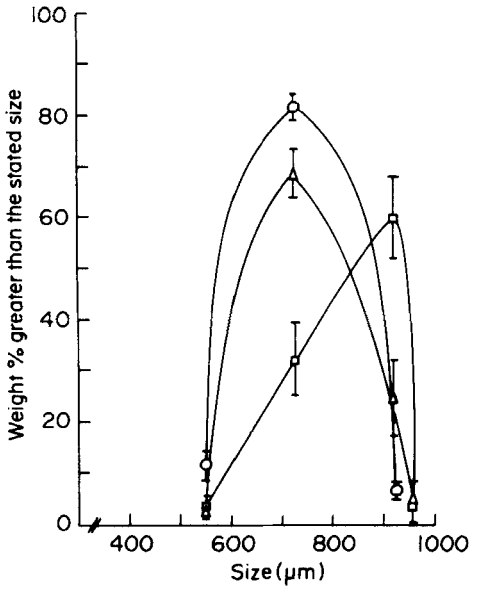

FIGURE 1

Effect of drug-polymer ratio on the size-distribution of ethyl cellulose micropellets at a speed setting of 1175 r.p.m. key: Drug-polymer ratio : (0) ⊥ : 1, (Δ) 1.5 : 1, (□) 2 : 1.

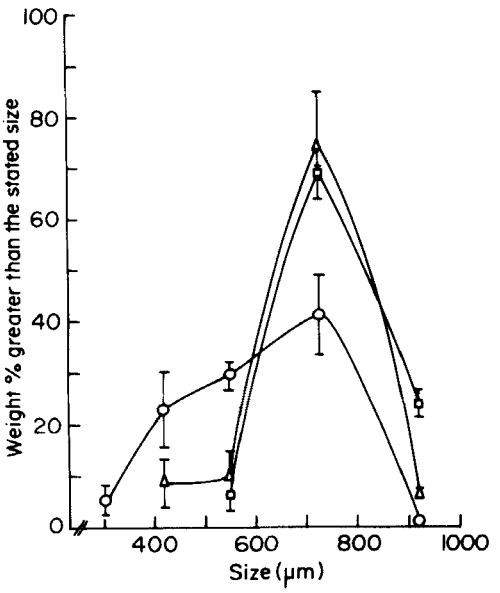

FIGURE 2

Effect of drug-polymer ratio on the size-distribution of ethyl cellulose micropellets at a speed setting of 1375 r.p.m. key: Drug : Polymer : (0) 1 : 1, (Δ) 1.5 : 1, (□) 2 : 1.

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are shown in Figure 1 and 2 respectively. At a constant stirring speed size-distribution curves shifted towards bigger micropellets as the drug - polymer ratio was increased. At higher stirring speed size - distribution curves moved towards the smaller micropellets while maintaining the same trend of shifting the curves towards bigger micropellets as the drug-polymer ratio was increased. A change in the dispersed phase changes both viscosity of the dispersed phase and interfacial tension between the dispersed phase and dispersion medium and consequently influences the size-distribution of micropellets (9). An increase in drug-polymer ratio increases relative viscosity of dispersed phase (theophylline-ethylcellulose suspension) and, therefore, sub-division of the dispersed phase into smaller sizes is prevented by the higher interfacial viscosity. At higher stirring speed resistance towards the sub-division of the dispersed phase into smaller particles is reduced.

Release of Theophylline from Micropellets

The influence of dissolution media on theophylline release from ethyl cellulose micropellets is depicted in Figure 3. The data for the acidic and the buffer media are almost superimposable. Similar observations were noted by McGinity et. al. (10), while studying the release of theophylline from tablets containing RLPM resin and from Theodur tablets. Figure 4 represents dissolution profiles of theophylline from ethyl cellulose micropellets in 0.1(N) Hcl as a function of drug- drug-polymer ratio and particle size of micropellets. For a particular size of micropellets, an increase in drug-polymer ratios causes faster release of theophylline. Plot of drug content versus time taken for 50% release of the drug (Figure 5) also indicates that higher the drug-polymer ratios, for a particular size of micropellets, less is the time for 50% release of the drug. At higher drug-polymer ratios, there are more drug particles per micropellet, resulting in a higher concentration gradient to boost dissolution. The linearity between

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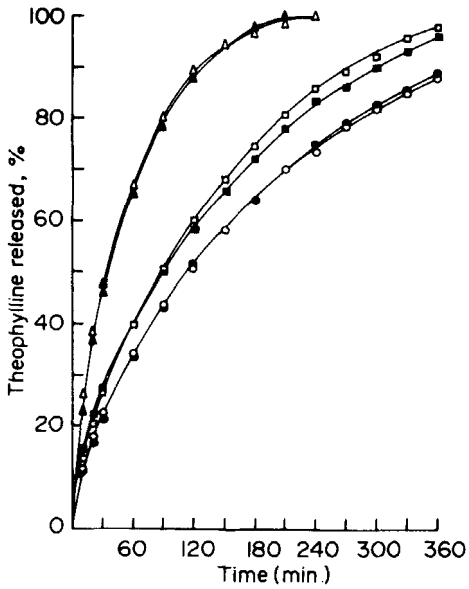

FIGURE 3

Influence of dissolution media on the release of theophylline from ethyl cellulose micropellets. Key : Drug - polymer ratio : (0) 1 : 1, mean diameter 727 μm, (Δ) 1.5 : 1, mean diameter 550 μm, (□) 2 : 1, mean diameter 922.5 μm. Open and closed symbols indicate dissolution media 0.1 (N) Hcl and phosphate buffer of pH 7.4 respectively.

drug content and time required to release 50% of the drug also indicate that a uniform diffusion gradient is set up and it may be possible to predict the 50% release time for micro-pellets of known size and drug content. This, in turn, can allow the preparation of micropelleted dosage form with a predictable release pattern. For a constant drug-polymer ratio, the release of theophylline increases with decreasing size of micro-pellets. Figure 6 depicts that release of theophylline is inversely proportional to the diameter of the spherical micro-pellets. This indicates that the fraction of sieve-analysed micropellets, taken for release studies, is a representative of uniform size distribution of the micropellets in that fraction and also indicates that the geometry of the micropellets is unaltered during dissolution study.

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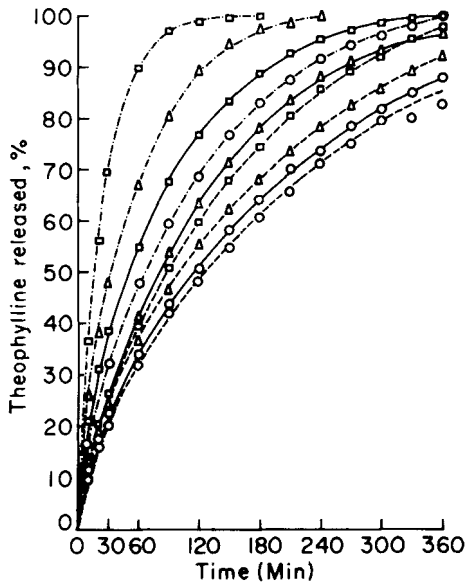

FIGURE 4

Effect of drug-polymer ratios and micropellet sizes on the dissolution profile of theophylline from ethyl cellulose micropellets in 0.1 (N) Hcl. Key : Drug-polymer ratio : (0) 1:1, (Δ) 1.5 : 1, (□) 2 : 1, mean micropellet diameter μm : (---) 922.5, (———) 727, (-.-.-) 550.

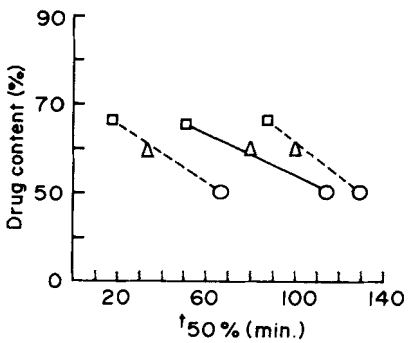

FIGURE 5

Effect of theophylline content on the time for 50% release from ethyl cellulose micropellets in 0.1 (N) Hcl. Key : Drug-polymer ratio : (0) 1 : 1, (Δ) 1.5 : 1, (□) 2 : 1. Mean micropellet diameter μm : (---) 922.5, (———) 727, (-.-.-) 550.

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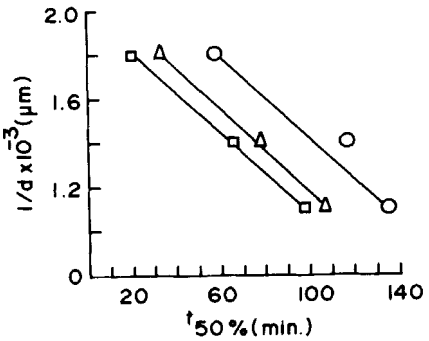

FIGURE 6

Effect of mean micropellet diameter on the time for 50% release of theophylline from ethyl cellulose micropellets in phosphate buffer of pH 7.4. Key : Drug-polymer ratio : (O) 1 : 1, (Δ) 1.5 : 1, (□) 2 : 1.

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Kinetic of Theophylline Release from Micropellets

Micropellets, in contrast to microcapsules, are actually monolithic or matrix systems and, therefore, release of a drug from micropelleted dosage form should be expected to follow diffusion controlled model in accordance with Higuchi equation (11) $Q = K t^{\frac{1}{2}}$ where Q = amount of drug released in time t per unit exposed area, K = Higuchi constant.

The plots of the amount of theophylline released from ethyl cellulose micropellets versus square root of time, Figure 7, indicated that the amount of theophylline released from micropellets increased linearly with square root of time.

In order to further verify that the release followed diffusion controlled model, Higuchi equation $Q = K t^{\frac{1}{2}}$ was converted into logarithmic form as $\log Q = \log K + 1/2 \log t$. A plot of log Q versus log t should yield a straight line having a slope of 0.5. Figure 8 shows that plots of log of amount of theophylline released versus log of time were also linear but the slopes, instead of being 0.5, varied from 0.5 to 0.62.

When logarithm of the percent of theophylline remaining to be released from the micropellets were plotted against

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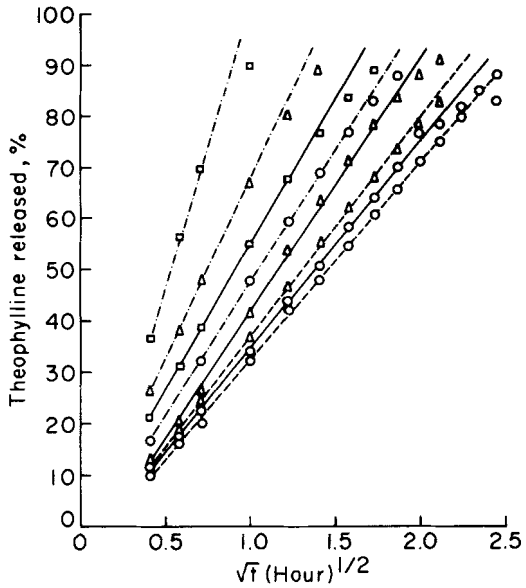

FIGURE 7

Apparent diffusion - controlled release profiles for the ophylline from ethyl cellulose micropellets. Key : Drug-polymer ratio : (0) 1 : 1, (Δ) 1.5 : 1, (□) 2 : 1. Mean micropellet diameter μm (---) 922.5, (———) 727, (-.-.-.-) 550.

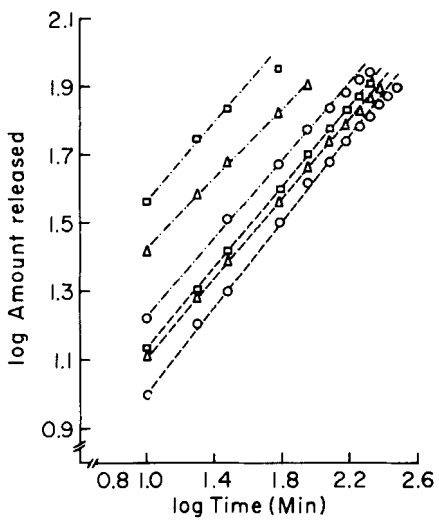

FIGURE 8

Plot of log of amount of theophylline released from ethyl cellulose micropellets against log of time. Key : Drug-polymer ratio : (0) 1 : 1, (Δ) 1.5 : 1, (□) 2 : 1. Mean micropellet diameter μm. (---) 922.5, (-.-.-) 550.

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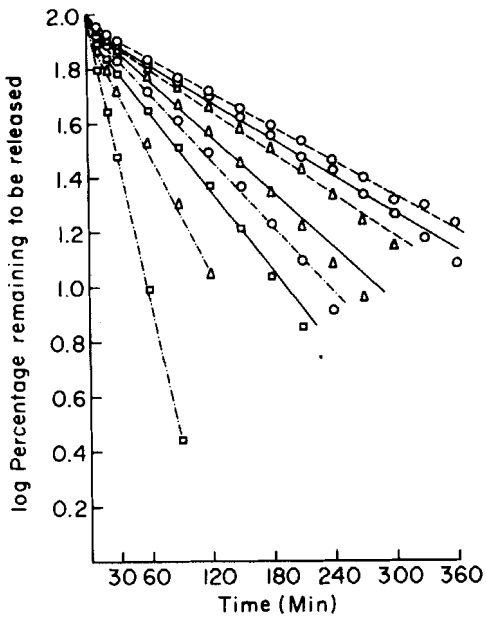

FIGURE 9

Release profiles of theophylline from ethyl cellulose micropellets plotted according to first-order kinetics. Key : Drug-polymer ratio : (O) 1 : 1, (Δ) 1.5 : 1 , (□) 2 : 1. Mean micropellet diameter μm. (---) 922.5 (——) 727 (-.-.-) 550.

time, as predicted by first order kinetics, linear relationship were obtained (Figure 9). The initial curvature can be attributed to the presence of surface drugs and can be ignored.

Since both the square root of time and first order release plots were linear, as indicated by correlation co-efficients (Table 2), it was necessary to distinguish between the mechanisms. The treatment was based upon use of the differential forms of the first order and square root-time equations (12). Similar treatment was used to identify correct release pattern of drugs from polymeric film (13) and microcapsule (14).

For diffusion controlled mechanism, the rate will be inversely proportional to the total amount of drug released Q' in accordence with equation : $\frac{dQ'}{dt} = \frac{K_H^2 S^2}{2Q'}$ where

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TABLE 2

Kinetics of Theophylline Release in 0.1(N) Hcl from Ethyl Cellulose Micropellets having different Drug-Polymer ratios and different Sizes.

Drug:Polymer	Mean Size (d) μm	k_1* $X10^{-3}$ min^{-1}		K_H** mg $min^{-1/2}$	
1 : 1	922.5	4.7887	(0.998)	4.9461	(0.998)
	727	5.2150	(0.999)	5.1959	(0.999)
	550	9.4983	(0.989)	6.6500	(0.989)
1.5 : 1	922.5	5.9228	(0.997)	5.5433	(0.999)
	727	7.9587	(0.997)	6.3568	(0.991)
	550	17.0764	(0.999)	9.1844	(0.982)
2 : 1	922.5	7.1919	(0.979)	6.1320	(0.997)
	727	11.1785	(0.999)	7.3131	(0.974)
	550	38.5760	(0.999)	13.7467	(0.978)

* Calculated from first-order equation

** Calculated from Higuchi equation ($Q=Kt^{1/2}$)
Figures in the parenthesis indicate correlation co-efficients.

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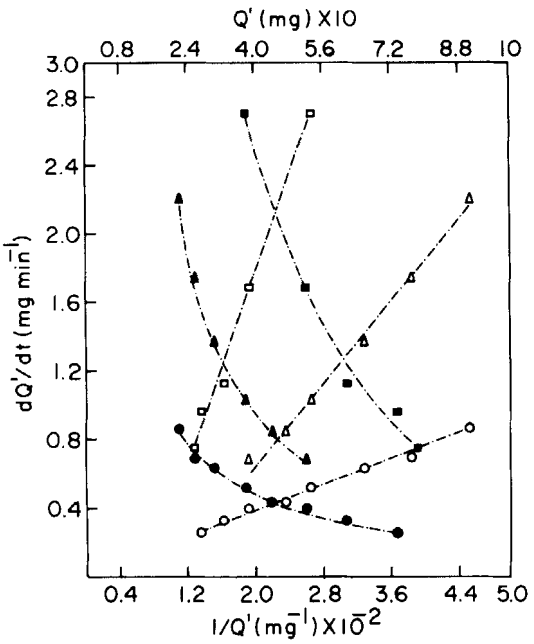

FIGURE 10

Plots of release rate (dQ'/dt) of theophylline against reciprocal of amount 1/Q' (open symbols) and the amount Q' (closed symbols) of drug released from micropellets having mean diameter of 550 μm. Key : Drug-polymer ratio : (0) 1 : 1, (Δ) 1.5 : 1 (□) 2 : 1.

Q' = Q x S (S is the surface area of micropellets). The rate predicted by first - order kinetics is given by :

$\frac{dQ'}{dt} = kC_0 - kQ'$ where $C = C_0 - Q'$. This indicated that rate will be proportional to Q'. The rates of release were determined by measuring the slopes at different points on the % of theophylline release versus time curves.

The plots of rates of release versus 1/Q' were linear and those of rates versus Q' were curved or non-linear (Figure 10). This was true for all the micropellets having different drug-polymer ratios and different sizes (Table-3) indicating

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TABLE 3

Comparison of Linearity between Plots of Rate of Release against Reciprocal Amount (1/Q') and Amount (Q') of Theophylline Released from Ethyl Cellulose Micropellets in 0.1(N) Hcl.

Drug:Polymer	Mean Size (d) μ m	Correlation coefficients Rate dQ'/dt Versus 1/Q'	Versus Q'
1 : 1	922.5	0.998	0.969
	727	0.994	0.967
	550	0.997	0.954
1.5 : 1	922.5	0.995	0.987
	727	0.996	0.983
	550	0.997	0.951
2 : 1	922.5	0.997	0.975
	727	0.999	0.979
	550	0.996	0.968

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that in the release of theophylline from the ethyl cellulose micropellets, diffusion controlled mechanism was operative.

Conclusion

A novel micropellet dosage form for theophylline has been developed using ethyl cellulose as a polymeric material. The method is simple and reproducible. Drug-polymer ratios and stirring speed during preparation influence the size-distribution of micropellets. The drug-polymer ratio and size of micropellets, in turn, control the release behavior of theophylline. The time for 50% release of theophylline varies linearly with drug content in micropellets and varies inversely with size of micropellets. Hence, a right release profile for sustained release dosage form can be obtained by combining appropriate portion of different sized micropellets having different drug-polymer ratios. The release of theophylline from such matrix system appears to follow both diffusion controlled and first order kinetics. However, differential rate treatment confirmed that release was controlled by diffusion controlled mechanism.

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