
Design of Controlled Release Non-erodible Polymeric Matrix Tablets of Theophylline Using Sintering Technique

A. KONDAIAH* AND K. PRAKASH

Department of Pharmaceutical Sciences, Andhra University, Visakhapatnam-530 003.

The objective of the present study is to formulate and evaluate theophylline polymeric matrix tablets for controlled release using sintering technique. The powder of ethylene vinyl acetate copolymer 1802 was prepared by a novel spray technique. The micromeritics of the powdered vinyl acetate copolymer were studied. Matrix tablets of theophylline in vinyl acetate copolymer were prepared in different drug and polymer ratios using direct compression and subsequent sintering technique at various temperatures. The sintered tablets were evaluated for various tablet characteristics including dissolution rate. A comparative dissolution rate study was conducted with the optimized formula against three commercial theophylline sustained release products. A simple process for powdering of vinyl acetate copolymer was developed. The sintering technique produced nonerodible matrix tablets. The *in vitro* dissolution studies have shown a considerable sustained release of theophylline from the matrix tablets of different drug polymer ratios. The control of release of theophylline from the sintered tablets depended on the polymer-drug ratio, temperature of sintering and time of sintering. Tablet formulation with a drug-polymer ratio of 75:25 sintered at 60° for a period of 1.5 h gave maximum percent of drug release in 12 h. The cumulative percent of drug released from this tablet formulation is better than two commercial products and comparable to the other one.

The objective in dosage form design is to optimize the delivery of medication so as to achieve a measure of control of therapeutic effect in the face of uncertain fluctuations *in vivo* environment in which drug release takes place¹. There are several physical approaches by which the drug release from a dosage form can be retarded. One such method to retard drug release is a heterogeneous dispersion of drug particles in a solid matrix which can be either biodegradable or non-biodegradable and which controls drug release by diffusion through the matrix, by erosion of the matrix, or by a combination of both diffusion and erosion.

Controlled release systems for macromolecules can be formulated by dissolution of ethylene vinyl acetate copolymer in an organic solvent (dichloromethane), adding powdered macromolecules, casting the mixture in a mold at low

temperature and vacuum². Cohen *et al.*³ developed a method for making polymeric systems for the controlled release of macromolecular drugs, which involved mixing drug and vinyl acetate copolymer (EVA) powders below the glass transition temperature of the polymer and sintering the compressed mixture at a temperature above the glass transition point. The kinetic studies indicated that there was sustained release, and the bioactivity of macromolecules tested was unchanged throughout the sintering and release processes. Verhoeven *et al.*⁴ studied the effect of hydrophilic excipients on drug release from the matrix tablets. In that they reported that adding more drug creates more pores between the polypropylene particles thereby greater release of drug.

The investigations of Jambhekar and Breen⁵ about the factors that control drug release from non-disintegrating cylindrical slow release tablets using sodium salicylate as model drug showed that the drug release was controlled by

*For correspondence:

porosity of the tablet and the mass of the drug present per unit of tablet volume. However, the pH and the flow rate of dissolution fluid did not influence the release of the drug; thus these factors are less critical in controlling drug release from such matrix formulations.

The present work was conducted based on the non-biodegradable system. This system involves usage of non-erodible retardant polymer matrix. The polymer matrix system considered for this work is EVA copolymer in which the drug was dispersed. Theophylline (TH) is a drug of choice for asthma therapy as a second line drug and many marketed sustained release formulations are available. Hence TH was selected as a model for the present study.

EXPERIMENTAL

EVA 1802 copolymer was obtained as gift sample from Polyolefins Industries Ltd., Mumbai. TH was obtained as gift sample from Tablets India Ltd., Chennai. Chloroform was procured from Ranbaxy Laboratories Ltd. Tween 85 was obtained from Sigma Chemical Co., St. Louis. Magnesium stearate, talc, lactose, glycerin IP, PEG 6000, tribasic sodium phosphate were procured from S.D. Fine Chemicals, Mumbai.

Spray powdering technique:

A 5% solution of EVA in chloroform was prepared and sprayed with the help of a Painter's Spray Gun (Simplex, capacity 600 ml) into a fabricated cylindrical spray drum made of galvanized iron sheeting measuring 0.46 m diameter and 1.22 m length. The air pressure was maintained at 2.5 kg/cm² using a Kirloskar compressor. The spraying end of the drum was kept at an elevated angle of 30° to horizontal and a fine nylon cloth was fastened at the collection end of the drum. The powder was left to dry at room temperature (32°) for 0.5 h. The powder was collected by brushing the cloth and inner walls of the drum. Micromeritic properties like tapped and untapped bulk density, compressibility index and angle of repose⁶ were studied.

Formulation of sintered tablets:

Matrix tablets were prepared with polymer: drug ratios of 50:50 (F1), 40:60 (F2), 30:70 (F3) and 25:75 (F4). Magnesium stearate (0.5% w/w) and Talc (1% w/w) were used as lubricants. All materials were dried overnight in a desiccator before compressing them into tablets. The materials were mixed using a mortar and pestle and finally in a glass bottle by tumbling action. The powder mass was compressed into tablets using a Cadmach single punch tablet press with

11 mm punch and die set, each tablet containing 200 mg of TH. The matrix tablet formulations viz. F1, F2, F3 and F4 containing different ratios of polymer-drug were sintered at 60°, 70°, 75° and 80° for 1.5 h (S1) and matrix tablet formulations F3 and F4 were sintered at 60°, 70°, 75° and 80° for 3 h (S2) in constant temperature ovens.

Evaluation of sintered tablets:

The diameter and thickness of the tablets were measured using vernier calipers. The hardness was tested using Stokes-Monsanto hardness tester. The Friability test was conducted using Roche friabilator. Weight variation test and drug content uniformity for TH in tablets was carried out as per IP⁷.

In vitro dissolution rate studies:

The *in vitro* dissolution rate studies were conducted for all the sintered tablet formulations using USP XXI dissolution apparatus (Type 1), (Thermonik, Campbell Electronics, Mumbai). Dissolution test was carried out for a period of 12 h using 0.1 N HCl (900 ml) as dissolution medium for the first 2 h and pH 6.8 phosphate buffer for the rest of the period. At appropriate time intervals 5 ml samples were withdrawn and replaced with the same volume of dissolution medium. The absorbance of these samples were measured at 271 nm against blank using Shimadzu UV-140-02 double beam spectrophotometer to determine the amount of TH released from the tablets.

Studies on the effect of hydrophilic excipients and sintering time on drug release from the optimized formulation:

The effect of hydrophilic excipients like lactose, Tween 85, glycerin and PEG 6000 (formulations LF4, TF4, GF4 and PF4 respectively) at 10% w/w level on the drug release characteristics from the matrix tablet formulation F4 sintered at 60° and for a sintering time of 1.5 h was studied. An *in vitro* dissolution testing of three commercial sustained release products, X, Y and Z was also conducted for comparison with the prepared sintered tablets.

RESULTS AND DISCUSSION

A new technique was developed for the controlled release of TH from the non-erodible plastic matrix tablets prepared from EVA. A novel method for powdering of EVA was achieved by a spray technique from a chloroform solution of the polymer. The powder recovery was 70-75% of the polymer load in solution. The powder contained fine particles to thread like masses (fig. 1). The untapped and tapped bulk

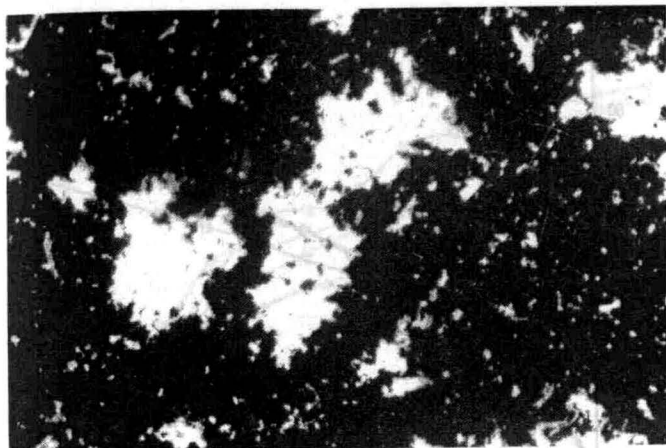


Fig. 1: Photomicrograph of ethylene vinyl acetate 1802 copolymer powder (100X magnification).

densities of EVA powder are 0.119 g/ml and 0.174 g/ml respectively suggesting that the material is fluffy and a high bulk material. The high value of angle of repose, 59.04° for the powder suggest poor flow, and the flow was increased upon addition of the drug. Polymer matrices of EVA and TH in various proportions were prepared and compressed into tablets to contain 200 mg of TH. The average thickness of the matrix tablets was found to be 5.3, 4.0, 3.2 and 3.0 mm for F1, F2, F3 and F4 respectively, with an average diameter of about 11.5 mm before sintering, which is slightly more than the punch diameter (11 mm). This expansion of diameter could be due to the plastic nature of the EVA powder. There was no change in the dimensions of the tablets after sintering. The zero friability indicates that sintered tablets are compact and hard. The hardness of the sintered tablets ranged between 2.0 and 4.8 kg/cm². The hardness has in-

creased when the sintering temperature and time are increased. This may be due to the firm bonding of EVA particles at higher temperatures. The weight variation test for all the prepared tablet formulations complies with the IP⁷ limits for compressed tablets. The drug content was found to be within 10% variation of the label claim of 200 mg in all formulations thus complying with IP limits for content uniformity.

In vitro drug release studies were carried out for all formulations for a period of 12 h. The non-erodible nature of the tablets was established by intactness of tablets at the end of the dissolution period. The dissolution data for all the prepared and commercial tablets were given in Table 1.

The cumulative percent of drug release (CPR) from tablet formulations (F1, F2, F3 and F4) sintered at various temperatures revealed that the release of TH decreased gradually as the EVA content of the tablets increased (Table 1). Dissolution profiles of the tablet formulations (F1, F2, F3 and F4) sintered at 60° for 1.5 h are shown in fig. 2. The cumulative percent of TH released was decreased marginally as the sintering temperature was increased from 60 to 80° for all the tablet formulations. This may be due to the fact that higher polymer content and higher temperature give more compact sintered matrices so that the inner core is relatively inaccessible to the dissolution media whereby both cumulative percent released and rates of release of the drug were slowed down. As the cumulative percent release of TH in 12 h was less than 55%, further studies on formulations F1 and F2 were discontinued.

Further the effect of sintering time on the matrix formu-

TABLE 1: RELEASE OF THEOPHYLLINE FROM SINTERED FORMULATIONS.

Formulation	Sintering Temperature							
	60°		70°		75°		80°	
	CPR	Kx10 ⁻²	CPR	Kx10 ⁻²	CPR	Kx10 ⁻²	CPR	Kx10 ⁻²
F1S1	47.81	4.7	46.72	4.0	46.63	3.56	42.77	3.84
F2S1	55.50	7.19	54.40	6.77	54.60	6.22	51.81	5.62
F3S1	71.71	9.03	64.21	7.31	63.69	7.08	63.34	7.37
F4S1	82.81	11.23	75.56	10.23	74.08	10.12	73.58	10.01
F3S2	67.42	7.42	65.70	6.67	63.24	6.77	62.88	6.58
F4S2	78.57	11.23	70.60	8.69	74.89	10.23	63.21	8.52

CPR is the average cumulative percent of Theophylline released in 12 h. (n=3) and k is the first order release rate constant.

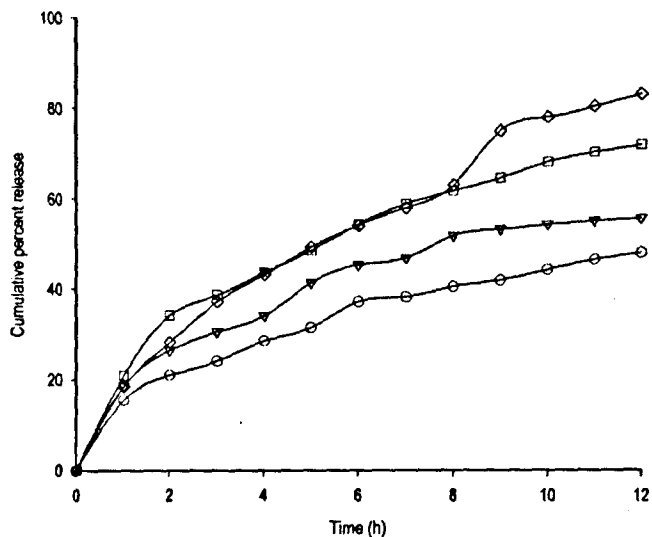


Fig. 2: *In vitro* release profiles of theophylline from matrix tablets.

In vitro release of theophylline was studied from matrix tablets sintered at 60° for 1.5 h. The various formulations studied are F1 (-O-), F2 (-∇-), F3 (-□-) and F4 (-◇-).

lations F3 and F4 at various temperatures was studied. When the duration of sintering of matrix formulations F3 and F4 was increased to 3 h (i.e., F3S2 and F4S2), the cumulative percent release of TH decreased when compared to the corresponding CPR values of 1.5 h sintering time (i.e., F3S1 and F4S1). This may be due to the increase in the extent and firmness of sintering which compacts the mass further so that the drug release was affected. The dissolution profiles of these formulations F3 and F4 sintered at 60° for 1.5 and 3 h are shown in fig. 3.

From the foregoing discussion, it is clear that tablets made from formulation F4 with EVA content of 25% w/w and TH content of 75% w/w which were sintered for 1.5 h at 60° provided maximum percent of drug release. This finding may be due to the fact that the sintering compaction was sufficient to yield pores as the drug dissolves out from the matrix. When the dissolution data of the prepared and commercial tablets were fitted to various release models (zero order⁸, First order⁹, Higuchi model¹⁰ and Power law model¹¹), the data of all the formulations fitted well to both the first order and Higuchi square root of time models as indicated by its correlation coefficient (*r*) values near to unity. This showed that the release of TH from both the prepared and commercial formulations was mediated through the process of diffusion and the release followed first order rate kinetics.

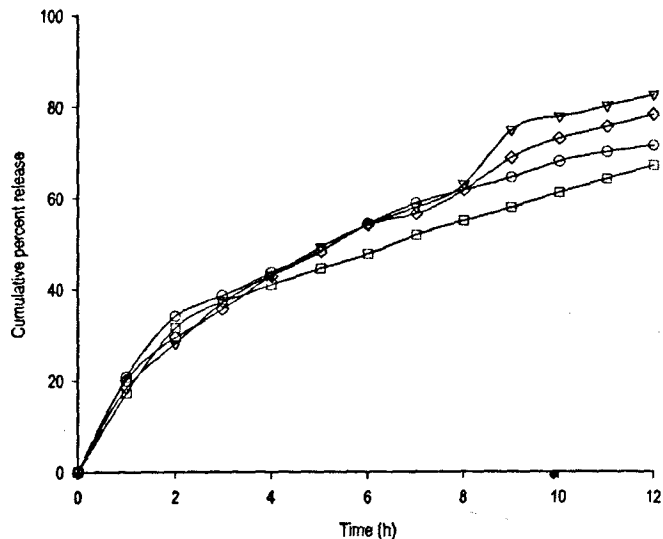


Fig. 3: *In vitro* release profiles of theophylline from matrix formulations F3 and F4.

In vitro release of theophylline was studied from matrix formulations F3 and F4 sintered at 60° for 1.5 h (S1) and 3 h (S2), F3SI (-O-), F4SI (-∇-), F3S2 (-□-) and F4s2 (-◇-).

To further enhance the drug release, the effect of hydrophilic additives like lactose, tween 85, glycerin and PEG 6000 on drug release pattern in matrix formulation F4 sintered at 60° for 1.5 h were studied. The cumulative percent release was found to be 66.34, 85.84, 65.25 and 62.30 for the formulations LF4, TF4, GF4 and PF4 respectively (fig. 4). The release rate constant *k* was found to be 6.77, 16.45, 8.86 and 6.22 ($\times 10^{-2} \text{ h}^{-1}$) for the above formulations. Incorporation of lactose (L) and PEG 6000 (P) at 10% w/w levels in the above optimized formulation did not improve the release rate of TH from the tablets. Further when tween 85 (T) and glycerol (G) were incorporated at 10% w/w levels, though the release of TH was high the tablets lost their shape and partial erosion occurred towards end of the dissolution study.

The dissolution profile of formulations F4 sintered at 60° and for 1.5 h (F4S1 at 60°) was compared with those of three commercial TH sustained release tablets (fig. 5). The cumulative percent of drug release for the commercial tablets X, Y and Z in 12 h was found to be 95.74, 67.56 and 70.54 respectively. The *k* values were found to be 19.1, 9.03 and 8.85 ($\times 10^{-2} \text{ h}^{-1}$) for the formulations X, Y and Z respectively. These findings shows that the cumulative percent release of TH and *k* values of the optimized formulation (F4) were quite comparable to that of the studied marketed sustained release products, viz., X, Y and Z of TH.

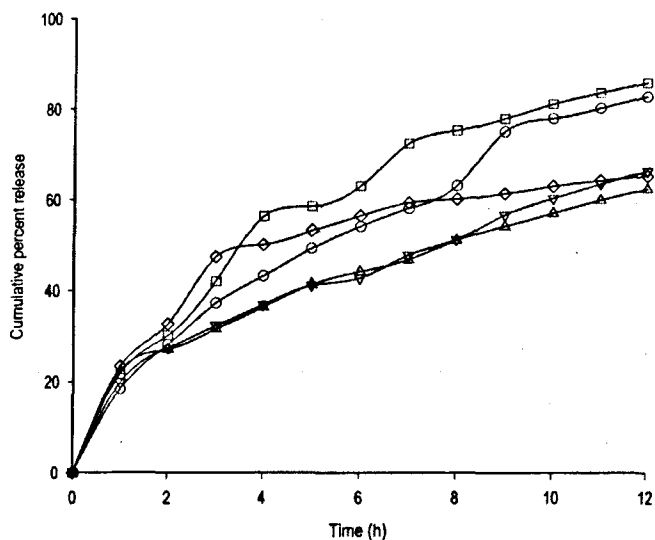


Fig. 4: Effect of hydrophilic excipients on the release behaviour of F4.

Effect of hydrophilic excipients (10% w/w) on the release behaviour of theophylline from F4 sintered at 60° for 1.5 h; F4SI (-O-), lactose (-∇-), Tween 85 (-□-), glycerin (-◇-) and PEG 6000 (Δ).

A simple technique for powdering of EVA 1802 was developed. The EVA powder contained fine particles to thread like masses. The sintering technique produced non-erodible matrix tablets. Sintering at 60° for a period of 1.5 h gave maximum percent of TH release from the matrix formulation F4 in 12 h dissolution study. When the time of sintering and/or temperature was increased, the percent of TH released was reduced irrespective of the drug: polymer ratio in the formulation. The cumulative percent of drug released from the optimized tablet [matrix formulation F4, sintered at 60° for 1.5 h (F4S1)] is better than two commercial products Y and Z and comparable to the other X. By selecting proper polymer-drug ratio, sintering temperature and sintering time, an effective controlled release tablet dosage form can be formulated.

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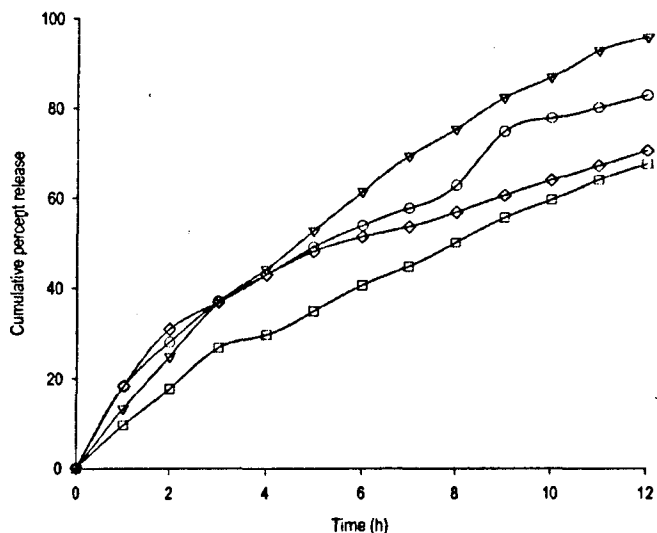


Fig. 5: Comparative release profiles of formulation F4 with commercial products.

Comparison of release pattern of theophylline from matrix formulation F4 sintered at 60° for 1.5 h, F4SI (-O-) with commercial products X (-∇-), Y (-□-) and Z (-◇-).

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