RESEARCH PAPER

Accepted 5 August 2003
Revised 3 July 2003
Received 12 June 2002
Indian J. Pharm. Sci., 2003, 65(5): 496-502

Design and Evaluation of Ethylene Vinyl Acetate Sintered Matrix Tablets

B. SREENIVASA RAO, A. SESHASAYANA, K. HIMASANKAR, Y. PRASANNA RAJU AND K. V. RAMANA MURTHY*
Department of Pharmaceutical Sciences, Andhra University, Visakhapatnam-530 003.

A new method of preparation of sintered matrix tablets of rifampicin with ethylene-vinyl acetate copolymer is developed for controlling its release rate. This method is very simple. Drug and polymer powder (ethylene-vinyl acetate copolymer) were mixed and compressed at room temperature. The compressed fluffy matrices were kept at 60°, 70° and 80° for 1.5, 3 and 4.5 h for sintering. The sintered tablets were characterized for their physical characteristics and evaluated for *in vitro* dissolution studies. The sintering time markedly affected the drug release properties from the matrices. The release rate of rifampicin from EVA 1408 matrices was inversely related to the time of sintering due to the increase in the extent and firmness of sintering which compacts the mass further so that the drug release is affected. The drug release followed diffusive mechanism with first-order release kinetics.

In controlled release drug delivery systems the drug is released at a predetermined rate based on a desired therapeutic concentration (in either systemic circulation or a target site) and the drug's pharmacokinetic characteristics[1]. Earlier studies relating to the use of plastic polymers as the matrix have shown that controlled release was possible for macromolecules. Sintering technique for the preparation of polymer matrix has attracted wide attention in the controlled release of drugs. Cohen *et al.* developed a new method for the controlled release of macromolecular drugs, which involved mixing drug and EVA copolymer powder below the glass transition temperature of the polymer and compressing the mixture at a temperature above the glass transition (T_g) point[2]. Nesic and Cvetkovic developed controlled release oral dosage form by sintering the polymer matrix with different organic solvent vapors[3]. The process of sintering affects the pore structure and strength of plastic matrix tablets[4,5].

Rifampicin, a semisynthetic hydrazine derivative of rifamycin B, one of the most potent and powerful mycobactericidal drugs is used both in tuberculosis and leprosy treatment. Its short biological half-life, high doses, adverse side effects and prolonged period of treatment with conventional doses necessitate its formulation into controlled release drug delivery systems, promoted the development of controlled release formulations.

Ethylene vinyl acetate (EVA) copolymer is a random copolymer has a pendent acetate group. EVA 1408 is a tough material having 18% w/w vinyl acetate content. In the present investigation, a new technique was developed for the controlled release of rifampicin from EVA 1408 by sintering technique.

MATERIALS AND METHODS

Rifampicin IP was obtained from Aristo Pharmaceuticals Limited, Mandeep, Maharastra. Sodium starch glycolate was procured from Veco Pharma, Visakhapatnam. Aerosil was obtained from Knoll Pharmaceuticals, Pune. Potassium dihydrogen orthophosphate, sodium hydroxide, and ascorbic acid used were of analytical grade, purchased from S. D. Fine Chemicals Ltd., Mumbai.

Powdering of EVA 1408:

Powdering of small pellets of EVA 1408 is difficult due to high tensile strength and polymeric nature. Generally EVA

*For correspondence
E-mail: drkvrmurthy@rediffmail.com

polymer was converted into a powder by two methods, both these methods requiring liquid nitrogen. But these processes were time consuming and uneconomical. In the present study, powdering of EVA 1408 copolymer was achieved by a simple procedure. EVA 1408 beads were soaked in sufficient amount of chloroform for 8 h, and then the swollen beads were passed through sieve No. 60 by applying low pressure. The powder was spread evenly over oily paper and dried at ambient temperature by continuous mixing with a spatula. The dried polymer powder was then sieved through mesh No. 30. Polymer powder passed through mesh No. 30 was used in the present study.

Flow properties of polymer powder:

The static angle of repose (θ) was measured according to the fixed funnel and free standing cone method[6]. A funnel with the end of the stem cut perpendicular to its axis of symmetry is secured with its tip 2 cm above a graph paper placed on a flat horizontal surface. Powder is carefully poured through the funnel until the apex of the cone thus formed just reaches the tip of the funnel. The mean diameter of the base of the powder cone is determined and the tangent of the angle of repose is obtained.

Compressibility on tamping[7] was measured with a sample of 25 g placed in a 100 ml graduated cylinder and the occupied volume (V_0) was determined. After 10 and 500 vibrations, occupied volumes V_{10} and V_{500} were determined. With these data we obtained the compressibility index (CI) using the formula, $CI=V_{500}-V_{10}/V_{500}x100$.

Preparation of tablets:

For the preparation of tablets rifampicin and different proportions of additives are mixed as shown in Table 1. Quantity sufficient for a batch of 40 tablets was mixed thoroughly to ensure complete mixing. Tablets containing 300 mg equivalent to rifampicin were compressed to an applied force of 500-kg/cm² and compression time of 11 sec using 11 mm round, flat and plain punches (surface lubricated with talc) on single stroke tabletting machine (Cadmach Machinery Co. Pvt. Ltd., Ahmedabad). The prepared tablets were sintered at various temperatures like 60, 70 and 80° for 1.5, 3.0 and 4.5 h in constant temperature ovens. The temperature of ovens was maintained within a degree Celsius.

Differential scanning calorimetry (DSC):

Thermal analysis was performed on the drug, polymer and other additives using a Shimadzu DSC-50 thermal analyzer. Samples (5 mg) were accurately weighed into an aluminum pan and then sealed. The thermograms of the samples were obtained at a scanning rate of 10°/min conducted over a temperature range of 30-300° with an empty pan as reference.

Thin layer chromatography (TLC):

Stability of rifampicin which was treated at 80° for 4½ h was performed by TLC method, official in British Pharmacopoeia[8], using silica gel G as the coating substance, preparing the suspension using citro phosphate buffer pH 6.0. A mixture of 85 volumes of chloroform and 15 volumes of methanol was used as the mobile phase and the solvent front was allowed to ascend 12 cm above the line of application. Rifampicin was dissolved in chloroform.

Microbiological assay:

Potency of rifampicin, which was treated at 80° for 4.5 h, was determined by microbiological assay that is official in Indian Pharmacopoeia[9], using cylinder-plate or cup-plate method. Nutrient agar was used as the medium. *Bacillus subtilis* was the test organism. Incubation period was 18 h at 35°.

Dissolution of rifampicin:

The dissolution test was carried out using USP rotating basket method. Stirring speed was maintained at 100 rpm. Phosphate buffer (pH 7.4) containing 0.02% W/V of ascorbic acid was used as dissolution medium (900 ml) and was maintained at 37°±1. Samples of 5 ml volume were withdrawn at predetermined time intervals, filtered, diluted suitably and assayed spectrophotometrically. An equal volume of fresh medium was immediately replaced to

TABLE 1: COMPOSITION OF RIFAMPICIN MATRIX TABLETS.

Ingredients	Formulation Code			
	E_1 (mg)	E_2 (mg)	E_3 (mg)	E_4 (mg)
Rifampicin	300	300	300	300
EVA 1408powder	60	90	120	150
Sodium starch glycolate	15	15	15	15
Aerosil 1	1	1	1	

Composition of Rifampicin matrix tablets prepared and their formulation codes, EVA is Ethylene vinyl acetate

maintain the dissolution volume. The samples were analyzed spectrophotometrically at 475 nm using double beam UV spectrophotometer to assay the amount of rifampicin released at each time interval. Dissolution studies were performed in triplicate and the results were expressed as mean of the three values.

At the end of 12 h of testing, the tablet remains were suspended in methanol and the residual drug content was estimated. This is to make sure that the amount of drug remained, when added to the cumulative amount of drug released up to 12 h equals to the average drug content of the tablets estimated prior to subjecting them to drug release studies.

Standard physical tests of sintered tablets:

To study the variations in physical properties, sintered tablets were subjected to the following tests. Friability (F) was determined by weighing 10 tablets after dusting with a camel-hair brush, placing them in a Roche-friability tester and rotating the basket vertically at 25 rpm for 4 min. After dusting again the total remaining weight of the tablets was recorded and percent friability was calculated.

Hardness was determined by taking 6 tablets from each formulation, placing each tablet between the jaws of a Stokes-Monsanto hardness tester and noting the pressure (kg/cm^2) required to crush each tablet. Results were expressed as mean±SD. Uniformity of weight was determined by weighing 20 tablets individually and calculating the percentage deviation of each tablet from the average weight.

RESULTS AND DISCUSSION

The advantages of sintering method used in this study, when compared with solvent casting method and compressed at elevated temperature method include, elimination of shrinkage, elimination of the need for potentially expensive scale up steps such as vacuum drying and usage of liquid nitrogen, reduction of processing time (slabs were produced in 1.5-4.5 h) compared to 4 h required for solvent casting and simple (scalpel and forceps need not be used as in the case of the method of compression at elevated temperature).

It is necessary to characterize flow properties of the powders that make it possible to make sure that they are suitable for using as direct compression excipients. In this investigation we used angle of repose and compressibility index on tamping to characterize the flow properties of the polymer powder. These tests are generally used to characterize bulk solids routinely before compression. So, better optimization of flow properties can be achieved in experimental formulations.

Although the determination of flow rate (g/s) through a circular orifice is the direct assessment of flow properties of a powder material, the flow rate determination of EVA 1408 copolymer powder was not possible due to development of electrostatic charge during flow. Therefore, the angle of repose was considered an indirect measurement of powder flowability[10]. According to the Delattre classification, EVA 1408 copolymer powder is classified as poor-flowing powder because the angle of repose is higher than 40°[10]. The compressibility index also indirectly measures the flowability of powder mass[11], the CI value of EVA 1408 copolymer powder was measured and found to be 28.5. This result indicated that the drug mixture was not ideal due to slower transport through the hopper into the feed frame and for subsequent die filling. It is generally accepted that CI values above 23% are indicative of poor flowability of a material.

DSC was used to examine thermal behaviour of pure drug and formulation. DSC thermograms (not shown in figure) indicated the qualitative composition of the drug formulations and verified the identity of each of the components. No drug interaction or complexation occurred during the manufacturing process.

TLC method was used to detect the degradative products that might have formed after exposing rifampicin to 80° for 4.5 h. The TLC indicated no additional spots other than the principal spot of rifampicin, whose Rf value matched, with that of the standard. This indicated that rifampicin did not degrade even after heating at 80° for 4.5 h. This result is in agreement with similar findings of others[12]. Microbiological assay also confirmed that the potency of rifampicin was unaltered even after heating at 80° for 4.5 h.

Tablets from all formulations passed the test for weight uniformity (not more than two tablets differed from the average weight by more than the 5% and no tablet differed by more than 10% (data not shown). Tablets of all formulations passed the test for friability (<1%)[13]. Hardness of the tablets increased as the polymer content was increased and hardness also depended on sintering time as well as sintering temperature (Table 2).

Drug release from EVA polymer matrix tablets (heterogeneous, nonerodible, nonbioadhesive) was

TABLE 2: BREAKING STRENGTH OF SINTERED MATRICES.

Temperature	Time (h)	Breaking strength (kg/cm²) of Formulations			
		E_1	E_2	E_3	E_4
60°	1.5 h	2.1	2.4	2.7	2.9
	3.0 h	2.5	3.1	3.2	3.4
	4.5 h	2.7	3.3	3.6	3.8
70°	1.5 h	2.6	3.3	3.7	4.2
	3.0 h	3.1	3.7	4.0	4.8
	4.5 h	3.4	3.8	4.3	5.1
80°	1.5 h	3.3	3.6	4.1	4.8
	3.0 h	3.7	4.0	4.3	5.1
	4.5 h	3.9	4.3	4.6	5.5

Breaking strength in kg/cm^2 of various Rifampicin tablet formulations coded E_1, E_2, E_3, E_4 sintered at different temperatures (60°, 70°, 80°) for durations of 1.5 h. 3.0 h, and 4.5 h.

examined during the dissolution of matrices. At the end of 12 h, the matrix shape was not disturbed, suggesting that the drug release is controlled by diffusion. Dissolution profiles of rifampicin from EVA 1408 matrices sintered at different temperatures for various times are shown in figs. 1-4. The sintering time markedly affected the drug release properties of EVA 1408 matrices. It is notable that the release rate of rifampicin from EVA 1408 matrices was inversely related to the time of sintering. This may be due to the increase in the extent and firmness of sintering which compacts the mass further so that the drug release is affected. Furthermore, the dissolution pattern of rifampicin from EVA 1408 matrices revealed that the drug release was increased as the EVA 1408 copolymer percent was decreased. The cumulative percent of rifampicin released was decreased as the sintering temperature was increased for all formulations.

Higuchi[14] has described drug release mechanism from matrix dosage forms using the following equation, $Q=\sqrt{D(2W-C_s)C_s t}$. In this equation, D is the diffusion coefficient of the drug in the matrix, W is the total amount of the drug per unit volume of the matrix, C_s is the solubility of the drug in the matrix and t is the drug release time. When $W>>C_s$, the above equation can be simplified to as $Q=\sqrt{2WDC_s t}$.

This equation indicates that the amount of drug released is proportional to the square root of time from the diffusional release of a drug from a matrix-type system. The linear correlation coefficients of the slopes, shown in Table 3 indicated that the drug release from EVA 1408 polymeric matrix follows Higuchi diffusion model. The pattern of drug

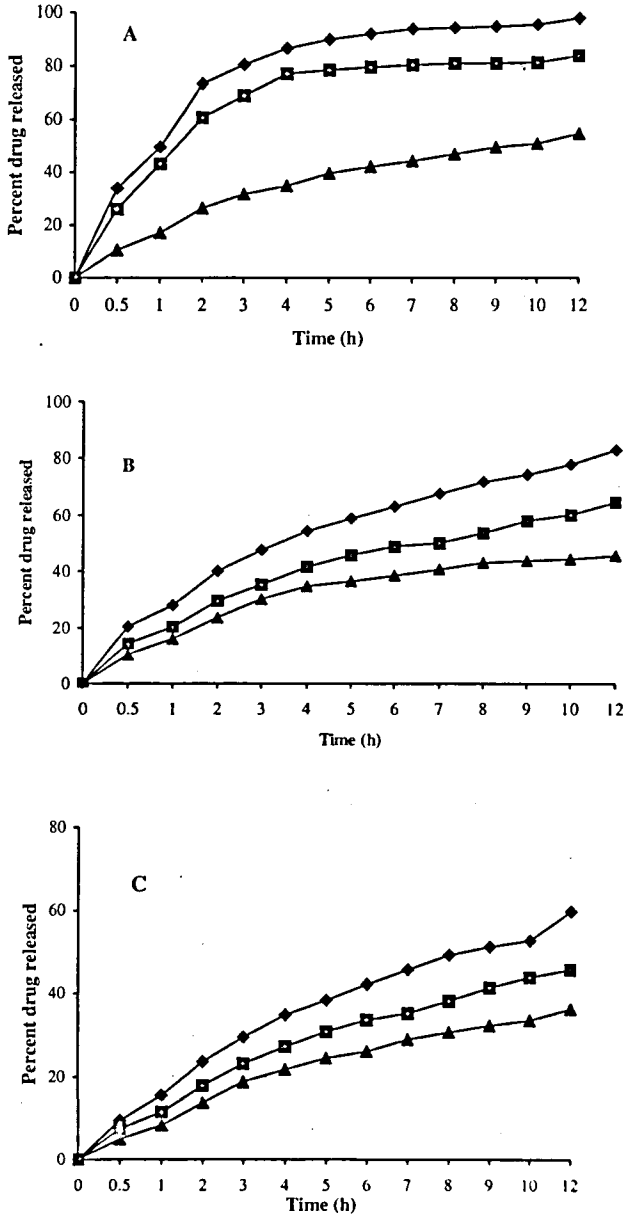

Fig. 1: Dissolution profiles of rifampicin from formulation E_1.

Formulation E_1 was sintered at (A) 60°, (B) 70° and (C) 80° for different time intervals , 1.5 h (-▲-), 3.0 h (-■-) and 4.5 h (-♦-). (n=3)

release form the EVA 1408 copolymer sintered tablets was linear with the square root of time through out the entire period. This fact supports the conclusion that the drug is released by a diffusion process. The correlation coefficients of the slopes of these matrices also showed an adequate fit to the first order model. It had been reported that the EVA 1408 matrices sintered at increased temperature might result more extent of sintering due to firmness between EVA 1408 particles (shown in Table 3).

The surface of the sintered matrix after dissolution was porous in appearance (figure not shown) whereas the matrix before dissolution was quite smooth. This difference indicated that the matrix size and shape was not altered. Appearance of the porous structure is because of the release of dispersed rifampicin and other additives in sintered matrix. Tablets throughout the experiments maintained their original shape without any kind of erosion.

The very low hardness obtained when the tablets

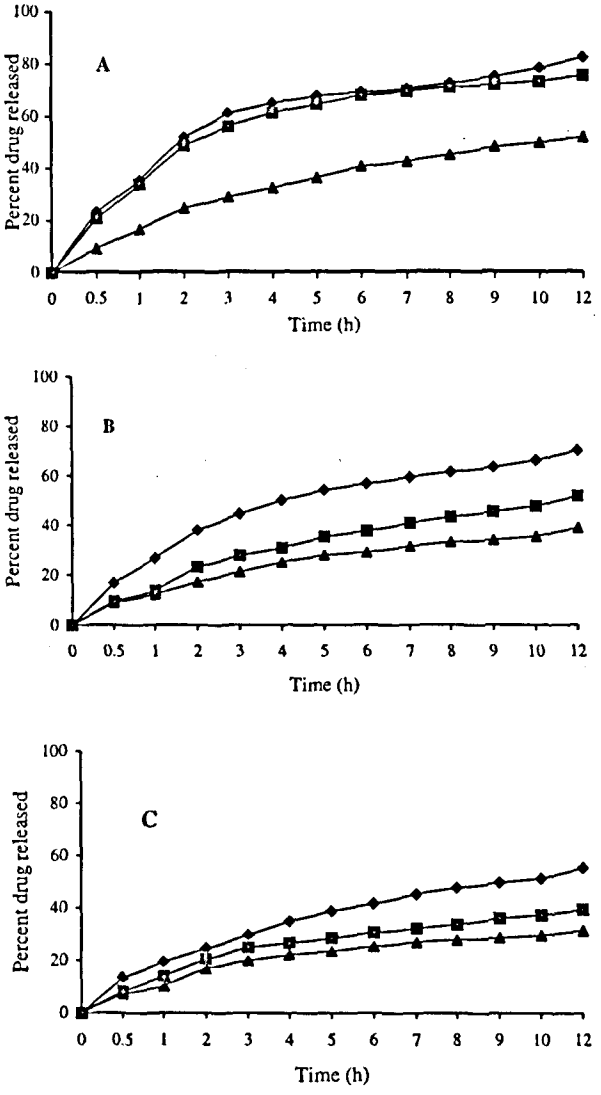

Fig. 2: Dissolution profiles of rifampicin from formulation E_2

Formulation E_2 was sintered at (A) 60°, (B) 70° and (C) 80° for different time intervals , 1.5 h (-▲-), 3.0 h (-■-) and 4.5 h (-♦-). (n=3)

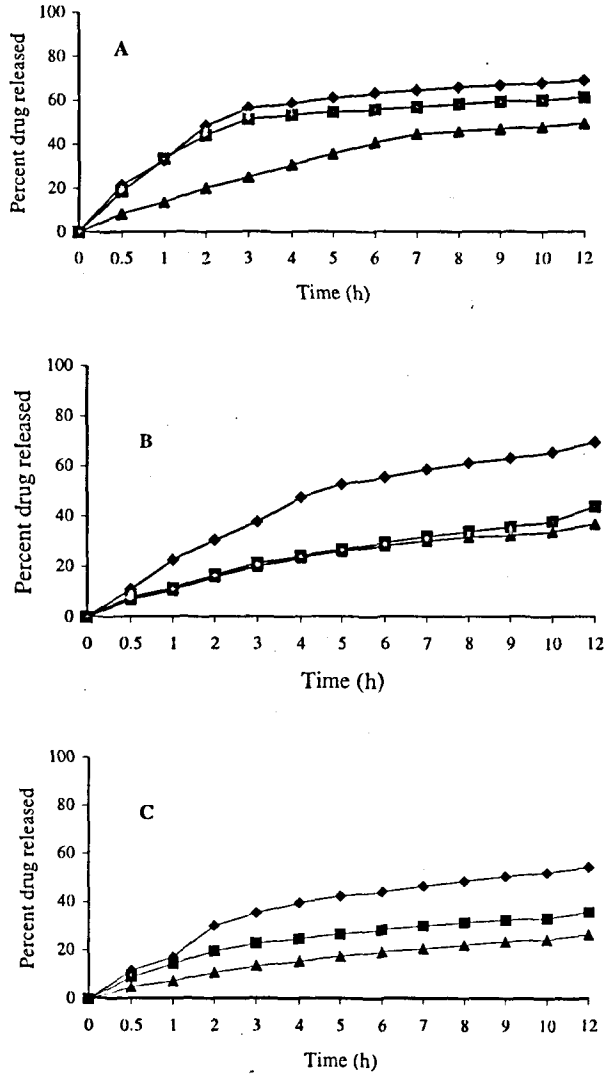

Fig. 3: Dissolution profiles of rifampicin from formulation E_3

Formulation E_3 was sintered at (A) 60°, (B) 70° and (C) 80° for different time intervals, 1.5 h (-▲-), 3.0 h (-■-) and 4.5 h (-♦-). (n=3)

TABLE 3: REGRESSION COEFFICIENTS AND RELEASE RATE CONSTANTS OF RIFAMPICIN FROM THE SINTERED FORMULATIONS.

Matrices	First order kinetics		Higuchi model
	r	K (hr^{-1})	r
E_4 at 60° for 1.5 h	0.954	0.0522	0.977
for 3.0 h	0.962	0.0496	0.988
for 4.5 h	0.861	0.0409	0.980
E_4 at 70° for 1.5 h	0.964	0.0419	0.988
for 3.0 h	0.964	0.0356	0.989
for 4.5 h	0.964	0.0293	0.988
E_4 at 80° for 1.5 h	0.952	0.0329	0.983
for 3.0 h	0.953	0.0288	0.982
for 4.5 h	0.970	0.0200	0.988
E_3 at 60° for 1.5 h	0.875	0.0711	0.944
for 3.0 h	0.854	0.0521	0.991
for 4.5 h	0.953	0.0502	0.995
E_3 at 70° for 1.5 h	0.965	0.0510	0.975
for 3.0 h	0.969	0.0386	0.988
for 4.5 h	0.957	0.0313	0.985
E_3 at 80° for 1.5 h	0.941	0.0555	0.987
for 3.0 h	0.942	0.0292	0.987
for 4.5 h	0.970	0.0226	0.989
E_2 at 60° for 1.5 h	0.948	0.1104	0.961
for 3.0 h	0.925	0.0928	0.961
for 4.5 h	0.966	0.0552	0.984
E_2 at 70° for 1.5 h	0.961	0.0822	0.995
for 3.0 h	0.969	0.0526	0.987
for 4.5 h	0.982	0.0342	0.987
E_2 at 80° for 1.5 h	0.974	0.0580	0.988
for 3.0 h	0.940	0.0321	0.988
for 4.5 h	0.932	0.0255	0.992
E_1 at 60° for 1.5 h	0.957	0.2674	0.991
for 3.0 h	0.861	0.1170	0.890
for 4.5 h	0.953	0.0557	0.992
E_1 at 70° for 1.5 h	0.983	0.1285	0.989
for 3.0 h	0.975	0.0730	0.989
for 4.5 h	0.780	0.0411	0.986
E_1 at 80° for 1.5 h	0.968	0.0659	0.996
for 3.0 h	0.967	0.0455	0.996
for 4.5 h	0.964	0.0351	0.995

First order release rate constants and Higuchi diffusion correlation coefficients of rifampicin sintered matrix formulations.

sintered at low temperature indicates that the main forces holding the particles together are probably van der Waal's and mechanical forces due to interlocking of irregularities on the surfaces of particles. Little if any, may be due to asperity melting or sintering that occurred at this temperature. Increasing the temperature or time of exposure to a particular temperature often decreased the release rate. This is probably due to the fusion of polymer granules or formation of welded bonds between the polymer particles.

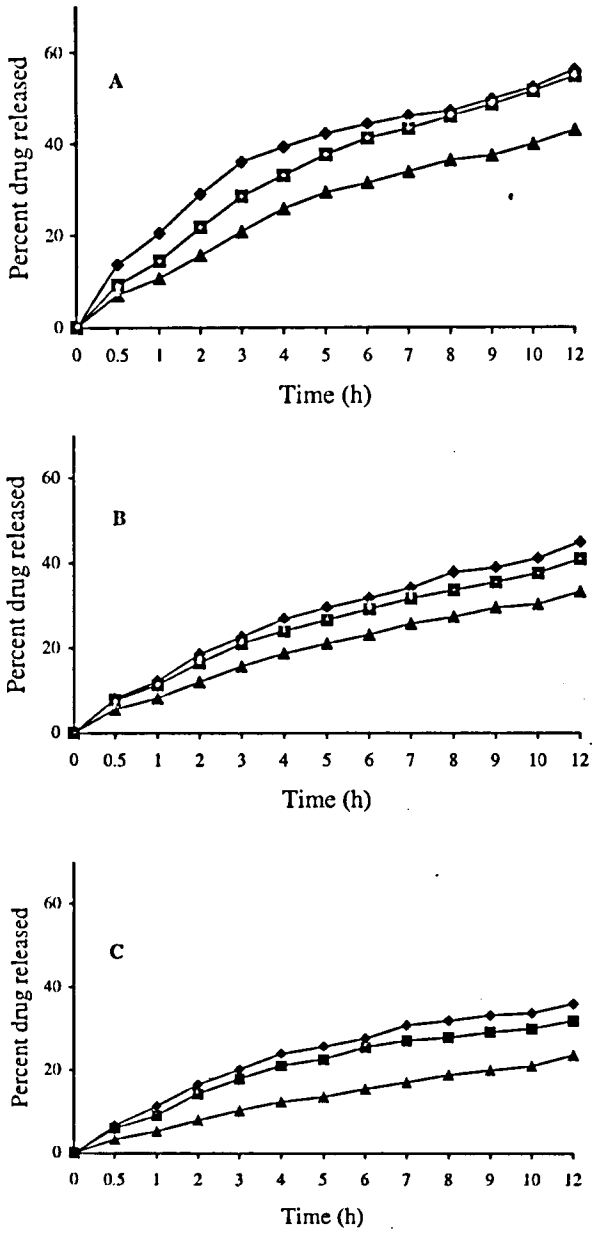

Fig. 4: Dissolution profiles of rifampicin from formulation E_4

Formulation E_4 was sintered at (A) 60°, (B) 70° and (C) 80° for different time intervals, 1.5 h (-▲-), 3.0 h (-■-) and 4.5 h (-♦-). (n=3)

In conclusion, among the different strategies employed for the design of controlled release dosage forms, sintering technique for the preparation of polymer matrices for the controlled release of rifampicin is an alternative technique. This new method for controlling the rate of release of rifampicin has been developed and tested here. The rifampicin stability was not affected by the higher temperatures used for sintering indicating the suitability of the method. At elevated temperature EVA 1408 powder particles were fused or welded where the particles were contacted. The extent of fusion depends on sintering temperature and sintering time. This type of system provides a simple and convenient method of achieving controlled release in oral dosage form.

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