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Studies on Release of Rifampicin from Sintered Matrix Tablets

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The new methods for making polymeric systems for the controlled release of rifampicin drug is described. This method is very simple, it consists of mixing drug and polymer powder (ethylene-vinyl acetate copolymer) and compressed at room temperature. The compressed fluffy matrices were kept at 60°, 70° and 80° for 1½, 3 and 4½ h for sintering. The sintering tablets were charcterised for their physical parameters and conducted *in vitro* dissolution tests. The sintering time markedly affected the drug release properties of EVA (ethylene vinyl acetate copolymer) matrices. It is notable that the release rate of rifampicin from EVA 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. The cumulative percent of rifampicin release decreased as the sintering temperature was increased, for all formulations. The drug release follows diffusive mechanism with first-order release kinetics.

Controlled release drug delivery systems are dosage forms which the drug is released by a predetermined rate, which is 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].

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Rifampicin, the semisynthetic hydrazine derivative of rifamycin B, is one of the most potent and powerful mycobactericidal drug. It is used mainly in intermittent therapy, both in tuberculosis and leprosy, because of its high cost and adverse side effects[15]. This has promoted the development of controlled release formulations.

Ethylene vinyl acetate (EVA) copolymer is a random copolymer has a pendent acetate group. EVA 1802 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 1802 by sintering technique.

MATERIALS AND METHODS

Rifampicin IP was obtained from Aristo Pharmaceuticals Limited, Mandideep, Madhya Pradesh. 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 1802:

Powdering of small pellets of EVA is difficult due to its high tensile strength and polymeric nature. Powdering of EVA polymer is generally achieved by two methods. But this process is time consuming and uneconomical. In the present study, powdering of EVA copolymer was achieved by a simple procedure. EVA 1802 beads were soaked in sufficient amount of chloroform for 8 h, then the swollen beads were passed through sieve No. 60 under low pressure. The powder was spread evenly over oily paper immediately and continuously rubbed with a spatula for drying at ambient temperature. The ground 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 conc 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 were determined, V_{10} and V_{500} respectively. With these data we obtained the compressibility index (CI).

$$CI = \frac{d_{500} - d_{10}}{d_{500}} \times 100$$

Preparation of tablets:

Rifampicin and different proportions of additives are 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/cm^2 and compression time of 11 sec, using 11 mm round, flat and plain punches (surface lubricated with talc) on single stroke tableting machine (Cadmach Machinery Co. Pvt. Ltd., Ahmedabad, India). 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 ± 1°.

Differential scanning calorimetry (DSC):

Thermal analysis was performed on the drug, polymer and other additives using a Shimadzu DSC-50 thermal analyszer. 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[8], using silica gel G as the coating substance, preparing the suspension using citrophosphate 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 4½ h was determined by microbiological assay. Microbiological assay is official in Indian Pharmacopoeia[9], using cylinder-plate or cup-plate method. Nutrient agar

TABLE 1: COMPOSITION OF RIFAMPICIN MATRIX TABLETS

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

The quantities in mg of all ingredients that were used in the preparation of rifampicin matrix tablets, E_1, E_2, E_3 and E_4 are tabulated.

was taken as medium. *Bacillus subtilis* was taken as test organism. Incubation period is about 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 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 three times and the mean values were taken.

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

Standard physical test of the tablets:

To study the variations in the physical properties the sintered tablets were subjected for 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 at 25 rpm for 4 min. After dusting, the total remaining weight of the tablets was recorded and the percent friability was calculated.

Hardness was determined by taking 6 tablets from each formulation and placing one tablet between the jaws of Stokes-Monsanto hardness tester. The applied pressure (kg/cm^2) for crushing the tablet was noted. Weight uniformity was determined by weighing 20 tablets, individually, taken the average weight and the percent deviation of each tablet with respect to average weight was calculated.

RESULTS AND DISCUSSION

The advantages of sintering method used in this study, when compared with solvent casting method or compression at elevated temperature method includes (1) elimination of shrinkage (2) elimination of the need for potentially expensive scale up steps such as vacuum drying and liquid nitrogen (3) reduction of processing time compared with 4 h required for solvent casting and (5) simple [no need to use scalpel and forceps, which are required for compression at elevated temperature method].

Pharmaceutical industry needs to characterize flow properties of the powders that make it possible to estimate their suitability for direct compression excipients[16]. In this work we have used some of these tests: angle of repose and compressibility index on tamping, for characterizing

TABLE 2: HARDNESS OF SINTERED MATRICES

		Formulation Code			
		E_1	E_2	E_3	E_4
60°	1½ h	2.2	2.6	2.7	2.8
	3.0 h	2.4	3.0	3.2	3.4
	4½ h	2.8	3.4	3.6	3.8
70°	1½ h	2.6	3.3	3.7	4.2
	3.0 h	3.0	3.7	4.0	4.8
	4½ h	3.5	3.9	4.3	5.1
80°	1½ h	3.2	3.8	4.1	4.8
	3.0 h	3.5	4.0	4.3	5.0
	4½ h	3.9	4.3	4.5	5.3

The hardness of all the four formulations, E_1, E_2, E_3 and E_4 are shown. Each value is an average of hardness determinations of 6 tablets and is expressed as kg/cm^2.

the flow properties of polymer powder. In the development laboratory, these tests are used routinely to characterize bulk solids 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 copolymer powder was not possible due to development of electrostatic charge during flow. The angle of repose is considered an indirect measurement of powder flowability[10]. According to the Delattre classification, EVA 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 copolymer powder was measured and found to be 30.81. This result is an indication that the transport through the hopper into the feed frame and for subsequent die filling could not be better for the drug mixtures because it is known that the CI value above 23% indicates bad flowability (poor flow) 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 find out the degradative products in treated rifampicin at 80° for 4½ h. After removal of the plate from TLC chamber, allowed it to dry in air at room temperature. No colored spot other than the principal spot of rifampicin was observed in the chromatogram with test sample and gave same R_f value as that of standard. This indicated that there is no degradation in rifampicin even if heated at 80° for 4½ h. This result is in agreement with similar finding of others[12]. Microbiological assay also conformed, in potency wise, that the rifampicin was stable in solid state upto 80°.

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

Drug release from heterogeneous, nonerodible, nonbiodegradable, nonbioadhesive matrix formulations examined during the dissolution of matrices. At the end of 12 h, the matrix shape was not disturbed, suggesting that the release of the drug is controlled by diffusion from the matrix.

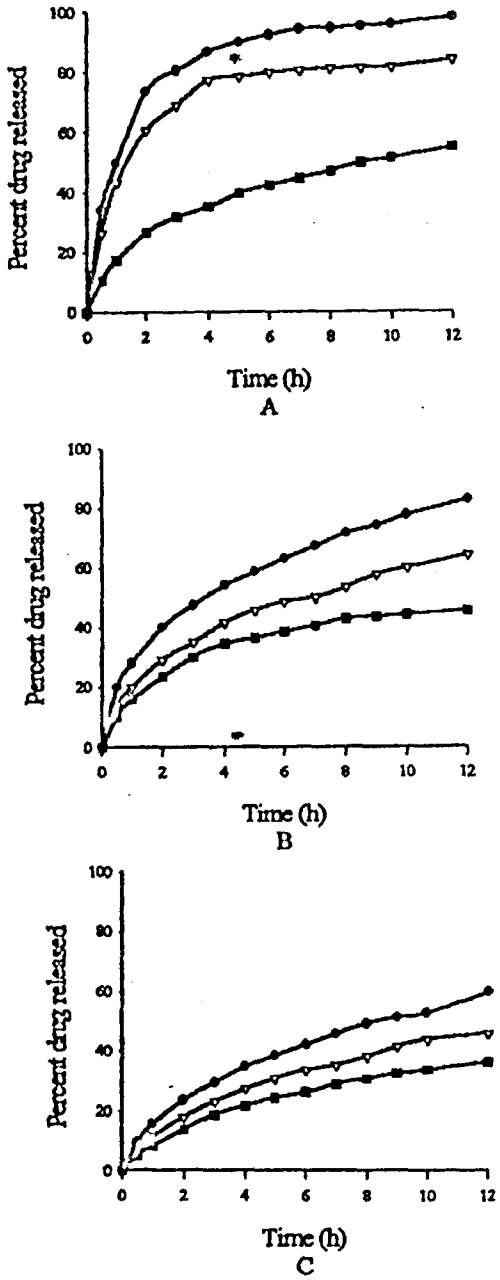

Fig. 1: Dissolution profiles of rifampicin from formulation E1 Rifampicin release from formulation E1 sintered at 60°(A), 70° (B) and 80°(C) for 1.5 h (-●-), 3.0 h (-∇-) and 4.5 h (-□-). Each point is an average of 3 determinations (n=3).

The dissolution profiles of rifampicin from EVA 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 matrices. It is notable that the release rate of rifampicin from EVA 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 matrices revealed that

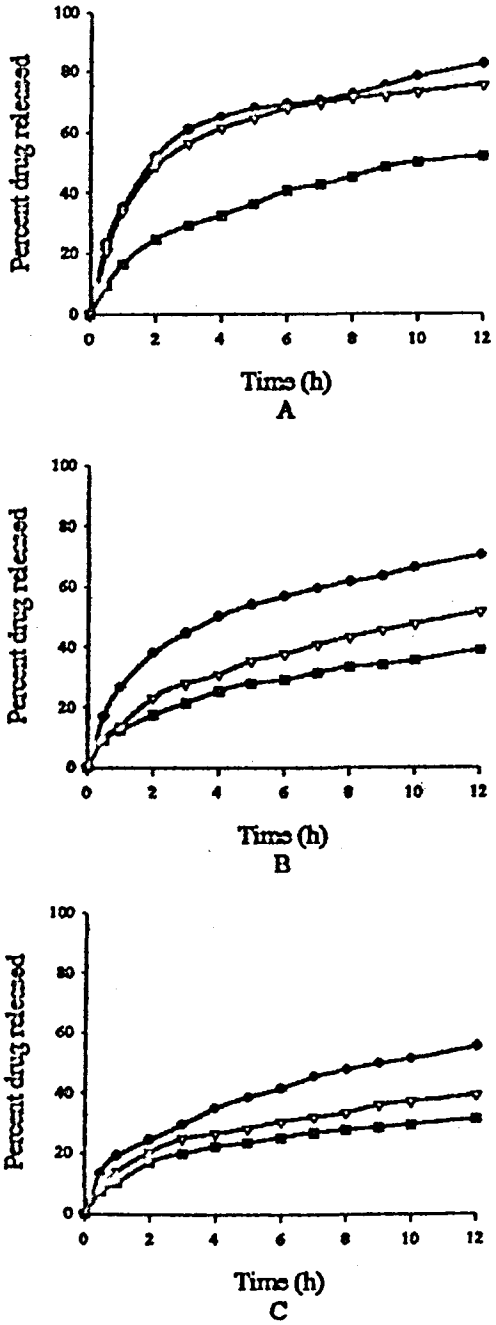

Fig. 2: Dissolution profiles of rifampicin from formulation E2

Rifampicin release from formulation E1 sintered at 60°(A), 70° (B) and 80°(C) for 1.5 h (-o-), 3.0 h (-∇-) and 4.5 h (-□-). Each point is an average of 3 determinations (n=3).

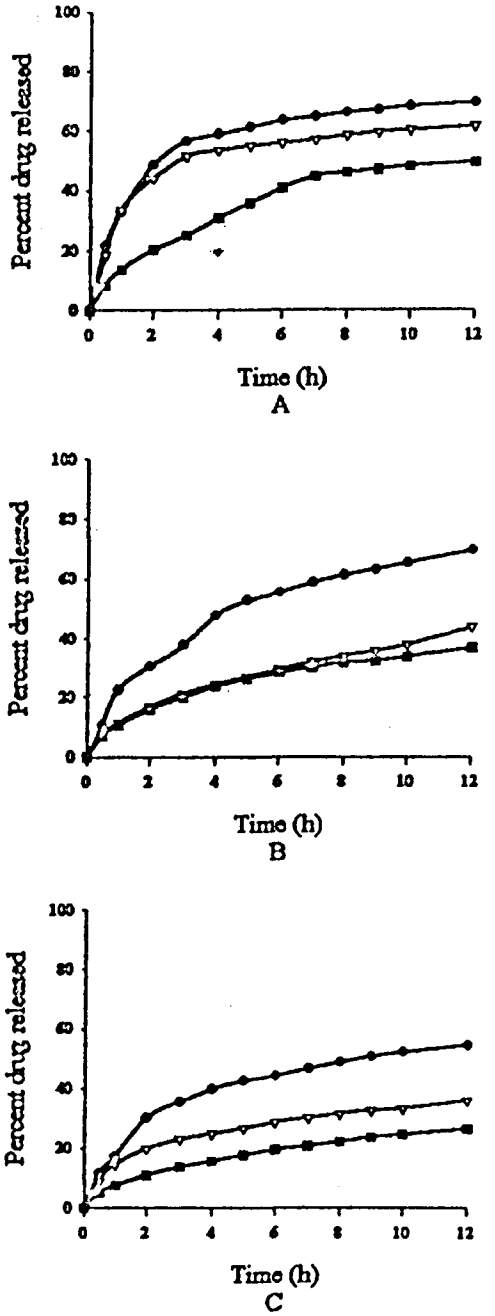

Fig. 3: Dissolution profiles of rifampicin from formulation E3

Rifampicin release from formulation E1 sintered at 60°(A), 70° (B) and 80°(C) for 1.5 h (-o-), 3.0 h (-∇-) and 4.5 h (-□-). Each point is an average of 3 determinations (n=3).

TABLE 3: RELEASE RATE CONSTANTS AND CO-EFFICIENTS

Matrices		First order kinetics		Higuchi model
		r^2	K (hr^{-1})	r^2
E_4 at 60°	for 1.5 h	0.968	0.0534	0.987
	for 3.0 h	0.987	0.0508	0.998
	for 4.5 h	0.886	0.0421	0.998
E_4 at 70°	for 1.5 h	0.989	0.0431	0.999
	for 3.0 h	0.989	0.0378	0.999
	for 4.5 h	0.989	0.0303	0.998
E_4 at 80°	for 1.5 h	0.966	0.0319	0.993
	for 3.0 h	0.965	0.0277	0.992
	for 4.5 h	0.994	0.0202	0.998
E_3 at 60°	for 1.5 h	0.899	0.0724	0.939
	for 3.0 h	0.869	0.0531	0.983
	for 4.5 h	0.965	0.0512	0.988
E_3 at 70°	for 1.5 h	0.979	0.0501	0.988
	for 3.0 h	0.993	0.0398	0.998
	for 4.5 h	0.972	0.0323	0.995
E_3 at 80°	for 1.5 h	0.953	0.0546	0.977
	for 3.0 h	0.956	0.0281	0.987
	for 4.5 h	0.982	0.0219	0.999
E_2 at 60°	for 1.5 h	0.961	0.1110	0.951
	for 3.0 h	0.937	0.0942	0.951
	for 4.5 h	0.980	0.0544	0.994
E_2 at 70°	for 1.5 h	0.976	0.0826	0.985
	for 3.0 h	0.984	0.0518	0.997
	for 4.5 h	0.997	0.0333	0.997
E_2 at 80°	for 1.5 h	0.989	0.0568	0.998
	for 3.0 h	0.955	0.0321	0.998
	for 4.5 h	0.947	0.0244	0.992
E_1 at 60°	for 1.5 h	0.972	0.2670	0.991
	for 3.0 h	0.876	0.1160	0.899
	for 4.5 h	0.978	0.0567	0.993
E_1 at 70°	for 1.5 h	0.998	0.1280	0.997
	for 3.0 h	0.990	0.0739	0.997
	for 4.5 h	0.805	0.0403	0.976
E_1 at 80°	for 1.5 h	0.983	0.0668	0.998
	for 3.0 h	0.982	0.0460	0.998
	for 4.5 h	0.979	0.0343	0.997

Coefficients and release rate constants of rifampicin release functions of sintered matrix for formulations, E_1, E_2, E_3 and E_4 sintered at 60, 70 and 80° for 1.5, 3.0 and 4.5 h.

the drug release increased as the EVA copolymer percent was decreased. The cumulative percent of rifampicin released, decreased as the sintering temperature was increased for all formulations.

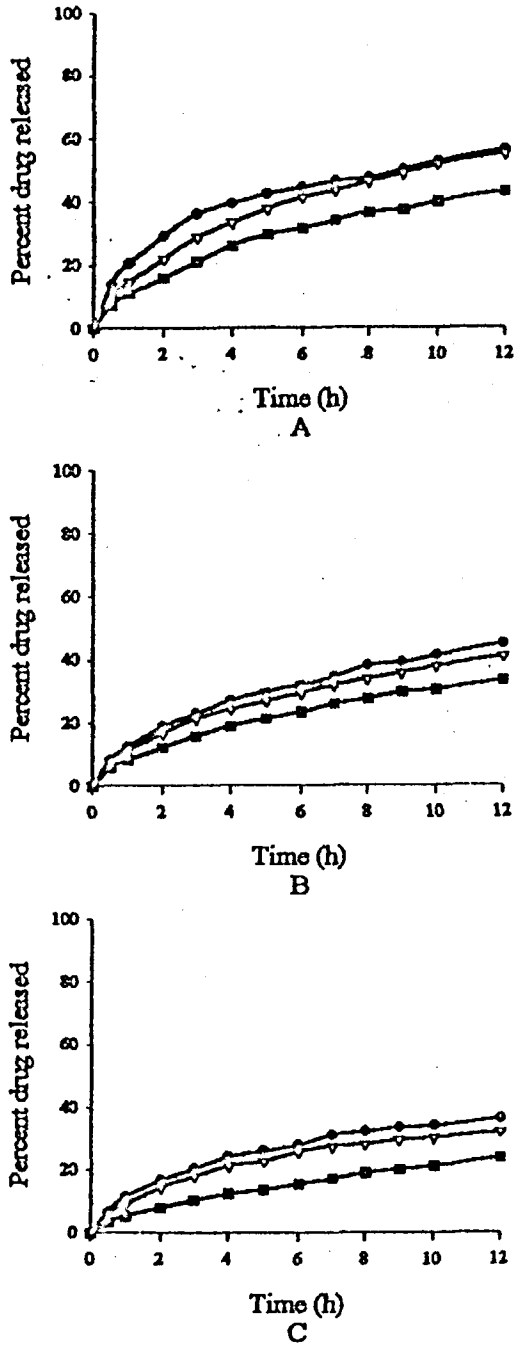

Fig. 4: Dissolution profile of rifampicin from formulation E4

Rifampicin release from formulation E1 sintered at 60°(A), 70° (B) and 80°(C) for 1.5 h (-o-), 3.0 h (-∇-) and 4.5 h (-□-). Each point is an average of 3 determinations (n=3).

Higuchi[14] has described drug release mechanism from matrix dosage forms using the following equation:

$$Q = \sqrt{D(2W-Cs)\ C_{st}}$$

In the above 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 the following:

$$Q = \sqrt{2WDC_{st}}$$

This equation indicates that the amount of drug released is proportional to the square root of time for the diffusional release of a drug from a matrix-type system. The linear correlation coefficients of the slopes, shown in Table 3 indicating that the drug release from EVA polymeric matrix follows Higuchi diffusion model. 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 matrices sintered at increased temperature might result more extent of sintering due to firmness between EVA 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 between these two matrices indicated that the matrices size and shape was not altered. The porous structure appeared because of the release of dispersed rifampicin and other additives in sintered matrix. Tablets throughout the experiments maintained their original shape and no erosion of any kind occurred. The pattern of drug release form the EVA copolymer sintered tablets was linear with the square root of time through out the entire period.

The very low hardness obtained when the tablets 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 asperity melting or sintering has occurred at this temperature. Increasing the temperature or time of exposure to a particular temperature often decreases the release rate. This is probably due to the fusion of polymer granules or formation of welded bonds between the polymer particles.

In conclusion, among the different strategies employed for the design of a 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 rifampicin release rate has been developed and tested here. The increased temperature has not affected the rifampicin stability. At elevated temperature EVA powder particles were fused or welded where the particles were in contact. 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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