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## Design and Evaluation of Eudragit RL 100 Sintered Matrix Tablets

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A simple technique for making polymeric matrix systems for the controlled release of rifampicin using Eudragit RL100 is described. This method consisted of mixing drug and Eudragit RL100 powder (polymethacrylates) and compressed at room temperature. The compressed fluffy matrices were kept in acetone chamber for 1.5, 3 and 4.5 h for sintering. The sintered tablets were characterized for physical characteristics and subjected to *in vitro* dissolution studies. The sintering time markedly affected the drug release properties of Eudragit RL100 matrices. It is notable that the release rate of rifampicin from Eudragit RL100 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 drug release followed first-order release kinetics with diffusive mechanism.

Controlled release dosage forms are becoming increasingly important, either to achieve the desired level of therapeutic activity required for a new drug entity or to extend life cycle of an existing drug through improved performance or patient compliance. The long period of treatment with conventional drug delivery systems and adverse effects of rifampicin often lead to discontinuation of treatment by a substantial proportion of patients as soon as they begin to feel better<sup>1</sup>.

Earlier studies reporting the use of plastic polymers as the matrix have shown that controlled release was possible for macromolecules. Sintering technique for the preparation of a 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<sup>2</sup>. Nestic and Cvetkovic developed

controlled release oral dosage form by sintering the polymer matrix with different organic solvent vapors<sup>3</sup>. The process of sintering appears to affect the pore structure and strength of plastic matrix tablets<sup>4,5</sup>.

Rifampicin, one of the most potent and powerful mycobactericidal drugs, is used mainly in intermittent therapy, both in tuberculosis and leprosy. Its high cost and adverse side effects<sup>6</sup> prompted the development of controlled release formulations.

Eudragit RL100 is described in USP NF XVII as ammonio methacrylic acid copolymer consisting of fully polymerized copolymers of acrylic acid and methacrylic acid esters with a low content of quaternary ammonium groups. No work is reported on sintering technique using Eudragit polymer in the literature. Hence in the present investigation eudragit sintered matrix tablets were prepared, physical characteristics were evaluated and *in vitro* dissolution profile was studied.

### MATERIALS AND METHODS

Rifampicin IP was obtained from Aristo Pharmaceuticals

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Limited, Mandeep, Maharashtra; 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 Eudragit RL100:

Powdering of small pellets of Eudragit RL100 is difficult due to high tensile strength and polymeric nature. In the present study, powdering of Eudragit RL100 copolymer was achieved by a simple procedure. Eudragit RL100 beads were soaked in sufficient amount of Acetone for 5 h, then the swollen beads were passed through sieve No. 60 by applying low pressure. The powder was spread evenly over butter paper and dried while mixing at ambient temperature. The dried polymer powder was 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 ( $\theta$ ) was measured according to the fixed funnel and freestanding cone method<sup>7</sup>. Compressibility on tamping<sup>8</sup> 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 done manually, occupied volumes were determined,  $V_{10}$  and  $V_{500}$  respectively. With these data we obtained the compressibility index (CI) using the formula,  $CI = \frac{V_{500} - V_{10}}{V_{500}} \times 100$ .

#### Preparation of matrix tablets:

For the preparation of tablets, rifampicin and different proportions of additives were mixed whose compositions have been 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 using 11 mm round, flat and plain punches

TABLE 1: COMPOSITION OF RIFAMPICIN MATRIX TABLETS

Ingredients	E <sub>1</sub> (mg)	E <sub>2</sub> (mg)	E <sub>3</sub> (mg)	E <sub>4</sub> (mg)
Rifampicin	300	300	300	300
Eudragit RL100	60	90	120	150
Sodium starch glycolate	15	15	1515	
Aerosil	1	1	1	1

(surface lubricated with talc) on single stroke tableting machine (Cadmach Machinery Co. Pvt. Ltd., Ahmedabad).

The compressed tablets were exposed to acetone vapor in a desiccator. After exposure for predetermined time intervals (1.5, 3.0 and 4.5 h), the tablets were removed from the desiccator, dried at ambient temperature to evaporate adhering free acetone for 24 h and were finally dried in a vacuum desiccator over fused calcium chloride for 24 h.

#### Differential Scanning Calorimetry (DSC):

Thermal analysis was performed on the drug, polymer, other additives and drug-additive mixtures 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 exposed to acetone vapors in a dessicator for 6 h, was evaluated using a TLC method, which is official in British Pharmacopoeia<sup>9</sup>, employing silica gel G as the stationary phase prepared from a slurry made with citrophosphate buffer at pH 6.0. A mixture of 85 volumes of chloroform and 15 volumes of methanol was used as the mobile phase. The TLC plates were kept in the chamber till the mobile phase ascended to 12 cm above the line of application. Rifampicin solution was prepared in chloroform.

#### Microbiological assay:

Potency of rifampicin, which was exposed to acetone vapors in a dessicator for 6 h, was determined using the official microbiological assay<sup>10</sup>. The assay was performed according to a cylinder-plate or cup-plate method, using nutrient agar as medium and *Bacillus subtilis* as test organism. Incubation was carried out for 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<sup>11</sup> was used as the dissolution medium (900 ml) and was maintained at 37±1. Samples of 5 ml volume were withdrawn at predetermined time intervals, filtered, diluted and assayed spectrophotometrically. An equal volume of fresh medium was immediately replaced to maintain the dissolution volume constant. The samples were analyzed spectrophotometrically

at 475 nm using a double beam UV spectrophotometer to assay the amount of rifampicin released at each time interval. Dissolution studies were performed in triplicate and mean values were reported.

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 up to 12 h equaled the average drug content of the tablets estimated prior to the drug release studies.

#### Standard physical test of sintered tablets:

To study the physical properties, the sintered tablets were subjected to the following tests. Friability (F) was determined with a Roche-friabilator, hardness was determined using a Monsanto hardness tester. Uniformity of weight was determined by the following method. Twenty tablets were weighed individually, the average weight was calculated and percent deviation of each tablet from average weight was computed.

### RESULTS AND DISCUSSION

It is necessary to characterize the flow properties of powders in order to estimate their suitability for employing them as direct compression excipients. In this work, we used angle of repose and compressibility index on tamping to characterize the flow properties of a polymer powder. In the development laboratory, these tests could be 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. The angle of repose is considered an indirect measurement of powder flowability<sup>12</sup>. According to the Delattre classification, EVA 1408 copolymer powder is classified as poor-flowing powder because the angle of repose is higher than 40°<sup>12</sup>. The compressibility index also indirectly measures the flowability of powder mass<sup>13</sup>. The CI value of Eudragit RL100 powder was measured and found to be 29.11, which indicated that Eudragit RL100 has poor flow properties since it is known that the CI value above 23% indicates poor flowability of a material. Hence Aerosil was added to improve the flow characteristics of these mixtures for compression. DSC was used to examine the thermal behavior of pure drug and drug additive mixtures in

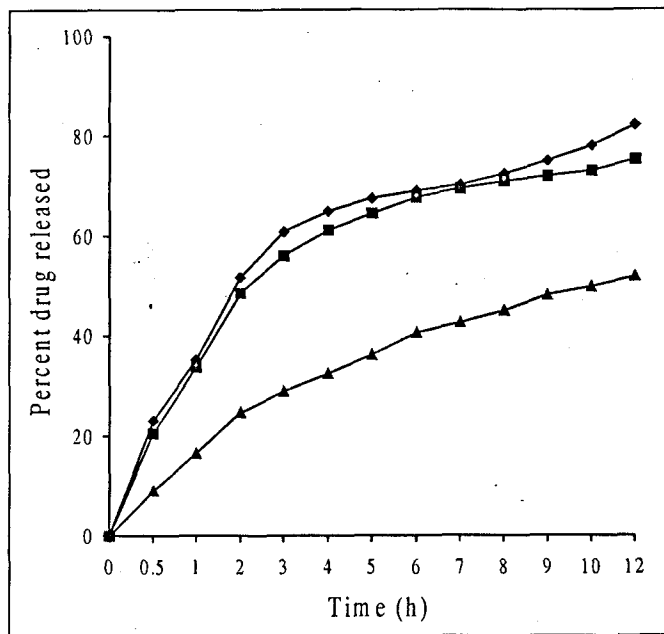
the formulation. DSC thermograms (not shown in figure) indicated the qualitative composition of the drug in the drug additive mixtures and verified the identity of each of the components. No drug interaction or complexation occurred during the manufacturing process.

TLC method was used to find out if any degradation products formed after treating rifampicin with acetone vapors for 6 h. After removing the plate from TLC chamber, it was allowed 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, which also showed similar R<sub>f</sub> value as that of standard. This indicated that rifampicin did not degrade even after exposed to acetone vapors for 6 h. This result is in agreement with similar finding of others<sup>14</sup>. Microbiological assay also conformed, in potency wise, that the rifampicin was stable in solid state even after treatment with acetone vapors.

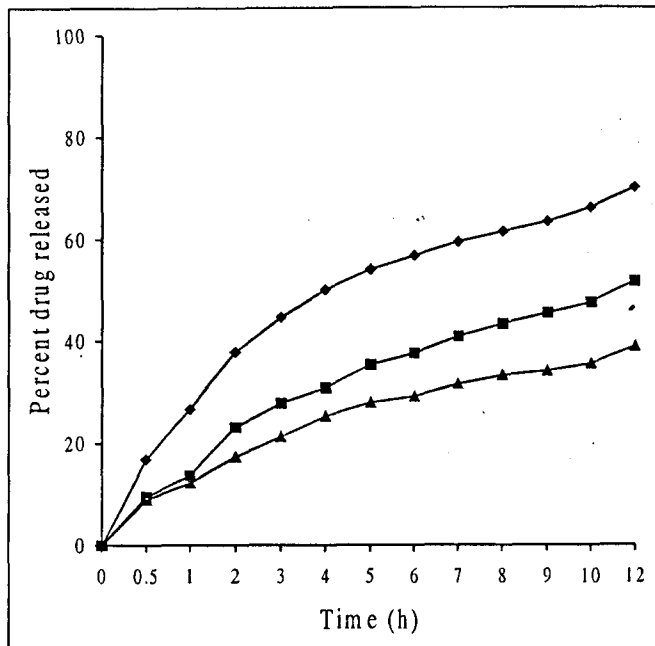
Tablets from all formulations passed the test for weight uniformity (not more than two of the tablets differ from the average weight by more than the 5% and no tablet differs by more than 10% (not shown). Tablets of all formulations passed the test for friability (<1%)<sup>15</sup>. The hardness of the tablets of formulation E<sub>1</sub> was 2.2, 3.6 and 4.1 Kg/cm<sup>2</sup>, formulation E<sub>2</sub> was 2.3, 3.9 and 4.9 Kg/cm<sup>2</sup>, formulation E<sub>3</sub> was 2.5, 4.9 and 5.4 Kg/cm<sup>2</sup> and for formulation E<sub>4</sub> was 2.7, 5.2 and 6.2 Kg/cm<sup>2</sup> at sintering times of 1.5, 3.0 and 4.5 h, respectively. Hardness of tablets increased as the polymer content was increased and hardness also depended on sintering time as well as sintering temperature.

Drug release from heterogeneous, nonerodible, nonbiodegradable, nonbioadhesive matrix formulations was 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.

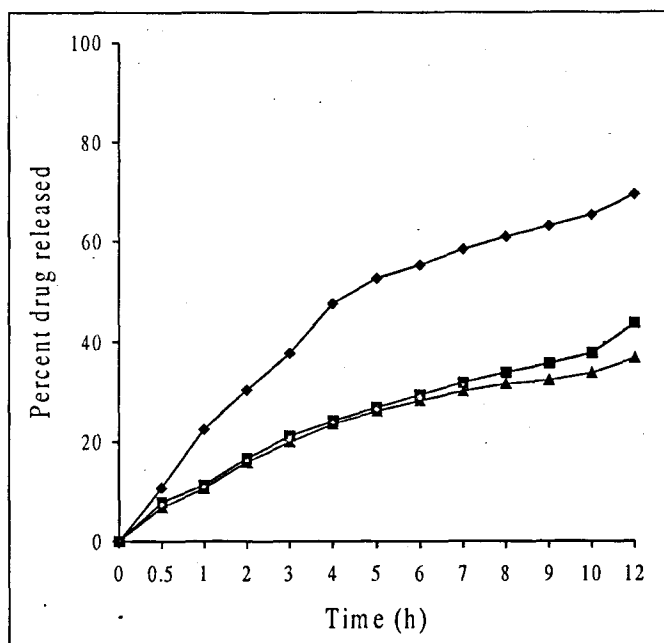
The dissolution profiles of rifampicin from Eudragit RL100 sintered matrix tablets for various times are shown in figs. 1-4. The sintering time markedly affected the drug release properties of Eudragit RL100 matrices. It is notable that the release rate of rifampicin from Eudragit RL100 matrices was 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 Eudragit RL100 matrices revealed that the drug release was increased as the Eudragit RL100 copolymer percent was decreased.



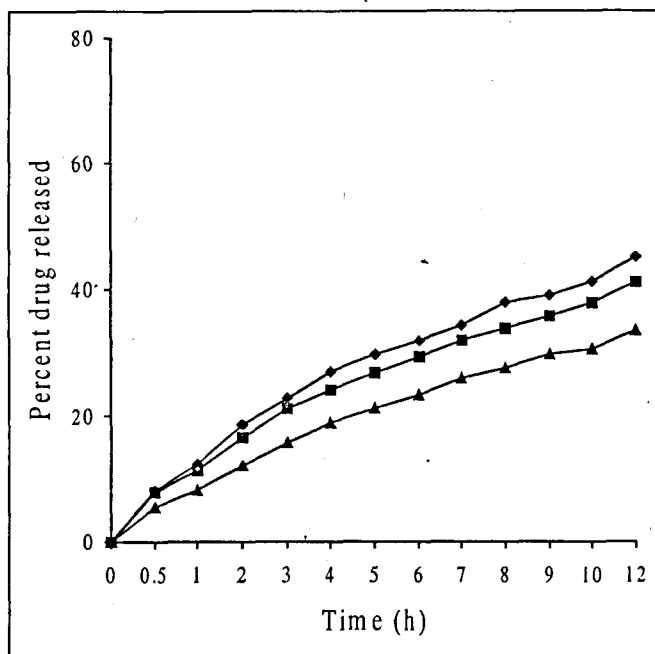
**Fig. 1: Formulation E<sub>1</sub>, dissolution profiles of rifampicin.** Dissolution profiles of rifampicin from formulation E<sub>1</sub> sintered matrix tablets (n=3) sintered in acetone chamber (-♦-) for 1.5 h, (-■-) for 3.0 h and (-▲-) for 4.5 h.



**Fig. 2: Formulation E<sub>2</sub>, dissolution profiles of rifampicin.** Dissolution profiles of rifampicin from formulation E<sub>2</sub> sintered matrix tablets (n=3) sintered in acetone chamber (-♦-) for 1.5 h, (-■-) for 3.0 h and (-▲-) for 4.5 h.



**Fig. 3: formulation E<sub>3</sub>, dissolution profiles of rifampicin.** Dissolution profiles of rifampicin from formulation E<sub>3</sub> sintered matrix tablets (n=3) sintered in acetone chamber (-♦-) for 1.5 h, (-■-) for 3.0 h and (-▲-) for 4.5 h.



**Fig. 4: Formulation E<sub>4</sub>, dissolution profiles of rifampicin.** Dissolution profiles of rifampicin from formulation E<sub>4</sub> sintered matrix tablets (n=3) sintered in acetone chamber (-♦-) for 1.5 h, (-■-) for 3.0 h and (-▲-) for 4.5 h.

Higuchi<sup>16</sup> has described drug release mechanism from matrix dosage forms using the equation  $Q = \sqrt{D(2W - C_s)C_s t}$ , where 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  $W \gg C_s$ , The above equation can be simplified to the following  $Q = \sqrt{2WDC_s t}$ .

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 2 indicating that the drug release from Eudragit RL100 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 (Table 2).

The surface of the sintered matrix after dissolution exhibited porous appearance (not shown in figure) 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 appearance was the result the release of dispersed rifampicin and other additives from the sintered matrix. Tablets throughout the experiment maintained their original shape, no erosion of any kind occurred. The pattern of drug release from the Eudragit RL100 sintered tablets was linear with the square root of time through out the entire period.

The very low hardness obtained when the tablets compressed at room temperature indicates that the main forces holding the particles together are probably van der Waals 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 time of exposure to acetone vapors 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 form, sintering technique for preparing polymer matrices for controlled release of rifampicin appears to be an alternative technique. This new method for controlling the release rate of rifampicin has been developed using Eudragit and was tested. At room temperature when exposed to acetone vapors Eudragit RL100 powder particles fused or welded to each other due

TABLE 2: COEFFICIENTS AND RELEASE RATE CONSTANTS OF DRUG RELEASE FUNCTIONS

Matrices	First order kinetics		Higuchi model	
	r <sup>2</sup>	K (hr <sup>-1</sup> )	r <sup>2</sup>	
E <sub>4</sub>	for 1.5 h	0.989	0.0399	0.912
	for 3.0 h	0.964	0.0311	0.889
	for 4.5 h	0.985	0.0264	0.973
E <sub>3</sub>	for 1.5 h	0.991	0.0486	0.962
	for 3.0 h	0.872	0.0391	0.991
	for 4.5 h	0.982	0.0256	0.935
E <sub>2</sub>	for 1.5 h	0.954	0.1084	0.974
	for 3.0 h	0.975	0.0502	0.901
	for 4.5 h	0.990	0.0421	0.869
E <sub>1</sub>	for 1.5 h	0.988	0.2758	0.984
	for 3.0 h	0.903	0.1356	0.905
	for 4.5 h	0.994	0.0622	0.994

to coming in contact with other particles where the particles were contacted. The extent of fusion was depends depended on sintering time. This type of a system provides a simple and convenient method for achieving controlled release in oral dosage forms.

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