Iranian Journal of Basic Medical Sciences
Vol. 10, No. 3, Autumn 2007, 197-205
Received: Jun 9, 2007; Accepted: Oct 9, 2007

Effect of Particle Size, Compaction Force and Presence of Aerosil 200 on the Properties of Matrices Prepared from Physical Mixture of Propranolol Hydrochloride and Eudragit RS or RL

*[1] Fatemeh Sadeghi, [2] Fatemeh Mosaffa, [3]Hadi Afrasiabi Garekani

Abstract

Objective

Eudragits are widely used polymers in the production of oral sustained release dosage forms. The application of these polymers in the production of inert insoluble matrices has been investigated. However the effect of particle size, compaction force and presence of Aerosil 200 as a glidant on the properties of Eudragit RS and RL matrices prepared by direct compression of their physical mixtures with drug have not been fully investigated. This study was performed in order to investigate the effect of above mentioned factors on physicomechanical and release properties of propranolol hydrochloride and Eudragit RS or RL matrices.

Materials and Methods

Polymers were separated to different size fractions using series of sieves. Matrices were prepared in 1:3 ratio by direct compression of physical mixture of drug and polymer. To study the effect of Aerosil 200, matrices were prepared from different size fractions containing 1%w/w Aerosil 200. To investigate the effect of compaction force, the 125-177µm size fraction of polymer was chosen and compression carried out at 5, 10, 15, 20 and 30 kN compaction force. Matrices were characterized for their hardness and dissolution.

Results

The results showed that due to decrease in tablet hardness the release rate increased with increase in polymer particle size. Drug release rates were almost the same for both polymers at similar particle size range. The same trend was also observed for matrices containing Aerosil 200. Addition of Aerosil 200 decreased the rate of drug release from all matrices except those prepared from 250-350 µm size fraction. This was attributed to increase in the tablet hardness. Increase in compaction force from 5kN to 20kN increased the tablet hardness and consequently decreased the release rate, however, further increase in compaction force from 20 to 30 kN did not significantly affect the release rates of drug.

Conclusion

Polymer particle size, presence of Aerosil and compaction force are important factors affecting drug release from Eudragit RS or RL matrices. Eudragit RS and RL polymers alone are not suitable for preparation of sustained release matrices containing water soluble drugs.

Keywords: Sustained release matrices, Eudragit, particle size, Aerosil 200, compaction force

1,3 –Department of Pharmaceutics, School of Pharmacy and Pharmaceutical Research Center, Mashhad University of Medical sciences, Mashhad, Iran
*Corresponding author: Tel: +98-511-8823255-66; Fax: +98-511-8823251; email: sadeghif@mums.ac.ir
2- School of Pharmacy, Mashhad University of Medical Sciences, Mashhad, Iran

Introduction

Design of oral sustained release dosage forms have been the focus of many research activities. Matrices are considered as the simplest and cheapest systems in formulation of sustained release dosage forms. Eudragit RS and RL are among inert insoluble polymers which due to their several proper properties namely, lack of toxicity and independency of their solution to pH of dissolution medium have been used as a vehicle in preparation of sustained release dosage forms. These polymers have been used in coating of granules and pellets (1) and in preparation of matrices either in the form of solid dispersion systems (2-4) or in direct compression (5).

Direct compression of drug and polymers along with a proper excipient is a simple method for preparation of matrices. In this method the amount of polymers needed for preparation of matrices are different depending on drug solubility and desired drug release profile. Other excipients that may be necessary to optimize drug release include soluble and or swellable materials like lactose and starch to facilitate drug release and variety of insoluble excipients such as calcium phosphate or calcium sulphate to delay drug release. In contact with dissolution medium the release of drug starts after drug dissolution in pores of matrices which has been filled with dissolution medium. Drug release continues with diffusion of dissolved drug through water filled pores. Therefore the structure of pores plays a major role in drug release. Studies have shown that many parameters such as drug: polymer ratio (6), the ratio of different polymers (7), drug type (8), the method of matrix preparation (3, 9) and compaction force (3, 10) can affect the structure of pores in matrices and consequently affect drug release from these matrices. While there are studies investigating the influence of polymer particle size, compaction force and presence of lubricant on drug release from ethylcellulose matrices prepared by physical mixing of drug and polymer (11, 12) literature survey shows that the effect of above mentioned factors on properties of Eudragit RS and/or RL matrices prepared from physical mixtures of drug and polymer have not been investigated. This study was performed in order to investigate the effect of polymer particle size, compaction force and presence of Aerosil 200 as glident on mechanical properties and release rate of drug from matrices containing physical mixture of propranolol hydrochloride (as a water soluble model drug) and Eudragit RS or RL.

Materials and Methods

Propranolol hydrochloride (prepared from Daroopaksh, Iran), Eudragit RS and RL (Rohm GmbH, Germany), Aerosil 200 (Colloidal silicon dioxide) (prepared from Tehran Chemi) were used in this study.

Preparation of different size fraction of polymers and drug

Different size fraction of polymers (53-88, 88-125, 125-177, 177-250, 250-350 μm) were prepared by grinding of polymer powder in mortar and pestle, and sieving the resulted powder using series of sieve with proper mesh size.

The size fraction of 88- 125 μm of drug was also prepared after grinding and sieving the drug powder and then used for the preparation of matrices.

Preparation of physical mixture of polymer and drug

In order to prepare the physical mixture of drug and polymer in 1:3 ratio, proper amount of each material in proper size fraction was weighed and then mixed in tumbling mixer for 10 minutes. To investigate the effect of glidant, Aerosil 200 (1%) was added to the

mixture and mixing continued for another 5 minutes.

Determination of drug content in mixtures

This test was performed in order to evaluate the method of mixture preparation. At first 200 mg of each physical mixture weighed accurately and then transferred to 1000 mL volumetric flask containing 700 mL distilled water. The volumetric flask was put aside and shook intermittently for 2 hours. After this period the solution brought to volume by distilled water and the absorption of filtrate was obtained at 290 nm. The amount of drug in the mixture was determined, using the calibration curve prepared for propranolol hydrochloride at 290 nm wave length.

Preparation of matrices

Matrices were made from physical mixture of drug and polymers using Korcsh single punch tableting machine (EK- 0- 72) equipped with strain gauge. In order to investigate the effect of polymer particle size on properties of matrices the compaction force of 15 kN was selected. To study the effect of compaction force on properties of matrices the size fraction 125-177 μm of polymers was used and matrices, were prepared at compaction forces of 5, 10, 20 and 30 kN.

The proper amount of each mixture containing 80 mg drug was weighed accurately and then compressed using a flat faced die and punch with 12 mm diameter. Before preparation the surface of die and punch was lubricated with the suspension of magnesium stearate in acetone (%1).

Determination of crushing strengths of matrices

The crushing strengths of the matrices were measured using a hardness tester (Erweka TBH-28, Germany) 24 h after compaction. Five tablets were used in each study. Test of one way analysis of variance was used for comparison of crushing strengths of matrices.

Determination of friability of matrices

The friability of matrices was measured using Erweka friablator (TA3R). Ten tablets were weighed accurately and then the test was run for 4 minutes at 25 rpm. After this period the tablets were weighed again and their friability was determined from their weight change.

Dissolution test

Dissolution tests were carried out in a USP dissolution apparatus I (Pharmatest PTWS 3E, Germany). The release profiles of matrices containing 80 mg of propranolol hydrochloride in 1000 mL distilled water at a rotation speed of 100 rpm and at 37±0.5 °C were determined using Shimadzu U.V, A160 spectrophotometer (Japan) at 290 nm wavelength. The mean of six determinations was used to calculate drug release for each formulation.

The kinetics of drug release was determined by fitting the dissolution data with Higuchi kinetic model using regression analysis. The slope of the line was used for comparison of release rates.

Results

The results for crushing strength, friability and release rate constant of matrices prepared from different size fractions of polymers are shown in table 1. These results show that with decrease in particle size of both polymers, the crushing strengths of matrices increased ($p< 0.001$). The results of friability test are in agreement with the results of crushing strength and indicate that with decrease in particle size of polymers matrices are more resistant against the friability.

Table 1. The results of crushing strength, friability and Higuchi release rate for matrices prepared from different size fractions of Eudragit RS or RL polymers (at compaction force of 15 kN)

Size fraction (μm)	Eudragit RS			Eudragit RL		
	Crushing strength (kg ± SD)	Friability %	Release rate constant $\%min^{-1/2}$	Crushing strength (kg ± SD)	Friability %	Release rate constant $\%min^{-1/2}$
53-88	8.2 ± 0.4	0.8	27.9	5.0 ± 0.5	1.3	28.4
88-125	5.6 ± 0.4	1.0	30.7	3.6 ± 0.2	1.9	29.1
125-177	3.4 ± 0.3	1.7	34.5	2.9 ± 0.6	2.1	35.9
177-250	2.7 ± 0.3	2.3	42.6	2.3 ± 0.2	2.6	40.9
250-350	1.6 ± 0.2	7.4	41.7	1.6 ± 0.1	7.5	42.6

The results for crushing strength and release rate constant for matrices containing Aerosil 200 (1%) are shown in table 2. These results show that in the presence of Aerosil 200 also, decrease in particle size fraction of polymer increased the crushing strength of matrices of both polymers ($p< 0.01$).

Table 2. The results of crushing strength, friability and Higuchi release rate for matrices prepared from different size fractions of Eudragit RS or RL polymers containing 1% Aerosil 200 (at compaction force of 15 kN)

Size fraction (μm)	Eudragit RS		Eudragit RL	
	Crushing strength (kg ± SD)	Release rate constant $\%min^{-1/2}$	Crushing strength (kg ± SD)	Release rate constant $\%min^{-1/2}$
53-88	9.5 ± 0.4	17.0	8.6 ± 0.3	14.1
88-125	7.3 ± 0.6	18.8	7.2 ± 0.7	18.3
125-177	4.3 ± 0.2	19.1	4.6 ± 0.3	19.6
177-250	3.2 ± 0.2	24.9	3.5 ± 0.4	25.8
250-350	2.0 ± 0.2	38.8	2.1 ± 1.5	38.4

Table 3 shows the results for the effect of compaction force on crushing strength of matrices. As it can be seen with increase in compaction force from 5 to 30 kN, the crushing strength of matrices increased significantly.

Table 3. The results of crushing strength (kg ± SD) for Eudragit RS or RL matrices prepared from 125-177 μm size fraction and compressed under different compaction forces

Compaction force (kN)	Eudragit RS	Eudragit RL
5	1.4 ± 0.1	1.2 ± 0.1
10	2.8 ± 0.3	2.6 ± 0.2
15	3.4 ± 0.3	2.9 ± 0.6
20	4.4 ± 0.3	4.0 ± 0.1
30	5.1 ± 0.2	4.4 ± 0.1

The release profiles for matrices prepared from different size fraction of Eudragit RS and RL polymers are shown in figures 1 and 2 respectively. Figure 3 and 4 show the release profiles for matrices containing Aerosil 200 (1%). Addition of this material decreased the percentage of drug release at each sampling time. The comparison of release profiles for matrices prepared at different compaction forces are shown in figures 5 and 6. The results show that increase in compaction force from 5 to 30 kN did not affect drug release profiles from the Eudragit matrices considerably.

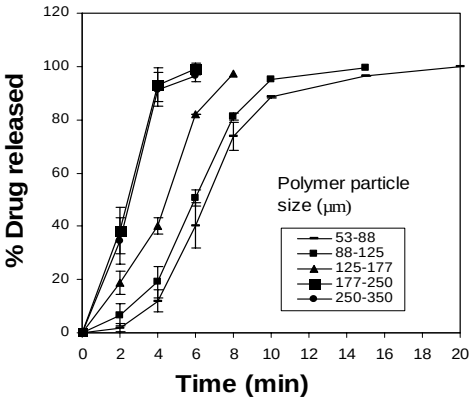

Figure 1. The release profiles of propranolol hydrochloride from matrices prepared of different size fractions of Eudragit RS polymer.

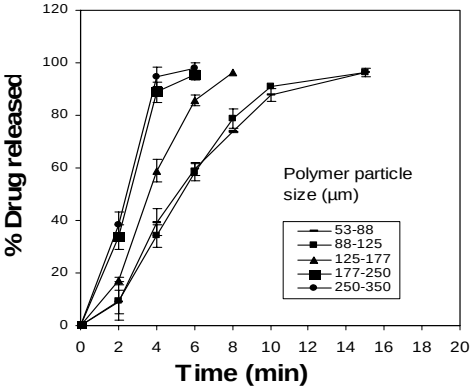

Figure 2. The release profiles of propranolol hydrochloride from matrices prepared of different size fractions of Eudragit RL polymer.

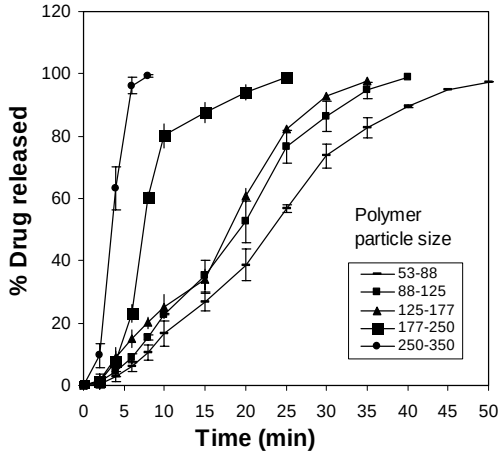

Figure 3. The release profiles of propranolol hydrochloride from matrices prepared of different size fractions of Eudragit RS polymer containing 1% Aerosil 200.

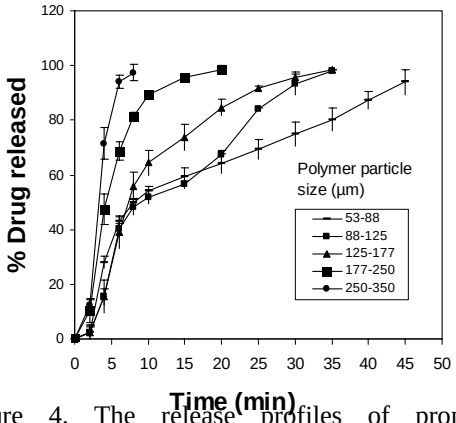

Figure 4. The release profiles of propranolol hydrochloride from matrices prepared of different size fractions of Eudragit RL polymer containing 1% Aerosil 200.

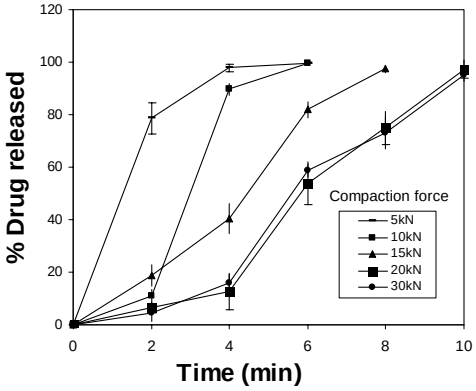

Figure 5. The release profiles of propranolol hydrochloride from matrices prepared of 125-177 μm size fraction of Eudragit RS polymer at different compaction force.

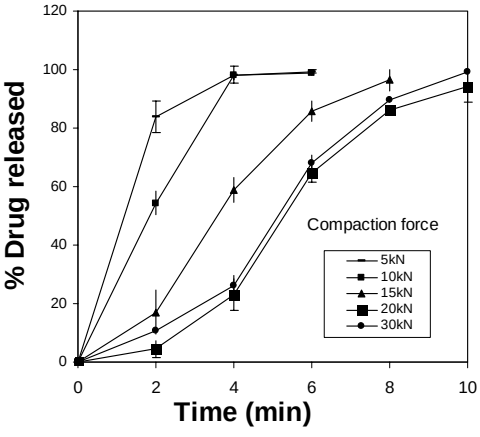

Figure 6. The release profiles of propranolol hydrochloride from matrices prepared of 125-177 μm size fraction of Eudragit RL polymer at different compaction force.

Discussion

The results of crushing strengths for matrices prepared from different size fraction of either Eudragit RS or RL (Table 1) show that with decrease in polymer particle size, the crushing strength of matrices increased ($p< 0.001$). These results are in agreement with those published by Katikaneni et al. (11) and Dabbagh et al. (12) for ethylcellulose matrices. These authors showed that with decrease in ethylcellulose particle size which is similar to Eudragit RS and RL and belongs to insoluble inert polymers the crushing strength of pseudoepherine hydrochloride and propranolol hydrochloride increased. The results obtained in these studies were attributed to increase in contact points between particles with decrease in particle size which resulted in better bounding. From the comparison of two polymers it can be seen that in small size fractions (53-88, 88-125 μm) the crushing strength of Eudragit RS matrices are more than Eudragit RL matrices ($p< 0.01$). This effect could be due to more compressibility of Eudragit RS compare to RL. However, in larger particle size fractions the difference between two polymers is faded. Cameron et al. reported that at similar compaction forces (3.1, 5.3, 6.7 and 8.4 kN) the crushing strength of theophylline and Eudragit RS matrices are slightly more than theophylline and Eudragit RL matrices. The authors attributed these results to the more compressible character of Eudragit RS (13).

The results for friability test which are shown in table 1, are in agreement with results of crushing strength test and show that with decrease in particle size of both polymers, matrices become more resistant against friability.

The results for crushing strength of matrices containing Aerosil 200 (1%) are shown in table 2. Since the proper amount of Aerosil as a glidant has been reported to be 0.5-1% (14), the effect of 1% Aerosil was investigated in this study. The results of crushing strength of matrices containing 1% Aerosil show that in the presence of Aerosil 200 with decrease in particle size of polymers the crushing strength increased for both polymers ($p<0.01$). Also, the comparison of the results presented in table 2 with those of table 1 indicate that addition of Aerosil 200 in all size fractions increased the crushing strength of matrices slightly ($p< 0.01$), compared to matrices without this material. Similarly it was shown that addition of colloidal silicon dioxide increased the crushing strength of tablets made from crosslinked polyalkylammonium (15). In a study of Katikaneni et al. it was shown that presence of magnesium stearate as a lubricant, even in small amounts had a negative effect on crushing strength of ethylcellulose matrices (11). The results of this study also showed that in the presence of Aerosil 200 there was no significant difference between crushing strength of Eudragit RS and RL matrices in all size fractions.

The effect of compaction force on crushing strength of matrices (table 3) shows that increase in compaction force from 5 to 30 kN increased the crushing strength of matrices significantly ($p< 0.001$). This effect was due to increased binding between particles. Similar results were reported in study of matrices containing theophylline and Eudragit RS and RL and it was shown that with increase in compaction force from 700 to 1900 pounds the crushing strength of matrices increased (13). The results in table 1 also indicate that there is little difference between crushing strengths of Eudragit RS and RL matrices in 125-177 μm size fraction.

The release profiles for matrices prepared from different size fractions of either polymer which are shown in figure 1 and 2 indicate that both type of matrices released all their drug content rapidly (between 6 and 15 minutes). In other words none of matrices

retained their shape for long period and after contact with dissolution medium disintegrated rapidly and therefore, could not have any control on drug release rate. This may be due to the high water solubility of propranolol hydrochloride. After contact with dissolution medium and upon rapid dissolution of drug, pores are developed inside the matrix and weaken the structure of matrices and led to disintegration of it. However, the comparison of release rates for matrices prepared from different size fractions of polymers (Table 1) show that with increase in polymer particle size the release rate increased for both polymers. This result could be attributed to the decrease in crushing strength and therefore, increased porosity of matrices which facilitate the ingress of dissolution medium into the matrix structure. Similar findings have been reported by other authors for the release of drug from ethylcellulose matrices (11, 12) and slower release of drug from small size fraction of polymer have been attributed to the ability of matrices prepared from them to retain their shape during dissolution test.

Comparison of figures 1 and 2 shows that release rates for matrices prepared from different size fractions of both polymers are similar. These results are not in agreement with other reports which indicate that Eudragit RS are more effective in controlling drug release rate (2, 5). With close examination of figures 1 and 2 it can be seen that in matrices prepared from smaller size fractions of polymers, there is difference between Eudragit RS and RL matrices especially in the early stages of dissolution test. Matrices of Eudragit RS released their drug content more slowly compared to Eudragit RL. This effect could be attributed to the more water permeability character of Eudragit RL due to higher percentage of quaternary ammonium groups in its structure. However, after tablet disintegration the release of drug from both polymers was similar. The results also indicate that these polymers alone are not suitable for control of water soluble drugs in the form of matrices due to rapid disintegration and therefore, rapid drug release and there is need for addition of other excipients in order to sustain drug release.

Figure 3 and 4 show that addition of Aerosil 200 into formulation of matrices, caused considerable reduction in drug release at different sampling time and also, drug release rates (Table 2) (except matrices prepared from 250-350 μm size fraction). This effect could be due to increased crushing strength of matrices upon addition of Aerosil 200 which slowed down the entrance of dissolution medium into the matrices. In the presence of Aerosil 200 also, increase in polymer particle size increased the release rate of drug from both type of matrices.

Comparison of release profiles for matrices compressed at different compaction forces in figure 5 and 6 show that increase in compaction forces from 5 to 30 kN did not have considerable influence on drug release from Eudragit matrices. In other words the release rates of drug from these matrices are rapid even at high compaction forces. A little difference observed in release profiles with increase in compaction force from 5 to 20 kN could be due to increase in crushing strength of matrices with increase in compaction force. However, with increase in compaction force from 20 to 30 kN the release profile remained nearly unchanged. Similarly Stamm and Tritsch reported that increase in compaction forces and consequently increase in crushing strength of ethyclecllulose and methoclopramide hydrochloride matrices decreased drug release rate to a certain degree (16). However, further increase in compaction force did not influence the release rate of drug (16). Similar results were obtained in the study of Katikaneni et al. on ethylcellulose matrices (11). While Sarisuta

and Mahahpunt reported that increase in compaction force did not have any influence on diclofenac sodium release from Eudragit RS and Emcompress matrices and drug release rate was independent on compaction force from these matrices (17). These authors claimed that the compact would deform elastically when the compaction force increases beyond the critical value so that at first with increase in compaction force porosity decrease and then remain constant (17).

Conclusion

The results of this study showed that matrices prepared from physical mixture of water soluble propranolol hydrochloride and different size fractions of either Eudragit RS or RL polymers could retain their structure only for a short period of time after contact with dissolution medium and therefore, were not suitable to sustain drug release. Although, decrease in polymer particle size increased the crushing strength of matrices and decreased the rate of drug release, the release was rapid even from the smallest size fraction. In comparison between two polymers it was shown that both polymers behaved similarly in controlling drug release rate at similar size fractions. Addition of Aerosil 200 increased crushing strength of matrices prepared from each size fraction (except 250-350 μm size fraction) and decreased the release rate considerably. In these formulations also, decrease in polymer particle size decreased the drug release rate. With increase in compaction force from 5 to 20 kN, crushing strength of matrices increased and consequently the rate of drug release decreased slightly. However further increase in compaction force from 20 to 30 kN despite its effect on crushing strength did not influence the rate of drug release. Overall, the results presented in this study showed that Eudragit RS or RL alone are not suitable vehicle to sustain release of water soluble drug from their matrices. However, it is easily possible to have more control on drug release with selection of proper size fraction of polymer and addition of small amount of excipient such as Aerosil.

References

1. Zheng W, Sauer D, McGinity J. Influence of hydroxyethylcellulose on the drug release properties of theophylline pellets coated with Eudragit® RS 30 D**.** Eur J Pharm Biopharm 2005; 59:147-154.
2. Pignatello R, Ferro M, De Guidi G, Salemi G, Vandelli M A, Guccione S, et al. Preparation, Characterization and photosensitivity studies of solid dispersions of diflunisal and Eudragit RS100 and RL100. Inter J Pharma 2001; 218: 27-42.
3. Sadeghi F, Afrasiabi Garekani H, Goli F. Tableting of Eudragit RS and propranolol hydrochloride solid dispersion: effect of particle size, compaction force, and plasitcizer addition on drug release. Drug Develop and Indust Pharm 2004; 30: 759-766.
4. Aceres JM, Cruz, R, Hernandez E. preparation and characterization of furosemide – Eudragit controlled release systems. I J pharm 2000; 195: 45 – 53.
5. Azarmi S, Farid J, Nokhodchi A, Bahari-Saravi S M, Valizadeh H. Thermal treating as a tool for sustained release of indomethacin from Eudragit RS and RL matrices. Inter J Pharm 2002; 246 171-177.
6. Kaul D, Venkatarum S. Sustained release tablet formulation for a new iron chelator. Drug Develop and Industl Pharm 1992; 18: 1023-1035.
7. Ceballos A, Cirri M, Maestrelli F, Corti G, Mura P. Influence of formulation and process variables on in vitro release of theophylline from directly-compressed Eudragit matrix tablets .I J Farm 2005, 60: 913-918.
8. Jenquin MR, McGinity JW. Characterization of acrylic resin matrix films and mechanisms of drug polymer interactions. Inter J Pharm 1994; 101: 23-34.

9. Effentakis M, Buckton G. Modeling drug release from hydrophobic matrices by use of thermodynamic activation parameters. Inter J Pharm 1990; 60: 229-234.
10. Fassihi A, Parker M, Pourkavoos N. Solid dispersion controlled release: effect of particle size, compression force and temperature. Drug Develop and Indust Pharm 1985; 11: 523-535.
11. Katikaneni PR, Upadrashta SM, Neau SH, Mitra AK. Ethylcellulose matrix controlled release tablets of a water soluble drug. Interl J Pharm 1995; 123: 119-125.
12. Dabbagh MA, Ford JL, Rubinstein M H, Hogan JE. Effect of polymer particle size, compaction pressure and hydrophilic polymers on drug release from matrices containing ethylcellulose. Inter J Pharm 1996; 140: 85-95.
13. Cameron CG, McGinity JW. Controlled release theophylline tablet formulations containing acrylic resins: II. Combination resin formulations. Drug Develop and Indust Pharm1987; 13: 1409-1427.
14. Collet J, Moreton C. Modified-release peroral dosage forms. In: Aulton M E. (2nd Ed). Pharmaceutics. The Science of Dosage Form Design: Churchill Livingstone; 2002. p. 298.
15. Chang RK, Leonzio M, Hussain MA. Effect of colloidal silicon dioxide on flowing and tableting experimental crosslinked polyalkylammonium polymer. Pharm Deve Tech 1999; 4: 285-289.
16. Stamm A, Tritsch JC. Some consideration on the liberation of drug from inert matrices. Drug Develop and Indust Pharm 1986, 12: 2337-2353.
17. Sarisuta N, Mahahpunt P. Effect of compression force and type of fillers on release of diclofenac sodium from matrix tablets. Drug Develop and Indust Pharm 1994; 20: 1049-1061.