DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY®
Vol. 30, No. 7, pp. 759–766, 2004

# Tableting of Eudragit RS and Propranolol Hydrochloride Solid Dispersion: Effect of Particle Size, Compaction Force, and Plasticizer Addition on Drug Release

**F. Sadeghi,[1,2,*] H. Afrasiabi Garekani,[1,2] and F. Goli[1]**

[1]School of Pharmacy, Mashhad University of Medical Sciences, Mashhad, Iran
[2]Pharmaceutical Research Centre, Buali Research Institute, Mashhad, Iran

## ABSTRACT

The application of a solid dispersion (SD) system of propranolol HCl and Eudragit RS was evaluated in the preparation of prolonged release tablets. The effects of SD size fraction, compaction force, and inclusion of plasticizers [namely diethylphtalate (DEP) and triethylcitrate (TEC)] on crushing strengths of matrices and release profile of drug were also investigated. The results showed that when compressed as a tablet, the SD system was more efficient in prolonging drug release than physical mixture. This effect was due to formation of much harder tablets of the SD system (crushing strength 8.5 kg) compared with those of physical mixtures (crushing strength 2.7 kg). All matrices of the SD system showed release rate patterns that were best described by the Higuchi equation. It was also shown that the rate of drug release decreased from 19.8% to 9.13% $min^{-1/2}$ as the SD size fraction decreased from 300–350 to 125–250 μm. However, further reduction of size fraction did not significantly affect tablet crushing strength and drug release rate. Increase in compaction force from 5 to 30 kN increased the crushing strength of matrices from 2.9 to 13.6 kg. However, the rate of drug release remained nearly unchanged beyond compaction pressure of 10 kN, indicating that crushing strength of matrices in the range of 8.5–13.6 kg did not affect drug release rate. The addition of 5% or 10% of either plasticizer (DEP or TEC) led to an increase in crushing strength of

*Correspondence: F. Sadeghi, School of Pharmacy, Mashhad University of Medical Sciences, Mashhad, Iran; E-mail: fatemehsadeghi@hotmail.com.



DOI: 10.1081/DDC-120039652
0363-9045 (Print); 1520-5762 (Online)

matrices and more retardation of drug release. This effect was more pronounced for higher concentrations of plasticizers. This effect was probably due to more plastic deformation of matrices under the compaction force, which helped matrices to retain their shape throughout the dissolution test.

*Key Words:* Sustained release; Matrix; Solid dispersion; Eudragit RS; Particle size; Compaction force plasticizer.

## INTRODUCTION

Several approaches have been used in the attempt to sustain drug release from dosage forms. The solid dispersion technique, which at first had been used to enhance the dissolution rate of poorly water-soluble drugs,[1,2] is now used to sustain drug release.[3–5] It has been shown that preparation of matrices using solid dispersion (SD) systems is a valuable method in the production of sustained-release matrices using insoluble polymers. This can result in less polymer consumption in order to control drug release rate, compared with physical mixing of drug and polymer.[3,6,7]

Many studies have been conducted in order to investigate the effect of formulation and process variables on drug release from tablets of physical mixture of drug and polymer. It has been shown that polymer particle size, compaction force, and the presence of soluble or insoluble additives are among the factors affecting drug release from tablets of physical mixtures.[8,9] However, there are a few studies investigating the effect of these factors on drug release from tablets of SD systems. Khan et al. reported that the presence of diluents and compression pressure considerably affected the drug release from coprecipitates of ibuprofen and Eudragit S100.[10] Sadeghi, Afrasiabi Garekani, and Sadr showed that the addition of plasticizer into SD of ethylcellulose and diclofenac sodium resulted in more retardation of drug release.[3]

Our preliminary studies showed that the SD system of propranolol HCl and Eudragit RS in a 1:3 ratio as a powder form did not provide much control on the drug release rate. Therefore, the aim of this study was to investigate the effect of compression of the SD system into tablets in the preparation of prolonged-release, inert, insoluble matrices and to compare with those prepared from physical mixtures. The effects of SD size fraction, compaction force, and plasticizer addition on drug release from tablets of the SD system were also investigated. Propranolol HCl was used as a water-soluble model drug, which, due to its short biological half-life, was also a suitable candidate for formulation as a sustained-release dosage form.

## MATERIALS

Eudragit RSPO (supplied by Rohm GmbH, Darmstadt, Germany), propranolol hydrochloride (supplied by Daroopakhsh, Tehran, Iran), triethylcitrate (TEC) and ethanol (Merck, Darmstadt, Germany), and diethylphtalate (DEP) (supplied by Sobhan, Tehran, Iran) were used in this study.

## METHODS

### Preparation of Matrices

Solid dispersion systems of drug and polymer were prepared by dissolving 8 g of drug and 24 g of polymer (1:3 ratio) separately in 100 mL and 50 mL ethanol, respectively. The drug solution then was added to the polymer solution and mixed thoroughly. Equal amounts of the resulting solution were spread evenly on teflon-coated surfaces and oven-dried at 50°C to constant weight. The dried thin films were ground using a mortar and pestle and passed through a series of sieves. To prepare SD systems containing plasticizer, the above procedure was repeated, except that the required amount of each plasticizer (DEP or TEC) was added to the polymer solution before addition of the drug solution. The concentration of plasticizer used in this study was 5% or 10% with respect to polymer weight.

To prepare the physical mixture, a size fraction of 125–250 μm of drug and Eudragit RS in a 1:3 ratio was used and mixed in a tumbling mixer for 10 min.

To determine drug content in the SD systems and the physical mixture, 300 mg of each accurately weighed sample was dissolved in 96% ethanol in a 100-mL volumetric flask. The drug content in each sample was determined by ultraviolet (UV) spectroscopy at 290 nm after appropriate dilution based on the calibration curve prepared for propranolol HCl in

ethanol at this wavelength. The presence of Eudragit RS, TEC, or DEP did not interfere with propranolol HCl absorption at this wavelength.

Flat-faced tablets (10 mm in diameter) of physical mixture or SD system equivalent to 80 mg propranolol HCl were compressed without the addition of any other excipients on an instrumented single-punch tableting machine (Korsch EK-72, Berlin, Germany) at 10 kN compaction force. The surfaces of punches and die were lubricated using a suspension of 1% magnesium stearate in acetone prior to each tableting.

To investigate the effect of SD size fraction, the fractions of 300–350, 125–250, 90–125, and <90 μm of SD systems were collected and compressed as above.

To investigate the effect of compaction force, the size fraction of 125–250 μm was selected and tablets were prepared as above at 5-, 10-, 20-, or 30-kN compaction force.

To investigate the effect of incorporation of plasticizer, tablets were prepared from 125–250 μm size fraction of SD systems containing either 5% or 10% plasticizer at 10 kN compaction force.

### Evaluation of Matrices

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

Dissolution tests were carried out in a U.S. Pharmacopoeia (USP) dissolution apparatus I (Pharmatest PTWS 3E, Hainburg, Germany). The release profiles of matrices containing 80 mg of propranolol HCl 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 (Kyoto, 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 zero-order and Higuchi kinetic models using regression analysis. The correlation coefficient and sums of squares of errors were taken as the criteria to choose the best model.

### Infrared Studies

A Fourier-transform infrared (FT-IR) spectrophotometer (Perkin Elmer Paragon 1000 IR, Beaconsfield Bucks, UK) was used to obtain IR spectra of the pure drug, Eudragit RSPO, their physical mixtures, and also their solid dispersion systems using KBr disks.

## RESULTS AND DISCUSSION

### Effect of Solid Dispersion System on the Dissolution of Propranolol Hydrochloride

Dissolution studies were conducted to compare tablets prepared from the SD system (125–250-μm size fraction) with tablets from physical mixture to determine whether the SD system provides better control of drug release rate than the physical mixture. The comparison of release profiles for tablets of physical mixture and SD system is depicted in Fig. 1. The corresponding release rates and correlation coefficients calculated based on the Higuchi and zero-order equations are shown in Table 1. While the release of drug from tablets of SD was best described by the Higuchi model, for tablets of physical mixture, the zero-order model gave the better fit. It is evident from the results that tablets prepared from the SD system show more retardation in drug release. Tablets of physical mixture showed 100% drug release within 10 min, whereas the tablets of SD showed only 27% drug release during this time interval, followed by continuous release until 100% release was achieved within 2.5 h. This indicates that the SD system is more efficient than the physical mixture in retarding drug release from tablets. Similar results were reported for the release of diclofenac sodium from ethylcelluose SD[3] and also for indomethacin from the Eudragit RS SD system.[11]

In our study, tablets of physical mixtures disintegrated rapidly in dissolution medium, resulting in rapid drug release. However, tablets of the SD system retained their shape until the end of the dissolution test, and only a small amount of erosion of the edges of the tablets was observed. This is very important for proper performance of inert, insoluble matrices. The IR spectra of the samples showed lack of strong interaction between drug and polymer, as all characteristic bands of propranolol HCl were observed in IR spectra of the physical mixture and the SD system (data are not shown). Crushing strengths were 2.7±1.5 and 8.5±0.5 kg for matrices of the physical mixture and the SD system, respectively. The tablets of SD systems were significantly harder than those of the physical mixtures ($p<0.001$). Opposite results were reported for ethylcellulose matrices, and it was shown that tablets of SD of diclofenac sodium and ethylcellulose were significantly softer than those of physical mixtures.[3] This effect was attributed to the formation of a hard SD system, which resisted deformation under the compaction force. However, it

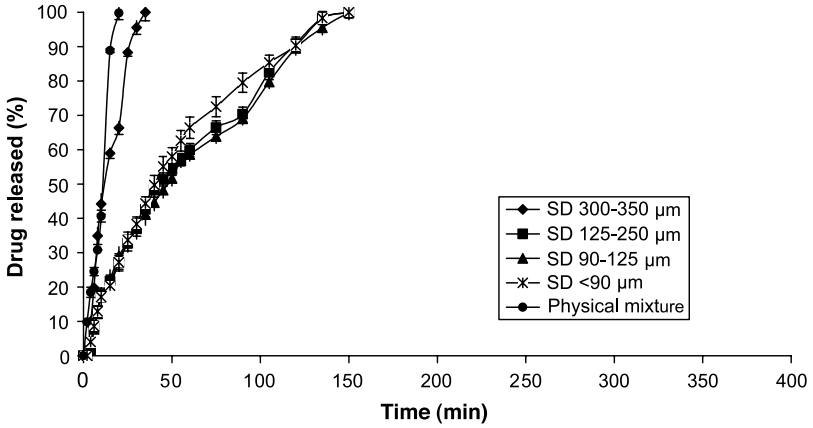


***Figure 1.*** Comparison of release profiles for matrices of physical mixture (prepared from 125–250-μm size fraction of drug and polymer) and SD system with different size fractions. (Each point represents mean ± SD of six determinations.)

has been reported that in some cases, solute molecules in solid solutions may serve as a plasticizer for the polymeric vehicle, leading to reduction in its glass transition temperature.[12]

The plasticizing effect of propranolol HCl on Eudragit RS film may be the best possible explanation for the observed increase in hardness of tablets of SD systems in this study. The effect of propranolol HCl on physical and mechanical properties of Eudragit RS was not studied. However, in a study by Wu and McGinity, it was shown that drugs such as cholorpheniramine maleate or ibuprofen have the ability to change the physical and mechanical properties of Eudragit RS and act as plasticizers.[13] It has also been reported that plasticizers influence the drug release rate from matrix-type tablets.[14] The rate and extent of release of cholorpheniramine maleate from dicalcium phosphate dihydrate and Eudragit RS matrices decreased with increasing DEP plasticizer, and this was attributed to the better adhesion of matrix materials in the presence of the plasticizer.[14] Therefore, the slow rate of propranolol HCl release from tablets of the SD system compared with those of the physical mixture could be mainly due to higher crushing strengths of former matrices. This slowed down the diffusion of dissolution medium into and dissolved drug out of the matrices. Also, formation of a film barrier around drug particles, which provides more resistance to drug release, could be another explanation for the observed slower rate of drug release from matrices of SD systems.

## Effect of SD Size Fraction on Drug Release

The release profiles for matrices prepared from different size fractions of the SD system are shown in Fig. 1 and the corresponding release rates are depicted in Table 2. The reduction of size fraction from 300–350 to 125–250 μm in each sampling time decreased the percent of drug release as well as the release rate, but further reduction in size fraction did not affect the drug release rate. Matrices prepared from the coarsest size fraction disintegrated rapidly and released their drug content fast. This indicated that the SD system of drug and polymer in powder form was not able to retard drug release. However, tablets prepared from

***Table 1.*** Slopes and correlation coefficients calculated based on fitting of release data to zero-order and Higuchi kinetic models for matrices of SD system (125–250 μm size fraction) and physical mixture.

| | Kinetic model | | | |
|---|---|---|---|---|
| | Zero order | | Higuchi | |
| Type of matrices | Slope (% $min^{-1}$) | r | Slope (% $min^{-1/2}$) | r |
| Physical mixture | 5.29 | 0.980 | 23.34 | 0.908 |
| Solid dispersion | 0.68 | 0.970 | 9.12 | 0.994 |

***Table 2.*** Influence of size fractions on crushing strengths and Higuchi rate constants for matrices of SD system.

| Size fraction of SD system (μm) | Crushing strength (kg) ± SD | Higuchi release rate (% $min^{-1/2}$) |
|---|---|---|
| 300–350 | 5.1 ± 0.6 | 19.87 |
| 125–250 | 8.5 ± 0.5 | 9.13 |
| 90–125 | 8.1 ± 0.7 | 8.84 |
| < 90 | 7.5 ± 0.7 | 9.52 |

smaller size fractions remained nearly intact during dissolution testing. In a study on release of drug from different size fractions of the SD system with either Eudragit RS or RL, it was shown that the release rate of indomethacin was reduced by increasing the particle size of the SD system in the untableted system.[11] It has also been reported that polymer particle size could affect drug release rate as well as the hardness of inert, insoluble matrices prepared from physical mixtures. The finer the particle size of the polymer, the more retardation in the drug release rate.[8,9]

The results observed in this study can be explained noting the crushing strength of matrices. The crushing strengths of matrices, which are listed in Table 2, show that the lowest value belongs to matrices prepared from the coarsest size fraction. However, there were no significant differences between the crushing strengths of matrices prepared from other size fractions ($p > 0.05$). Reduction in size fractions may increase the interparticle contacts during the compaction procedure, leading to an increase in crushing strength and therefore slower ingress of dissolution medium into the matrices. But with further reduction of size fraction, the crushing strength of matrices remained nearly unchanged.

## The Effect of Compaction Force on Drug Release

Figure 2 represents the effect of compaction force on drug release from matrices. Comparisons of release profiles and release rates (Table 3) indicate that an increase in compaction force from 5 to 10 kN reduced the rate of drug release. However, further increase in compaction force did not noticeably influence the release rate. These results are somewhat different from those reported by Khan et al., who showed that increase in compaction pressure from 5 to 40 kN decreased the rate of ibuprofen release from coprecipitate with Eudragit S100.[10] All the tablets except those prepared at 5-kN compaction force remained nearly intact during the dissolution test. But those prepared at 5-kN compaction force disintegrated rapidly in the dissolution medium. The effect of the compaction force on crushing strengths of matrices (Table 3) shows that with increasing the

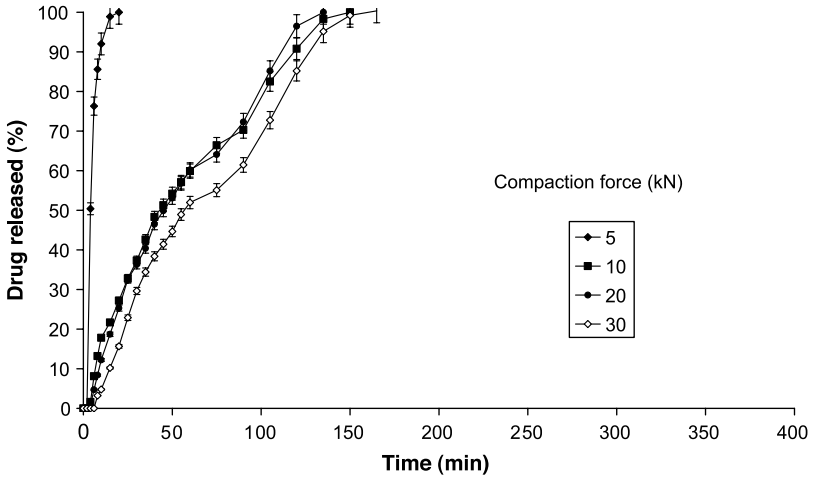


***Figure 2.*** Influence of compaction force on release profiles for matrices of SD system prepared from 125–250-μm size fraction. (Each point represents mean ± SD of six determinations.)

*Table 3.* Influence of compaction forces on crushing strengths and Higuchi rate constants for matrices prepared from 125–250-μm size fraction of SD system.

| Compaction force (kN) | Crushing strength (kg) ± SD | Higuchi release rate (% $min^{-1/2}$) |
|---|---|---|
| 5 | 2.9 ± 0.2 | 27.17 |
| 10 | 8.5 ± 0.5 | 9.13 |
| 20 | 12.4 ± 0.2 | 9.60 |
| 30 | 13.6 ± 0.6 | 9.11 |

compaction force from 5 to 20 kN, the crushing strengths of matrices increased considerably ($p < 0.001$). However, increase in the compaction force beyond 20 kN did not significantly affect the crushing strength of matrices ($p > 0.05$). The faster dissolution of drug from matrices prepared at 5-kN compaction force may be due to insufficient bonding of particles under low pressure, allowing easy penetration of the dissolution medium into matrices, which leads to rapid disintegration and drug release. However, the more compact nature of matrices prepared at higher compaction forces precludes rapid drug release. There were no considerable differences in drug release rates from matrices prepared at compaction forces higher than 10 kN. As shown by the release profiles, matrices prepared at higher compaction forces exhibit longer lag times prior to drug release. However, the rate constants are nearly the same (Table 3). It has been previously shown that tablet hardness in the range of 7–15 kg had a minimal influence on theophylline release profiles from Eudragit RSPM and L100 matrices.[15] Similarly, Sarisuta and Mahahpunt reported that compaction force as well as tablet crushing strength were not important factors in modifying the release pattern of diclofenac sodium from matrices containing Eudragit RS, lactose, and Emcompress within the range of 300–600-kg forces and 4–10-kg tablet crushing strength.[16] It has been also reported that although increasing the compaction pressure from 56 to 492 $MNm^{-2}$ resulted in a large reduction of the pore volume and a shift of pore-size distributions towards the smaller sizes, this did not influence the water penetration into the compacts and release profiles of aspirin from Eudragit RS matrices.[17]

## The Effect of Plasticizer Type and Concentration on Drug Release

It has been shown that plasticizer type and concentration have great influence on drug diffusivity in drug-loaded films.[18] It was also reported that inclusion of plasticizer into the SD system of ethylcellulose and diclofenac sodium profoundly affected crushing strengths of matrices and drug release rates. This effect was dependent on plasticizer type.[3] The effects on drug release profiles of plasticizer addition, Higuchi rate constants, and crushing strength of tablets of the SD system of propranolol HCl and Eudragit RS

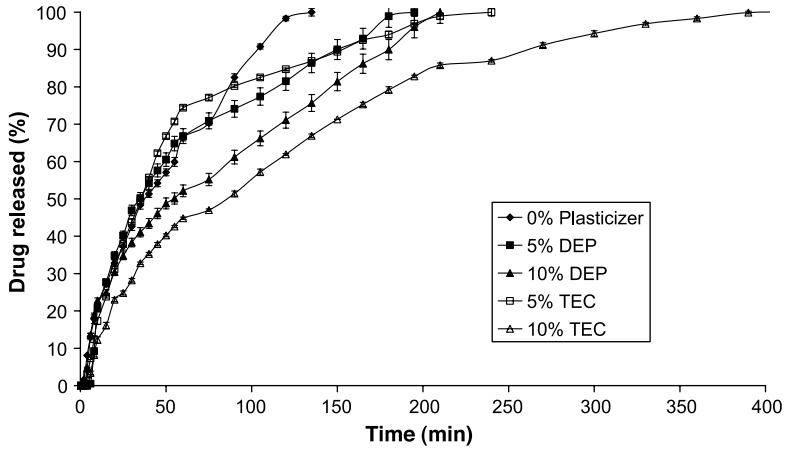


*Figure 3.* Influence of plasticizer incorporation [diethylphtalate (DEP) and triethylcitrate (TEC)] on release profiles for matrices of SD system prepared from 125–250-μm size fraction. (Each point represents mean ± SD of six determinations.)

*Table 4.* Influence of plasticizer type and concentration on crushing strengths and Higuchi rate constants for matrices of SD system.

| Plasticizer type and concentration | Crushing strength (kg) ± SD | Higuchi release rate (% $min^{-1/2}$) |
|---|---|---|
| DEP 5% | 10.2 ± 0.8 | 8.18 |
| DEP 10% | 13.8 ± 0.3 | 6.89 |
| TEC 5% | 10.5 ± 0.5 | 8.55 |
| TEC 10% | 12.5 ± 0.6 | 6.16 |

are depicted in Fig. 3 and Table 4. It is evident from the results that incorporation of 5% of either plasticizer had a minimal effect on the drug release rate. However, the addition of 10% plasticizer decreased the rate of drug release to a greater extent. Crushing strengths of matrices containing 10% plasticizer were significantly higher than those without any plasticizer ($p<0.001$). However, this was not responsible for the slower drug release rate, as in the study of the effect of compaction force, it was shown that crushing strength of matrices had minimal effect on drug release rate in the range of 8.5 to 13.6 kg. The tablets containing plasticizer remained completely intact during dissolution testing and no sign of erosion was observed even on the edges of the tablets. Probably, in the presence of a plasticizer, a more uniform film has been formed around drug particles, and also, the improved plastic deformation of tablets under compaction pressure caused the tablets to retain their shape as intact as possible during dissolution testing. Zhu et al. showed that the presence of TEC decreased the release rate of chlorpheniramine maleate in tablets prepared by direct compression and tablets made from compressed granules that had been prepared by high-shear, hot-melt granulation.[19] This was attributed to the presence of TEC in the interstices of the polymer, which increased the binding of drug to the polymer and therefore facilitated the formation of a continuous matrix structure.[19] Also, in a study by Wang et al., the ability of plasticizers to change the mechanical properties of pellets has been shown.[20] These authors investigated the influence of different plasticizers on the mechanical properties of single pellets containing Eudragit RS 30 D as a granulating binder. They showed that pellets containing low levels of plasticizers exhibited a brittle fracture behavior under compression, while a ductile property was observed at higher plasticizer concentration.[20] As both DEP and TEC were suitable plasticizers for Eudragit acrylic films,[20,21] they behaved similarly and no considerable differences were observed in the effects of these two plasticizers.

## CONCLUSION

This study has confirmed that the SD system is more efficient than physical mixing in the preparation of sustained-release, inert, insoluble matrices of propranolol HCl and Eudragit RS. Neither matrix prepared from physical mixture nor the SD system as a powder form could provide control on drug release. However, proper matrices with sustained-release properties could be prepared from the compressed SD system. It has also been shown that reduction of size fraction of the SD system from 300–350 to 125–250 μm had a great influence on the drug release rate, but beyond that it did not influence the release rate. Increase in compaction force up to 10 kN slowed the drug release rate to a great extent, but further increase in compaction forces did not have any profound effect on drug release although it led to an increase in crushing strengths of matrices. Incorporation of DEP or TEC into SD systems affected drug release profiles and crushing strength of matrices and provided better control of drug release. The effect was dependent on plasticizer concentration. Therefore, the drug release rate can be further modified by the addition of a suitable plasticizer into the SD system.

## ACKNOWLEDGMENTS

The authors express their thanks to the School of Pharmacy, Mashhad University of Medical Sciences for financial support and also to Rhom Pharma Gmbh for supplying Eudragit RS.

## REFERENCES

1. Goldberg, A.H.; Gibaldi, M.; Kanig, J.L. Increasing dissolution rates and gastrointestinal absorption of drugs via solid solutions and eutectic mixtures. I. Theoretical considerations and discussion of literature. J. Pharm. Sci. **1965**, *54*, 1145–1148.

2. Chiou, W.L.; Riegelman, S. Pharmaceutical applications of solid dispersion systems. J. Pharm. Sci. **1971**, *60*, 1281–1302.
3. Sadeghi, F.; Afrasiabi Garekani, H.; Sadr, A. Influence of polymer viscosity and plasticizer addition on ethylcellulose matrix characteristics prepared from solid dispersion system. STP Pharma Sci. **2003**, *13*, 105–110.
4. Pignatello, R.; Ferro, M.; De Guidi, G.; Salemi, G.; Vandelli, M.A.; Guccione, S.; Geppi, M.; Forte, C.; Puglisi, G. Preparation, characterization and photosensitivity studies of solid dispersions of diflunisal and Eudragit RS100 and RL100. Int. J. Pharm. **2001**, *218*, 27–42.
5. Aceves, J.M.; Cruz, R.; Hernandez, E. Preparation and characterization of furosemide–Eudragit controlled release systems. Int. J. Pharm. **2000**, *195*, 45–53.
6. Hernandez, J.I.; Ghalj, E.S.; Malave, A.; Marti, A. Controlled release matrix of acetaminophen ethylcellulose solid dispersion. Drug Dev. Ind. Pharm. **1994**, *20*, 1253–1265.
7. Goracinova, K.; Klisarova, L.J.; Simov, A. Physical characterization and dissolution properties of verapamil HCl coprecipitates. Drug Dev. Ind. Pharm. **1995**, *21*, 383–391.
8. Dabbagh, M.A.; Ford, J.L.; Rubinstein, M.H.; Hogan, J.E. Effect of polymer particle size, compaction pressure and hydrophilic polymers on drug release from matrices containing ethylcellulose. Int. J. Pharm. **1996**, *140*, 85–95.
9. Katikaneni, P.R.; Upadrashta, S.M.; Neau, S.H.; Mitra, A.K. Ethylcellulose matrix controlled release tablets of a water-soluble drug. Int. J. Pharm. **1995**, *123*, 119–125.
10. Khan, M.A.; Karnachi, A.A.; Singh, S.K.; Sastry, S.V.; Kislalioglu, S.M.; Bolton, S. Controlled release coprecipitates: formulation considerations. J. Control. Release **1995**, *37*, 131–141.
11. Oth, M.P.; Moes, A.J. Sustained release solid dispersions of indomethacin with Eudragit RS and RL. Int. J. Pharm. **1989**, *55*, 157–164.
12. Leuner, C.; Dressman, J. Improving drug solubility for oral delivery using solid dispersions. Eur. J. Pharm. Biopharm. **2000**, *50*, 47–60.
13. Wu, C.; McGinity, W. Non-traditional plasticization of polymeric films. Int. J. Pharm. **1999**, *177*, 15–27.
14. Mulye, N.V.; Turco, S.J. Matrix type tablet formulation for controlled release of highly water soluble drugs. Drug Dev. Ind. Pharm. **1994**, *20*, 2633–2643.
15. Cameron, C.G.; McGinity, J.W. Controlled release theophyline tablets formulations containing acrylic resins. II. Combination resin formulations. Drug Dev. Ind. Pharm. **1987**, *13*, 1409–1427.
16. Sarisuta, N.; Mahahpunt, P. Effect of compression force and type of fillers on release of diclofenac sodium from matrix tablets. Drug Dev. Ind. Pharm. **1994**, *20*, 1049–1061.
17. Carli, F.; Capone, G.; Colombo, I.; Magarotto, L.; Motta, A. Surface and transport properties of acrylic polymers influencing drug release from porous matrices. Int. J. Pharm. **1984**, *21*, 317–329.
18. Siepmann, J.; Lecomte, F.; Bodmeier, R. Diffusion controlled drug delivery systems: calculation of the required composition to achieve desired release profiles. J. Control. Release **1999**, *60*, 379–389.
19. Zhu, Y.; Shah, N.H.; Malick, A.W.; Infeld, M.H.; McGinity, J.W. Solid state plasticization of an acrylic polymer with chlorpheniramine maleate and triethyl citrate. Int. J. Pharm. **2002**, *241*, 301–310.
20. Wang, C.C.; Zhang, G.; Shah, N.H.; Infeld, M.H.; Malick, A.W.; McGinit, J.W. Influence of plasticizers on the mechanical properties of pellets containing Eudragit RS 30 D. Int. J. Pharm. **1997**, *152*, 153–163.
21. Lin, S.Y.; Chen, K.S.; Run-Chu, L. Organic esters of plasticizers affecting the water absorption, adhesive property, glass transition temperature and plasticizer permanence of Eudragit acrylic films. J. Control. Release **2000**, *68*, 343–350.