# *In vitro* Release Kinetics Study of Ambroxol Hydrochloride Pellets Developed by Extrusion Spheronization Technique Followed by Acrylic Polymer Coating

**Ishtiaq Ahmed, Monzurul Amin Roni, Golam Kibria, Muhammad Rashedul Islam and Reza-ul Jalil**

Department of Pharmaceutical Technology, Faculty of Pharmacy, University of Dhaka, Dhaka-1000, Bangladesh

**ABSTRACT:** The aim of the present study was to investigate the effect of Ammonio Methacrylate Copolymer Dispersion Type A (Eudragit RL 30 D) and Ammonio Methacrylate Copolymer Dispersion Type B (Eudragit RS 30 D) combination in different weight ratios on the release kinetics of Ambroxol Hydrochloride from coated pellets. Microcrystalline cellulose, lactose, maize starch, hydroxypropyl methylcellulose and the drug was incorporated in the nuclei prepared by Extrusion-Spheronization technique which was coated with Eudragit RL 30D and Eudragit RS 30D in 1:1,1:1.5,1:2,1:2.5 and 1:3 ratios. The *in vitro* dissolution studies were carried out in 0.1N HCl for 1 hour followed by phosphate buffer (pH 6.8) for 11 h with USP dissolution apparatus Type-II. Drug release decreased with increasing amount of Eudragit RS 30 D in all cases. The drug release followed first order and Higuchi release kinetics. The Korsmeyer plot revealed n=0.50-0.61 or non-Fickian transport mechanism for drug release. From one way ANOVA it was found that the ratio of binary polymer mixer had significant ($p<0.05$) effect on drug release.

**Key words:** Aqueous coating, Eudragit, release kinetics, pellet, extrusion-spheronization

## INTRODUCTION

Pellets are small, near spherical and free flowing agglomerates which can be incorporated in hard gelatin capsule shell. After their introduction in 1960s by Smith Kline and French (SK & F) the delivery system was adopted by pharmaceutical industry to produce modified release dosage forms. Pellets formulations have some advantages over conventional solid dosage forms. They have lesser chance of dose dumping than tablets coated with controlled release coating. They are also less sensitive to the effect of stomach emptying.[1] These properties made them one of the most promising dosage forms for the development of sustained release drug delivery systems.

Sustained release pellets are prepared usually by coating the nuclei with different release retarding polymers.[2-8] The most widely used pelletization processes in the pharmaceutical industry are extrusion-spheronization, solution/suspension layering and powder layering.[9] The techniques of solution, suspension and powder layering was reported by some of the authors using conventional coating pan or in fluid bed coater.[10,11] Extrusion-Spheronization is a multiple-step compaction process comprising dry mixing of the ingredients with excipients, wet granulation of the mass, extrusion of the wetted mass,

Correspondence to: Golam Kibria
Tel: 88-01816105604, Fax: 88-02-8615583
E-mail: gkibria123@yahoo.com

Dhaka Univ. J. Pharm. Sci. **7**(1): 75-81, 2008 (June)

charging the extrudates into spheronizer to produce a spherical shape, drying the wet pellets in a dryer and, finally, screening to achieve the required size distribution.[12-19]

Acrylic polymers are widely used for the coating of sustained release pellets and tablets.[20-22] Two acrylic polymers namely Ammonio Methacrylate Copolymer Dispersion Type A (Eudragit RL 30D, Rohm GmbH) and Ammonio Methacrylate Copolymer Dispersion Type B (Eudragit RS 30D, Rohm GmbH) were used in the experiment. These polymers are available as 30% aqueous dispersion.[23] Both polymers are insoluble in water but Eudragit RL is more permeable than Eudragit RS. The quaternary groups occur as salts and are responsible for the permeability of films made from these polymers. Depending on the type of polymer used, films of different solubility characteristics can be produced. Film coatings prepared from both polymers give pH-independent release of active substance. Combination of these two gives the formulator more control over the release pattern of the drug.

Sparingly soluble Ambroxol hydrochloride was used in the experiment as a model drug. It is indicated in productive cough and 75 mg sustained release capsule is available in the market (Ambrolan® by Lannacher, Austria). The drug is chemically trans-4-[(2-amino-3,5-dibromobenzyl) amino] cyclohexanol hydrochloride with molecular weight of 414.6.

## MATERIALS AND METHODS

Materials used in the experiment were Ambroxol hydrochloride (Alchymars ICM SM Pvt. Ltd., India), Lactose (The Lactose Co. of New Zealand Ltd.), Microcrystalline cellulose (Ming Tai Chemical co. Ltd., Taiwan), Maize starch (Cerestar, Netherlands), HPMC 5 cps (Shin Etsu Chemical Company Ltd., Japan), Eudragit RL30 D (Rohm GmbH, Germany), Eudragit RS 30D (Rohm GmbH, Germany), Purified talc (Asian Mineral Resources Co. Ltd., Thailand) and triethyl citrate (Morflex Inc., USA). Other materials used were reagent grade.

**Preparation of sustained release pellets.** The nuclei containing Ambroxol Hydrochloride was manufactured using extrusion-spheronization technique. The drug and the diluents (Lactose, Maize starch, Microcrystalline Cellulose) were dry-mixed in a laboratory scale planetary mixer (Umang Pharmatech Pvt. Ltd., India) to achieve homogenous powder dispersion and then wet granulated using binder solution (HPMC 5 cps in purified water). The composition of nuclei is shown in Table 1. The wet mass was extruded using screen extruder (Caleva, UK) having 1 mm screen to form rod shaped extrudes of uniform diameter. The extrudes were charged into spheronizer (Caleva, UK) and rounded off at 600 rpm for one minute. The spherical particles were then dried in a tray dryer (Indo-German PVT Ltd., India)

**Table 1. Composition of coated pellets**

| Materials | Formulation | | | | |
|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | 5 |
| *Core Formula (g)* | | | | | |
| Ambroxol hydrochloride | 140 | 140 | 140 | 140 | 140 |
| Lactose | 60 | 60 | 60 | 60 | 60 |
| Maize starch | 20 | 20 | 20 | 20 | 20 |
| MCC | 160 | 160 | 160 | 160 | 160 |
| HPMC 5 cps | 20 | 20 | 20 | 20 | 20 |
| Purified water | 200 | 200 | 200 | 200 | 200 |
| *Coating Formula (g)* | | | | | |
| Eudragit RL 30D | 26.67 | 21.34 | 17.77 | 15.24 | 13.34 |
| Eudragit RS 30D | 26.67 | 32.00 | 35.57 | 38.10 | 40.00 |
| Purified Talc | 2.40 | 2.40 | 2.40 | 2.40 | 2.40 |
| Triethyl Citrate | 0.96 | 0.96 | 0.96 | 0.96 | 0.96 |
| Purified water | 23.30 | 23.30 | 23.30 | 23.30 | 23.30 |

to achieve the desired moisture content. The pellets were then screened using ASTM 20 mesh followed by ASTM 24 mesh to achieve the targeted size distribution (710-850 μm).

Coating suspension was prepared by adding Talc in the purified water followed by Triethyl Citrate, Eudragit RL 30 D and Eudragit RS 30 D with stirring (Table 1). Coating of Nuclei was done with 4% polymer load on 400 g nuclei using fluid bed coater (Labcoater; Umang Pharmatech, India) according to process parameters of Table 2. The ratio of Eudragit RL 30 D and Eudragit RS 30 D was 1:1, 1:1.5, 1:2, 1:2.5 and 1:3. The coated pellets were dried in the labcoater for 15 minutes at $40^0$C to avoid twinning and agglomeration. The picture of coated pellets have shown in Figure 5.

**Table 2. Machine parameters set up during coating**

| Machine | Fluid bed coater (Wurster, Umang Pharmatech Ltd.) |
|---|---|
| Batch size | 400 g |
| Inlet air temperature | 50-55 $^0$C |
| Outlet air temperature | 29-32 $^0$C |
| Product temperature | 35-40 $^0$C |
| Chamber humidity | 55% |
| Air flow | 90 $m^3$/h |
| Spraying pressure | 1.20 bar |
| Spraying rate | 3.0 g/min |
| Secondary drying | 40 $^0$C/15 min |

**Physical characterization of coated pellets.** Loss on drying (LOD) was determined on 1.0 g pellet at $60^0$C under vacuum for 4 h. Resistance to abrasion was determined using a Roche TAR 10 friabilator (Erweka, Ensenstam, Germany). Friability was measured with 10 g of drug-loaded pellets (nuclei) mixed with 25 glass spheres (5μm in diameter) and uniformly tumbled for 10 minutes at 25 rpm. Weight loss from the pellets were measured afterwards.

***In vitro* dissolution study.** The dissolution of ambroxol hydrochloride sustained release pellets was studied by Erweka (Germany) dissolution tester USP (XXVIII) using USP apparatus 2 (Paddle method). Ambroxol hydrochloride sustained release pellets equivalent to 75 mg of ambroxol hydrochloride was poured in 900 ml of 0.1 N HCl medium at $37^0$ ± $0.5^0$C with a rotation of 50 rpm for 1 hour. At the end of 1 hour the media was removed and drug content was determined spectrophotometrically at 244 nm. Then 900 ml of phosphate buffer ($Na_3PO_4$) pH 6.8 was placed in each vessel and rotated at 50 rpm at $37^0$ ± $0.5^0$C for 11 hours. 10 ml samples were drawn every one hour and replaced by fresh medium to maintain the volume constant and drug content was determined spectrophotometrically at 244 nm using UV-Visible Spectrophotometer (Shimadzu, Japan).

## RESULTS AND DISCUSSION

The color of the drug-loaded pellets was found almost white and round shaped. As the nuclei was prepared by wet massing, little amount of moisture is expected. The moisture content of nuclei was determined with LOD (Loss on Drying) of 0.18% which indicates that the layering process as well as the raw materials are suitable to manufacture stable pellets having low moisture content, as moisture plays a vital role in case of pellets stability. The balance between moisture and friability is critical as over dried pellets tend to be fragile. The friability of nuclei was 0.26% which is very well within the requirement (below 1%). Tapped bulk density of the pellets plays an important role during encapsulation which was found 0.78 g/$cm^3$. This value will be suitable to fill the pellets in empty hard gelatin capsule shell. Before coating the pellet size distribution was 710 - 850 μ and after coating it was slightly increased (710 - 1000 μ). For acceptable film coating, a narrow size distribution of pellets is a prerequisite (in addition to spherical shape and smooth surface). The size distribution affects both the performance of the coating and the release rate of the drug.[4,6,24] Thus the physical characteristics of the nuclei prepared by extrusion-spheronization was satisfactory and further studies were carried out with the sample.

After 12 h of dissolution 96.82 ± 0.76%, 93.71 ± 1.04%, 91.05 ± 1.57%, 88.6 ± 1.98% and 83.00 ± 1.59% drug was released from formulations containing Eudragit RL and Eudragit RS 1:1, 1:1.5,

1:2, 1:2.5 and 1:3 ratios respectively. The dissolution profile is shown in Figure 1. Mean Dissolution Time (MDT) of pellets are given in Table 3. The data indicates MDT values increased with the increase of Eudragit RS 30 D in the coating. It is due to lower permeability of Eudragit RS 30 D film that increases its release retarding capability.[25]

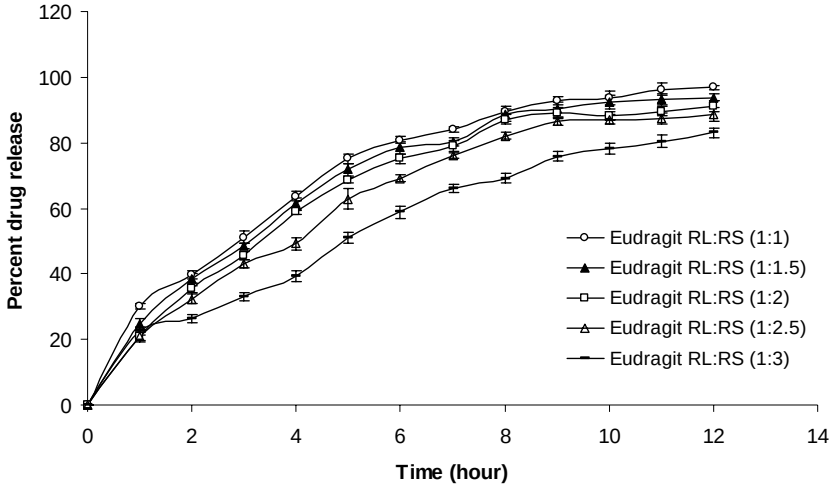


Figure 1. Zero order release profile of Ambroxol HCl from coated pellets (mean ±S.D., n=3)

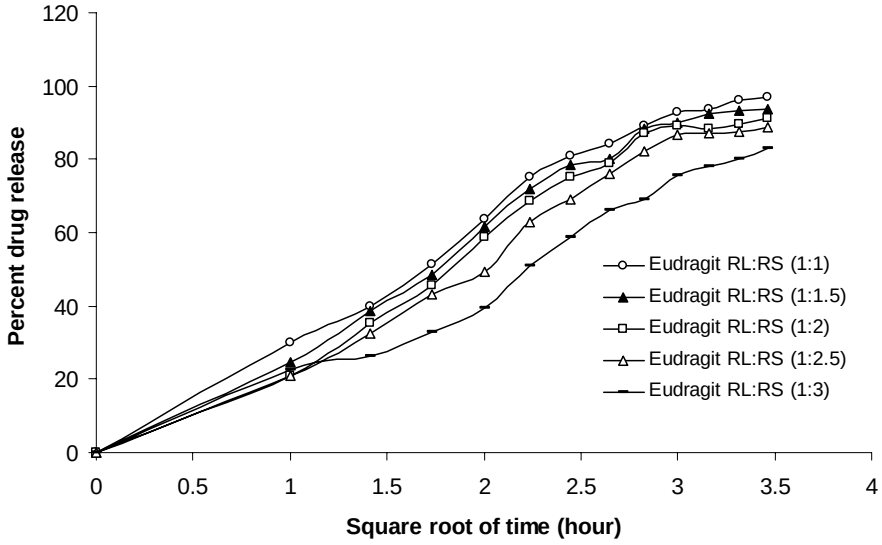


Figure 2. Higuchi release profile of Ambroxol HCl from coated pellets. (n=3)

The release curve of the drug showed poor fit for zero order kinetics (Table 3). The regression coefficient values ($r^2$) increased gradually with increasing Eudragit RS content in coating. It implies the release may follow zero order kinetics at higher amount of Eudragit RS. On the other hand, the delivery system showed better linearity for Higuchi release kinetics ($r^2$>0.97). It indicates that drug release was a diffusion process. The release profile also fitted well with first order kinetics suggesting release was drug concentration dependant (Table 3).

The dissolution data was fitted to the Korsmeyer equation (Equation 1), which is often used to describe the drug release behavior from polymeric systems. [26]

$$\text{Log}\left(\frac{M_t}{M_f}\right) = \text{Log}\, k + n\, \text{Log}\, t \qquad (1)$$

Where $M_t$ is the amount of drug release at time t; $M_f$ is the amount of drug release after infinite time; k is a release rate constant incorporating structural and geometric characteristics of the dosage form; n is the diffusional exponent indicative of the mechanism of drug release.[27]

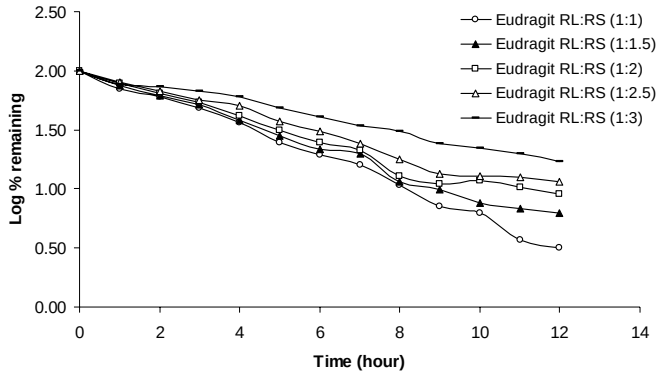


Figure 3. First order release profile of Ambroxol HCl from coated pellets (n=3)

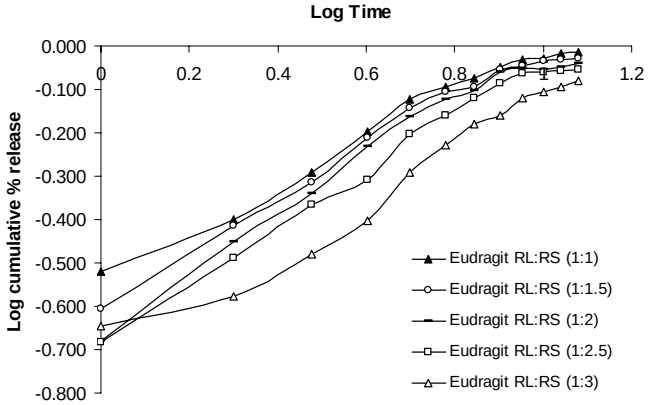


Figure 4. Korsmeyer release profile of Ambroxol HCl from coated pellets (n=3)

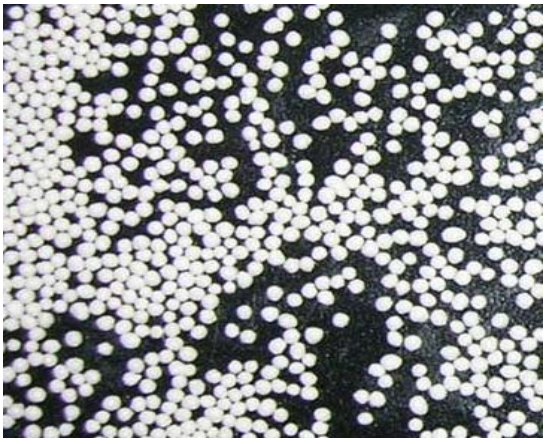

Figure 5. Ambroxol Hydrochloride sustained release pellets coated with Eudragit RL 30D & Eudragit RS 30D

The log value of percent drug dissolved is plotted against log time for each formulation according to equation 1. In a sphere the value of $n \leq 0.43$ indicates Fickian (case I) release; $> 0.45$ but $< 0.85$ for non-Fickian (anomalous) release; and $> 0.85$ indicates super case II type of release. Case II generally refers to the erosion of the polymeric chain and anomalous transport (Non-Fickian) refers to a combination of both diffusion and erosion controlled drug release. [28]

All the formulations showed diffusion coefficient value (n) greater than 0.43 but less than 0.85 (Table 3) after fitting to the Korsmeyer's

equation. It indicates anomalous or non-Fickian transport mechanism. Therefore the drug is released by both diffusion and erosion mechanism.

The statistical evaluation was performed by one-way ANOVA and results are shown in Table 4. From the data it is evident that p value is less than 0.05 in all formulations for 1h (in acid media), 2h (buffer media starts), 6h (middle point of test) and 12 h (end point of the test). Therefore it can be derived that the change in polymer ratio had significant effect on the release of the drug.

**Table 3. Kinetic parameters of coated pellets**

| Code | Zero order | | First order | | Higuchi | | Korsmeyer | | MDT (h) |
|---|---|---|---|---|---|---|---|---|---|
| | $r^2$ | $K_0$ | $r^2$ | $K_1$ | $r^2$ | $K_H$ | $r^2$ | n | |
| F1 | 0.86 | 7.21 | 0.99 | 0.13 | 0.98 | 29.71 | 0.98 | 0.50 | 3.57 |
| F2 | 0.87 | 7.18 | 0.99 | 0.11 | 0.98 | 29.45 | 0.97 | 0.55 | 3.87 |
| F3 | 0.87 | 7.13 | 0.97 | 0.09 | 0.97 | 29.14 | 0.97 | 0.60 | 4.20 |
| F4 | 0.90 | 7.11 | 0.98 | 0.08 | 0.98 | 28.56 | 0.98 | 0.61 | 4.61 |
| F5 | 0.95 | 6.57 | 0.99 | 0.06 | 0.98 | 25.79 | 0.97 | 0.57 | 5.86 |

**Table 4. One way ANOVA of drug release at different hours**

| Hour | Source of Variation | SS | df | MS | F | P-value | F crit |
|---|---|---|---|---|---|---|---|
| 1 | Between Groups | 187.122 | 4 | 46.780 | 16.500 | 0.000 | 3.478 |
| | Within Groups | 28.352 | 10 | 2.835 | | | |
| | Total | 215.474 | 14 | | | | |
| 2 | Between Groups | 351.695 | 4 | 87.924 | 50.129 | 0.000 | 3.478 |
| | Within Groups | 17.540 | 10 | 1.754 | | | |
| | Total | 369.235 | 14 | | | | |
| 6 | Between Groups | 976.677 | 4 | 244.169 | 97.977 | 0.000 | 3.478 |
| | Within Groups | 24.921 | 10 | 2.492 | | | |
| | Total | 1001.598 | 14 | | | | |
| 12 | Between Groups | 328.967 | 4 | 82.242 | 46.526 | 0.000 | 3.478 |
| | Within Groups | 17.677 | 10 | 1.768 | | | |
| | Total | 346.644 | 14 | | | | |

## CONCLUSION

In this study, nuclei containing Ambroxol Hydrochloride were prepared successfully using extrusion-spheronization technique. Coating was done in fluid bed coating system using Eudragit RL 30 D and Eudragit RS 30 D as rate retarding polymer. The release mechanism was explored and explained with zero order, first order, Higuchi equation and Korsmeyer's equation. Release profiles showed a tendency to follow anomalous transport mechanism. More extensive *in vitro-in vivo* correlation studies on similar formulations are essential to establish a successful formulation from the biopharmaceutical viewpoint.

## ACKNOWLEDGEMENT

The authors are thankful to Eskayef Bangladesh Ltd. for providing raw materials, reagents as well as manufacturing facilities.

## REFERENCES

1. Andrew, B.C. and Shargel, L. 1941. Modified release Drug Products and Targeted Drug Delivery System. In: Applied Biopharmaceutics and Pharmacokinetics, 3rd ed., Appleton & Lange, Connecticut, pp. 225-264.
2. Mehta, A.M., Valazza, M.J. and Abele, S.E. 1986. Evaluation of fluid-bed processes for enteric coating systems. *Pharm. Technol.* **10**, 46-56.
3. Ragnarsson, G., Sandberg, A., Johansson, M.O. and Sjogren, J. 1987. Development of a new controlled release metoprolol product. *Drug Dev. Ind. Pharm.* **13**, 1495-1509.
4. Ragnarsson, G. and Johansson, M.O. 1988. Coated drug cores in multiple-unit preparations. Influence of particle size. *Drug Dev. Ind. Pharm.* **14**, 2285-2297.
5. Bianchini, R. and Vecchio, C. 1989. Oral controlled release optimization of pellets prepared by extras ion-spheronization processing. *Il Farmaco.* **44**, 645-654.
6. Wesdyk, R., Joshi, Y.M., Jain, N.B., Morris, K. and Newman, A. 1990. The effect of size and mass on the film thickness of beads coated in fluidized bed equipment. *Int. J. Pharm.* **65**, 69-76.

7. Marvola, M., Nykanen, P., Rautio, S., Isonen, N. and Autere, A.M. 1999. Enteric polymers as binders and coating materials in multiple-unit site-specific drug delivery systems. *Eur. J. Pharm. Sci.* **7**, 259-267.
8. Umprayn, K., Chitropas, P. and Amarekajom, S. 1999. Development of terbutaline sulfate sustained-release coated pellets. *Drug Dev. Ind. Pharm.* **25**, 477-491.
9. Ghebre-Sellassie, I. 1989. Pharmaceutical Pelletization Technology. Marcel Dekker Inc., New York, pp.1-3, 50-52,145-164.
10. Absar, M. S., Kibria, G. and Jalil, R. 2007. Effect of Acrylic Polymers on the Physical Parameters and in vitro Release Kinetics of Diclofenac Sodium Sustained Release Pellets. *Bangladesh J. Sci. Ind. Res.* **42**, 239-248,
11. Kibria, G. and Jalil, R. 2007. *In vitro* Release Kinetics Study of Diltiazem Hydrochloride from Pellets using an Ethylcellulose Pseudolatex Coating System. *Dhaka Univ. J. Pharm. Sci*. **6**, 87-92,
12. Conine, J.W. and Hadley, H.R. 1970. Small solid pharmaceutical spheres. *Drug Cosmet. Ind.* **90**, 38-41.
13. Reynolds, A. D. 1970. A new technique for the production of spherical particles. Manuf. Chem. 39-43.
14. O'Connor, R.E. and Schwartz, J. B.1989. Extrusion and spheronization technology. In: Ghebre-Sellassie, I (ed.). Pharmaceutical Pelletization Technology, Marcel Dekker Inc., New York. pp. 187-215.
15. Hellen, L., Yliruusi, J., Muttonen, E. and Kristoffersson, E. 1992. Process variables of the radial screen extruder. Part II: Size and size distribution of pellets. *Pharm. Techn. Int,* **5** (2).
16. Erkoboni, D.F. 1997. Extrusion-Spheronization as a Granulation Technique. In: Handbook of Pharmaceutical Granulation Technology (Parikh, D. M.,Eds.), Vol. 81, Marcel Dekker Inc. New York, pp. 333-365.
17. Gazzaniga, A., Sangalli, M. E., Bruni, G., Zema, L., Vecchio, C. and Giordano, F. 1998. The use of β-cyclodextrin as a pelletization agent in the extrusion/spheronization process. *Drug Dev. Ind. Pharm.* **24**, 869-873.
18. Thoma, K. and Ziegler, I. 1998. Investigations on the influence of the type of extruder for pelletization by extrusion-spheronization.II. Sphere characteristics. *Drug Dev. Ind. Pharm.* **25**, 413-422.
19. Schmidt, C. and Kleinebudde, P. 1999. Influence of the granulation step on pellets prepared by extrusion/spheronization. *Chem. Pharm. Bull*. **47**, 405-412.
20. Dreher, D. and Lehmann, K. 1973. The use of aqueous synthetic polymer dispersions for coating pharmaceutical dosage forms. *Drugs made Ger.* 16 , 126, 131, 132, 134, 136.
21. Dreher, D. and Lehmann, K. 1981. Coating of tablets and small particles with acrylic resins by fluid bed technology. *Int. J. Pharm. Technol. Prod. Manuf.* **2**, 31-43.
22. Obi, C.E. and Okor, R.S. 1990. Drug release through aqueous-based film coatings of acrylatemethacrylate, a water-insoluble copolymer. *Int. J. Pharm.* **58,** 89-91.
23. Kibbe, H.A. 2000. Handbook of Pharmaceutical Excipients. 3rd Edn., American Pharmaceutical Association and Pharmaceutical Press, Washington DC, pp. 599-601.
24. Hey, W.J. 1991. Effect of particle size and porosity on particle film coatings. *Powder Tech.* **65**, 441-445.
25. Kibria, G. and Jalil, R. 2007. *In vitro* release kinetics study of Diclofenac Sodium from acrylic polymer coated pellets. *Dhaka Univ. J. Pharm. Sci.* **6**, 1-7.
26. Ritger, P.L. and Peppas. N.S. 1987. J. Control Release, **5**, 37-42.
27. Korsmeyer, R.W., Gurny, R., Doelker, E., Buri, P. and Peppas, N.A. 1983. Mechanisms of solute release from porous hydrophilic polymers. *Int. J. Pharm*. **15**, 25-35.
28. Siepmann, J. and Peppas, N.A. 2001. Modeling of drug release from delivery systems based on hydroxypropyl methylcellulose (HPMC). *Adv. Drug Deliv. Rev.* **48**, 139-157.