*S. J. Pharm. Sci.* 2(2): 53-58

# Effects of coating on the release profile of drug combination from hydrophilic matrix pellets

Muhammad Shahidul Islam[1*], Md. Moniruzzaman[2], Ruknuzzaman Rony[1], Tasnuva Haque[1]

Department of Pharmacy, Stamford University Bangladesh[1]
Product Development Section, Incepta Pharmaceuticals Lts. Bangladesh[2]

***Corresponding Author**
Muhammad Shahidul Islam
Lecturer, Department of Pharmacy
Stamford University Bangladesh
Contact no.: +88-01819559297
E-mail: shahidul.pharmdu@yahoo.com

*Received- 15 June, 2009* *Accepted for Publication- 15 July, 2009*

## ABSTRACT

In this work zinc sulfate, ferrous sulfate and ascorbic acid was formulated on the same pellet by combination pelletization technique and their and in vitro dissolution studies were performed by using United States Pharmacopoeia (USP) apparatus type II. In addition, effect of different types of polymers, formulation variables and variations in coating composition on the release of drug were studied. The desired release profile for ferrous sulfate was 35% for 1st hour, 45-75% for 2nd hour and 60-85% for third hour and not less than 85% for 4th hour. The release rate controlling polymer used was various concentrations of Methoccel K15M CR with different concentrations of Microcrystalline cellulose (Avicel PH 101). The maximum release percentage of Ferrous Sulphate was obtained from 2.5 % of Methocel K15M CR and 30 % Avicel PH 101 containing pellets (F-4) and it was 92.32%. And the minimum release percentage of Ferrous Sulphate was obtained from 10 % of Methocel K15M CR and 35.7 % Avicel PH 101 containing pellets (F-1) and it was 86.36%. The release profile from other formulations containing 35.4 % Methocel K 15M CR & 7.5 % Avicel (F-2) and 32% Methocel K 15M CR & 4 % Avicel (F-3) were also within desired range. The effect of Eudragit coating (enteric) and the presence of PEG and HPMC in the film coating composition on the drug release were also investigated. Hydrophobic matrix pellets prepared using lower concentrations of Methocel K15M CR were found to be best suited for modulating the delivery of the ferrous sulphate from the combination.

**Key words:** Non Pariel Seeds (NPS), Pan Coater, Ascorbic acid, Methocel K15M CR, Pelletization, PEG, Avicel PH 101, Xanthan gum.

## INTRODUCTION

Given the enormous advantage of multi particulate systems over single unit oral dosage forms, extensive research has focused recently on refining and optimizing existing pelletization techniques as well as on the development of novel manufacturing approaches that uses innovative formulations and processing equipment. The most commonly used and intensely investigated pelletization processes are powder layering, solution/suspension layering, and extrusion-spheronization (Issac Ghebre- Sellassie *et al*. 2006). Pellets consist of spherical or semi spherical solid units, typically from about 0.5 mm to 1.5 mm, and are intended for oral administration (Gadjos 1983, Kristensen *et al.* 1987).

In the last two decades pellets have established their position for many reasons (Ghebre-Sellassie 1989, Hellen 1992). Pellets offer a great flexibility in pharmaceutical solid dosage form design and development. They flow easily and pack easily without significant difficulties, resulting in uniform and reproducible fill weight for capsules and tablets (Conine and Hadley 1970, Lyne *et al.* 1981, Ghebre-Sellassie *et al*. 1985, Reynolds 1990, Niskanen 1992, Vuppala *et al*. 1997). Successful film coating can be applied onto pellets due to their ideal spherical shape and a low surface area to volume ratio (Rowe 1985, Vertommen *et al*. 1997). Pellets consisting of different drugs can be blended and formulated into a single dosage form. This approach facilitates the delivery of two or more drugs, chemically compatible or incompatible, at the same site or different sites in the gastrointestinal tract. Even pellets with different release rates of the same drug can be supplied in a single dosage form (Ghebre-Sekkasue *et al*. 1989, Wan *et al*. 1991).The most important reason for the wide acceptance of pellets is the rapid increase in popularity of oral controlled release dosage forms. Controlled release oral dosage forms are usually intended for delivery of the drug at a site within the gastrointestinal tract or to sustain the action over an extended period of time. With pellets, the above mentioned goals can be obtained through the application of coating materials (mainly different polymers), providing desired functions (Mehta *et al*. 1986) or through the formulation of matrix pellets to provide the desired effect (O'Conner *et al.* 1985). In pellets

prepared by combination of ferrous sulfate, zinc sulfate and ascorbic acid, all the three active ingredients are retained in a single pellet. So, mixing is not required before encapsulation. The objective of the present research work was to scrutinize whether it would be possible to formulate pellets in combined way. The objective of the current study was to observe the binder solution consumption for the individual and combination pellets.

## MATERIALS AND METHODS

### *Drugs and chemicals*

Ferrous Sulfate (Nanming Wuxing Feed Additive Co. Ltd), Ascorbic Acid (BASF Southeast Asia Pvt. Ltd.), Zinc Sulfate (Changsha Yili Chemical Factory), Avicel PH 101 (Mingtai Chemical Co Ltd), Povidone K 30 (BASF Southeast Asia Pvt. Ltd.), Methocel K 15M (The Dow Chemical Company), HPMC 15 cps (Colorcon Asia Pvt Ltd), HPMC 5 cps (Colorcon Asia Pvt Ltd), PEG 6000 (Weichers & Helm GmbH & Co.), Purified Talc (Tuhin Chemicals), Methanol (Zhejiang Sunrise Fine Chemicals Company Ltd), Methylene Chloride (Shangdong Dongyne Chemical Co. Ltd.), Triethyl Citrate (Vertellus Performance Materials Inc), Iron Oxide Yellow (Shangdong Dongyne Chemical Co. Ltd.), Eudragit L 100 (Degussa) and other reagents and solvents used were of analytical or pharmaceutical grade.

### *Preparation of ferrous sulfate pellets*

Ferrous sulfate, Avicel PH 101, Povidone K 30, Methocel K15 MCR, ascorbic acid etc. are blended in a polybag for 10 minutes. Water added to the blend to make wet mass. The wet mass is extruded with extruder. The mixture is then processed in the spheronizer. The formulation of ferrous sulfate pellets for sample 1, sample 2, sample 3, and sample 4 are shown in Table

### *Drying of ferrous pellets*

The pellets were dried at 40℃ for 5 hours by fluid bed processor. The final LOD of the pellets was 3.03%.

### *Sub-coating of the dried pellets:*

Coating solution was prepared with HPMC 15 cps, HPMC 5 cps, PEG 6000, purified talc, methanol and methylene chloride. Methanol and methylene chloride were taken is a beaker and PEG 6000 was added to dissolve with stirring. HPMC 15 cps and HPMC 5 cps were added and stirred to make clear suspension. Purified talc was homogenized by homogenizer and added to the previous suspension. The suspension was stirred for 30 minutes. Ferrous sulfate pellets was sub-coated at the wurster coater. The inlet temperature was set to 50℃ and outlet temperature was set to 40℃. The sub coated pellets were dried for 1 hour. The formulation of sub-coating of ferrous sulfate pellets for sample 1, sample 2, sample 3, and sample 4 are shown in Table

### *Enteric Coating of ferrous sulfate pellets*

Methanol was taken is a beaker. Eudragit L 100 was added while stirring. Triethyl citrate was added to the solution and stirred. Purified talc and iron oxide yellow was homogenized by homogenizer. This was then added to the previous solution and stirred for 10 minutes. The sub coated pellets was coated with the enteric coating solution in wurster coating machine. The inlet temperature and outlet temperature was set 50℃ and 40℃ respectively. After completion of coating, the pellet was dried for 1 hour.The formulation for enteric coating of ferrous sulfate pellets for sample 1, sample 2, sample 3, and sample 4 are shown in Table

### *Drug loading of ascorbic acid*

Ascorbic acid was dissolved in water with continuous stirring. PEG 6000 was added to the solution and stirred to make clear solution. HPMC 15 cps and HPMC 5 cps were added to the previous solution and stirred to make clear dispersion. Purified talc and titanium dioxide are homogenized by homogenizer and added to the previous dispersion. This dispersion was loaded on the previous pellets with wurster coater. The inlet temperature was set to 60℃ and outlet temperature was set to 50℃. The formulation for drug loading of ascorbic acid for sample 1, sample 2, sample 3, and sample 4 are shown in Table

### *Film coating of the pellets*

Methanol and methylene chloride were taken in a beaker. PEG 6000 was added to the beaker and stirred to make clear solution. HPMC 15 cps and HPMC 5 cps were added to the previous solution and stirred to make clear dispersion. Purified talc is homogenized in methanol and methylene

chloride and added to the previous dispersion. The formulation for film coating of ascorbic acid loaded pellets for Formula 1, Formula 2, Formula 3, and Formula 4 are shown in Table 3.

**Table: 3. Formulations of Ferrous Sulphate pellets (Individual pelletization and combination pelletization).**

| Ingredients | Amount (Gm) | |
|---|---|---|
| | For Individual Pelletization | For Combination Pelletization |
| Ferrous sulfate | 100 | 100 |
| Ascorbic acid | 50 | 50 |
| Zinc sulfate | 50 | 50 |
| Avicel PH 101 | 930 | 380 |
| Povidone K 30 | 26 | 10 |
| Methocel K 15 M CR | 42 | 42 |
| HPMC 15 cps | 45 | 45 |
| HPMC 5 cps | 45 | 45 |
| PEG 6000 | 7.5 | 27 |
| Purified Talc | 7.5 | 727 |
| Methanol | 836 | 636 |
| Methylene Chloride | 900 | 600 |
| Eudragit L 100 | 25 | 25 |
| Triethyl Citrate | 2.5 | 2.5 |
| **Total** | 3066.5 | 2739.5 |

***Drug loading of zinc sulfate***

Water was taken in a beaker. Zinc sulfate was added to water with continuous stirring. PVA and PEG were added to the solution with continuous stirring. Purified talc and titanium dioxide are homogenized by homogenizer and added to the previous dispersion. This dispersion was loaded on the pellets with wurster coater. The dispersion was coated on the pellets with wurster coater. The inlet temperature was set to 60℃ and outlet temperature was set to 50℃. The formulation for drug loading of zinc sulfate for sample 1, sample 2, sample 3, and sample 4 are shown in Table

***In-vitro* Dissolution testing procedure for ferrous sulfate**

The water bath was checked, if necessary and water added to maintain desired water level. 800 ml buffer pH 1.2 was taken into each of the six vessels of the apparatus. The thermostat was adjusted to 37.8℃. After attaining this temperature, the rotation was adjusted at 50 rpm. 100 mg test sample was placed in each of the six baskets. The apparatus was operated for 1 hour. After completion of rotation, 10 ml of samples from each of the vessel were withdrawn. The sample was filtered and filtrate was collected. 10 ml of buffer pH 1.2 was added in each of the vessels. 5 ml of the filtrate was diluted with water q.s to 25 ml. (Solution a). The dissolution medium pH was adjusted to 2.5 by addition of 2.5625 gm of potassium hydrogen phthalate in each of vessels. The instrument was run for 1 hour. After completion of rotation, 10 ml solution from each of the vessels was taken. The solution was filtered and filtrate was collected. 10 ml buffer pH 2.5 was added in each of the vessels.5 ml filtrate was diluted with q.s. to 25 ml of water. (Solution b).The dissolution medium pH was adjusted to 4.5 by addition of 2 ml 5N potassium hydroxide solution in each of vessels. The instrument was run for one hour. After completion of rotation, 10 ml solution from each of the vessels was taken. The solution was filtered and filtrate was collected. 10 ml buffer pH 4.5 was added in each of the vessels. 5 ml filtrate was diluted with q.s. to 25 ml of water. (Solution c). The instrument was run for another one hour. After completion rotation, 10 ml sample from each of the vessels was taken. The solution was filtered and filtrate was collected. 2 ml of filtrate was diluted with water q.s. to 25 ml. Three 100 ml standard solutions of Iron (0.5 ppm, 1 ppm and 2 ppm were prepared by diluting the reference working standard solution of iron (1000 ppm) in suitable amount of water.

Absorbance reading of the above standard and sample solutions was taken in Atomic Absorption Spectrophotometer using hollow cathode lamp of iron. Dissolution was calculated using the following equation:

$$\text{Dissolution} = \frac{A_s \times P \times D\ F_s}{A_{st}}$$

Where, $A_s$ = absorbance of sample solution, Ast = absorbance of standard solution, P = Potency of standard in ppm, DFs = dilution factor of sample.

***Drug content assay***

***Assay for ferrous sulfate***

10 gm of test sample was ground into fine powder. 150 mg fine powder was taken in a 250 ml volumetric flask. 50 ml water and 25 ml hydrochloric acid were added to it. The volumetric flask was placed on a hot plate and allowed to boil. Then this was cooled for 30 minutes at room temperature. Water added to make the final volume 250 ml. The solution was filtered and filtrate was collected. 1 ml of filtrate was transferred into a 100 ml volumetric flask and diluted with water q.s. to 100 ml. This is the sample solution.

Three 100 ml standard solutions of working standard solutions of iron (0.5 ppm, 1 ppm and 2 ppm) by diluting of reference working standard solution of iron (1000 ppm) in suitable amount of water.

Absorbance reading of the working standard solution was taken in Atomic Absorption Spectrophotometer using hollow cathode lamp of iron. Absorbance of the test sample was recorded. Amount of active present in the pellet is calculated by using the following equation:

$$Q = \frac{A_s \times W_{st} \times DF_s \times 100 \times 3.044}{A_{st} \times DF_{st} \times W_s}$$

Where Q = amount of ferrous sulfate monohydrate per 100 mg pellets, As = absorbance of sample solution, Ast = absorbance of standard solution at known concentration, Ws = amount of sample taken, Wst = amount of standard, DFs = dilution factor of sample solution, DFst = dilution factor of standard solution

***Assay for Zinc Sulfate***

10 gm of sample was ground into fine powder. 150 gm of powder was taken in a 250 ml volumetric flask and 50 ml water, 25 ml of hydrochloric acid and 25 ml nitric acid was added. The flask was placed on hot plate and allowed to boil. Then it was cooled for 30 minutes at room temperature. Water was added q.s. to 250 ml. The solution was filtered and filtrate was collected. 1 ml filtrate was taken in a volumetric flask and diluted with water to 100 ml. 100 ml standard solution of zinc (0.5 ppm, 1 ppm and 2 ppm) was prepared by diluting reference working standard solution of zinc (1000 ppm) in suitable amount of water. Absorbance of standard and test sample was taken in Atomic Absorption Spectrophotometer using hollow cathode lamp of zinc.

***Assay for Ascorbic Acid***

10 gm sample was ground to powder. 430 mg powder was taken in a 100 ml volumetric flask and 60 ml water was added. The volumetric flask was sonicated for 15 minutes. Water was added to make 100 ml solution. The solution was filtered and filtrate was collected. 1 ml of filtrate was taken in 100 ml volumetric flask and diluted with water to 100 ml. This was sample solution. 50 mg of ascorbic acid was dissolved in water in a 100 ml volumetric flask. The volumetric flask was sonicated for 15 minutes. 1 ml solution was diluted to 100 ml with sufficient amount of water. Absorbance of sample and standard solutions was taken at 264 nm in an ultraviolet spectrophotometer using water as a blank.

***Kinetic modeling of drug release***

After completing *in vitro* dissolution of all the batches for eight hours, the data were treated with zero order equation and Higuchi equations (equation 1-2 respectively).

$M_t = M_0 + k_0 t$ .....(1)

$Mt = M_0 - k_H t^{1/2}$ .....(2)

In these equations, $M_t$ is the cumulative amount of drug released at any specified time (t) and $M_0$ is the dose of the drug incorporated in the delivery system. $k_0$ and $k_H$ are rate constants for zero

order and Higuchi model respectively. These models failed to explain drug release mechanism due to swelling (upon hydration) along with gradual erosion of the matrix. Therefore the dissolution data were also fitted to well-known Korsmeyer kinetic equation to ascertain the mechanism of drug release.

$log (M_t/M_\infty) = logk + nlogt$……(3)

Where $M_\infty$ is the amount of drug release after infinite time; k is the release rate constant which considers structural and geometric characteristics of the tablet; and n is the diffusional exponent or release exponent; indicative of the mechanism of drug release. For a tablet having cylindrical shape, when n is below 0.45, the Fickian diffusion phenomenon dominates, and n between 0.45 and 0.89 is an anomalous transport (non-Fickian diffusion), often termed as first-order release. After the n value reaches 0.89 and above, the release can be characterized by case II and super case II transport, which means the drug release rate does not change over time and the release is characterized by zero order. In this case, the drug release is dominated by the erosion and swelling of the polymer. Mean dissolution time (MDT) was calculated from dissolution data according to Mockel and Lippold using the following equation.

$$MDT = \left(\frac{n}{n+1}\right) k^{-\frac{1}{n}}$$

## RESULTS AND DISCUSSION

From the above data, it is observed that concentration of polymer plays important role on the release kinetics of drugs. The desired release of ferrous sulfate from combination pellets in 35% for the 1st hour, 45 to 75% for the 2nd hour, 60 to 85% for the 3rd hour, and not less than 85% for the 4th hour. When Methocel K15M CR is used at a concentration of 5% of the ferrous sulfate pellets, the release was faster than the desired rate. 8% concentration of Methocel K15 M CR controlled the release of ferrous sulfate from pellets more slowly. In this case, the desired release profile was achieved. When Methocel K4M CR was used at a concentration of 15% of the ferrous sulfate pellets, the release was faster than the desired rate. 20% concentration of Methocel K4M CR controlled the release of ferrous sulfate from pellets more slowly.

To investigate the effects of polymer and their content level on drug release four formulations were prepared (Table 1). Formulation F-2 and F-4 fits with Korsmeyer kinetic model ($R^2$ =0.989 and $R^2$=0.976 respectively) (Table 2). The values of release exponent (n) for the above mentioned formulations are 1.095 and 1.124 respectively which indicates case II and super case II transport, i.e. the drug release rate does not change over time and the release is characterized by zero order. In this case, the drug release is dominated by the erosion and swelling of the polymer. F-1 ($R^2$=0.833) and F-3 ($R^2$=0.945) has a value of release exponent (n) is 0.969 and 0.854 which also indicates case II and super case II transport.

## CONCLUSION

Both PVA and acrylic polymers are useful for the preparation of zinc sulfate, ferrous sulfate and ascorbic acid pellets. Due to the different chemical and physical nature of the two polymers the release profiles were not similar. The pellets coated with Kollicoat® SR 30D retarded drug releases more than the Eudragit® NE 30D dispersion. It is possible to modify the release profile of ambroxol pellets by choosing suitable polymers at a suitable level to meet the desired drug concentration.

## REFERENCES

Agyilirah, G., Bullens, Lee, L., Dimemmo, L. and Wheatley, T., 1995. Use of microcrystalline cellulose cores (MCC cores) as substrates for drug layering. Pharm. Res. 12(9), 149, (abstract).

Appelgren, C., 1985. Recent advances in granulation technology and equipment. Drug Dev. Ind. Pharm. 11, 725-741.

Aulton, M.E. and Banks, M., 1981. Fluidised bed granulation - Factors influencing the quality of the product. Int. J. Pharm. Tech. & Prod. Mfr. 2, 24-29.

Bauer, K.H., 1979. Rotor-Einbauten in Wirbelshichten zur Verbesserung Gutbewegung. Pharm. Ind. 41, 973-976.

Bechgaard, H., Christensen, F. N., Davis, F. N., Davis, S. S., Hardy, J. G., Taylor, M. J., Whilley, D. R., Wilson, C. G., 1985. Gastrointestinal transit of pellet systems in ileostomy subjects and the effect of density. J. Pharm. Pharmacol. 37(10), 718-21.

Capes, C. E., 1980. Particle size enlargement. In Handbook of Powder Technology. Vol. I, Williams, J. C. and Allen, T. (Eds.), Elsevier, Amsterdam, pp. 23-31.

Chien W. Y, 1992. Novel Drug Delivery Systems. Marcel Dekker, Inc., New York, vol. 50, p.p. 156-165.

Davies, S. S., Hardy, J. G., Taylor, M. J., Whalley, D.R. and Wilson, C. G., 1984. A comparison study of the gastrointestial transit of a pellet and tablet formulation. Int. J. Pharm. 21, 167-177.

Davies, S. S., Wilson, C. G. and Washington, N., 1987. Gastrointestinal transit of a controlled-release pellet formulation of tiaprofenic acid and the effect of food. Int. J. Pharm. 35, 253-258.

Peppas, N.A. 1985. Analysis of Fickian and non-Fickian drug release from polymers. *Pharm. Acta. Helv*. **60,** 110-111.

Feely, L. C., Khosla, R. and Davis, S, S., 1987. Investigating the gastric emptying of different sizes of non-disintegrating tablets in humans using gamma scintigraphy. J. Pharm. Pharmacol. 39, 31P.

Gajdos, B., 1984. Rotary granulators - Evaluation of process technology for pellet production using factorial design. Drugs Made Ger. 27, 30-36.

Ghali, E. S., Contractor, A. M., Mankad, A. D., O'Connor, R. E. and Schwartz, 1990.A high-speed mixer for continuous wet granulation. Pharm. Tech. April 60-66.

Juslin, L., 1997. Measurement of droplet size distribution and spray angle of pneumatic nozzle, and granule growth kinetics and properties of lactose, glucose and mannitol granules made in a fluidized bed granulator. Doctor's thesis, University of Helsinki.

Kader, A. and Jalil, R., !998. In vitro release of theophylline from poly (lactic acid) sustained-release pellets prepared by direct compression. Drug Dev. Ind. Pharm. 24 (6), 527-534 .

Kapur, P. C. and Fuerstenau, D. W., 1964. Kinetics of green pelletization. Trans. AIME 229, 348-355.

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.

Nakahara, N., 1964. Method and apparatus for making spherical granules, US patent 3 277 520.

Niskanen, M., 1992. Powder layering and coating in a centrifugal granulator: Effect of binder-solution concentration, powder particle size and coating amount on pellets properties. Doctor's Thesis, University of Helsinki.

Vertommen, J. and Kinget, R., 1997. The influence of five selected processing and formulation variables on the particle size, particle size distribution, and friability of pellets produced in a rotary processor. Drug Dev. Ind. Pharm. 23 (1), 39-46