Development and evaluation of omeprazole pellets fabricated by sieving-spheronization and extrusion – spheronization process

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Abstract: Pelletized dosage forms can be prepared by different methods which, in general, are time consuming and labor intensive. The current study was carried out to investigate the feasibility of preparing the spherical pellets of omeprazole by sieving-spheronization. An optimized formulation was also prepared by extrusion-spheronization process to compare the physical parameters between these two methods. The omeprazole pellets were consisted of microcrystalline cellulose, polyvinylpyrrolidone K 30, sodium lauryl sulphate and polyethylene glycol 6000. The omeprazole delay release system was developed by coating the prepared pellets with aqueous dispersion of Kollicoat 30 DP. The moisture content, spheronization speed and residence time found to influence the final properties of omeprazole pellets prepared by extrusion-spheronization and sieving-spheronization. The Mann-Whitney test revealed that both methods produced closely similar characteristics of the pellets in terms of, friability (p=0.553), flowability (p=0.677), hardness (p=0.103) and density (bulk, p=0.514, tapped, p=0.149) except particle size distribution (p=0.004). The percent drug release from the coated formulation prepared by sieving-spheronization and extrusion spheronization was observed to be 84.12 ± 1.10% and 82.67 ± 0.96%, respectively. Dissolution profiles of both formulations were similar as indicated by values of f1 and f2, 1.52 and 89.38, respectively. The coated formulation prepared by sieving-spheronization and commercial reference product, Zimore® also showed similar dissolution profiles (f1=1.22, f2=91.52). The pellets could be prepared using sieving-spheronization. The process is simple, easy, less time- and labor-consuming and economical as compared to extrusion-spheronization process.

Keywords: Omeprazole, pellets, sieving-spheronization extrusion-spheronization.

INTRODUCTION

Pelletilization is an attractive approach to formulate multiparticulate dosage form due to several advantages over single unit dosage forms (Bechgaard and Nielsen, 1978; Hellen *et al*., 1993). Pelletized products offer flexibility in dosage form design and development can be formulated as capsules, tablets and suspensions and with improved drug safety and efficacy (Ghebre-Sellasssie, 1989; Bechard and Leroux, 1992). They are dispersed freely in the gastrointestinal tract, show maximum drug absorption, decreased gastrointestinal irritation and minimum chances of dose dumping (Wilson and Washington, 1989; Tang *et al.,* 2005). Pelletized dosage forms can be formulated by using different methods. Extrusion-spheronization is one of the methods which, in general, is time consuming and labor intensive. The current study was carried out to assess the feasibility of preparing spherical omeprazole pellets by sieving the wet powder mass followed by spheronization. This simple method was compared with extrusion-spheronization process in terms of physical characteristics and *in-vitro* dissolution profile of the developed formulations. Omeprazole is susceptible to heat, moisture, organic solvents and, to some degree, to light. Omeprazole, if exposed to unfavorable environmental conditions, decolorizes which range from light beige to deep purple color. The susceptibility of omeprazole to the environmental conditions poses challenges in designing its stable formulation. The omeprazole is unstable in acidic environment which reduces its oral bioavailability. The enteric coating technology is the most efficient means to protect acid unstable drugs from the attack of gastric fluid and to release drug in the small intestine (Storpirtis and Rodrigues, 1998). The omeprazole pellets are generally coated with organic composition of Eudragit L100-55 and Eudragit L3 D-55. These coatings have been reported to be toxic, costly and require the time consuming process. Thus, in the current study aqueous colloidal dispersion of Eudragit L100 (Kollicoat 30 DP) was used to coat pellets (Li and Jasti, 2006).

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MATERIALS AND METHODS

Materials

Omeprazole and magnesium stearate were purchased from Chemi Pharm (India) and lactose monohydrate from HMS, (Holland). Microcrystalline cellulose (Avicel® PH 101) was obtained from FMC Corporation (USA) and polyvinylpyrrolidone, K30 from BASF (USA). Polyethyleneglycol (PEG, 400, 2000, 4000, and 6000), talc and propylene glycol were purchased from Merck (Germany). Sodium lauryl sulphate, sodium starch glycolate, disodium hydrogen orthophosphate and dipotassium hydrogen phosphate were obtained from

Euro Chemo Pharm (Malaysia). Glycerol and mannitol were purchased from Fisher Scientific (USA). Kollidone® CL was obtained from BASF, (USA). Eudragit® L100, 30% neutral copolymer (Kollicoat® MAE 30 DP methacrylic acid/ethyl acrolate dispersion) was purchased from BASF (Baden Aniline and Soda Factor) Ludwigshafen (Germany), magnesium stearate from Ackros Chemicals (India) and Zimor® 20 mg capsule manufactured by Rubio (Barcelona-Spain) was purchased from local market in Malaysia. All the raw materials were of British pharmacopoeia grade and used as received.

Pelletization by sieving-spheronization

Several pellet formulations of omeprazole (F1 to F21) were prepared using various excipients and formulation conditions shown in table 1 employing the sieving-spheronization method. For each formulation, 150 grams of the wet mass was prepared which contained a fixed amount (20 g) of omeprazole, varied amounts of excipients and granulating liquid (water + phosphate buffer, pH 8) according to table 1 until spherical pellets with the required release rate were achieved. In all formulations microcrystalline cellulose (MCC), lactose and the other excipients were mixed in a granulator (Kenwood, UK) at 140 rpm for 10 minutes, sieved through 0.8 mm sieve (Endicott, England) and added Polyvinypyrrolidone (PVP K30) as binder. Mixing was continued for another 10 minutes to form a wet mass of suitable consistency. The required amounts of different grades of polyethylene glycol (PEG) for different formulations and omeprazole were dissolved separately in small amount of water. The omeprazole solution was immediately neutralized with phosphate buffer, pH 8 prior to adding in the wet mass. The wet mass was then sieved using 1.25 mm sieve to obtain extrudates. The extrudates were spheronized (Caleva Model 380, UK) at speed 1000 rpm for 10 min, the optimum speed and residence time, respectively previously obtained from pilot experimentation. The amount of granulating liquid was changed according to the requirement of the formulation. The resultant pellets were dried in a fluidized bed dryer at 30°C until the loss on drying, was less than 2.5 wt %.

Pelletization by extrusion-spheronization

A formulation with yield greater than 80%, maximum particle size within 0.8-1.25 mm and the release rate of above 80% at pH 6.8 within 45 min was selected for pelletization by extrusion-spheronization process. Based upon the above desired criteria, a formulation labeled as $F21_{E-S}$ was prepared by extrusion-spheronization using the same excipients, spheronization speed and the residence time, but with slightly lesser quantity of water as granulation liquid employed for preparation of $F21_{S-S}$ (table 2). To formulate $F21_{E-S}$, a wet mass was prepared as stated under the sieving-spheronization method and was extruded using a rotary gear extruder (Caleva Model 40, UK) with a cylindrical die of 14 cm length and perforations of 1 mm diameter. The extrudates were then spheronized in a spheronizer (Caleva Model 380, UK) at 1000 rpm with 10 min residence time. The resultant pellets were dried and sieved in the same way as mentioned above for sieving-spheronization process.

Coating of pellets

One hindered fifty gram of the each selected formulations $F21_{S-S}$ and $F21_{E-S}$ were coated separately using different coating dispersions (table 3). Three coating dispersions were prepared using different compositions (table 3). Propylene glycol was dissolved in distilled water prior to the addition of talc and Kollicoat30 DP and mixed using a magnetic stirrer for 15 min.

Batches of 150 grams of omeprazole formulations, $F21_{S-S}$ (prepared by sieving-spheronization) and $F21_{E-S}$ (prepared by extrusion-spheronization) were coated separately using the bottom spray fluidized bed coater (Aromatic–Fielder AG, Switzerland) fitted with a cylindrical partition tube (Wurster insert, diameter =47mm, height =180 mm). Prior to the use of coating dispersion, magnesium stearate (2% w/v) sub coat, prepared by dissolving magnesium stearate 2g in 100 ml water and stirred for 1 hour was applied.

The 150 ml coating dispersion while stirred throughout the coating process was sprayed via two-fluid spray nozzle using a peristaltic pump (Rota Consulta, Model 1B, 100S-R/65, Germany) at pre-selected conditions given in table 4. The omeprazole pellets were coated at three different coating thicknesses corresponding to 13%, 15% and 17.5% of theoretical weight gained by the pellets. The coating level was the quotient of the weights of polymer and uncoated pellets. The coated pellets were dried by further fluidizing them for an additional 15 minutes. The curing time is also crucial to complete the film formation (Young and Ghebre-Sellassie, 1990). The pellets were cured at 40ºC for 15 minutes after magnesium stearate coating and for 2 hours at the same temperature after the coating with Kollicoat 30 DP.

Characterization of pellets

All the formulations F1 to F21 shown in table 1, selected optimized formulations $F21_{S-S}$, $F21_{E-S}$ and the coated formulations of $F21_{S-S}$, $F21_{E-S}$ were evaluated for percent yield, particle size, size distribution and drug release at 45 min. Based upon the characterizations, $F21_{S-S}$ was selected due to the desired properties, yield greater than 80%, 70% pellets within range of 0.08-1.25mm and above 80% drug release within 45 minutes. The coated and un-coated formulations of $F21_{S-S}$, $F21_{E-S}$ were characterized as above and additionally for friability, flowability, densities, hardness, roundness, release kinetics analysis, and time for 75% drug release ($T_{75\%}$), respectively.

Percentage yield of pellets

The percentage yield of omeprazole pellets was determined mathematically using the Equation 1 (Khan *et al*., 2010; Shavi *et al*, 2009).

$$\text{Yield \%} = \frac{\text{Weight of pellets}}{\text{Weight of powder ingredients fed initially}} \times 100 \quad (1)$$

Pellet size analysis

Sieves with aperture sizes of 0.40, 0.63, 0.80, 1.25, 1.70 and 2.00 mm diameters were used for the size analysis of the dried pellets. One hundred grams of pellets were taken and the sieves were vibrated mechanically (Retsch AS200 analytical sieve shaker, Germany) at amplitude of 1.00 mm for 10 minutes. The weight of pellets retained on each sieve was recorded. The geometric weight mean diameter (d_{gw}) and geometric standard deviation (S_g) were calculated using Equations 2 and 3, respectively to characterize pellet size and size distribution, respectively (Schaefer and Worts, 1977).

$$d_{gw} = \log^{-1} \frac{\sum(w_i \log d_i)}{\sum w_i} \quad (2)$$

$$S_g = \log^{-1} \left[\frac{\sum w_i (\log d_i - \log d_{gw})^2}{\sum w_i} \right]^{0.5} \quad (3)$$

Where d_i is the mean diameter of sieve fraction number i and W_i is the weight of sieve fraction number i.

Friability

The 5 g of pellets were rotated at 25 rpm in a friabilator (Model TA3 R, Eureka, Germany) for 4 minutes, sieved through a sieve of aperture size 6.3 mm and weighed the pellets retained on the sieve. The percentage of difference in weight before and after the test provided a measure for friability (Dreua *et al.,* 2005) and was calculated using the Equation 4 (Rasool *et al*., 2012).

$$\text{Friability\%} = \frac{\text{Initial weight - Final weight}}{\text{Initial weight}} \times 100 \quad (4)$$

The experiment was repeated six times for each batch.

Flowability assessment

For flow rate, poured 100 g of pellets into a glass tube (70.0 cm in length and 4.5 cm in diameter) fitted with an orifice of 8 mm in diameter at the bottom of the tube. The pellets were allowed to flow out from the tube through the orifice into a beaker. After pellets flow for 5 seconds when the flow was considered at steady state, the pellets were collected for 10 seconds and the weight was determined. The experiment was carried out six times for each batch. The flow rate was calculated using the Equation 5 (Shah *et al*., 2012; Harun *et al.,* 2001).

$$\text{Flow rate (g/s)} = \frac{\text{Weight of pellets collected in 10s}}{\text{10s}} \quad (5)$$

To calculate the angle of repose the pellets were poured carefully through the funnel until the apex of the conical pile just touched the tip of the funnel and the angle was calculated using the relationship in equation 6.

$$Tan\text{Ø} = H/R \quad (6)$$

Where Ø is the angle of repose, R is the radius of the base of cone and H is the distance between the tip of the funnel and the base (Khan *et al*., 2011; Umprayn *et al.,* 1999).

For assessment of Carr's index, bulk and tapped densities were required. For bulk density, 50 grams of pellets were poured into a 100 ml graduated glass cylinder kept at an angle of 45° to the horizontal. The cylinder was straightened up and the volume occupied by the pellets was read to the nearest 1 ml (Harun *et al*., 2001). To calculate the tapped density, 50 gram of pellets was poured into a 100 ml graduated glass cylinder kept at an angle of 45° to the horizontal. The cylinder was straightened up and tapped 200 times by dropping at constant rate from a height of 2 cm and the volume occupied by the pellets was noted. The bulk and tapped density of pellets was measured six times for each batch using the Equation 7 (Murtaza *et al*., 2010; Varshosas *et al*., 1997; Umprayn *et al*., 1999).

$$\text{Density (g/ml)} = \frac{\text{Weight of pellets}}{\text{Volume occupied by pellets}} \quad (7)$$

Carr index greater than 25 is considered to be an indication of poor flowability and below 15% good flowability (Bouffard *et al.,* 2007; Shah *et al.,* 2008). This parameter was calculated by using Equation 8 (Aamir *et al*., 2011).

$$\text{Carr's Index} = \frac{P_p - P_b}{P_p} \quad (8)$$

Where P_b is the bulk density and P_p is the tapped density.

Hardness test

The hardness of 10 pellets from each batch was determined by using a texture analyzer (Schmidt and Kleinebudde, 1999; Steckle and Mindermann, 2004). A stainless steel cylindrical probe of 5 mm diameter was used to rupture the pellets. The ambient temperature and humidity were also noted. The temperature was 25±2°C and the relative humidity (RH) was 65±5% (Hassan *et al*., 2013). The data was analyzed using Texture Expert™ software using the instrumental settings given in table 5.

Estimation of roundness

The roundness of 20 pellets was assessed for the selected un-coated and coated pellets formulations prepared by sieving-speronization and extrusion-speronization using microscope (Meiji, Japan). The microscope was fitted with a standard graticules (Graticules Ltd, England, validated according to BS2625). The calibration distance of the graticule was verified using a stage micrometer diameter. The length (long diameter) and width (short diameter) of the pellets were used to calculate the elongation ratio by the following equation:

$$\text{Elongation ratio} = \frac{\text{Short diameter}}{\text{Long diameter}} \quad (9)$$

The pellets with elongation ratio near to one were considered round (Baert and Remon, 1993).

Morphology

The surface and cross section view of the pellets were taken using scanning electron microscope (SEM) (Leica Cambridge S- 360, UK). The pellets were mounted onto stubs using double-sided adhesive tape. The mounted samples were sputter coated with gold under argon atmosphere (Emitech K750, Kent, UK) for SEM (Baseer *et al*., 2013).

In- vitro release study

The *in-vitro* drug release of uncoated pellets was determined using basket method of USP 26 dissolution test apparatus 1 (Distek premiere, 5100, Dissolution test apparatus, USA) in 1000 ml phosphate buffer, pH 6.8 maintained at 37.0°C±2.0. One gram of uncoated pellets was taken in baskets which were rotated at 100 rpm. Samples of 5 ml were collected at 10, 20, 30 and 45, minutes, using autosampler and replaced with 5 ml of fresh dissolution medium.

The coated formulations were tested first in acidic dissolution media, pH 1 prepared by 0.01 N HCl for 120 min (2 hr) and then in phosphate buffer, pH 6.8 for 90 min (1.5 hr). Samples (5 ml) at 10, 20, 30, 45, 60 and 120 min for pH 1 and 130, 140, 150, 160, 170,180, 190, 200, and 210 min were taken for quantification of release in phosphate buffer, pH 6.8. The amount of drug released was quantified in each sample after suitable dilution using a UV/VIS spectrophotometer (U-2000, Hitachi, Japan) at a detection wavelength of 300 nm. For each batch of product, six determinations were carried out.

Release kinetics analysis and computation of time for 75% drug release

The kinetics of coated omeprazole pellets formulations, $F21_{S\text{-}S}$ $F21_{E\text{-}S}$ and Zimor® capsule were determined by finding the best fit of the dissolution data to the following models.

$$Q = Q_o - K_o \quad (10)$$

Where Q is the amount of drug released at time t, Q_o is the amount of drug in the solution at time t = 0 (Q_o =0), and K_0 is the zero order release rate constant.

$$LnQ = LnQ_o - K_1 t \quad (11)$$

Where K_1 is the first order release rate constant, Q_o is the initial amount of drug.

$$Q = K_H t^{1/2} \quad (12)$$

Where Q is the amount of drug release at time t and K_H is the Higuchi rate constant which represents the diffusion rate constant (Shahzad *et al.,* 2013).

The time for 75% release ($T_{75\%}$) was computed by forecast function in Microsoft Excel® with two values of percent release at corresponding time points for coated $F21_{S\text{-}S}$ and $F21_{E\text{-}S}$. The computed values of $T_{75\%}$ were compared for the pairs of $F21_{S\text{-}S}$ versus $F21_{E\text{-}S}$ and that of $F21_{S\text{-}S}$ versus a reference formulation, Zimor® capsule.

Similarity factors for drug dissolution profiles

The similarity of release profiles between the pairs of coated $F21_{S\text{-}S}$ & $F21_{E\text{-}S}$ and $F21_{S\text{-}S}$ & Zimor® capsule (Reference) were assessed with dissimilarity factor f1 and similarity factor f2 as shown in equations 13 and 14.

$$f1 = \frac{\Sigma[R_t - T_t]}{\Sigma R_t} \quad (13)$$

$$f2 = 50 \log\left[\frac{1}{\sqrt{1+\frac{1}{n}[\Sigma(R_t - T_t)^2}} \times 100\right] \quad (14)$$

Where R_t and T_t are the percentages of drugs dissolved at each time point for the reference and test preparations respectively; n is the number of time points considered.

Statistical data analysis

The data are given as mean ± SD. The statistical analysis was carried out employing SPSS (Version14 USA) to compare the characteristics of omeprazole uncoated and coated pellets prepared either by sieving-spheronization or extrusion-spheronization method using Mann Whitney test. The difference was considered statistically significant at $p<0.05$.

RESULTS

Several formulations from F1 to F20 (table 6) were prepared with sieving-spheronization to find the best formulation based on the pellets yield >80%, maximum pellets within size range 0.8-1.25 mm, roundness within range and release >80% within 45 min at pH 6.8. The findings for the physical characterization for the formulations prepared by sieving-spheronization, $F1_{S\text{-}S}$ to $F20_{S\text{-}S}$ are shown in table 6.

In formulation F1, the extrudates after sieving could not be spheronized appropriately and resulted in the lower yield, 40.8%. In formulation F2, the percentage yield was higher, 68.2%. Pellets yield was improved with the addition of polyvinylpyrrolidone K 30 (PVP), but the resulting pellets exhibited wider particle size range. With increasing PVP K30 from 0.5 to 1 % and addition of 0.5 % of polyethylene glycol 400 (PEG) ($F3_{S\text{-}S}$), the yield was increased up to 89.5 %, might be due to the PEG's spheronization enhancing properties and PVP's binding characteristics.

A lower yield of 78.31% was observed in formulation F5, might be attributed to an increased stickiness of the wet mass observed might be due to the higher content of

sodium starch glycolate. With increasing Kollidone® (CL) up to 10% (F8), the percentage yield was 80.53 % as compared to 87.81 ± 0.79% and 88.85 ± 1.75 % for F6 and F7 containing, respectively 2% and 5%, Kollidone® (CL). A lower yield in F8 as compared to F6 and F7 might be due to the high amount of disintegrant. Formulation F9 exhibited the highest yield of 91.18 % due to 1% sodium lauryl sulfate, which might also acted as spheronizing enhancer besides its surfactant properties.

The spheronization speed, residence time and the amount of granulating liquid played a major role on the rheological behavior of the wet mass. Spheronization speed of 1000 rpm and residence time of 10 minutes were optimized based on a pilot study. By increasing the amount of granulating liquid the wet powder mass was too tacky to be processed and hence, resulted in a reduction of the percentage yield.

The most of the formulations (F3, F4, F6, F7 and F9 to F18) showed 78 to 84% of pellets within the desired size range of 0.80 to 1.25 mm. The % of pellets with the above size range for formulations F19 and F20 was observed to be 73.88% and 72.36%, respectively which was below the accepted range and might be due to decrease in the amount of MCC.

Due to lesser yield, lower particle size within desire size range, the formulations F1 and F2 were not further studied for roundness and drug release. The geometric mean and geometric standard deviation from formulation F3 to F20 was not affected by the composition (table 7).

Drug release study of pellets formulations F3 to F20

Drug release study was carried out in phosphate buffer, pH 6.8 to find out the best formulation based on the release rate above 80%. The release data of formulations (F3-F20) are illustrated in table 6 and release profiles in fig. 1. With changing the composition of the formulation, the drug release within 45 min was increased from 28.80 ± 1.30% in formulation F3 to 74.34 ± 0.98% in formulation F20.

DISCUSSION

Characterization of pellets formulations F1 to F20

Several formulations from F1 to F20 (table 6) were prepared with sieving-spheronization. The omeprazole pellet formulation F1 with MCC, lactose, and water, as moistening liquid was not spherical, showed wider particle size distribution and lower yield (18%) within 0.8-1.25 mm particle size. A lower yield might be attributed to the absence of binder in F1. The color of the pellets was noted to be changed from off-white to light purple after spheronization. In formulation F2 polyvinylpyrrollidone K30 (PVP K30) was added as 0.5% by weight of the formulation. Being a binder, PVP K30 imparted sufficient mechanical strength to the pellets (Shivakumar *et al.,* 2006). However, the wet mass could not be spheronized properly and the resultant pellets were not spherical and were with lower yield of 39.25% for the required pellets size. This might be due to the less amount of PVP K30 added in the formulation. Similar observation was reported by Tomer *et al.* (2001).

Sodium lauryl sulfate, besides the surface active properties possibly, also acted as a good spheronization enhancer (Tomer *et al.,* 2001). With lower MCC and increasing lactose with a slight increase in the quantity of sodium lauryl sulfate (0.2%), the drug release could be enhanced in phosphate buffer, pH 6.8. In formulation F19 the amount of MCC was further decreased to 26%, sodium lauryl sulfate was increased to 0.28% and the quantity of PVP K30 to 2% in order to increase the binding properties of wet mass during spheronization process. The F19 presented increased release of drug to 64.34%.

In formulation F20, MCC was further decreased to 20% and the release rate from this omeprazole pellet formulation was noted to be 74.25% within 45 minutes (fig. 1).

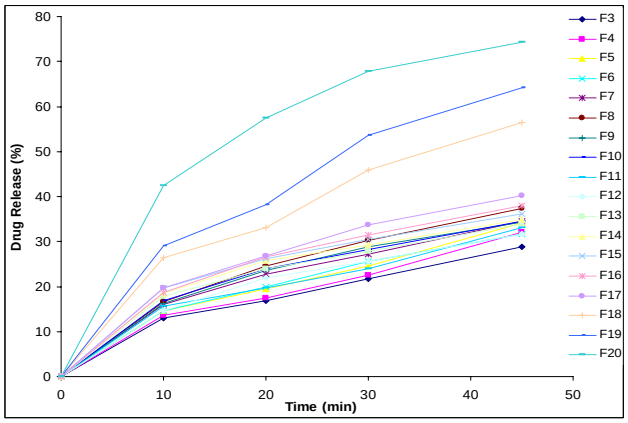


Fig. 1: Percent release of omeprazole from different pellets formulations prepared by sieving-speronization process

Characterization of optimized formulations F21$_{S\text{-}S}$ and F21$_{E\text{-}S}$

By adjusting the composition of different formulations (table 1), an optimized composition was achieved and is given in table 2. A formulation F21$_{S\text{-}S}$ met the criteria of yield greater than 80%, maximum particle size within 0.80 and 1.25 mm and release rate greater than 80% in phosphate buffer, pH 6.8 within 45 min. A formulation, F21$_{E\text{-}S}$ was prepared using extrusion speronization-with the same composition employed for F21$_{S\text{-}S}$ i.e., 16% MCC, 2.5% PVP K30, 0.39% sodium lauryl sulfate and PEG 6000, 2.6%. The Formulations F21$_{S\text{-}S}$ and F21$_{E\text{-}S}$ were selected for further studies such as coating and release kinetic analysis besides the other necessary characterization.

Two methods, sieving-spheronization and extrusion-spheronization were compared for the physical properties of selected formulations using the Mann-Whitney test at $p \leq 0.05$. As shown in table 7 statistically significant difference was noted between the uncoated pellets produced by sieving-spheronization and extrusion-spheronization in terms of total amount of pellets yielded (80.34±0.89% vs 78.80±0.49 %, p=0.004). This was due to sticking of a wet mass inside the extruder rollers and die during extrusion process.

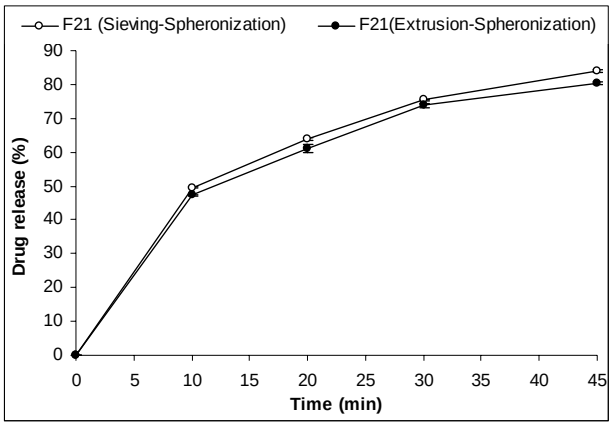


Fig. 2: Release of omeprazole at pH 6.8 from pellets $F21_{S\text{-}S}$ (prepared by sieving-spheronization) and $F21_{E\text{-}S}$ (prepared by extrusion-spheronization). Mean.±SD, N=6.

The value of angle of repose (30.45±0.062 vs 29.72±0.025, p=0.006) and Carr's Index (11.07±0.092 vs 12.23±0.11, p=0.01) differed significantly in extrusion-spheronization process as compared to the sieving-spheronization. This might be due to smooth and fine pellets obtained from a high force of compression during extrusion process which increased the flowability of pellets. However, formulation prepared by two methods exhibited a good flowability as indicated by Carr's index below 15 and angle of repose less than 30°. No statistically significant difference was observed between the two methods for the rest of the physical characteristics (table 7). The roundness of pellets is important for flowability and the uniform coating. The incorporation of sodium lauryl sulfate and PEG 6000 in this study enhanced the combined characteristics of cohesiveness, firmness and plasticity of the prepared mass and played role to maintain the sphericity of the pellets. No significant difference was noted for the roundness of the pellets prepared by any method (p>0.155). These above findings suggested that the sieving-spheronization method is equally good for pelletization process for the model drug.

The release rate of $F21_{S\text{-}S}$ was 84.12 % within 45 minutes at pH 6.8 (table 7). The $F21_{S\text{-}S}$ contained 2.6% PEG 6000, a hydrophilic carrier exhibited higher dissolution rate due to the dissolution enhancing properties of the PEG. Increased dissolution with the use of sodium lauryl sulfate in *in-vitro* dissolution media of water-insoluble drug has already been reported (Crisen *et al.,* 1997; Wong *et al.,* 2006; Prajapati *et al.,* 2007).

Among three levels of coating, the coating level of 17.5% produced the appropriate pellets in terms of drug release. The table 8 shows the comparative physical characters of the omeprazole coated pellets prepared by sieving-spheronization ($F21_{S\text{-}S}$) and extrusion-spheronization ($F21_{E\text{-}S}$). The percentage of particle in size range (0.80-1.25mm) of pellets formulated through sieving-spheronization and extrusion-spheronization after coating was 79.75% and 81.34%, respectively which was different significantly (p=0.004). This difference in particle size range might be due to a smooth and even coating on pellets prepared by extrusion-spheronization which led them more spherical. The geometric weight mean diameter of the pellets formulated by sieving-spheronization and extrusion-spheronization were 1.06 mm and 1.05mm, respectively (p> 0.05).

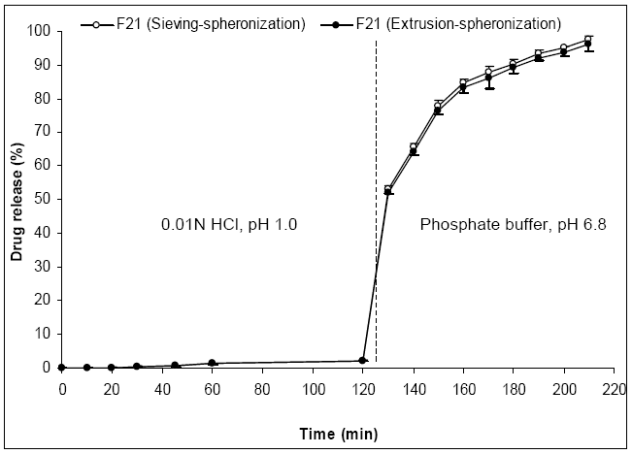


Fig. 3: Release of omeprazole in 0.01 N HCl, pH 1 and phosphate buffer, H 6.8 from coated pellets $F21_{S\text{-}S}$ (prepared by sieving-spheronization) and $F21_{E\text{-}S}$ (prepared by extrusion-spheronization). Mean.±SD, N=6.

The friability of the coated omeprazole pellets prepared by sieving-spheronization (0.17%) was higher, though within specifications and non-significant than that of the pellets prepared by extrusion-spheronization (0.15%). Coating with Kollicoat 30 DP improved the friability as indicated by lower values than that of the uncoated pellets. According to Hellen *et al.* (1993), pellets with friability value lower than 1.7 % are considered mechanically acceptable. Thus, the pellets prepared by two methods possessed good mechanical properties.

The assessment of density of pellets is necessary for the technological purposes for determination of the fill weight which is critical for filling into the fixed volume dosage form such as hard shell capsules. The values of bulk and

tapped densities of the coated pellets prepared by sieving-spheronization and extrusion-spheronization process were slightly higher in coated pellets as compared to that of the uncoated pellets prepared by both methods and higher in coated pellets prepared by sieving-spheronization.

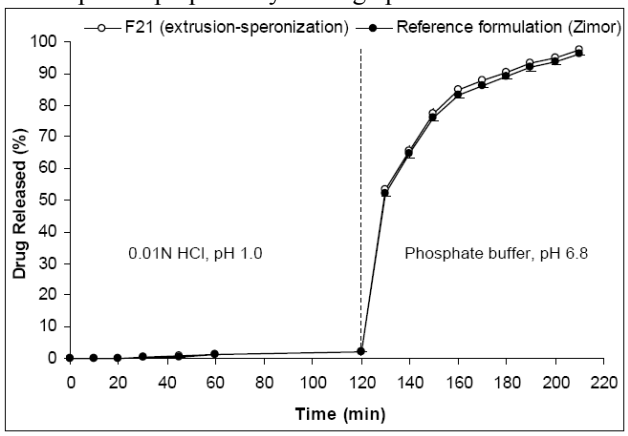


Fig. 4: Release of omeprazole in 0.01 N HCl, pH 1 and phosphate buffer, pH 6.8 from coated pellets $F21_{S\text{-}S}$ (prepared by sieving-spheronization) and the Reference formulation (Zimor®). Mean±SD, N=6.

Though the angle of repose of the coated pellets $F21_{E\text{-}S}$ was different (p=0.008) as compared to coated $F21_{S\text{-}S}$, the flow rate of the coated pellets was similar (p=0.677) for both formulations prepared by two methods due to the reason given before. The Carr's index for the both formulations was below 15, indicating good flow. This finding is suggestive of a little role of the bulk and tapped density of pellets in determining the pellet flowability which was in line with the findings of Ganderton (1968). The particle size, particle shape, roughness of the particle surface, chemical nature of the excipients and moisture content have been reported to affect the pellets flowability (Carstensen, 1980; Amidon and Houghton, 1995) which was in parallel to the present findings.

Lower hardness was expected in the coated pellets prepared by sieving-spheronization as compared to that prepared by extrusion-spheronization due to a low magnitude of compaction and cohesive strength to bind the particles closely during sieving-spheronization process. However, as shown in table 8, the difference between the hardness of pellets prepared by both methods was not significant (p=0.103). The uncoated pellets demonstrated tendency to break into small fragments while the coated pellets showed breakage without fragmentation.

Film coating is effectively used to modify the release of active ingredients from pellets. The aqueous colloidal dispersion is used extensively to coat the solid dosage forms (Tang *et al.,* 2005). The advantages of such dispersions are the avoidance of the use of toxic organic solvents, pellets without agglomeration during coating process and achieving the efficient and predictable drug release. The mechanism of film formation from aqueous dispersion is complex. The aqueous dispersion is sprayed onto the solid particles with a suitable equipment and as water evaporates; colloidal particles of coating dispersion are forced to come together to form a film. Plasticizers are added to the aqueous dispersions to improve the film forming characteristics and to achieve a film with desired permeability and drug release.

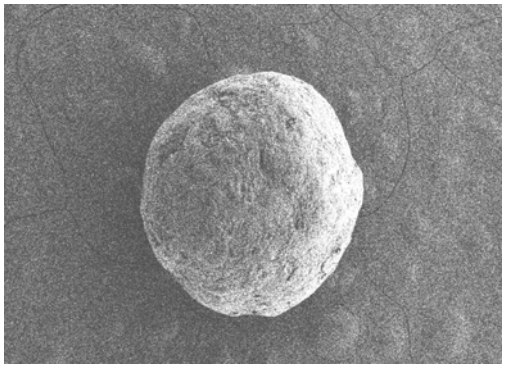
The pellet formulation $F21_{S\text{-}S}$ was found to be slightly less round as compared to that of the $F21_{E\text{-}S.}$ In this study, the spherical pellets were obtained with lesser quantity of MCC in formulation $F21_{S\text{-}S}$ and $F21_{E\text{-}S}$ which was in line with the findings of Fekete *et al.,* (1998) but contrarily to the Holm *et al.,* (1996) who report that increasing MCC content improves the pellet sphericity. Nevertheless, these contradictory experimental findings showed that the MCC contents may influence the properties of a formulation.

The incorporation of sodium lauryl sulfate and PEG (6000) in this study did not alter remarkably, the cohesiveness, firmness and plasticity of the desired mass but influenced the sphericity of pellets. The spheronizer friction plate is also responsible for providing the smoothing stage that creates the spherical pellets by generating rotational motion of each granule about its axes in constantly changing planes (O, Connor and Schwartz, 1989). Roundness of both pellet formulations was further improved after coating. No significant difference was observed between the roundness of the pellets prepared by the two methods (p=0.394).

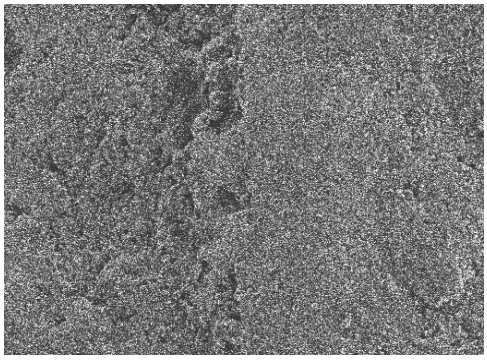
The sphericity of the pellets was further supported by the SEM micrographs (Plate 1). Both formulations of the pellets were appeared to be spherical discrete units. The surface of pellets prepared by extrusion-spheroniztion was slightly smooth as compared to that prepared by sieving-spheronization.

In -vitro drug release from selected uncoated and coated formulations, $F21_{S\text{-}S}$ and $F21_{E\text{-}S}$

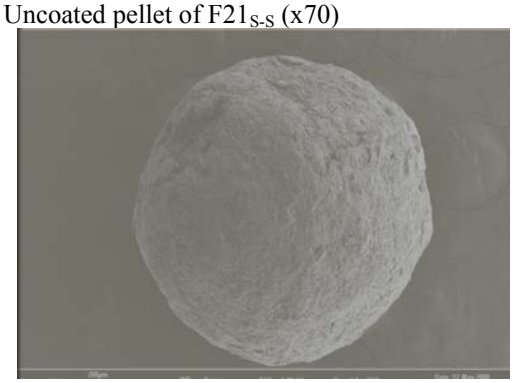
In the current study the sieving-spheronization and extrusion-spheronization were found to be successful to formulate omeprazole pellets with high percent yield and narrow particle size distribution. However, it was challenging to achieve the required release rate greater than 80% within 45 minutes at pH 6.8 (US Pharmacopoeia, 1999). For this purpose different processing aids such as surfactants, spheronization enhancers, plasticizers, fillers and disintegrants were used in the present study. The required release of omeprazole from pellet formulations $F21_{S\text{-}S}$ and $F21_{E\text{-}S}$ was achieved by lower MCC, higher amount of lactose and addition of PEG 6000 and sodium lauryl sulfate. Polyethylene glycol 6000, a carrier enhanced the dissolution rate of the drug due to its hydrophilic nature and dissolution enhancing



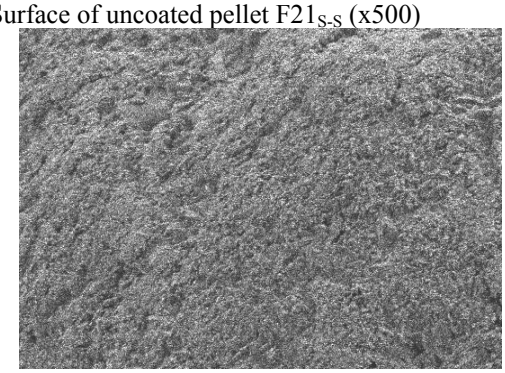
(A) Uncoated pellet of $F21_{S-S}$ (x70)



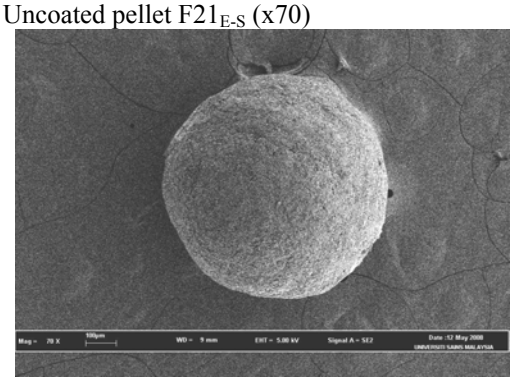
(B) Surface of uncoated pellet $F21_{S-S}$ (x500)



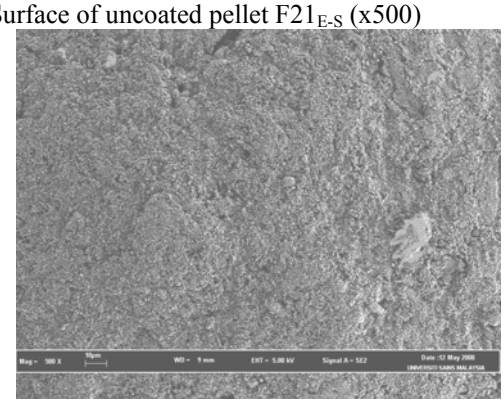
(C) Uncoated pellet $F21_{E-S}$ (x70)



(D) Surface of uncoated pellet $F21_{E-S}$ (x500)



(E) Coated pellets at 17.5% coating level 70x



(F) Surface of coated pellets at 17.5% coating pellet 500x

Plate 1: Scanning electron micrographs of uncoated pellets formulation $F21_{S-S}$ prepared by sieving-shperonization (A and B), pellet formulation $F21_{E-S}$ prepared by extrusion-spheronization (C and D) and coated pellets formulation prepared by sieving-spheronixation (E and F)

properties. Similar observation was reported by Prajapati *et al,* (2007). The addition of sodium lauryl sulfate also enhanced the dissolution of omeprazole (fig. 2). Recent literature cites an increased dissolution of water insoluble drugs with the use of surfactant, sodium lauryl sulfate in dissolution media (Crisen *et al.,* 1997; Wong *et al.,* 2006; Prajapati *et al.,* 2007).

The percent release data of the coated pellet formulation and the reference formulation are presented in tables 9 and 10. The fig. 3 shows the omeprazole release profiles from coated formulations prepared by sieving-spheronization ($F21_{S-S}$) and by extrusion-spheronization ($F21_{E-S}$). Prior to coating the pellets with Kollicoat 30 DP, a subcoat of magnesium stearate was applied to protect the drug from moisture absorption. The total weight gained with subcoat (magnesium stearate) for 150 grams pellets was 3%. The application of subcoat to a solid dosage form of an enteric film coating has also been reported in the literature (Lovgren *et al*., 1988; Felton *et al*., 1995; Dangel *et al.,* 2000 and Crotts *et al.,* 2001). The rate of drug released from coated formulation prepared by sieving-spheronization ($F21_{S-S}$) and that of the reference formulation (Zimor®) was similar (fig. 4).

Kollicoat 30 DP dispersion was applied at three different coating levels. The pellets prepared by sieving-spheronization process at coating levels of 13%, 15% and

Table 1: Formulation ingredients and different conditions for preparation of omeprazole pellets

Formu-lation Code	MCC g	Lactose g	PVP (K30) g	Sodium starch glycolate g	Glycerol g	Sodium lauryl sulphate g	Kollidone (CL) G	Polyethylene glycol G (grade)	Mannitol g	Water ml	Phosphate buffer, pH-8 ml
F1	100	30	_	–	–	–	–	–	_	102	_
F2	89.25	40	0.75	_	_	_	_	_	_	50	46
F3	89	38.75	1.5	_	–	_	_	0.75 (400)	_	50	45
F4	89	35.75	1.5	3	_	_	_	0.75 (400)	_	50	44
F5	89	32.75	1.5	6	–	–	–	0.75 (400)	–	50	42
F6	89	35.75	1.5	–	–	–	3	0.75 (400)	–	50	44
F7	89	31.25	1.5	_	_	_	7.5	0.75 (400)	_	50	46
F8	89	23.75	1.5	_	_	_	15	0.75 (400)	_	50	44
F9	89	37.25	1.5	_	_	1.5	_	0.75 (400)	_	50	48
F10	89	37.34	1.5	_	1.5	_	_	0.75 (400)	_	50	47
11	60	52.75	1.5	_	_	_	_	0.75 (400)	15	38	32
F12	76	51.25	1.5	_	_	_	_	1.5 (2000)	_	50	47
F13	751	50.50	1.5	_	_	_	_	3 (2000)	_	50	46
F14	77	50	1.5	_	_	_	_	1.5 (4000)	_	50	47
F15	75	50.50	1.5	_	_	_	_	3 (4000)	_	50	46
F16	76	51	1.5	_	_	_	_	1.5 (6000)	_	50	46
F17	74 (60%)	50.08	1.5	_	_	_	_	3 (6000)	_	50	46
F18	60 (40%)	65.30	1.5	_	_	0.2	_	3 (6000)	_	34	30
F19	40 (26.66)	84.10	3	_	_	0.4	_	3 (6000)	_	27	23
F20	30 (20%)	93.58	3.03	_	_	0.4	_	3 (6000)	_	26	22
F21	24 (16%)	97.75	3.75	_	_	0.6	_	3.90 (6000)	_	21	17

17.5% of Kollicoat 30 DP, released 16.21%, 11.56% and 2.18%, respectively at pH 1 after two hours. At the same coating levels the pellets prepared by extrusion-spheronization process exhibited release of 16.14, 11.60 and 2.16%. Thus, the coated pellets prepared by either method ($F21_{S\text{-}S}$ and $F21_{E\text{-}S}$) with coating level of 17.5 % of Kollicoat 30 DP exhibited the drug release less than 10 % at acidic pH within two hours which was 82 to 84 % at pH 6.8 within 45 minutes. The thicker the coat, the longer would be the diffusional path length during passage of molecules across the coat and thus, delaying the drug release. A similar inverse relationship between the thickness of polymer coat and the rate of drug release has been reported (Ghebre-Sellassie *et al.,* 1985; Li *et al*., 1991; Schultz and Kleinebudde, 1997).

Release kinetics T75% of selected coated and uncoated pellet formulation $F21_{S\text{-}S}$ and $F_{E\text{-}S}$

The release kinetics for the coated pellets formulated by sieving-spheronization and extrusion-spheronization was tested for the zero order, first order and Higuchi models. The best linear coefficient was obtained for first order kinetics showing a higher value of R^2>0.987 and >0.9913, respectively for the coated pellets prepared by sieving-spheronization and that formulated through extrusion-spheronization than the rest of the kinetic models. Both release data of the reference and the coated formulation prepared by sieving-spheronization ($F21_{S\text{-}S}$) were fitted to first order kinetic model (R^2>0.987 and >0.9916, respectively) indicating dependency of the release rate on the drug concentration in the above formulations.

Table 2: Composition of the optimized omeprazole pellet formulations, $F21_{S\text{-}S}$ and $F21_{E\text{-}S}$

Ingredients (Grams)	Formulation	
	$F21_{S\text{-}S}$	$F21_{E\text{-}S}$
Omeprazole (g)	20.00	20.00
Microcrystalline cellulose (g)	24.00	24.00
Lactose (g)	97.75	97.75
Polyvinylpyrrolidone (K30) (g)	3.75	3.75
Polyethylene glycol-6000 (g)	3.90	3.90
Sodium lauryl sulfate (g)	0.6	0.6
Distilled water (ml)	21.0	20.0
Phosphate buffer-pH 8 (ml)	17.0	17.0

The values of $t_{50\%}$ could not be calculated since the release of omeprazole pellets was greater than 50% within the first 10 minutes in basic media. Thus, $T_{75\%}$ was calculated for the coated pellet formulations $F21_{S\text{-}S}$ and $F21_{E\text{-}S}$ and found to be 27.75 min and 28.90 min, respectively which was statistically insignificant (p>0.05).

The $t_{75\%}$ values of test formulation (coated $F21_{S-S}$) and reference formulation (Zimor®) were 27.92 min and 29.32 min, respectively which was statistically insignificant as well ($p>0.05$). The above $t_{75\%}$ values indicated the delayed release pattern of the drug from coated pellets.

Table 3: Composition of coating dispersion used for coating 150 g omeprazole pellet formulations, $F21_{S-S}$ and $F21_{E-S}$

Kollicoat MAE 30DP (ml)	Propylene glycol (ml)	Talc (g)	Distilled water (ml)	Coating level (%)
50	7.5	2	150	13.0
60	9	2.4	150	15.0
75	11.50	3	150	17.5

Table 4: Coating process conditions and coater settings

Process conditions	Setting
Batch size (g)	150
Inlet temperature (°C)	30/40
Outlet temperature (°C)	35-40
Atomizing air (bar)	1
Flow rate (ml/min)	3-3.3
Fluidized air (m^3/h)	90/100
Spray nozzle diameter (mm)	0.8
Centre pipe diameter (mm)	47
Center pipe length (mm)	180

Similarity and dissimilarity factors for the selected coated formulations

Determination of the similarity and dissimilarity factors is a FDA-recommended approach to compare two release profiles. The factor f1 calculates the percentage difference between the two drug release profiles as curves at each time interval and describes the relative error between the two profiles. The percentage is zero when the reference and test formulations are identical. The factor f2 is a logarithmic reciprocal square root transformation of the sum of squared error and is the measurement of the similarity in the percentage of dissolution between the curves. Generally the $f1 \leq 15$ and $f2 \geq 50$ indicates the average difference between two release profiles is not more than 10% at the sampling time points. This ensures equivalence of the profiles and hence the same performance of the test and the reference formulations (Moore and Flanner, 1996; Shah, 1998). The values of f1 and f2 for pellets coated at 17.5% coating level were 1.52 and 89.38 respectively, indicated the similarity between profiles.

Table 5: Settings of texture analyzer for hardness testing of pellets

Mode	Force in Compression
Pre-test speed	2.5 mm/s
Test speed	1.5 mm/s
Post-test speed	2.5mm/s
Distance	0.6 mm

Table 6: Characterization of omeprazole pellet formulations (F1-F20) prepared by sieving-spheronization (Mean± SD, n=6)

Formulation Code	Total amount of pellets Yield (%)	Pellets with size range 0.8-1.25mm (%)	Geometric weight mean diameter (dgw)	Geometric Standard deviation (Sg)	Drug Released (%) at 45 min pH 6.8
F1	40.08	18.06	-	-	-
F2	68.2	39.43	-	-	-
F3 (PEG 400, 0.5%)	89.5±2.19	79.9 0±.90	1.02±0.001	1.2±0.01	28.80±1.30
F4 (sodium starch glycolate, 2%)	88.1±1.94	76.37±1.09	1.01±0.002	1.14±0.006	32.02±1.13
F5 (sodium starch glycolate4%)	78.31±1.05	64.19±1.42	1.04±0.004	1.25±0.012	34.21±1.42
F6 (Kollidone (CL 2%)	87.81±0.79	79.35±1.17	1.07±0.006	1.25±0.035	36.34±1.02
F7 (Kollidone (CL 5%)	88.85±1.75	79.28±0.87	1.03±0.103	1.25±0.040	38.52±0.93
F8 (Kollidone (CL 10%)	80.53±1.01	76.39±1.16	1.06±0.019	1.24±0.02	39.95±1.67
F9 (SLS 0.5% -1%)	91.18±1.28	82.28±0.93	1.04±0.002	1.17±0.006	35.31±1.25
F10 (Glycerol 1%)	88.2±1.02	80.86±0.95	1.09±0.002	1.21±0.006	34.47±1.09
F11 (Mannitol 10 %)	86.03±1.14	80.45±0.96	1.07±0.003	1.22±0.006	33.09±1.06
F12 (PEG 2000-1%)	87.9±1.01	79.97±1.13	1.06±0.003	1.21±0.015	31.73±1.03
F13 (PEG 2000-2%)	86.34±0.97	80.45±0.91	1.05±0.005	1.20±0.006	33.89±1.25
F14 (PEG-4000-1%)	84.93±1.41	80.87±1.02	1.06±0.003	1.21±0.006	35.04±1.06
F15 (PEG-4000-2%)	84.36±0.96	80.87±1.06	1.07±0.002	1.21±0.015	36.19±1.48
F16 (PEG-6000-1%)	88.26±1.06	83.17±1.02	1.01±0.001	1.16±0.006	37.93±1.29
F17 (PEG-6000-2%) (60% MCC)	89.66±1.11	84.20±1.36	1.04±0.001	1.22±0.006	40.14±1.01
F18 (PEG-6000-2%) 40%MCC	85.23±0.96	78.49±0.96	1.07±0.005	1.23±0.010	56.50±0.99
F19 (PEG-6000-2%) (26.66%MCC)	85.04±1.07	73.88±0.87	1.07±0.009	1.25±0.021	64.19±1.27
F20 (PEG-6000-2%) (20%MCC)	84.30±1.02	72.36±1.01	1.05±0.07	1.25±0.01	74.34±0.98

Table 7: Comparative characteristics of the uncoated omeprazole pellets produced by sieving-spheronization ($F21_{S-S}$) and extrusion-spheronization ($F21_{E-S}$)

Parameters	Formulation		P value
	Sieving-spheronization	Extrusion-spheronization	
Pellets yield (%)	80.34±0.89	78.80±0.49	004
Pellets within 0.08-1.25 mm	71.53±0.61	72.02±0.70	0.262
Geometric weight (d_{gw}) (mm)	1.06± 0.005	1.06±0.07	0.802
Geometric standard deviation (sg)	1.25 ± 0.006	1.26 ±0.006	0.562
Friability (%)	0.19±.006	0.18±0.015	0.805
Flowability			
Flow rate(g/m)	5.71±0.015	5.76±0.006	0.090
Angle of repose (°)	30.45±0.062	29.72±0.025	0.006
Bulk density (g/ml)	0.89±0.006	0.88±0.006	0.249
Tapped density	0.993±0.002	0.989±0.005	0.128
Carr's Index	11.07±0.092	12.23±0.11	0.010
Hardness (kg)	1.34±0.02	1.39±0.01	0.434
Roundness (ratio)	0.90±0.010	0.91±0.006	0.155
Drug Released (%) 45 min pH 6.8	84.12 ± 1.10	82.67 ± 0.96	-

Table 8: Comparative characteristics of omeprazole coated pellets prepared by sieving-spheronization ($F21_{S-S}$) and extrusion-spheronization ($F21_{E-S}$). Mean ± SD, N=6

Parameters	Sieving-spheronization	Extrusion-spheronization	P value
Total amount of uncoated Pellets	150 g	150 g	
Pellets within 0.08-1.25 mm	79.75±0.484	81.34±0.486	0.004
Geometric weight mean diameter(d_{gw}) (mm)	1.06±0.012	1.05±0.18	0.93
Geometric standard deviation (sg)	1.25 ±0.012	1.26±0.15	0.553
Friability (%)	0.17 ± 0.005	0.16±0.008	0.553
Flowability			
Flow rate (g/m)	5.75 ±`0.18	5.76±0.019	0.677
Angle of repose	30.25 ±0.407	29.45±0.344	0.008
Bulk density (g/ml)	0.90±0.026	0.89±0.019	0.514
Tapped density	0.995±0.006	0.992±0.017	0.149
Carr's Index	10.66±0.53	11.54±0.60	0.157
Hardness (kg)	2.23. ±0.172	2.27±0.046	0.103
Roundness (ratio)	0.91±0.002	0.92. ±0.001	0.394

Table 9: Omeprazole release at pH 1 (0.01N) from coated pellets prepared by sieving-spheronization and extrusion-spheronization and from Zimor®

Time (min)	Percent release		
	$F21_{S-S}$ (Prepared by sieving-spheronization) *	$F21_{E-S}$ (prepared by extrusion-spheronization)	Zimor®**
0	0	0	0
10	0.14±0.01	0.13±0.01	0.14±0.01
20	0.17±0.02	0.15±0.0	0.15±0.00
30	0.43±0.101	0.4 2±0.01	0.35±0.01
45	0.67±0.10	0.62±0.10	0.61±0.13
60	1.26±0.04	1.24±0.01	1.09±0.01
120	2.18±0.14	2.15±0.06	1.12±0.06

*=Also considered as Test formulation, **=Reference formulation

Table 10: Omeprazole release at pH 6.8 from coated pellets prepared by sieving-spheronisation and extrusion-spheronization and from Zimor®

Time (min)	Percentage release		
	$F21_{S-S}$ (Prepared by sieving-spheronization)*	$F21_{E-S}$ (prepared by extrusion-spheronization)	Zimor®**
130	53.24±0.93	52.12±0.54	52.14±0.54
140	65.57±1.09	64.85±1.05	64.71±1.10
150	77.33±1.64	76.24±1.05	76.85±1.69
160	84.74±1.15	83.16±1.68	83.24±1.76
170	87.86±1.86	86.17±3.19	86.27±3.19
180	90.28±1.45	89.14±1.77	89.20±1.75
190	93.44±0.90	91.92±0.71	92.32±1.11
200	95.04±0.53	93.78±0.92	94.81±0.96
210	97.44±1.16	96.25±2.09	96.31±2.19

*=Also considered as Test formulation, **=Reference formulation

The *in-vitro* dissolution profiles of reference omeprazole capsule (Zimor® 20 mg) and the test formulation (coated $F21_{S-S}$) were observed to be similar throughout the entire dissolution period The similarity of the release profiles was further supported with the values of f1 and f2, 1.22 and 91.52, respectively. The f1 value less than 15 and f2 more than 50 indicates the similarity of dissolution profiles (More and Flannel, 1996).

CONCLUSION

The sieving-spheronization and extrusion-spheronization methods produced closely similar characteristics of the omeprazole pellets. However, extrusion-spheronization process caused the blockage of die opening of extruder rollers which led to the difficulty in the immediate re-usability of the instrument after preparation of a batch. Contrarily, sieving-spheronization was found to be a continued process and several batches of formulations could be prepared within a day without the above limitation. Thus, being the simple technique, sieving-spheronization had been shown as a successful approach for pellets preparation.

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