Production variables affecting characteristics of pellets in melt pelletization with wax combination in a laboratory scale spheronizer

SUDARSAN BISWAL1*
JAGANNATH SAHOO1
PADALA NARASIMHAM MURTHY1
RAJESH PANDURANG GIRADKAR2
SUBASH DAS2
JASMINE GEV AVARI2

1Royal College of Pharmacy and Health Sciences, Andhapasarsa Road
Berhampur-760002 Orissa, India
2Department of Pharmaceutical Sciences Rashtrasant Tukadoji Maharaj, Nagpur University Campus, Nagpur-440033 (M.S.), India

The purpose of the study was to evaluate the suitability of laboratory scale spheronizer for the production of spherical pellets loaded with diltiazem hydrochloride by wax combination. The 1:1 combination of cetyl alcohol and hydrogenated castor oil, as low and high melting point waxes, were used. The various production variables affecting the different characteristics of pellets and the process efficiency were evaluated. Drug loaded pellets were evaluated for drug release in distilled water. Bowl temperature primarily affects the sphericity and adhesion of pellets to the bowl. Mass temperature has a pronounced effect on size, size distribution and sphericity of pellets. Wax concentration affects all characteristics of pellets but adhesion was least affected. The effect of these three variables can be compensated by optimizing the friction plate speed. It has been found that the highest yield of pellets (850–1400 \( \mu \text{m} \)) with maximum sphericity can be produced by using 45 °C bowl temperature, 52 °C mass temperature and 1400 rpm friction plate speed.

Keywords: pellets, diltiazem hydrochloride, spheronizer, bowl temperature, cetyl alcohol, hydrogenated castor oil

* Correspondence; e-mail: sudarsan_mpharm@yahoo.co.in

Use of a meltable binder seems to be suitable to produce pellets of water-sensitive materials such as hygroscopic drugs. Natural meltable binders such as wax and some high molecular mass alcohols are suitable for melt pelletization because of their non-toxicity, economy and wide availability. Thereby, water and organic solvents can be avoided during granulation pellet production, which is desirable for both environmental and economic reasons. Melt pelletization in a laboratory scale spheronizer is advantageous because of the simplicity of the process. The pellets are formed without extrusion, so it is economical in terms of time and energy (1–3). Use of a laboratory scale spheronizer permits a small batch size (100–500 g).
Melt agglomeration can be carried out in a high shear mixer, fluid bed granulator, rotary processor and by hot extrusion-spheronization, each with their respective disadvantages. Hot extrusion-spheronization is a two-step process, whereas high shear mixers have the risk of uncontrolled coalescence caused by melting of the whole binding material due to high shear produced by impellers during spheronization (4). Fluid bed granulator and rotary processor require highly specialized equipment and critical controlling parameters (5). The only limiting factor of melt spheronization is wider size distribution of pellets compared to those obtained by extrusion.

In the present study, a cetyl alcohol and hydrogenated castor oil in ratio of 1:1, as low and high melting point waxes, were used (6). Cetyl alcohol and hydrogenated castor oil have been used in melt granulation and matrix type sustained release formulations (7). During spheronization the low melting cetyl alcohol remains in molten form and promotes spheronization by providing plasticity to the mass, whereas hydrogenated castor oil remains in unmelted form and acts as a lipophilic diluent. The rationale of using wax combination is to enable spheronization at a relatively low temperature and to avoid any overwetting during the process (1, 8).

The purpose of this study was to evaluate the feasibility of melt pelletization with wax combination in a laboratory scale spheronizer and to formulate sustained release pellets of diltiazem hydrochloride.

Diltiazem hydrochloride is a calcium channel blocker widely used in the treatment of angina pectoris, systemic hypertension and supraventricular arrhythmias. It has an extensive and highly variable hepatic first pass metabolism following oral administration, having a half life of 4.5 h. Diltiazem hydrochloride is a BCS class-I (highly soluble highly permeable) drug. Thus it is a suitable candidate for sustained drug delivery system to avoid frequent dose administration and improve patient compliance and therapeutic efficacy. The melting point of the drug is higher (214–218 °C) than the melting point of waxes, so it is an ideal candidate for the melt pelletization.

EXPERIMENTAL

Materials

Cetyl alcohol (CA) (Central Drug House Pvt. Ltd., India) and hydrogenated castor oil (HCO) (Hindustan Lever Ltd., India) were used as meltable binders. Dibasic calcium phosphate dihydrate 0.0686 mm (Himedia, India) (DCP) was used as a diluent.

Equipment

A laboratory scale spheronizer (Umang Pharmatech Pvt. Ltd., India) equipped with an electrically heated jacket and a transparent lid with an opening was used for the production of pellets. The temperature of the mass inside the bowl was continuously determined using a thermo-resistance probe fixed onto the bowl lid and dipped in the mass. The bowl capacity was 1800 mL and the friction plate used had the cross-hatched grooves of 1.0 mm size. The friction plate rotational speed can be varied between 0 to 3000 rpm.
Pellet manufacture

Cetyl alcohol (melting range 46–52 °C) and hydrogenated castor oil (melting range 76–84 °C) in the ratio 1:1 were melted completely in a glass beaker with a heating jacket. Diltiazem hydrochloride was added to the molten mass followed by dibasic calcium phosphate dihydrate at a temperature of 84 °C under continuous stirring, so the waxes could coat the solid particles to form uniform molten dispersion. Then the mass was allowed to attain the required temperature (48, 52, 56 and 60 °C) and was transferred into the spherization bowl which was maintained at a temperature lower than mass temperature. While transferring the molten mass into the bowl, it remains in the form of soft granules because the cetyl alcohol remains in molten form in which DCP, HCO and drug are dispersed. The dispersed drug, DCP, and HCO in molten cetyl alcohol provide a granular semisolid consistency.

To achieve the maximum yield of spherical pellets, the friction plate speed was kept at 1400 rpm for initial 2 min and thereafter 1200 rpm for 6 min. During the last 2 min the friction plate speed was lowered to 1100 rpm and the bowl temperature was lowered to 46 °C to harden pellets. Spheronization process takes 10 min to complete.

The pelletization procedure was standardized on the basis of preliminary trials to obtain spherical pellets of desired size and maximum yield. The effects of various production variables and their levels were determined experimentally and were targeted to obtain pellets in the size range of 850–1400 μm. Production variables studied were bowl temperature of 42, 45 and 48 °C, mass temperature 48, 52, 56 and 60 °C, wax concentration 30, 40 and 50 % (m/m) in 1:1 ratio (CA: HCO) along with the friction plate speed of 1000, 1200, 1400 and 1600 rpm. Two variables were studied at a time keeping the other two constant. Step by step optimization of production variables was carried out. Each experiment was repeated three times and the effect on pellet characteristics and process efficiency was determined by further characterization of cooled pellets from each batch.

Pellet characterization

Size distribution. – The cooled product was sieved in order to remove lumps and pellets larger than 2000 μm and smaller than 600 μm. The pellet size and size distribution were estimated by sieve analysis using a set of four standard sieves (ASTM sieves). The sieve fractions were 1400–2000, 850–1400 and 600–850 μm. The pellets in the size range 850–1400 μm were regarded as the desired % yield.

Scanning electron microscopy (SEM). – Microphotographs of the pellets of the size fraction 850–2000 μm from the selected experiment were taken for the scanning electron microscopy study (SEM 515, Phillips, The Netherlands). The pellets were sputtered with gold (E5200 Autosputter coater, BioRad, UK) before microscopy.

Sphericity. – The shape of the pellets was examined with a Traveling light microscope (Unilab®, India) at 10x magnification. Sphericity was determined by the two dimensional shape factor calculated as the ratio of minor and major axes of 120 particles from each experiment and was expressed as the mean value.

Adhesion. – Adhesion of the material to the friction plate and bowl wall was estimated as the difference between the amount of material placed in the bowl and the amount
freely emptied. The adhesion was expressed as the percentage of the amount of starting material.

Drug release study. – Dissolution studies of different formulations were performed using the United States Pharmacopoeia (9) model digital tablet dissolution test apparatus-2 (LABINDIA, India) at the paddle rotation speed of 100 rpm in 900 mL distilled water as dissolution medium at 37 ± 0.5 °C. The samples withdrawn were filtered through Whatman filter paper No. 1 and the drug content in each sample was analyzed after suitable dilution using a UV spectrophotometer at 237 nm (9). The release profile of optimized batches was compared with that of the commercial product Angizem 60 mg SR capsule (Sun Pharmaceutical Industries, India) using the similarity factor method (f²) and the best batch was selected.

RESULTS AND DISCUSSION

Effect of bowl temperature and friction plate speed on pellet characteristics

Pellet size decreases at 42 and 45 °C bowl temperature by increasing the friction plate speed from 1000 to 1600 rpm (Fig. 1). Low friction plate speed might be not sufficient to break the mass but higher speed breaks the mass, which causes the production of smaller pellets. An increase in plate speed leads to the formation of larger size pellets at 48 °C bowl temperature. At higher speed of the plate, the temperature of the product increases due to the heat generated by friction. Heat develops soft agglomerates and higher liquid saturation on the surface of pellets (10, 11). So the agglomerates start to coalesce rapidly and form larger size pellets. Uncontrolled ball growth (> 2000 μm) was observed at 48 °C bowl temperature at 1400 and 1600 rpm.

The yield of pellets of size range 1400–2000 μm is 39 % (Fig. 1) at 1000 rpm speed and 42 °C bowl temperature, but percentage yield of the same decreases again at higher speed. The yield of larger size pellets increases on increasing the bowl temperature. The yield of pellets of size range 850–1400 μm was 56 % at 1200 rpm speed and 42 °C bowl temperature, but increased when the temperature was raised to 45 °C and decreased with further increase in bowl temperature to 48 °C at the same speed. The yield of pellets having a size range of 600–850 μm is highest (22 %) at 1600 rpm speed and 42 °C bowl temperature. The higher friction plate speed breaks the agglomerates into small sized pellets.

Table I. Composition of different batches

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Diltiazem hydrochloride</th>
<th>DCP (%)</th>
<th>CA (%)</th>
<th>HCO (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>B₁</td>
<td>20</td>
<td>45</td>
<td>17.5</td>
<td>17.5</td>
</tr>
<tr>
<td>B₂</td>
<td>20</td>
<td>40</td>
<td>20.0</td>
<td>20.0</td>
</tr>
<tr>
<td>B₃</td>
<td>20</td>
<td>35</td>
<td>22.5</td>
<td>22.5</td>
</tr>
<tr>
<td>B₄</td>
<td>20</td>
<td>30</td>
<td>25.0</td>
<td>25.0</td>
</tr>
</tbody>
</table>

CA – cetyl alcohol, HCO – hydrogenated castor oil, DCP – dibasic calcium phosphate
Fig. 1. Effect of bowl temperature and friction plate speed on pellet characteristics at mass temperature of 52 °C and 40 % (m/m) wax concentration (mean ± SD, n = 3).
Development of more spherical pellets was observed with an increase in friction plate speed from 1000 to 1600 rpm. Similarly, the sphericity also increased when bowl temperature increased from 42 to 45 °C. It might be due to the fact that the amount of heat generated by the friction plate increases with an increase in speed, which leads to the increase in liquid saturation on the agglomerate surface. The increased liquid saturation on the surface of agglomerates makes their surface more plastic, which results in more rounded agglomerates (11, 12). The sphericity decreases at 48 °C compared to 45 °C bowl temperature and increased speed of the plate. This is due to the fact that increased bowl temperature causes sticking of mass to the bowl wall and friction plate, causing coalescence and finally deformation of agglomerates (13).

The adhesion of agglomerates to the bowl wall decreases by increasing the friction plate speed from 1200 to 1600 rpm at 42 °C bowl temperature (Fig. 1). In comparison with 45 °C bowl temperature, more adhesion was observed at 42 °C. This might be due to the fact that the difference between bowl and mass temperature (52 °C) is higher, so the more mass sticks to the bowl wall and friction plate. The adhesion was significantly increased at 45 and 48 °C bowl temperature at 1000 and 1200 rpm plate speed. At higher bowl temperature and higher speed more sticky mass was observed which stuck strongly to the bowl wall. This causes an increase in contact area between bowl wall and agglomerates resulting in more adhesion (11, 12). The bowl temperature and friction plate speed affected the size and size distribution, sphericity and adhesion of pellets significantly ($p < 0.05$).

**Effect of mass temperature and friction plate speed on pellet characteristics**

Fig. 2 shows that the pellet size increased significantly by increasing the mass temperature from 48 to 60 °C. This might be due to the increase in the amount of the molten form of cetyl alcohol with increased mass temperature, which led to strong cohesion of particles within the agglomerates, resulting in larger size pellets. At 60 °C mass temperature and at 1000 and 1200 rpm friction plate speed, the size and size distribution can be controlled but at higher plate speed the uncontrolled ball growth and adhesion was observed. This is due to complete melting of cetyl alcohol, which remains in the liquid state for a longer time due to higher friction plate speed. Desired size pellets with narrow size distribution were obtained at 52 °C mass temperature. It was observed that the size of pellets decreases with the increase in friction plate speed from 1000 to 1600 rpm at 48, 52 and 56 °C mass temperature, but the effect of the friction plate speed diminishes with increased mass temperature.

The yield of pellets of size 600–850 μm is 43 % (Fig. 2) at a speed of 1600 rpm and 48 °C mass temperature. The yield of pellets of size range 850–1400 μm is 66 % at 1400 rpm and 52 °C mass temperature. At 60 °C mass temperature the yield of larger size pellets was higher. The percentage yield of smaller sized pellets (600–850 μm) was higher at 48 °C mass temperature but the percentage yield of larger size pellets (> 1400 μm) was more at higher mass temperature, 56 and 60 °C due to the low meeting point of wax which remains in molten form for a larger time.

Fig. 2 shows that at 48 and 52 °C mass temperature, the sphericity increases by increasing the friction plate speed from 1200 to 1600 rpm. At 56 °C mass temperature, the sphericity increases from 1000 to 1400 rpm but it decreases at 1600 rpm. At 60 °C mass temperature, the sphericity was found to decrease with the increase in friction plate
Fig. 2. Effect of mass temperature and friction plate speed on pellet characteristics at bowl temperature of 45 °C and 40 % (m/m) wax concentration (mean ± SD, n = 3).
speed from 1000 to 1200 rpm. This is due to the fact that at higher mass temperature there is more liquid saturation on the agglomerate surface, which causes coalescence of two or more agglomerates and adhesion of agglomerates to the bowl wall and friction plate making it difficult to spheronize properly. Below 48 °C mass temperature, very poor sphericity ($< 0.745$) was observed due to insufficient molten binder in the agglomerates.

Fig. 2 also shows that the least adhesion takes place at 48 °C mass temperature and at 45 °C bowl temperature. But as the mass temperature increases from 52 to 60 °C, the percentage adhesion increases with increased speed. At 60 °C mass temperature at 1400 and 1600 rpm, uncontrolled ball growth and more adhesion were observed. The mass temperature and friction plate speed also affect the size and size distribution, sphericity and adhesion of pellets significantly ($p < 0.05$).

**Effect of wax concentration and friction plate speed on pellet characteristics**

The size of pellets decreases significantly and more fines are obtained with increasing the friction plate speed at 30 % ($m/m$) wax concentration (14) (Fig. 3). This is because the wax concentration was insufficient form cohesive mass. The yield of large sized pellets ($> 1400 \mu m$) was higher at 50 % ($m/m$) wax concentration. At 40 % ($m/m$) wax concentration and at 1200 and 1400 rpm, the maximum yield of 850–1400 μm pellets was obtained. It was also found that wax concentration in the range 30 to 50% ($m/m$) does not have any effect on the yield of 850–1400-μm pellets at a constant mass temperature (52 °C). The effect of wax concentration on the size and size distribution can be compensated by optimizing the friction plate speed (3, 15, 16).

The yield of pellets of size range 600–850 μm is 40 % at 30 % ($m/m$) of wax and at 1600 rpm speed, but again the yield of this size range decreased upon an increase in wax concentration (Fig. 3). Maximum yield of 850–1400 μm size pellets (65%) was obtained at 40 % ($m/m$) of wax and at 1200 rpm. The yield of larger size pellets ($> 1400 \mu m$) decreased at 30% ($m/m$) of wax compared to 50 % ($m/m$) of wax.

It is difficult to get spherical pellets at 30 % ($m/m$) wax concentrations due to insufficient binder available for spheronization; however, above 50 % ($m/m$) wax concentration larger pellets are obtained ($> 1400 \mu m$) at 1000–1600 rpm. This is due to strong cohesion provided by a higher amount of wax.

Poor sphericity was observed at 30 % wax concentration. Sphericity was increased with increasing friction plate speed at 40 % and 50 % ($m/m$) wax concentration. The highest sphericity (0.930) was observed at 50 % ($m/m$) wax concentration and 1600 rpm due to the softening of mass as well as increased surface plasticity with increased wax concentration. The wax concentration and friction plate speed affect sphericity and adhesion of pellets significantly but not the size and size distribution ($p < 0.05$).

From Fig. 3 it is clear that at optimum bowl temperature (45 °C), wax concentration has little effects on percent of adhesion and it was slightly increased with the increase in friction plate speed from 1000 to 1600 rpm. But, above 50 % ($m/m$) wax, more adhesion and larger pellets ($> 2000 \mu m$) were obtained. Increase in wax concentration with increasing friction plate speed could not affect the sticking tendency significantly in the range of wax concentration 30 to 50 % ($m/m$) and at friction plate speed from 1000 to 1600 rpm.
Fig. 3. Effect of wax concentration and friction plate speed on pellet characteristics at bowl temperature of 45 °C and mass temperature of 52 °C (mean ± SD, n = 3).
Scanning electron microphotographs (Fig. 4) of different size pellets show that the sphericity and the surface smoothness decrease with a decrease in the size of pellets. The shape factor of different size pellets was found to be 0.857, 0.903 and 0.922 for 850, 1400 and 2000 μm, respectively. This might be due to the fact that the binder hardens in smaller size agglomerates before complete rounding, but in larger agglomerates it remains in molten state for comparatively longer time, enabling complete rounding within the period of spheronization (10 min).

Drug release

As shown in Fig. 5, diltiazem hydrochloride release is remarkably lowered when the amount of lipidic binder is increased from 35 % (almost 93 % release after 15 h) to 50 % (m/m) (only 78 % drug release after 15 h). An important decrease of the diltiazem hydrochloride release is achieved for the formulation B3 containing 45 % (84 % drug release after 12 h) and even more for the formulation B4 containing 50 % lipidic binder (78 % drug release after 15 h). The reason for slow drug release is either increase in the coating level or saturation of drug particles with increasing wax concentration. During the spheronization process HCO solidifies rapidly, then cetyl alcohol coats it. As the concentration of wax increases, the coating level increases. This slows down the entry of dissolution medium into the core of the drug particle, resulting in retardation of drug release. The in vitro drug release profile of B3 and B4 formulations matched with the USP (9) test.
2 release profiles (amount of the drug released after 1, 3 and 8 h not less than 15, 45–75 and 80 %, resp.). By comparison of release profiles of optimized batches with that of marketed Angizem 60 mg SR, the similarity factor ($f_2$) of optimized batches (B3 and B4) was found to be more than 50.

CONCLUSIONS

The present investigation has revealed that the laboratory scale spheronizer might be a suitable alternative for the production of sustained release spherical pellets for dil-tiazem hydrochloride. Use of the combination of low and high melting point waxes having a distinct melting range makes the process easily controllable and less time consuming. The various production variables of pellets, such as bowl temperature, mass temperature and wax concentration, affect significantly different pellet characteristics and process efficiency, the effect of which can be compensated by optimizing the friction plate speed. It was observed that the production variables have to be optimized according to the melting behaviour of the low melting wax used.

Acknowledgements. – The authors thank Umang Pharmatech (India) for developing the laboratory scale spheronizer for melt spheronization and U. G. C., New Delhi, for providing financial aid.

REFERENCES


**S AŽE T A K**

**Proizvodne varijable koje utječu na svojstva peleta u peletiranju taljenjem sa smjesom voskova u sferonizatoru za laboratorijsku proizvodnju**

SUDARSHAN BISWAL, JAGANNATH SAHHOO, PADALA NARASIMHAM MURTHY, RAJESH PANDURANG GIRADKAR, SUBASH DAS i JASMINE GEV AVARI


**Ključne riječi:** pelete, sferonizator, temperatura peletiranja, cetilni alkohol, hidrogenirano ricinusovo ulje, diltiazem hidroklorid

*Royal College of Pharmacy and Health Sciences, Andhapasarsa Road, Berhampur-760002 Orissa, India*

*Department of Pharmaceutical Sciences, Rashtrasant Tukadoji Maharaj Nagpur University Campus, Nagpur-440033, (M.S.), India*