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Wax-based sustained release matrix pellets prepared by a novel freeze pelletization technique
I. Formulation and process variables affecting pellet characteristics

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ABSTRACT

A novel freeze pelletization technique was evaluated for the preparation of wax-based matrix pellets. Pellets containing either theophylline or diltiazem HCl were prepared using various waxes. In this technique, molten waxes along with a dispersed active ingredient were introduced as droplets into an inert and immiscible column of liquid to form pellets. An 80% (w/w) aqueous glycerol solution was found to be the most suitable column liquid for preparing spherical wax pellets. The physical stability of the molten wax suspensions was substantially improved by the addition of a 5% (w/w) colloidal silica gel. Pellet size obtained was directly proportional to the cubic root of the outer radius of the needle tip used to form pellets. Pellet size increased as the ratio of interfacial tension (γ_{LL}) to the density difference ($\Delta\rho$) between the molten matrix and the column liquid increased. Moreover, an increase in the drug load of theophylline increased the pellet size. However, an addition of a surfactant to the matrix slightly decreased the pellet size. Microscopic studies indicated that theophylline was homogenously dispersed throughout the matrix and existed in a crystalline state at higher drug loads. The percent drug recoveries ranged from 90.7 to 102.3% with acceptable drug loads up to 20% (w/w). Therefore, wax pellets containing drugs of varying aqueous solubility were successfully prepared using this technique.

1. Introduction

The freeze pelletization technique is a simple and novel technique for producing spherical matrix pellets containing active ingredients (Cheboyina et al., 2004). In this technique, a molten solid carrier along with a dispersed active ingredient is introduced as droplets into an inert and immiscible column of liquid. These droplets can move either in upward or downward directions, depending on their density with respect to the liquid in the column and solidify into spherical pellets. If the density of the molten solid matrix is more than that of the liquid in the column, then the droplets are introduced from the top of the column and pellets solidify in the bottom portion of the column. Conversely, if the density of the molten solid matrix is less than that of the liquid in the column, then the droplets are introduced from the bottom of the column, and pellets solidify in the top portion of the column as shown in the apparatus II (Fig. 1). A variety of carrier solids and liquids that can be used as pellet forming liquids and column liquids, respectively in this freeze pelletization process were also discussed previously (Cheboyina et al., 2004).

A mathematical model was derived (Cheboyina et al., 2006) based on the various forces acting on the droplets at the time of droplet formation to predict the size of the pellets formed in the freeze pelletization process. In this study a molten solid carrier (without any actives/excipients) was slowly injected in such a way that individual droplets were formed at the tip of the needle. An equation for predicting the size of the wax pellets formed in apparatus II was given as

$$d_P = \left[\frac{12 r_N \gamma_{LL} \rho_{PL} \varphi(r_N/a)}{\Delta\rho g \rho_P}\right]^{1/3} \quad (1)$$

where d_P is the diameter of the pellet at room temperature, r_N is the inner or outer radius of the circular needle tip depending on the wetting characteristics between the molten carrier and the material of construction of the needle tip, γ_{LL} and $\Delta\rho$ are interfacial tension and density difference between the column liquid and the molten solid carrier at the initial column temperature, respectively, ρ_{PL} and ρ_P are the densities of molten solid carrier at the initial column and room temperatures, respectively, $\varphi(r_N/a)$ is the Harkins and Brown's droplet correction factor, a is the capillary constant of the molten

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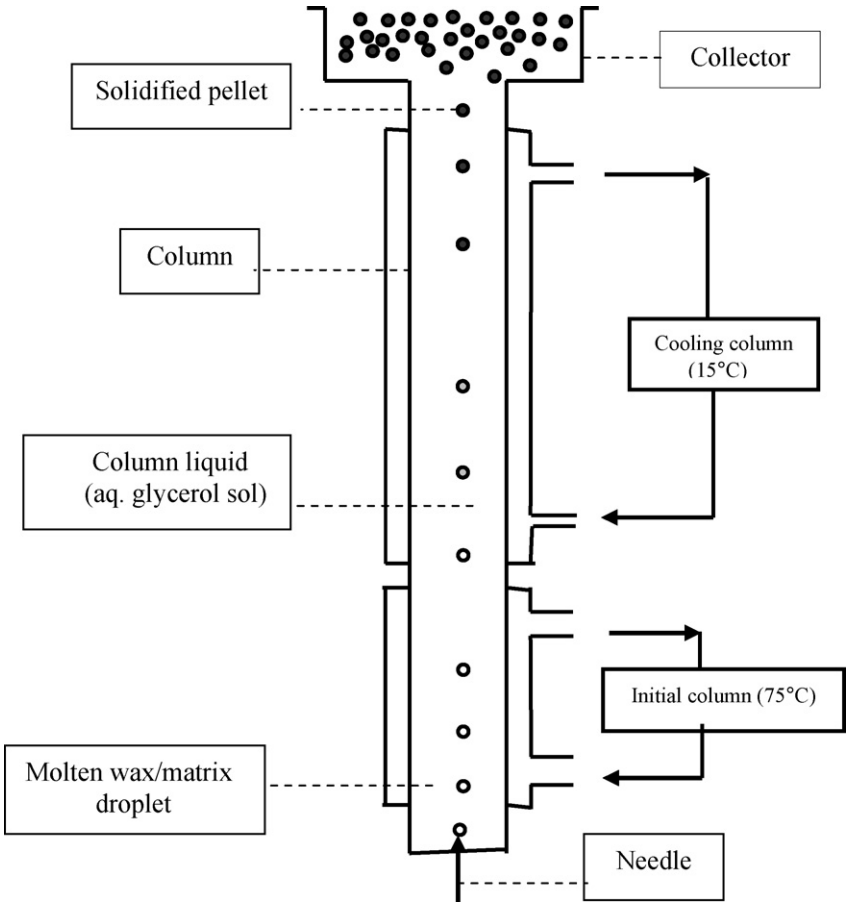

Fig. 1. Schematics of the freeze pelletization apparatus II.

solid carrier and is defined as $(2\gamma_{LL}/\Delta\rho g)^{1/2}$ and g is the acceleration due to gravity.

At a given initial column temperature, neglecting the droplet correction factor and liquid–solid volume contraction fraction ($[\rho_{PL}/\rho_P]^{1/3}$), Eq. (1) was simplified as

$$d_p = Kr_N{}^{1/3}P^{1/3} \quad (2)$$

where $K=(12/g)^{1/3}$ is a constant and $P=\gamma_{LL}/\Delta\rho$. Eq. (2) indicates that diameter of the needle tip, interfacial tension and density difference between molten solid carrier and column liquid are the most important factors affecting the pellet size. The following conclusions were also drawn previously with respect to the parameters affecting pellet size; the viscosity of neither the column liquids nor the molten waxes affected the pellet size in the range of viscosities studied, the shape and wetting characteristics of the needle tips were found to have a significant effect on the pellet size in addition to the gauge size of the needle, and the pellet size slightly decreased as the temperature maintained in the initial column increased. However, the viscosity of the aqueous glycerol solutions significantly affected the shape of the wax pellets formed in apparatus II. Therefore, further studies were conducted to determine the most suitable viscosity to produce spherically shaped pellets.

A previous study (Cheboyina et al., 2004) successfully demonstrated the applicability of freeze pelletization process in the preparation of immediate release dexamethasone matrix pellets using apparatus I. The present study primarily investigated the feasibility of using a variety of waxes in the preparation of sustained release matrix pellets containing water soluble drugs using apparatus II. These waxes when melted are completely immiscible with some hydrophilic liquids such as aqueous glycerol/sugar/polymeric solutions. Moreover, their densities are usually less than that of the hydrophilic liquids. Therefore, apparatus II was evaluated for the applicability of preparing wax-based sustained release matrix pellets. Further, the effect of various parameters including wax type, needle gauge size, drug loading, and addition of a surfactant to the matrix on the pellet size were studied. Pellets were also evaluated for the drug encapsulation efficiency, uniformity of drug distribution, physical state of the drug in the matrix, hardness and friability. Two model drugs of varying aqueous solubility were chosen for this study; theophylline, a sparingly water soluble drug (~6 mg/ml) and diltiazem hydrochloride, a highly water soluble drug (~600 mg/ml).

2. Materials and methods

2.1. Materials

Theophylline anhydrous, diltiazem hydrochloride (DHCl), glyceryl monostearate (GMS), cetyl ester wax (CEW), cetyl alcohol (CA), yellow beeswax (BW), glycerol and colloidal silica gel were purchased from Spectrum Chemical Mfg. Corp., New Brunswick, NJ. Precirol® ATO 5 (glyceryl palmitostearate or GPS) was generously supplied by Gattefossé Corp., Paramus, NJ. Brij®76 was purchased from Aldrich Chemical Co. Inc., Milwaukee, WI. The model drugs were sieved and 74–44 μm fraction (mesh #200–mesh #325) was used in the studies.

2.2. Equipment

Pelletization apparatus was built in-house with borosilicate glass tubes. In this apparatus, the lengths of initial and cooling columns are 30 and 50 cm, respectively. These columns have an inner diameter of 2 cm. A Nikon CoolPix 5700 digital camera, a VWR Chiller, Model No. 1171PD, VWR International (Buffalo Grove, Illinois) and water circulators, Polyscience (Niles, Illinois) were used. PrecisionGlide® needles with stainless steel (SS) circular tips (12G 1″, 16G 1″, 18G 1″, 20G 1″ 22G 1″ and 25G 1″) and 10 ml polypropylene (PPE) syringes were purchased from Becton Dickinson (Franklin Lakes, New Jersey).

2.3. Methods

2.3.1. Effect of viscosity of aqueous glycerol solutions on the pellet shape

To evaluate the effect of column liquid viscosity on pellet shape and to determine an optimum viscosity for producing spherically shaped pellets, a series of aqueous glycerol solutions ranging from ~1 to 219 mPa s at 20 °C (10, 50, 70, 75, 80 and 90% (w/w) glycerol solutions) were studied. Approximately 10 g of Precirol (without any drug) was melted and poured into a jacketed syringe attached with a 22-G stainless steel (SS) needle having a circular tip. Then the needle was pierced through the rubber septum attached at the bottom portion of the column and the molten wax was slowly injected drop wise (manually) into the glycerol solution in apparatus II. In this apparatus, the initial column jacket temperature was maintained at 75 °C, and the cooling column jacket was kept around 15 °C using a water circulator. The typical time of drop formation was kept constant at 2–3 s to ensure pellets of uniform size. The droplets moved up the column and solidified into pellets as shown in Fig. 1. The pellets that were collected at the top of the column were removed and washed three times with deionized water. Later they were dried under a vacuum at 25 °C for 24 h.

2.3.2. Evaluation of silica gel as a suspending agent in the molten carrier solid suspensions

In the freeze pelletization process, a suspending agent was considered necessary to maintain the homogeneity of drug distribution in the wax suspensions. Therefore, colloidal silica gel was chosen as a suspending agent in all the molten carrier solid suspensions. Colloidal silica gel is submicroscopic fumed silica with a particle size of about 15 nm and has been frequently used in wax-based formulations such as suppositories to increase viscosity and prevent sedimentation during molding (Morefield and Seyer, 2003).

The molten carrier solid suspensions containing a 10% (w/w) theophylline were prepared without any suspending agent. Theophylline was sieved and a 44–74 μm size fraction (US mesh #325–US mesh #200) was selected for the studies. The suspensions were placed in 10 ml graduated measuring cylinders and immersed in a water bath maintained at a temperature of 75 °C. All the suspensions were evaluated for their physical stability by measuring the sedimentation volumes up to 30 min. The sedimentation volume at time, t is defined as the ratio of the sediment volume at time, t to the initial volume of the suspension, before settling. The molten carrier solids studied were GMS, beeswax, Precirol, cetyl alcohol and cetyl ester wax. The molten carrier solid suspension with the least physical stability was identified and varying amounts of colloidal silica gel including 1, 3, 5, 7 and 10% (w/w) were added. The lowest concentration of silica gel, which provided highest physical stability, was chosen as the optimum concentration of silica gel in all the molten carrier solid suspensions.

2.3.3. Preparation of drug loaded wax matrix pellets

The molten wax matrix was prepared by dispersing theophylline anhydrous or diltiazem HCl in a molten wax containing colloidal silica gel as a suspending agent. Approximately 10 g of molten wax matrix was prepared and poured into a jacketed syringe having a circular SS needle tip. This molten solid matrix was slowly introduced as droplets into a column containing an 80% (w/w) glycerol solution. The initial column jacket temperature was maintained at 75 °C, and the cooling column jacket temperature was kept at 15 °C for all the studies. The pellets that were collected at the top of the column were removed and washed three times with deionized water. Later they were dried under a vacuum at 25 °C for 24 h. The compositions of various wax matrix pellets containing either theophylline or diltiazem HCl are shown in Table 1.

2.3.4. Factors affecting the size of wax matrix pellets

2.3.4.1. Effect of wax type on the pellet size. The effect of wax type on the pellet size was studied by preparing different wax pellets containing 10% (w/w) theophylline using 22 G needles. The waxes studied were beeswax, cetyl ester wax, cetyl alcohol, Precirol and GMS.

2.3.4.2. Effect of needle gauge size on the pellet size. The effect of needle gauge size on the pellet size was studied by preparing GMS

Table 1
The composition of various wax matrix pellets

Wax matrix pellets	Theophylline (%, w/w)	Diltiazem HCl (%, w/w)	Wax type (%, w/w)	Colloidal silica gel (%, w/w)	Brij 76 (%, w/w)	Needle gauge size used (G)
F#1	10	–	Cetyl ester wax: 85	5	–	22
F#2	10	–	Beeswax: 85	5	–	22
F#3	10	–	Cetyl alcohol: 85	5	–	22
F#4	10	–	Precirol: 85	5	–	22
F#5	10	–	GMS: 85	5	–	22
F#6	10	–	GMS: 85	5	–	12
F#7	10	–	GMS: 85	5	–	16
F#8	10	–	GMS: 85	5	–	20
F#9	10	–	GMS: 85	5	–	25
F#10	2	–	GMS: 93	5	–	20
F#11	5	–	GMS: 90	5	–	20
F#12	15	–	GMS: 80	5	–	20
F#13	20	–	GMS: 75	5	–	20
F#14	10	–	Precirol: 83	5	2	22
F#15	10	–	Precirol: 80	5	5	22
F#16	10	–	Precirol: 75	5	10	22
F#17	–	10	Precirol: 85	5	–	22
F#18	–	10	GMS: 85	5	–	20

pellets containing 10% (w/w) theophylline. GMS pellets were prepared using 12, 16, 20, 22 and 25 G needle tips.

2.3.4.3. Effect of drug loading on the pellet size. The effect of drug loading on the pellet size was studied by preparing GMS pellets containing increasing loads of theophylline including 2, 5, 10, 15 and 20% (w/w). These pellets were prepared using 20 G needles. Pellets containing drug loads higher than 20% (w/w) could not be prepared because these molten matrices were very viscous and could not be extruded through the needles.

2.3.4.4. Effect of surfactant concentration on the pellet size. The effect of surfactant concentration on the pellet size was studied by preparing Precirol pellets containing 10% (w/w) theophylline and increasing amounts of Brij 76 (HLB = 12.4) including 2, 5 and 10% (w/w). These pellets were prepared using a 22-G needle. Preliminary studies indicated that surfactants having higher HLB values increased the miscibility between molten waxes and aqueous glycerol solutions in the column. Therefore, a surfactant with only an intermediate HLB value was chosen.

2.3.5. Evaluation of pellet size

For different batches of the pellets prepared, around 30–40 pellets were randomly selected, and their diameters were measured using a digital vernier caliper. To determine whether the pellet sizes were significantly different among various batches of pellets, analysis of variance (ANOVA) and Tukey–Kramer multiple comparison tests were performed (at $\alpha = 5\%$) using the statistical software, JMP 3.2.1, SAS Institute Inc.

2.3.6. Efficiency of drug loading

To determine the efficiency of the drug encapsulation process, wax matrix pellets were assayed for their drug content. The drug assays were conducted in triplicate. Pooled samples weighing approximately 100 mg were accurately weighed and transferred into a 100-ml volumetric flask containing 50 ml of deionized water. The flasks were immersed in a water bath maintained at 75 °C for 2–3 min and shaken vigorously until all the pellets were completely melted and uniformly dispersed. The flasks were cooled and water was added to bring the volume to 100 ml. The resulting suspensions was filtered through a 0.45-μm syringe filter and the drug content was analyzed using a UV spectrophotometer (Lambda EZ201, PerkinElmer, Norwalk, CT) at 271 and 236 nm for theophylline and diltiazem HCl, respectively, using the calibration data.

2.3.7. Hardness and friability

The hardness of selected batches of pellets was measured using a texture analyzer, TA.XT2*i* (Texture Technologies Corp., NY). A stainless steel cylinder probe with a bottom surface area of 1 cm^2 was used in the study. The probe advanced onto a single pellet at a speed of 0.5 mm/s. The force required to crack a pellet was measured. Around 10–15 pellets were tested to determine the average hardness of the pellets in each of the batches. A 25-kg load capacity and 1 g sensitivity were used for the tests. The friability of the pellets was evaluated using a tablet friability apparatus (Vankel, NC) by noting a change in the weight of 500 mg of pellets after the pellets were subjected to 100 free falls.

2.3.8. Microscopy

The shape and surface morphology of the pellets were observed using a Leica DMIL optical microscope (Wetzlar, Germany) with PictureFrame 5.0 software. Thin sections of the pellets were also prepared and observed for the presence or absence of drug particles. Further, the homogeneity of drug distribution in the pellets was examined.

2.3.9. Differential scanning calorimetry

Differential scanning calorimetric (DSC) studies were performed in a PerkinElmer DSC 6 (Norwalk, CT) and analyzed using Pyris 6 software. The temperature axis was calibrated with indium. The runs were performed under nitrogen gas flow (20 ml/min) in crimped aluminum pans with a sample weight around 5–10 mg. A heating rate of 10 °C/min was used over the temperature range of 20–300 °C. DSC thermograms of wax matrix pellets and drug–wax physical mixtures were examined to determine the physical state of the drug in the matrix.

3. Results and discussion

3.1. Effect of viscosity of aqueous glycerol solutions on the pellet shape

Precirol pellets prepared in 10 and 50% (w/w) aqueous glycerol solutions were highly irregular in shape but the sphericity of the pellets improved considerably as the concentration of glycerol increased to 80% (w/w) (see Fig. 2). The viscosities of the aqueous glycerol solutions at 20 and 75 °C are given in Table 2. The reason for obtaining irregularly shaped pellets in 10 and 50% (w/w) glycerol solutions was found to be mainly due to the turbulence generated by the movement of column liquid in apparatus II. In this apparatus, the initial column (bottom portion of the column) was heated to 75 °C, but the cooling column (upper portion of the column) was maintained at 15 °C. Because of this temperature difference, a density gradient exists throughout the length of the column liquid. Therefore, in this apparatus unlike in apparatus I (Cheboyina, 2006), the temperature and the density gradients run in opposite directions. Since denser liquid is present at the top and less dense liquid at the bottom, there is a constant movement of column liquid because of convection. The strength of these convection currents depends on the temperature difference between the initial and the cooling columns, viscosity and thermal conductivity of the column liquid, and dimensions and design of the apparatus. It was found that the pellet shape considerably improved in 50% glycerol solutions when the temperature difference between the initial and cooling columns was reduced (initial column maintained at 75 °C and cooling column at 45 °C). However, it was observed that at higher viscosities, (>70% (w/w) glycerol solutions) there was no significant effect of temperature/density gradient in the column on the pellet shape. At these viscosities, convection of the column liquid was not found to significantly influence the pellet shape.

It was also observed that in low viscosity column liquids (<70% (w/w) glycerol solutions), the spherical shape of the droplets distorted as they rapidly ascended the column resulting in disc shaped particles upon solidification. Therefore, sphericity of the pellets was related to the movement of the droplets in the column liquid, which in turn, depended on the viscosity of column liquid. As the viscosity of column liquid increased, convection of the liquid medium was minimized and also the droplets ascended the column at a slower rate, which helped in preserving the spherical shape of the droplets. However, at much higher viscosities (>80% (w/w) glycerol solutions), movement of the droplets was very slow and led to the agglomeration of pellets. Therefore, 80% (w/w) glycerol solution was chosen as a suitable column liquid for producing spherically shaped pellets in apparatus II.

3.2. Evaluation and determination of optimum amount of silica gel in molten matrix suspensions

The physical stability of various molten wax suspensions containing a 10% (w/w) theophylline was studied at 75 °C for a period

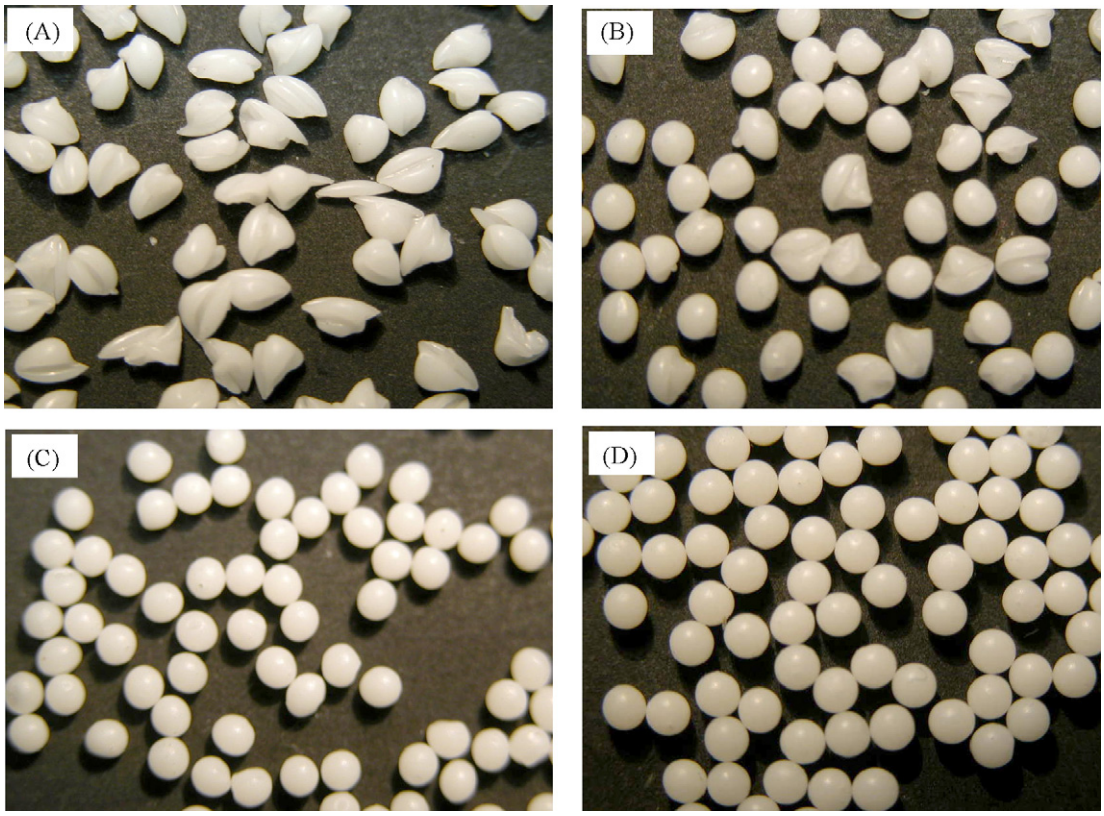

Fig. 2. Photographs of Precirol pellets prepared in apparatus II: (A) pellets formed in 10% (w/w) glycerol solution; (B) pellets formed in 50% (w/w) glycerol solution; (C) pellets formed in 70% (w/w) glycerol solution; (D) pellets formed in 80% (w/w) glycerol solution.

of 30 min. It was observed that sedimentation rate of theophylline particles in each of the molten carrier solid suspensions was different as shown in the Fig. 3(A). The increasing physical stability of the suspensions was found to be in the following rank order; GMS > beeswax > Precirol > cetyl alcohol > cetyl ester wax. The molten GMS matrix was found to be the most stable suspension with a sedimentation volume of 73%. The sedimentation velocity of a particle in dilute suspensions was described by Stokes law (Martin, 1993) as follows:

$$v = \frac{d^2(\rho_S - \rho_L)g}{18\eta} \quad (3)$$

where v is the velocity of the sedimentation, d is the diameter of the particle, ρ_S and ρ_L are the densities of the particles and the liquid, respectively, g is the acceleration due to gravity and η is the viscosity of the liquid. From the Eq. (3), it can be observed that the sedimentation rate of the particles is directly related to the particle size and density difference between the particles and the liquid and inversely related to the viscosity of the liquid. The highest physical stability of GMS suspension was mainly due to its high density and viscosity when compared to other waxes. The densities and viscosities of these carrier solids are given in Table 2.

Fig. 3(A) shows that cetyl ester wax suspension is least physically stable with a sedimentation volume of only 20%. Therefore, cetyl ester wax suspensions were chosen to determine the optimum amount of colloidal silica gel required to produce stable suspensions. The cetyl ester wax suspensions containing a 10% (w/w) theophylline and increasing amounts of colloidal silica gel (1, 3, 5, 7 and 10% (w/w)) were prepared. It was observed that as the amount of silica gel increased, physical stability of the suspensions substantially increased (see Fig. 3(B)). However, there was no significant difference between sedimentation volumes of suspensions containing 5 and 7% (w/w) silica gel. Although suspension containing a 10% (w/w) silica gel was highly stable, it was too viscous to be extruded through a 22-G needle. Therefore, a 5% (w/w) silica gel was chosen as an optimum concentration. The concentration of

Table 2
Densities and viscosities[a] of various waxes and aqueous glycerol solutions

	Density (g/cm^3)	Viscosity (mPa s)
Precirol	0.990 at 20 °C, 0.885 ± 0.001 at 75 °C	17 at 90 °C
Glyceryl monostearate	1.030 at 20 °C, 0.906 ± 0.002 at 75 °C	21 at 90 °C
Cetyl ester wax	0.940 at 20 °C, 0.819 ± 0.001 at 75 °C	7 at 90 °C
Cetyl alcohol	0.890 at 20 °C, 0.806 ± 0.003 at 75 °C	8 at 90 °C
10% (w/w) aqueous glycerol solution	1.021 at 20 °C, 1.003 ± 0.001 at 75 °C	1.31 at 20 °C, 0.5 at 75 °C
50% (w/w) aqueous glycerol solution	1.124 at 20 °C, 1.097 ± 0.002 at 75 °C	6 at 20 °C, 1.53 at 75 °C
70% (w/w) aqueous glycerol solution	1.178 at 20 °C, 1.146 ± 0.001 at 75 °C	22 at 20 °C, 3.8 at 75 °C
75% (w/w) aqueous glycerol solution	1.192 at 20 °C, 1.169 ± 0.002 at 75 °C	35 at 20 °C, 5 at 75 °C
80% (w/w) aqueous glycerol solution	1.205 at 20 °C, 1.172 ± 0.002 at 75 °C	60 at 20 °C, 6 at 75 °C
90% (w/w) aqueous glycerol solution	1.235 at 20 °C	219 at 20 °C, 13.5 at 75 °C

[a] Cheboyina et al. (2006).

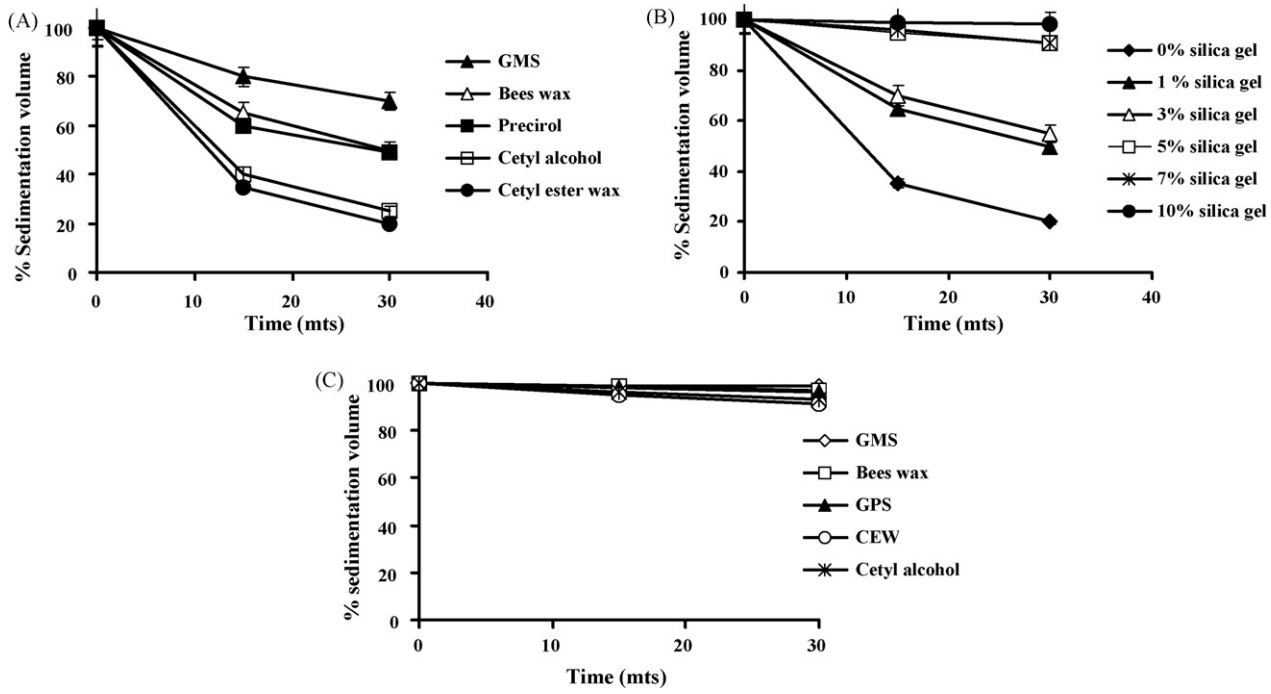

Fig. 3. Percent sedimentation volume of the (A) suspensions containing 10% (w/w) theophylline (without a suspending agent); (B) cetyl ester wax suspensions containing a 10% (w/w) of theophylline and increasing amounts of silica gel; (C) suspensions containing a 10% (w/w) theophylline and a 5% (w/w) colloidal silica gel.

silica gel is known to influence drug release rates (Realdon et al., 1997). Therefore, silica gel concentration was kept constant at 5% (w/w) in all the wax matrix formulations so that the release profiles could be compared. The percent sedimentation volumes of various molten wax suspensions containing a 10% (w/w) theophylline and a 5% (w/w) colloidal silica gel are given in Fig. 3(C).

3.3. Pellet size

The average sizes of the pellets and their corresponding standard deviations are given in Table 3. The standard deviations of different batches of the pellets indicate that the pellets have a very narrow size distribution or monodisperse.

3.4. Factors affecting the size of wax matrix pellets

3.4.1. Effect of wax type on the pellet size

Eq. (2) indicates that the pellet size primarily depends on the ratio of interfacial tension (γ_{LL}) to the density difference ($\Delta\rho$) between the molten matrix and the column liquid for a particular needle gauge size. $P(=\gamma_{LL}/\Delta\rho)$ values as determined for cetyl ester wax, beeswax, cetyl alcohol, Precirol and GMS (pure waxes) against 80% (w/w) glycerol solutions at 75 °C were 45.67, 44.78, 28.01, 22.94 and 9.846 $cm^3\ s^{-2}$, respectively (Cheboyina et al., 2006; Cheboyina, 2006). However, *P*-values of wax–drug dispersions against 80% (w/w) aqueous glycerol solutions might be different from the above determined values because of the changes induced in density and interfacial tension after the addition of suspending agent and drug to the molten wax. The interfacial tension between the molten wax matrix suspensions (which have different surface characteristics compared to neat liquids) and the aqueous glycerol solutions could not be determined at this time considering the complexity and uncertainty in the measurement techniques. However, it was observed that each of the wax matrices containing theophylline and silica gel yielded a different pellet size even though the needle size was kept constant. The size of the drug loaded wax pellets obtained, confounded well with the *P*-values of the pure waxes. As the *P*-value increased pellet size increased (Fig. 4).

3.4.2. Effect of needle gauge size on the pellet size

It was observed that as the gauge size of the needle increased from 12 to 25 G, the size of GMS pellets containing a 10% (w/w) theophylline decreased from 2.55 ± 0.1 to 1.27 ± 0.04 mm (see Table 3). The nominal outer radii of 12, 16, 20, 22 and 25 G needle tips were 1.385, 0.825, 0.451, 0.355 and 0.254 mm, respectively (Aldrich catalog, 2003-04, p T698). Fig. 5 shows the effect of cubic root of outer

Table 3
The average sizes and percent drug recoveries[a] of various wax matrix pellets

Sustained release pellets	Pellet size (mm)	Drug recovery (%)	Sustained release pellets	Pellet size (mm)	Drug recovery (%)
F#1	2.82 ± 0.10	94.5 ± 1.5	F#10	1.57 ± 0.06	99.5 ± 1.0
F#2	2.79 ± 0.07	100 ± 1.6	F#11	1.69 ± 0.05	99 ± 1.0
F#3	2.24 ± 0.06	96.5 ± 2.5	F#12	1.74 ± 0.04	100.5 ± 1.5
F#4	2.09 ± 0.06	98.5 ± 2.0	F#13	1.76 ± 0.04	99.3 ± 1.0
F#5	1.51 ± 0.04	100.4 ± 1.3	F#14	2.08 ± 0.04	98.5 ± 1.5
F#6	2.55 ± 0.08	101.5 ± 1.5	F#15	2.05 ± 0.06	97.5 ± 2.0
F#7	2.05 ± 0.1	99 ± 0.5	F#16	2.02 ± 0.07	96.7 ± 1.2
F#8	1.71 ± 0.05	99.5 ± 1.0	F#17	1.96 ± 0.07	90.7 ± 2.0
F#9	1.27 ± 0.04	98 ± 1.5	F#18	1.67 ± 0.06	96.3 ± 2.4

[a] Pooled samples and $n = 3$.

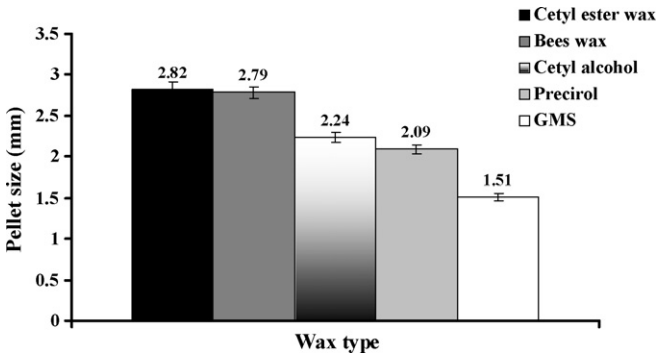

Fig. 4. Effect of wax type on the size of pellets containing a 10% (w/w) theophylline and prepared using a 22-G needle tip.

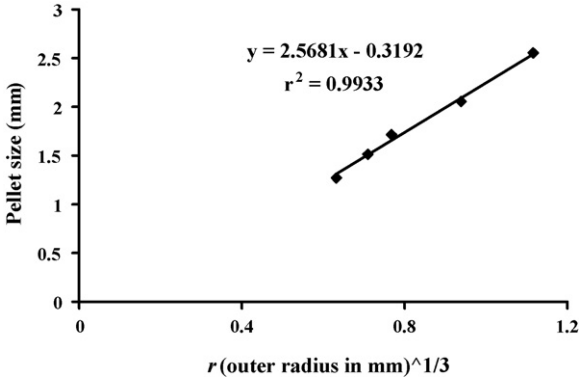

Fig. 5. Effect of cubic root of outer radius of the needle tip on the size of GMS pellets containing a 10% (w/w) theophylline.

radius of the needle tip ($r_N{}^{1/3}$) on the size of pellets formed. It was observed that as $r_N{}^{1/3}$ increases, pellet size increases linearly ($r^2 = 0.9933$) as indicated by Eq. (2). Outer radii were considered because molten waxes were found to wet the stainless steel circular needle tips (Cheboyina et al., 2006).

3.4.3. Effect of drug loading on the pellet size

It was observed that as theophylline loading increased from 2 to 20% (w/w), pellet size increased from 1.57 ± 0.05 to 1.76 ± 0.04 mm as shown in the Fig. 6. However, Tukey–kramer multiple comparison tests indicated that there was no significant difference in size

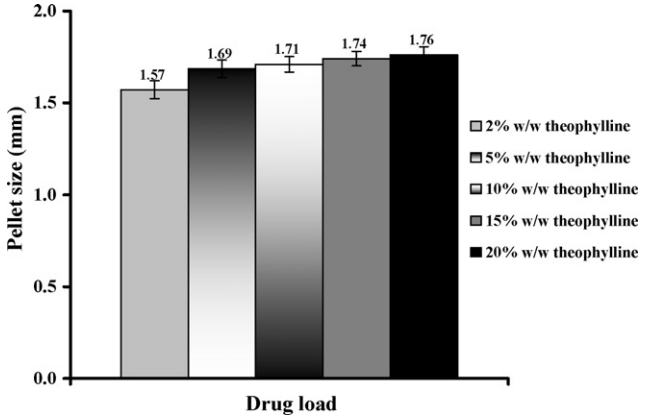

Fig. 6. Effect of increase in theophylline loading on the size of GMS pellets prepared using a 20-G needle tip.

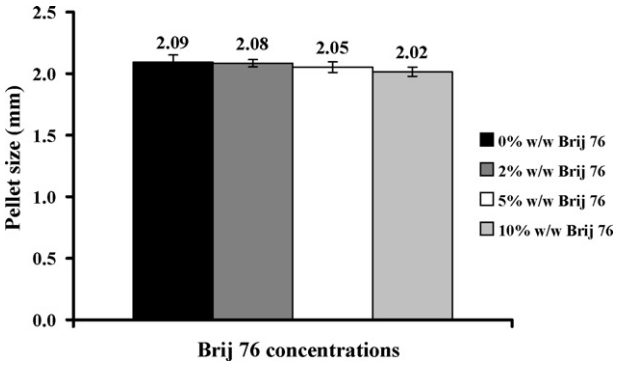

Fig. 7. Effect of increase in Brij 76 concentration on the size of Precirol pellets containing a 10% (w/w) theophylline and prepared using a 22-G needle tip.

among GMS pellets containing 10, 15 and 20% (w/w) theophylline. There was also no significant difference in size between GMS pellets containing 5 and 10% (w/w) theophylline. However, GMS pellets containing 5% (w/w) theophylline were smaller than the pellets containing 15 and 20% (w/w) theophylline but larger than the pellets containing 2% (w/w) theophylline. GMS pellets containing 2% (w/w) theophylline were significantly smaller than all other pellets.

As explained in the Section 3.4.1, pellet size can be affected by the changes in the interfacial tension and the density difference. As the theophylline concentration increases in the matrix, the density of the matrix also increases (theophylline being denser than GMS). This increase in the matrix density decreases the density difference between the matrix and the 80% glycerol solution. Eq. (2) indicates that as the density difference decreases, an increase in the pellet size is expected primarily if interfacial tension increases or remains constant. However, from the experimental results (Fig. 6) it appeared that this slight increase in pellet size with increase in drug loading was due to the increase in the density of the matrix with no appreciable change in the interfacial tension.

3.4.4. Effect of surfactant concentration on the pellet size

A reduction in the surface/interfacial tension can be achieved by the addition of a surfactant, which may result in smaller pellets. The pellet size may also depend upon the surface activity of the drug itself (Knoch, 1994). It was observed that as the surfactant concentration increased from 2 to 10% (w/w), pellet size slightly decreased from 2.08 ± 0.03 to 2.02 ± 0.04 mm as shown in the Fig. 7. However, Tukey–Kramer multiple comparison tests indicated that there was no significant difference in size among Precirol pellets containing 0, 2 and 5% (w/w) Brij 76. There was also no significant difference in size between Precirol pellets containing 5 and 10% (w/w) Brij 76. But Precirol pellets containing 0 and 2% (w/w) Brij 76 were significantly larger than the pellets containing 10% (w/w) Brij 76.

As Brij concentration increases in the matrix, the density of the matrix also increases because Brij replaces some parts of Precirol and the density of Brij is higher than that of Precirol ($\rho_{Brij} = 0.946\,g/cm^3$ at 75 °C and $\rho_{Precirol} = 0.885\,g/cm^3$ at 75 °C). This increase in matrix density decreases the density difference between the matrix and the 80% glycerol solution. Based on Eq. (2), as the density difference decreases, pellet size decreases only if the interfacial tension decreases. Therefore, this slight decrease in pellet size with increase in surfactant concentration was due to the decrease in interfacial tension between the molten matrix and 80% glycerol solution.

3.5. Efficiency of drug loading

The average drug content of pooled samples ($n = 3$) for all the batches of wax matrix pellets are given in Table 3. It was observed that efficiency of drug loading primarily depended on the wax type and the aqueous solubility of the drug. For the pellets prepared using various waxes (F#1–F#5) containing a 10% (w/w) theophylline (nominal), the drug content seemed to depend on the physical stability of the molten matrix suspensions. The encapsulation efficiency of these pellets were of the following rank order; GMS ≥ beeswax > Precirol > cetyl alcohol > cetyl ester wax. This is the same order as the increasing physical stability of these suspensions.

In the case of theophylline, the average drug content in Precirol and GMS pellets ranged from 98.5 to 101.5% of the nominal amount. However, the average drug contents in Precirol and GMS pellets containing diltiazem HCl were 90.7 and 96.3%, respectively. The lower drug content values obtained for diltiazem HCl pellets was likely due to the leaching of drug from the pellets into the column liquid (80% glycerol solution) and deionized water during the pelletization and washing steps, respectively, as diltiazem HCl is a more water soluble drug (~100 times) when compared to theophylline. The reason for the higher recovery of diltiazem HCl in GMS pellets than in Precirol pellets at the same theoretical concentration might be due to the greater physical stability of molten GMS suspensions when compared to Precirol suspensions.

3.6. Hardness and friability

The hardness of GMS pellets containing varying theophylline content (2–20% (w/w)) was determined. The average hardness of pellets for each of the batches is presented in Table 4. From the results, it was observed that as the theophylline loading increased, hardness of the pellets increased. The average hardness values indicate that pellets have sufficient strength to withstand potential destructive forces encountered in the GI tract (Kamba et al., 2002). The friability of all the pellet batches was found to be less than 0.5%.

Table 4
The average hardness of GMS pellets containing increasing loads of theophylline

Formulation	Hardness (*N*)
F#10	2.54 ± 0.31
F#11	2.79 ± 0.29
F#8	3.27 ± 0.69
F#12	4.17 ± 0.31
F#13	4.53 ± 0.40

3.7. Microscopic analysis

Microscopic images (Fig. 8A and B) of the thin sections indicated the presence of theophylline crystals in GMS pellets containing 10 and 20% (w/w) theophylline. Moreover, they also showed that the drug particles were homogenously distributed throughout the matrix. But theophylline crystals were not evident in the GMS pellets containing 2% (w/w) (photograph not shown) and 5% (w/w) theophylline (Fig. 8C).

3.8. Differential scanning calorimetry

DSC scans of theophylline anhydrous, GMS, GMS pellets containing 20% (w/w) theophylline and GMS–theophylline physical mixture containing 20% (w/w) theophylline are shown in Fig. 9.

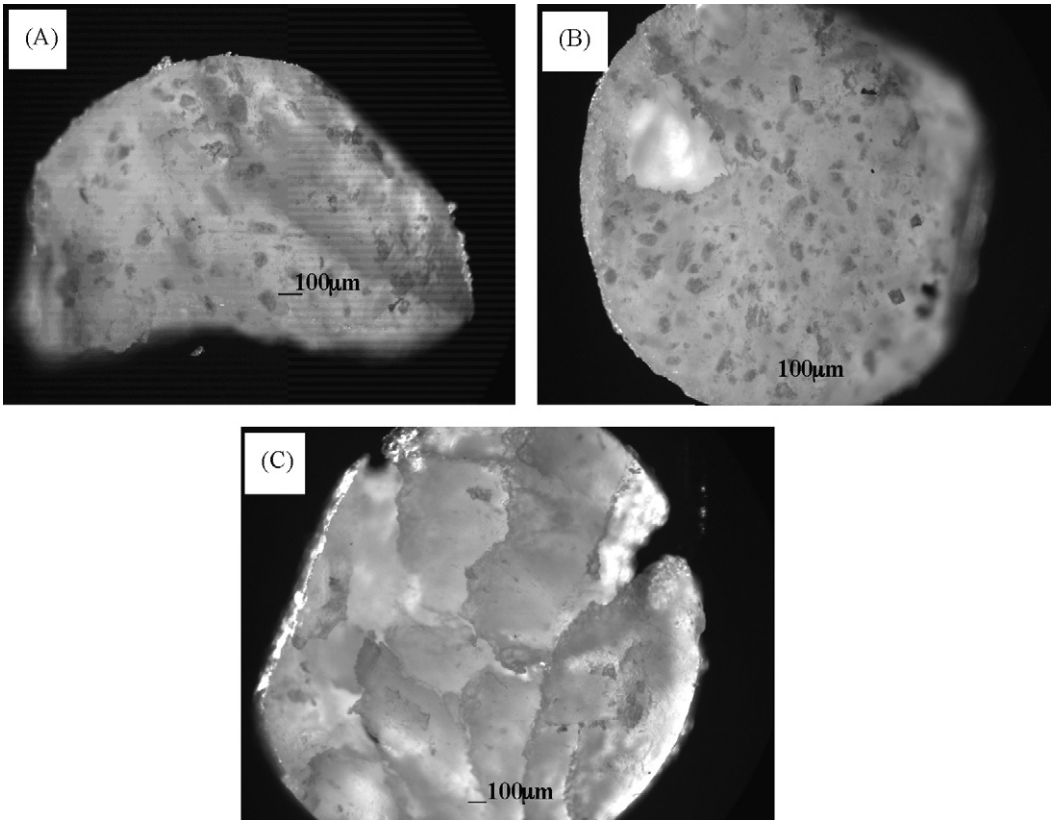

Fig. 8. Microscopic images (100×) showing the presence (A and B) and absence (C) of theophylline particles in thin sections of GMS pellets: (A) 10% (w/w) theophylline pellets; (B) 20% (w/w) theophylline pellets; (C) 5% (w/w) theophylline pellets.

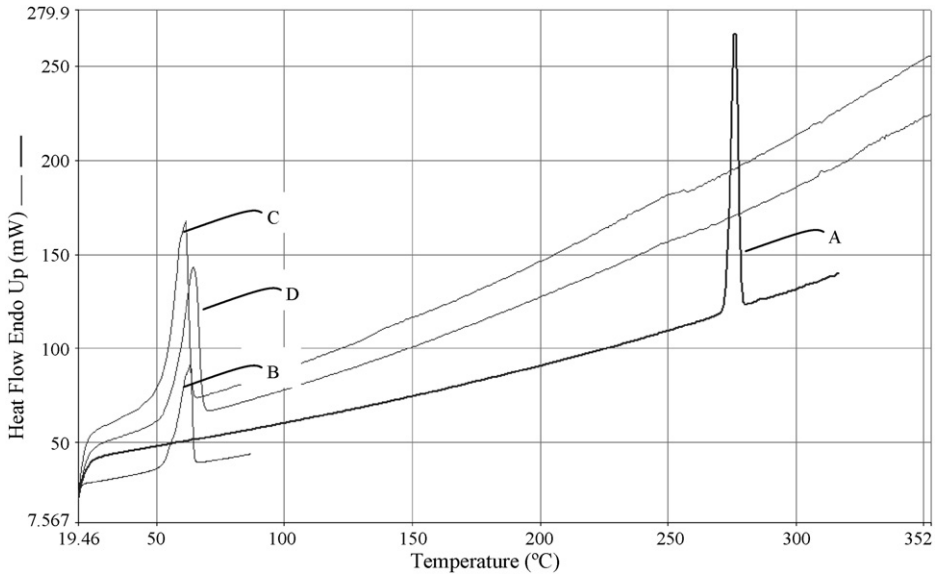

Fig. 9. DSC thermographs: (A) theophylline; (B) GMS; (C) GMS pellets containing 20% (w/w) theophylline; (D) GMS–theophylline physical mixture containing 20% (w/w) theophylline.

Thermogram of theophylline showed endothermic melting peak at 273.6 °C. However, it was observed that neither the pellet formulation nor the physical mixture showed any endotherms corresponding to the melting point of theophylline. This suggests that theophylline dissolved in the wax matrix as the temperature was raised up to its melting point during the DSC run because it is unlikely for theophylline to form a solid solution in the physical mixture. Moreover, microphotographs clearly indicated the presence of theophylline crystals in the GMS matrices at higher drug loads. The small endothermic peaks observed in the pellet formulation and the physical mixture near the melting point of drug might be due to enthalpic changes occurring during the process of drug dissolution in the wax matrix. Therefore, DSC studies alone cannot be used to conclusively determine the physical state of theophylline in GMS matrices. Even though, there is evidence that theophylline exists in a crystalline state at higher drug loads, its physical state at lower drug loads is unclear. Even the powder X-ray diffraction studies were inconclusive as this technique is not sensitive enough to detect crystalline materials present at these low concentrations (2 and 5% (w/w)). However, DSC studies and microphotographs suggest that theophylline may exit in a dissolved state at low drug loads. Moreover, the evidence that theophylline existed in dissolved and crystalline states at low and high drug loads, respectively, also came from the dissolution studies which will be presented in the second part of this article.

From the scans, it was also observed that untreated GMS (as received) and GMS in the physical mixture (B and D in Fig. 9) showed endothermic melting peaks at 63.03 and 64.40 °C, respectively, and GMS in the pellet formulations (C in the Fig. 9) showed an endothermic melting peak at 61.491 °C. The enthalpy values (ΔH) of GMS in the pellet formulation, physical mixture and untreated sample were 98.68, 135.72 and 141.75 J/g, respectively. The lower enthalpy value and melting endothermic peak of GMS in the pellet formulations was due to the formation of unstable polymorphic forms in the melt-cooled GMS pellets which are known to transform into a more stable polymorphic form on ageing and/or storage conditions. These polymorphic transitions in the melt-cooled waxes are well documented in the literature (Eldem et al., 1991a,b; Hamdani et al., 2003).

4. Conclusions

The freeze pelletization technique is a novel and simple pelletization technique for the preparation of wax matrix pellets. To demonstrate the applicability of this technique, wax-based spherical matrix pellets containing water soluble drugs were successfully prepared using a variety of waxes in apparatus II. The effect of various formulation and process related variables on shape, size and other pellet characteristics were evaluated. This technique produced pellets with acceptable drug loads (up to 20% (w/w)) and percent drug recoveries ($100 \pm 10\%$). Therefore, freeze pelletization technique can produce wax matrix pellets containing drugs of varying aqueous solubility, which can be potentially used for various sustained release applications.

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