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Wax-based sustained release matrix pellets prepared by a novel freeze pelletization technique
II. *In vitro* drug release studies and release mechanisms

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ABSTRACT

A novel freeze pelletization technique was evaluated for the preparation of wax-based sustained release matrix pellets. Pellets containing water-soluble drugs were successfully prepared using a variety of waxes. The drug release significantly depended on the wax type used and the aqueous drug solubility. The drug release decreased as the hydrophobicity of wax increased and the drug release increased as the aqueous drug solubility increased. In glyceryl monostearate (GMS) pellets, drug release rate decreased as the loading of theophylline increased. On the contrary, the release rate increased as the drug loading of diltiazem HCl increased in Precirol pellets. Theophylline at low drug loads existed in a dissolved state in GMS pellets and the release followed desorption kinetics. At higher loads, theophylline existed in a crystalline state and the release followed dissolution-controlled constant release for all the waxes studied. However, with the addition of increasing amounts of Brij 76, theophylline release rate increased and the release mechanism shifted to diffusion-controlled square root time kinetics. But the release of diltiazem HCl from Precirol pellets at all drug loads, followed diffusion-controlled square root time kinetics. Therefore, pellets capable of providing a variety of release profiles for different drugs can be prepared using this freeze pelletization technique by suitably modifying the pellet forming matrix compositions.

1. Introduction

The freeze pelletization technique is a simple and novel pelletization 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 an upward or downward direction, depending on their density with respect to the liquid in the column, and solidify into spherical pellets. A mathematical model to predict the size of the pellets formed in this freeze pelletization process was derived previously (Cheboyina et al., 2006). In a more recent study (Cheboyina and Wyandt, 2008), a variety of wax-based spherical matrix pellets were successfully prepared using this technique in apparatus II. Further, the effect of various formulation and process related parameters on the pellet size and shape was studied. Pellets were also evaluated for drug encapsulation efficiency, uniformity of drug distribution, physical state of the drug in the matrix, hardness and friability.

The present study primarily focused on the effect of wax type, pellet size, aqueous solubility of the drug, drug loading and addition of surfactant to the wax matrix on the *in vitro* drug release characteristics of these wax matrix pellets. Two different model drugs of varying aqueous solubility were used in this study; theophylline, a sparingly water-soluble drug and diltiazem hydrochloride, a highly water-soluble drug. The dissolution data obtained was fitted to various mathematical models corresponding to possible release mechanisms. The mathematical equations that were used to characterize these release profiles are presented below.

In matrix systems, a drug is homogeneously dissolved or dispersed throughout the carrier solid. If the drug is dissolved in the rate controlling carrier solid, then the system is called a monolithic solution. On the contrary, if the drug has a limited solubility in the carrier solid and only a portion of the drug is dissolved in the carrier solid and the remaining is dispersed as particulates, such a system is called monolithic dispersion. The mechanism of drug release from a non-swellable and non-erodible wax matrix system is primarily diffusion. The release rate of a dissolved drug from a matrix system is similar to the desorption process (desorption of an adsorbed

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drug) and it can be approximated using two equations for a planar system (Baker, 1987) as follows:

$$\frac{dM_t/M_0}{dt} = 2\left(\frac{D}{\pi l^2 t}\right)^{1/2} \quad \text{for } 0 \le M_t/M_0 \le 0.6 \tag{1}$$

and

$$\frac{dM_t/M_0}{dt} = \frac{8D}{l^2}\exp\left(\frac{-\pi^2 Dt}{l^2}\right) \quad \text{for } 0.4 \le M_t/M_0 \le 1.0. \tag{2}$$

where M_t/M_0 is the fractional drug release at time t, D is the diffusion coefficient of the drug in the matrix and l is the length of the slab.

In the case of monolithic dispersions, a mathematical model to describe the drug release process from a homogenous slab is (Higuchi, 1961):

$$\frac{dM_t}{dt} = A\left(\frac{DC_sC_0}{2t}\right)^{1/2} \quad \text{for } C_0 \gg C_s \tag{3}$$

where A is the total surface area, C_0 is the amount of the drug per unit volume of the slab, M_t is the drug release at time t and C_s is the saturation solubility of the drug in the matrix. However, a mathematical equation to describe the drug release process from a granular slab is (Higuchi, 1963):

$$\frac{dM_t}{dt} = A\left(\frac{D_e\varepsilon C_sC_0}{2\tau t}\right)^{1/2} \quad \text{for } C_0 \gg C_s \tag{4}$$

where ε and τ are the porosity and tortuosity of the matrix that exists after the amount of drug M_t is released, and D_e is the effective diffusion coefficient for the drug in the fluid filled matrix pores. For a homogenous monolithic sphere of radius, r, a mathematical equation to describe the drug release process is (Higuchi, 1963; Baker and Lonsdale, 1974):

$$\frac{3}{2}\left[1-\left(1-\frac{M_t}{M_0}\right)^{2/3}\right] - \frac{M_t}{M_0} = \frac{3DC_s}{r^2C_0}t \tag{5}$$

In monolithic solutions (Eqs. (1) and (2)), the release rate decreases in proportion to $t^{-1/2}$ until around 60% of the drug has been desorbed/released (square root of time kinetics) and after that the release rate falls off exponentially (first-order kinetics). However, in monolithic dispersions Eqs. (3) and (4), the release rate decreases in proportion to $t^{-1/2}$ for the complete release profile (when $C_s \sim 0$). Higuchi models for monolithic dispersions have been applied extensively in the literature with good results. However, instances have been reported (Haleblian et al., 1971; Ayres and Laskar, 1974; Bottari et al., 1974) where the drug release kinetics from drug-dispersed matrices could not be adequately described by these models because the models all assume instantaneous drug dissolution. Chandrasekran and Paul, 1982, developed a simplified dissolution rather than a diffusion-controlled model. In this model, the dissolution rate is proportional to the difference between the solubility of the drug in the matrix, C_s, and the actual concentration of the drug in the matrix at any point, C.

$$\frac{\partial C}{\partial t} = k(C_s - C) \tag{6}$$

where k is the dissolution rate constant. Applying the appropriate boundary conditions for the dissolved drug with respect to time and distance, the fractional release at any time t from a slab of length, l, was given as

$$\frac{M_t}{M_0} = 2\sqrt{\frac{Dk}{l^2}}\frac{C_s}{C_0}\left(\frac{1}{2k}+t\right) \tag{7}$$

From the above equation, it can be observed that the fractional release is directly proportional to time (zero-order kinetics) and inversely related to the initial drug load.

2. Materials and methods

2.1. Materials

Theophylline anhydrous (Theo), diltiazem hydrochloride (DHCl), glyceryl monostearate (GMS), cetyl ester wax, cetyl alcohol, yellow beeswax, glycerol and colloidal silica gel were purchased from Spectrum Chemical Mfg. Corp., New Brunswick, NJ. Precirol® ATO 5 (glyceryl palmitostearate) 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. Methods

2.2.1. Preparation of wax-based sustained release matrix pellets

The wax matrix pellets were prepared by dispersing either theophylline anhydrous or diltiazem HCl in a molten wax containing a 5% (w/w) colloidal silica gel and introducing the molten matrix as droplets into apparatus II. A detailed description of this apparatus and wax matrix pellet preparation methods were described previously (Cheboyina and Wyandt, 2008).

2.2.2. Factors affecting the release characteristics of sustained release wax pellets

2.2.2.1. Effect of wax type on the release of theophylline from matrix pellets. The effect of wax type on the release of theophylline was studied by preparing different wax matrix pellets including beeswax, cetyl ester wax, cetyl alcohol, Precirol and glyceryl monostearate. It was observed that each of the wax matrices containing a 10% (w/w) theophylline yielded a different pellet size even though the needle gauge size was kept constant (Cheboyina and Wyandt, 2008). Therefore, needle sizes were chosen in such a way that the pellet sizes obtained for all the waxes were approximately of the same size. Consequently, GMS, Precirol, cetyl alcohol, cetyl ester wax and beeswax pellets containing a 10% (w/w) theophylline were prepared using 12, 18, 20, 25 and 25 G needles respectively to produce pellets of size 2.55 ± 0.1 mm.

2.2.2.2. Effect of pellet size on the release of theophylline. The effect of pellet size on the release of theophylline was studied by preparing GMS and Precirol pellets containing a 10% (w/w) theophylline. GMS pellets were prepared using 12, 16, 20 and 25 G needles and Precirol pellets were prepared using 18, 22 and 25 G needles.

2.2.2.3. Effect of aqueous drug solubility on the release profiles. The effect of aqueous drug solubility on the release profiles was studied using theophylline, a sparingly water-soluble model drug (~6 mg/ml) and diltiazem hydrochloride, a highly water-soluble model drug (~600 mg/ml). Pellets containing a 10% (w/w) model drug were prepared with GMS and Precirol waxes using 20 and 22 G needles respectively.

2.2.2.4. Effect of drug loading on the release profiles. The effect of drug loading on the release was studied by preparing pellets containing increasing loads (from 2 to 20% (w/w)) of theophylline and diltiazem HCl in GMS and Precirol pellets respectively. GMS pellets were prepared using 20 G needles and Precirol pellets were prepared using 22 G needles.

2.2.2.5. Effect of surfactant concentration on the theophylline release from Precirol pellets. All the Precirol pellets containing theophylline exhibited very low dissolution rates. Therefore, in order to enhance the dissolution rate of theophylline, increasing amounts of Brij 76 (HLB = 12.4) including 2, 5 and 10% (w/w) were added to the Precirol pellets containing a 10% (w/w) theophylline. These pellets were prepared using a 22-G needle.

2.2.3. In vitro release studies of sustained release wax matrix pellets

In vitro release studies were conducted in triplicate by placing 200 mg of pellets in 1-l dissolution flasks containing 900 ml of deionized water. USP apparatus I (Hanson SR 6, Hanson Research Corp., Chatsworth, CA) was used at a rotation speed of 100 ± 2 rpm and maintained at $37 \pm 0.5\,^{\circ}$C. 10 ml samples were withdrawn from the dissolution flasks using a syringe, and filtered before analysis. Samples were collected at 0.25, 0.5, 1, 2, 4, 6, 9, 12 and 24 h. But in selected pellet formulations, samples were also collected at 16 and 20 h. The amount of drug released was analyzed using a UV spectrophotometer (Lambda EZ201, PerkinElmer, Norwalk, CT) at 271 and 236 nm for theophylline and diltiazem HCl respectively.

2.2.4. Dissolution data analysis

The dissolution data obtained was fitted to various mathematical models corresponding to possible release mechanisms. Approximately first 90% of the total drug released was fitted into the following equations except Eq. (9) to determine the goodness of fit of release data. The fractional drug release data between 0.4 and 1 was fitted to Eq. (9).

Zero-order release kinetics

$$F = k_1 t + c_1 \text{ (based on Eq. (7))} \quad (8)$$

First-order release kinetics

$$1 - F = e^{-k_2 t + c_2} \text{ (based on Eq. (2))} \quad (9)$$

Square root of time release kinetics

$$F = k_3 t^{1/2} + c_3 \text{ (based on Eq. (1) or (3))} \quad (10)$$

Higuchi spherical matrix release kinetics/Baker–Lonsdale model

$$3/2[1 - (1 - F)^{2/3}] - F = k_4 t + c_4 \text{ (based on Eq. (5))} \quad (11)$$

where F is the fraction of drug released, c_{1-4} are constants and k_{1-4} are the release rate constants.

In order to discriminate any two release profiles, a two-way ANOVA was performed using JMP 3.2.1, SAS Institute Inc., NC. In this test, $p < 0.05$ indicated that any two release profiles were statistically significantly different and $p > 0.05$ indicated the similarity between the two release profiles. The release profiles were also compared pair wise using a similarity factor (f_2) approach; where f_2 was defined as

$$f_2 = 50 \log \left\{ \left[1 + \frac{1}{n} \sum_{1}^{n} (R_t - T_t)^2 \right]^{-0.5} \times 100 \right\} \quad (12)$$

where R_t and T_t are the cumulative percent releases at time t, for any two release profiles. A f_2 value between 50 and 100 suggests that the two dissolution profiles are similar (Shah et al., 1998). However, it was observed that release profiles with f_2 values between 65 and 100 correlated well with the release profiles having p values greater than 0.05. Therefore, in this study, any two release profiles were considered similar if the f_2 values were between 65 and 100.

3. Results and discussion

3.1. Factors affecting the release characteristics of sustained release wax pellets

3.1.1. Effect of wax type on the release of theophylline from matrix pellets

The *in vitro* release studies indicated that the release of theophylline significantly depended on the type of wax used as a carrier solid (Fig. 1). The cumulative theophylline releases in 24 h were 3, 13, 19, 90 and 97% for beeswax, Precirol, cetyl ester wax, GMS and cetyl alcohol pellets respectively. This difference in the release profiles can be attributed to the chemical nature and the relative hydrophobicity of the waxes (Adeyeye and Price, 1994; Thomsen et al., 1994; Duclos et al., 1999). Beeswax primarily consists of various esters of straight-chain monohydric alcohols with even-numbered carbon chains (C_{24}–C_{36}) esterified with straight-chain acids. Precirol is a mixture of mono-, di- and triglycerides of fatty acids (C_{16} and C_{18}) and cetyl ester wax is a mixture of esters of saturated fatty alcohols (C_{14}–C_{18}) and saturated fatty acids. GMS is a monoglyceride of stearic acid (C_{22}) and has two free hydroxyl groups. Cetyl alcohol is an aliphatic alcohol (C_{16}) with one hydroxyl group.

GMS and cetyl alcohol, which have hydroxyl groups, are more susceptible to hydration by the dissolution media. Therefore, release rates of theophylline were found to be much higher for GMS and cetyl alcohol pellets when compared to the release rates obtained for other wax pellets. The relative hydrophobicities can be ranked depending on the length of carbon chains present in the waxes as follows: beeswax > Precirol > cetyl ester wax > GMS > cetyl alcohol. But the drug release rates were found to be in a reverse order. Therefore, as the hydrophobicity of the wax increased, theophylline release rate decreased.

3.1.2. Effect of pellet size on the release of theophylline from matrix pellets

The release profiles of GMS and Precirol pellets containing theophylline are shown in Fig. 2. From the release profiles, it was observed that the release rate slightly increased as the pellet size decreased in both GMS and Precirol pellets. There was higher than 90% drug release within 24 h for all the GMS pellets. However, in the case of Precirol pellets only 25, 21 and 13% of the total drug was released from 1.75, 2.09 and 2.55 mm pellets respectively in a 24-h time period. The release data were analyzed using a similarity factor approach (f_2) to discriminate any two selected release profiles. It was found that all the release profiles obtained for GMS and Precirol pellets prepared using different needle gauge sizes were

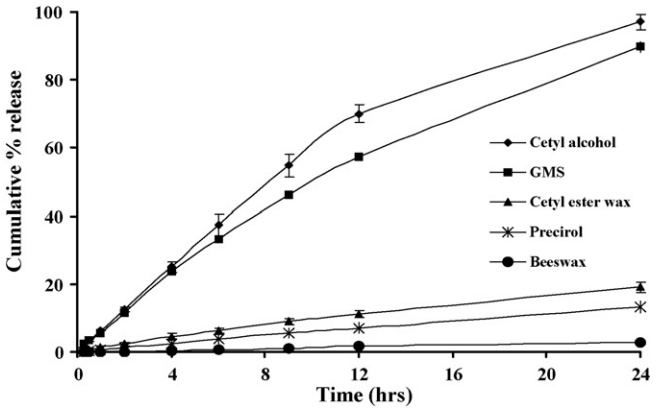

Fig. 1. Effect of wax type on the release of theophylline from different wax pellets of size 2.55 mm and containing a 10% (w/w) theophylline.

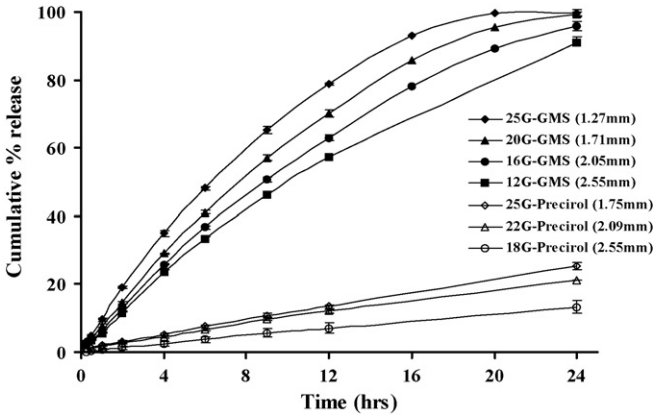

Fig. 2. Effect of pellet size on the release of theophylline from GMS and Precirol pellets containing a 10% (w/w) theophylline.

Table 1
Similarity factors (f_2)

Sustained release wax matrix pellets	f_2 value
GMS pellets—10% (w/w) Theo (12 G vs. 16 G)	46.19
GMS pellets—10% (w/w) Theo (16 G vs. 20 G)	46.94
GMS pellets—10% (w/w) Theo (20 G vs. 25 G)	40.67
Precirol pellets—10% (w/w) Theo (18 G vs. 22 G)	48.12
Precirol pellets—10% (w/w) Theo (22 G vs. 25 G)	64.88
GMS pellets (10% (w/w) Theo vs. 15% (w/w) Theo)	44.65
GMS pellets (15% (w/w) Theo vs. 20% (w/w) Theo)	46.3
Precirol pellets (10% (w/w) DHCl vs. 20% (w/w) DHCl)	23.75

significantly different from each other (refer Table 1). This increase in release rate with decreasing pellet size can be attributed to the increase in surface area exposed to the dissolution medium and decrease in diffusion path length (Voinovich et al., 2000; Guo et al., 2005).

3.1.3. *Effect of aqueous drug solubility on the drug release profiles of wax pellets*

The release profiles of GMS and Precirol pellets containing either a 10% (w/w) theophylline or diltiazem HCl are shown in Fig. 3. From the release profiles, it was observed that aqueous drug solubility had a significant effect on the release of drugs from the wax pellets. In the case of GMS, pellets containing theophylline and diltiazem HCl, 90% of the total drug was released in about 20 and 4 h

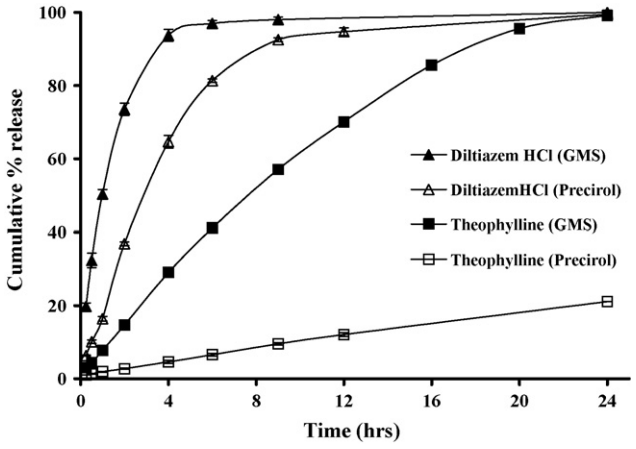

Fig. 3. Effect of aqueous drug solubility on the drug release from GMS and Precirol pellets containing a 10% (w/w) drug and prepared using 20 and 22 G needles respectively.

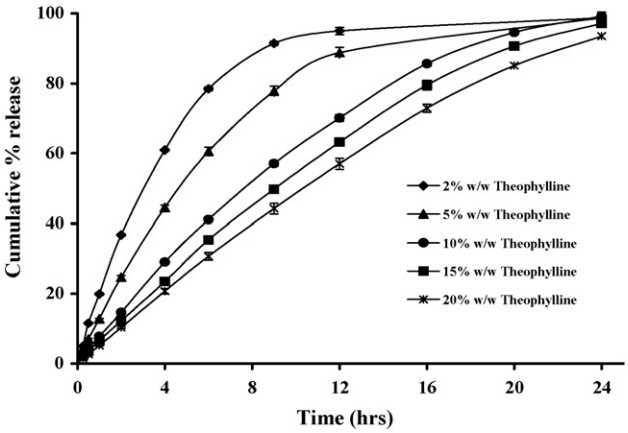

Fig. 4. Effect of drug loading on the release of theophylline from GMS pellets prepared using a 20-G needle.

respectively. In the case of Precirol pellets containing diltiazem HCl, 90% of the total drug was released in about 9 h. However, Precirol pellets containing theophylline released only 21% in 24 h of dissolution. These differences in the release profiles can be attributed to the higher aqueous solubility of diltiazem HCl when compared to theophylline (100 times more soluble). For drugs with high aqueous solubility, drug dissolution and diffusion are much faster than for sparingly water-soluble drugs (Brossard et al., 1991; Hamdani et al., 2002) and hence faster release rates were observed for diltiazem HCl.

3.1.4. *Effect of drug loading on the release profiles of wax pellets*

The release profiles of GMS pellets containing theophylline and Precirol pellets containing diltiazem HCl are given in Figs. 4 and 5 respectively. All the release profiles were found to be statistically significantly different from each other (selected f_2 values are given in Table 1). It was observed that drug release significantly decreased as the concentration of theophylline increased in GMS matrices. This decrease in the drug release was not associated with the slight increase in pellet size, which was observed as the concentration of theophylline increased. It was found that there was no significant size difference in GMS pellets containing 10, 15 and 20% (w/w) theophylline and pellets containing 5 and 10% (w/w) theophylline (Cheboyina and Wyandt, 2008). Moreover, the effect of pellet size on theophylline release was marginal. Even when the pellet size decreased as low as 0.5 mm, there was less than 10% increase in percent cumulative dissolutions at all time points (see Fig. 2). GMS

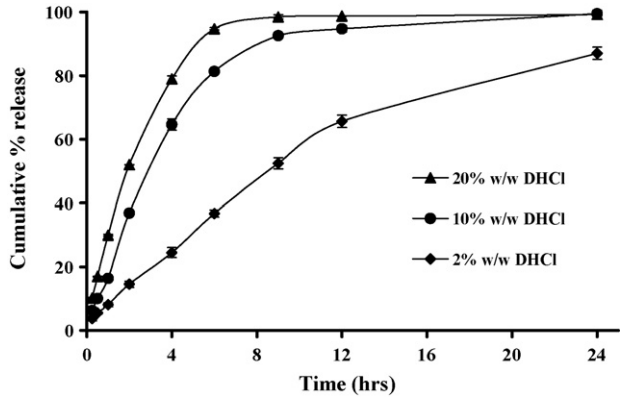

Fig. 5. Effect of drug loading on the release of diltiazem HCl from Precirol pellets prepared using a 22-G needle.

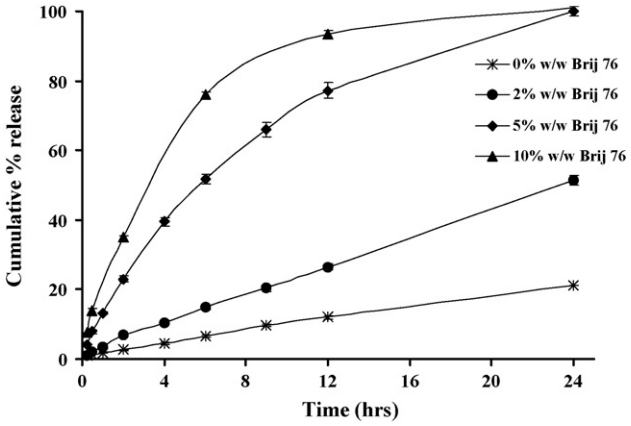

Fig. 6. Effect of Brij 76 concentration on theophylline release from Precirol pellets containing a 10% (w/w) theophylline and prepared using a 22-G needle.

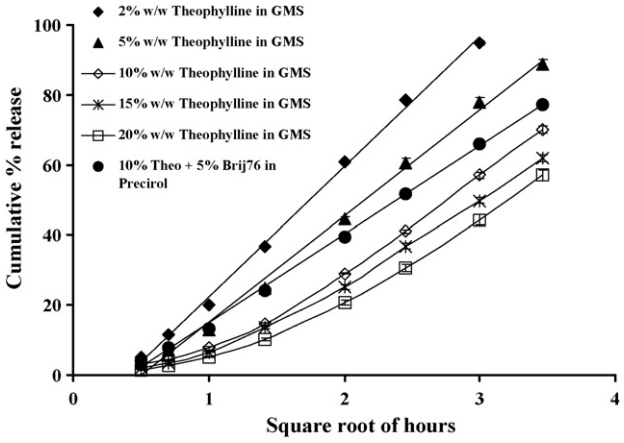

Fig. 7. Release data of pellets containing theophylline fitted to square root model.

pellets containing 2, 5, 10, 15 and 20% (w/w) theophylline released 90% of the total drug in about 9, 12, 18, 20 and 22 h respectively. Moreover, the drug release profiles appeared to have changed from a non-linear to linear kinetics with an increase in theophylline drug loading. On the contrary, the drug release increased significantly as diltiazem HCl loading increased in Precirol pellets. Precirol pellets containing 10 and 20% (w/w) diltiazem HCl released more than 90% of the drug in about 9 and 6 h respectively. However, only 87% of the total drug was released at the end of 24 h from pellets containing 2% (w/w) diltiazem HCl. Mechanisms corresponding to these release profiles will be explored in Section 3.2.

3.1.5. *Effect of surfactant concentration on theophylline release from Precirol pellets*

Fig. 6 shows the release of theophylline from Precirol pellets containing increasing amounts of Brij 76. From the release profiles, it was observed that there was a significant increase in the drug release as the surfactant concentration increased. This increase in the drug release was not associated with the slight decrease in pellet size, which was observed as Brij concentration increased. It was found that there was no significant difference in pellet size among Precirol pellets containing 0, 2 and 5% (w/w) Brij 76 and pellets containing 5 and 10% (w/w) Brij 76 (Cheboyina and Wyandt, 2008). Moreover, the effect of pellet size on theophylline release was marginal (Fig. 2).

Precirol pellets containing 5 and 10% (w/w) Brij 76 released 100% theophylline by the end of 24 h. However, only 21 and 51% of the total drug were released at the end of 24 h from Precirol pellets containing 0 and 2% (w/w) Brij 76 respectively. Moreover, the drug release profiles appeared to have changed from a linear to non-linear kinetics as the Brij concentration increased. The increase in the release of theophylline can be explained in two ways; first, the addition of Brij 76 could enhance the hydration of the wax matrix by the dissolution medium and thereby increase the diffusion of the dissolved drug from the matrix. It was observed that Brij 76 and Precirol were completely miscible in all proportions. Second, the addition of Brij 76 could enhance the dissolution rate of sparingly water-soluble theophylline crystals. It is well known that surfactants can enhance the solubility and dissolution rate of sparingly water-soluble drugs (Javadzadeh et al., 2005; Kawakami et al., 2006).

3.2. *Release mechanisms and mathematical modeling of release profiles*

Release data obtained from the pellet formulations were fitted to various mathematical models corresponding to possible release mechanisms. The goodness of fit (r^2) values for the various models are given in Table 2. Fig. 7 shows plots of the release data of theophylline pellets fitted to the square root of time model. These plots and the results in Table 2 indicated that there was a change in the release mechanism of theophylline in GMS matrices as the drug loading increased from 2 to 20% (w/w). *F*-test used to compare the models indicated that the dissolution data of GMS pellets containing 10, 15 and 20% (w/w) theophylline fitted very closely to zero-order kinetics but fitted poorly to square root, Higuchi spherical matrix and first-order kinetics ($p < 0.001$, goodness of fit for zero-order model was significantly more than that of other models). From the above analysis, it appears that release of theophylline followed a dissolution-controlled process at a higher drug load ($\geq$10%). In this model Eq. (7), the amount of drug released varies directly with time (zero-order). It is possible to visualize three steps which govern the drug release from wax pellets; penetration of the dissolution medium into the wax matrix, dissolution of dis-

Table 2
Goodness of fit (r^2) of dissolution data for the drug release mathematical models

Sustained release wax matrix pellets		Square root kinetics	Zero-order kinetics	Higuchi spherical matrix kinetics	First-order kinetics
GMS pellets	2% (w/w) theophylline	0.9947	0.9463	0.9862	0.9961
	5% (w/w) theophylline	0.9955	0.9659	0.9687	0.9933
	10% (w/w) theophylline	0.9821	0.9946	0.9448	0.9619
	15% (w/w) theophylline	0.9847	0.9948	0.9582	0.9765
	20% (w/w) theophylline	0.9827	0.992	0.9153	0.9548
Precirol pellets	2% (w/w) diltiazem HCl	0.9975	0.9301	0.9752	0.9838
	10% (w/w) diltiazem HCl	0.9974	0.9352	0.9566	0.9851
	20% (w/w) diltiazem HCl	0.9915	0.9507	0.9831	0.9895
	10% (w/w) theophylline+5% (w/w) Brij 76	0.9895	0.8847	0.9719	0.9411

persed drug particles and diffusion of the dissolved drug through the wax matrix. The slowest step will control the release rate. If diffusion of the drug is the rate-limiting step, the drug release follows Higuchi square root kinetics. However, if the dissolution of the drug is the rate-limiting step, the drug release follows zero-order kinetics. Since, theophylline is a sparingly water-soluble drug, dissolution may be the rate-limiting step.

It was also observed that there was a significant difference in the release profiles of Precirol pellets containing 10% (w/w) theophylline and varying concentrations of Brij 76. The pellets containing 0 and 2% (w/w) Brij 76 were found to follow zero-order kinetics whereas pellets containing 5 and 10% (w/w) Brij 76 followed square root kinetics (see Fig. 6, Fig. 7 and Table 2). The concentrations of Brij 76 at or above 5% (w/w) enhanced the dissolution rate of sparingly water-soluble theophylline crystals. Hence, a shift in the drug release profile of theophylline from zero-order to Higuchi square root kinetics was observed. Moreover, microphotographs indicated that theophylline particles were homogenously distributed throughout the matrix and existed in a crystalline state at higher drug loadings (Cheboyina and Wyandt, 2008). Therefore, wax matrices being non-swellable and non-erodible, a dissolution-controlled release mechanism is the logical explanation for the constant release rates observed at higher theophylline loadings. It was also previously observed that theophylline release from polyethylene oxide (PEO) matrices followed a zero-order model (Kim, 1995; Kim, 1998). The author noted that diffusion did not play an important role in the release of theophylline from PEO tablets. Similar linear dissolution profiles were also observed by other researchers for various sparingly water-soluble drugs (Haleblian et al., 1971; Ayres and Laskar, 1974; Bottari et al., 1974). The dissolution-controlled release model Eq. (7) also indicates that the fractional drug release is inversely proportional to the initial drug load. For GMS pellets containing theophylline (10, 15 and 20% (w/w)), the decrease in fractional drug release with increasing drug content might be due to the presence of more crystal domains in the pellets. At low loads, drug particles are well separated and result in faster dissolution rates. This decrease in fractional drug release with an increase in drug load was also observed for other poorly water-soluble drugs (Haleblian et al., 1971; Bottari et al., 1974; Rubio and Ghaly, 1994; Zhou et al., 1996).

The drug release from the matrix pellets where the drug exists in a dissolved state are described by Eq. (9) (based on Eq. (2)) and Eq. (10) (based on Eq. (1)). *F*-test was used to compare the models and it indicated that the dissolution data of GMS pellets containing 2 and 5% (w/w) theophylline fit both the square root and first-order kinetics very closely ($p = 0.165$ for 2% (w/w) Theo and $p = 0.202$ for 5% (w/w) Theo) but had a poor fit to the zero-order and Higuchi spherical matrix kinetic models ($p < 0.001$, goodness of fit for square root and zero-order models was significantly more than that of other models). Even the microscopic studies did not indicate the presence of any drug crystals in these pellets (Cheboyina and Wyandt, 2008). Therefore, theophylline at low concentrations existed in a dissolved state in GMS matrices and the release followed desorption kinetics. This conclusion can be further supported by the fact that the terminal release profiles (after 85 or 90% drug release) of the pellets containing higher loads of theophylline (>10%, w/w) are non-linear (Fig. 4). This non-linearity was due to the release of the dissolved drug remaining in the matrix after the crystalline drug was depleted. And since there is no dissolution step involved in drug release from the pellets containing low drug loads (2 and 5% (w/w)), a higher release rate was observed from them when compared to pellets containing higher drug loads. Similar conclusions were drawn on the release behavior of nifedipine from polyacrylate microspheres (Benita et al., 1990).

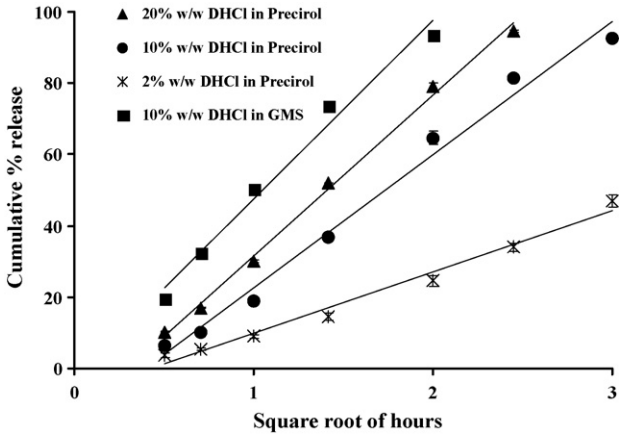

Fig. 8. Release data of pellets containing diltiazem HCl fitted to square root model.

In the case of Precirol pellets containing diltiazem HCl, *F*-test indicated that the release profiles fitted very closely to the square root model but fitted poorly to zero-order, first-order and spherical matrix kinetics ($p < 0.0001$, goodness of fit for square root model was significantly more than that of other models). Therefore, the release mechanism for diltiazem HCl was diffusion controlled. It was also observed from Figs. 5 and 8 that as the drug loading increased, release rate increased. In diffusion-controlled systems as the drug loading increases, cavities resulting from the dissolution of drug provide extended pathways for the escape of the residual drug within the system. These cavities increase the overall apparent permeability of the drug resulting in higher release rates (see Eq. (4)). For a three-dimensional matrix, the critical drug loading above which a continuous network of pathways form is only 15% v/v (Zaller, 1977).

4. Conclusions

The freeze pelletization technique is a novel and simple pelletization technique for the preparation of wax-based sustained release pellets. These pellets are of the matrix type and do not require any additional coating. The drug release profiles from these wax matrix pellets primarily depended on the nature of the carrier solid, pellet size, aqueous solubility of the drug, physical state of the drug in the matrix, drug load and the presence of additives such as surfactants. From the above results, it can be concluded that this technique can be used to produce pellets with a variety of release profiles for different drugs by suitably modifying the pellet forming matrix compositions.

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