Original Article

Comparative study on the different techniques for the preparation of sustained-release hydrophobic matrices of a highly water-soluble drug

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ABSTRACT: The objective of the present study was to control the release of freely water-soluble salbutamol sulphate (SS) over a prolonged period of time by embedding the drug into slowly eroding waxy matrix materials such as Precirol® ATO 5, Compritol® 888 ATO, beeswax, paraffin wax, carnauba wax, and stearyl alcohol. The matrices were prepared by either direct compression or hot fusion techniques. The compatibility of the drug with the various excipients was examined using differential scanning calorimetry (DSC). A factorial design was employed to study the effect of polymer type, polymer concentration (15% and 35%), and filler type (Avicel® PH101 and dibasic calcium phosphate dehydrate (DCP) on the *in vitro* drug release at 6 h. Results of DSC confirmed drug-excipient compatibility. Increasing the polymer ratio resulted in a significant retardation of drug release. The use of DCP resulted in significant retardation and incomplete drug release while the use of Avicel did not. The hot fusion method was found to be more effective than the direct compression method in retarding SS release. A Precirol formulation, prepared using the hot fusion technique, had the slowest drug release, releasing about 31.3% of SS over 6 h. In contrast, Compritol, prepared using the direct compression technique, had the greatest retardation, providing sustained release of 59.3% within 6 h. A hydrophobic matrix system is thus a useful technique for prolonging the release of freely water-soluble drugs such as salbutamol sulphate.

Keywords: Salbutamol sulphate, controlled release, waxy materials, direct compression, hot fusion

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1. Introduction

A hydrophobic matrix system is the earliest oral sustained-release platform for medicinal use (*1*). A wax matrix system is a well developed matrix system used for sustained drug delivery because of its effectiveness, low cost, ease of manufacture, and drug stability due to the chemical inertness of wax (*2,3*). Wax matrix dosage forms are used to embed a drug in an inert water insoluble matrix material in order to formulate sustained or slow release formulations, and especially those containing freely water-soluble drugs such as potassium chloride and tramadol hydrochloride (*4-6*).

Lipophilic matrix agents are frequently used in the preparation of sustained-release tablets (*7*). Materials such as Precirol® ATO5 (glyceryl palmitostearate), Compritol® 888 ATO (glyceryl behenate), beeswax (white wax), paraffin wax, carnauba wax, and stearyl alcohol provide several advantages ranging from good stability at varying pH values and moisture levels to chemical inertness, safe application, and lower cytotoxicity in humans due to the absence of solvents in the production process (*8-10*).

For highly water-soluble drugs, drug release for a prolonged period using a hydrophilic matrix system is limited because of rapid diffusion of the dissolved drug through the hydrophilic gel network or shearing of the hydrated polymer gel layer by the food present in the gastrointestinal tract, leading to dose dumping. Hydrophobic polymers (waxes) are suitable matrixing agents for such drugs, allowing the development of sustained-release dosage forms since they are water-insoluble and non-swelling materials (*6,9,11,12*).

When lipophilic matrix tablets are placed in dissolution media, several cracks, channels, and pores are reportedly formed on their surface (*3*). These channels are formed due to a rapid dissolution of the drug particles present on the surface of the matrix (*13*). The dissolution medium enters the channels, allowing more dissolution of the drug present at deeper sites of the matrix and leaching the dissolved drug through these channels (*9,14*).

Salbutamol sulphate is a direct acting sympathomimetic drug with predominantly β-adrenergic activity and selective action on β2 receptors (*15,16*). Since SS is a freely water-soluble drug (*17*) and the half-life of orally administered salbutamol is approximately 5 h, the drug must be administered three to four times daily to maintain bronchodilatation (*18*). Therefore, this drug would be a suitable target for controlled-release formulations.

The purpose of the present study was to prolong SS release, thus increasing patient compliance by reducing the frequency of administration. This study also sought to investigate the effect of some formulation factors on the physical properties and on *in vitro* drug release at 6 h from different tablets prepared either by a direct compression or hot fusion technique.

2. Materials and Methods

2.1. *Materials*

Salbutamol (Albuterol) sulfate (SS) was donated by Sedico Company (6th October City, Egypt). Compritol® 888 ATO (glyceryl behenate) and Precirol® ATO5 (glyceryl palmitostearate) were donated by Gattefosse Co. (Saint-Priest, France). Beeswax, carnauba wax, paraffin wax, and stearyl alcohol were donated by Luna Cosmetics (Cairo, Egypt). Aerosil® was donated by Delta Pharm (10th of Ramadan City, Egypt). Avicel® PH 101 and dibasic calcium phosphate dihydrate (DCP) were purchased from Morgan Chemical Industrial Company (10th of Ramadan City, Egypt).

2.2. *Drug-excipient interactions*

Differential scanning calorimetric (DSC) analysis was used to investigate the physicochemical compatibility of the drug and the excipients used. Samples (2-4 mg) of drug alone, excipients, and a drug-excipient physical mixture (1:1, w/w) were sealed in a 30-µL aluminum pans and heated in the DSC instrument (DSC-50, Shimadzu, Kyoto, Japan) in a dynamic nitrogen atmosphere with a flow rate of 50 mL/min. A temperature range of 30 to 300ºC was used and the heating rate was 10ºC/min.

2.3. *Preparation of matrices by the direct compression (DC) method*

A 2^3 factorial design was used to study the effect of three different formulation variables, namely polymer type (Precirol® ATO5 or Compritol® 888 ATO), polymer concentration (15% or 35%), and filler type (DCP or Avicel® PH 101), on the *in vitro* release of SS at 6 h from matrices prepared using the DC technique. Each variable was set at two levels. Eight formulations were prepared according to the compositions shown in Table 1, with each containing 10.6 mg SS. The calculated amounts of the drug, hydrophobic polymer, and filler were mixed by geometric dilution in a glass mortar and then the calculated amount of lubricant (Aerosil® 0.5%) was added. Dry blend formulations were compressed into 200 mg tablets using a single punch (7 mm) machine (Model EKO-9920; Erweka, Heusenstamm, Germany). The compression force (6-8 kN) was kept constant throughout the experiment.

2.4. *Preparation of matrices by the hot fusion method*

A 6.2^2 multiple factorial design was used to study the effect of the same formulation variables on the *in vitro* release of SS at 6 h from matrices prepared using the hot fusion technique. The first variable, polymer type, was set at six levels (Precirol® ATO5, Compritol® 888 ATO, beeswax, carnauba wax, paraffin wax, or stearyl alcohol) while the second and third variables, polymer concentration and filler type, were set at two levels for polymer concentration (15% or 35%) and filler type (DCP or Avicel® PH 101), respectively. Twenty-four formulations were prepared according to the compositions shown in Table 2, with each containing 10.6 mg SS. The accurately weighed amount of the hydrophobic polymer or wax was melted. When a homogenous melt was obtained, the mixture of the drug and filler was continuously stirred until a homogenous dispersion was obtained. The molten mass was allowed to cool to room temperature and screened through a No. 20 sieve. Those granules retained on a No. 60 sieve were collected and mixed with the predetermined amount of lubricant (Aerosil® 0.5%) and compressed

Table 1. Composition of different formulations of directly compressed salbutamol sulphate hydrophobic matrix tablets

Formulation No.	Precirol® ATO5 (mg)	Compritol® 888 ATO (mg)	DCP* (mg)	Avicel® (mg)
B1	30	–	158.4	–
B2	70	–	118.4	–
B3	30	–	–	158.4
B4	70	–	–	118.4
B5	–	30	158.4	–
B6	–	70	118.4	–
B7	–	30	–	158.4
B8	–	70	–	118.4

All tablet formulations contain 10.6 mg salbutamol sulphate equivalent to 8.8 mg salbutamol base and 1 mg Aerosil® as lubricant.
* DCP indicates dibasic calcium phosphate dihydrate.

Table 2. Composition of different formulations of salbutamol sulphate hydrophobic matrix tablets prepared using a hot fusion technique

Formulation No.	Precirol® ATO5 (mg)	Compritol® 888 ATO (mg)	Beeswax (mg)	Carnauba wax (mg)	Paraffin wax (mg)	Stearyl alcohol (mg)	DCP* (mg)	Avicel® (mg)
C1	30	–	–	–	–	–	158.4	–
C2	70	–	–	–	–	–	118.4	–
C3	30	–	–	–	–	–	–	158.4
C4	70	–	–	–	–	–	–	118.4
C5	–	30	–	–	–	–	158.4	–
C6	–	70	–	–	–	–	118.4	–
C7	–	30	–	–	–	–	–	158.4
C8	–	70	–	–	–	–	–	118.4
C9	–	–	30	–	–	–	158.4	–
C10	–	–	70	–	–	–	118.4	–
C11	–	–	30	–	–	–	–	158.4
C12	–	–	70	–	–	–	–	118.4
C13	–	–	–	30	–	–	158.4	–
C14	–	–	–	70	–	–	118.4	–
C15	–	–	–	30	–	–	–	158.4
C16	–	–	–	70	–	–	–	118.4
C17	–	–	–	–	30	–	158.4	–
C18	–	–	–	–	70	–	118.4	–
C19	–	–	–	–	30	–	–	158.4
C20	–	–	–	–	70	–	–	118.4
C21	–	–	–	–	–	30	158.4	–
C22	–	–	–	–	–	70	118.4	–
C23	–	–	–	–	–	30	–	158.4
C24	–	–	–	–	–	70	–	118.4
C24	–	–	–	–	–	70	–	118.4

All tablet formulations contain 10.6 mg salbutamol sulphate equivalent to 8.8 mg salbutamol base and 1 mg Aerosil® as a lubricant.
* DCP indicates dibasic calcium phosphate dihydrate.

into 200 mg tablets using a single punch (7 mm) machine. The compression force (6-8 kN) was kept constant throughout the experiment.

2.5. *Quality control tests of the prepared tablet formulations*

2.5.1. *Weight variation*

Twenty tablets of each formulation were individually weighed on an electronic balance (Type AGE-220, Shimadzu) and their average weight was calculated (*19*).

2.5.2. *Uniformity of tablet thickness and diameter*

Ten tablets of each formulation were measured for the uniformity of their thickness and diameter using Vernier Calipers (Steco, Wuppertal, Germany) at two different positions. The average value of the diameter and thickness was then calculated in millimeters.

2.5.3. *Friability test*

Ten tablets were weighed and placed in a friabilator (model PTF; Pharma Test, Hainburg, Germany). The drum was rotated 100 times, and then the tablets were removed, brushed, and reweighed. The percentage loss in weight was calculated as a measure of friability. The percentage loss was not to exceed 1% (*20*).

2.5.4. *Content uniformity*

Ten tablets of each formulation were selected and each was individually assayed for drug content. Each tablet was crushed and dissolved in 100 mL distilled water in a volumetric flask with the aid of a sonicator (type USR3; Julabo Labortechnik, Seelbach, Germany). The mixture was filtered using a Millipore filter (0.2 μm) and measured spectrophotometrically at a λ_{max} of 276 nm using a UV/VIS Spectrophotometer (UV-1601 PC, Shimadzu) with distilled water as a blank (*20*).

2.5.5. *In vitro release studies*

In vitro release of SS from the prepared tablet formulations was performed using the USP Dissolution Tester, Apparatus II, Rotating paddle, (Type PTW, Pharma Test) at a rotation of 50 rpm (*19,21*). Studies were carried out at 37 ± 0.5ºC in 250 mL of 0.1 N HCl (pH 1.2) for a period of two hours and then continued in phosphate buffer (pH 7.4) for 10 h after shifting the pH from pH 1.2 to pH 7.4 using a 2.5 M KH_2PO_4 solution containing 16.72% (w/v) NaOH (*22*). Samples were collected, filtered using a Millipore filter (0.2 μm), and analyzed for SS content by measuring the absorbance at a λ_{max} of 276 nm. All release studies were done in triplicate.

2.5.6. *Release kinetics*

The release data were analyzed according to the

well-known Korsmeyer-Peppas diffusion model (*23,24*). Peppas *et al*. introduced an exponential model to analyze drug release from polymeric devices with various geometrical shapes (*3,4*) according to the following equation:

$$M_t/M_\infty = kt^n \quad \text{--- Eq. 1}$$

where M_t/M_∞ is the fraction of the drug released at time t and K is the kinetic constant; n is the release exponent indicative of the mechanism of release. This model is, however, valid only for the early stages (≤ 60%) of drug release (*25-27*). The values of n have no definite relationship with polymer content (*28*). The value of 0.43 < n < 0.5 for Fickian (Case I) release, 0.5 < n < 0.89 for non-Fickian (Anomalous) release, n = 0.89 for Case II (Zero-order) release, and n > 0.89 for the super Case II type of release (first-order) (*29-31*). The release exponent, n, is the slope of the log fraction of drug release *versus* the log time curve.

A model independent parameter, the mean dissolution time (MDT), was employed for comparison of dissolution profiles of the different formulations of salbutamol sulphate tablets prepared and was calculated according to the following equation:

$$MDT_{in\text{-}vitro} = \frac{\sum_{i=1}^{n} t_{mid}\,\Delta M}{\sum_{i=1}^{n} \Delta M} \quad \text{--- Eq. 2}$$

where *i* is the sample number, *n* is the number of dissolution samples, t_{mid} is the time at the midpoint between *i* and *i – 1*, and ΔM is the additional amount of drug dissolved between *i* and *i – 1* (*32-34*).

2.6. *Statistics*

Statistical analysis of the *in vitro* SS release from the different prepared formulations after 6 h was done by one-way analysis of variance (ANOVA) for multiple comparisons at $p < 0.05$. Statistical analysis was performed using StatView software version 4.53.

3. Results and Discussion

3.1. *Drug-excipient interactions*

Figure 1 shows the thermograms of SS and its physical mixtures (1:1 ratio, w/w) with the different excipients used. The DSC thermogram of the drug alone had two main prominent sharp endothermic peaks at 204.25ºC and 280.32ºC which were reported to be corresponding to the decomposition of the SS molecules (*35*). The thermograms of physical mixtures of the drug with the excipients used showed drug endothermic peaks together with characteristic peaks of the excipients used, indicating that there was no interaction between the drug and the excipients used.

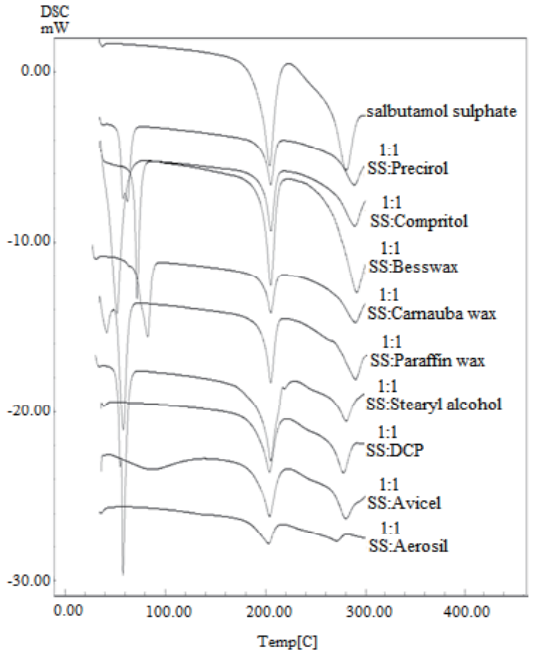

Figure 1. DSC thermograms of salbutamol sulphate and its physical mixtures (1:1, w/w) with the excipients used.

3.2. *Quality control tests of the prepared tablet formulations*

The physical properties of the prepared tablets are presented in Table 3. Data revealed that the content uniformity of all formulations complied with the pharmacopeial limits (85-115%) (*20*).

3.3. *In vitro release studies*

Figures 2 and 3 show the *in vitro* release profiles of SS from the prepared tablet formulations. Statistical analysis was carried out to compare the different SS release profiles after 6 h (Q at 6 h) using one-way ANOVA. A high initial release of SS from the prepared tablet formulation was observed in the first hour and might be due to the fast dissolution of the drug particles present at the tablet surface, while the drug present in the deeper interstices of the tablet was released at a slower rate (*9*).

3.3.1. *Influence of filler type*

Clearly, as shown in Figure 4, more significant ($p < 0.05$) retardation of *in vitro* drug release at 6 h was observed upon use of DCP as a filler. This finding agrees with those of Liu *et al*. (*36*) and El-Shanawany (*37*), who reported that DCP was an insoluble and non-swelling filler. Thus, the tablets will remain intact throughout the dissolution process and the drug will be released by diffusion through small inter- and intra-particle spaces.

Table 3. Physical characterizations of the hydrophobic matrix tablets prepared

Formulation No.	Weight (mg)*	Thickness (mm)	Diameter (mm)	Friability (%)	Content uniformity (%)*
B1	199 ± 1.73	4.1	7	1.00	99.21 ± 1.53
B2	200 ± 1.03	4.2	7	0.97	97.20 ± 2.60
B3	203 ± 2.36	4.7	7	0.41	102.30 ± 1.92
B4	201 ± 1.59	4.9	7	0.26	99.20 ± 1.71
B5	200 ± 1.51	4.1	7	0.90	98.62 ± 2.04
B6	199 ± 1.03	4.2	7	0.85	97.85 ± 3.20
B7	202 ± 2.80	4.8	7	0.60	100.51 ± 2.72
B8	201 ± 2.18	4.9	7	0.30	98.50 ± 2.42
C1	197 ± 2.34	4.0	7	0.41	98.12 ± 1.73
C2	200 ± 1.93	4.1	7	0.70	96.69 ± 3.01
C3	201 ± 1.79	4.8	7	0.15	101.61 ± 2.62
C4	202 ± 2.04	4.9	7	0.10	97.68 ± 2.97
C5	201 ± 2.78	4.0	7	0.60	98.10 ± 1.94
C6	199 ± 1.53	4.0	7	0.46	95.30 ± 2.60
C7	203 ± 2.75	4.9	7	0.23	99.31 ± 2.02
C8	202 ± 2.34	5.0	7	0.20	97.61 ± 3.32
C9	199 ± 2.98	4.1	7	0.31	97.52 ± 2.82
C10	198 ± 2.53	4.0	7	0.20	95.49 ± 2.90
C11	201 ± 2.93	4.9	7	0.23	99.20 ± 1.81
C12	201 ± 2.71	5.0	7	0.15	98.02 ± 2.91
C13	200 ± 1.89	4.0	7	0.90	98.40 ± 2.37
C14	200 ± 2.03	4.1	7	0.50	96.01 ± 2.59
C15	202 ± 3.31	4.8	7	1.00	99.03 ± 2.93
C16	203 ± 3.13	4.9	7	0.50	97.43 ± 2.41
C17	200 ± 1.63	4.1	7	0.63	99.61 ± 1.96
C18	199 ± 1.51	4.2	7	0.10	97.01 ± 2.80
C19	201 ± 3.03	4.9	7	0.54	100.60 ± 2.91
C20	202 ± 2.37	5.0	7	0.10	98.51 ± 3.43
C21	200 ± 1.33	4.0	7	0.95	99.73 ± 2.08
C22	197 ± 3.14	4.0	7	0.80	97.71 ± 2.45
C23	201 ± 1.97	4.9	7	0.68	101.23 ± 2.04
C24	201 ± 1.59	5.0	7	0.32	99.10 ± 1.72

* Data are presented as means ± S.D.

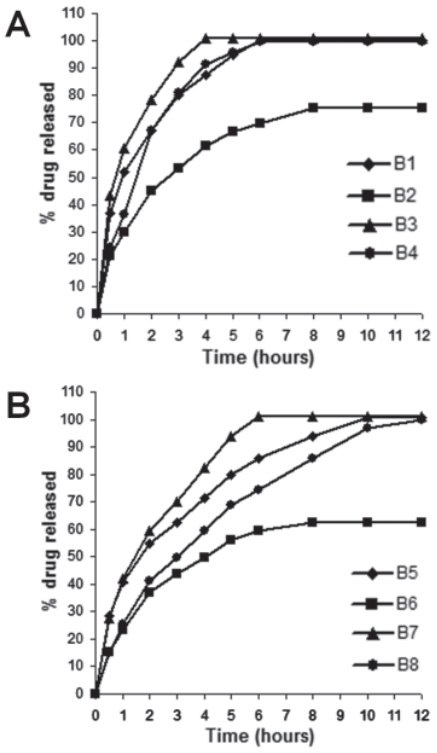

Figure 2. *In vitro* release profile of salbutamol sulphate from tablets prepared with a direct compression technique using Precirol® ATO5 (A) and Compritol® 888 ATO (B).

When Avicel® was used as a filler, water was absorbed into the tablet through capillaries, leading to swelling and formation of new cracks and channels from which a further amount of the drug was dissolved and released with no disintegration of the tablet. Unlike formulations prepared using Avicel®, tablet formulations prepared using DCP were found to have incomplete drug release, so no further investigations were carried out on those formulations prepared using DCP as a filler (*36,37*).

3.3.2. *Influence of polymer type*

One of the directly compressed formulations (Figure 2), Compritol® was significantly more successful ($p < 0.05$) at retarding drug release than Precirol®, as shown in Figure 4A. The least significant release (Q at 6 h = 74.5%) was obtained from formulation B8 prepared using 35% Compritol® and Avicel® as fillers. This might be due to the high melting range of Compritol® compared to Precirol®. These results are in accordance with previously published results (*38,39*) indicating that this phenomenon might be due to the greater loss of structure or weakening of bonds between particles at 37°C in the compressed matrices prepared from glyceride esters of fatty acids with a low melting point. Thus, the higher melting range of the used polymer, the less

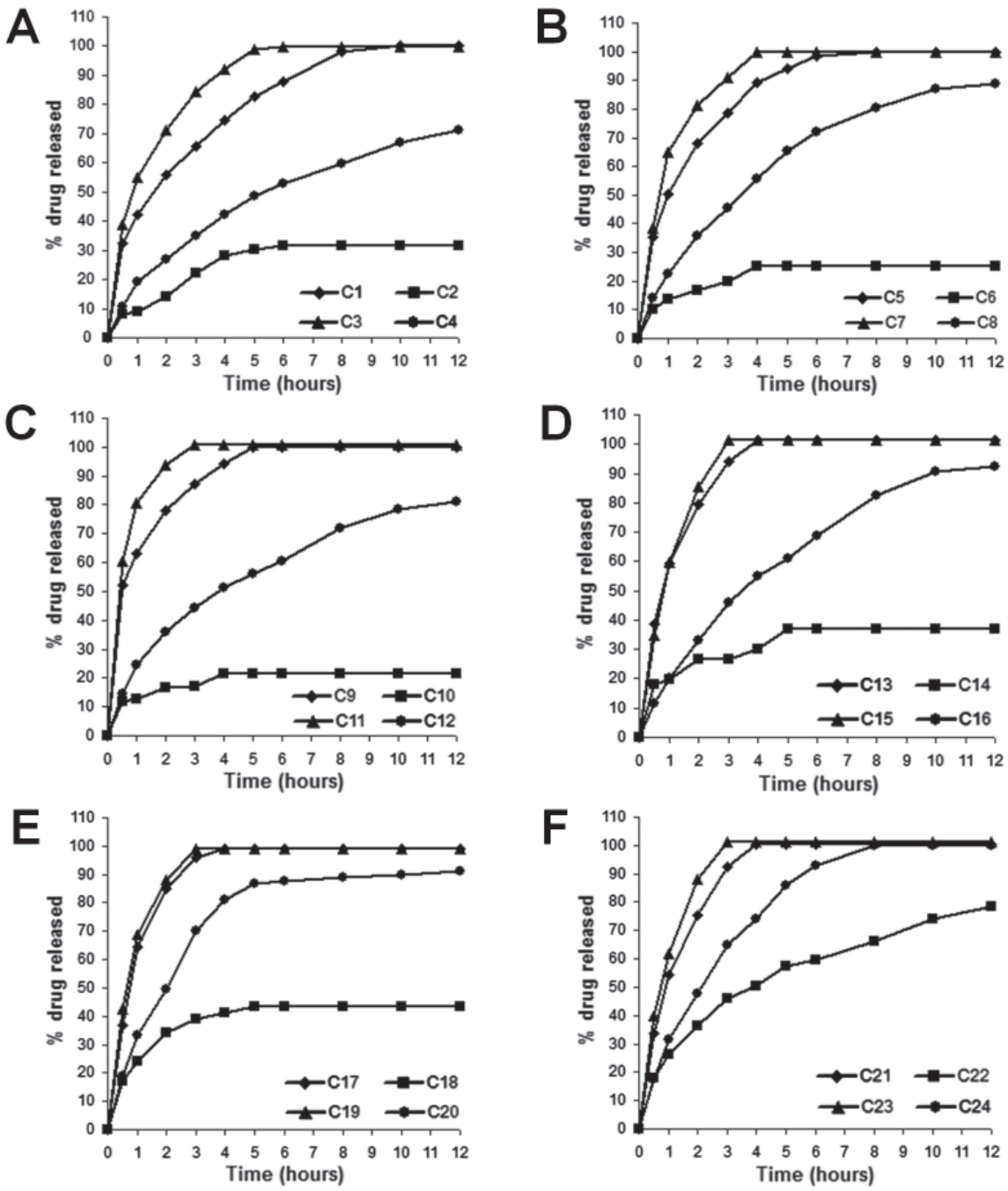

Figure 3. ***In vitro*** **release profile of salbutamol sulphate from tablets prepared with a hot fusion technique using Precirol® ATO5 (A), Compritol® 888 ATO (B), beeswax (C), carnauba wax (D), paraffin wax (E), and stearyl alcohol (F).**

drug released. Prepared using the hot fusion method (Figure 4B), 35% Precirol® (formulation C4) and 35% beeswax (formulation C12) retarded drug release more significantly ($p < 0.05$) than did other polymers, releasing about 52.8% and 60.5% after 6 h, respectively, when using Avicel® as a filler. In contrast, stearyl alcohol had the most significant release (Q at 6 h = 92.9%, $p < 0.05$) from formulation C24 prepared using a 35% stearyl alcohol concentration and Avicel® as a filler. The highest drug release from stearyl alcohol is in accordance with the findings of Karasulu *et al*. (*40*), who explained that, on the basis of polymeric structure, stearyl alcohol was more convenient for drug diffusion. Stearyl alcohol also has a lower melting point and higher water absorption capacity than the other polymers, allowing more dissolution medium to penetrate the matrix system and resulting in faster drug release (*40,41*).

3.3.3. *Influence of polymer concentration*

As shown in Figure 4 reveal, increasing the polymer concentration from 15% to 35% resulted in greater retardation of drug release ($p < 0.05$). This might be due to an increased polymer concentration resulting in

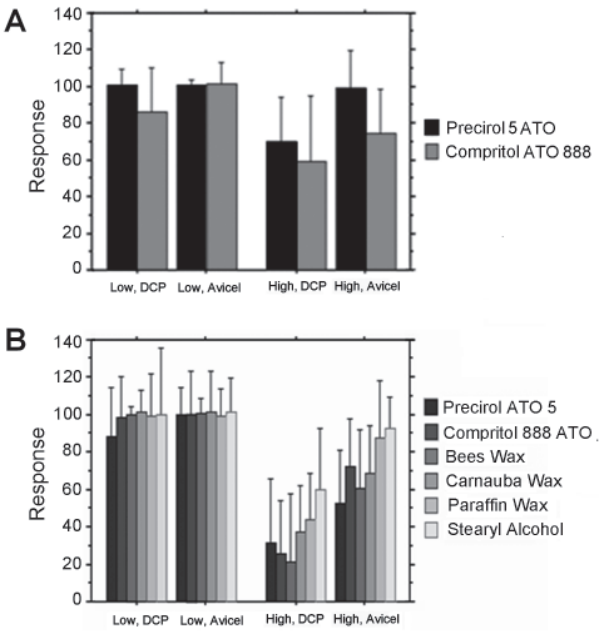

Figure 4. Interaction bar plot for the effect of polymer type, polymer concentration, and filler type on *in vitro* release at 6 h from hydrophobic tablet formulations prepared with a direct compression technique (A) and hot fusion technique (B).

a decrease in the total porosity of the matrices (initial porosity plus porosity due to dissolution of the drug), decreasing the penetration of the dissolution medium into the matrix system and thus reducing drug dissolution. In addition, increasing the polymer content led to an increase in the drug diffusion path length, which in turn retarded drug diffusion from the matrix (*42*).

3.3.4. *Influence of the method of preparation*

Drug release was greater from the matrices prepared by direct compression relative to that from matrices prepared by hot fusion. The slower release from the latter matrices could be due to the complete coating of the drug particles by the melted polymer. In such instances, there would presumably be less penetration of the dissolution medium into the matrix compared to that into matrices prepared by direct compression, and hence, dissolution and release of the drug would occur at a slower rate (*36,43,44*).

3.4. *Release kinetics*

The release exponent (n) and kinetic constant (k) were calculated from equation 1 and are shown in Table 4.

Table 4. MDT values of different formulations of salbutamol sulphate tablets and fitting of salbutamol sulphate release data to Korsmeyer-Peppas model

Formulation No.	MDT (h)*	Correlation coefficient (r^2)	Release exponent (n)	Kinetic constant (K)	Mechanism
B1	1.63	–	–	–	–
B2	2.17	0.998	0.53	0.304	Anomalous transport
B3	1.14	–	–	–	–
B4	1.73	–	–	–	–
B5	2.75	0.996	0.48	0.399	Case I (Fickian release)
B6	2.19	0.997	0.60	0.235	Anomalous transport
B7	2.03	0.996	0.55	0.409	Anomalous transport
B8	3.77	0.994	0.68	0.246	Anomalous transport
C1	2.46	0.999	0.40	0.425	Case I (Fickian release)
C2	2.16	0.903	0.55	0.105	Anomalous transport
C3	1.42	–	–	–	–
C4	3.92	0.984	0.63	0.177	Anomalous transport
C5	1.67	–	–	–	–
C6	1.45	0.993	0.36	0.133	Case I (Fickian release)
C7	1.09	–	–	–	–
C8	3.45	0.999	0.66	0.222	Anomalous transport
C9	1.17	–	–	–	–
C10	1.19	0.948	0.24	0.134	Case I (Fickian release)
C11	0.67	–	–	–	–
C12	3.52	0.992	0.62	0.231	Anomalous transport
C13	1.15	–	–	–	–
C14	1.61	0.927	0.25	0.208	Case I (Fickian release)
C15	1.04	–	–	–	–
C16	3.80	0.999	0.76	0.198	Anomalous transport
C17	0.99	–	–	–	–
C18	1.27	0.996	0.47	0.339	Case I (Fickian release)
C19	0.88	–	–	–	–
C20	2.12	0.990	0.70	0.314	Anomalous transport
C21	1.25	–	–	–	–
C22	3.48	0.999	0.51	0.260	Anomalous transport
C23	0.98	–	–	–	–
C24	2.55	0.992	0.72	0.298	Anomalous transport

* MDT indicates mean dissolution time.

According to the Korsmeyer-Peppas diffusion model, formulations B5, C1, C6, C10, C14, and C18 fell under Case I (Fickian release) in which the rate of drug diffusion was much lower than that of polymer relaxation (*i.e.*, erosion) while formulations B2, B6, B7, B8, C2, C4, C8, C12, C16, C20, C22, and C24 exhibited anomalous transport in which the drug was delivered by the combined effect of drug diffusion and polymer relaxation (*30,45*). The release exponent for the remaining formulations is not shown because there were insufficient data points in the release profiles below 60% release to provide accurate values.

The MDT value was used to characterize the drug release rate from the dosage form and the retarding effect of the polymer. MDT values calculated from equation 2 are shown in Table 4. As is readily apparent, the higher the polymer level, the higher the value of MDT and the greater the retarding effect of the polymer. These findings are in accordance with those reported by Abdelkader *et al*. and Roni *et al*. (*46,47*).

4. Conclusion

A hydrophobic matrix system in which a drug is embedded into a slowly eroding waxy material was found to be a viable technique to produce sustained-release tablets, and especially those containing freely water-soluble drugs such as SS. The *in vitro* drug release profile can be modified by the selection of the filler excipient. Formulations prepared using DCP were found to hold little promise as DCP led to incomplete drug release. In contrast, those prepared using Avicel® proved more promising. Compared to the direct compression technique, the hot fusion method was found to be more efficient at retarding drug release. C4, the formulation of choice, succeeded in controlling drug release up to 52.8% within six hours.

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References

1. Qiu Y. Rational design of oral modified-release drug delivery systems. In: Developing Solid Oral Dosage Forms: Parmaceutical Theory and Practice (Qiu Y, Chen Y, Zhang G, Liu L, Porter W, eds.). Academic Press, San Diego, CA, USA, 2009; pp. 469-499.
2. Qiu Y, Flood K, Marsh K, Carroll S, Trivedi J, Arneric SP, Krill SL. Design of sustained-release matrix systems for a highly water-soluble compound, ABT-089. Int J Pharm. 1997; 157:43-52.
3. Sato H, Miyagawa Y, Okabe T, Miyajima M, Sunada H. Dissolusion mechanism of diclofenac sodium from wax matrix granules. J Pharm Sci. 1997; 86:929-934.
4. Ozyazici M, Gökçe EH, Ertan G. Release and diffusional modeling of metronidazole lipid matrices. Eur J Pharm Biopharm. 2006; 63:331-339.
5. Dredan J, Antal I, Racz I. Evaluation of mathematical models describing drug release from lipophilic matrices. Int J Pharm. 1996; 145:61-64.
6. Tiwari SB, Murthy TK, Pai MR, Mehta PR, Chowdary PB. Controlled release formulation of tramadol hydrochloride using hydrophilic and hydrophobic matrix system. AAPS PharmSciTech. 2003; 4:18-23.
7. Zhang Y, Schwartz JB. Melt granulation and heat treatment for wax matrix-controlled drug release. Drug Dev Ind Pharm. 2003; 29:131-138.
8. Uner M, Gönüllü U, Yener G, AltInkurt T. A new approach for preparing a controlled release ketoprofen tablets by using beeswax. Farmaco. 2005; 60:27-31.
9. Obaidat AA, Obaidat RM. Controlled release of tramadol hydrochloride from matrices prepared using glyceryl behenate. Eur J Pharm Biopharm. 2001; 52:231-235.
10. Obaidat AA. Evaluation of the mechanism of release of water soluble drug from a waxy inert matrix. Acta Pharma Turc. 1999; 61:199-202.
11. Reddy KR, Mutalik S, Reddy S. Once-daily sustained-release matrix tablets of nicorandil: Formulation and *in vitro* evaluation. AAPS PharmSciTech. 2003; 4:E61.
12. Huang HP, Mehta SC, Radebaugh GW, Fawzi MB. Mechanism of drug release from an acrylic polymer-wax matrix tablet. J Pharm Sci. 1994; 83:795-797.
13. Collett JH, Moreton RC. Modified-release peroral dosage forms. In: Aulton's Pharmaceutics: The Design and Manufacture of Medicines (Aulton ME, ed.). 3rd Ed., Churchill Livingstone, London, UK, 2007; pp. 483-499.
14. Cao QR, Kim TW, Lee BJ. Photoimages and the release characteristics of lipophilic matrix tablets containing highly water-soluble potassium citrate with high drug loadings. Int J Pharm. 2007; 339:19-24.
15. Pacifici GM, De Santi C, Mussi A, Ageletti CA. Interindividual variability in the rate of salbutamol sulphation in the human lung. Eur J Clin Pharmacol. 1996; 49:299-303.
16. Collomp K, Candau R, Lasne F, Labsy Z, Prefaut C, De Ceaurriz J. Effects of short-term oral salbutamol administration on exercise endurance and metabolism. J Appl Physiol. 2000; 89:430-436.
17. Galichet LY, Moffat AC, Osselton MD, Widdop B. Monographs: Salbutamol Sulfate. In: Clarke's Analysis of Drugs and Poisons. 3rd ed., Pharmaceutical Press, London, UK, 2005; pp. 1546-1547.
18. San Vicente A, Hernández RM, Gascón AR, Calvo MB, Pedraz JL. Effect of aging on the release of salbutamol sulfate from lipid matrices. Int J Pharm. 2000; 208:13-21.
19. The USP NF. Asian ed. US Pharmacopoeial Convention, Twinbrook Parkway, Rockville, MD, USA, 2009; pp. 264-269, 386-387.
20. The British Pharmacopoeia. The Stationary Office, London, UK, 2008; pp. 1918-1920, A303-304, A423-424.
21. Sanghavi NM, Bijlani CP, Kamath PR, Sarwade VB. Matrix tablets of salbutamol sulphate. Drug Dev Ind Pharm. 1990; 16:1955-1961.
22. Kondo N, Iwao T, Hirai K, Fukuda M, Yamanouchi K, Yokoyama K, Miyaji M, Ishihara Y, Kon K, Ogawa Y, Mayumi T. Improved oral absorption of enteric coprecipitates of a poorly soluble drug. J Pharm Sci. 1994; 83:566-570.
23. Korsmeyer RW, Gurny R, Doelker E, Buri P, Peppas NA.

Mechanism of solute release from porous hydrophilic polymers. Int J Pharm. 1983; 15:25-35.
24. Ritger PL, Peppas NA. A simple equation for description of solute release II. Fickian and anomalous release from swellable devices. J Control Release. 1987; 5:37-42.
25. Costa P, Sousa Lobo JM. Modeling and comparison of dissolution profiles. Eur J Pharm Sci. 2001; 13:123-133.
26. Siepmann J, Peppas NA. Modeling of drug release from delivery systems based on hydroxypropyl methylcellulose (HPMC). Adv Drug Deliv Rev. 2001; 48:139-157.
27. Gren T, Nyström C. Porous cellulose matrices containing lipophilic release modifiers – a potential oral extended-release system. Int J Pharm. 1999; 184:7-19.
28. Reza MS, Quadir MA, Haider SS. Comparative evaluation of plastic, hydrophobic and hydrophilic polymers as matrices for controlled-release drug delivery. J Pharm Pharmaceut Sci. 2003; 6:282-291.
29. Avachat A, Kotwal V. Design and evaluation of matrix-based controlled release tablets of diclofenac sodium and chondroitin sulphate. AAPS PharmSciTech. 2007; 8:E88.
30. Sarfraz MK, Nisar-Ur-Rehman, Ahmed S, Ashraf M, Mohsin S. Ethyl cellulose-based solid matrix system for sustaining release of naproxen. Pak J Biol Sci. 2007; 10:668-672.
31. Jagan MS, Kishan V, Madhusudan RY, Chalapathi RNV. Formulation of controlled release Levodopa and Carbidopa matrix tablets: Influence of some hydrophilic polymers on the release. Curr Trends Biotech Pharm. 2009; 3:204-209.
32. Barakat NS, Elbagory IM, Almurshedi AS. Controlled-release carbamazepine matrix granules and tablets comprising lipophilic and hydrophilic components. Drug Deliv. 2009; 16:57-65.
33. Varshosaz J, Tavakoli N, Kheirolahi F. Use of hydrophilic natural gums in formulation of sustained-release matrix tablets of tramadol hydrochloride. AAPS PharmSciTech. 2006; 7:E24.
34. Varshosaz J, Tavakoli N, Eram SA. Use of natural gums and cellulose derivatives in production of sustained release metoprolol tablets. Drug Deliv. 2006; 13:113-119.
35. Larhribh H, Martin GP, Marriott C, Prime D. The influence of carrier and drug morphology on drug delivery from dry powder formulations. Int J Pharm. 2003; 257:283-296.
36. Liu J, Zhang F, McGinity JW. Properties of lipophilic matrix tablets containing phenylpropanolamine hydrochloride prepared by hot-melt extrusion. Eur J Pharm Biopharm. 2001; 52:181-190.
37. El-Shanawany S. Sustained release of nitrofurantoin from inert wax matrices. J Control Release. 1993; 26:11-19.
38. Shaikh NH, De Yanes SE, Shukla AJ, Block LH, Collins CC, Price JC. Effect of different binders on release characteristics of theophylline from compressed microspheres. Drug Dev Ind Pharm. 1991; 17:793-804.
39. Almurshedi AS. Formulation and evaluation of extended-release carbamazepine granules prepared with inert fatty matrices (M. Sc. Thesis). College of Pharmacy, King Saud University, Saudi Arabia, 2007.
40. Karasulu E, Yeşim Karasulu H, Ertan G, Kirilmaz L, Güneri T. Extended release lipophilic indomethacin microspheres: Formulation factors and mathematical equations fitted drug release rates. Eur J Pharm Sci. 2003; 19:99-104.
41. Mahalingam R, Li X, Jasti BR. Semisolid dosages: Ointments, creams and gels. In: Pharmaceutical Manufacturing Handbook: Production and Processes (Gad SC, ed.). John Wiley & Sons, Inc., New Jersey, NJ, USA, 2008; pp. 267-288.
42. Quadir MA, Rahman MS, Karim MZ, Akter S, Awkat MT, Reza MS. Evaluation of hydrophobic materials as matrices for controlled-release drug delivery. Pak J Pharm Sci. 2003; 16:17-28.
43. Savolainen M, Khoo C, Glad H, Dahlqvist C, Juppo AM. Evaluation of controlled-release polar lipid microparticles. Int J Pharm. 2002; 244:151-161.
44. Li FQ, Hu JH, Deng JX, Su H, Xu S, Liu JY. *In vitro* controlled release of sodium ferulate from Compritol 888 ATO-based matrix tablets. Int J Pharm. 2006; 324:152-157.
45. Saha RN, Sajeev C, Sahoo J. A comparative study of controlled release matrix tablets of diclofenac sodium, ciprofloxacin hydrochloride, and theophylline. Drug Deliv. 2001; 8:149-154.
46. Abdelkader H, Abdalla OY, Salem H. Formulation of controlled-release baclofen matrix tablets: Influence of some hydrophilic polymers on the release rate and *in vitro* evaluation. AAPS PharmSciTech. 2007; 8: E100-E108.
47. Roni MA, Kibria G, Jalil R. Formulation and *in vitro* evaluation of alfuzosin extended release tablets using directly compressible eudragit. Indian J Pharm Sci. 2009; 71:252-258.

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