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Research Article

Exploring the Potential of A Highly Compressible Microcrystalline Cellulose as Novel Tabletting Excipient in the Compaction of Extended-Release Coated Pellets Containing an Extremely Water-Soluble Model Drug

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Abstract. Compaction of controlled-release coated pellets into tablets is challenging because of the fusion of pellets and the rupturing of coated film. The difficulty in compaction intensifies with the use of extremely water-soluble drugs. Therefore, the present study was conducted to prepare and compact pellets containing pseudoephedrine hydrochloride as an extremely water-soluble model drug. The pellets were produced using an extrusion–spheronization technique. The drug-loaded pellets were coated to extend the drug release up to 12-h employing various polymers, and then they were compressed into tablets using microcrystalline cellulose Ceolus KG-801 as a novel tabletting excipient. The *in vitro* drug release studies of coated pellets and tablets were undertaken using the USP basket method in dissolution test apparatus I. The amount of drug released was analyzed at a wavelength of 215 nm. The combined coatings of hydroxypropyl methylcellulose and Kollicoat SR-30D yielded 12-h extended-release pellets with drug release independent of pH of dissolution medium following zero-order kinetics. The drug release from the tablets prepared using inert Celous KG-801 granules as tabletting excipient was found faster than that of coated pellets. However, a modification in drug release rate occurred with the incorporation of inert Ceolus KG-801 pellets. The drug dissolution profile from tablets containing 40% w/w each of coated pellets and inert granules along with 20% w/w inert pellets was found to be closely similar to that of coated pellets. Furthermore, the friability, tensile strength, and disintegration time of the tablets were within the USP specifications.

KEY WORDS: ceolus KG-801; compaction of coated pellets; microcrystalline cellulose; pseudoephedrine hydrochloride; tabletting excipients.

INTRODUCTION

The controlled-release coated pellets can either be filled into hard gelatin capsules or compressed into multiple-unit tablets. The compression of pellets into tablets is a modern technological process (1), which is much more ideal than enclosing them into hard gelatin capsules (2). The advantages of tabletted pellets include a reduced risk of tampering and less difficulty in oesophageal transport when compared with capsules. Large-volume tablets generally have a higher patient compliance than capsules. Tablets from pellets can be prepared at lower cost compared to pellet-filled capsules because of the higher production rate of the tablet press. The expensive control of capsule integrity is also eliminated (1,3). Nonetheless, compaction of coated pellets into tablets is extremely challenging, especially if the coated pellets are loaded with highly water-soluble drugs. So far, only a few pellet-containing tablet products are available, such as Beloc® ZOK and Antra® MUPS (4).

There are numerous challenges associated with formulating coated pellets into tablets, such as that pellets may fuse into a non-disintegrating matrix during compression, thus losing their integrity and advantages as multiple units. With the reservoir-type coated pellets, the polymeric coating may rupture during compression, leading to immediate loss in the controlled-release characteristics in the case of water-soluble drugs. Lastly, the multiple-unit tablets may not possess adequate hardness, friability, and disintegration time. Several approaches have been attempted to overcome the problems associated with the compaction of coated pellets into tablets. These approaches include modulation of tabletting excipients, addition of "cushioning agents," and the enhancement of coated film flexibility. Different tabletting excipients such as microcrystalline cellulose (MCC) granules, polyethylene glycol 3350, crospovidone, lactose, and dicalcium phosphate were used in the compression of theophylline pellets coated with Eudragit RS (5). The authors suggested that tabletting excipients composed of MCC, polyethylene glycol 3350, and crospovidone were the most appropriate for minimum damage to the coated film. In another approach, pellets were

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mixed with cushioning agents (placebo particles) such as α-lactose monohydrate granules, MCC (Avicel-PH101) pellets, and paraffinic wax/starch beads to protect coated film of diltiazem pellets from rupture during compression (6). The results showed that the addition of deformable wax beads minimized the damage to coated pellets. Other methods included (a) increasing the flexibility of the coat by the incorporation of plasticizers (7,8), (b) varying the amount of coating applied to the pellets to maintain the controlled-release characteristics after compression (9,10), and (c) addition of hydrophobic polymer prior to compression to maintain the drug release profiles from pellets with damage coatings (11). Nevertheless, the success of the above techniques is often conflicting, case-specific, and dependent on the size and properties of the pellets and the polymer film used (6). The key factors affecting the compression of coated pellets into tablets are (a) the magnitude of the compression force; (b) flexibility, thickness, and type of the coated films; and (c) the proportion of tabletting excipients (powder, granules, or placebo pellets) (1,3).

Ceolus KG-801 possesses the highest compressibility among all MCC grades with special high binding function in tablets. The compression force required to compact Ceolus KG into tablets is low. Tablets with higher hardness (tensile strength) and low friability can be made using Ceolus KG even at a low content (12). The hardness of tablets produced with Ceolus KG grade is 1.5 times higher than that of Avicel PH grade, although both tablets have nearly the same disintegration time (13). Since the force of compression to form tablets is low with Ceolus KG, it may find its applications in the tabletting of coated pellets where the coating film is ruptured because of the higher compression force during the compression process.

The objective of the study was to explore the potential of a highly compressible MCC grade, namely, Ceolus KG-801, as a novel tabletting excipient in the compression of extended-release coated pellets containing an extremely water-soluble model drug, pseudoephedrine hydrochloride. The study is novel in two ways. Firstly, it is aimed at the compression of coated pellets into tablets containing an extremely water-soluble drug at a relatively higher loading of 30% w/w than previously reported studies. Secondly, the use of Ceolus KG-801 as tabletting excipient is a new approach. The rationale for employing Ceolus KG-801 as a tabletting excipient in the present study is its reported physical properties, as mentioned earlier. Thus, the research hypothesis of this study was as follows: it is possible to compact the 12-h, extended-release, extruded–spheronized, coated pellets of pseudoephedine hydrochloride into tablets using Ceolus KG-801 as tabletting excipient. Furthermore, the formed tablets may have a drug release rate closely similar to those of coated pellets and possess adequate friability, tensile strength, and disintegration time.

MATERIALS AND METHODS

Materials

The materials used were high-compressibility MCC (Ceolus KG-801, Asahi Chemicals, Tokyo, Japan), pseudoephedrine hydrochloride (Emmellen Biotech and Pharmaceuticals, Mumbai, India), Eudragit RS-30D (Rohm Gmbtt, Germany), Kollicoat SR-30D (BASF, Ludwigshafen, Germany), hydroxypropyl methylcellulose (HPMC; Metolose-90SH, 100,000SR, viscosity: 100,000 cps of 2% w/v aqueous solution at 20°C Shin-Etsu Chemicals, Tokyo, Japan), triethyl citrate (TEC; Merck-Schuchardt, Hohenbrunn, Germany), polyethylene glycol 4000 (PEG 4000, Merck-Schuchardt), lactose monohydrate (impalpable grade; HMS, Uitgeest, Holland), and magnesium stearate (CM, Meditech, Petaling Jaya, Malaysia).

Preparation of Pseudoephedrine HCl Core Pellets (F1)

Five batches of pseudoephedrine hydrochloride core pellets, each of size 200 g containing 140 g Ceolus KG-801, 60 g of pseudoephedrine HCl, and 75 ml of distilled water (F1), were prepared using extrusion–spheronization. Ceolus KG-801 and pseudoephedrine HCl were weighed (Denver Instrument, Denver, CO, USA), screened through a 0.80-mm-diameter sieve (Endecotts, London, UK) and mixed at a speed of 160 rpm for 10 min in a mixer (Kenwood Chef Classic, Watford, UK). Distilled water (the granulation liquid) was added slowly, followed by mixing to form a wet mass of suitable consistency. The wet mass was extruded at a speed of 100 rpm using a rotary gear extruder (Caleva Model 40, Dorset, UK) with a cylindrical die 14 cm in length and perforations 1.00 mm in diameter. The extrudates were spheronised in a spheroniser (Caleva Model 380) at a speed of 1,000 rpm for 10 min. The resultant pellets were dried in a fluidized bed dryer (Burkard FBD, 350 S, Rickmansworth, UK) at 60°C for 30 min. The dried pellets were sieved through a nest of sieves having mesh sizes of 0.40, 0.63, 0.80, 1.25, 1.70, and 2.00 mm using a mechanical shaker (Retsch AS200, Haan, Germany) at an amplitude of 1.00 mm for 10 min. Pellets with diameters between 0.80 and 1.25 mm were selected for further studies.

Determination of Pellet Yield

The percent yield depicts the amount of pellets achieved from the wet mass after the pelletization process and was determined mathematically using the following equation:

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

Pellet Size Analysis

A series of sieves with aperture sizes of 0.40, 0.63, 0.80, 1.25, 1.70, and 2.00 mm diameter were used for the size analysis of pellets obtained after drying. The sieves were vibrated mechanically (Retsch AS200 analytical sieve shakers, Germany) at an amplitude of 1.00 mm for 10 min. The weight of pellets retained on each sieve was recorded.

The geometric weight mean diameter and geometric standard deviation were used to characterize pellet size

and size distribution. The equations used (14) are given below:

$$d_{gw} = antilog \frac{\sum(w_i.\ \log\ d_i)}{\sum w_i} \quad (2)$$

$$(S_g)^2 = \frac{1}{\sum w_i}\left[\sum w_i(\log d_i)^2 \frac{(\sum w_i.\log d_i)^2}{\sum w_i}\right], \quad (3)$$

where

Nomenclature

d_{gw} Geometric-weight mean diameter
S_g Geometric standard deviation
d_i Mean diameter of sieve fraction number i
w_i Weight of sieve fraction number i

Preparation of Polymeric Coating Solutions

The formulations of the various coating solutions and the coating process conditions for this study are shown in Tables I and II, respectively. The aqueous dispersion of Eudragit RS-30D (an ammonio methacrylate copolymer) was mixed with TEC (a plasticizer) and stirred for 30 min. The resultant solution was then diluted with distilled water and mixed continuously up to 1 h. A similar procedure was adopted for the preparation of coating solution Kollicoat SR-30D (a copolymer of 27% polyvinyl acetate, 2.7% povidone, and 0.3% sodium lauryl sulfate). In the preparation of HPMC (Metolose-90SH, 100,000SR) coating solution, PEG 4000 was employed as a plasticizer in place of TEC because PEG 4000 is a plasticizer recommended exclusively for HPMC and sodium carboxymethylcellulose coating solution. Nonetheless, because of the high viscosity grade of HPMC, only 0.25% w/v solution was possible. In order to prepare the HPMC coating solution, HPMC was dissolved in half of the total amount of water after heating up to 70–80°C with constant stirring until the solution was formed. The remaining amount of water along with PEG 4000 was added and stirred until PEG was dissolved. The solution was allowed to stand at room temperature for 24 h.

Coating of Pseudoephedrine HCl Core Pellets

Batches of 200 g of pseudoephedrine HCl core pellets were coated in a bottom-spray fluidized bed coater (Aromatic-Fielder AG, Bubendorf, Switzerland) fitted with a cylindrical partition tube (Wurster insert, diameter=47 mm, height=180 mm). The coating polymer was sprayed via the two-fluid spray nozzle using a peristaltic pump (Rota Consulta, Model 1B.100 S-R/65, Germany) at pre-selected conditions. In order to reduce sticking of pellets during storage, an HPMC (Metolose-90SH, 100,000SR) overcoat was applied up to 1% weight gain of the total weight for all coated pellet formulations, except for F3 because it was composed of HPMC coating only. Coating of pellets with HPMC solution (F3) was conducted using only 100-g pellets to reduce the coating time. On completion of the coating, the coated pellets were fluidized for an additional 15 min to ensure complete drying.

Compression of Coated Pseudoephedrine HCl Core Pellets into Tablets

Coated pseudoephedrine HCl pellets exhibiting 12-h extended release were chosen for tabletting. The tabletting excipients were composed of inert Ceolus KG-801 granules and inert Ceolus KG-801 pellets. The inert tabletting granules consisting of Ceolus KG-801 (70% w/w), lactose monohydrate (29% w/w), and magnesium stearate (1% w/w) were prepared using wet granulation method. Ceolus KG-801, lactose monohydrate, and magnesium stearate were passed through a 0.80-mm-diameter sieve (Endecotts) and mixed (Kenwood Chef Classic) for 10 min. Distilled water (the granulating liquid) was added to the powder mixture and mixing was continued for another 10 min to produce a wet mass of suitable consistency, which was passed through 0.80-mm-diameter sieve (Endecotts). The resulting granules were dried in an oven (Carbolite, Hope, UK) at 50°C. On the other hand, the inert Ceolus KG-801 pellets were prepared following the extrusion–spheronization technique using 140 g of Ceolus-KG801, 60 g of lactose monohydrate and 75 ml of distilled water. The coated pseudoephedrine HCl pellets and inert Ceolus KG-801 granules, with/without inert Ceolus KG-801 pellets, were compressed into tablets using a single punch-tabletting machine (Manesty, Keswick, UK) fitted with round, flat-faced, 10-mm-diameter punches and dies. The compositions of various tablet formulations are shown in Table III. The tablets demonstrating drug dissolution profiles closely similar to that of un-compressed coated pellets were subjected to friability, tensile strength, and disintegration time tests as described in US Pharmacopeia 26.

In Vitro Drug Release Study

The *in vitro* drug release study of 1 g of extended-release coated pellets or tablets made from coated pellets was carried out in 900 ml of distilled water maintained at 37.0±0.5°C, using the basket method of USP 26 dissolution test apparatus 1 (Distek Premiere, 5100, dissolution test apparatus, North Brunswick, NJ, USA), at a stirring speed of 100 rpm. At time intervals of 10, 30, 60, 120, 240, 480, and 720 min, samples of 5 ml were collected using auto-sampler (Distek) and replaced with 5 ml of fresh dissolution medium. The amount of drug released was quantified after suitable dilution using a UV/VIS spectrophotometer (U-2000, Hitachi, Tokyo, Japan) at a detection wavelength of 215 nm. The effect of the dissolution medium on drug release was studied using phosphate buffer of pH7 (BP) and 0.1 M hydrochloric acid of pH1. The drug release data were presented as the percentage of drug released and $t_{50\%}$ (time for 50% of drug released). For each batch of product, six determinations were carried out.

Table I. Coating Formulations and Dissolution $t_{50\%}$ Values of Various Coated Pseudoephedrine HCl Pellets

	Coating Polymers			Plasticizers			Inner Coat		Outer Coat		
Formulation Code	HPMC (g)	Eudragit (ml)	Kollicoat (ml)	TEC (ml)	PEG (g)	Diluting Liquid (water)	Polymer	Coating Level (% w/w)	Polymer	Coating Level (% w/w)	$t_{50\%}$ (min)[a]
F2	–	200	–	3	–	400	–	–	–	–	–
F2a							Eudragit	10.0	–	–	6.84±0.39
F2b							Eudragit	20.0	–	–	20.08±0.57
F2c							Eudragit	30.0	–	–	31.77±2.99
F3	20	–	–	–	3	8,000	–	–	–	–	–
F3a							HPMC	10.0	–	–	11.10±1.90
F3b							HPMC	15.0	–	–	28.10±6.23
F3c							HPMC	20.0	–	–	61.66±9.02
F4	–	–	200	3	–	400	–	–	–	–	–
F4a							Kollicoat	10.0	–	–	66.68±4.13
F4b							Kollicoat	20.0	–	–	485.30±10.49
F4c							Kollicoat	30.0	–	–	849.06±5.32
F5	–	–	200	3	–	400	–	–	–	–	–
F5a							Kollicoat	12.5	–	–	123.29±3.56
F5b							Kollicoat	15.0	–	–	166.98±25.15
F5c							Kollicoat	17.5	–	–	285.12±41.18
F6	5	–	200	3	0.75	400	–	–	–	–	–
F6a							HPMC	2.5	Kollicoat	12.5	128.29±7.95
F6b							HPMC	2.5	Kollicoat	15.0	300.61±19.55
F6c							HPMC	2.5	Kollicoat	17.5	480.89±35.81

[a] Mean±SD, N=6

Table II. Coating Process Conditions

Process Conditions	Setting
Batch size (g)[a]	200/100
Inlet temperature (°C)[b]	45/60
Outlet temperature (°C)[c]	42–43/56–57
Atomizing air (bar)	1.0
Flow rate (ml/min)	5.5–6.0
Fluidized air (m^3/h)	90–110
Spray nozzle diameter (mm)	0.8
Center pipe diameter (mm)	47
Center pipe length (mm)	180

[a] Batch size: 200 g for all coating formulations except F3, where it was 100 g
[b] Inlet temperature: 45°C for Eudragit RS-30D and Kollicoat SR-30D and 60°C for HPMC
[c] Outlet temperature: 42–43°C for Eudragit RS-30D and Kollicoat SR-30D and 56–57°C for HPMC

Release Kinetics of Extended-Release Coated Pellets and Tablets made from Coated Pellets

The drug release kinetics was determined for the extended-release pellets and tablets that were able to sustain the drug release for 12 h. The goodness of fit of the selected drug release data was tested with mathematical models such as zero-order kinetic (Eq. 4), first-order kinetic (Eq. 5) and Higuchi's square root of time release (Eq. 6) (15).

$$w = w_0 - k_0 t \tag{4}$$

$$\ln w = \ln w_0 - k_1 t \tag{5}$$

$$Q = K\sqrt{t}, \tag{6}$$

where w is undissolved amount of drug at time t; w_0 is undissolved amount of drug at time t equals zero; Q is the amount of drug released at time t; and k_0, k_1, and K are the corresponding release rate constants. Lag time was the calculated value of time (t) corresponding to the amount of drug undissolved (w)=100%, or the amount of drug released at time (t) when Q=0.

Statistical Analysis

The statistical analysis was carried out using SPSS software (version 11.5, Chicago, IL, USA). Independent-samples T test and one-way analysis of variance (ANOVA) with post-hoc Tukey honestly significant difference (Tukey-HSD) test were applied, where appropriate. The difference was considered statistically significant at $p<0.05$.

RESULTS AND DISCUSSION

The pellets containing pseudoephedrine HCl at 30% w/w loading were produced successfully using the extrusion–spheronization method. The percent yield of pseudoephedrine HCl loaded pellets (F1) was 91.10±11.66%. It was evident that the percent yield of drug-loaded pellets prepared using Ceolus KG-801 as the pellet core was satisfactory. The pellet size analysis showed that the majority of the pellets were within the desired size range of 0.80–1.25 mm (76.89±0.63%). The geometric weight mean diameter and the geometric standard deviation of the pseudoephedrine HCl pellets were 0.77±0.02 mm and 3.04±0.04, respectively.

In Vitro Drug Release from Coated Pseudoephedrine HCl Pellets

The drug dissolution profiles of pellets coated with Eudragit RS-30D are shown in Fig. 1. It could be seen that increasing the polymer coating level from 10% to 30% caused a significant reduction in the drug release. The $t_{50\%}$ values of Eudragit RS-30D coated pellets at the coating levels of 10%, 20%, and 30% were 6.84, 20.08, and 31.77 min ($p<0.05$), respectively. Nevertheless, Eudragit RS-30D could not extend the drug release for more than 2 h even at the 30% coating level. A similar inability to extend the release of an extremely water-soluble drug at high drug loading (more than 20% w/w) from pellets using a polymeric coating system has been reported previously (16–18).

In this regard, a high-viscosity grade of HPMC was chosen as the coating polymer. In order to prevent agglomeration of pellets during the coating process, a dilute coating solution of 0.25% w/w was prepared and used. Figure 2 shows the release of pseudoephedrine HCl from pellets coated with various coating levels of HPMC. An increase in the HPMC coating levels from 10% to 20% drastically delayed the drug release rate. However, even at 20% HPMC coating level, almost 80% of drug was released in 8 h. The $t_{50\%}$ values at 10%, 15%, and 20% HPMC coating levels were 11.10, 28.10, and 61.66 min ($p<0.05$), respectively.

As for Kollicoat SR-30D, this polymer was found to extend the drug release for more than 12 h at a coating level

Table III. Formulations and Dissolution $t_{50\%}$ Values of Tablets made of Various Tabletting Excipients

		Tabletting Excipients		
Formulation Code	F6b (% w/w)	Ceolus KG-801 granules (% w/w)	Ceolus KG-801 pellets (% w/w)	$t_{50\%}$ (min)[a]
F7	50	50	–	100.54 (±12.79)
F8	45	55	–	139.30 (±6.86)
F9	40	60	–	179.11 (±13.80)
F10	40	50	10	162.81 (±7.02)
F11	40	45	15	226.78 (±11.85)
F12	40	40	20	284.53 (±6.85)

[a] Mean±SD, N=6

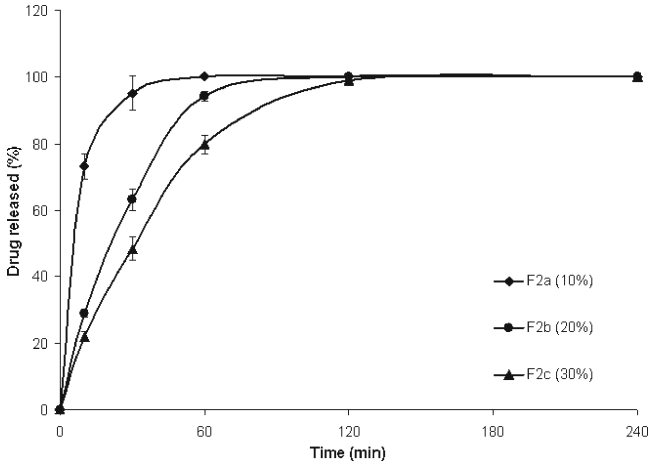

Fig. 1. Effect of coating levels of Eudragit RS-30D on pseudoephe drine HCl release in distilled water. Mean±SD, N=6

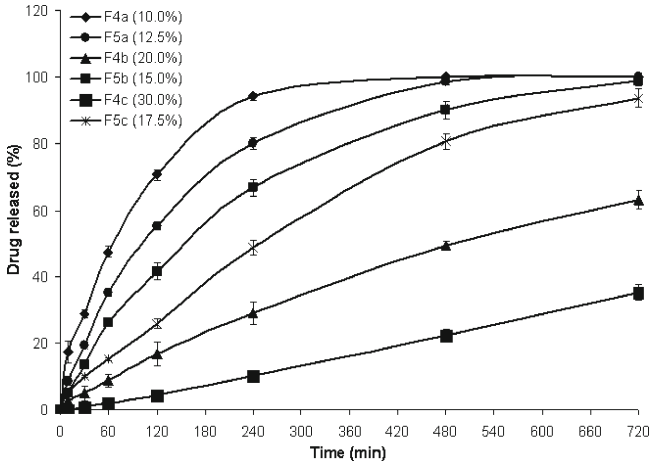

Fig. 3. Effect of coating levels of Kollicoat SR-30D on pseudoephe drine HCl release in distilled water. Mean±SD, N=6

of 30% (Fig. 3). The $t_{50\%}$ values at the coating levels of 10%, 20%, and 30% were 66.68, 495.30, and 849.06 min ($p<0.05$), respectively. The drug release data of F4b and F4c were subjected to release kinetic models, which indicated that F4b and F4c followed first-order ($R^2=1$) and zero-order ($R^2=0.997$) release kinetic models, respectively. When the coating levels of Kollicoat SR-30D were reduced to 12.5%, 15.0%, and 17.5%, the drug release could still be extended to 12 h, with $t_{50\%}$ values of 123.29, 166.98, and 285.12 min, respectively. On the basis of $t_{50\%}$ values, F5c was deemed to be the most suitable coating formulation for this study. It was found that both F5b and F5c followed the first-order release kinetics with R^2 values of 0.98 and 0.99, respectively. To achieve a zero-order release, a modification in the coating pattern was made. HPMC was applied as an inner coat over the drug-loaded pellets at a coating level of 2.5% w/w, followed by Kollicoat SR-30D as a middle coat at the coating levels of 12.5%, 15.0%, and 17.5% w/w. These pellets (F6a, F6b, and F6c) were eventually coated with additional HPMC solution to a coating level of 1% to eradicate the sticking problem.

The dissolution studies of the pellets coated with a combination of polymers, namely, HPMC and Kollicoat SR-30D, are shown in Fig. 4. The presence of HPMC as an inner coat not only reduced the initial burst release of pseudoephedrine HCl but also increased the $t_{50\%}$ values of the formulations. The dissolved drug in the pellet core has to cross the HPMC gel barrier before diffusing through Kollicoat SR-30D coated film, thus contributing to a reduction in the initial drug release, delaying the drug release rate. Nevertheless, the drug release rate from F6a was comparatively faster than that of F6b and F6c. It was found that both F6b and F6c followed the zero-order release kinetics with R^2 values of 0.9924 and 0.9972, respectively. The drug release from F6c was relatively slow; hence, F6b was selected as the optimum coating formulation for further studies. To examine the effect of the pH of the dissolution medium on the drug release, F6b was subjected to dissolution studies at pH1 and pH7. Figure 5 shows that the drug release from F6b was independent of the dissolution medium pH. Out of all coating formulations, only F6b emerged as the formulation of choice, accomplishing the drug release rate up to 12 h with zero-

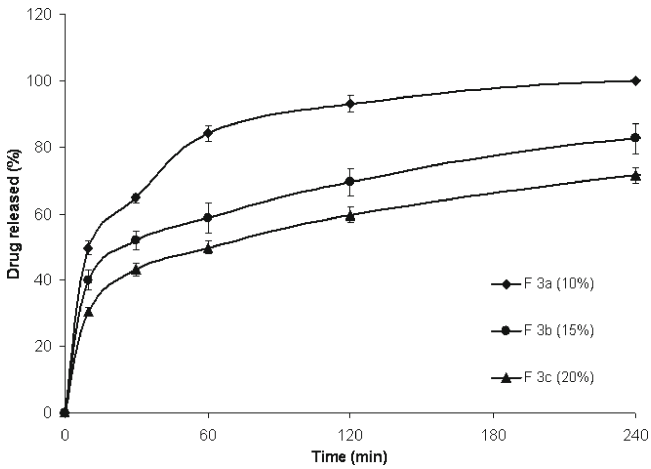

Fig. 2. Effect of coating levels of HPMC on pseudoephedrine HCl release in distilled water. Mean±SD, N=6

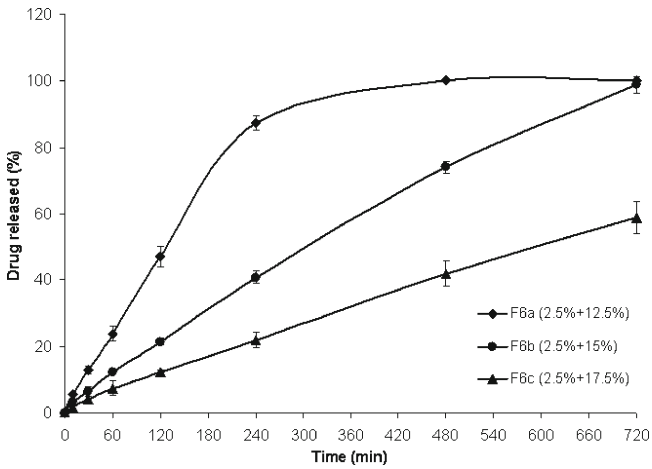

Fig. 4. Pseudoephedrine HCl release profiles from pellets with an inner coat of HPMC and an outer coat of Kollicoat SR-30 D in distilled water

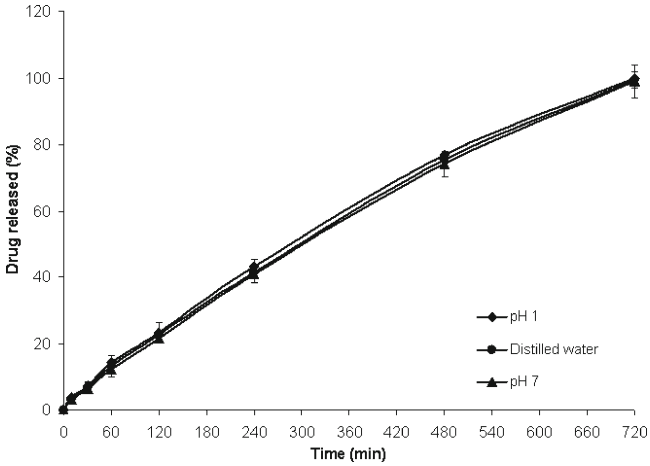

Fig. 5. Effect of the pH of dissolution medium on pseudoephedrine HCl release from coated pellets F6b. Mean±SD, N=6

order kinetics. Therefore, F6b was selected as the final coated pellet formulation to be compressed into tablets.

In Vitro Drug Release from Tablets made from Extended-Release Coated Pseudoephedrine HCl Pellets

The drug release profiles of tablets made from coated pellets with various compositions are shown in Fig. 6. Increasing the content of inert Ceolus KG-801 granules in the tablet from 50% to 60% or decreasing the coated pellets from 50% to 40% has markedly delayed the drug release rate (F7–F9). The damage to coated film was reduced gradually upon increasing the amount of inert Ceolus KG-801 granules. This might be attributed to the filling of void spaces between the densely packed coated pellets by the inert Ceolus KG-801 granules. The compression of coated or uncoated pellets needs tabletting excipients in the form of granules. This is because the tablets prepared only from coated drug-loaded pellets might have too low tensile strength (19). Theoretically, 29% of tabletting excipient is needed to fill the void space between the pellets (3). Although at a low compression force, the presence of inert Ceolus KG-801 granules facilitated the compaction of coated pellets into tablet, yet, significant damage to the coating film was still observed. The damage incurred could be visualized as fine crack lines and indicated by a faster drug release from tablets made of coated pellets as compared to un-compressed coated pellets. The failure of Ceolus KG-801 to circumvent the disruption of the coated film during compression might be ascribed to two factors, namely, an elevated loading (40–50% w/w) of the coated pellets in the compacted formulations and the high aqueous solubility of pseudoephedrine HCl, which promptly affects the drug release, even if minor damage to the coated membrane occurred. Hence, it is apparent that Ceolus KG-801 granules alone could not emerge as a suitable tabletting excipient in the preparation of tablets made of coated pellets with a high loading of an extremely water-soluble drug.

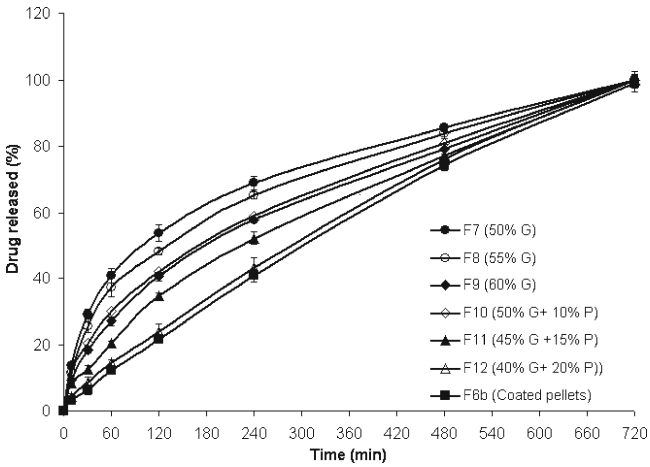

Fig. 6. Drug release profiles of tablets made of coated drug pellets with various tabletting excipients and non-tabletted coated pellets (G granules, P pellets). Mean±SD, N=6

In order to overcome this problem, inert Ceolus KG-801 pellets were incorporated along with inert Ceolus KG-801 granules during the tabletting process of coated pellets. Since the inert Ceolus KG-801 pellets have relatively weaker mechanical strength than the coated drug pellets, the inert pellets tend to fragment easier during compression and functioned as a cushioning agent that protected the coating film of the drug pellets. Wax beads acting as cushioning agents during the compression of coated diltiazem pellets has been reported previously (6). Furthermore, the inert Ceolus KG-801 pellets could also fill the void space between the coated pellets and provide a good bond (20).

The dissolution profiles of tablets made of coated pellets and different tabletting excipients are shown in Fig. 6. An increase in inert Ceolus KG-801 pellets in the formulations (F10, F11, and F12) further reduced the drug release rate due to a reduction in disruption in the coated film incurred during compression. The drug release profiles of tablet F12 and coated drug pellets F6b were found to be closely similar. The $t_{50\%}$ values of F12 and F6b were 284.53 and 300.61 min ($p>0.05$), respectively. The $t_{50\%}$ values for the various tablets made of coated pseudoephedrine HCl pellets (F7–F12) varied from 100.54 to 284.53 min and are shown in Table III. Furthermore, the drug release of F12 followed zero-order release kinetics with an R^2 value of 0.9877.

Formulation F12 was subjected to physical evaluation tests, namely, friability, tensile strength, and disintegration time. The results showed that the friability, tensile strength, and disintegration time values were 0.55±0.08%, 5.14 kg± 0.49, and 7.83 min±0.75, respectively. All these values were within the acceptable limits as specified by the US Pharmacopeia. Tablets made of coated drug pellets disintegrated rapidly, yet pellets maintained both their integrity as multiple units, as well as extended-release characteristics thereafter.

CONCLUSIONS

Coated pellets can be compressed into tablets using MCC Ceolus KG-801 granules as tabletting excipient. However, tabletting excipient composed only of inert Ceolus KG-801 granules is insufficient to minimize the damage incurred to the coated film during compression. A combination of inert Ceolus KG-801 granules and inert Ceolus KG-801 pellets is essential to further reduce the damage that occurred on the coated film during the tabletting process.

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