AAPS PharmSciTech, Vol. 11, No. 2, June 2010 (© 2010)
DOI: 10.1208/s12249-010-9456-2

Research Article

Development and Evaluation of a Novel Modified-Release Pellet-Based Tablet System for the Delivery of Loratadine and Pseudoephedrine Hydrochloride as Model Drugs

Farrukh Zeeshan[1,2] and Nadeem Irfan Bukhari[1]

Received 18 February 2010; accepted 27 April 2010; published online 22 May 2010

Abstract. Modified-release multiple-unit tablets of loratadine and pseudoephedrine hydrochloride with different release profiles were prepared from the immediate-release pellets comprising the above two drugs and prolonged-release pellets containing only pseudoephedrine hydrochloride. The immediate-release pellets containing pseudoephedrine hydrochloride alone or in combination with loratadine were prepared using extrusion–spheronization method. The pellets of pseudoephedrine hydrochloride were coated to prolong the drug release up to 12 h. Both immediate- and prolonged-release pellets were filled into hard gelatin capsule and also compressed into tablets using inert tabletting granules of microcrystalline cellulose Ceolus KG-801. The *in vitro* drug dissolution study conducted using high-performance liquid chromatography method showed that both multiple-unit capsules and multiple-unit tablets released loratadine completely within a time period of 2 h, whereas the immediate-release portion of pseudoephedrine hydrochloride was liberated completely within the first 10 min of dissolution study. On the other hand, the release of pseudoephedrine hydrochloride from the prolonged release coated pellets was prolonged up to 12 hr and followed zero-order release kinetic. The drug dissolution profiles of multiple-unit tablets and multiple-unit capsules were found to be closely similar, indicating that the integrity of pellets remained unaffected during the compression process. Moreover, the friability, hardness, and disintegration time of multiple-unit tablets were found to be within BP specifications. In conclusion, modified-release pellet-based tablet system for the delivery of loratadine and pseudoephedrine hydrochloride was successfully developed and evaluated.

KEY WORDS: extrusion–spheronization; loratadine; modified-release multiple-unit tablet; pseudoephedrine hydrochloride.

INTRODUCTION

The oral drug delivery systems are classified broadly into single-unit dosage forms (capsules or tablets) and multiple-unit dosage forms or pelletized dosage forms (pellets or pellets containing capsules or tablets) (1). Although closely similar drug release profiles can be obtained with both single-unit and multiple-unit dosage forms, pellets offer several added therapeutical advantages (2). The pellets spread uniformly throughout the gastrointestinal tract. They are also found to empty gradually from the stomach with less intra- and inter-individual variations, thus giving better predictability for an administered dose. In contrast, the gastric emptying of a single unit dosage form is at random and with inherently large intra- and inter-subject variations (3). With the use of pellets, the risk of high local drug concentrations and toxicity associated with the intake of locally restricted tablets can also be avoided (4). Premature drug release from enteric-coated tablets in the stomach, potentially resulting in drug degradation or gastric mucosal irritation, can also be reduced with the coated pellets owing to their rapid transit time. The better distribution of pellets in the gastrointestinal tract could also improve the bioavailability of the drug they contain, leading to a possible reduction in drug dose and adverse effects. The risk of dose dumping from pellets is equally divided, and it is less likely that the pellets are disrupted (5). Incomplete drug release of the preparation is less likely to happen. Inter- and intra-individual variations in the bioavailability caused for instance by food effects are also reduced. Furthermore, modified-release profiles can be obtained by simply mixing pellets with different release characteristics (1).

With regard to final dosage form, pellets can either be placed into hard gelatin capsule (multiple-unit capsule) or compressed into tablets (multiple-unit tablets). However, compression of pellets into tablets is becoming more popular than filling them into capsules (1). The compression of pellets into tablets is a modern technological process (6) and is much more ideal than enclosing them into capsule (7). The advantages of tabletting pellets include reduced risk of tampering and lesser difficulty in esophageal transport compared to capsules. Tablets could administer higher dose strength and can be prepared from pellets at lower cost compared to pellet-filled capsules because of the higher production rate of tablet press. The expensive control of

[1] Department of Pharmaceutical Technology, School of Pharmacy and Allied Health Sciences, International Medical University, Bukit Jalil, 57000, Kuala Lumpur, Malaysia.
[2] To whom correspondence should be addressed. (e-mail: farrukh_zeeshan@yahoo.com; farrukh_zeeshan@imu.edu.my)

capsule integrity is also eliminated in tabletting from pellets (2,6). Nevertheless, compaction of pellets, especially coated pellets, containing freely water-soluble drugs into tablets is an extremely challenging area, and thereby to date, only a few pellets containing tablet products such as Beloc® ZOK and Antra® MUPS are commercially available (8). Several problems associated with compression of coated pellets include rupturing of coated film leading to the immediate loss of controlled-release characteristics particularly for water-soluble drugs. Compression without rupturing coated film on pellets may still not ensure the formation of multiple unit tablets with appropriate tensile strength, friability, and disintegration time. Research is being carried out to address the aforementioned problems encountered during compression of pellets. A study has documented the potential of highly compressible microcrystalline cellulose, Ceolus KG-801, as a suitable tabletting excipient to protect coated pellets containing a freely water-soluble drug from damage incurred during the compression. The multiple-unit tablets were also reported to possess adequate tensile strength with short disintegration time and less friability (9).

It has been documented that combination therapy comprising an antihistamine, such as loratadine, fexofenadine, and cetirizine, and a decongestant, such as pseudoephedrine hydrochloride and phenylephrine hydrochloride, is more effective in relieving the symptoms of allergic rhinitis than either component alone (10–12). Consequently, the combined immediate-release or modified-release products of antihistamine and decongestant are available in the market either in the form of single-unit tablets or multiple-unit capsules. A couple of commercially available modified-release products containing loratadine and pseudoephedrine are Clarinase®, Clarityne-D®, Chlor-Tripolon ND®, Claritin Extra®, Colbid®, Loridin-D®, Rhilor-D®, and Carinox® . Once-a-day modified-release products contain 10 mg of loratadine and 240 mg of pseudoephedrine, whereas twice-a-day products comprise 5 mg loratadine and 120 mg pseudoephedrine. The products are formulated in such a way that the entire loratadine and half of pseudoephedrine are intended for immediate release, while the balance of pseudephedrine is for prolonged/extended release (13). Nevertheless, documented studies on the development of modified-release multiple-unit capsules and tablets containing an antihistamine such as loratadine and a decongestant such as pseudoephedrine are scant.

In view of the aforementioned limitations, the objective of the present study was to develop modified-release multiple-unit tablets containing two drugs with different release profiles using loratadine and pseudoephedrine hydrochloride as model drugs. The multiple-unit tablets were produced from the compression of immediate-release pellets containing both loratadine and pseudoephedrine hydrochloride and prolonged-release pellets containing only pseudoephedrine hydrochloride. The potential therapeutic advantages of pellets over single-unit capsules or tablets and the growing popularity of multiple-unit tablets compared to multiple-unit capsules was the rationale behind the present study. The study might be novel in the sense that no documented study was found on the development of modified-release pellet-based tablet system for the delivery of an antihistamine and a decongestant despite the growing popularity of multiple-unit tablets compared to multiple-unit capsules. The drug dissolution profile of the multiple-unit tablets was compared with that of the multiple-unit capsules as compaction could alter the release profile of drugs.

MATERIALS AND METHODS

Materials

The different materials used were highly compressible microcrystalline cellulose (MCC; Ceolus KG-801 (KG-801), Asahi Chemicals, Japan), pseudoephedrine hydrochloride (P.HCl; Emmellen Biotech and Pharmaceuticals Limited, Mumbai, India), loratadine (Emmellen Biotech and Pharmaceuticals Limited, Mumbai, India), lactose monohydrate (Impalpable Grade; HMS, Holland), Kollicoat SR-30D aqueous dispersion 30%, *w/v* (KLC; 30 g of dispersed substances consisting of 27% polyvinyl acetate, 2.7% povidone, and 0.3% sodium lauryl sulfate in 100 ml of dispersion; 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, Japan), triethyl citrate (TEC; Merck-Schuchardt, Germany), polyethylene glycol 4000 (PEG 4000, Merck-Schuchardt), hydrochloric acid 12.06 M (Lab-Scan Asia, Bangkok, Thailand), acetonitrile HPLC grade (J.T.Baker, Mexico), ammonium dihydrogen orthophosphate (BDH Limited, Poole, England), and phosphoric acid (Ajax Chemicals, Sydney, Australia).

Preparation of Immediate-Release Pellet Formulations

Two different types of immediate-release pellets (F1 and F2), each with a batch size of 150 g, were prepared in triplicate using extrusion–spheronization method. For the preparation of F1 pellets, 5 g of loratadine, 60 g of pseudoephedrine hydrochloride, and 85 g of microcrystalline cellulose were screened through a 0.80-mm diameter sieve (Endecotts Ltd., London, England) and mixed in a planetary mixer (Kenwood Chef Classic, UK) at 160 rpm for 10 min. Distilled water as granulating liquid was added slowly and the mixing was continued to obtain a wet mass of suitable consistency. The wet mass was extruded at 1,000 rpm using a rotary gear extruder (Caleva, model 40, UK) with a cylindrical die of 14-cm length and perforations of 1.00-mm diameter. The extrudates were subjected to the spheronizer (Caleva, model 380) at 1,000 rpm for 10 min. The formed pellets were dried in a fluidized bed dryer (Burkard, FBD 350S, UK) at 60°C for 30 min. A similar procedure was used to prepare F2 pellets comprising 60 g of pseudoephedrine hydrochloride and 90 g of microcrystalline cellulose.

Percent Yield and Size Analysis of Immediate-Release Pellet Formulations

The percent yield of the three batches of immediate-release pellet formulations (F1 and F2) was determined individually using the following equation (9):

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

The size range of each batch of pellets obtained after drying was determined using a series of sieves with aperture sizes of 0.40-, 0.63-, 0.80-, 1.25-, 1.70-, and 2.00-mm diameter. All the pellets of each batch obtained after drying were used in the size analysis study. The sieves were vibrated mechanically (Retsch AS200 Analytical Sieve Shakers, Germany) at amplitude of 1.00 mm for 10 min. The weight of pellets retained on each sieve was recorded. Pellets of size range between 0.80- and 1.25-mm diameter were selected for further study. The geometric weight mean diameter and geometric standard deviation for each pellet batch were also determined (14) and were used to characterize the pellet size and size distribution.

Preparation of Prolonged-Release Pellet Formulations by Polymeric Coating System

Three different types of prolonged-release coated pellets (F3, F4, and F5) as shown in Table I were prepared by coating 150 g of F2 pellets with two different polymeric coating solutions. The outer coating dispersion was prepared by mixing and stirring 1.5 g of TEC with 100 ml of Kollicoat SR-30D aqueous dispersion for 30 min. The dispersion was further diluted and mixed well with 200 ml of distilled water. The inner coating solution was prepared by dissolving 3.75 g of HPMC (Metolose-90SH, 100,000SR) and 565 mg of PEG 4000 in water to a final volume of 1.5 L. The solution was allowed to stand at room temperature for 24 h. TEC was replaced by PEG 4000 as a plasticizer in the preparation of aqueous coating of HPMC due to its better efficacy as a plasticizer in preparation of HPMC coating solution (15).

Batches of 150 g of F2 pellets were coated initially with HPMC at 2.5% (*w*/*w*) coating level followed by coating using Kollicoat SR-30D at three different coating levels, namely, 15%, 17.5%, and 20% (*w*/*w*, Table I) in a bottom spray fluidized bed coater (Aromatic-Fielder AG, Switzerland) fitted with a cylindrical partition tube (Wurster insert, diameter=47 mm, height=180 mm). The coating level is the quotient of the dry weight of polymer and the weight of the uncoated pellets, expressed as a percentage. The coating level was determined experimentally by determining the percentage increase in pellet weight upon coating. The coating solution was sprayed via the two-fluid spray nozzle using a peristaltic pump (Rota Consulta, model 1B.100 S-R/65, Germany) at preselected coating conditions as shown in Table II. A specific sequence of coating was followed; the pellets were subjected firstly to HPMC coating followed by coating with Kollicoat SR-30D aqueous dispersion. Lastly, in order to reduce sticking of coated pellets during storage, an HPMC overcoat of 1% (*w*/*w*) of the total weight of coated pellets was also applied using the similar coating conditions as were followed for its initial coat of 2.5 % (*w*/*w*). On the completion of the coating, the coated pellets were fluidized for an additional 15 min to ensure complete drying.

Modified-Release Multiple-Unit Capsules and Tablets Containing Immediate-Release Loratadine and Pseudoephedrine Hydrochloride Pellets and Prolonged-Release Pseudoephedrine Hydrochloride-Coated Pellets

Immediate-release pellets with a weight of 150 mg containing 5 mg of loratadine and 60 mg of pseudoephedrine hydrochloride (F1) were mixed with 185 mg 12-h prolonged-release pseudoephedrine hydrochloride-coated pellets (F4) containing approximately 60 mg of pseudoephedrine hydrochloride. Thus, a total weight of 335 mg of pellets containing 5 mg of loratadine and 120 mg of pseudoephedrine hydrochloride were filled into a size "0" hard gelatin capsule. Fifty capsules were prepared manually, labeled as F6, and were employed as reference to compare the drug dissolution profiles of the multiple-unit tablets. In order to ensure the uniformity of the drug content in multiple-unit capsules containing both immediate and prolonged-release pellets, the assay of the total drug content was conducted (16).

To produce multiple-unit tablets (F7), inert Ceolus KG-801 tabletting granules consisting of 140 g of Ceolus KG-801 and 60 g of lactose monohydrate and distilled water were first prepared using wet granulation method. The weighed amount of Ceolus KG-801 and lactose were passed through a 0.80-mm diameter sieve (Endecotts Ltd.) 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 Ltd.). The resulting granules were dried in an oven (Carbolite Company, England) at 50°C and sieved manually using a series of sieves with aperture sizes of 0.16, 0.40, and 0.80 mm (Endecotts Ltd.). The granules with size range between 0.40 and 0.80 mm were only used in the compaction process. Each multiple-unit tablet containing 5 mg of loratadine and 120 mg of pseudoephedrine hydrochloride comprised 150 mg of F1, 185 mg of F4, and 150 mg of inert Ceolus KG-801 granules.

Table I. Formulations of Modified-Release Multiple-Unit Capsules and Multiple-Unit Tablets Containing Loratadine and Pseudoephedrine Hydrochloride

Formulation code	Dosage form	Release profiles	Composition	HPMC inner coat (%, *w*/*w*)	Kollicoat outer coat (%, *w*/*w*)	F1 pellets (mg)	F4 pellets (mg)	Inert MCC, Ceolus KG-801 granules (mg)
F1	Pellets	Immediate	P.HCl+Loratadine	–	–	–	–	–
F2	Pellets	Immediate	P.HCl	–	–	–	–	–
F3	Coated pellets	Prolonged	P.HCl	2.5	15.0	–	–	–
F4	Coated pellets	Prolonged	P.HCl	2.5	17.5	–	–	–
F5	Coated pellets	Prolonged	P.HCl	2.5	20.0	–	–	–
F6	Multiple-unit capsule	Modified	P.HCl+Loratadine	-	–	150	185	–
F7	Multiple-unit tablet	Modified	P.HCl+Loratadine	–	–	150	185	150

HPMC Hydroxypropyl methylcellulose, *MCC* Microcrystalline cellulose

Table II. Coating Process Conditions

Process conditions	Setting
Batch size (g)	150
Inlet temperature (°C)	45 (Kollicoat SR-30D) 60 (HPMC)
Outlet temperature (°C)	42–43 (Kollicoat SR-30D) 56–57 (HPMC)
Atomizing air (bar)	1
Flow rate (ml/min)	5.5–6
Fluidized air (m^3/h)	90–110
Spray nozzle diameter (mm)	0.8
Center pipe diameter (mm)	47
Center pipe length (mm)	180

HPMC Hydroxypropyl methylcellulos

The tabletting procedure was conducted using a single punch-tabletting machine (Manesty, England) fitted with round, flat-faced 10-mm diameter punches and dies. One batch comprising 100 tablets was prepared and subjected to testing the uniformity of the drug content study (16), *in vitro* drug release study, friability, tensile strength (17), and disintegration time tests (18).

In Vitro Drug Release Study

The *in vitro* drug release study of prolonged-release pellet formulations (F3–F5) was carried out in 900 ml of distilled water as dissolution medium maintained at 37.0±0.5°C using the basket method of USP 26 dissolution test apparatus l (Distek Premiere, 5100, dissolution test apparatus, USA) at a stirring speed of 100 rpm. One gram of coated pellets containing approximately 325 mg of pseudoephedrine hydrochloride was used in the study. At predetermined time intervals of 10, 30, 60, 120, 240, 480, and 720 min, 5 ml sample was collected using an autosampler (Distek) and replaced with 5 ml of fresh dissolution medium. The amount of drug released was quantified using a UV/VIS spectrophotometer (U-2000, Hitachi, Tokyo, Japan) at a detection wavelength of 215 nm after suitable dilution with distilled water such that the absorbance value follows Beer–Lambert law. The goodness of fit of the drug release data was tested with mathematical models such as zero-order kinetics, first-order kinetics, and Higuchi's square root of time release (19).

The *in vitro* drug dissolution studies of multiple-unit capsules (F6) and tablets (F7) were carried out using the basket method of USP 26 dissolution test apparatus1 for 12 h at pH 1.2. The amount of drug released was quantified using the high-performance liquid chromatography (HPLC) method instead of UV spectrophotometry. This is because in both multiple-unit capsules and tablets, loratadine and pseudoephedrine hydrochloride were present in combination and could not be measured using a UV spectrophotometer. The samples containing both drugs were injected directly to the HPLC system without any dilution. The HPLC system comprised a Waters 510 pump (Waters Corporation, Milford, MA, USA) equipped with a six-valve sample injection port (Rheodyne7725 Cotati, CA, USA), fitted with a 20-µl sample loop, a Jasco 875-UV/VIS detector (Japan), and a D-2500 chromato-integrator (Hitachi). A reversed phase Luna 5 µ C-18 (2) Phenomenex column (150×4.6 mm ID, 5 µm) fitted with a refillable guard column was used for chromatographic separation. The mobile phase consisted of 30 mM ammonium dihydrogen orthophosphate and acetonitrile (4:6, *v*/*v*) adjusted to pH 3.5 with phosphoric acid. The analysis was run at ambient room temperature with a flow rate of 1 ml/min at a detection wavelength of 265 nm. The drug release profiles in terms of the percentage of drug released, $t_{50\%}$ (time for 50% of loratadine released) and $t_{75\%}$ (time for 75% of pseudoephedrine hydrochloride released), were determined from the corresponding drug release against time release curves. For each batch of product, six determinations were carried out.

Statistical Analysis

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

RESULTS AND DISCUSSION

Percent Yield and Size Analysis of Immediate-Release Pellet Formulations

Immediate-release pellets containing pseudoephedrine hydrochloride alone or in combination with loratadine were prepared successfully using extrusion–spheronization method. The coating of pseudoephedrine hydrochloride pellets to prolong the drug release rate was also conducted smoothly under the predetermined coating conditions as specified in Table II. In addition, the modified-release multiple-unit capsules and tablets containing immediate-release as well as prolonged-release pellets were also produced successfully.

The total amount of powder ingredients of each of three batches of immediate-release pellet formulations was 150 g. The mean percent yield of three batches of F1 after drying (moisture content < 2%) was found to be 92.5±1.40%. On the other hand, the mean percent yield of three batches of F2 after drying (moisture content < 2%) was 91.76±1.45%. However, the slightly lower pellet yield of F2 compared to that of F1 was not statistically significant ($p>0.05$). The percent yield obtained from both types of immediate-release pellets seems to be acceptable as it was more than 90%.

The size distribution profiles of immediate-release pellet formulations (F1 and F2) are shown in Fig. 1. All the pellets obtained after drying were used in the size analysis study. Both types of the immediate-release pellets exhibited a narrow size distribution, and approximately 75% of the pellets were within the desirable size range of 0.80–1.25 mm, though only about 68% (75% of 90%) of total pellets obtained using extrusion–spheronization method were found to be in desired size range of 0.80–1.25 mm. Nevertheless, percent yield of pellets and consequently the amount of pellets in the desired size range of 0.80–1.25 mm might be further improved by increasing the batch size of the powder ingredients fed into the extruder. During the extrusion process, loss of a certain amount of powder ingredients is inevitable due to their adherence to the perforations of the extruder. Therefore, an increase in the batch size is expected to increase the percent yield, thereby more pellets within the desired size range are also predicted.

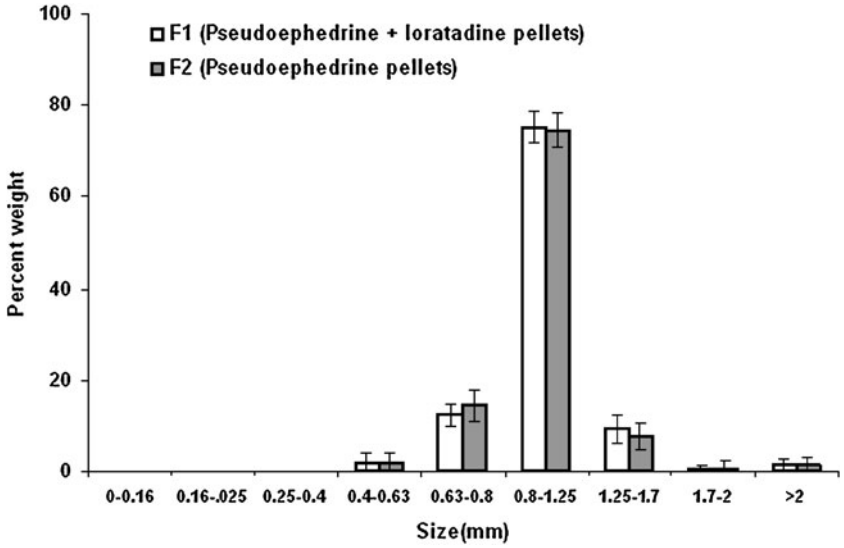

Fig. 1. Size distribution of immediate-release pellets containing pseudoephedrine hydrochloride in combination with loratadine (Formulation 1) and pseudoephedrine hydrochloride alone (Formulation 2)

Prolonged-Release Pseudoephedrine Hydrochloride Pellet Formulations

The release profiles of F3–F5 pellets are shown in Fig. 2. The approach of using mixed polymeric coating to prolong the drug release has been reported in previous studies (20–24). It is evident that increasing the coating level of Kollicoat SR-30D from 15% (*w*/*w*) to 20% (*w*/*w*) caused a significant reduction in the drug release rate. The dissolution $t_{50\%}$ values for F3, F4, and F5 at coating levels of 15%, 17.5%, and 20% (*w*/*w*) of Kollicoat SR-30D were 239.35±1.56, 318.57±2.43, and 385.58±3.23 min, respectively ($p<0.05$). The drug release kinetics of F3 fitted Higuchi's diffusion equation with a correlation coefficient (R^2) value of 0.990, while the drug release kinetics of F4 and F5 best fitted the zero-order kinetics with correlation coefficient (R^2) values of 0.998 and 0.999, respectively. The intended drug release rate for F3–F5 pellet formulations was 5–6 mg/h with a dissolution $t_{50\%}$ value closer to 300 min. In addition, the drug dissolution profile of these pellets must follow zero-order release kinetics. This is because only the zero-order release with a drug release rate between 5 and 6 mg/h would ensure the gradual and almost complete release of pseudoephedrine hydrochloride within a time period of 12 h. Since the drug release characteristics of F4 were found closest to the intended drug release rate and the $t_{50\%}$ value and followed zero-order drug release kinetics, therefore F4 pellets were selected to be combined with the immediate-release F1 pellets in the preparation of the multiple-unit capsules and tablets.

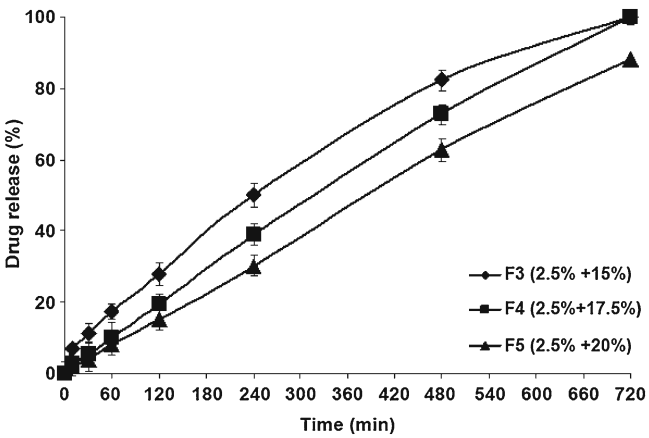

Fig. 2. *In vitro* dissolution profile of prolonged-release pseudoephedrine hydrochloride coated pellets (Formulations 3-5)

In Vitro Drug Release from Modified-Release Multiple-Unit Capsules and Tablets

The chromatogram of pseudoephedrine hydrochloride and loratadine is shown in Fig. 3. The retention time of pseudoephedrine hydrochloride was 1.31 min, while loratadine was retained at 3.45 min. The standard calibration curve of pseudoephedrine hydrochloride was linear at the concentration range between 5 and 200 μg/ml, while loratadine depicted linearity at the concentration range between 0.25 and 10.00 μg/ml. The limit of detection for pseudoephedrine hydrochloride was 1.25 μg/ml while that for loratadine was 62.50 ng/ml. The limits of quantification for pseudoephedrine hydrochloride and loratadine were 5 and 0.25 μg/ml, respectively. The within-run and between-run precision and accuracy values of both pseudoephedrine hydrochloride and loratadine were found to be within the acceptable limits (25). This simple yet sensitive HPLC method was employed successfully to quantify drug released from both the multiple-units capsules and tablets containing loratadine and pseudoephedrine hydrochloride.

The drug dissolution profiles of multiple-unit capsules F6 and tablets F7 at pH 1.2 are shown in Fig. 4. Despite the fact that residence time of any oral solid dosage form in the stomach is much shorter than 12 h, the drug dissolution studies were carried out for 12 h at pH 1.2 because loratadine demonstrates the best solubility at pH 1.2 (26). Pseudoephedrine hydrochloride, on the other hand, is freely soluble at acidic and

alkaline pH. It is evident that all the loratadine from both F6 and F7 was released within 2 h, with a $t_{50\%}$ value of 39.74± 1.23 min for F6 and 38.14 (±1.44) min for F7. The difference between loratadine $t_{50\%}$ values obtained from multiple-unit capsules and tablets was not statistically significant ($p>0.05$). This finding was encouraging since the normal residence time of oral solid dosage forms in the stomach is approximately 2 h. Hence, the insolubility problem of loratadine at the higher intestinal pH is non-existing. On the contrary, from both F6 and F7, approximately 60 mg of the pseudoephedrine hydrochloride was released within 10 min, while the remaining 60 mg was released gradually within 12 h, with a $t_{75\%}$ value of 307.46±14.20 min for F6 and 302.50±10.95 min for F7. The slight difference between pseudoephedrine hydrochloride $t_{75\%}$ values obtained from multiple-unit capsules and tablets was not statistically significant ($p>0.05$). Thus, the drug dissolution profiles of multiple-unit tablets was found closely similar to that of capsules, indicating that compaction process exerted, if any, a negligible effect on the dissolution profiles of pseudoephedrine hydrochloride. Furthermore, friability, tensile strength, and disintegration time values of multiple-unit tablets F7 were found to be 0.50± 0.06 %, 5.35±0.62 kg, and 6.44±0.53 min, respectively. All these values were within the acceptable limits as specified (17,18).

The closely similar pseudoephedrine hydrochloride release profile of multiple-unit tablets to that of capsules might be ascribed to the integrity of coated membrane on prolonged-release pseudoephedrine hydrochloride pellets due to the presence of compressible microcrystalline cellulose Ceolus KG-801 in the form of tabletting granules and pellets. This finding was in agreement with that of a previously reported study (9). The compression of coated or uncoated pellets needs tabletting excipients in the form of granules.

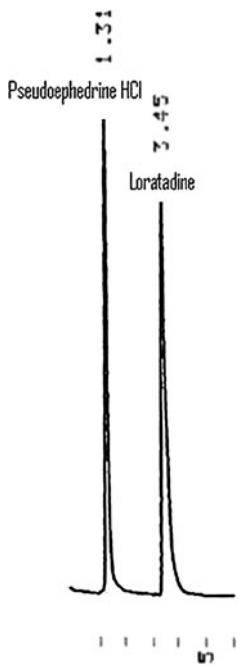

Fig. 3. Chromatogram of pseudoephedrine hydrochloride and loratadine. Retention time: Pseudoephedrine hydrochloride=1.31 min; Loratadine=3.45 min

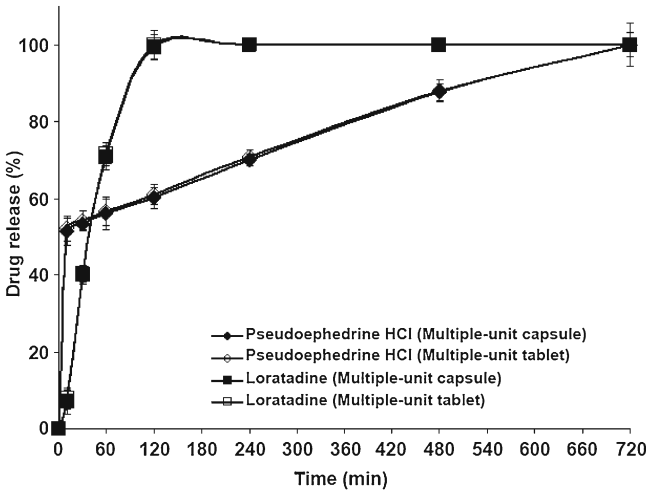

Fig. 4. Loratadine and pseudoephedrine hydrochloride release profiles of multiple-unit capsules (Formulation 6) and of multiple-unit tablets (Formulation 7) at pH 1.2. Mean ± SD, $N=6$

This is because the tablets prepared only from coated drug-loaded pellets might have too low tensile strength (27). Theoretically, at least 29% of tabletting granules are required to fill the void space between the pellets undergoing compaction (1). Nevertheless, tabletting excipients provided only in the form of granules are not sufficient to minimize the damage incurred upon compaction to the coated film, especially if freely water-soluble drugs are employed (9), and may require other ingredients/cushioning agents (28). In the present study, the immediate-release pellets prepared using microcrystalline cellulose Ceolus KG-801containing both loratadine and pseudoephedrine hydrochloride (F1) might have served as the cushioning agents. Since immediate-release pellets (F1) were uncoated, hence they possess a relatively weaker mechanical strength than that of the coated pellets, which might have caused them to fragment easily during compression, thus forming the protective film for the coated pellets. In addition, the immediate release pellets (F1) also filled the void space between the coated pellets and thus provided a good bond (29).

CONCLUSION

Modified-release multiple-unit tablets were prepared successfully by compressing immediate release pellets containing both loratadine and pseudoephedrine hydrochloride and prolonged release coated pellets containing only pseudoephedrine hydrochloride using microcrystalline cellulose Ceolus KG-801 as tabletting excipient. The drug release profile of the multiple-unit tablets was found to be closely similar to that of the multiple-unit capsules, indicating that compression did not alter the release profiles of drugs. The findings of the present study suggest that multiple-unit tablet systems could be applied to deliver multiple drugs with different release profiles in the treatment of certain diseases.

DECLARATION OF INTEREST

The authors report no declaration of interest.

REFERENCES

1. Bodmeier R. Tableting of coated pellets. Eur J Pharm Biopharm. 1997;43:1–8.
2. Bechgaard H, Neilson GH. Controlled release multiple units and single-unit doses. Drug Dev Ind Pharm. 1978;4:53–67.
3. Bechgaard H. Critical factors influencing gastrointestinal absorption—what is the role of pellets? Acta Pharm Technol. 1982;28(2):149–57.
4. Wilson CG, Washington C, Washington N. Overview of epithelial barriers and drug transport. In: Wilson CG, Washington N, editors. Physiological pharmaceutics: biological barriers to drug absorption. Chichester: Ellis Horwood Limited; 1989. p. 60–70.
5. Beckett AH. Proceedings of an International Symposium on Recent Advances in the Design, Development and Assessment of Sustained Release Drug Delivery Systems.1985; Liverpool.
6. Wieslaw S, Rafal L. Compressibility of floating pellets with verapamil hydrochloride coated with dispersion Koollicoat SR 30 D. Eur J Pharm Biopharm. 2005;60:153–58.
7. Tunon A, Borjesson E, Frenning G, Alderborn G. Drug release from reservoir pellets compacted with some excipients of different physical properties. Eur J Pharm Biopharm. 2003;20:469–79.
8. Dashevsky A, Kolter K, Bodmeier R. Compression of pellets coated with various aqueous polymer dispersions. Eur J Pharm Sci. 2004;279:19–26.
9. Zeeshan F, Peh KK, Tan YTF. 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. AAPS PharmSciTech. 2009;10(3):850–57.
10. Connell JT. A novel method to assess antihistamine and decongestant efficacy. Ann Allergy. 1979;42:278–85.
11. Falliers CJ, Redding MA. Controlled comparison of a new antihistamine–decongestant combination to its individual components. Ann Allergy. 1980;45:75–80.
12. Connell JT, Williams BO, Allen S, Cato A, Perkins JG. A double- blind controlled evaluation of Actifed and its individual constituents in allergic rhinitis. J Int Med Res. 1982;10:341–47.
13. Sznitowska M, Cal K, Kupiec K. Development of modified-release dosage forms containing loratadine and pseudoephedrine sulphate. Acta Pol Pharm. 2004;61:72–4.
14. Schaefer T, Worts O. Control of fluidized bed granulation: effects of spray angle, nozzle height and starting materials on granule size and size distribution. Arch Pharm Chem Sci. 1977; 5:51–60.
15. Tan YTF, Heng PWS, Wan LSC. Mixed polymer coating for modified release from coated spheroids. Pharm Dev Technol. 1999;5(4):561–70.
16. British Pharmacopoeia. Vol IV. London, UK: British Pharmacopoeia Commission Office; 2008: Appendix XII C A303-5.
17. British Pharmacopoeia. Vol IV. London, UK: British Pharmacopoeia Commission Office; 2008: Appendix XVII H A423-4.
18. British Pharmacopoeia. Vol IV. London, UK: British Pharmacopoeia Commission Office; 2008: Appendix XII A A283-4.
19. Laakso L, Kristoffersson E, Marvola M. Bi-exponential first-order release kinetics of indomethacin from tablets containing polysorbate 80. Eur J Pharm Sci. 1984;19:35–42.
20. Lippold BC, Monells Pagés R. Control and stability of drug release from diffusion pellets coated with the aqueous quaternary polymethacrylate dispersion Eudragit RS 30 D. Pharmazie. 2001;56(6):477–83.
21. Nisar ur Rahman, Yuen KH, Khan NA, Wong JW. Drug–polymer mixed coating: a new approach for controlling drug release rates in pellets. Pharm Dev Technol. 2006;11(1):71–7.
22. Chen S, Zhu J, Cheng J. Preparation and *in vitro* evaluation of a novel combined multiparticulate delayed-onset sustained-release formulation of diltiazem hydrochloride. Pharmazie. 2007;62 (12):907–13.
23. Huang HF, Lu Y, He HB, Tang X. Preparation and bioavailability of sustained-release doxofylline pellets in beagle dogs. Drug Dev Ind Pharm. 2008;34(7):676–82.
24. Ghaffari A, Avadi MR, Moghimi HR, Oskoui M, Bayati K, Rafiee-Tehrani M. Mechanistic analysis of drug release from theophylline pellets coated by films containing pectin, chitosan and Eudragit RS. Drug Dev Ind Pharm. 2008;34(4):390–02.
25. Mikatos A, Panderi I. Determination of the carboxylic acid metabolite of clopidogrel in human plasma by liquid chromatography–electrospray ionisation mass spectrometry. Analytica Chim Acta. 2004;505:107–14.
26. Zahirul M, Khan I, Dragica Raušl, *et al*. Classification of loratadine based on the biopharmaceutics drug classification concept and possible *in vitro–in vivo* correlation. Biol Pharm Bull. 2004;27:1630–35.
27. Flament MP, Leterme P, Gayot A, Gendrot E, Bruna E, Cousin G. Development and industrial scale-up of tablets containing modified-release pellets. Pharm Technol Eur. 1994;2:19–25.
28. Vergote GJ, Kiekens F, Vervaet C, Remon JP. Wax beads as cushioning agents during the compression of coated diltiazem pellets. Eur J Pharm Sci. 2002;17:145–51.
29. Celik M. Compaction of multiparticulate oral dosage forms. In: Ghebre-Sellasie, editor. Multiparticulate oral drug delivery. New York: Marcel Dekker; 1994. p. 181–15.