International Journal of Pharmaceutics 419 (2011) 121–130

Contents lists available at ScienceDirect

International Journal of Pharmaceutics

journal homepage: www.elsevier.com/locate/ijpharm

Dual coating of swellable and rupturable polymers on Glipizide loaded MCC pellets for pulsatile delivery: Formulation design and *in vitro* evaluation

Deepak Yadav, Sachin Survase, Neeraj Kumar*

Department of Pharmaceutics, National Institute of Pharmaceutical Education and Research (NIPER), Sector 67, S.A.S. Nagar, Punjab 160067, India

ARTICLE INFO

Article history:
Received 13 June 2011
Received in revised form 15 July 2011
Accepted 18 July 2011
Available online 22 July 2011

Keywords:
Pulsatile
Glipizide
Pellet
Swellable
Rupturable

ABSTRACT

This study is aimed to develop and evaluate time dependent rupturable multiparticulate pulsatile delivery system for Glipizide. Microcrystalline cellulose (MCC) based pellets containing Glipizide were prepared by extrusion–spheronization technique (Type I pellets). These were further coated with two consecutive layers, a swellable layer of hydroxypropylmethylcellulose (HPMC) and a rupturable layer of plasticized ethylcellulose (EC) with fluidized bed coating to yield Type II pellets. Drug release and water uptake studies were carried out on formulated pellets. SEM was used to monitor the pellets' morphology and change on exposure to dissolution medium. Both types of pellets were evaluated for particle size, flow, friability, dissolution and content uniformity. Immediate release pattern was optimized for Type I pellets to achieve more than 80% drug release within 30 min. Type II pellets displayed burst release and a lag period of 6–8 h. After selection of appropriate proportions of these pellets (Type I and Type II), drug release studies were performed which showed a pulsatile dissolution profile with a lag-time of 6–8 h. Multiparticulate approach with a blend of the two types of pellets was successfully used to develop a pulsatile release product for Glipizide.

1. Introduction

Diabetes mellitus is one of the major causes of death and disability in the world. Although the prevalence of both Type-I and Type-II diabetes is increasing worldwide, the prevalence of Type-II diabetes is expected to rise more rapidly in future because of sedentary lifestyle, increasing obesity and reduced activity levels. In USA, about 90% of all diabetic patients have Type-II diabetes (Davis, 2006). Glipizide is a second generation sulfonylurea and is one of the most widely used agents against Type II diabetes. It is a weak acid ($pK_a = 5.9$), practically insoluble in water and acidic environment but highly permeable drug belonging to BCS class 2 (Jamzad and Fassihi, 2006). It has a short biological half-life (3.4 ± 0.7 h) and requires 2–3 doses of 2.5–10 mg per day for treatment (Martindale, 1996; Shivakumar et al., 2007). This drug is usually intended to be taken for a long period of time, which often leads to non-compliance. Thus, there is a strong clinical need and market potential for pulsatile delivery system for Glipizide, thereby resulting in better patient compliance.

Pulsatile drug delivery systems are characterized by at least two distinctive drug release phases following a predetermined lag time. Drug release may be controlled by time, by site or a combination of the two parameters. Pulsatile systems have been developed in the past based on a variety of mechanisms, including erosion (Gazzaniga et al., 1994; McConville et al., 2005) and rupturable systems (Bussemer and Bodmeier, 2003). The latter were developed either as single unit hard/soft gelatin capsules (Bussemer and Bodmeier, 2003; Bussemer et al., 2003a) and tablets (Sungthongjeen et al., 2004) or in the form of multiparticulates (Ueda et al., 1994). Rupturable systems usually consist of a core containing the drug, a swelling layer, and an external water insoluble, but permeable polymer coating (Bussemer and Bodmeier, 2003). Gastrointestinal fluids penetrate through the polymer coating, the swelling layer expands until the outer polymer coating ruptures and the drug is then released rapidly. Parameters such as surfactants, pH, and ionic strength of the *in vitro* dissolution medium were investigated previously, in an attempt to predict in vivo performance of drug formulations (Galia et al., 1998). A marketed pulsatile product (Chronotopic® or Time Clock® system) consists of two coating layers a hydrophilic (HPMC) or lipophilic (carnauba or beeswax) coating layer and an enteric coating layer in order to prevent premature drug release from the drug containing core (Maroni et al., 2005). Bar-Shalom also described release of drug

Abbreviations: MCC, Microcrystalline cellulose; HPMC, Hydroxypropylmethylcellulose; EC, Ethylcellulose; SLS, Sodium laurylsulfate; BCS, Biopharmaceutics classification system; h, hours; min, minutes; ρ_{tapped}, Tapped density; ρ_{bulk}, Bulk density; rpm, rotations per minute.

* Corresponding author. Tel.: +91 172 2292057; fax: +91 172 2214692.
E-mail address: neeraj@niper.ac.in (N. Kumar).

0378-5173/$ – see front matter © 2011 Elsevier B.V. All rights reserved.
doi:10.1016/j.ijpharm.2011.07.026

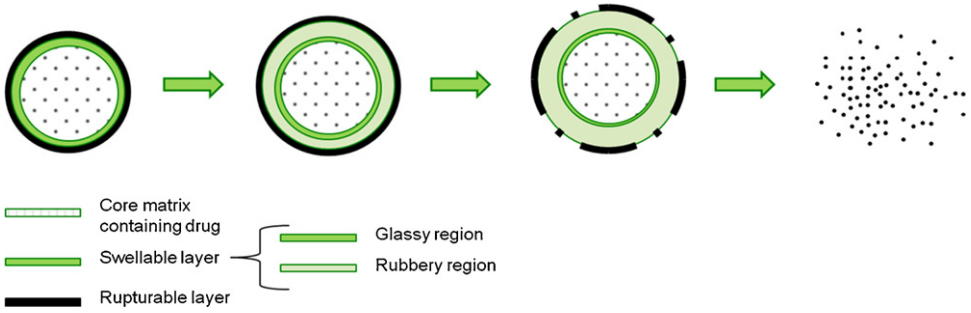

Fig. 1. Expected behaviour and drug release mechanism from a pellet system provided with swellable/rupturable coating layers for oral pulsatile delivery.

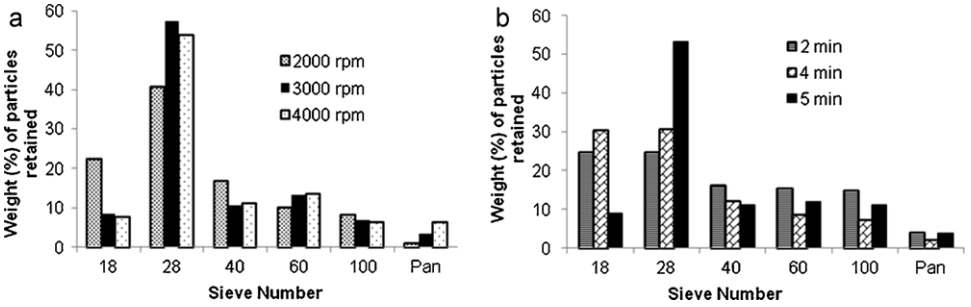

Fig. 2. Effect of (a) spheronization speed and (b) spheronization time on particle size distribution of pellets.

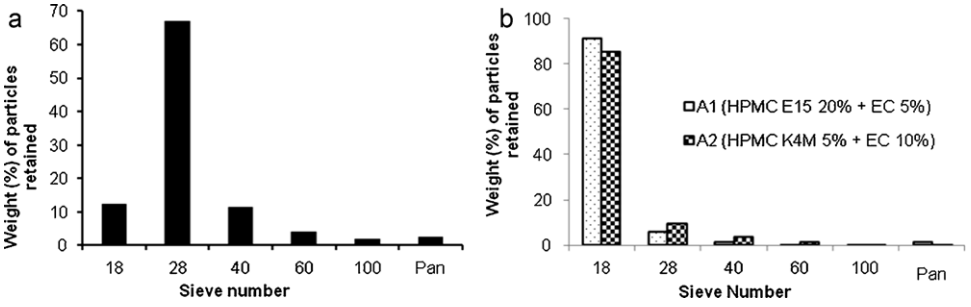

Fig. 3. *In vitro* dissolution profiles of Glipizide showing optimization of immediate release pattern from pellets.

from a composition occurring at a predetermined time (1–12 h). The composition comprised of one layer of an active substance homogeneously dispersed in filler and another layer of water soluble crystalline polymer or mixture of water soluble crystalline polymers and surface active agent. Finally, the formulation comprises a coating with an opening exposing one of the layers to the aqueous environment (Bar-Shalom et al., 1993).

In the present study, a multiple unit time dependent oral pulsatile delivery system has been developed in which drug reservoir is provided with two polymeric coatings, the outer coating undergoes breakup within a prespecified time period after the formulation is immersed in the aqueous fluids, thus allowing the inner drug content of the formulation to be exposed directly to the bulk medium. The film rupture responsible for drug release occurs as a consequence of pressure build-up within the system, which results from liquid uptake and expansion of the inner swellable coating (Fig. 1). Pressure developed by the swelling layer as well as the water permeability and the mechanical strength of the outer coating are the main factors controlling the lag time (Bussemer and Bodmeier, 2003; Bussemer et al., 2003a; Sungthongjeen et al., 2004). The immediate release drug-containing (Type I) pellets prepared by extrusion–spheronization process were used as the core pellets

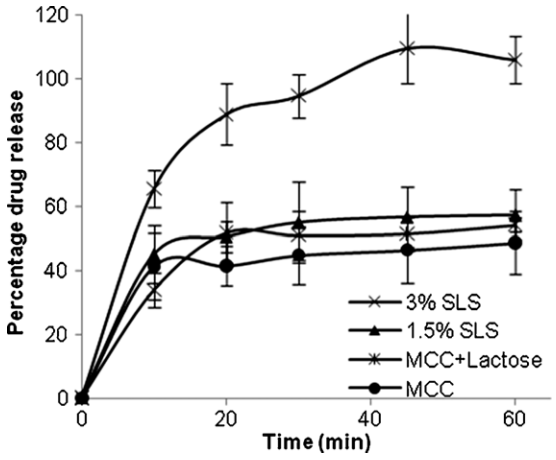

Fig. 4. Particle size distribution of (a) Type I pellets prepared with optimized formula and (b) Type II pellets, A1 and A2 (coated with swellable HPMC and rupturable EC coatings, coating levels are shown in parenthesis).

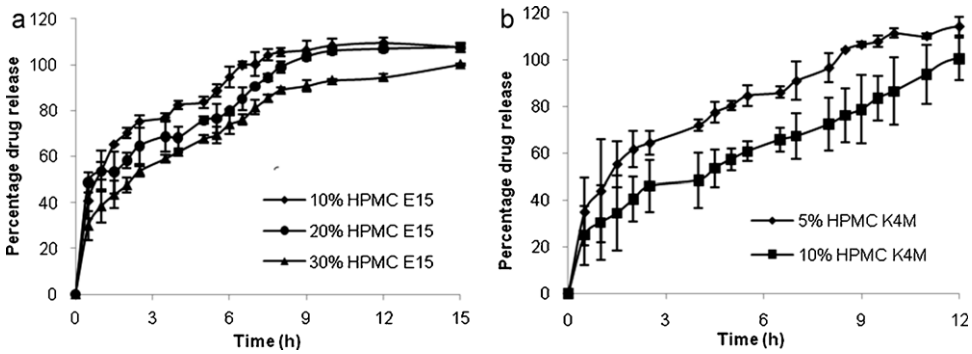

Fig. 5. *In vitro* dissolution profiles of Glipizide from pellets coated with only swelling layer (a) HPMC E15 grade at 10%, 20% and 30% coating levels and (b) HPMC K4M grade at 5% and 10% coating levels.

for coating and coated with swellable and rupturable polymeric layers to produce Type II pellets. The material used for swellable coating was HPMC (E15 and K4M grade). The rupturable coating consisted of a plasticized ethylcellulose film which ruptures easily upon exposure to the dissolution medium and the resultant internal pressure developed within the pellet cores (Krögel and Bodmeier, 1999; Sungthongjeen et al., 2004). Both of these types of pellets (Type I + Type II) were combined together in appropriate proportions to get pulsatile release of Glipizide.

2. Materials and methods

2.1. Materials

The matrix material selected for this study was microcrystalline cellulose (Signet, Mumbai, India). Lactose (Lactose, India), was used as a soluble diluent. The active ingredient Glipizide was purchased from Oceanic Laboratories, Mumbai, India. Hydroxypropylmethylcellulose was supplied by Signet India (HPMC 15 CPS USP 2910, Pharmacoat 615 USP, Mfd. by Shin etsu, Japan and HPMC 4000 CPS USP 2208, Metolose 90 SH 4000, Mfd. by Shin etsu, Japan). Ethyl cellulose and polyvinylpyrrollidone (PVP) were supplied by Signet, India. Triethyl citrate (Morflex, USA), Sodium laurylsulfate (Loba chemie, India). All other chemicals were of analytical reagent grade and were used as received.

2.2. Preparation of pulsatile release pellets

2.2.1. Preparation of Type I (immediate release) pellets

A uniform powder mixture of all the ingredients was wet massed by the addition of polyvinylpyrrolidone (PVP) solution as binder. The dough was then passed through an extruder (Caleva, Model 10) to form cylindrical extrudates, which were subsequently broken into smaller cylindrical rods and rounded into spherical pellets by means of a fast-rotating friction plate (Spheronizer, Caleva, Model 120) and finally dried. MCC, the gold standard to manufacture pellets via extrusion–spheronization was used as matrix forming material. Glipizide is a low dose drug, so lactose was used as diluent which also improves pellet disintegration and drug release from MCC based pellets.

Initially blank (without drug) pellets were prepared with MCC alone to optimize extrusion and spheronization process and get the desired particle size range with adequate flow properties and friability. The optimized process was then used to prepare Glipizide loaded pellets and drug release pattern was studied. Lactose and sodium laurylsulphate were added to improve the dissolution rate and to get an immediate drug release pattern from the pellets.

2.2.2. Preparation of Type II pellets

Type II pellets were prepared by coating the optimized Type I pellets in a Glatt GmbH fluidized bed coater (Systemtechnik, Germany). The coating process required a progressive set-up of the operating conditions. Bottom spray technique was optimized for different parameters like batch size, inlet air temperature, spray rate, atomization, bed pressures, etc. During optimization each parameter was varied sequentially based on its relative impact on the film coating process while keeping other parameters constant. Initially the balance between polymer content and "sprayability" of the coating solutions (i.e. possibility of being sprayed at reasonable rate resulting in adequate atomization) was sought for HPMC and EC individually i.e. single coating was done on Type I pellets with HPMC and EC separately to optimize coating parameters. The polymer solution concentrations were adjusted such that the spray-coating could be carried out with reasonably limited clogging or powdering problems. Aqueous solution (5%, w/v) of HPMC and ethanolic solution (5%, w/v) of EC were used for coating. Triethyl citrate (25%, w/w of EC) was used as plasticizer during EC coating to improve the film coat flexibility and processability (Ensslin et al., 2009). After the optimized process of single coatings, double coating was done with swellable polymer HPMC followed by rupturable polymer EC. Final pulsatile release formulation was prepared by combining Type I and Type II pellets in appropriate proportion. Type II pellets were selected on the basis of drug release profiles.

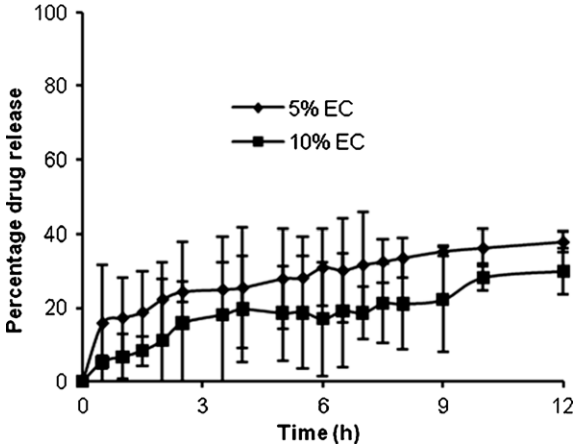

Fig. 6. *In vitro* dissolution profiles of Glipizide from pellets coated with only rupturable layer EC at 5% and 10% coating levels.

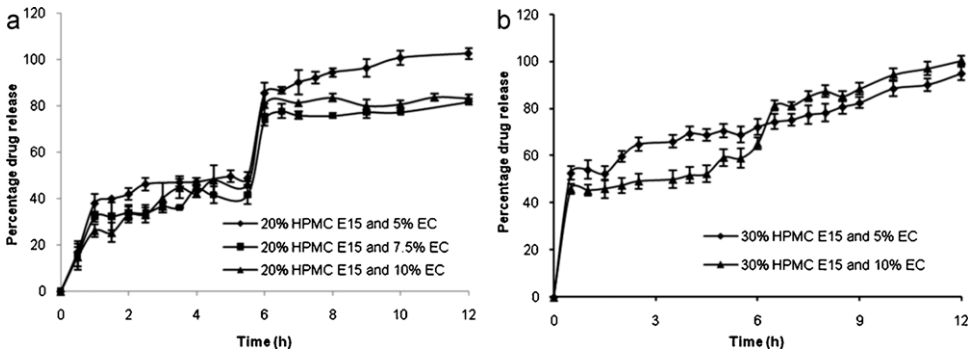

Fig. 7. *In vitro* dissolution profiles of Glipizide from pellets coated with swellable and rupturable layers, (a) HPMC E15 (swellable) coating at 20% coating level and varying coating levels of EC (rupturable) layer, (b) HPMC E15 (swellable) coating at 30% coating level and varying coating levels of EC (rupturable) layer.

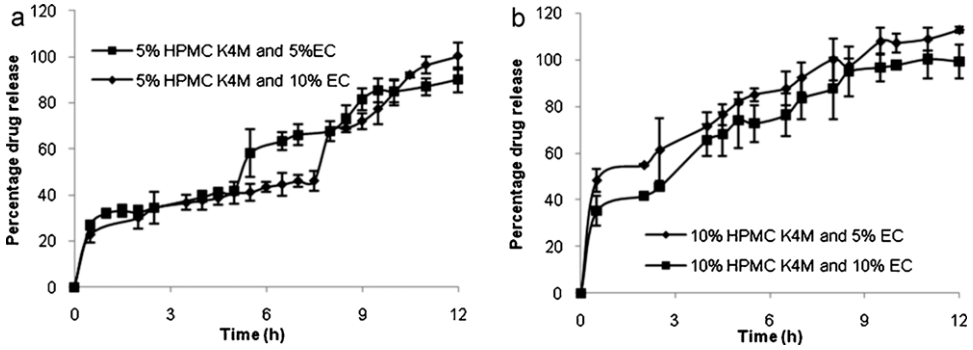

Fig. 8. *In vitro* dissolution profiles of Glipizide from pellets coated with swellable and rupturable layers, (a) HPMC K4M (swellable) coating at 5% coating level and varying coating levels of EC (rupturable) layer, (b) HPMC K4M (swellable) coating at 10% coating level and varying the coating levels of EC (rupturable) layer.

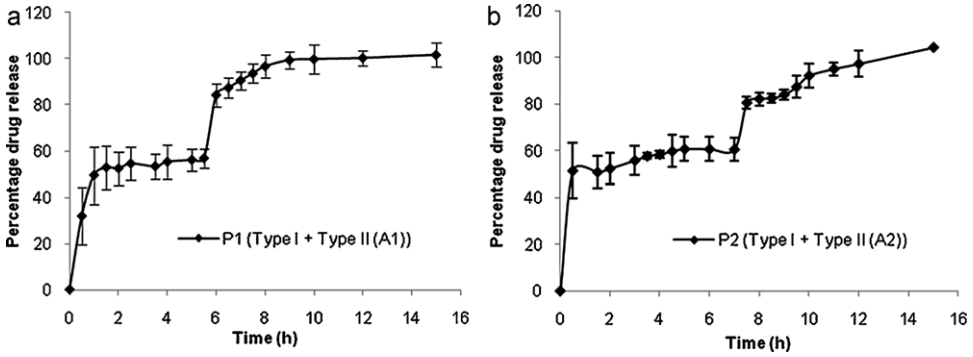

Fig. 9. *In vitro* dissolution profiles of Glipizide from pulsatile release formulations: (a) pulsatile formulation P1 {Type I and Type II (with HPMC E15 coating at 20% and EC coating at 5%)}, (b) pulsatile formulation P2 {Type I and Type II (with HPMC K4M coating at 5% coating level and EC coating at 10% coating level)}.

2.3. Evaluation of pellets

2.3.1. Particle size analysis

In case of pellets, shape and size distribution are important parameters during tabletting, capsule filling operation and also for good coating efficiency. Particle size distribution of pellets was evaluated by sieve analysis. Fixed weight of pellets was sieved through a nest of sieves (900–150 μm) on a vibratory sieve shaker (Retsch® Model AS 200 digit, Retsch, Germany), and the percentage weight of pellets retained on each of the sieves was determined. Table 1 shows correlation between sieve numbers and particle size retained.

2.3.2. Flow properties

Flowabilty of pellets formed was assessed by measuring angle of repose (Granulator tester Erweka GT) and compressibility index (Table 2). Compressibility index was calculated by determining bulk density and tapped density (Electrolab tap density tester, USP) of pellets using the equation:

$$\text{Compressibility index} = 100 \times \left(\frac{\rho_{\text{tapped}} - \rho_{\text{bulk}}}{\rho_{\text{tapped}}} \right)$$

Table 1
Correlation between the particle diameter and sieve number.

Sieve number	Diameter (μm) of particle retained on the sieve
18	900 and above
28	600–900
40	450–600
60	250–450
100	150–250
Pan	150 and below

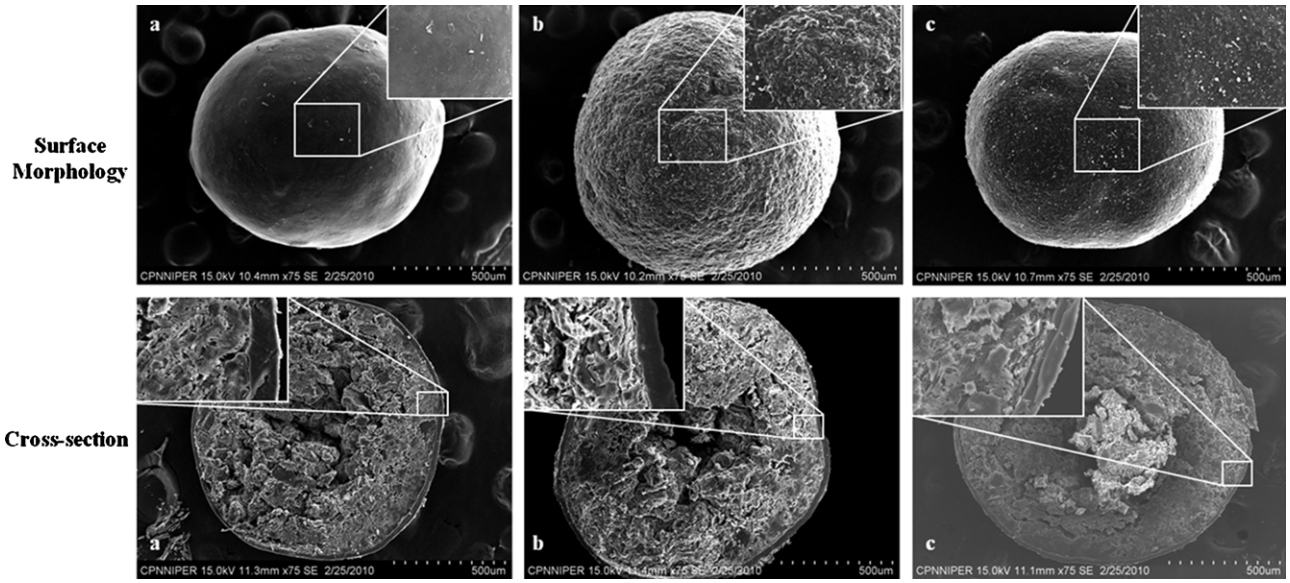

Fig. 10. Scanning electron microscopic images of surface morphology (upper row) and cross-section (lower row) of pellets at 75× magnification coated with (a) HPMC K4M (swellable coating) at 5% coating level, (b) EC (rupturable coating) at 10% coating level and (c) both (swellable and rupturable coatings i.e. Type II pellet) HPMC K4M at 5% and EC at 10% coating levels. Inset: magnified images from the indicated boxes for surface morphology at 300× magnification and cross-section at 1000× magnification. Core matrix and coating can be easily distinguished in cross-sections and both swellable and rupturable coatings can be seen in inset of cross-section image c.

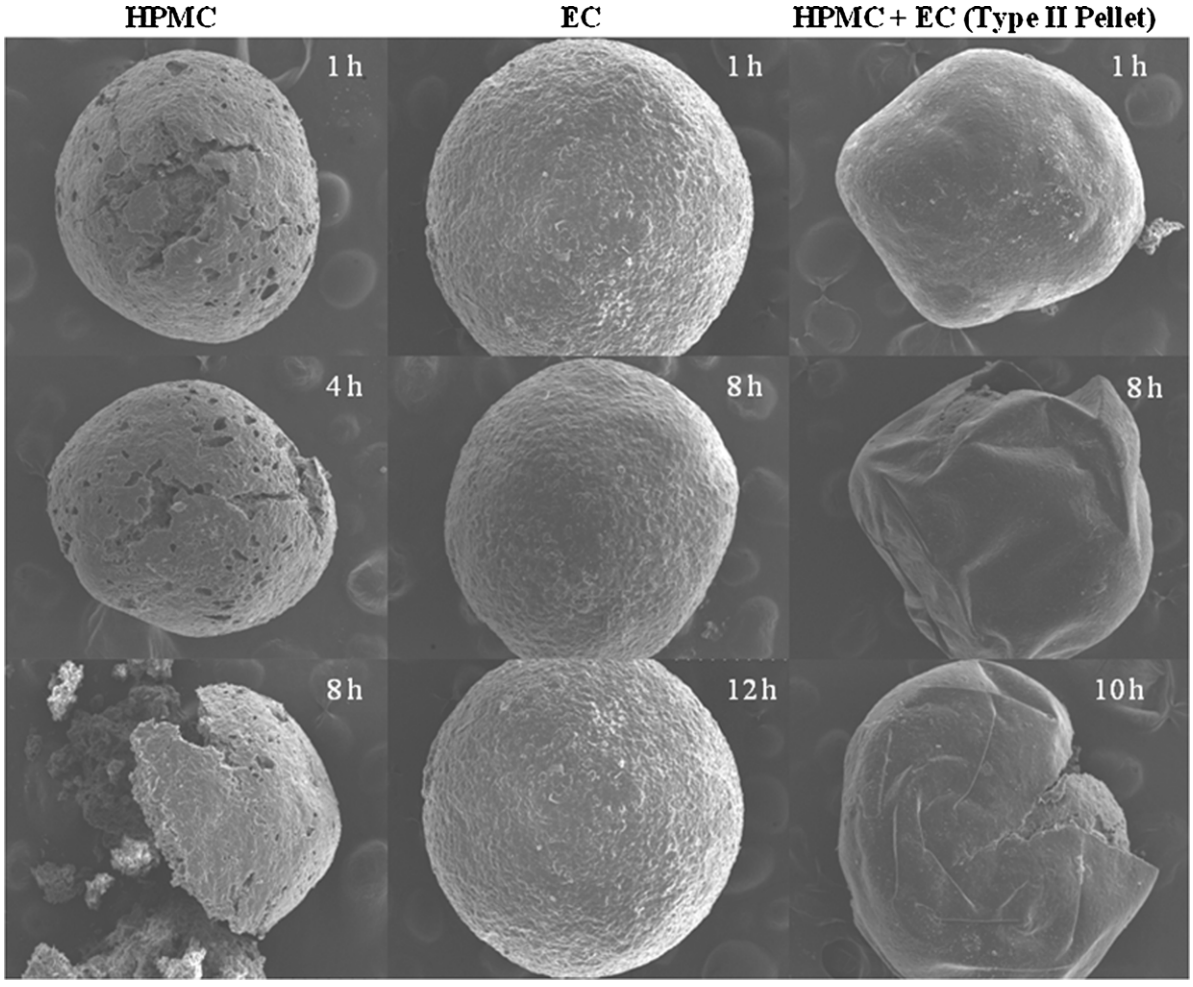

Fig. 11. Scanning electron microscopic images of pellets exposed to phosphate buffer pH 6.8 for different periods of time, coated with HPMC K4M (swellable coating) at 5% coating level, EC (rupturable coating) at 10% coating level and both (swellable and rupturable coatings i.e. Type II pellet) HPMC K4M at 5% and EC at 10% coating levels. HPMC dissolves and erodes from surface creating pores while EC coating remains intact. Rupture sequence of Type II pellet at $t = 1$ h (h), $t = 8$ h (start of rupture) and $t = 10$ h (ruptured pellet exposing core matrix).

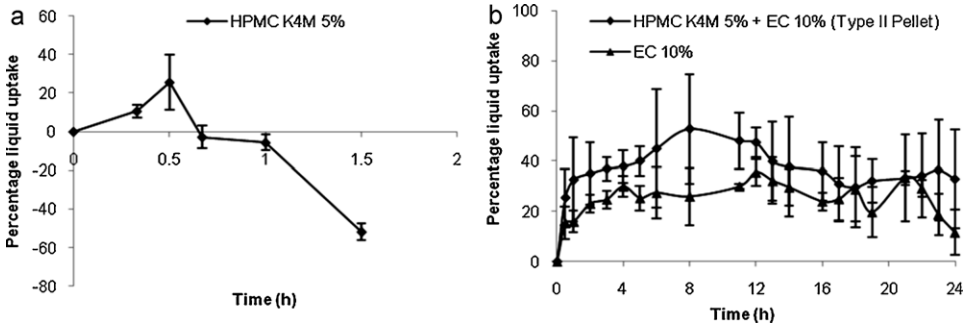

Fig. 12. Percentage water uptake by pellets coated with (a) HPMC K4M (swellable coating) at 5% coating level, (b) EC (rupturable coating) at 10% coating level and both (swellable and rupturable coatings i.e. Type II pellet) HPMC K4M at 5% and EC at 10% coating levels.

Table 2
Scale of flowability.

Flow property	Angle of repose (°)	Compressibility index (%)
Excellent	25–30	≤10
Good	31–35	11–15
Fair-aid not needed	36–40	16–20
Passable-may hang up	41–45	21–25
Poor-must agitate, vibrate	46–55	26–31
Very poor	56–65	32–37
Very, very poor	>66	>38

2.3.3. Friability

Accurately weighed sample (10 g pellets) was placed in the drum of Electrolab friabilator (USP XXIII) and rotated for 100 times. The sample was removed and weighed accurately to determine percentage weight loss of pellets.

2.3.4. Content uniformity

Glipizide is a low dose drug, so content uniformity test was done. Pellets equivalent to 5 mg Glipizide were placed in a vial containing 10 ml methanol and subjected to probe sonication (Misonix Sonicator 3000) for 2–3 min in order to ensure complete breakage of the pellets. It was then filtered and analysed after suitable dilutions for drug content by at 276 nm using UV–visible spectrophotometer (Specord 200, Jena analytica).

2.3.5. Dissolution testing

Pellets equivalent to 5 mg Glipizide were studied for dissolution testing by using USP Type II (paddle) dissolution test apparatus (Electrolab, USP XXI/XXII) at 37 °C and 50 rpm employing phosphate buffer (pH 6.8, 1000 ml) as a dissolution media. At predetermined time intervals 5 ml aliquots were withdrawn and replaced with the pre-warmed fresh medium to maintain initial volume of dissolution fluid. The samples were filtered and analysed for drug content by validated UV method.

2.3.6. Scanning electron microscopy (SEM)

The surface morphology and cross-section of fresh (dried) pellets as well as morphology of pellets upon exposure to dissolution medium (phosphate buffer pH 6.8) for different time periods was monitored using scanning electron microscopy.

The sphere of a single pellet (Type I and Type II) was taken as a whole or was sectioned into two halves by means of a sharp blade. The pellets were mounted on a metal slab using a double-sided adhesive tape and vacuum coated with a thin layer of gold, using E1010 ion sputter with Au target assembly (Hitachi, Model 03E-1211). The samples were analysed, using a Hitachi-S 3400N scanning electron microscope.

2.3.7. Water uptake studies

Water uptake studies were performed on a single pellet of different formulations (coated and uncoated pellets), where a pellet was placed in a container filled with phosphate buffer (pH 6.8) for predetermined time intervals; the pellet was removed from the medium, carefully blotted with tissue paper to remove surface water, weighed and then placed back in the medium. Water uptake (%) was calculated using the following equation:

$$\text{Water uptake}\,(\%) = \left(\frac{W_t - W_0}{W_0}\right) \times 100$$

where W_0 = initial weight of dry pellet, W_t = weight of wet pellet at time t.

2.3.8. Swelling studies

Swelling studies were also performed on single pellets. A pellet was placed in a container filled with phosphate buffer (pH 6.8) and its image was captured periodically (without removing it from the medium) using an inverted microscope (TC 5500, Meiji Techno, Japan) equipped with IMT i-solution software. The diameter of the pellet was measured at different time points and swelling was calculated in percentage from increase of average diameter related to the first measured diameter.

Table 3
Optimized parameters for extrusion and spheronization process.

Parameter	Quantity
Concentration of binder solution	2% (w/v)
Speed of extruder	50%
Speed of spheronizer	3000 rpm
Spheronization time	5 min
Volume of binder solution	q.s.
Time for drying	2 h

2.3.9. Release kinetic analysis of dissolution data

Glipizide release kinetics were analysed by various mathematical models. Seven kinetic models including the zero order, first order, Higuchi matrix, Baker–Lonsdale, Peppas–Korsmeyer, Hixson–Crowell and Weibull release equations were applied to process the *in vitro* release data. Regression analysis was performed and best fits were calculated on the basis of correlation factors as r^2.

Table 4
Particle flow properties and content uniformity of Type I and Type II pellets.

Parameter	Type I pellets	Type II pellets	
		A1 (20% HPMC E15 + 5% EC)	A2 (5% HPMC K4M + 10% EC)
Weight retained (sieve #)	70% (#28)	91.5% (#18)	85.4% (#18)
Angle of repose	28°	26.3°	26.8°
Compressibility index	13.80%	10.23%	10.45%
Friability	0.03%	0.02%	0.02%
Content uniformity (%)	98.73 ± 8.23	101.23 ± 7.26	98.45 ± 6.94

3. Results and discussion

3.1. Preparation and evaluation of Type I (immediate release) pellets

3.1.1. Particle size and flow properties (Type I pellets)

Particle size distribution and shape are prerequisites for good coating efficiency of the multi-particulate dosage form. Particle size of 600–900 μm i.e. pellets retaining on sieve #28 (Table 1) was selected as desired particle size because pellets of this size can be efficiently coated using fluidized bed coater. Pellets prepared at different speeds of spheronization (2000, 3000 and 4000 rpm) showed that 3000 rpm gave maximum proportion of pellets with desired particle size range retained on sieve #28 (Fig. 2a) Spheronization time was optimized as 5 min (Fig. 2b). The optimized parameters for extrusion and spheronization process are shown in Table 3. The pellets so produced were found to be having good to excellent flow properties and very low friability (Table 4).

3.1.2. Dissolution studies (Type I pellets)

The pellets prepared with MCC alone showed a poor dissolution profile, where only 49% Glipizide was released in 60 min (Fig. 3). Addition of lactose, a hydrophilic diluent in 2:3 ratio to MCC did not improve dissolution of Glipizide. This was not the case with other drugs like paracetamol, theophylline and indomethacin as reported by Blanque et al. where the *in vitro* dissolution of these drugs was influenced by addition of lactose (Blanque et al., 1995). Addition of sodium laurylsulfate (SLS) a surfactant at 3% concentration significantly enhanced the dissolution rate of glipizide providing 89% drug release within 30 min (Fig. 3), thereby complying with regulatory requirements for immediate release dosage form (FDA, 1997). Based on dissolution studies, immediate release (Type I) formula was optimized (Table 5). Type I pellets formulated with the optimized formula yielded maximum proportion of pellets retained on sieve #28 (having size 600–900 μm) as depicted in Fig. 4a. Content uniformity of Glipizide loaded Type I pellets was also found to be within acceptable limits (Table 4).

3.2. Preparation and evaluation of coated pellets

Sixty grams of glipizide immediate release (Type I) pellets were coated with HPMC (grades E15 and K4M) and EC to achieve percentage weight gain of coatings in Glatt GmbH fluidized bed coater to yield Type II pellets. The optimized coating parameters are reported in Table 6. The pellets coated with single coatings (swellable/rupturable) and double coatings (inner-swellable and outer-rupturable) were subjected to *in vitro* dissolution studies.

3.2.1. Single coatings

On comparing release of pellets coated with HPMC E15 (lower viscosity) with that of HPMC K4M (higher viscosity), it was observed that glipizide release from higher viscosity grade coated pellets is much slower than with lower viscosity grade coated pellets (Fig. 5). This is because drug release through HPMC (swellable) layer depends not only on erosion and dissolution of polymeric coating but also on the permeability and mechanical characteristics of the resulting gel (rubbery region) layer. The gel layer formed in case of K4M grade was thicker (because of higher viscosity) as compared to that of E-15 grade thereby decreasing drug release rate. So E15 grade was used at higher coating levels (20% and 30%, w/v) and K4M grade was used at lower coating levels (5% and 10%, w/v) for further studies.

Plasticized EC forms water insoluble and much less permeable film as compared to HPMC thereby reducing the drug release. Only 30–35% of drug release was observed in 12 h at 5% and 10% coating levels (Fig. 6).

On the basis of Glipizide dissolution profiles from single polymer coated pellets, low viscosity HPMC E15 was further explored at 20% and 30% coating and high viscosity HPMC K4M was explored at 5% and 10% with rupturable EC coatings from 5% to 10% coating levels.

3.2.2. Double coatings (Type II pellets)

In case of low viscosity HPMC E15 (swellable coating) at 20% coating level (Fig. 7a) it was observed that after initial burst of Glipizide in first hour, a lag phase was observed for further 3.5–4 h and a clear burst after 6 h when the outer EC layer ruptures, followed by slow release at the end. Different levels of initial burst were observed depending on the percentage of EC (rupturable) coating. When coating of (swellable) HPMC E15 was increased to 30% level, initial burst release of Glipizide was higher and also no clear lag phase was observed both at 5% and 10% rupturable (EC) coatings (Fig. 7b).

In case of pellets coated with higher viscosity grade HPMC K4M (swellable) at 5% and EC (rupturable) at 5% level (Fig. 8a), the outer EC layer ruptured within 5 h while in case of 10% EC coating it ruptured at 7.5–8 h as indicated by sudden release after a lag phase. Also when swellable coating level was increased to 10% (Fig. 8b) no

Table 5
Optimized formula of Type I (immediate release) pellets.

S. No.	Name of ingredient	Quantity (percentage)
1	Glipizide	3%
2	Microcrystalline cellulose (MCC)	54%
3	Lactose	40%
4	Sodium lauryl sulphate (SLS)	3%
5	Binder solution (2% PVP)	q.s.

Table 6
Optimized parameters for film coating process.

Parameter	Swellable coating	Rupturable coating
Polymer used	HPMC	EC
Batch size	60 g	60 g
Inlet air temperature	70 °C	40 °C
Spray rate	2.5 ml/min	2.5 ml/min
Spraying pressure	2 Bar	1.5 Bar
Height of partition gap	10 mm	10 mm
Air distribution plate	Type B	Type B
Fluidization pressure	3 Bar	4 Bar

Table 7
Mathematical model fits for pulsatile formulations (release parameters and regression coefficients).

Release model	Parameter	Pulsatile formulations			
		P1 {Type I + Type II (A1)}		P2 {Type I + Type II (A2)}	
		Immediate release profile	Second dose release profile	Immediate release profile	Second dose release profile
Zero order	r^2	0.466	0.686	0.439	0.951
	k_0	6.411	1.767	5.222	3.409
First order	r^2	0.533	0.966	0.539	0.938
	k_1	−0.044	−0.484	−0.038	−0.199
Higuchi	r^2	0.740	0.742	0.690	0.963
	k_H	20.883	11.586	18.473	22.638
Baker & Lonsdale	r^2	0.624	0.993	0.671	0.953
	k	0.010	0.080	0.009	0.048
Peppas & Korsmeyer (Power law)	r^2	0.705	–	0.992	–
	k_p	0.436	–	0.475	–
	n	0.188	–	0.151	–
Hixson & Crowell	r^2	0.510	0.968	0.503	0.893
	k_β	0.029	0.095	0.024	0.119
Weibull	r^2	0.726	0.980	0.805	0.934
	a	1.723	49.522	1.370	24.615
	b	0.258	2.476	0.126	1.784
	T_d	8.253	4.837	12.210	6.021

r_2: correlation coefficients of regression line; k_0; k_1; k_H; k_b; k_p and k_β are release rate constants; n: diffusion exponent; a: scale parameter; b: shape parameter; T_d: time interval necessary to release 63.2% of drug.

clear lag time was observed, indicating rupture of the EC layer (both at 5% and 10% coating levels) during first hour of release study.

3.3. Effect of amount of swelling layer on release profile of Type II pellets

Swelling layer was found to affect initial burst release of Glipizide as well as lag time for rupture of EC coating.

3.3.1. On initial burst release of Glipizide

In case of HPMC E15 at 20% coating level (Fig. 7), 35–50% of burst release was achieved while at 30% coating level burst release was 45–55% within half hour. While HPMC K4M grade at 5% coating level (Fig. 8) showed 20% of burst release in the first hour, at 10% coating level burst release showed 40–50% within half hour. So with increase in HPMC coating level (i.e. amount of swelling layer) the extent of burst release of Glipizide increased and also burst release occurs more rapidly.

3.3.2. On lag period

With HPMC E15 at 20% coating level (Fig. 7a) EC layer (at 5, 7.5 and 10% coatings) ruptured at 6 h as indicated by a lag period followed by sudden release in Glipizide release profile, while at 30% coating level (with 5% EC coating) EC layer ruptured during first half hour as indicated by a linear drug release profile (Fig. 7b) and absence of any lag phase. Similarly with HPMC K4M grade at 5% coating level (Fig. 8a), EC layer ruptured at 5–8 h while at 10% coating level (with both 5% and 10% EC coating) EC layer ruptured during first half hour (Fig. 8b). This is because higher amounts of swelling layer absorbs water more rapidly thus creating pressure on outer EC layer to rupture earlier than at lower coating levels of swelling layer.

3.4. Effect of amount of rupturable coating on release profile of Type II pellets

The mechanical properties of outer rupturable membrane are very important for the performance of the pulsatile system (Dashevsky and Mohamad, 2006). Mechanically weak and nonflexible films are suitable, while highly flexible films expand and often do not rupture during release test (Bussemer et al., 2003b). Amount of rupturable (EC) layer was also found to affect burst release of Glipizide as well as lag time. When comparing the lag time, keeping swelling layer (HPMC E15) constant at 20% coating level (Fig. 7a), lag time was found to be the same i.e. 6 h at all the three EC levels (5%, 7.5% and 10%). Reason for this may be the pressure generated by swelling of HPMC layer was sufficient enough to break the EC coat at all coating levels.

With higher viscosity grade HPMC (K4M at 5% coating level), the lag time increased from 5 h to 8 h when EC coating level was increased from 5% to 10%. At higher amounts of swelling layer (K4M at 10% coating level) the pressure generated by swelling of HPMC layer was sufficient enough to break the EC coat at all coating levels so no lag periods were observed.

3.5. Selection of Type II pellets

Considering the desired lag time of 6–8 h and the observed *in vitro* drug release profiles, two formulations of Type II pellets were finalised, the first was designated as A1 (with HPMC E15 at 20% coating level and EC at 5% coating level) and the second was designated as A2 (with HPMC K4M at 5% coating level and EC at 10% coating level). Particle size distribution of these coated pellets (Fig. 4b) showed that most of the pellets (85–90%) were retained on sieve #18 (Maximum proportion of uncoated pellets was retained on sieve #28) indicating an increase in particle size of pellets. Coating did not affect the particle flow properties and both the angle of repose and compressibility index showed good to excellent flow (Table 4). In fact friability of pellets was reduced as a result of coating. Content uniformity of Type II pellets was also found to be in acceptable range. All these results suggested that coating did not have any negative effect on pellet properties rather it improved some of pellet properties like friability.

3.6. Pulsatile formulation

In order to have a pulsatile release pattern showing 50% drug release in first (immediate release) phase and remaining 50% after a lag period of 6 to 8 h, Type I and Type II pellets were combined in two different proportions. With Type II pellets A1 (20% HPMC E15 + 5% EC), a proportion of Type I:Type II pellets was selected as 2:3 considering the dose and *in vitro* release profile of Glipizide. Similarly with Type II pellets A2 (5% HPMC K4M + 10% EC), a proportion of Type I:Type II pellets was selected as 3:7. Dissolution

testing of combined pulsatile formulations (Fig. 9a and b) showed that 50% of drug was released as immediate release (within first hour) followed by a lag period of about 6–8 h and then again release of second dose thus providing a pulsatile release pattern.

3.6.1. Release kinetic analysis of dissolution data

The dissolution profiles of the two final pulsatile formulations (Fig. 9a and b) can be divided into two portions i.e. immediate release and second dose release. Therefore these two portions of dissolution curves were separately fitted into drug release kinetic models (Table 7) so that Glipizide release mechanisms for immediate release and second dose release can be investigated.

For immediate release profile of pulsatile formulation P1, the fits were insufficient; indicating that no single drug release mechanism was responsible for dissolution of Glipizide, while second dose release profile best fits into Baker–Lonsdale model (Table 7). For pulsatile formulation P2 the immediate release profile best fits into Peppas–Korsmeyer model, while second dose release profile best fits into Higuchi model. Modelling showed that immediate release from both the formulations, P1 and P2 was a result of more than one type of mechanisms and second dose release was diffusion controlled and not dependent on the intrinsic dissolution rate of the drug substance (O'Connor and Schwartz, 1993).

3.6.2. Scanning electron microscopy

To confirm drug release mechanisms, the internal and external morphology of pellets coated with single coatings of HPMC (swellable) and EC (rupturable) as well as Type II pellets (double coating with internal coating of HPMC and outer coating of EC) was studied using scanning electron microscopy. HPMC coated pellets were having smooth surface while EC coating produced a rough surface (Fig. 10). Surface of Type II pellets was comparatively smooth than that of EC coated pellet. The three components of a Type II pellet namely pellet core, swelling layer containing HPMC and outer rupturable EC coating can be clearly seen in cross section.

Disintegration behaviour of core and coatings after exposure to phosphate buffer pH 6.8 for different periods of time can be seen in Fig. 11. Pores can be seen on the surface of pellet coated with HPMC alone within 1 h during dissolution which increase in size because of erosion and dissolution of HPMC and finally the pellet disintegrates after 8 h. EC forms a tight coating which does not dissolve or erode in dissolution medium maintaining the pellet integrity even after 12 h that is the reason that drug release was only 30–35% in 12 h from these pellets as confirmed by dissolution studies (Fig. 6). A Type II pellet (coated with both HPMC and EC) ruptures after 8 h. Water influx and the subsequent volume expansion of the swelling layer caused the rupturing of the EC coating (Fig. 11) which is in good agreement with the observed drug release profile (lag phase till 8 h and then sudden burst release, Fig. 8a).

3.6.3. Water uptake and swelling studies

The liquid content of pellets coated with HPMC (swellable coating), EC (rupturable coating) and both HPMC and EC (Type II pellets) upon exposure to phosphate buffer pH 6.8 for different periods of time are illustrated in Fig. 12a and b. HPMC coated pellets imbibe 20% of their weight of liquid within half hour, after that HPMC rapidly started eroding and dissolving because of which pellet weight becomes half of its original weight in 1.5 h. EC coated pellets did not disintegrate and absorbed water comparatively at a slower rate reaching up to 25% in 4 h. A Type II pellet (both HPMC and EC coated) absorbed more water than single polymer coated pellets reaching up to 50% in 8 h (maximum weight when EC coating ruptures) after that its weight started decreasing.

In swelling studies (Fig. 13) HPMC coated pellet showed around 1% swelling within first hour while EC coated pellet swells with

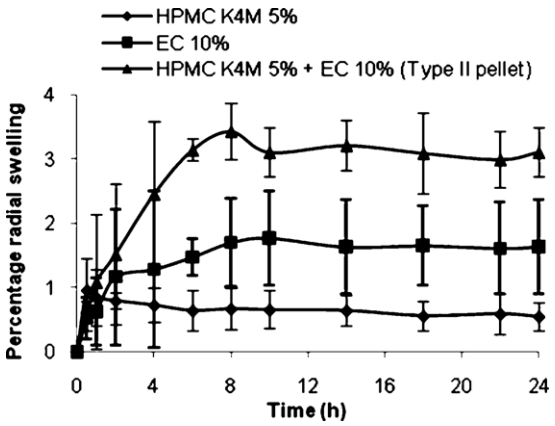

Fig. 13. Percentage radial swelling of pellets coated with HPMC K4M (swellable coating) at 5% coating level, EC (rupturable coating) at 10% coating level and both (swellable and rupturable coatings i.e. Type II pellet) HPMC K4M at 5% and EC at 10% coating level.

comparatively slower rate but to a greater extent (1.5% in 9 h). A Type II pellet (both HPMC and EC coated) swells to a much greater extent (3.5%) in 8 h and then decreases to a constant level. These results of Type II pellet swelling are in line with liquid uptake (Fig. 12), SEM (Fig. 11) and drug release studies (Fig. 8a) which indicate rupturing of EC layer after 7–8 h.

4. Conclusion

Extrusion and spheronization process was optimized for desired particle size distribution, shape, flowability and friability. Sodium laurylsulfate at 3% concentration improved dissolution rate of Glipizide to achieve 100% release in 1 h from Type I pellets. Fluidized bed coating was used successfully to coat Type I pellets with swellable and rupturable polymers to give Type II pellets which released the drug after a certain lag time due to rupture of ethylcellulose film. The lag time of the system could be modified by level of swelling layer and rupturable coating. Finally two formulations were obtained by combination of appropriate proportions of Type I and Type II pellets which showed pulsatile release pattern for Glipizide with a lag time of 6–8 h. Mathematical modelling showed that Glipizide immediate release profiles from the combined pulsatile formulations followed more than one type of release mechanisms and the second dose followed release mechanism of matrix type delivery systems.

Acknowledgments

Authors are thankful to Director, NIPER for financial assistance through grant C-11 to carry out the present research work. Finally the support from Signet, India for gift samples of film coating polymers is acknowledged.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.ijpharm.2011.07.026.

References

Bar-Shalom, D., Kindt-Larsen, T., Buhk, M.A., 1993. Buhk, Meditec A/a (Hellerup, DK) Controlled Release Article with Pulsatile Release.

Blanque, D., Sternagel, H., Podczeck, F., Newton, J.M., 1995. Some factors influencing the formation and in vitro drug release from matrix pellets prepared by extrusion/spheronization. Int. J. Pharm. 119, 203–211.

Bussemer, T., Bodmeier, R., 2003. Formulation parameters affecting the performance of coated gelatin capsules with pulsatile release profiles. Int. J. Pharm. 267, 59–68.

Bussemer, T., Dashevsky, A., Bodmeier, R., 2003a. A pulsatile drug delivery system based on rupturable coated hard gelatin capsules. J. Control. Release 93, 331–339.

Bussemer, T., Peppas, N.A., Bodmeier, R., 2003b. Time-dependent mechanical properties of polymeric coatings used in rupturable pulsatile release dosage forms. Drug Dev. Ind. Pharm. 29, 623–630.

Dashevsky, A., Mohamad, A., 2006. Development of pulsatile multiparticulate drug delivery system coated with aqueous dispersion Aquacoat® ECD. Int. J. Pharm. 318, 124–131.

Davis, S.N., 2006. Diabetes mellitus and the physiological effects of insulin. In: Brunton, L.L., Lazo, J.S., Parker, K.L. (Eds.), Goodman & Gilman's the Pharmacological Basis of Therapeutics. , 11th ed. McGraw-Hill, New York.

Ensslin, S., Moll, K.P., Haefele-Racin, T., Mäder, K., 2009. Safety and robustness of coated pellets: self-healing film properties and storage stability. Pharm. Res. 26, 1534–1543.

FDAUS, 1997. Dissolution Testing of Immediate Release Solid Oral Dosage Forms. Center for Drug Evaluation and Research (CDER), Rockville.

Galia, E., Nicolaides, E., Hörter, D., Löbenberg, R., Reppas, C., Dressman, J.B., 1998. Evaluation of various dissolution media for predicting in vivo performance of class I and II drugs. Pharm. Res. 15, 698–705.

Gazzaniga, A., Sangalli, M.E., Giordano, F., 1994. Oral Chronotopic® drug delivery systems: achievement of time and/or site specificity. Eur. J. Pharm. Biopharm. 40, 246–250.

Jamzad, S., Fassihi, R., 2006. Development of a controlled release low dose class II drug-Glipizide. Int. J. Pharm. 312, 24–32.

Krögel, I., Bodmeier, R., 1999. Floating or pulsatile drug delivery systems based on coated effervescent cores. Int. J. Pharm. 187, 175–184.

Maroni, A., Zema, L., Cerea, M., Sangalli, M.E., 2005. Oral pulsatile drug delivery systems. Expert Opin. Drug Deliv. 2, 855–871.

Martindale, W., 1996. Antidiabetic drugs. In: Reynolds, J.E.F. (Ed.), Martindale: The Extra Pharmacopoeia. , 31st ed. Royal Pharmaceutical Society, London, pp. 347–348.

McConville, J.T., Ross, A.C., Florence, A.J., Stevens, H.N.E., 2005. Erosion characteristics of an erodible tablet incorporated in a time-delayed capsule device. Drug Dev. Ind. Pharm. 31, 79–89.

O'Connor, R.E., Schwartz, J.B., 1993. Drug release mechanism from a microcrystalline cellulose pellet system. Pharm. Res. 10, 356–361.

Shivakumar, H.N., Patel, P.B., Desai, B.G., Ashok, P., Arulmozhi, S., 2007. Design and statistical optimization of glipizide loaded lipospheres using response surface methodology. Acta Pharm. 57, 269–285.

Sungthongjeen, S., Puttipipatkhachorn, S., Paeratakul, O., Dashevsky, A., Bodmeier, R., 2004. Development of pulsatile release tablets with swelling and rupturable layers. J. Control. Release 95, 147–159.

Ueda, S., Ibuki, R., Kimura, S., Murata, S., Takahashi, T., Tokunaga, Y., Hata, T., 1994. Development of a novel drug release system, time-controlled explosion system (TES). III: relation between lag time and membrane thickness. Chem. Pharm. Bull. 42, 364–367.