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Research Article

Development of Push–Pull Osmotic Tablets Using Chitosan–Poly(Acrylic Acid) Interpolymer Complex as an Osmopolymer

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Abstract. The objectives of this study were to prepare push–pull osmotic tablets (PPOT) of felodipine using an interpolymer complex of chitosan (CS) and poly(acrylic acid) (PAA) as an osmopolymer, and to study the mechanisms of drug release from these tablets. The interpolymer complexes were prepared with different weight ratios of CS to PAA. Preparation of PPOT involved the fabrication of bilayered tablets with the drug layer, containing felodipine, polyethylene oxide, and the polymeric expansion layer, containing the CS–PAA complex. The effects of polymer ratios, type of plasticizers, and compression forces on release characteristics were investigated. It was found that drug release from PPOT exhibited zero-order kinetics and could be prolonged up to 12 or 24 h depending on the plasticizer used. PPOT using dibutyl sebacate showed a longer lag time and slower drug release than that using polyethylene glycol 400. In the case of polyethylene glycol 400, an increase in the CS proportion resulted in an increase in the drug release rate. The compression force had no effect on drug release from PPOT. Drug release was controlled by two consecutive mechanisms: an osmotic pump effect resulting in the extrusion of the drug layer from the tablet and subsequent erosion and dissolution of the extruded drug layer in the dissolution medium. The mathematical model (zero-order) related to extrusion and erosion rates for describing the mechanism of drug release showed a good correlation between predicted and observed values.

KEY WORDS: chitosan; felodipine; interpolymer complex; poly(acrylic acid); push–pull osmotic tablet.

INTRODUCTION

Osmotically controlled release dosage formulations have gained considerable interest due to distinct and practical advantages compared with other oral controlled delivery systems such as matrices and reservoirs. Since osmotic drug delivery systems utilize osmotic pressure as the energy source and driving force, drug release can be controlled at a constant rate. In addition, drug release is not affected by motility, pH, or the presence of food. Many different systems have been developed based on principles of osmotic pressure, including one chamber systems, *e.g.*, elementary osmotic pump (EOP) (1), swellable elementary osmotic pump (2), monolithic osmotic tablet (3), and also multiple chamber systems, *e.g.*, push–pull osmotic pump (PPOP; 4,5), push–stick system (6), push–melt osmotic pump (7), OROS CT® (8), and sandwiched osmotic tablet (9). Currently, two osmotically controlled delivery mechanisms that are widely used by the pharmaceutical industry are EOP and PPOP. The EOP is a simple system that is only suitable for the delivery of moderately water-soluble drugs. To overcome this limitation, the PPOP was developed for very soluble and insoluble drugs. PPOP consists of two compartments, one containing drug along with an osmotic agent and the other containing a hydrophilic expansion polymer or osmopolymer (10). To assist the release of the drug, the second layer swells in an aqueous environment and thereby supplying the driving force against the drug layer. Subsequently, the drug suspension generated in the first layer is delivered via the orifice.

The osmopolymer is a hydrogel which exhibits the ability to swell in water and retains a significant portion of the imbibed water within the polymer structure. The swelling capacity of the hydrogel is very high, usually exhibiting a two- to 50-fold volume increase. The swellable hydrophilic materials commonly used as osmopolymers are polyethylene oxide (4,5), sodium carboxymethyl cellulose (11), and poly(acrylic acid; 4,5). In the present study, the alternative hydrogel of chitosan–poly(acrylic acid) interpolymer complex is introduced for use as an osmopolymer. Chitosan (CS) is a partially *N*-deacetylated product from the natural polymer chitin, which is found widely in nature. When CS, a cationic polymer, interacts with poly(acrylic acid) (PAA), an anionic polymer, an interpolymer complex between CS and PAA can be formed due to electrostatic interaction. Recently, there are some studies where the CS–PAA interpolymer complex has been used as a matrix (12–14), mucoadhesive (15,16), and nanoparticles (17,18) in oral drug delivery systems. However, to date, there are no reports of the use of the CS–

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PAA interpolymer complex in osmotically controlled release drug delivery systems. This interpolymer complex is a swellable polymer, producing a stiff gel-like matrix which helps maintain an integrated consistency in the push compartment without significant erosion that is found in the case of individual polymers (12). In addition, since the CS–PAA interpolymer complex does not exhibit pH-sensitive swelling due to a semi-permeable membrane limiting the passage of ions from the environment, it is expected that this complex might offer some advantages when used in osmotic controlled systems.

In this study, an attempt has been made to develop a push–pull osmotic tablet (PPOT) using the CS–PAA interpolymer complex as an osmopolymer to effect the controlled delivery of felodipine over a period of time (12–24 h). Complexes with different ratios of CS/PAA were investigated, and the influence of plasticizer type in semi-permeable film and compression pressure on drug release from PPOT were studied to obtain useful information for the design of the dosage form. The mechanisms for drug release from the PPOT were also investigated and mathematical models developed to describe and explain the drug release patterns observed in the dissolution studies.

MATERIALS AND METHODS

Materials

CS (MW 600,000, 85% deacetylation) was purchased from Fluka Biochemica (Buchs, Switzerland). PAA (Carbopol 934P) was obtained from BF Goodrich (OH, USA). Felodipine was purchased from Zhejiang Yiyuan Pharmaceutical Chemical (Zhejiang, China). Polyethylene oxide (PEO; MW 300,000), cellulose acetate (CA, 39.8% acetylation), polyethylene glycol 400 (PEG 400), and dibutyl sebacate (DBS) were purchased from Aldrich (Milwaukee, USA). Microcrystalline cellulose (MCC; Avicel PH102) was purchased from Asahi Chemical Industrial (Tokyo, Japan). Pregelatinized starch (PS; Starch 1500) was purchased from Colorcon (Tokyo, Japan). Potassium chloride, sodium hydrogen phosphate, and potassium dihydrogen phosphate were purchased from Univar (Seven Hills, Australia). All other reagents used in this study were analytical grade and were used as received.

Methods

Preparation of CS–PAA Interpolymer Complex

The 3.3% *w/v* polymeric mixtures of various CS/PAA weight ratios (1:2, 1:1, 2:1) were prepared by dissolving CS and PAA (Carbopol 934P) in 1 M acetic acid. The mixtures were then titrated with 3 M sodium hydroxide to achieve a pH of 5.0. The mixtures were kept at room temperature overnight and then filtered. The filtrate was washed with distilled water, and the remaining wet mass dried at 50°C for 24 h and pulverized to a fine powder by cutting mill.

Characterization of CS–PAA Complex Via Infra-red Spectroscopy

Nicolet, Magna-IR 500 infra-red spectrometer was used. Powdered CS–PAA complex (1 mg) was mixed with dried KBr powder (1 g) and the mixture compressed at 390 MPa for 2 min. The compressed disk was scanned in the range was 400–4,000 cm^{-1} using a blank KBr disk as a reference.

Preparation of Push–Pull Osmotic Tablets

Preparation of the Core Tablets. The bilayered tablets were prepared by the double compression method. The composition of core tablets is shown in Table I. The drug layer (total weight, 100.25 mg) comprised felodipine as an active ingredient, PEO as a suspending agent, potassium chloride as an osmotic agent, a mixture of MCC and PS (1:1) as filler, and magnesium stearate as a lubricant. The push layer (total weight, 50.05 mg) comprised the CS–PAA complex with different polymer weight ratios as an osmopolymer, potassium chloride as an osmotic agent, a mixture of MCC and PS (1:1) as a filler, and FD&C red No.2 as a coloring agent. The ingredients for both layers were mixed separately and the bilayered tablet compressed on an instrument tablet machine (Colton model 216, Vector Corporation, USA) with a 7-mm standard concave punch by the following procedure. Firstly, the drug layer mixture was filled in the die cavity as usual by the tablet machine; the push layer mixture was then manually loaded on after stopping the machine. Finally, the tablet was made by compression using pressure at 156 MPa. The total weight of the 10 mg felodipine PPOT was about 150 mg.

Table I. Formulation Composition of PPOT

Formulation code	C1-2	C1-1	C2-1	P60	C40	C20
Drug compartment composition, mg/tab						
Felodipine	10	10	10	10	10	10
Polyethylene oxide	40	40	40	60	40	40
Potassium chloride	10	10	10	10	10	10
Filler	40	40	40	20	40	40
Push compartment composition, mg/tab						
CS–PAA complex; various polymer weight ratios						
1:2	20	–	–	–	–	–
1:1	–	20	–	20	40	20
2:1	–	–	20	–	–	–
Potassium chloride	10	10	10	10	10	10
Filler[a]	20	20	20	20	–	20

[a] Filler is the mixture of Avicel PH102 and Starch 1500 (1:1). Results are means±SD where applicable

Table II. Operative Coating Condition of PPOT

Process conditions	
Batch size	2 kg
Volume of spray liquid	3,024 mL
Preheating time	15 min
Air inlet temperature	40–45°C
Air outlet temperature	30–35°C
Pumping rate	25 mL/min
Atomizing pressure	0.8 kg/cm^2
Pan speed	6–9 rpm
Coating time	120 min
Drying air temperature	35°C
Drying time	10 min

Evaluation of the Core Tablets

Thickness and Hardness. Tablet thickness and hardness were monitored using a multipurpose measuring device (Model PTB311, Pharma Test, Hainburg, Germany). Twenty tablets were measured individually.

Friability. Tablet friability test was performed on 20 tablets at 25 rpm for 4 min using friabilator (Model PTF3 RA, Pharma Test, Hainburg, Germany). The loss in weight (%) was calculated after the test.

Content Uniformity. Content uniformity of tablets was determined by the assay of 10 individual tablets. Each tablet was powdered and quantitatively transferred into a 100-mL volumetric flask. The high pressure liquid chromatography (HPLC) assay method followed was exactly as described for content uniformity in felodipine extended-release tablets in the USP 31.

HPLC Analysis. The samples were analyzed by HPLC assay using a mixture of 40% *v/v* acetonitrile, 20% *v/v* methanol, and 40% *v/v* of buffer (0.05 M NaH_2PO_4, adjusted to pH 3 with H_3PO_4) as mobile phase delivered at 1 mL/min by high pressure pump (Model LC-10AT VP, Shimadzu, Kyoto, Japan). Samples (20 µl) were injected onto a C-8 column (4.6×250 mm, Lichropher RP-8, Merck, Darmstadt, Germany) at room temperature and the eluent monitored at 362 nm using a UV detector (Model SPD-10 VP, Shimadzu, Kyoto, Japan). Three determinations were performed for each tablet formulation.

Porosity of the Core Tablets

The influence of compression force on drug release was studied by compressing tablets using three different pressures, *i.e.*, 156, 234, and 312 MPa. The porosity of tablets was analyzed (in duplicate) using mercury porosimeter (PoreSizer 9320, Micromeritics, Norcross, Germany). Measurements were performed with the pressure ranging from 0.5 to 30,000 psia, which corresponded to pore diameters in the range of 400 µm to 6 nm. Total pore volume (V_{tot}), mean pore diameter, % porosity, bulk, and apparent density were calculated with PoreSizer 9320 software, Version 2.05.

Coating of the Core Tablets

The core tablets were coated with 3% *w/v* cellulose acetate in acetone, using 5% *w/w* DBS or PEG 400 as a plasticizer, to achieve 10% additional weights by using a perforated pan coater (Thai coater, Model 15L, Pharmaceutical and Medical Supply, Thailand). The operative coating conditions are shown in Table II.

Drilling the Orifice Using a Laser Beam

The coated tablets were automatically drilled on the drug side by CO_2-laser equipment (GCC Venus, Taiwan) with a computer-based control for batch production. A batch size of 50 tablets was drilled accurately by the laser head moving automatically above each tablet by focusing and emitting the laser beam at the center of the coated tablets. The speed and power of the laser equipment were set up by a computer program, Corel Draw 12, to achieve an orifice size of 0.5 mm. The orifice size was also measured microscopically to make sure that right orifice size had been achieved.

In Vitro Release Studies

Drug release from the PPOT was determined as described in the USP 28 dissolution test for felodipine extended-release tablets, using a stationary tablet basket (Electrolab, Mumbai, India) with the dissolution apparatus (Model SR8 Plus, Hanson, Chatsworth, USA). A paddle method was used at a rotational speed of 50 rpm. Five hundred milliliters of 0.1 M phosphate buffer (pH 6.5) with 1% sodium lauryl sulfate was used as the dissolution medium. The temperature of medium was maintained at 37°C. Six tablets of each formulation were placed individually in each of the six dissolution flasks for this study (*i.e.*, n=6). The dissolution apparatus used was automated, with a pumping system that circulated the dissolution media through a UV cell. This allowed the determination of absorbance values at a wavelength of 362 nm (λ_{max} for felodipine) every 30 or 60 min over the range of 12 or 24 h.

Table III. Drug Content and Physical Properties of PPOT Formulations

Properties of PPOT	C1-2	C1-1	C2-1
Drug content (%) (n=3)	100.4 ±1.3	99.6 ±2.3	101.1 ±1.4
Tablet weight (mg) (n=20)	154.2 ±1.3	152.7 ±2.2	155.4±2.0
Hardness (kg) (n=20)	3.8 ±0.4	4.3 ±0.5	3.9 ±0.6
Thickness (mm) (n=20)	4.01 ±0.05	3.97 ±0.03	4.07 ±0.03
Friability (%) (n=2)	0.65	0.22	1.7

Results are means±SD where applicable

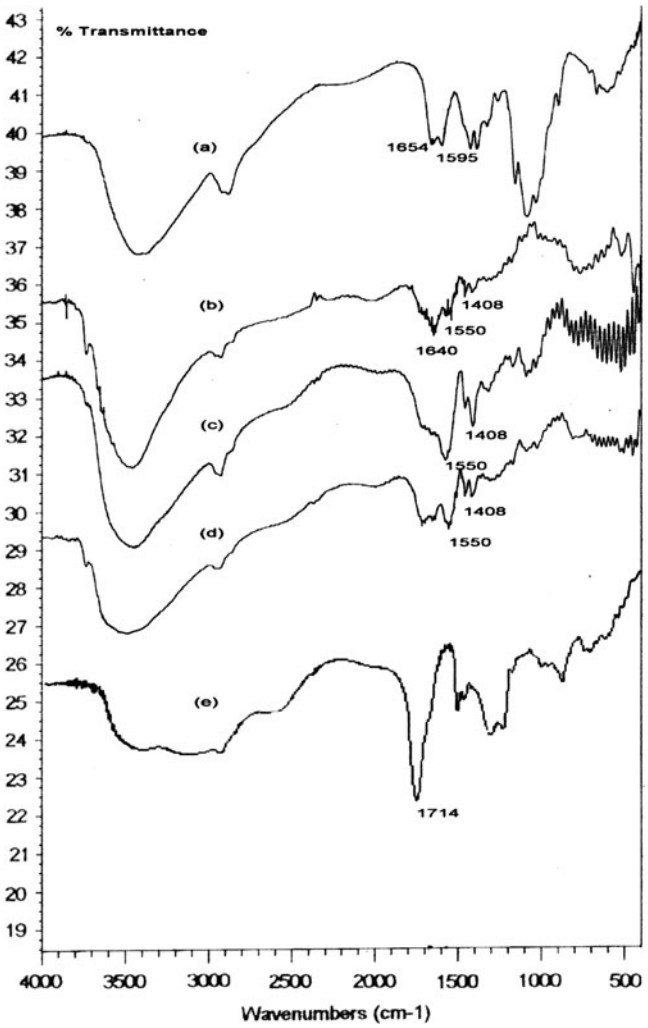

Fig. 1. FTIR spectra of CS **a**, CS–PAA complex at various ratios of 2:1 **b**, 1:1 **c**, 1:2 **d**, and PAA **e**

Osmotic Delivery Mechanism

Drug release mechanisms were investigated based on the assumption that release was most likely controlled by two consecutive mechanisms, *i.e.*, extrusion and erosion. Therefore, the extrusion rate constant (K_{ext}) and erosion rate constant (K_{ero}) due to both mechanisms were determined.

Extrusion Rate Constant (K_{ext})

The amount of extruded drug at a definite time could be determined as follows. For each time point, three tablets of each formulation were exposed to 500 mL of 0.1 M phosphate buffer (pH 6.5) with 1% sodium lauryl sulfate under conditions similar to the dissolution test. At pre-determined sampling times, the tablets were physically removed from the dissolution vessel, any extruded material at or near the delivery orifice was carefully wiped off, and the residual undelivered drug from the tablet was extracted for analytical quantification. The amount of extruded drug was then calculated by subtracting the amount recovered from the known initial drug loading. The sample-collection times were 2, 3, 4, 5, 6, and 7 h. The extrusion rate constant (K_{ext}) was obtained from the slope of the linear regression plot between amount of extruded drug and time. The amount of drug dissolved at sampling times was also determined to acquire the dissolution data corresponding to the drug extrusion.

Erosion Rate Constant (K_{ero})

The wet mass of drug layer composition of PPOT was prepared by an aqueous wet granulation method. The wet mass was then transferred to a glass syringe and extruded via an exit port with a 0.5-mm diameter (by taking off the needle). The extrudates were shortened to lengths of 5 mm and dried in a hot air oven at 45°C. Dissolution tests of the drug-based extrudates were performed in a manner similar to that described for PPOT. Erosion rate constant (K_{ero}) was calculated from the slope of linear regression plot between fractions of drug dissolved (F_d) and time.

$$Fd = \frac{Qt}{Qo} \tag{1}$$

where Q_t and Q_o are amount of drug dissolved in each sampling time and initial amount of drug in extrudates, respectively.

Table IV. Linear Regression Analyses of Dissolution Data Corresponding to 10–80% of Drug Release Using Different Mathematical Models

	Zero-order		First-order		Higuchi	
	$F_t = K_o t + C$		$\log(1 - F_t) = K_1 t + C$		$F_t = K_H t^{1/2}$	
Formulation	K_0	R^2	K_1	R^2	K_H	R^2
PEG 400						
C1-2	0.0990	0.9874	−0.0725	0.9852	0.4162	0.9857
C1-1	0.0950	0.9919	−0.0833	0.9715	0.4409	0.9852
C2-1	0.0990	0.9894	−0.0934	0.9714	0.4563	0.9881
DBS						
C1-2	0.0536	0.9959	−0.0434	0.9798	0.3211	0.9904
C1-1	0.0 524	0.9964	−0.0419	0.9780	0.3352	0.9931
C2-1	0.0549	0.9938	−0.0444	0.9866	0.3313	0.9954

DBS dibutyl sebacate, F_t=fraction of drug release at time t ($F_t = Mt/M_\infty$) K_0 is the zero-order release constant (min^{-1}), K_I is the first-order release constant (min^{-1}), and K_H is the Higuchi dissolution constant (min^{-2})

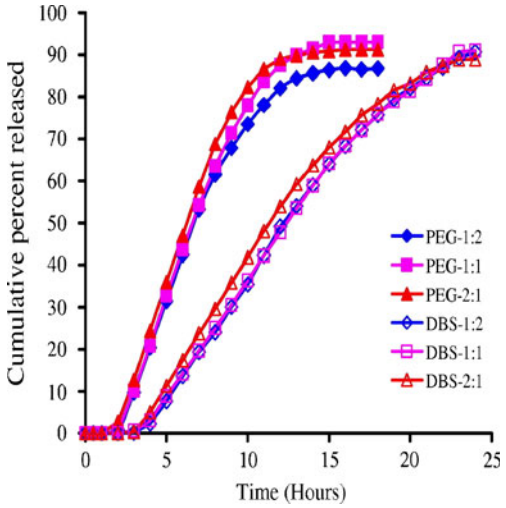

Fig. 2. Effect of various ratios of CS/PAA and plasticizers on drug release from felodipine PPOT

Three distinct formulations of PPOT were prepared to exhibit the different drug release rates. The composition of core tablets is shown in Table III. The core tablets were coated with 3% *w/v* cellulose acetate in acetone, with 10% *w/w* polyethylene glycol 400 as a plasticizer, to achieve 10% additional weights and were drilled to achieve an orifice size of 0.5 mm.

RESULTS AND DISCUSSION

Infra-red Spectroscopic Analysis

Figure 1a–e show FTIR spectra of CS, CS–PAA complex of various ratios, *i.e.*, 2:1, 1:1, 1:2, and PAA which confirm of complex formation between CS and PAA. Characteristic peaks of CS were located at 1,595 cm^{-1} for the amine group of 2-aminoglucose unit and 1,654 cm^{-1} for the carbonyl group of the 2-acetaminoglucose unit of CS (19), as the percent of deacetylation of CS was 85%. The peak of 1,714 cm^{-1} in the spectrum of PAA (Fig. 1e) was assigned to C=O stretching vibration of the carboxylic groups. The comparison of Fig. 1a, b–d show important changes in the spectrum of the CS–PAA complex. In Fig. 1b–d, two peaks at 1,654 and 1,595 cm^{-1} decreased, and two new peaks at 1,408 $cm^{-1}$and 1,550 cm^{-1} were observed. The peak of 1,408 cm^{-1} corresponded to the asymmetrical stretching of the carboxylate anion present in the complex (20). In addition, the complex at the ratio of 2:1 (Fig. 1b) showed the peak of 1,640 cm^{-1}, indicating that the amine group was protonated to a NH_3^+ group in the complex (12). This peak was not found clearly in the other ratios (Fig. 1c–d). On the contrary, the other ratios showed the increase of peak at 1,550 and 1,408 cm^{-1}. It could be explained that the amine group of chitosan was more protonated in the case of the complex at the ratio of 2:1 due to higher amount of chitosan, but carboxylic group was more ionized in the case of the complex at the ratio of 1:1 and 1:2 due to higher amount of polyacrylic acid. These results suggested that the carboxylic groups of PAA were dissociated into COO^- groups, which complexed with the protonated amino groups of CS through electrostatic interaction to form the interpolymer complex.

Physical Evaluation of Osmotic Core Tablets

Felodipine core tablets were evaluated for their physical properties. The weight variation, thickness, hardness, and friability are shown in Table III. The results show that all formulations had low weight variation, indicating that direct compression is an acceptable method for preparing PPOT. The hardness of all formulations was moderately high enough to carry through the coating process, including coating condition in Table II. However, the result of friability in the case of PPOT with the polymer ratio of 2:1 gave the high percent friability. This suggests that the complex at the ratio of 2:1 had lower binding property than the others; therefore, the lower particulate bonding in the polymer layer causes the high fine powder formation during the friability test.

Drug Release from Push–Pull Osmotic Tablets

Drug Release Kinetics

Three mathematical models, *i.e.*, zero-order, first-order, and Higuchi were used to explain the drug release kinetics of the various formulations. The dissolution curves plotted according to each mathematical expression were subjected to linear regression analyses, and the data are shown in Table IV. It was found that the zero-order model could provide good correlation coefficients for most of the formulations (R^2=0.9874–0.9964), suggesting that this system could deliver the drug at an approximately constant rate.

Influence of Plasticizer

Figure 2 depicts the dissolution profiles of PPOT using two different kinds of plasticizers in the polymer film. It is well known that plasticizers modify the physical properties of films by changing viscoelastic behavior. In addition, different plasticizers may affect the aqueous permeability of the

Fig. 3. Cross-section of felodipine PPOT using dibutyl sebacate as plasticizer after dissolution in time sequence

polymer film as well as the release of the drug. As can be seen in Fig. 2, drug release could be prolonged up to 12 or 24 h depending on the plasticizer. At the same polymer ratio, drug release from PPOT using DBS as plasticizer gave longer a lag time (3–4 h) and slower drug release. This can be attributed to the differences in hydrophobicity of DBS and PEG 400. Since DBS is a hydrophobic plasticizer, it was difficult to leach, and the residual DBS prevented water penetration through the membrane. As a consequence, the permeability of the membrane and drug release both decreased. On the other hand, hydrophilic PEG 400 is easily leached from the membrane, leading to a porous structure which increased permeability of the membrane and drug release from PPOT.

Influence of Polymer Ratios

The influence of polymer ratio on drug release is also shown in Fig. 2. It shows that the percent release at 8 h from PPOT containing complex at ratio of 1:2, 1:1, and 2:1 were 61.43%, 63.44%, and 68.66%, respectively for PPOT containing PEG 400, and were 24.13%, 25.06%, and 29.65%, respectively, for PPOT containing DBS. The extent of drug release during the testing period was between 86% and 93%. To compare drug release among these PPOT, the release rate according to zero-order kinetics was determined from the slope of the drug release profile by linear regression as shown in Table IV. The effect of the polymer ratio on the release rate was further analyzed statistically using analysis of variance (ANOVA) at α=0.05. In the case where PEG 400 is used as the plasticizer, it was found that the release rate increased significantly as chitosan proportion increased from 1:2 to 2:1. In the case where DBS is used, no significant difference was exhibited in the release rate for polymer ratio ranging from 1:2 to 2:1. However, the release was somewhat rapid with the polymer ratio of 2:1. It may be that the drug release from PPOT is correlated with the swelling of CS–PAA complex used as an osmopolymer. This can be demonstrated by the photographs of cross-sections of PPOT after dissolution at specified times in Fig. 3. It shows that the core progressively hydrates and that the volume occupied by the polymer layer increases with time to assist in the release of drug layer extrudates. It is believed that the increase in swelling ability of the complex results in an increase in drug release from PPOT due to the higher driving force for pumping out the drug layer. In previous studies in our laboratory, the results of swelling studies showed that the complex at ratio of 2:1 exhibited markedly higher swelling than those at ratios of 1:1 and 1:2 (unpublished data). Consequently, higher release rate could be obtained with the polymer ratio of 2:1. In case where DBS is the plasticizer, the drug release from PPOT with a polymer ratio of 1:1 was not different to that of 1:2. This may be due to less water permeation through the membrane with DBS, resulting in fewer differences in the swelling of both complexes.

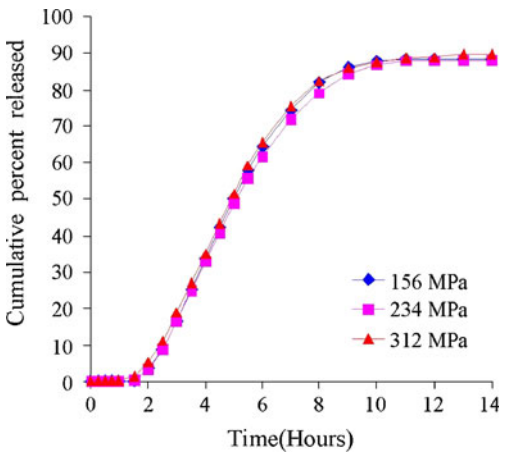

Fig. 4. Effect of compression pressure on drug release from felodipine PPOT

Table V. Porosity and Pore Diameter of Felodipine PPOP Core Tablet at Different Compression Pressures

Formulation[a]	Avg. porosity (%)	Avg. pore diameter (μm)
C1-1/F156	18.40	0.1364
C1-1/F234	17.57	0.1159
C1-1/F312	14.55	0.080

[a] The compositions of core tablets were the same as the formulation C1-1 shown in Table I

Influence of Compression Pressure

Figure 4 shows drug release profiles from PPOT prepared with different compression pressures, and the data were analyzed statistically using ANOVA at α=0.05. The result shows that no significant difference was exhibited in the release rate among the three compression pressures. It is noteworthy that the percent porosity of the PPOT with three different compression pressures (Table V) was not very different (18.40%, 17.57%, 14.55% for compression pressures of 156, 234, and 312 MPa, respectively). Moreover, it was observed that a highly viscous gel was formed in the drug layer and expelled via the delivery orifice as seen in Fig. 5. It is possible that this viscous gel acts as a barrier within PPOT, limiting the amount of water penetrating into the glassy drug layer and subsequently controlled the drug release, regardless to the influence of compression pressures.

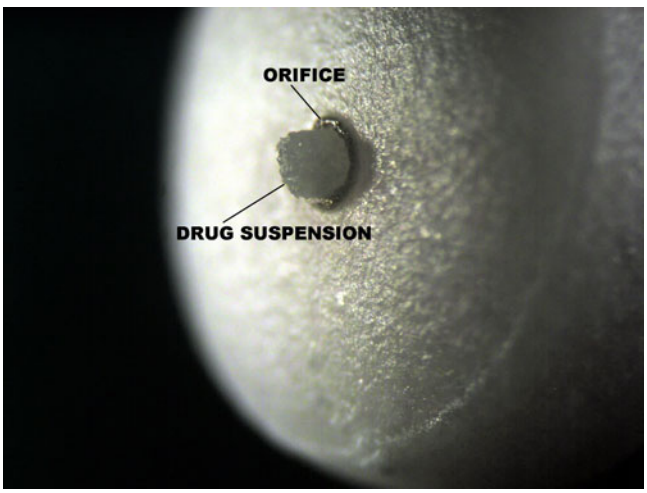

Fig. 5. Photograph of PPOT shows extrusion of high viscous gel of drug layer through the delivery orifice

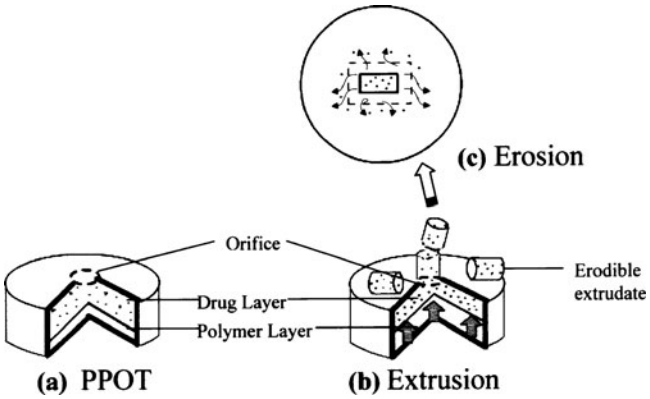

Fig. 6. Mechanism of drug release from felodipine PPOT **a** before ingress of water **b** after ingress of water, causing extrusion of the drug layer **c** erosion of extrudate and drug dissolution

Osmotic Drug Delivery Mechanism

Based on the above results, the mechanism for release of drug from PPOT may be proposed as follows. Initially, water penetrates through the CA membrane and enters into the PPOT by diffusion. Subsequently, the delivery system involves an osmotic mechanism, KCl (osmotic agent) imbibing water from the external environment. The function of the imbibed water in the drug layer is to liquefy the contents of the drug layer and in the presence of PEO a viscous gel-like liquid is produced. Meanwhile, the push layer also imbibes water steadily. The imbibed water is retained within the CS–PAA complex, resulting in a considerable increase in the volume of the push layer. This expansion enables the drug layer to be extruded through the delivery orifice of PPOT. This mechanism is probably similar to that described for other push–pull osmotic systems (9).

In the present study, visual observation was made during dissolution tests of PPOT. It was found that the composition forming the drug layer was expelled from the PPOT in a plug-like state, the composition being so highly viscous that it did not flow like a liquid, as shown in Fig. 5. The drug layer was exposed to the environment as an erodible composition, in contrast to usual push–pull osmotic system in which the drug layer was pumped out as a suspension or slurry. The explanation for this may be the fact that the drug layer in our PPOT contained high amount of fillers, Avicel PH102 and Starch 1500, which are not well hydrated and helped maintain the integrity of the drug layer by less loss of the water-soluble constituents from the drug layer. Nevertheless, the extruded plug-like drug layer would readily be eroded to release the drug to the environment. The drug release mechanism is considered to proceed as depicted in Fig. 6.

Mathematical Model of Drug Release

Based on the release mechanism illustrated in Fig. 6, it was hypothesized that there were two mechanisms that contributed to drug release: osmotic pump and erosion. The first step was the extrusion of the drug layer via the orifice to the environment, and then the erosion of the extruded drug layer in the environment and ultimate drug dissolution. According to these mechanisms, the following equations can describe drug release from PPOT.

I. Osmotic pump mechanism: (21)

$$\frac{dM}{dt} = \left[\frac{K}{h}.A_p\pi_{p+}\frac{K}{h}.A_d\pi_d\right].F_dC_o \tag{2}$$

where A_p, A_d, π_p, π_d, h, C_o, F_d, and K are the area of the push compartment, the area of the drug compartment, the osmotic pressure of the push compartment, the osmotic pressure of the drug compartment, membrane thickness, the solid concentration of the suspension dispensed from the system, the initial drug fraction in the drug compartment, and membrane permeability coefficient, respectively.

By controlling the various parameters defining the total mass delivery rate in Eq. 2, the push–pull osmotic system can be programmed for various delivery rate profiles. If the osmotic pressure of the push chamber is very high, $\pi_p >> \pi_d$, the expansion of push layer governs the rate of drug release. Therefore, Eq. 2 can be rewritten as following:

$$\frac{dM}{dt} = \left[\frac{K}{h}.A_p\pi_p\right].F_dC_o \tag{3}$$

The zero-order delivery profile can been achieved if $A_p.\pi_p$ is kept constant during operation, while the rest of parameters were invariable. Therefore, the mass delivery rate in Eq. 3 can define the extrusion rate of drug layer and be written as Eq. 4.

$$\begin{aligned}\tfrac{dM}{dt} &= K'F_dC_o \\ &= K_{ext}\end{aligned} \tag{4}$$

where K_{ext} is the extrusion rate constant.

II. Erosion mechanism: (22)

$$\frac{dM}{dt} = \frac{DAC_s}{h} \tag{5}$$

where D, A, C_s, and h are the diffusion coefficient, the surface area of erosion, the solubility of drug layer composition, and the thickness of boundary layer, respectively.

Table VI. Mathematical Parameters for PPOT Formulations Obtained from the Regression Plots of Extrusion and Erosion

Formulation code	K_{ext} (R^2)	C_{ext}	K_{ero} (R^2)	C_{ero}
P60	1.179 (0.977)	−0.923	0.873 (0.985)	0.036
C40	1.337 (0.992)	−0.432	1.203 (0.998)	−0.136
C20	1.194 (0.990)	−0.602	1.203 (0.998)	−0.136

E is amount of drug erosion per hour per milligrams of drug
K_{ext} is extrusion rate (mg h^{-1})
K_{ero} is erosion rate (per hour)
C_{ext} and C_{ero} are regression constant

Table VII. Comparison of Amount of Drug Released by Erosion (Predicted) to Amount of Drug Dissolved During Dissolution (Observed*) from Three Formulations of PPOT with PEG 400 Used as Plasticizer

	Drug release of P60 (mg)		Drug release of C40 (mg)		Drug release of C20 (mg)	
Time (h)	Observed	Predicted	Observed	Predicted	Observed	Predicted
2	0.12 (±0.26)	0.23	0.92 (±0.14)	0.97	0.79 (±0.17)	0.61
3	1.24 (±0.20)	1.30	2.39 (±0.11)	2.39	1.99 (±0.20)	1.84
4	2.37 (±0.19)	2.38	3.87 (±0.13)	3.82	3.19 (±0.23)	3.08
5	3.49 (±0.12)	3.45	5.34 (±0.15)	5.25	4.39 (±0.19)	4.31
6	4.62 (±0.15)	4.52	6.82 (±0.28)	6.68	5.59 (±0.17)	5.54
7	5.74 (±0.12)	5.59	8.29 (±0.21)	8.10	6.79 (±0.19)	6.77
8	6.86 (±0.22)	6.62	9.77 (±0.28)	9.53	7.99 (±0.26)	8.00

*n=3 (results are means±SD) for observed values

In Eq. 5, the erosion mechanism governs the rate of drug release from the extrudates. This mechanism can be considered to be matrix-dissolution controlled and described by Noyes–Whitney equation (22). Zero-order drug delivery will be achieved due to the invariable parameters in the right-hand side of the equation and can be written as;

$$\frac{dM}{dt} = K_{\text{ero}} \tag{6}$$

where K_{ero} is the erosion rate constant, derived from D, A,C_s, and h in Eq. 3.

(A could be kept constant due to the constant extrusion rate, resulting in consistency of the extrudate existing in dissolution medium.)

The amount of drug released by erosion from Eq. 6 should be consistent to the amount of drug dissolved in the dissolution test. This is because the drug released by erosion is a rate limiting step prior to subsequent drug dissolution in the medium. To verify this assumption, the amount of drug released by erosion is calculated to compare with the dissolution data. The calculation can be done as follows:

$$E_t = \sum_{n=2}^{t} W_n = W_2 + W_3 + W_4 \ldots\ldots + W_t \tag{7}$$

where E_t and W_t are the amount of drug release by erosion at time t (t=2,3,4,….) and the amount of drug release by erosion in each hour, respectively.

$$W_t = (X_{t-1} - X_{t-2}).E \tag{8}$$

where X_t, E are the amounts of drug released by extrusion at time t (t=1,2,3,4,….) and the amount of drug released by erosion per hour per milligram of extruded drug, respectively.

Thus, Eq. 7 becomes:

$$\begin{aligned} E_2 &= X_1.E \\ E_3 &= X_1.E + (X_2 - X_1).E \\ E_4 &= X_1.E + (X_2 - X_1).E + (X_3 - X_3).E \\ E_t &= X_1.E + (X_2 - X_1).E + (X_3 - X_2).E + \ldots\ldots\ldots(X_{t-1} - X_{t-2}).E \\ &= X_{t-1}.E \end{aligned} \tag{9}$$

if the amount of drug extrusion at time t is represented by Eq. 10

$$X_t = K_{\text{ext}}.t + C_{\text{ext}} \tag{10}$$

where K_{ext}, C_{ext} are the slope and y-intercept of linear regression plot between amount of drug extruded and time; K_{ext} represents the extrusion rate constant as described in Eq. 4.

Thus, Eq. 9 becomes:

$$E_t = [K_{\text{ext}}.(t-1) + C_{\text{ext}}].E \tag{11}$$

if the amount of drug erosion/hour/mg is represent by Eq. 12

$$E = K_{\text{ero}} + C_{\text{ero}} \tag{12}$$

where K_{ero} and C_{ero} are the slope and y-intercept of linear regression plot between fraction of drug eroded from extrudates and time; K_{ero} represents the erosion rate constant as described in Eq. 6.

$$E_t = [K_{\text{ext}}.(t-1) + C_{\text{ext}}].(K_{\text{ero}} + C_{\text{ero}}) \tag{13}$$

All the parameters mentioned, *i.e.*, K_{ero}, C_{ero}, K_{ext}, and C_{ext} could be experimentally determined. K_{ext} played an important role in the overall drug release process and was further used to determine amount of drug released by erosion (E_t) according to Eq. 13. Table VI shows the values of K_{ero}, C_{ero}, K_{ext}, and C_{ext} which were obtained for three different formulations of PPOT. The correlation coefficients were between 0.9772 and 0.9987. Finally, E_t could be calculated and was compared with the dissolution data of PPOT as shown in Table VII.

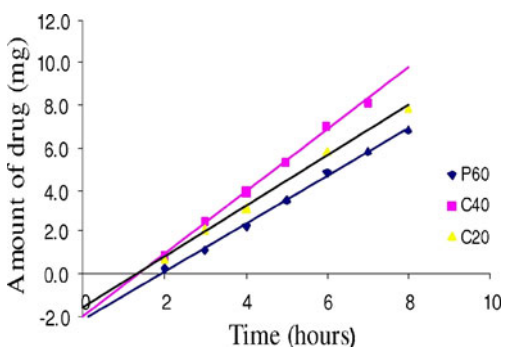

Fig. 7. Drug release from different PPOT formulations in the study of drug release mechanism

The predicted values of three formulations were in close agreement with the experimental values. This supports the validity of the model which was proposed to verify the drug release mechanism.

Three formulations of PPOT (C20, C40, P60) were prepared, and the different drug releases obtained can be explained by this model. The first mechanism concerning drug release is implied as osmotic pump engine by expanding the volume of push layer to extrude the drug layer to the environment. From Fig. 7, drug release from PPOT-C40 (containing 40 mg of CS–PAA complex) was faster than that of PPOT–C20 (containing 20 mg of CS–PAA complex). This may be explained as an increase in amount of CS–PAA complex resulting in an increase in expansion of the push layer, leading to the higher amount of extrudates. As seen in Table VI, the extrusion rate (K_{ext}) of PPOT–C40 was higher than that of PPOT–C20. The second mechanism concerning drug release is erosion of the extrudates in the environment. Figure 7 shows that the drug release rate of PPOT–P60 (containing 60 mg of PEO) was slower than that of PPOT–C20 (containing 40 mg of PEO). This may be ascribed to the physicochemical character of PEO in this study. This type of PEO is of medium molecular weight (300,000), and can swell after uptake of water, forming gel. The increase in amount of PEO may be responsible for the lower erosion rate (K_{ero}) of PPOT–P60, in comparison with PPOT–C20, as shown in Table VI. The decreased erosion is caused because the extrudate remains more viscous and as a result, drug release is slower and amount of drug dissolved is delayed in the dissolution medium.

CONCLUSION

The interpolymer complex of CS and PAA showed a great potential for use as an osmopolymer in push–pull osmotic tablets. The release of felodipine from this device exhibited zero-order kinetics and could be prolonged up to 12 or 24 h with the use of polyethylene glycol 400 or dibutyl sebacate as plasticizers, respectively. In the case of PPOT containing polyethylene glycol 400, an increase in CS proportion resulted in the increase of drug release. Compression force had no significant effect on drug release. The mathematical model related to extrusion (K_{ext}) and erosion rate constant (K_{ero}) for describing the mechanism of drug release showed a good correlation between predicted and observed values. In further studies, the push–pull osmotic tablets will be programmed for desired release of felodipine by controlling formulation factors related to both parameters, with appropriately selected polymer ratios and plasticizer.

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