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Modified push–pull osmotic system for simultaneous delivery of theophylline and salbutamol: development and in vitro characterization

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Abstract

An oral osmotic system which can deliver theophylline and salbutamol sulphate simultaneously for extended period of time was developed and characterized in a view to reduce the problems associated with the multidrug therapy of asthma. Simple controlled porosity osmotic pump contained both drugs (in freely soluble form) did not provide satisfactory extended release of theophylline. A modified two-layered, push–pull osmotic system was developed by using the basic designs of various oral osmotic pumps, such as controlled porosity osmotic pump (CPOP), elementary osmotic pump (EOP) and push–pull osmotic pump (PPOP). Scanning electron microscopy of cellulose acetate coating membrane after dissolution revealed that 25% (w/w) of sorbitol can be used as an optimized concentration of pore forming agent with 25% (w/w) of plasticizer, which was kept constant. Formulations were initially developed for theophylline and the release was optimized by using two different soluble forms of theophylline with varying amount of hydrophilic polymer mixture in upper layer and polyethylene oxide (expandable hydrogel) in lower layer. Further, the release of salbutamol sulphate was optimized by keeping the drug in upper or lower layer or both layers. In vitro release studies showed satisfactory controlled release profiles of both drugs. The release profiles of both drug statistically compared with respective marketed controlled release formulations. An optimized system was selected to study the effect of concentration of pore forming agent and orifice diameter on the release of both drugs.

Keywords: Oral osmotic pumps; Theophylline; Salbutamol sulphate; Multidrug therapy; Oral controlled drug delivery

1. Introduction

There has been increasing interest in the development of oral osmotic pumps in the past 20 years, and various types of oral osmotic pumps have been devel-

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oped and studied to deliver drugs possessing different aqueous solubility. Oral osmotic pumps can deliver drugs in a controlled manner over a long period. Various types of oral osmotic pumps, their advantages and formulation aspects were recently reviewed by Verma et al. (2000, 2002). Elementary osmotic pump (EOP) is the simple version of oral osmotic pump in which drug delivered through an aperture at approximate zero order rate. EOPs are suitable for moderately soluble drugs (Theeuwes, 1975; Santus and Baker, 1995). Later, controlled porosity oral osmotic pumps (CPOP) have been developed for the delivery of drugs to avoid the aperture making and its optimization (Haslam and Rork, 1989; Zentner et al., 1990). The release of highly water-soluble drugs from CPOPs and EOPs can be controlled by different solubility modulated approaches such as by using sodium chloride (McClelland et al., 1991), by using resin (Zentner et al., 1991) and by the addition of appropriate amount of hydrophilic polymer to the core (Prabakaran et al., 2003), respectively. To deliver slightly water-soluble drugs, a two-layered push–pull oral osmotic pump (PPOPs) was developed and marketed by Pfizer (e.g. Adalat® nifedipine tablet). Also, β-cyclodextrin was used as solubilizing as well as osmotic pumping agent to deliver slightly water-soluble drugs (Okimoto et al., 1998, 1999). A number of design options are available in the field of oral osmotic pumps to deliver various drugs possessing different solubility properties.

Chronic diseases such as asthma, tuberculosis, heart diseases and diabetes are treated using multi-drug therapies, which are vulnerable to incidences of side effects, poor patient compliance and slow improvement of patients. Asthma is an extremely common disorder accounting for 1–3% of all office visits, 500,000 hospital admissions per year, and more pediatric hospital admissions than any other single illness. Asthma should be viewed primarily as an inflammatory illness that has bronchial hyperactivity and brochospasm as a result and this has led to marked changes in the recommendation regarding prevention and treatment of asthma (Undem and Lichtenstein, 2001). Bronchodilators such as salbutamol (a beta-adrenergic drug) and theophylline are used to treat asthma effectively either alone or in combination. Though controlled drug delivery systems are available separately for both drugs, a system, which can deliver both drugs simultaneously at a controlled rate, may ensure improved patient compliance. For this purpose an osmotically regulated multi-drug delivery system has been proposed in the present study. This system made a promising possibility of simultaneous administration of two or more drugs for the treatment of various chronic diseases. This system may reduce the problems associated with multi-drug therapy by delivering drugs at near zero order rate, simultaneously. In addition to improved patient compliance, as once daily formulation, it may improve safety profile and activity of drugs exhibiting short biological half-life. Recently, osmotically regulated asymmetric capsular system was developed to deliver slightly aqueous soluble rifampicin and freely soluble isoniazid simultaneously (Prabakaran et al., 2004).

In the present study, the possibility of simultaneous controlled release of two drugs from a modified push–pull osmotic system was explored. The system designed by using the basic designs of EOP, CPOP and PPOP. The newer system coated with controlled porosity membrane instead of usual semipermeable membrane. Moreover, water-soluble drug was taken in the lower layer along with expandable hydrogel. Two different forms of theophylline such as theophylline base (TB) (slightly water-soluble) and choline theophylline (CT) (freely water-soluble), and salbutamol sulphate (SS) (freely water-soluble drug) were used to challenge the design. The developed systems were evaluated in vitro, statistically compared with marketed sustained release formulations and an optimized formulation was selected to study the effect of coating composition (concentration of pore forming agent) and aperture diameter on the drug release.

2. Materials and methods

2.1. Materials

Theophylline base (TB), choline theophylline (CT) and salbutamol sulphate (SS) were gift samples from Zoetic formulations (P) Ltd., Chennai, India. Cellulose acetate (CA) (320 S) was obtained from Sun Pharmaceutical Advanced Research Center, Mumbai, India (manufactured by FMC Corp., USA). Polyethylene glycol (PEG) 400, mannitol and microcrystalline cellulose (MCC) were purchased from Himedia, India. Hydroxy-propyl methyl cellulose (HPMC) (200–300 cps, medium viscosity grade) and sorbitol

were procured from Loba Chemie, India. Polyethylene oxide (PEO) with molecular weight of 8,000,000 g/mol was obtained from Aldrich, USA. Unicontin® Continus, controlled release (CR) (Modi-Mundi Pharma Ltd., India) matrix tablet of theophylline (400 mg) and Ventorlin® controlled release (CR) (Themis Laboratories Ltd., India) capsule containing spansules of salbutamol sulphate (8 mg) were purchased from local retail outlets. Solvents of reagent grade and double distilled deionised water were used in all experiments.

2.2. Drug analysis

A reverse phase high performance liquid chromatography (HPLC) method was developed for simultaneous estimation of theophylline and salbutamol sulphate in dissolution fluids. The instrument (Shimadzu, Japan) comprised of Shimadzu pump LC-10AT vp equipped with universal injector 7725I (Rheodyne) with injection volume 20 μl, SPD-10A vp variable wavelength UV-Vis detector (Shimadzu) and Shimadzu Class-VP software, Version 5.03. A C-18 reverse phase column (Luna, Particle size-5 μm, column size 250 mm × 4 mm) was used. Mixture of acetonitrile, 0.025% phosphoric acid and triethanolamine (65:33:2) was used as mobile phase with flow rate of 1.2 ml/min and detection was carried out at 254 nm for both drugs. Separate samples containing theophylline base and choline theophylline showed similar retention time. The mean calibration curve (concentration versus peak area) of theophylline ($y = 0.1364x + 0.0296$) ($n = 6$) was linear between 200 ng/ml and 2 μg/ml ($r^2 = 0.9996$). The correlation coefficient of separate calibration curve varied between 0.9987 and 0.9999. The recovery of the 500 ng/ml, 1 and 1.5 μg/ml of theophylline was 95.6 ± 4.21%, 96.8 ± 2.81% and 94.17 ± 3.44%, respectively. The retention time, tailing factor and theoretical plates were 1.52 ± 0.2 min, 0.72 and 1924, respectively. The mean calibration curve of salbutamol sulphate (SS) ($y = 0.1763x + 0.0118$) ($n = 6$) was linear between 20 and 200 ng/ml ($r^2 = 0.9992$). The correlation coefficient of separate calibration curves of SS varied between 0.9976 and 0.9996. The SS recovery of 50, 100 and 150 ng/ml were 96.4 ± 2.74%, 97.1 ± 1.93% and 96.6 ± 3.08%, respectively. The retention time, tailing factor and theoretical plates were 0.86 ± 0.3 min, 0.48 and 649, respectively. The drug content of the formulation and the amount of theophylline and SS released in dissolution fluids were determined (with appropriate dilution) by using the calibration curves.

2.3. Granulation and tablet compression

Granules were prepared by wet granulation method. In case of two-layered tablets granules were prepared separately for both layers. MCC and PEO exhibited adhesive and binding properties during granulation. The ingredients (listed in Tables 1 and 2) were mixed and passed through a mesh (250 μm). Isopropyl alcohol was used as granulating solvent and the wet mass was passed through a mesh (1150 μm). The resultant granules were dried at 45 °C for 5 h and dried granules were passed through a mesh (1000 μm). Granules were lubricated with talc and magnesium stearate (2:1). Granules were compressed by an automated single station-punching machine (CIP machinaries, Ahmedabad, India and Bro-Shell Remedies, Sagar, India) with concave punches (diameter 10 mm). Two-layered tablets were prepared manually by double compression method. First, the die cavity was adjusted for required

Table 1
Contents of core formulations containing only theophylline

Ingredients	T1 (mg)	T2 (mg)	T3 (mg)	T4 (mg)	T5 (mg)	T6 (mg)
Upper layer						
Theophylline base	100	100	100	100	100	100
MCC	–	5	10	15	10	10
HPMC	–	5	10	15	10	10
Mannitol	55	45	35	25	35	35
Lower layer						
Choline theophylline	300	300	300	300	300	300
PEO	50	50	50	50	100	150
Mannitol	75	75	75	75	25	–

Table 2
Contents of core formulations containing both theophylline and salbutamol sulphate

Ingredients	F1 (simple tablet) (mg)	F2 (two-layered tablet) (mg)	F3 (two-layered tablet) (mg)	F4[a] (two-layered tablet) (mg)
Upper layer				
Theophylline base	–	100	100	100
MCC	60	10	10	10
HPMC	–	10	10	10
Salbutamol sulphate	8	–	8	2
Mannitol	32	35	27	33
Lower layer				
Choline theophylline	400	300	300	300
PEO	–	100	100	100
Salbutamol sulphate	–	8	–	6
Mannitol	–	17	25	19

[a] Same ingredients of optimized system F4 was taken to formulate F5, F6 and F7. In case of F5 and F6 coating composition was varied and in F7 aperture size was varied.

weight of lower layer and was compressed. Then, the compressed lower layer was again pressed in to the die cavity, adjusted for required weight of upper layer and compressed to produce two-layered tablet. The average hardness of compressed tablets was found to be 6.2 ± 0.42 kg/cm^2. The drug content of the tablets was found to be within the limits of 95–105%.

2.4. Coating and drilling

Three coating solutions containing 15%, 25% and 35% (w/w) (based on coating membrane weight) of pore forming agent (sorbitol) were prepared. The components of coating solution are given in Table 3. The plasticizer concentration was kept constant (PEG 400, 25% (w/w)), which provided elegant coating with better membrane properties (Haslam and Rork, 1989; Zentner et al., 1990). Coating solution of 25% (w/w) of sorbitol was used as an optimized pore forming agent concentration and other coating solutions were used to study the effect of concentration of pore forming agent on the release rate. The coating was carried out by spray pan coating machine with hot air blower (Rowland Chem. and Machinaries, Hyderabad, India). Pan was made up of stainless steel, having diameter of 22 cm and rotating speed of 25 rpm. The spray rate was fixed at 4 ml/min. Coated tablets were dried at 50 °C for 12 h and the thickness of the coating membrane was controlled in the range of 475–550 μm. The average weight increase after coating was found to be 13.56 ± 1.46%. Two-layered tablets were drilled by a mechanical drill to obtain uniform orifice diameter of 612 ± 36 μm (Prabakaran et al., 2003, 2004).

2.5. In vitro drug release

In vitro drug release of the formulations was carried out by using USP paddle type apparatus (rotating speed of 100 rpm, at 37 ± 1 °C). The dissolution medium was simulated gastric fluid (SGF pH 1.2, 1000 ml) for first 2 h and simulated intestinal fluid (SIF pH 6.8, 1000 ml) for subsequent hours (Theeuwes et al., 1983). No enzymes were added in dissolution fluids. Samples of 1 ml were withdrawn at specified time

Table 3
Coating composition used for different formulations

Materials	Coating solution 1 (used to coat F1, 2, 3, 4 and 7[a])	Coating solution 2 (used to coat F5)	Coating solution 3 (used to coat F6)
Cellulose acetate (CA)	50% (w/w)	60% (w/w)	40% (w/w)
Sorbitol	25% (w/w)	15% (w/w)	35% (w/w)
Polyethylene glycol (PEG) 400	25% (w/w)	25% (w/w)	25% (w/w)

[a] F7 – the aperture size was reduced to 300 μm.

intervals (replaced with fresh dissolution medium), suitably diluted, centrifuged and supernatant (filtered through 0.2 μm filter) was analyzed immediately by HPLC method. Parameters such as percentage cumulative drug release, average release rate (including initial higher release and late time slow release rate) and $T_{80\%}$ values (time to release 80% of drug) were calculated.

2.6. Scanning electron microscopy

Coating membranes (varying in sorbitol concentration) obtained before and after complete dissolution of core contents were examined for their porous morphology by Jeol 6100 scanning electron microscope (SEM) (JEOL, Japan). Membranes were dried at 45 °C for 12 h and stored between sheets of wax paper in a dessicator before examination. The membrane samples were sputter coated for 5–10 min with gold by using fine coat ion sputter (JFC-1100, Jeol, Japan) and examined under SEM.

2.7. Statistical analysis

The cumulative amount of drug(s) released from simple CPOP and two-layered systems were statistically compared with those of marketed controlled release formulations. The statistical significance was tested by using Student's *t*-test with two-tailed *P*-value (GraphPad-Instat software, GraphPad Software Inc., CA, USA) and a value of $P < 0.05$ was statistically significant.

3. Results and discussion

3.1. Formulation design and development

3.1.1. Preliminary investigations with controlled porosity osmotic pumps

The present study was carried out to develop an oral controlled release system for a combination antiasthmatic therapy based on theophylline and SS. TB and SS possess extremely different solubility properties, hence, freely soluble CT was also used in formulations. Initially simple CPOP containing both drugs (in freely soluble form, i.e. CT and SS) was developed and studied for in vitro release. The systems showed higher release rate of theophylline and salbutamol initially, but after 10 h theophylline release rate reduced to negligible and release did not extend up to 16–20 h due to higher coating thickness. On the other hand the system ruptured with less coating thickness. Hence, the two-layered systems were designed (initially for theophylline only) to contain two different soluble form of theophylline such as TB and CT to achieve sufficient release rate.

3.1.2. Scanning electron microscopy (SEM) of coating membranes

Cellulose acetate (CA) membranes (containing various proportion of pore forming agent – sorbitol) obtained before and after complete dissolution, were studied by SEM. All membranes contained constant plasticizer concentration (PEG 400, 25% w/w) and CA concentration varied with different sorbitol level. Membrane (25% (w/w) sorbitol) obtained before dissolution showed non-porous region (Fig. 1A). After dissolution, membrane contained 25% (w/w) sorbitol showed microporous region (pore size $\leq$ 1 μm) surrounded by macroporous region (length 10–100 μm and width $\leq$ 10 μm) (Fig. 1B and 1C). After complete dissolution, the exhausted membrane showed the pore size lesser than 1 μm (Fig. 1C) and the formulation prepared with this membrane did not show swelling or rupturing. Membrane containing 35% (w/w) of sorbitol showed the pore size ranging between 1 and 5 μm (Fig. 1D). The formulation with this membrane showed slight swelling or elongation of lower layer towards negative direction during initial stage of dissolution, while the upper layer did not disintegrate completely. Membrane contained higher proportion of sorbitol (45% (w/w)) showed larger pores (up to 10 μm) (Fig. 1E) and net like structure. The formulation prepared with this membrane caused bursting. So, it can be assumed that more than 40% (w/w) of sorbitol would cause rupturing of membrane during dissolution. The SEM study suggested that 25% (w/w) of sorbitol can be used as an optimum concentration to obtain maximum release rate of drugs without rupturing of coating membrane for the core composition presented in this study. The possibility of diffusion of insoluble theophylline base particles through the porous membrane could be less during the initial hours of dissolution because the particle size of theophylline base was >20 μm.

3.1.3. Optimization of theophylline release from two-layered, modified push–pull system

The modified push–pull osmotic system initially prepared for theophylline only and optimized. The design is similar as shown in Fig. 2 but salbutamol sulphate was not taken. The optimization was carried out by varying the composition of upper and lower layer ingredients (Table 1). The two-layered, push–pull system contained TB in upper layer along with HPMC + MCC mixture (1:1) and CT in lower layer with PEO. The wettability and disintegration of upper layer were enhanced by the addition of MCC and HPMC because our preliminary studies showed very slow disintegration of compressed upper layer containing TB of low wettability. Lower layer contained PEO (Liu et al., 2000), which forms swelling hydrogel during contact with aqueous media and the swelling force may compensate the lowering osmotic pressure within the system

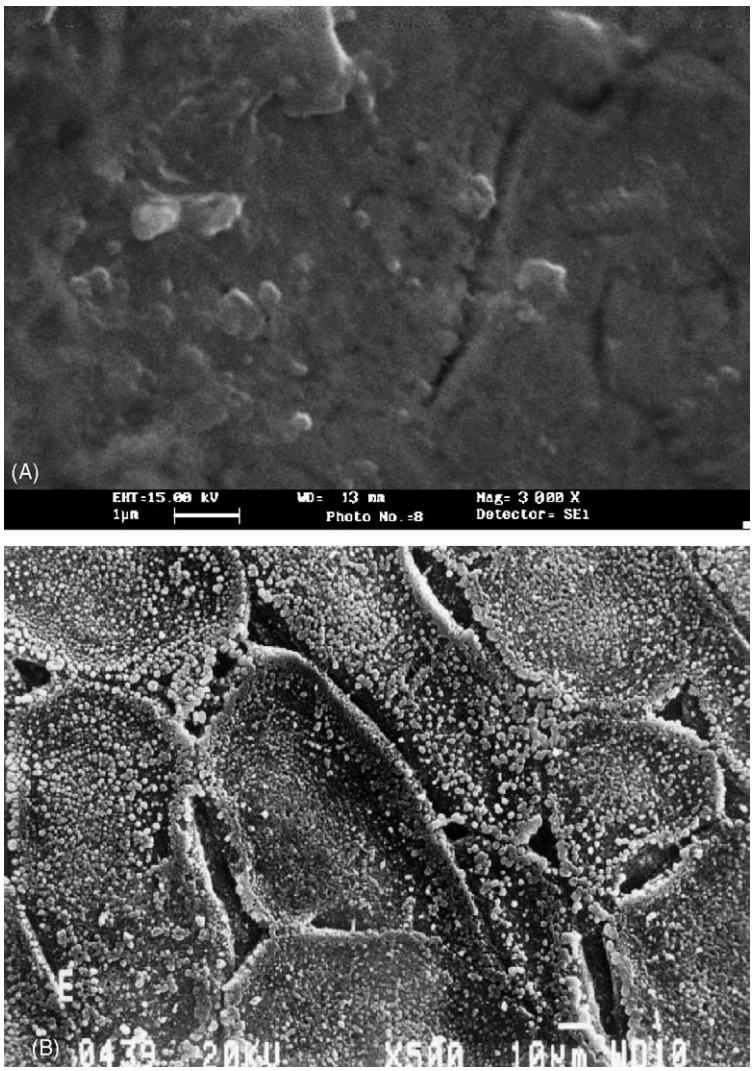

Fig. 1. Scanning electron microphotographs of coating membranes: (A) obtained before dissolution, non-porous region of membrane contained 25% (w/w) sorbitol (3000×); obtained after dissolution (B) porous region of membrane contained 25% (w/w) sorbitol (500×); (C) porous region of membrane contained 25% (w/w) sorbitol (3000×); (D) porous region of membrane contained 35% (w/w) sorbitol (3000×); (D) porous region of membrane contained 45% (w/w) sorbitol (500×).

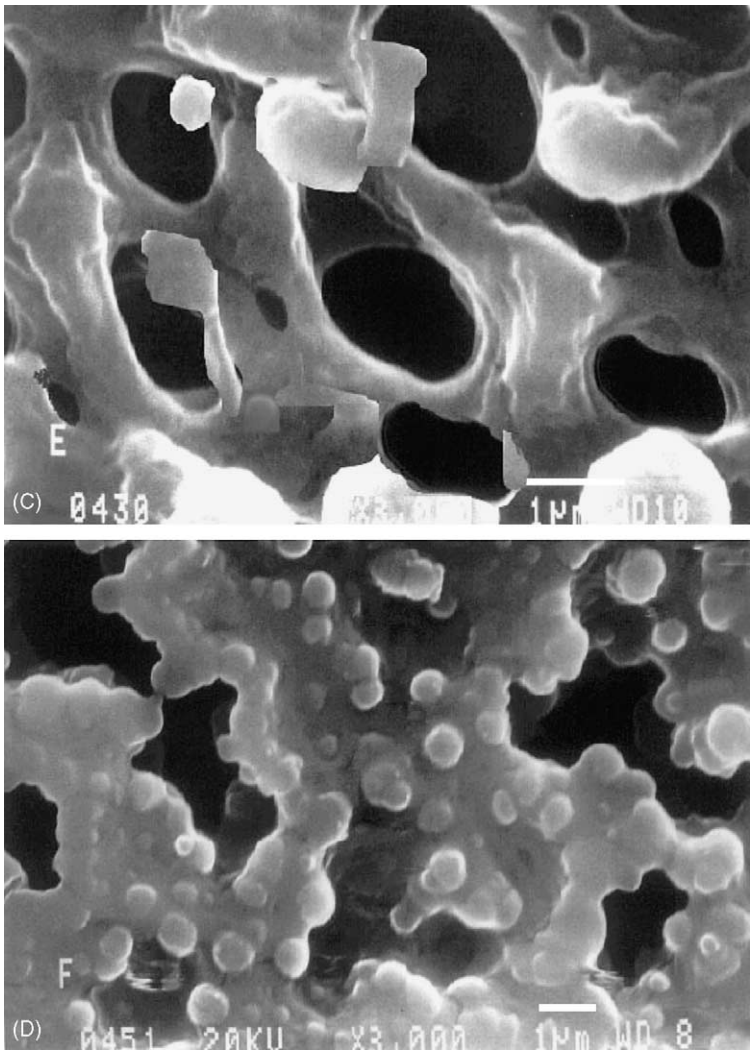

Fig. 1. (*Continued*)

due to pore formation in membrane and subsequent release of drugs during operation. At the same time, the upper layer contents disintegrated to become a suspension of less soluble materials. The swelling or expanding lower layer forced out the upper layer suspension through the aperture. Mannitol was used as a diluent also possessing little osmotic pressure (38 atm) (Verma et al., 2000). The formulations were coated with an in situ pore forming membrane (a membrane containing leachable materials). An aperture was made in the coating membrane of upper layer (Fig. 2) to deliver the contents. Parameters such as coating thickness, concentration of pore forming agent and aperture diameter were kept constant during the optimization studies. Moreover, moderately higher coating thickness was maintained throughout the studies to prevent the rupturing of coating membrane due to osmotic/hydrostatic pressure within the system and hydrogel formation. Lower layer contents were expected to release through the in situ forming pores. The release of freely soluble lower layer contents was expected to be more controlled by the PEO hydrogel formation. The system optimized for

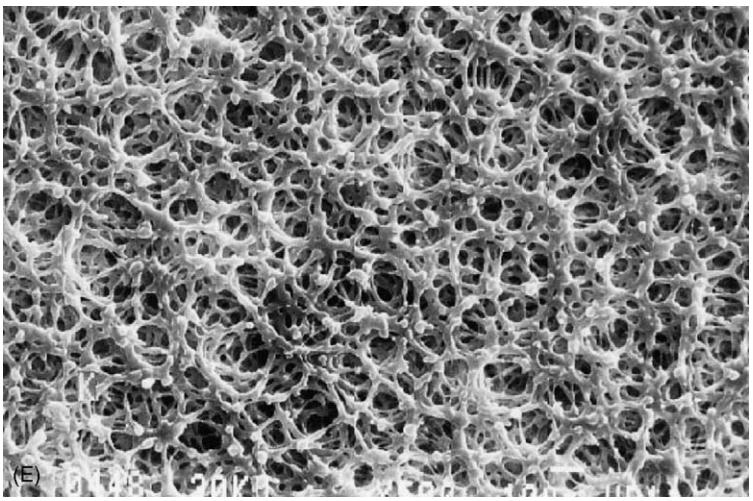

Fig. 1. (*Continued*).

ingredients such as amount of HPMC + MCC mixture and amount of PEO.

Four different concentrations (0%, 10%, 20% and 30% (w/w) of drug – 100 mg of TB in upper layer; formulation code – T1, T2, T3 and T4, respectively) of HPMC + MCC mixture (1:1) were used (Table 1) to observe the effect on the wettability and disintegration of upper layer and subsequent release of theophylline. Fifty milligram of PEO was taken in lower layer of T1, T2, T3 and T4, and in vitro release of theophylline was determined. T1 (0% (w/w)) did not show quick wetting and disintegration as observed visually. Since upper layer did not disintegrate, the pressure increased in lower layer, which expanded beyond the limit, eventually caused rupturing of the coating membrane. T2 and T3 showed considerable release of theophylline (Fig. 3), where later showed higher release. T4 provided theophylline release slower than T3 (Fig. 3), might be due to excess amount of polymer could act as release retardant. From the results, 20% (w/w) of polymer mixture was selected as an optimized concentration. However, release rate of theophylline was not sufficient. To improve the release rate, higher amount of PEO was taken in lower layer. 100 and 150 mg (coded as T5 and T6) of PEO mixed with lower layer contents whereas optimized 20% (w/w) of polymer mixture mixed with upper layer contents (Table 1). In vitro release study showed higher release rate of theophylline from T5 than T2 and T3 (Fig. 3) whereas excess swelling of lower layer and subsequent rupturing of coating membrane observed with T6. Hence, T5 (20% (w/w) polymer mixture in upper layer and 100 mg PEO in lower layer) was selected as an optimized formulation for further studies.

3.1.4. Modified push–pull osmotic system containing theophylline and salbutamol sulphate

The possibility of release of salbutamol sulphate (SS) from upper and lower layer was examined by adding SS in both layers of T5 and release of SS from both layers was found. Formulation T5 was optimized for required SS release profile by using three different designs (Fig. 2 and Table 2). The designs were: (1) A two-layered system, i.e. upper layer and lower layer comprised of TB and mixture of CT + SS, respectively (F2). (2) A two-layered system in which upper layer and lower layer comprised of mixture of TB + SS and CT, respectively (F3). (3) A two-layered system, i.e. upper layer composed of TB and a partial (1/4) amount of SS and lower layer contained CT and maximum (3/4) amount of SS (F4). Additionally, simple CPOP system (mixture of CT and SS with excipients compressed into tablet) was developed to observe the advantages of other systems by comparison study (F1). In case of F4, 2 mg of SS was taken in upper layer to compensate the initial slow release of SS (which can be observed from Fig. 4B) and this additional release may assist to achieve minimum effective concentration in

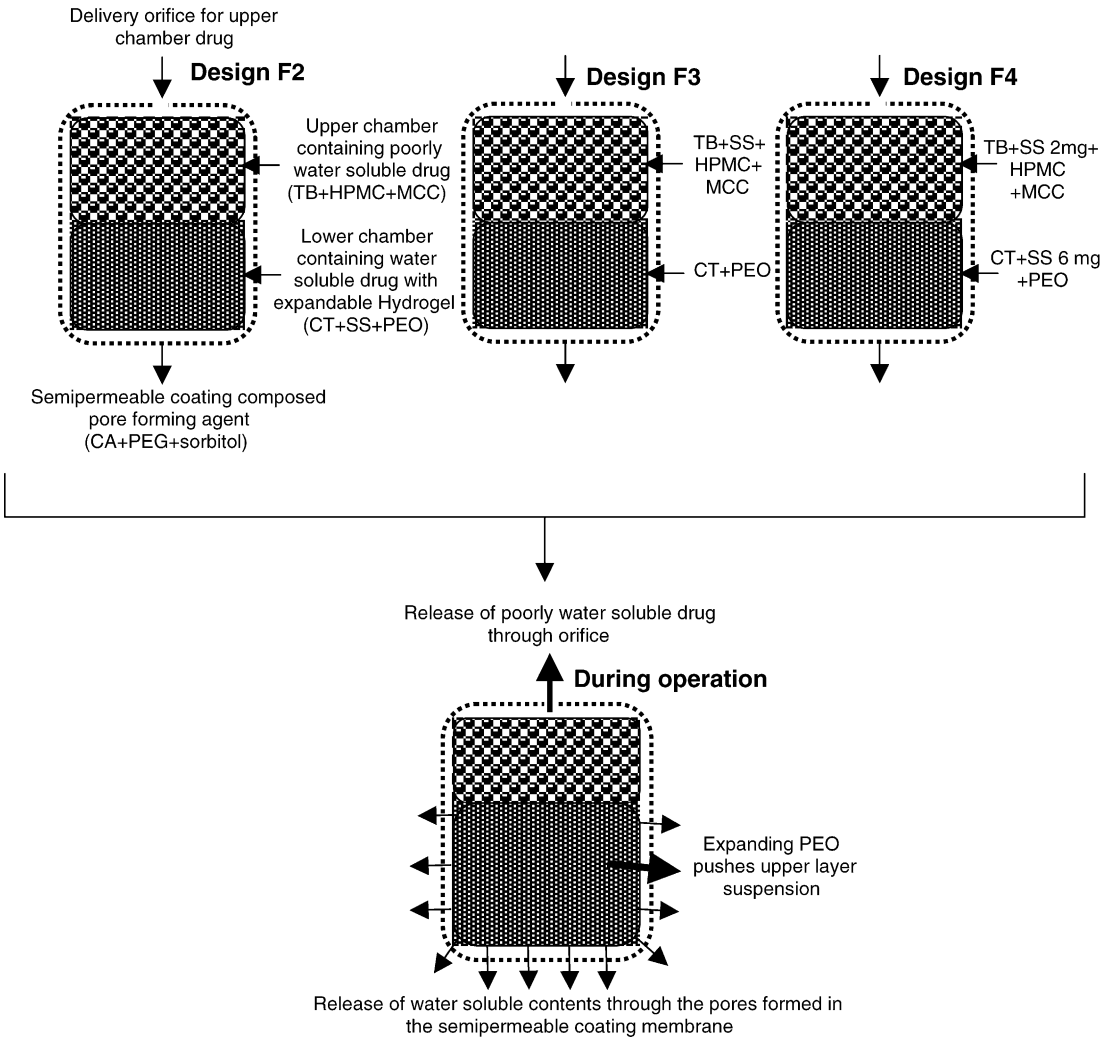

Fig. 2. Designing of theophylline and salbutamol modified push–pull osmotic systems.

blood. The formulations were coated and two-layered systems were drilled.

All the two-layered systems (F2, F3 and F4) showed satisfactory intactness of membrane during dissolution in SGF (pH 1.2) and SIF (pH 6.8) for 24 h, though slight swelling of lower layer was observed (1.5–3 h) due to PEO hydrogel formation. However, when the upper layer contents started to disintegrate, the swelling of lower layer stopped with compensatory release of upper layer contents. After third hour, a continuous pushing of upper layer by lower layer was observed up to 10–12 h.

3.2. Theophylline release from modified push–pull osmotic system containing both drugs

In vitro release of theophylline from system F1 (simple CPOP) showed higher average release rate of theophylline (5.68 ± 2.25%/h) and constant release rate was observed only up to 10 h ($T_{80\%}$ = 9.8 h). F1 contained only freely water soluble choline theophylline and opening of pores after 1 h triggered initial higher release rate, however, release rate gradually reduced to negligible within 10 h and this system may not be suitable for once a day dosage form. Theo-

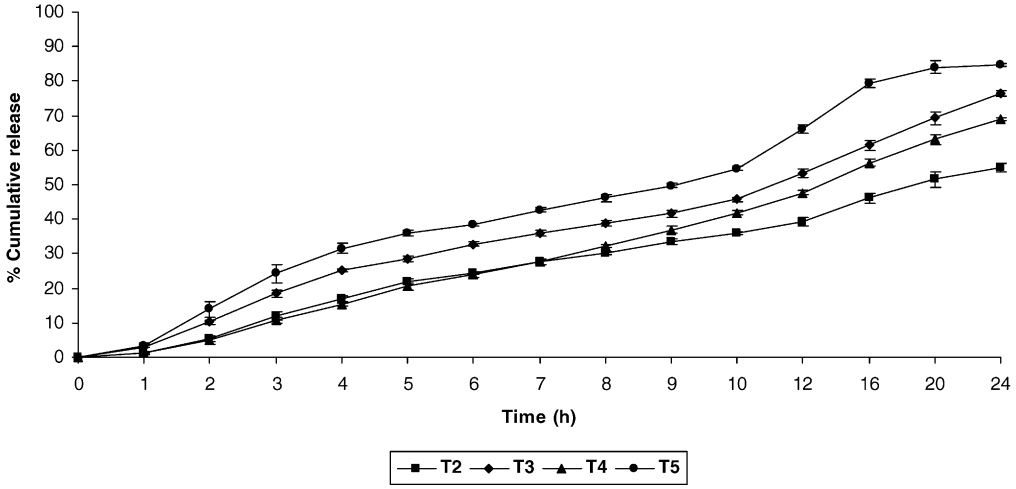

Fig. 3. Effect of different polymer mixture concentration (upper layer) and amount of PEO (lower layer) on the release of theophylline from modified push–pull osmotic system.

phylline release from the two-layered systems were comparatively longer with slower release rate (Table 4), which extended up to 16–20 h (Fig. 4A). All two-layered systems showed similar release profiles of theophylline, since no difference in the formulation design. Marketed theophylline matrix tablet, Unicontin-CR, showed comparatively slower average release rate of theophylline (5.26 ± 1.52%/h) up to 10 h and initial

Table 4
Average release rate, $T_{80\%}$ values and statistical analysis of formulations (n = 3)

Formulations	Theophylline release		Salbutamol sulphate release	
	Average release rate[a] (%/h)	$T_{80\%}$ (h)	Average release rate[a] (%/h)	$T_{80\%}$[b] (h)
F1	5.68 ± 2.25	9.8	5.49 ± 1.53	17.5
F2	5.03 ± 1.96	16.5	5.08 ± 1.25	18.5
F3	4.83 ± 1.52	16.6	7.22 ± 2.39	8.2
F4	5.36 ± 1.66	16.0	5.52 ± 1.86	15.8
Unicontin-CR	5.26 ± 1.52	16.4	–	–
Ventorlin-CR	–	–	5.83 ± 1.41	10.8
F5	4.86 ± 1.52	23	4.52 ± 1.56	>24
F6	5.76 ± 1.85	12.5	6.10 ± 3.26	7.9
F7	4.22 ± 1.62	>24	4.54 ± 1.52	23

Theophylline release				Salbutamol sulphate release			
Formulations compared	P-value	t-value	Result	Formulations compared	P-value	t-value	Result
Statistical analysis[c]							
F2 vs. Unicontin-CR	0.0891	1.827	ns[d]	F2 vs. Ventorlin-CR	<0.0001	11.459	s[e]
F3 vs. Unicontin-CR	0.0816	1.876	ns	F3 vs. Ventorlin-CR	0.1403	1.563	ns
F4 vs. Unicontin-CR	0.0509	2.135	ns	F4 vs. Ventorlin-CR	<0.0001	10.088	s

[a] Overall release rate including initial higher and late time slow release rate.
[b] Time to release 80% of drug content.
[c] The t-test was used to analyze the significance of the % cumulative drug release to those of marketed formulations.
[d] Not significant.
[e] Significant.

higher release was not found (Fig. 4A). These results confirmed that initial higher release of theophylline from developed osmotic pumps was triggered by opening of pores after 1 h imbibition in dissolution fluid. This initial higher release could be considered as an advantage to achieve minimum effective concentration in blood. Osmotic systems showed initial lag time of approximately one hour to imbibe aqueous media. Also controlled release of highly soluble CT attributed to the PEO hydrogel in lower layer and exposure of CT to porous membrane comparatively less than system F1.

Statistical analysis (Table 4) of the two-layered systems with marketed controlled release formulations revealed that all osmotic systems provided approximately similar release profiles of marketed product ($P > 0.05$, not significant). Simple CPOP (F1) resulted extremely significant difference as $P < 0.05$.

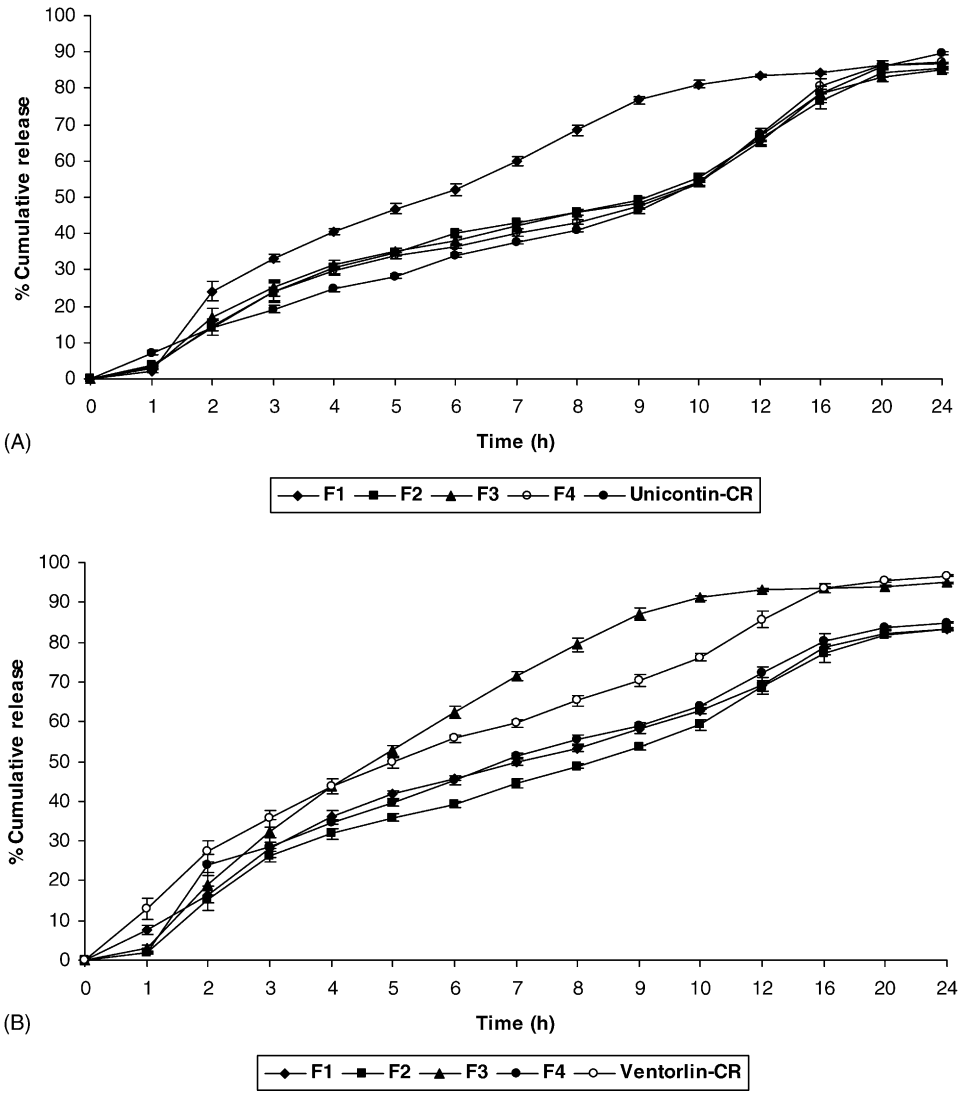

Fig. 4. In vitro release of (A) theophylline and (B) salbutamol sulphate from modified push–pull osmotic systems.

3.3. Salbutamol sulphate release from modified push–pull osmotic system containing both drugs

The designing of the system involved keeping SS in two different layers in varying amounts and different in vitro release profiles of SS obtained (Fig. 4B). System F3 showed higher and constant release rate of SS but up to 10 h only (7.22 ± 2.39%/h and $T_{80\%}$ = 8.2 h) because SS was kept in the upper layer, where the release occurred through the pores as well as the aperture. Though, HPMC and MCC attributed to little control in the release, release rate was higher with F3 when compared to other systems. SS in different layers did not affect the release of theophylline, which can be observed from Fig. 4A. Approximately 1 h lag time was observed with two-layered systems. Slower release rate of SS observed with system F2 (Table 4), in which SS was kept in lower layer where the release only occurred through the pores and release control also attributed to PEO. Similar release profiles of SS observed with system F1 and F4 (Table 4 and Fig. 4B), however, later showed 1 h lag time for the release. All systems except F3 showed comparatively slower release rate than the marketed capsule (containing spansules) Ventorlin – CR, which showed consistent release profile up to 16 h ($T_{80\%}$ = 10.8 h). Higher release rate of SS provided by F4 (compared to F2) attributed to partial amount of SS kept in the upper layer of F4. By considering initial higher release as well as extended release (up to 16 h) F1 and F4 could be the better formulations for the release of SS when compared to F2 and F3. Statistical analysis indicated that only system F3 showed approximately similar release profile of marketed product ($P > 0.05$) and release from other systems significantly varied from the marketed product ($P < 0.05$) (Table 4). However, system F3 provided release only up to 10 h.

The release mechanism of TB in upper layer of the system is similar to the usual push–pull osmotic system. The release mechanism of TB through the aperture attributed to the increasing osmotic and hydrostatic pressure in the upper layer by the lower layer containing CT, mannitol and expandable hydrogel (PEO) (Liu et al., 2000). Osmotic pumping is the primary mechanism of drug release from the oral osmotic pumps with simple diffusion playing a minor role (Haslam and Rork, 1989; Zentner et al., 1990, 1991). Freely water soluble drugs CT and SS in the lower layer released through the pores in a controlled manner. The release control of CT and SS attributed to the amount of PEO hydrogel in lower layer as well as the pore number and size. In addition to osmotic pumping, the release mechanism and kinetics of highly water-soluble drugs from oral osmotic pumps in the presence of appropriate amount of hydrophilic polymers was previously evaluated as non-Fickian diffusion (Prabakaran et al., 2003).

The release profiles of both the theophylline and SS from the developed systems revealed that system F4 could be the better formulation by considering satisfactory controlled release of SS (extended up to 16 h) with initial higher release rate. Though system F1 showed similar release profile of SS from F4, F1 was rejected even in the initial studies because of poor theophylline release profile. All developed systems showed 83–87% of drug release (both drugs) except release of SS from system F3, which showed 94.87 ± 0.18% at 24 h. As an optimized formulation F4 was selected to study the effect of variables such as concentration of pore forming agent and orifice diameter.

3.4. Effect of concentration of pore forming agent and orifice diameter on drug release

Fig. 5A and B clearly indicate the effect of concentration of pore forming agent and orifice diameter on the release of theophylline and SS from the system F4. Lower concentration of pore forming agent (15% (w/w), System F5) showed lower average release rate (4.86 ± 1.52 and 4.52 ± 1.56%/h for theophylline and SS, respectively) and higher concentration of pore forming agent (35% (w/w), system F6) showed higher average release rates (5.76 ± 1.85 and 6.10 ± 3.26%/h for theophylline and SS, respectively). System F6 released more than 80% of SS within 10 h and these results suggested that slightly higher concentration of pore forming agent may be useful to release maximum SS content from the systems. Reduction in orifice diameter (300 μm, system F7) caused the reduction of drug release as F7 showed lower average release rate of 4.22 ± 1.62 and 4.54 ± 1.52%/h for theophylline and SS, respectively. By reducing the concentration of pore forming agent and orifice size, release can be extended for longer period as F5 and F7 showed $T_{80\%}$ values of >20 h, however, release rate to be compromised. These results confirmed that in addition to number of pores and pore size, orifice diameter also possessed considerable role in the release of drugs. These two important

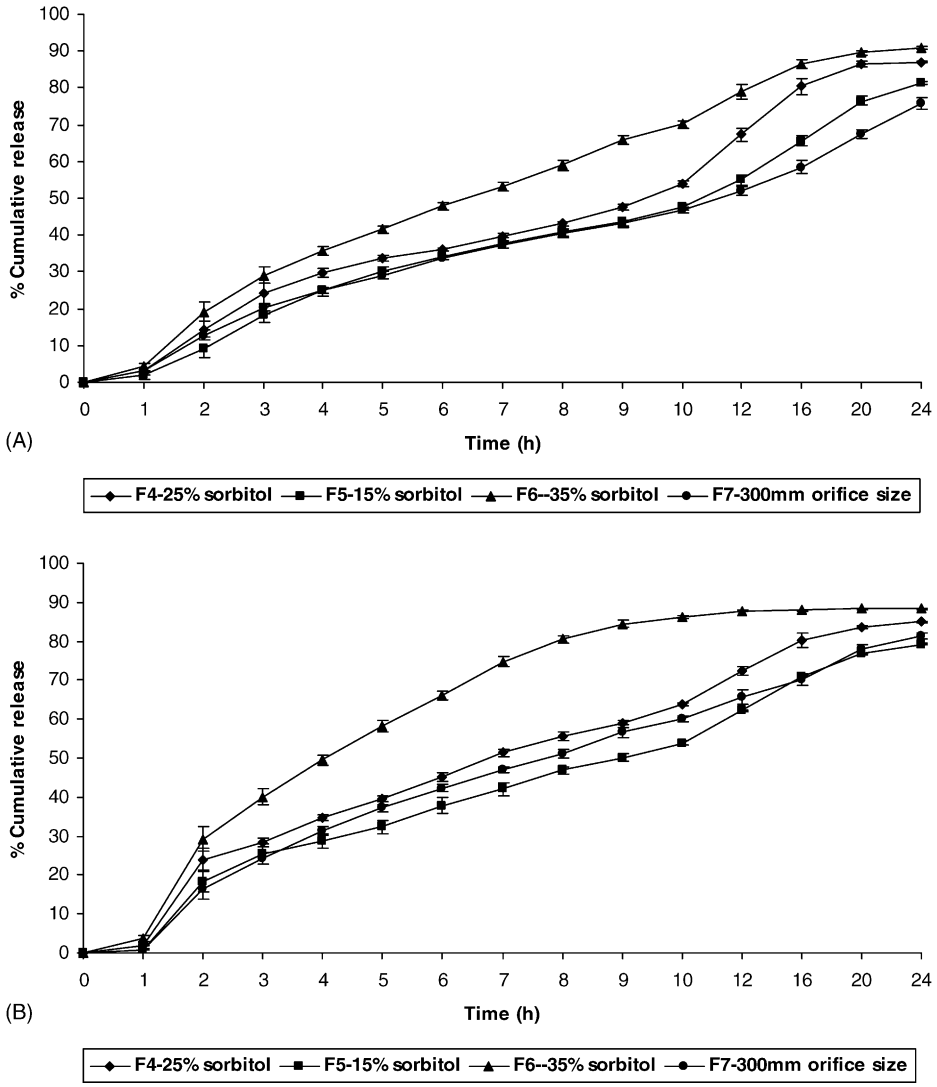

Fig. 5. Effect of concentration of pore forming agent and orifice size on the release of (A) theophylline and (B) salbutamol sulphate from system F4.

parameters can be effectively manipulated to obtain sufficient release rates of drugs.

4. Conclusion

The present study was aimed to develop an oral osmotic system which can deliver theophylline and salbutamol sulphate simultaneously. Modified push–pull osmotic system was designed since simple CPOP system failed to provide sufficient extended release of theophylline. By using two different, highly and poorly water soluble forms of theophylline, systems were developed and optimized. These systems further designed and optimized to deliver salbutamol sulphate at controlled rate for extended period. The optimized, modified push–pull osmotic system F4 was considered as better system since it provided controlled release of both drugs for extended period of time (16–20 h). Also, the release rate of drugs can be effectively modified by

manipulating the concentration of pore forming agent and orifice diameter. The modified push–pull osmotic system could be effective in the multi-drug therapy of asthma by delivering both drugs simultaneously at a controlled manner. The prototype design of the system could be applied for other combination of drugs (one water slightly soluble or insoluble drug and another freely water soluble drug) used for cardiovascular diseases, diabetes, etc. Furthermore, the applicability and in vivo efficacy of the system to be examined in suitable animal/human model.

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