AAPS PharmSciTech 2007; 8 (3) Article 53 (http://www.aapspharmscitech.org).

Formulation and Optimization of Porous Osmotic Pump–based Controlled Release System of Oxybutynin

Received: July 25, 2006; Final Revision Received: January 29, 2007; Accepted: January 31, 2007; Published: July 13, 2007

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ABSTRACT

The aim of the current study was to design a porous osmotic pump–based drug delivery system for controlled release of oxybutynin. The porous osmotic pump contains pore-forming water-soluble additives in the coating membrane, which after coming in contact with water, dissolve, resulting in an in situ formation of a microporous structure. The dosage regimen of oxybutynin is one 5-mg tablet 2 to 3 times a day. The plasma half-life ranges from ~2 to 3 hours. Hence, oxybutynin was chosen as a model drug with an aim to develop a controlled release system for a period of 24 hours. Linear and reproducible release similar to that of Ditropan XL was achieved for optimized formulation (f2 >50) independent of hydrodynamic conditions. The effect of different formulation variables, namely, ratio of drug to osmogent, membrane weight gain, and level of pore former on the in vitro release was studied. Cellulose acetate (CA) was used as the semipermeable membrane. It was found that drug release rate increased with the amount of osmogent because of the increased water uptake, and hence increased driving force for drug release. Oxybutynin release was inversely proportional to the membrane weight gain; however, directly related to the level of pore former, sorbitol, in the membrane. This system was found to deliver oxybutynin at a zero-order rate for 20 hours. The effect of pH on drug release was also studied. The optimized formulations were subjected to stability studies as per International Conference on Harmonisation (ICH) guidelines and formulations were stable after a 3 month study.

KEYWORDS: Osmotic system, oxybutynin, osmogent, cellulose acetate, pore former.

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INTRODUCTION

Oral controlled release (CR) systems continue to be the most popular amongst all the drug delivery systems.[1] Because pharmaceutical agents can be delivered in a controlled pattern over a long period by osmotic pressure, there has been increasing interest in the development of osmotic devices over the past 2 decades. A detailed review of various types of osmotic pumps has been done by Santus and Baker.[2] Drug delivery from this system is not influenced by the different physiological factors within the gut lumen, and the release characteristics can be predicted easily from the known properties of the drug and the dosage form.

Theeuwes introduced the elementary osmotic pump (EOP).[3] The EOP consists of an osmotic core, with the drug surrounded by a semipermeable membrane with a delivery orifice. In operation, the osmotic core acts by imbibing water from the surrounding medium via the semipermeable membrane. Subsequently, drug solution is generated within the device and delivered out of the device via the orifice. Various attempts to increase the permeability of the semipermeable coating have been reported, such as incorporating water-soluble pore-forming additives in the coating.[4] The release rate from these types of systems is dependent on the coating thickness, level of leachable components in the coating, solubility of the drug in the tablet core, and osmotic pressure difference across the membrane but is independent of the pH and agitation of the release media. It was observed that predominantly the drug was released through the pores at a constant rate. It was also observed that most of the core content released through pores at a constant rate, where the mechanism was primarily governed by osmosis with simple diffusion playing a minor role.[5,6] Osmotic tablets with an asymmetric membrane coating that can achieve high water fluxes have also been described.[7]

Oxybutynin, an antispasmodic and anticholinergic agent, was chosen as the model drug. Oxybutynin chloride is indicated for the relief of symptoms of bladder instability associated with voiding in patients with uninhibited neurogenic or reflex neurogenic bladder.[8-11] The usual dose of oxybutynin is 15 mg daily given in divided doses. Oxybutynin chloride is a white crystalline solid with a molecular weight

Table 1. Composition of Core Oxybutynin Tablets

Ingredients (mg/tablet)	Formulation Code			
	OXY/F01	OXY/F02	OXY/F03	OXY/F04
Oxybutynin chloride	10	10	10	10
Mannitol	0	50	100	200
Lactose	212	162	112	12
Povidone K30	12	12	12	12
Magnesium stearate	2.5	2.5	2.5	2.5
Talc	2.5	2.5	2.5	2.5
Colloidal silicon dioxide	1	1	1	1

of 393.9.[12] It is readily soluble in water and acids, but relatively insoluble in alkalis. The objective of the present study was to develop controlled porosity-based osmotically controlled release tablets of oxybutynin. Mannitol was used as the osmogent. The tablets were coated with cellulose acetate as the semipermeable membrane containing sorbitol as a pore forming / channeling agent.

Materials and Methods

Materials

Oxybutynin was obtained from Cadila Healthcare Ltd, Ankleshwar, India. Mannitol (Pearlitol SD 200, Roquette, France), Lactose (Pharmatose DCL 11, DMV International, Veghel, The Netherlands), Povidone (Kollidon30, BASF, Ludwigshafen, Germany), and Colloidal silicon dioxide (Aerosil 200, Degussa, Frankfurt, Germany) were procured from Cadila Healthcare Ltd, Ahmedabad, India. Cellulose acetate with 39.8% acetylene content (CA-398-10NF) was obtained from Eastman Chemical Inc, Kingsport, TN. Sorbitol and polyethylene glycol (PEG) 400 were purchased from S.D. Fine Chemicals Ltd, Mumbai, India. Ditropan XL (ALZA Corp, Mountain View, CA) tablets were obtained from retail pharmacy. All other solvents and reagents used were of analytical grade.

Drug-Excipient Interaction Studies

Assessment of possible incompatibilities between an active drug substance and different excipients forms an important part of the preformulation stage during the development of a solid dosage form. Differential scanning calorimeter (DSC) allows the fast evaluation of possible incompatibilities, because it shows changes in the appearance, shift or disappearance of melting endotherms and exotherms, and/or variations in the corresponding enthalpies of reaction.[13] The DSC thermograms of pure drug, core tablets, placebo of core tablets, and coated tablets were recorded. The samples were separately sealed in aluminum cells and set in PerkinElmer (Pyris 1) DSC (Waltham, MA). The thermal analysis was performed in a nitrogen atmosphere at a heating rate of 10°C/min over a temperature range of 50°C to 300°C.

Formulation of Core Tablets

The tablets were prepared by wet granulation technique. Drug was uniformly mixed with mannitol and lactose in a high shear mixer granulator. The dry blend was granulated with povidone, which was dissolved in isopropyl alcohol. The mass was dried at 50°C and sized through American Society of Testing and Materials (ASTM) 20 mesh and mixed with talc and colloidal silicon dioxide. The granules were lubricated with magnesium stearate and compressed into round tablets with standard concave punches (diameter, 9.52 mm) using 27-station rotary compression machine (CMB4 D-27, Cadmach Engg, Ahmedabad, India). Table 1 lists the composition of different formulations prepared using varying amounts of osmogents.

Coating

Table 2 summarizes the components of coating solution. The coating solutions were prepared using a mixture of dichloromethane and methanol (80:20) as the coating solvent. All coating compositions were clear solutions. Coating was performed by spray pan coating in a perforated pan (GAC-205, Gansons Ltd, Mumbai, India). The laboratory scale batch size was 700 g (350 g core tablets mixed with equal quantity of dummy tablets). Initially, tablets were preheated by passing hot air through the tablet bed and by rotating at a lower speed of 5 to 8 rpm. Coating process was started with rotation speed of 10 to 12 rpm. The spray rate and atomizing air pressure were 4 to 6 mL/min and 1.75 kg/cm^2, respectively. Inlet and outlet air temperatures were 50°C and 40°C, respectively. Coated tablets were dried at 50°C for 12 hours and the percentage weight gain and thickness (Digimatic

Table 2. Coating Composition for Oxybutynin Tablets*

Ingredients†	Coating Composition Code		
	C-I	C-II	C-III
Sorbitol	0	10	20
PEG-400	10	10	10

*PEG indicates polyethylene glycol.

†Composition based on percentage wt/wt of cellulose acetate. Total solids in the coating composition is 4% wt/vol.

Caliper, Mitutoyo, Japan) of the coating membrane were measured.

Weight Variation and Hardness Determination

Weight variation was determined by weighing 20 tablets of each formulation on an electronic balance (AG 64, Mettler-Toledo GmbH, Greifensee, Switzerland). The hardness of 10 tablets was measured using a hardness tester prior to coating (6-D, Dr Schleuniger Pharmatron Inc., Manchester, NH).

In Vitro Drug Release

In vitro drug release of the formulations was performed using United States Pharmacopeia (USP) type I apparatus (2100C, Distek Inc, North Brunswick, NJ) attached with auto-sampler, at 75 rpm. The dissolution medium consisted of 900 mL of degassed simulated gastric fluid (SGF, without enzymes) at 37°C ± 0.5°C. The drug release at different time intervals was analyzed by high-performance liquid chromatography (HPLC). The release studies were conducted in triplicate and parameters such as percentage cumulative drug release and drug release rate were calculated.

HPLC Analysis

Chromatographic separation of oxybutynin was performed on a Shimadzu LC-2010C_{HT} HPLC system using YMC-Pack-CN column (4.6 mm × 250 mm × 5µm particle size; Shimadzu, Kyoto, Japan). Mobile phase used was mobile phase-A (water:methanol [800:200] + 0.2 mL triethylamine, with pH 3.5. Temperature of the column was maintained at 30°C. Standard solution and dissolution samples were analyzed at 203 nm using a UV detector.

Scanning Electron Microscopy

Coating membranes of formulation obtained before and after complete dissolution of core contents were examined for their porous morphology by scanning electron microscope (XL30 ESEM TMP+EDAX, Philips, Eindhoven, The Netherlands). Membranes were dried at 45°C for 12 hours and stored between sheets of wax paper in a dessicator until examination.

Effect of pH

To study the effect of pH and to assure a reliable performance of the developed formulations independent of pH, in vitro release studies were conducted in media of different pH. The release media was SGF (pH 1.2), acetate buffer (pH 4.5), and simulated intestinal fluid (pH 6.8). Samples were analyzed by HPLC.

Effect of Agitational Intensity

In order to study the effect of agitational intensity of the release media, release studies were performed in dissolution apparatus at various rotational speeds. USP-I (rotating basket) type dissolution apparatus with rotational speeds of 50, 100, and 150 rpm was used. Degassed SGF (without enzymes) was used as dissolution media (pre-equilibrated to 37°C ± 1°C). Samples were analyzed by HPLC method.

Effect of Osmotic Pressure

To confirm the major mechanism of drug release, release studies of the optimized formulation were conducted in media of different osmotic pressure.[14,15] To increase the osmotic pressure of the release media (pre-equilibrated to 37°C ± 1°C), mannitol (osmotically effective solute) was added in SGF (without enzymes). Release studies were performed in 900 mL of media using USP-I dissolution apparatus (75 rpm). To avoid any interference in the analysis by mannitol, residual drug analysis methodology was used for construction of release profile. At predetermined time points, formulations were withdrawn from each vessel and cut open, and the contents were dissolved in sufficient volume of SGF. The samples were analyzed to determine the residual amount remaining in each formulation. Accuracy of this method was checked in SGF, where results after direct measurement of drug into the release media were similar to the results of residual drug analysis method.

Kinetics of Drug Release

The cumulative amount of drugs released from the optimized system at different time intervals were fitted to zero-order kinetics using least squares method of analysis to find out whether the drug release from the systems provides a constant drug release pattern.[14] The correlation coefficient between the time and the cumulative amount of drug released was also calculated to find the fitness of the data to zero-order kinetics. The fitness of the data to first-order kinetics was assessed by determining the correlation coefficient between the time and the amount of drug to be released from the formulations.

RESULTS AND DISCUSSION

The dosage form developed was designed as a tablet core coated with a rate-controlling membrane. Tablet core consists of drug along with osmogent, and other conventional excipients to form the core compartment. The core compartment is surrounded by a membrane consisting of a semipermeable membrane-forming polymer, water-soluble pore-forming additives, and at least 1 plasticizer capable of improving film-forming properties of the polymers. The semipermeable

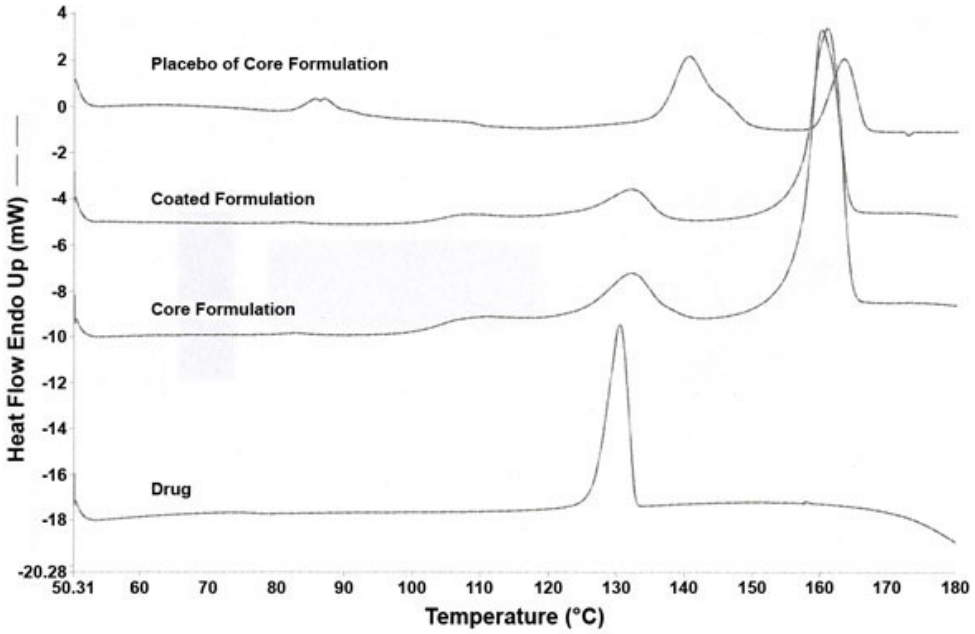

Figure 1. Differential scanning calorimetry thermograms of drug, core formulation, placebo of core formulation, and coated formulation.

membrane-forming polymer is permeable to aqueous fluids but substantially impermeable to the components of the core. In operation, the core compartment imbibes aqueous fluids from the surrounding environment across the membrane and dissolves the drug. The dissolved drug is released through the pores created after leaching of water-soluble additive(s) in the membrane. Cellulose acetate and sorbitol were used as water-insoluble polymer and water-soluble additive, respectively. PEG-400 was used as plasticizer.

Drug-Excipient Interaction Studies

Figure 1 depicts the DSC thermograms of oxybutynin and the formulation. No changes in the endotherms were observed as the drug exhibited a sharp melting endotherm in the core and coated formulation. From the DSC thermograms it was clear that no specific interaction between the drug and excipients used in the present formulation.

Drug Content and Physical Evaluation

The assay of drug in various formulations varied between 98.6% and 101.5% (mean 100.05%). Core tablet weights varied between 235 mg and 245 mg (mean 240 mg), thickness of the core tablets was found to be in the range of 3.05 and 3.45 mm (mean 3.25 mm). The hardness of core tablets was found to be between 3.8 and 5.2 kg cm^{-2} (mean 4.5 kg cm^{-2}), while the friability of prepared core tablets ranged between 0.12% and 0.23% (mean 0.17%). Thus, all the physical parameters of the compressed matrices were practically within limits.

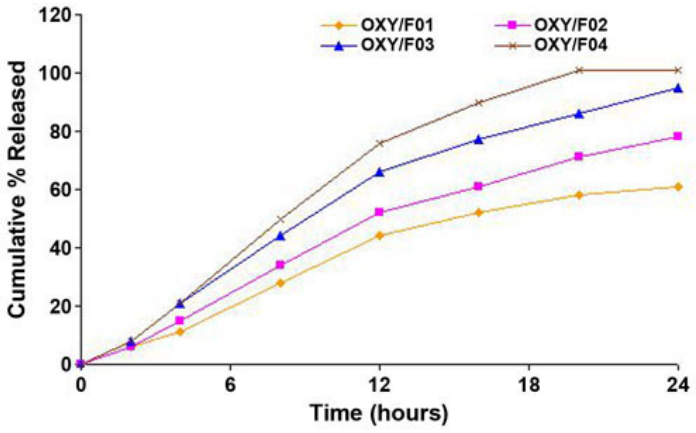

Figure 2. Effect of drug:osmogent ratio on drug release from developed formulation.

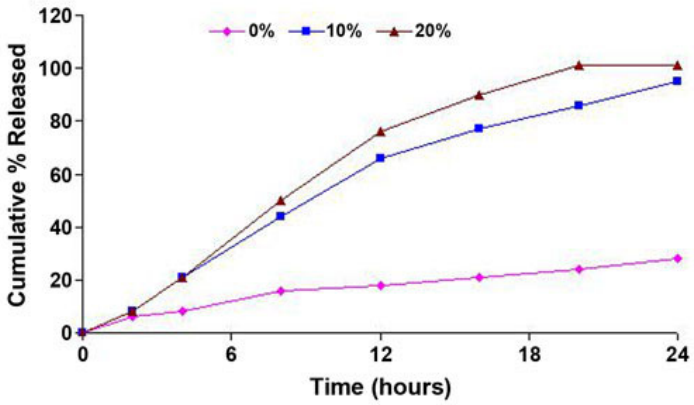

Figure 3. Effect of concentration of pore former on drug release from developed formulation.

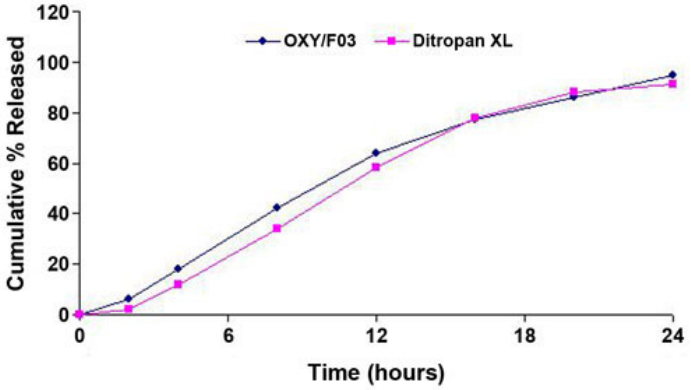

Figure 4. Release profile of optimized formulation in comparison with Ditropan XL.

Effect of Ratio of Drug to Osmogent

To optimize the amount of osmogent to be used in the formulation and to study the effect of drug-to-osmogent ratio, core formulations were prepared as shown in Table 1. The ratios of drug to osmogent studied were 1:0, 1:5, 1:10, and 1:20. All the core formulations were coated with coating composition, C-II containing 10% wt/wt (of cellulose acetate) of sorbitol. Release profile from these formulations is shown in Figure 2. It is clear from Figure 2 that osmogent enhances the release of drug and thus had a direct effect on drug release. This finding is evidenced from formulation OXY/F01 that was devoid of any osmogent in the core and showed 61% drug release at 24 hours. However, the use of osmogent enhanced the release beyond 80% drug release at 24 hours depending on the amount of osmogent present in the core formulation, which might be due to the increased water uptake and hence increased driving force for drug release.

Effect of Pore Forming Level

To study the effect of pore forming agent, core formulations of oxybutynin, OXY/F03, were coated with varying coating compositions of pore forming agent containing 0%, 10%, and 20% wt/wt (of cellulose acetate) of sorbitol. Release profile from these formulations is shown in Figure 3. It is clearly evident that the level of sorbitol had a direct effect on drug release. As the level of pore former increases, the membrane becomes more porous after coming into contact with the aqueous environment, resulting in faster drug release. The level of pore former also affects the burst strength of exhausted shells. The burst strength was inversely related to the initial level of pore former in the membrane. With the increase in the level of sorbitol, the membrane became more porous after exposure to water, leading to a decrease in its strength. The results in the present study are consistent with other reports.[14]

Statistical Analysis of Dissolution Data

Release profiles of tablets were compared by calculating 2 statistically derived mathematical indices, difference factor (*f1*) and similarity factor (*f2*) using Ditropan XL as the reference.[16] The pull points at 60-minute intervals, beginning from the first 60-minutes up to 1 point above 85% released were included in the calculations. OXY/F03 (coat C-II) formulation resulted in a more linear release profile (R^2 = 0.9886 for up to 80% release) having similarity to the reference product Ditropan XL (*f1*: 13.59 and *f2*: 62.51) as shown in Figure 4.

Performance Evaluation of Optimized Formulation

Scanning Electron Microscopy

Cellulose acetate (CA) membranes of optimized formulation, OXY/F03 (coat C-II), obtained before and after dissolution were studied by SEM. Membranes obtained before dissolution clearly showed nonporous region (Figure 5). After 24-hour dissolution, the membrane clearly showed pores in range of 1 to 15 μm (Figure 5) owing to dissolution of sorbitol. The leaching of sorbitol from the membrane leads to formation of pores, and thus the release of drug takes place.

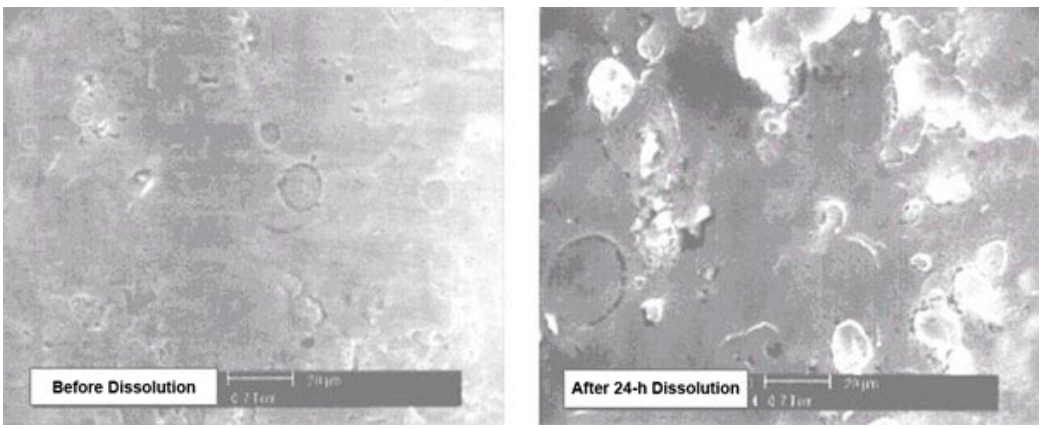

Figure 5. Scanning electron photomicrographs of membrane structure of optimized formulation before and after dissolution studies.

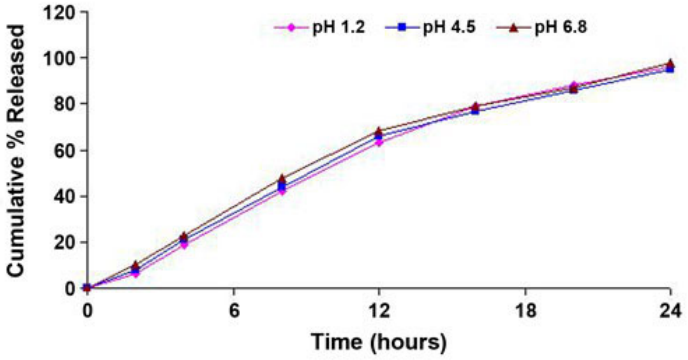

Figure 6. Effect of pH on drug release from optimized formulation.

Effect of pH

The optimized formulation, OXY/F03 (coat C-II), was subjected to in vitro release studies in buffers with different pH. As can be seen from Figure 6, there is no significant difference in the release profile, demonstrating that the developed formulation shows pH-independent release.

Effect of Weight Gain

To study the effect of weight gain of the coating on drug release, core tablets of oxybutynin OXY/F03 (coat C-II) were coated to obtain tablets with different weight gains (5%, 8%, and 12% wt/wt). Release profile of oxybutynin from these formulations is shown in Figure 7. It is clearly evident that drug release decreases with an increase in weight gain of the membrane.

Effect of Agitation Intensity

The release profile of oxybutynin from the optimized formulation OXY/F03 (coat C-II) was independent of the agitational intensity of the release media (figure not shown). The difference factor (*f1*) and similarity factor (*f2*) values were found to be 10.92 and 61.65 (for 50 and 100 rpm), 7.14 and 71.35 (for 50 and 150 rpm), and 6.02 and 76.89 (for 100 and 150 rpm). Therefore, the formulations can be expected to show a release profile, fairly independent of the hydrodynamic conditions of the body.

Table 3. Dissolution Parameters of Optimized Formulation With Varying Osmotic Pressure

Osmotic Pressure (atm)	Lag Time (hours)	Dissolution Rate (%/h)
8.15	1.38	8.52
32.45	2.84	6.08
94.89	4.10	3.89

Effect of Osmotic Pressure

The effect of osmotic pressure on the optimized formulation was studied in media of different osmotic pressure, and the dissolution parameters with varying osmotic pressure are depicted in Table 3. The drug release rate decreased with increase in osmotic pressure in the media; however, the lag time was prolonged. The drug release profiles with varying osmotic pressure are shown in Figure 8, and it is evident that the drug release from the formulation decreased as the osmotic pressure of the media increased. This finding confirms that the mechanism of drug release is by the osmotic pressure.

Kinetics of Drug Release

In order to understand the mechanism of drug release from the optimized system OXY/F03 (coat C-II), the data were treated according to first-order (log cumulative percentage of drug remaining vs time) along with zero-order (cumulative amount of drug released vs time) pattern using least squares method of analysis. When the data were plotted according to the first-order equation, the formulations showed a comparatively poor linearity, with regression value of

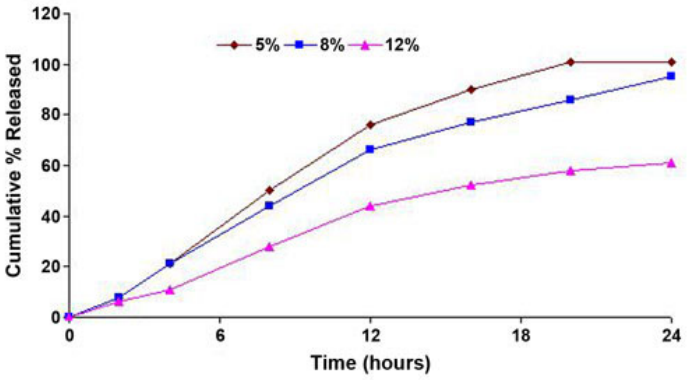

Figure 7. Effect of weight gain on drug release from optimized formulation.

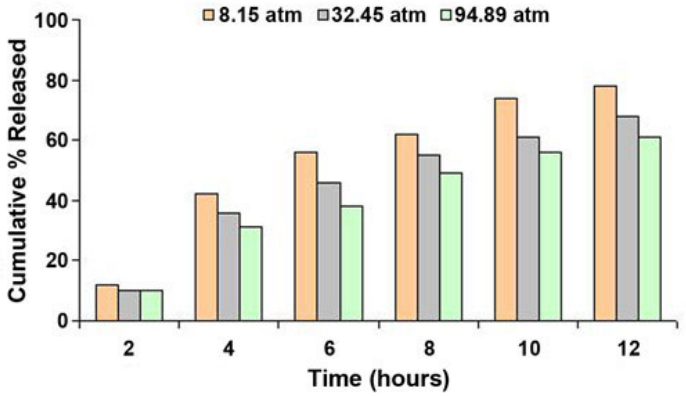

Figure 8. Effect of osmotic pressure of the release media on drug release from optimized formulation.

0.9358, whereas the regression value for zero-order equation was 0.9924, which indicated that drug release from optimized formulation was independent of drug concentration.

Accelerated Stability Studies

OXY/F03 (coat C-II) formulations were packed in strips of 0.04-mm thick aluminum foil laminated with polyvinyl chloride (PVC) and stored in ICH certified stability chambers maintained at 40°C and 75% relative humidity for 3 months. The tablets were withdrawn periodically and evaluated for drug content, hardness, burst strength, and release studies. The formulations were found to be stable in terms of drug content and dissolution stability (Figure not shown).

CONCLUSION

A porous osmotic pump–based drug delivery system can be designed for controlled release of highly water-soluble drug oxybutynin. It is evident from the results that the rate of drug release can be controlled through osmotic pressure of the core, level of pore former, and membrane weight with release to be fairly independent of pH and hydrodynamic conditions of the body. Oxybutynin release from the developed formulations was inversely proportional to the osmotic pressure of the release media, confirming osmotic pumping to be the major mechanism of drug release. Results of SEM studies confirmed the formation of pores in the membranes after coming into contact with the aqueous environment.

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