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Formulation and Evaluation of Osmotic Pump Delivery of Oxybutynin

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Abstract: 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. 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 Harmonization (ICH) guidelines and formulations were stable after a 3-month study.
Keywords: Controlled release drug delivery system (CDDS), osmotic system, oxybutynin, osmogent.

Introduction

OXB is a tertiary amine ester, [4-(diethylamino)-2-butynyl (±)-_ phenylcyclohexane-glycolate hydrochloride] indicated for relief of symptoms associated with uninhibited and reflex neurogenic bladder called urinary incontinence (UI) [1], which is a prevalent and costly condition that affects approximately 38% of older community-dwelling women [2,3]. This compound is a monoprotic base with p*K*a value of 8.04 and has a solubility of 0.012 mg/ml for free base at 37°C[4].OXBand/or its formulation(s) are official in USP, EP and BP. Being the drug of first choice in treating UI, OXB has been studied extensively for its pharmacodynamic properties[5,6]and pharmacokinetic parameters [7–9].Oral controlled release (CR) systems continue to be the most popular amongst all the drug delivery systems.[10] 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. The release rate from these types of systems is dependent on the coating thickness, level of leach able 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[11].

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 was 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), 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).

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, and 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[13, 14].

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 desiccators 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[15, 16, 17].

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. 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. 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

Drug-Excipient Interaction Studies: 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.

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.

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. The pull points at 60-minute intervals, beginning from the first 60-minutes up to 1 point above 85% released was 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)

Performance Evaluation of Optimized Formulation

Scanning Electron Microscopy: Cellulose acetate (CA) membranes of optimized formulation, obtained before and after dissolution were studied by SEM. Membranes obtained before dissolution clearly showed nonporous region. After 24-hour dissolution, the membrane clearly showed pores in range of 1 to 15 µm, 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.

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 that there is no significant difference in the release profile, demonstrating that the developed formulation shows pH-independent release.

Effect of Agitation Intensity: The release profile of oxybutynin from the optimized formulation was independent of the agitational intensity of the release media. 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.

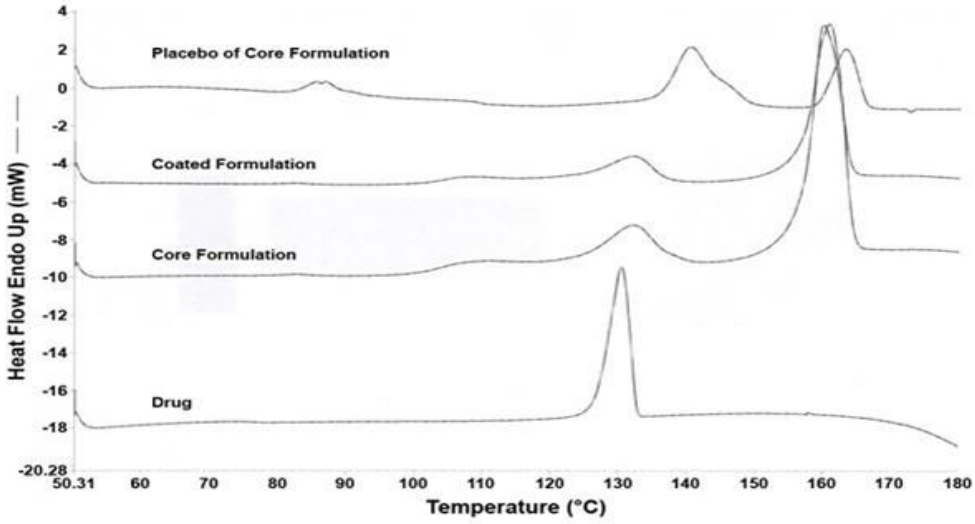
Effect of Osmotic Pressure: The drug release rate decreased with increase in osmotic pressure in the media; however, the lag time was prolonged. The drug release profiles with varying osmotic pressure are evident that the drug release from the formulation decreased as the osmotic pressure of the media increased. This finding confirms that the mechanism of drug release is by the osmotic pressure.

Conclusion

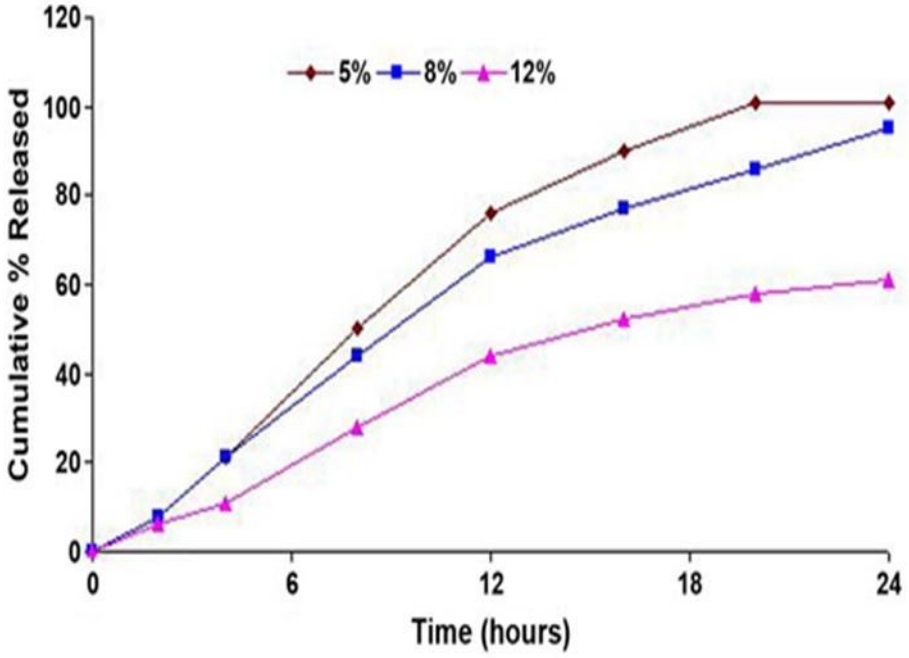
A porous osmotic pump–based drug delivery system can be designed for controlled release of highly water-soluble drug oxybutynin. It is evident from the results that the rate of drug release can be controlled through osmotic pressure of the core, level of pore former, and membrane weight with release 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.

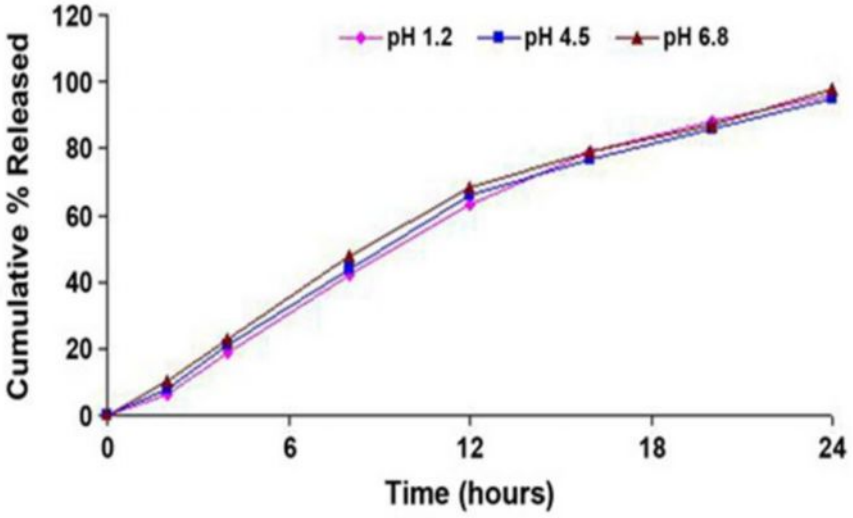
Composition of Core Oxybutynin Tablets: 1

Ingredients (mg/tablet)	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

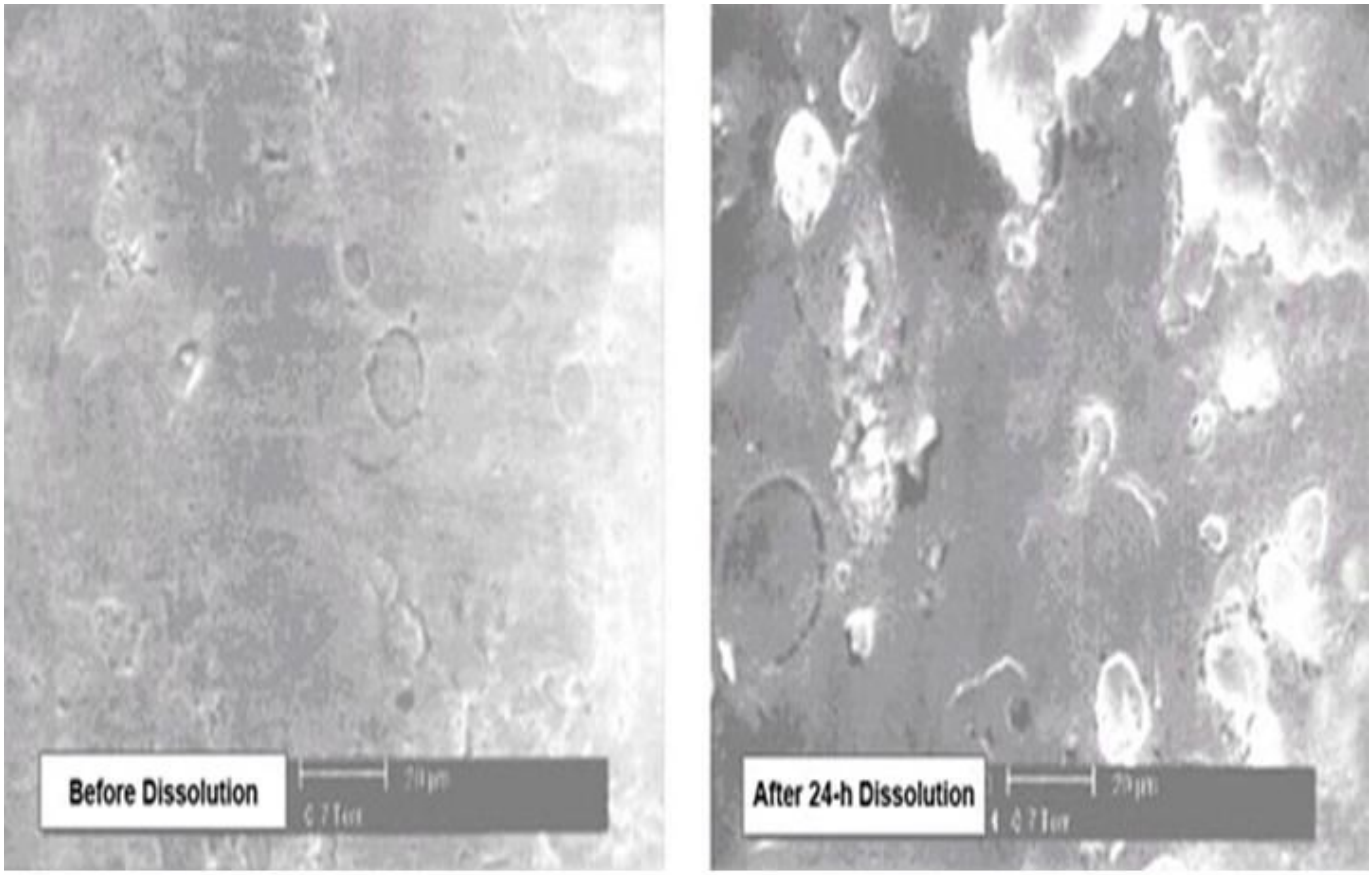


DSC Studies fig.

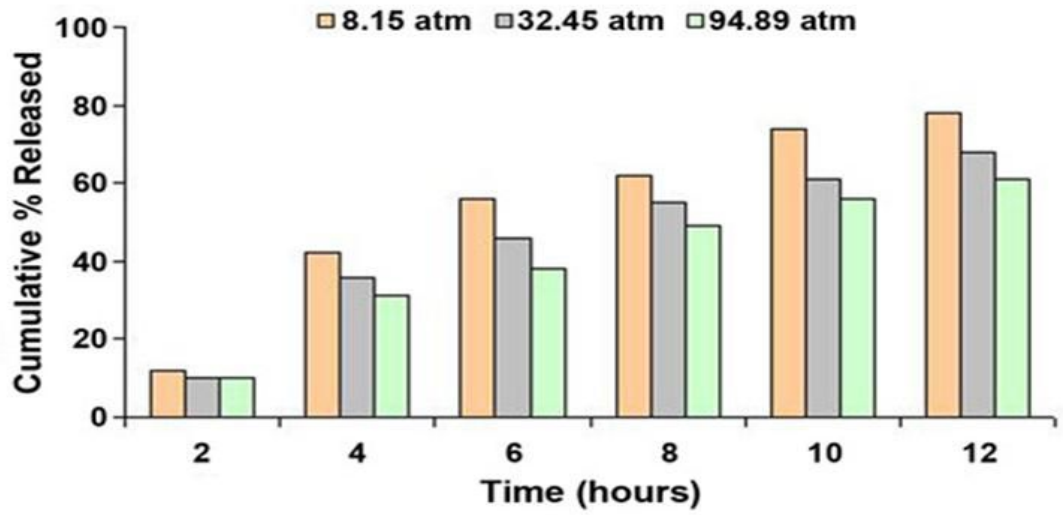




%CDR at different pH



Pore size before and after 24 hrs of dissolution



%CDR at various atmospheric pressure

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