RESEARCH ARTICLE

Formulation development and evaluation of controlled porosity osmotic pump delivery system for oral delivery of atenolol

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In the present study, we developed and evaluated the controlled porosity osmotic pump (CPOP) based drug delivery system of sparingly water soluble drug atenolol (ATL). We selected target release profile and optimized different variables to help us achieve this. Formulation variables, such as, the levels of solubility enhancer (0-15% w/w of drug), ratio of the drug to the osmogents, coat thickness of the semipermeable membrane (SPM) and level of pore former (0-20% w/w of polymer) were found to effect the drug release from the developed formulations. Cellulose acetate (CA 398-10) was used as the semipermeable membrane containing polyethylene glycol 400 as the Cplasticizer. ATL release was directly proportional to the level of the solubility enhancer, osmotic pressure generated by osmotic agent and level of pore former; however, was inversely proportional to the coat thickness of SPM. Drug release from developed formulations was independent of the pH and agitation intensities of release media. Burst strength of the exhausted shells decreased with increase in the level of pore former. The optimized formulations were subjected to stability studies as per International Conference on Harmonisation (ICH) guidelines, and formulations were found to be stable after 3 months study. Steady-state plasma levels of drug were predicted by the method of superposition.

Key words: *Atenolol, controlled porosity osmotic pump, osmogents, semipermeable membrane*

INTRODUCTION

Oral ingestion is one of the oldest and most extensively used routes of drug administration. It is also a convenient mean of effectively achieving both the local and systemic effects. Until recently, the drugs were almost always administered orally in conventional dosages. In the past few years, pharmaceutical research has developed innovative methods for drug delivery via the oral route.[1-3] Conventional preparation is usually in the form of two or three daily doses, which can lead to large fluctuations in the drug plasma concentration and cause side effects on the human body. Ideal oral drug delivery systems are those that progressively deliver a measurable, reproducible amount of drug over a prolonged period. Delivery systems capable of this are controlled-release dosage forms, which attempt to provide drug for absorption at a zero-order rate. Drug delivery at a zero-order rate provides a uniform concentration of drug for absorption and allows for maintenance of therapeutic plasma concentrations within a therapeutic window to avoid side effects and/or reduced frequency of administration. Despite these advantages, drug release from oral controlled-release dosage forms may be affected by pH, gastrointestinal tract (GIT) motility, and the presence of food.[4] One method with the potential to overcome these disadvantages is the osmotic drug delivery system.

Osmotic pumps are controlled drug delivery devices based on the principle of osmosis. Wide spectrums of osmotic devices are in exifstence. Amongst them, the osmotic pumps are unique, dynamic and widely employed in clinical practice.[5,6] Osmotic pumps offer many advantages, such as, (i) Easy to formulate and simple in operation, (ii) improve patient compliance by

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reducing dosing frequency (iii) provide good *in vitro in vivo* correlation[7] (iv) and, their industrial adaptability vis-a- vis production scale up is easy.[5,7] These drug delivery devices also prevent sudden increase and decrease in the plasma concentration of the drugs that may produce side effects or lower a drug's effectiveness, respectively.[8]

The first osmotic pump for delivery of active ingredients was invented by Rose Nelson in the 1950s.[9] The first commercial osmotic device was introduced by Theeuwes in the 1970s and was known as the elementary osmotic pump (EOP).[10] The EOP was in the form of a core tablet coated by a semipermeable membrane with a micro-orifice drilled on the surface. The EOP was very simple in preparation and could deliver water-soluble drugs at an approximately constant rate up to 24 hours. However, it was not feasible for the delivery of low solubility drugs and for the drugs that dissolved insufficiently and settled in the bottom of the tablet. Therefore, research was done in the fields of enhancing the solubility of the drugs,[11,12] and modifying the performance of the semipermeable the membrane;[13,14] however, these methods again were applicable only for a few drugs. One attempt in improving the delivery of the low solubility drugs was the development of controlled porosity solubility modulated osmotic pump. In majority of the cases, osmotic systems have a pre-formed passageway in the membrane from where the drug release takes place. Oral osmotic systems in which the delivery passage way is formed *in situ* are described in US patent no. 5,736,159.[15] Controlled porosity osmotic pumps (CPOP) contain water-soluble additives in the coating membrane, which after coming in contact with water, dissolve, resulting in an *in situ* formation of a microporous membrane. The resulting membrane is substantially permeable to both water and dissolved solutes, and the mechanism of drug release from these systems is found to be primarily osmotic, with simple diffusion playing a minor role.[16-18] Controlled porosity solubility modulated osmotic pumps for delivery of drugs having low water solubility are described in US patent nos. 4,946,686 and 4,994,273.[19,20] In the examples, tablet cores of two different drugs, namely, simvastatin and lovastatin, along with the solubility modulating agents were prepared and coated with a microporous membrane. The release of drug from the systems was controlled for an extended period of 4–24 hours.

Atenolol, also known as 4-[2-hydroxy-3-[(1-methylethyl) amino] propoxy] benzeneacetamide [Figure 1], is a cardio selective β 1-blocking agent, and can effectively reduce systolic and diastolic blood pressures, and it is widely used alone or in combination to treat hypertension.[21] Atenolol is slightly soluble in water, as reported in the Italian Pharmacopoeia,[22] and is characterized by a low oral bioavailability.[23] Atenolol is a sparingly soluble drug (27 mg/ml at 37 °C). Some methods had been attempted to improve its solubility. Ficarra *et al.*[24] prepared β-cyclodextrin inclusion complex. However, it was proved that atenolol solubility could not be significantly enhanced in this method. Moneghini *et al.*[25] prepared an

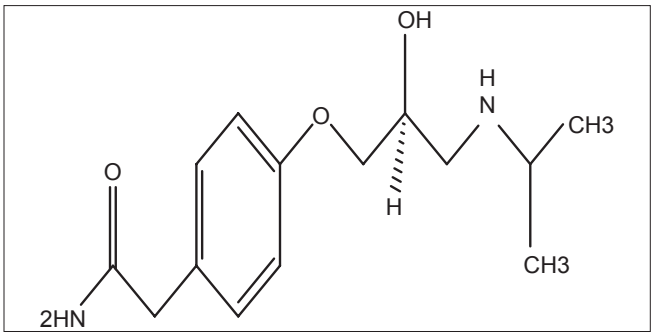

Figure 1: Atenolol

atenolol solid dispersion to improve the solubility. Although this method slightly improved the solubility of atenolol, large amounts of carrier were consumed. In addition, the solid dispersion method had some problems, such as the difficulty of scale-up, the physical stability of dispersion, and the reproducibility of physicochemical properties,[26] all which limited its commercial application. For some alkaline drugs, it was feasible to convert them into salt by reacting them with acid. Ayer and Theeuwes[27] used citric acid, maleic acid, malic acid and succinic acid as solubility promoters, and to increase the solubility of haloperidol substantially. Atenolol is an alkaline drug with an imide group. Appropriate solubility in tartaric acid made it a suitable candidate for modulating solubility of alkaline drugs.

The objective of the present study was to develop controlled porosity-based osmotically controlled release tablets of Atenolol. Tartaric acid was used as solubility modifier. Sodium chloride and Mannitol were used as osmogents. The tablets were coated with cellulose acetate (CA 398-10) as the semipermeable membrane, also containing sorbitol as a pore forming / channelling agent. The influences of tartaric acid, sodium chloride, level of pore former and membrane thickness on drug release profile were investigated. The influences of release media and agitation rate on *in vitro* release profile were also evaluated.

MATERIALS AND METHODS

Materials

Atenolol was obtained as a gift sample from Cadila Healthcare Ltd. Ahmedabad, India. Sodium chloride, tartaric acid, mannitol, and starch were purchased from Qualigens Fine Chemicals, Mumbai, India. PVP K30 and colloidal silicon dioxide were purchased from Signet chemical cooperation, Mumbai, India. Cellulose Acetate (CA 398-10) was obtained as a gift sample from Signet chemical cooperation Pvt. Ltd., Mumbai, India. PEG-400, PEG-4000, sorbitol, and glycerin were purchased from S.D. Fine Chem Limited, Mumbai, India. Isopropyl alcohol, Methanol and Acetone were purchased from Merck Limited, Mumbai, India. High performance liquid chromatography (HPLC) grade water was used for the HPLC analysis. All the other reagents used were of the analytical grade.

Methods

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. The DSC thermograms of pure drug, core tablets, placebo of core tablets, and coated tablets were recorded. The samples were separately sealed in aluminium cells and set in DSC (Universal V4.2E TA Instruments). The thermal analysis was performed in a nitrogen atmosphere at a heating rate of 10°C/minute over a temperature range of 50°C to 300°C.

Preparation of core tablets of atenolol

All formulations were prepared by the wet granulation method. All raw materials were sifted through 60 mesh. Atenolol powder was mixed with tartaric acid, sodium chloride, mannitol and starch in a mixer granulator for 10 minutes. The above mixture was passed through 30 mesh sieve. The dry blend was granulated with PVP K-30, and dissolved in Isopropyl Alcohol (IPA). The wet blend was granulated and dried at 40-50°C and sized through 20 mesh. Colloidal silicon dioxide was added to this mixture, and granules were lubricated with magnesium stearate for 10 more minutes. The resultant granules were then compressed into core tablets on 8 station single rotary compression machine (KMP-8, Cadmach Engg., Ahmedabad, India) with 8 mm round standard concave punches. The weight of each tablet was maintained within the range of 200 ± 5 mg and the drug loading was 50 mg/tablet. The composition of tablets is shown in Table 1.

Coating

Core tablets of ATL were coated in a conventional laboratory coating pan (Sehgal Industries Ltd., New Delhi) fitted with three baffles placed at angle of 120° each. The composition of coating solutions used for coating of core tablets is given in Table 2. Various components of coating solution were added to the solvent mixture in sequential manner. Coating solution was prepared by dissolving accurately weighed quantities of polymer, pore formers and plasticizer in the solvent (ethanol and acetone 1:9 mixture) using a stirrer. The component added first was allowed to dissolve before next component was added. Coating process was done on a batch of 250 tablets. Pan speed was set at 22 revolutions per minute (rpm) and inlet hot air temperature was set at 45°C. The manual coating procedure based on intermittent spraying and coating was used with a spray rate of 2ml/minute followed by 4 ml/minute. Coat weight and thickness were controlled by the volume of coating solution consumed in coating process.[28] After attaining the desired coat thickness, the tablets were dried in an oven at 60°C for 3 to 4 hours, followed by drying at room temperature for 8 to 10 hours. The prepared osmotic pump tablets were kept in a desiccator for future experiments.

Table 1: Composition of core atenolol tablets in the study

Ingredients (mg/tablet)	Formulation code				
	I	II	III	IV	V
Atenolol	50	50	50	50	50
Tartaric acid	2.5	5.0	7.5	7.5	7.5
Sodium chloride	15	15	15	20	25
Mannitol	50	50	50	50	50
Starch	70	67.5	65	60	55
Polyvinyl pyrrolidone K-30	10	10	10	10	10
Magnesium stearate	1.5	1.5	1.5	1.5	1.5
Colloidal silicon dioxide	1	1	1	1	1
Total	200	200	200	200	200

Evaluation of developed formulation

Evaluation of core and coated tablets

The core and coated tablets were evaluated for weight variation. Thickness and diameter of core and coated tablets were measured using screw gauze (Campbell Electronics Mumbai, India). Hardness of randomly selected tablets was tested using hardness tester (Monsanto hardness tester, Campbell Electronics Mumbai, India). Friability of core tablets was tested on the Electrolab friability tester (Electrolab, Mumbai, India) using 20 accurately weighed tablets.

Drug content uniformity

Accurately weighed 20 tablets (of all batches) were dissolved in 500 ml of distilled water. The samples were sonicated for 30 minutes and filtered through a 0.45µm nylon membrane filter. The filtered samples, after appropriate dilution were analyzed at 225 nm using ultraviolet (UV) Visible spectrophotometer (Shimadzu, 1601 and 1800, Japan).

In vitro drug release study

The developed formulations (n=3) of ATL were subjected to release studies using USP dissolution apparatus type I (Electrolab, TDT 06T, Mumbai, India) at 75 rpm. Dissolution media used was simulated intestinal fluid (SIF without enzymes, pH 6.8, 900ml) maintained at 37±0.5°C. The samples (5 ml) were withdrawn at different time intervals

Table 2: Composition of coating solutions in the study

Ingredients†	Coating code			
	A	B	C	D
Cellulose Acetate (gm)	3.4 gm	3.1 gm	2.8 gm	2.6 gm
PEG-400 (gm)	0.6 gm	0.6 gm	0.6 gm	0.6 gm
Sorbitol (gm)	–	0.3 gm	0.6 gm	0.8 gm
Ethanol (ml)	10 ml	10 ml	10 ml	10 ml
Acetone (ml)	90 ml	90 ml	90 ml	90 ml

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

and replaced with equivalent prewarmed (37± 0.5°C) volume of fresh medium. The withdrawn samples, after filtration through 0.45 µm nylon membrane filters, were analyzed using UV/Visible spectrophotometer at 225 nm. After analyzing the drug content in the dissolution samples, correction was made for the volume replacement and a graph of cumulative percentage of drug release versus the time was plotted.

High-performance liquid chromatography analysis

Chromatographic separation of atenolol was performed on a Shimadzu SDP-10 HPLC system using Kromasil C_{18} column (30 cm × 4.0 mm × 5µm particle size; Shimadzu, Kyoto, Japan). Mobile phase used was filtered mixture of buffer solution (1.1 gm of sodium 1-heptanesulfonatea and 0.71 gm of anhydrous disodium hydrogen phosphate was dissolved in 700 ml HPLC water and 2.0 ml of dibutylamine was added) and methanol prepared in the ratio of 70:30, with pH 3.5. Temperature of the column was maintained at 30°C. Injected volume was 20 µl and standard solution and dissolution samples were analyzed at 226 nm using a UV detector.

Statistical analysis

Experimental results were expressed as mean ± Standard Deviation (S.D.) values. Release profiles of various batches were compared using model independent pair wise approach, which included the calculation of 'difference factor' f_1 and 'similarity factor' f_2. The two release profiles were considered to be similar if f_1 value was lower than 15 (between 0 to15), and f_2 value was more than 50 (between 50 to100). Release profiles were also compared using mean dissolution time (MDT) which was calculated using following equation:[29]

$$MDT = \frac{\sum_{j=1}^{n} \hat{t}_j \Delta Mj}{\sum_{j=1}^{n} \Delta Mj} \quad (1)$$

where, j is the sample number, n is the number of dissolution sample times, $\hat{t}_j$ is the time at midpoint between t_j and $t_{(j=1)}$, and ΔMj is the additional amount of drug dissolve between t_j and $t_{(j=1)}$. One way analysis of variance test (ANOVA) was performed to check whether there is significant difference among the different formulations. Difference was considered statistically significant at $P<0.05$. In this study, mean dissolution time for 50% drug release ($MDT_{50\%}$) was used for comparison of release profiles from different batches.

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 (JSM-6390 LV SEM, Jeol Japan). Membranes were dried at 45°C for 12 hours and stored between sheets of wax paper in 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 were simulated gastric fluid (SGF) (pH 1.2), acetate buffer (pH 4.5), and simulated intestinal fluid (pH 6.8). Samples were analyzed by UV/Visible spectrophotometer.

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 75, 100, and 150 rpm was used. Degassed SIF (without enzymes) was used as dissolution media (pre-equilibrated to 37°C ± 1°C). Samples were analyzed spectrophotometrically after filtration through 0.45 µm nylon membrane filters.

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.[30] To increase the osmotic pressure of the release media (pre-equilibrated to 37°C ± 1°C), sodium chloride (osmotically effective solute) was added in SIF (without enzymes). Release studies were performed in 900 mL of media using USP-I dissolution apparatus (75 rpm). Samples were analyzed spectrophotometrically after filtration through 0.45 µm nylon membrane filters.

Burst strength

Burst strength of the exhausted shells, after 8 hour of dissolution, was determined to assure that the tablets would maintain their integrity in the GIT. Burst strength was determined as the force required to break/rupture the shells after dissolution studies. The texture analyzer (TAX T2i, Stable Micro systems, England) with a 5 kg load cell and 25 mm aluminium cylindrical probe was utilized for this purpose. Test speed of 0.8 mm/sec was selected and the distance moved was set at 2 mm.

Kinetics and mechanism of drug release

Dissolution data of the optimized formulation was fitted to various mathematical models (zero-order, first-order, and Higuchi) in order to describe the kinetics of drug release. Smallest value of sum of squared residuals (SSR) and best goodness-of-fit test (R^2) were taken as criteria for selecting the most appropriate model.

Accelerated stability studies

Optimized formulations of ATL were packed in blisters (10 tablets in one strip) of 0.25mm amber Polyvinyl chloride (PVC) with 0.05mm lidding aluminum foil. The packed formulations were stored in ICH certified stability chambers (NSW-175, Narang Scientific work, New Delhi, India) maintained at 40°C and 75% relative humidity (RH) for 3 months. The samples were withdrawn periodically and evaluated for drug

content, hardness, burst strength and release studies. The withdrawn samples, after filtration through 0.45 µm nylon membrane filters, were analyzed using the HPLC method

Prediction of in vivo performance

Using the known pharmacokinetic properties of ATL [Table 3] and various drug release parameters (R^0 and t_{Del}), which were calculated from *in vitro* release data, steady-state plasma levels of drug were predicted by the method of superposition.[31] It was assumed that after the administration of a test dose of formulation, the drug would be released at a release rate (R^0) for a period of time (t_{Del}), shorter than the selected dosing interval (τ). Time of delivery, t_{Del}, is the time taken to deliver 90% of the total drug within a selected dosing interval (τ = 12 hr). The predicted plasma levels of developed CPOP were compared with those of desired level by calculating the percent-predicted error (% PD) in C_{max} and AUC $_{0\text{-}\tau}$. Bioequivalence was anticipated if the average % PD was less than 15% for C_{max} and AUC $_{0\text{-}\tau}$.[32,33] The % PD was calculated using the following equation:

$$\% \text{ PD} = \frac{\text{Predicted value} - \text{Reference value}}{\text{Reference value}} \times 100 \qquad (2)$$

RESULTS AND DISCUSSION

The dosage form developed was designed as a tablet core coated with a rate-controlling membrane. Tablet core consisted 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 one plasticizer capable of improving film forming properties of the polymers. The semipermeable membrane-forming polymer is permeable to aqueous fluids; however, 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. Polyethylene glycol 400 (PEG-400) was used as plasticizer.

Table 3: Various pharmacokinetic parameters of atenolol

Pharmacokinetic parameters	Value	Reference (s)
Bioavailability (*f*)	56%	[35]
Elimination half life ($t_{1/2}$)	6 h	[34]
Terminal deposition rate constant (K_{el})	0.11 h^{-1}	[36]
Apparent volume of distribution (V_d)	0.95 l/kg	[34]
Maximum safe conc. (C_{max})	1 µg/ml	[34]
Minimum effective conc. (C_{min})	0.1 µg/ml	[34]
Clearance total (Cl_T)	2.0 ml/min/kg	[34]

Drug-excipient interaction studies

Figure 2 depicts the DSC thermograms of atenolol and the formulation. Some broadening of peaks leading to changes in area, onset of peak, and changes in peak temperature occur simply due to mixing of the components without indicating any significant interaction. If all the thermal features more or less remain the same, compatibility can be expressed. 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 was used in the present formulation.

Desired release profile

The purpose of this study was to select a release profile that could be used as a target for developed CPOP of ATL. The therapeutic range of ATL is between 100-1000 ng/ml,[34] and therefore, the desired maximum steady-state concentration, *C*ss max desired of ATL for 50 mg dose was selected as 400 ng/ml. In order to provide good therapeutic effect ATL plasma level should not fall below 150 ng/ml. Keeping this point in consideration desired minimum steady state concentration was kept at 250 ng/ml. Taking different pharmacokinetic parameters of ATL into consideration [Table 3] a zero-order based delivery strategy was designed to produce the desired plasma levels of ATL.[35] Series of simulations (using Sigma plot-10) were performed and it was found that a delivery rate of 4.46 mg/hour for a period of 8.0 hours was found to meet the above requirements. The simulated plasma concentration- time profile using this approach and the corresponding *in vitro* drug release profile are shown in Figure 3. Since, this delivery pattern was expected to maintain plasma levels of ATL within desired range, it was selected as target release profile.

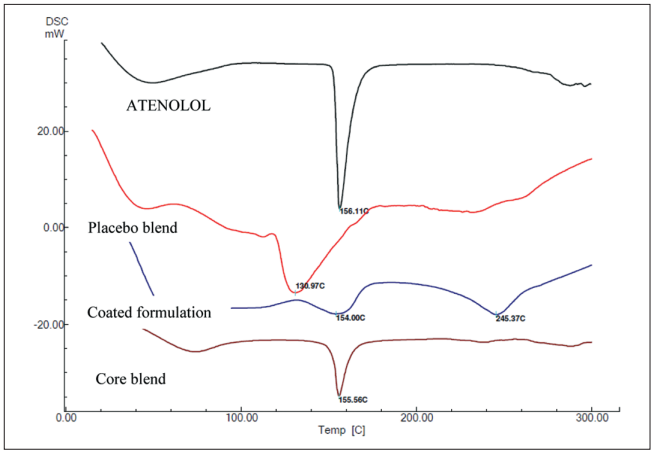

Figure 2: Differential Scanning Calorimetry thermograms of drug, placebo blend, coated formulation and core blend of atenolol

Drug content and physical evaluation

The content of drug as seen in various formulations varied between 98.6% and 101.5% (mean 100.05%). Core tablet weights varied between 195 mg and 207 mg (mean 200 mg and thickness of the core tablets was found to be in the range of 3.79 and 3.84 mm (mean 3.80 mm). The hardness of core tablets was found to be between 5.1 and 7.2 kg cm^2 (mean 6.2 kg cm^2); while the friability of prepared core tablets ranged between 0.12% and 0.26% (mean 0.17%). Thus, all the physical parameters of the compressed matrices were practically within limits.

Concentration of atenolol in tartaric acid aqueous Solutions

The concentration of atenolol in various concentrations of tartaric acid aqueous solution is shown in Figure 4. The solubility of atenolol (37°C) in deionized water was 21 mg/ml. It was clear that the concentration of atenolol in tartaric acid aqueous solution increased with the increase of original tartaric acid concentration. A more than 10-fold increase in atenolol concentration was achieved at original tartaric acid concentration of 100 mg/ml. This could be explained by its molecular structure. Atenolol had an imide group exhibiting alkalinity. When atenolol came in contact with the tartaric acid aqueous solution, it reacted and changed to salt. As a consequence, atenolol became freely soluble, and the concentration was increased markedly. It could be concluded that this method should be much more suited for the solubilisation of atenolol and the preparation of CPOP tablet compared with technologies of solid dispersion and cyclodextrin inclusion.

Effect of ratio of drug to osmogent and tartaric acid

To optimize the amount and type 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 (ATL) to osmogents (drug: sodium chloride: mannitol) studied were 1:0.3:1, 1:0.4:1, and 1:0.5:1 (formulation code III, IV and V respectively). The ratios of drug (ATL) to tartaric acid (drug: tartaric acid) studied were 1:0.05, 1:0.1, and 1:0.3 (formulation code I, II and III respectively). All the core formulations were coated with similar coating composition, C containing 15% w/w (of CA) of sorbitol. Release profile from these formulations is shown in Figure 5. It is clear from Figure 5 that osmogent and tartaric acid enhances the release of drug and thus had a direct effect on drug release. The drug release after 8 hours for formulation code I, II, III, IV, and V was 27.36, 39.37, 51.29, 69.49, and 71.52 % respectively. From the comparative release profiles it was found that release of ATL from formulation code IV is more controlled with highest zero-order coefficient of determination value ($R^2 = 0.991$) than other batches. Hence, formulation IV was chosen for further experimental studies.

Effect of coat thickness

To study the effect of coat thickness of SPM on drug release, core formulation of batch IV was coated with coating composition C so as to give different coat thickness (50 µm, 150 µm, 200 µm). Release profiles of ATL from

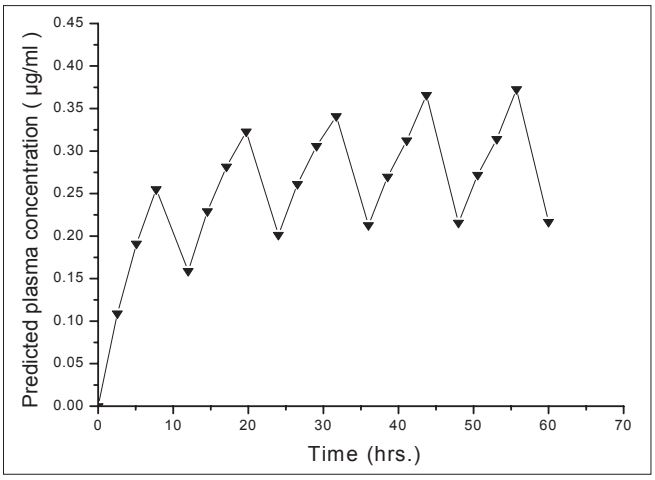

Figure 3: Predicted steady-state plasma levels of ATL using theoretically designed zero-order delivery approach

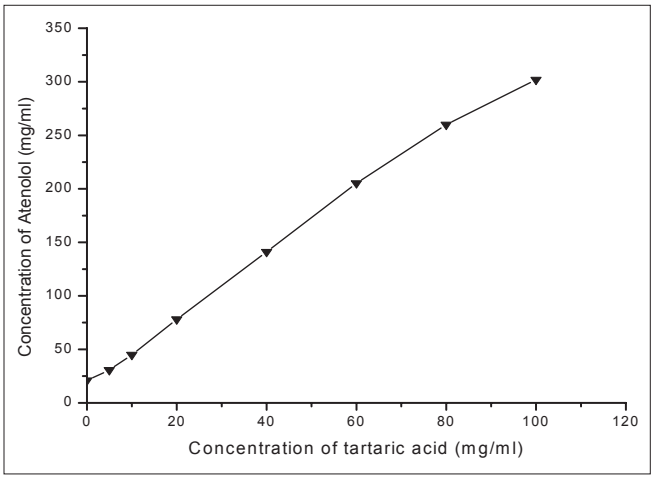

Figure 4: Concentration of atenolol in tartaric acid aqueous solution

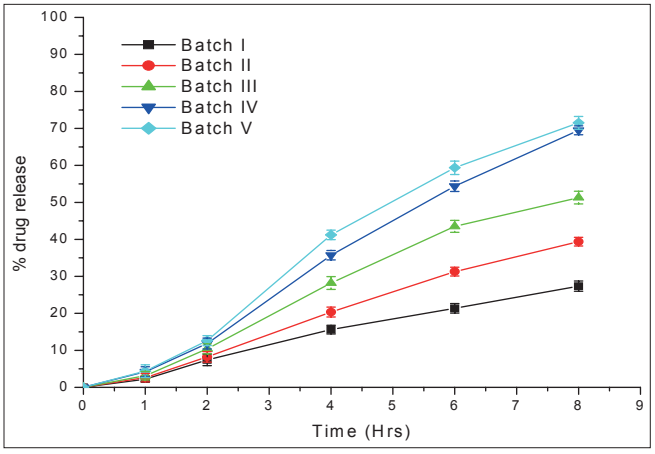

Figure 5: Effect of osmogent and tartaric acid on *in vitro* percent release of ATL CPOP tablets. Bars represent ± Standard Deviation (*n* = 3)

these formulations are shown in Figure 6. Drug release was decreased with increase in coat thickness of SPM. The increase of SPM thickness resulted in an increased resistance of SPM to water imbibition, causing a rate of decreased water imbibition, consequently causing a decrease in rate of liquefaction/ dissolution of drug in core, and ultimately resulting in a decline in the ATL release. $MDT_{50\%}$ value between different batches (2 hour 2 minutes., 3 hour 6 minutes. and 3 hour 44 minutes for formulation with coat thickness of 50 µm, 150 µm, 200 µm, respectively) w found to be statistically significant ($P < 0.05$). No bursting of the systems was observed during the dissolution run in any of the formulations.

Effect of pore forming level

To study the effect of pore forming agent, core formulations of atenolol of batch IV were coated with varying coating compositions of pore forming agent containing 0%, 7.5%, 15%, and 20% wt/wt (of total solids) of sorbitol. Release profile from these formulations is shown in Figure 7. 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. Exhausted tablets (after 8 hours of dissolution studies) were evaluated for burst strength to assure that the tablets maintain their integrity in GIT and do not lead to dose dumping. Figure 8 shows the dependency of burst strength of the exhausted shells on the level of pore former. 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. Since, satisfactory drug release and adequate burst strength were obtained in case of formulations with 15% pore level, this was selected as the "optimized" formulation and used for further evaluation.

Performance evaluation of optimized formulation

Scanning electron microscopy

Cellulose acetate (CA) membranes of optimized formulation, IV (coat C), obtained before and after dissolution were studied by SEM. Membranes obtained before dissolution clearly showed nonporous region. After 8 hour dissolution, the membrane clearly showed pores in range of 1 to 10 µm [Figure 9] owing to dissolution of sorbitol. The leaching of sorbitol from the membrane leads to formation of pores, and thus releasing the drug.

Effect of pH

The optimized formulation, IV (coat C), was subjected to *in vitro* release studies in buffers with different pH. As can be seen from Figure 10, there is no significant difference in the release profile, demonstrating that the developed formulation shows a pH-independent release.

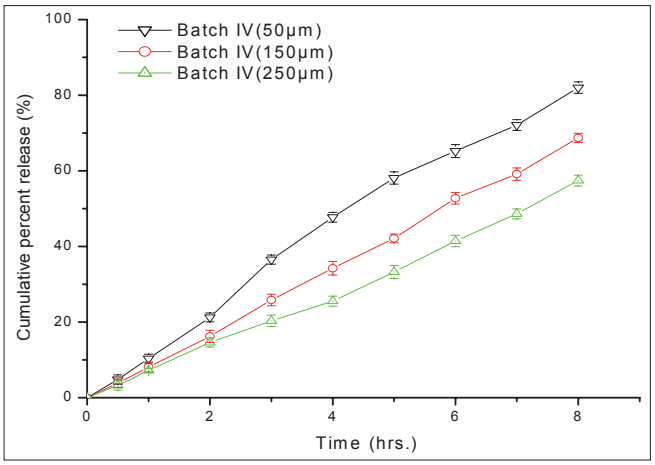

Figure 6: *In vitro* release profile of ATL CPOP tablets showing the effect of coat thickness. Bars represent ± Standard Deviation ($n = 3$)

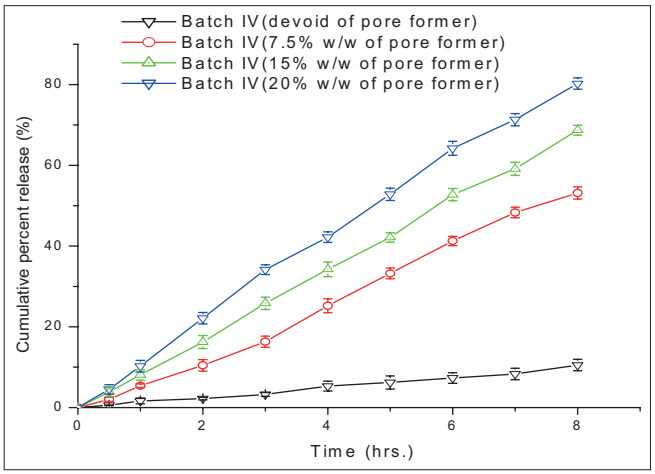

Figure 7: *In vitro* release profile of ATL CPOP tablets showing the effect of concentration of pore former. Bars represent ± Standard Deviation ($n = 3$)

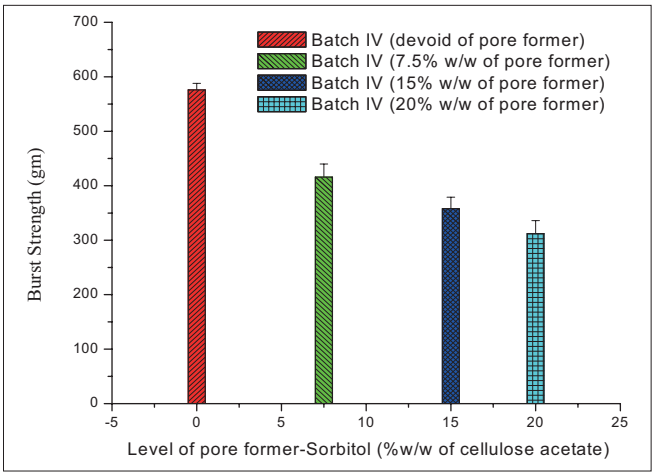

Figure 8: Bar diagram showing the effect of concentration of pore former on burst strength of SPM membrane. Bars represent ± Standard Deviation ($n = 3$)

Effect of agitation intensity

The release profile of atenolol from the optimized

formulation IV (coat C) was independent of the agitational intensity of the release media [Figure 11]. The difference factor (f_1) and similarity factor (f_2) values were found to be 3.03 and 91.33 (for 75 and 100 rpm), 2.74 and 93.63 (for 100 and 150 rpm), and 4.11 and 90.73 (for 75 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 effect of osmotic pressure on the optimized formulation was studied in media of different osmotic pressures, and the dissolution parameters with varying osmotic pressures are depicted in Table 4. 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 12, 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 and mechanism of drug release

Dissolution data of the optimized formulation was assessed with various mathematical models (zero-order, first-order, and Higuchi) in order to describe the kinetics of drug release. Smallest value of sum of squared residuals (SSR), best goodness-of-fit test (R^2) and higher correlation coefficient were taken as criteria for selecting the most appropriate model. Drug release from optimized formulations (batch- IV, coat C) fitted well into zero-order kinetics [Table 5] confirming that the release from formulation is close to the desired release.

Table 4: Dissolution parameters of optimized formulation with varying osmotic pressure in the study

Osmotic pressure atm.)	Lag time (hrs.)	Average release rate (cumulative percent)	Average release rate (mg/hr)
15	2.967±0.021	7.802±0.361	4.015±0.122
45	3.464±0.014	6.924±0.327	3.551± 0.157
60	5.207±0.016	6.421±0.882	3.158±0.241
90	6.341±0.011	5.735±0.692	2.853±0.116

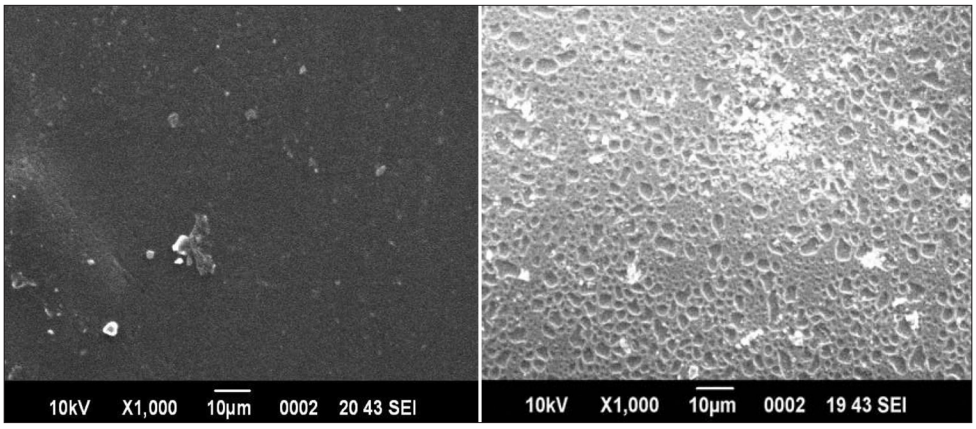

Figure 9: Scanning electron microphotographs of membrane structure of optimized formulation before and after dissolution studies

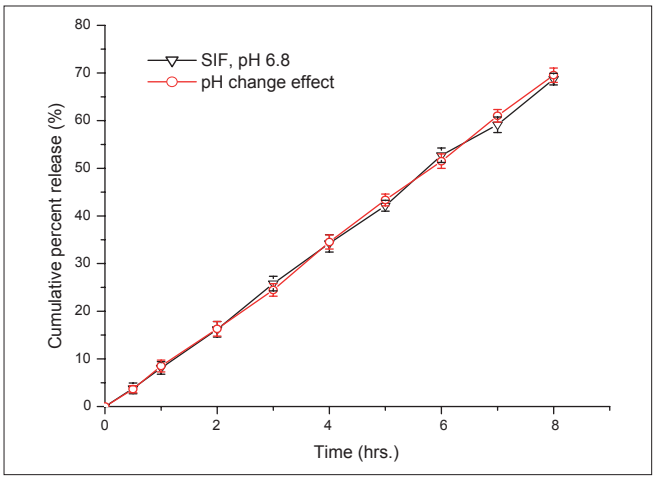

Figure 10: Release profiles showing the effect of pH on ATL release from optimized formulation. Bars represent ± Standard Deviation (n = 3)

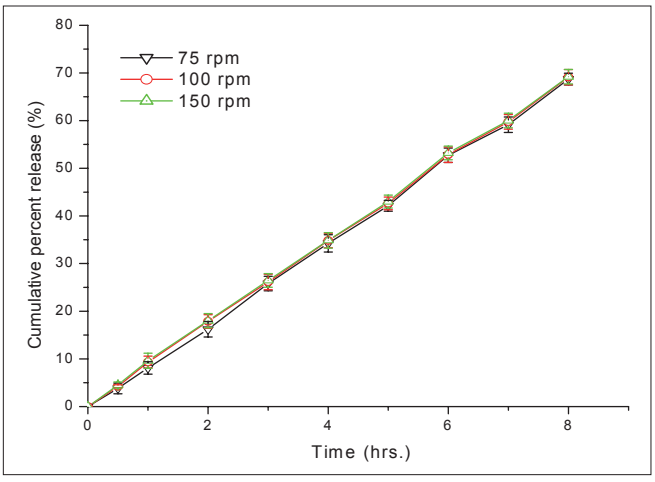

Figure 11: Release profiles showing the effect of agitation intensity on ATL release from optimized formulation. Bars represent ± Standard Deviation (n = 3)

Accelerated stability study

The stored formulations of batch-IV, coat C were found to be stable in terms of drug content and dissolution stability [Table 6]. In all the cases, the burst strength was higher than the reported values of mechanical destructive forces in the GIT, ensuring that the formulations remained intact in GIT without any incidence of dose dumping, even after storage.

In vivo prediction

Method of superposition was used to predict the steady state plasma levels of ATL after administration of a test dose (50 mg) of optimized formulation (Batch-IV C). Since osmotic pumps are reported to exhibit a significant *in vitro/in vivo* correlation, predicted data of steady-state plasma levels from drug release studies can be used for comparison with the desired plasma levels. The desired steady-state plasma levels of ATL were predicted from a theoretically designed zero order delivery system. Prediction of steady-state levels of ATL after administration of a test dose of optimized formulation showed that the plasma levels are between 250 ng/ml to 400 ng/ml. Figure 13 shows the predicted values of the steady-state plasma levels of the drug, after the administration of a test dose of Batch-IV C formulation, as compared to the desired steady state plasma levels. It is clearly evident from the figure that the predicted steady state plasma levels are very close to the desired levels. The predicted *C*ss max and AUC_{0-t} values after administration of optimized formulations of ATL, in comparison with the desired ones is listed in Table 7. The % PD of the steady-state parameters of the optimized formulations was calculated taking the data of the desired profile as the reference. The absolute % PD was found to be less than 15%, ensuring that the optimized formulations will produce plasma levels close to the desired ones. Thus, it can be concluded that the developed optimized formulation (batch-IV C) will produce plasma levels well within the therapeutic range. Since osmotic pumps are reported to exhibit a good *in vitro/in vivo* correlation, based on *in vivo* performance prediction, the developed formulations can be expected to perform similarly *in vivo*.

Table 5: Fitting drug release data of the optimized formulation (Batch-IV, Coat C) according to various mathematical models in the study

Models	R^2	r	Intercept (%)	k	SSR
Zero order	0.998	0.999	–0.559	4.328	4.217
First order	0.976	0.988	2.043	–0.0625	123.628
Higuchi model	0.973	0.986	–23.563	30.739	151.363

R^2: Goodness of fit; r: Correlation coefficient, SSR: Sum of squares of residuals, k: Release rate constant for respective models (k_0 in mg/h, k_1 in h^{-1} and k_h in % $h^{1/2}$ for zero-order, first order, and Higuchi rate equations respectively)

Table 6: Evaluation of batch IV, coat C formulation for 3 months of storage at 40°C and 75% Relative humidity (RH) in the study

Parameter	Initial	1 month	2 month	3 month
Drug content (%)	98.72± 1.04	98.34± 1.11	98.57± 1.21	98.11± 1.18
Hardness (kg/cm^2)	6	7	8	8
Burst strength (kg)	358±21	372±16	379±11	385±17
*f*1	–	2.6	2.9	3.1
*f*2	–	95.2	94.2	93.6
MDT 50% (hrs.)	3.102	3.074	3.063	3.011

Table 7: Predicted *In vivo* performance of the developed controlled porosity osmotic pump of atenolol in the study

Product	Predicted $C_{ss\ max}$ (ng/ml)	% PD	Predicted AUC_{0-t} (ng hr/ml)	% PD
Desired[a]	372.6	–	716	–
Batch IV coat C[b]	343.4	–7.83	704	–1.68

% PD= Percent predicted error. [a]Predicted from desired zero-order delivery profile (Dose = 50mg, R^0= 4.46mg/hr, and t_{Del} 7.73hr). [b]Predicted from drug release study (Dose = 50mg, R^0= 4.32mg/hr, and t_{Del} 8.00hr)

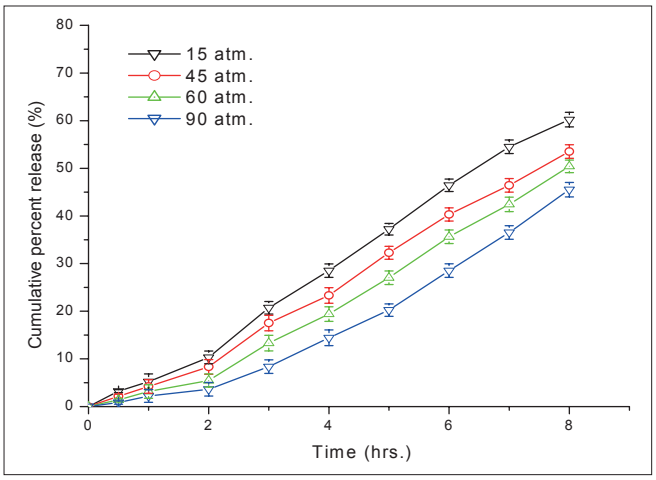

Figure 12: Profiles showing the effect of osmotic pressure of the release media on ATL release from optimized formulation. Bars represent ± Standard Deviation (*n* = 3)

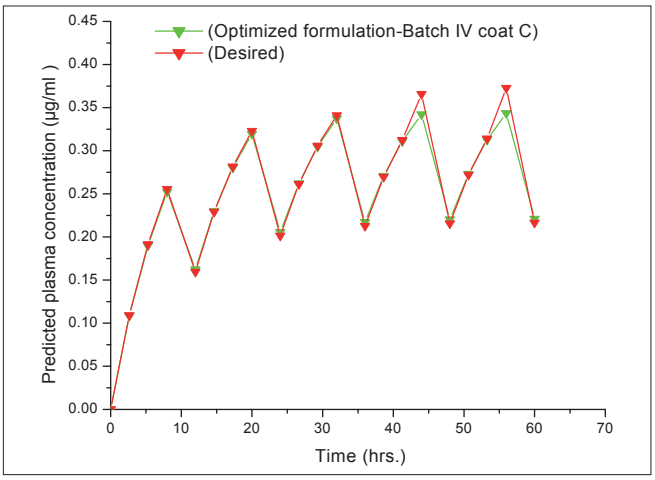

Figure 13: Predicted steady-state plasma levels of ATL following administration of test dose of optimized formulation (batch IV coat C) in completion with the desired profile

CONCLUSION

In the present study, CPOP of sparingly water soluble drug ATL was developed and evaluated. Target release profile was selected and different formulation variables were optimized to achieve the result. Drug release from the developed formulations was independent of pH and agitation intensity of the release media, assuring the release to be fairly independent of pH and hydrodynamic conditions of the absorption site. ATL release from developed CPOP was directly related to the level of osmogent and pore former; however, was inversely proportional to the level of coat thickness of SPM. Drug release data from ATL formulations fitted well into zero-order kinetics. From drug release studies, steady-state plasma levels were predicted using the method of superposition. The predicted steady-state plasma levels were within the desired range (250-400 ng/ml) to show a safe therapeutic effect. Since osmotic pumps are reported to exhibit a good *in vitro/in vivo* correlation, based on *in vivo* performance prediction, the developed formulations can be expected to perform similarly *in vivo*. Developed formulations were found to be stable during three months of storage at accelerated stability condition.

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