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Research Article

FABRICATION AND *IN VITRO* EVALUATION OF POROUS OSMOTIC PUMP BASED CONTROLLED DRUG DELIVERY OF METOPROLOL SUCCINATE

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ABSTRACT

An Osmotically controlled oral drug delivery system utilizes osmotic pressure for controlled delivery of active agents. It has gained wider acceptance due to drug release independent of pH and physiological condition of the GIT. Metoprolol Succinate, a highly soluble drug has been used as a model drug and attempt has been made to control the release of drug by two different approaches; one using an osmotic agent and a swelling agent. The core tablets were prepared by wet granulation technique and granules before compression were evaluated for micromeritic properties. The core tablets were coated with coating solution containing cellulose acetate, a pore former and a plasticizer to give good film properties. The effect of concentration of osmotic agent and swelling agent on *in vitro* release was studied and was found that drug release depend on both these factors. The formulation variables like amount of pore former, effect of pH, agitational intensity on *in vitro* release from optimized formulation was evaluated and was found that drug release directly depend on amount of pore former in the coating composition. The drug release was independent of pH and agitational intensity of the media. All the formulations showed more than 60% of drug release after 12 h and drug release from optimized formulation was found to follow zero order kinetics. The formulation was also found to be stable in terms of hardness, drug content and drug release after 3 months stability study.

Keywords: Osmotic pump, Controlled delivery, Metoprolol Succinate, Osmotic agent, Swelling agent.

INTRODUCTION

The treatment of acute diseases or chronic illnesses has been achieved by delivery of drugs to the patients for many years. These drug delivery systems include tablets, injectables, suspensions, creams, ointments, liquids and aerosols. Today these conventional drug delivery systems are widely used.[1] Conventional drug therapy requires periodic doses of therapeutic agents. These agents are formulated to produce maximum stability, activity and bioavailability. For most drugs, conventional methods of drug administration are effective, but some drugs are unstable or toxic and have narrow therapeutic ranges. Some drugs also possess solubility problems. In such cases, a method of continuous administration of therapeutic agent is desirable to maintain fixed plasma level.[2]

To overcome these problems, controlled drug delivery systems were introduced three decades ago. These delivery systems have a number of advantages over traditional systems such as improved efficiency, reduced toxicity, and improved patient convenience. The main goal of controlled drug delivery systems is to improve the effectiveness of drug therapies.

Controlled release (CR) drug delivery systems provide desired concentration of drug at the absorption site allowing maintenance of plasma concentrations within the therapeutic range and reducing the dosing frequency.

A number of design options are available to control or modulate the drug release from a dosage form. Majority of per oral CR dosage forms fall in the category of matrix, reservoir, or osmotic systems.

However, factors like pH, presence of food and other physiological factors may affect drug release from conventional CR systems (matrix and reservoir). Osmotic drug delivery is one of the most interesting and widely applicable. Osmotic drug delivery uses the osmotic pressure of drugs or other solutes (called *Osmotic agents*) for controlled delivery of drugs. Osmotic drug delivery has come a long way since Australian pharmacologists Rose and Nelson developed an implantable pump in 1955. This area of drug delivery has expanded into oral delivery and implants for humans and animals. Drug release from these systems is independent of pH and other physiological parameters to a large extent and it is possible to modulate the release characteristics by optimizing the properties of drug and system.[3, 4]

Hypertension is the most common cardiovascular disease & for this Metoprolol Succinate, a β_1-selective (cardioselective) adrenergic receptor blocking agent is used as an anti-hypertensive agent which is one of the most commonly prescribed drugs for the treatment of patients with hypertension. It is readily and completely absorbed from the GI tract but it is subject to considerable first pass metabolism, with a bioavailability of about 50%. Peak plasma concentrations vary widely and occur about 1.5 to 2 h after a single oral dose. It is moderately lipid soluble. Metoprolol is widely distributed; it crosses the blood brain barrier and placenta, and is distributed into breast milk. It is about 12% bound to plasma protein.

Metoprolol belongs to class - I of Biopharmaceutical Classification System (BCS). Metoprolol Succinate has a relatively short elimination half-life (3–4 h), thereby requiring two to four times daily dosing in large number of patients, which often leads to non-compliance. When dose is missing it may causes nocturnal attack, so attention was made to develop the controlled release tablets of Metoprolol Succinate by utilizing Osmotic agent and swelling polymer.[5]

Thus, there is a strong clinical need and market potential for a dosage form that will deliver Metoprolol Succinate in a controlled manner to a patient needing this therapy, thereby resulting in a better patient compliance.

The present study was aimed towards the development of controlled release formulations of Metoprolol Succinate based on osmotic technology because of its higher solubility and frequent dosing. Hence, in the present study an attempt has been made to control the release of Metoprolol Succinate by two different approaches i.e. one using osmotic agent and other by using swelling polymer. A semipermeable microporous membrane that regulates the drug release surrounds the system. The developed formulations were evaluated for physico-chemical parameters and effect of various formulation variables on in vitro drug release was studied i.e. effect of various concentrations of osmotic agent and swelling polymer and optimized formulation was further studied for effect of pH, effect of pore former and effect of agitational intensity.

MATERIALS AND METHODS

Materials

Metoprolol Succinate was obtained as a gift sample from The Madras Pharmaceuticals, Chennai. PVP K-30 was purchased from BASF Limited, India, Mannitol was purchased from S.D. Fine Chemicals,

Mumbai. India, Lactose was purchased from Himedia laboratories, Mumbai, Cellulose acetate was purchased from Signet chemicals, Mumbai, India, Sorbitol and Dibutyl Phthalate was purchased from Biodeal Laboratory Pvt. Ltd., India. All other solvents and reagents used were of analytical grade.

Formulation Development

Formulation of core tablets

Core tablets of Metoprolol Succinate were prepared by wet granulation and batch size was kept as 200 tablets. The composition of the core tablets were given in [Table No.1]. Metoprolol Succinate was mixed with mannitol, povidone K-30, lactose and microcrystalline cellulose and finally passed through 30 mesh screen. The blend was mixed for 10 min and the mixture was granulated with starch paste. The resulting wet mass was passed through 18 # sieve. The granules were dried at 60 °C in hot air oven for 30 min after which they were passed through 22 # sieve. These sized granules were then blended with magnesium stearate and talc for 10 min in a polybag and finally compressed into tablets having an average weight of 300 mg using a Rimek minipress-1 single stroke tablet punching machine fitted with a 9 mm round concave punches.[6]

Table 1: Formulation composition of osmotic pump tablets

Formulation Ingredients (mgs)	Formulation Code					
	F1	F2	F3	F4	F5	F6
Metoprolol Succinate	50	50	50	50	50	50
Mannitol	70	100	130	100	100	100
Povidone	10	10	10	20	30	40
Lactose	70	50	40	60	40	30
Microcrystalline Cellulose	97	87	67	67	77	77
Magnesium Stearate	2	2	2	2	2	2
Talc	1	1	1	1	1	1
Starch	qs	Qs	qs	qs	qs	qs
Purified Water	qs	Qs	qs	qs	qs	qs

Coating of core tablets

The core tablets of Metoprolol Succinate were coated with cellulose acetate in an automated perforated pan (Ganscoater, India). The compositions of the coating solution used for coating tablets were given in [Table No. 2]. All the tablets were coated with coating solution B i.e. 10% sorbitol. Various components of the coating solution were added to the solvent in a sequential manner. The component added first was allowed to dissolve before the next component was added. Core tablets of Metoprolol Succinate were placed in coating pan. The rotating speed of the pan was kept 15-18 rev/min. The coating was performed using spray gun at a spray rate of 3-5 ml/min. The atomization pressure was kept at 1 kg/cm^2 while outlet temperature was kept 40-45 °C. Coating was continued until desired weight gain (10%) was obtained and tablets were dried at 50 °C for 10 h before further evaluation.[7]

Table 2: Composition of the coating Solutions.

Ingredients	Coat Solution A	Coat Solution B	Coat Solution C
Cellulose Acetate (gms)	3.0	3.0	3.0
Sorbitol (ml)	0.23(7.5%)	0.3(10%)	0.38(12.5%)
Dibutyl phthalate (ml)	0.45(15%)	0.45(15%)	0.45(15%)
Acetone:Purified water	Up to 100ml	Up to 100ml	Up to 100ml

Compositions were given in terms of % W/W. Total solids in the coating compositions: 4.0%.

Evaluation of powder blend

Prior to the compression, Metoprolol Succinate powder blend were evaluated for their bulk and tapped density, USP method II on a tap density tester (ETD-1020, electrolab, India.) was used and from these values Carr's index and Hausner's ratio were calculated, while flow property of powder blend were accessed from the angle of repose.[8]

Drug analysis

Metoprolol Succinate was analyzed by ultraviolet (UV) spectrophotometric method at λmax 260 nm. Calibration curves were prepared in simulated gastric fluid (SGF pH 1.2) and simulated intestinal fluid (SIF pH 6.8) in the concentration range of 5–35 µg/ml (Shimadzu 1700 UV/visible double beam spectrophotometer). No enzymes were added to both SGF (pH 1.2) and SIF (pH 6.8). Correlation coefficients were found to be $r > 0.9950$ for all media and no interference of additives used in formulation was observed.[9]

Evaluation of developed formulation

The core and coated tablets were evaluated for weight variation by weighing 20 tablets on an electronic balance (OHAUS Corp. Pine, Brook, NJ, USA). Thickness of 3 tablets of each formulation was determined by using dial calliper (Mitutoyo, Japan). For Hardness, 10 tablets were randomly selected and tested using hardness tester (Campbell Electronics, Mumbai, India.). The friability of the core tablets was carried out on a friabilator (EF-2, electrolab, India.) for which 10 accurately weighed tablets were used. Content uniformity test was carried out on five tablets. The tablets were taken and powered. From the powder, an accurately weighed amount equivalent to 50 mg of Metoprolol Succinate was weighed and dissolved in distilled water. The solution was suitably diluted and dilute solution was then assayed for the drug content by measuring the absorbance at 260 nm using UV – Visible double beam spectrophotometer.

In vitro dissolution studies

The developed formulations of Metoprolol Succinate were subjected *in vitro* dissolution studies using USP – Type I dissolution apparatus (Electrolab, India) with a speed of 50 rpm. The dissolution study was carried out in 900 ml of two different dissolution media i.e. first 2 h in pH 1.2 followed by SIF of pH 6.8 buffer maintained at 37.0 ± 0.5 °C. At suitable time intervals, 10 ml samples were withdrawn and replaced with equivalent amount of fresh medium to maintain sink conditions. Samples withdrawn were filtered and analysed at 260 nm using a UV spectrophotometer. The release studies were conducted in triplicate and after analyzing the drug content in the dissolution samples plot of cumulative percentage of drug release versus time was plotted.[10]

Effect of concentration of pore former on drug release

In order to assess the effect of concentration of pore former on *in vitro* drug release, the optimized formulations were coated with coating solutions (A, B and C) containing varying amount of pore former (Sorbitol) i.e. 7.5%, 10% and 12.5% as per the procedure described earlier. The effect of increasing concentration of pore former on *in vitro* drug release was studied.[10]

Effect of pH on drug release

To study the effect of pH on *in vitro* drug release and to assure a reliable performance of the developed formulations independent of pH, release studies of the optimized formulations were conducted according to pH change method. The release media was simulated gastric fluid (SGF, pH 1.2) for first 2 h, acetate buffer (pH 4.5) for next 2 h, followed by SIF (pH 6.8) for the remaining period of 8 hrs. The samples (10 ml) were withdrawn at predetermined intervals and analysed spectrophotometrically for drug content.[10]

Effect of Agitational Intensity

In order to study the effect of agitational intensity of the release media, release studies of the optimized formulation were carried out in dissolution apparatus at various rotational speeds. Dissolution was carried at 75, 100 and 150 rpm in simulated intestinal fluid (pH 6.8) maintained at 37.0 ± 0.5 ^{o}C as the dissolution medium.[11]

Kinetics of drug release

The mechanism of Metoprolol Succinate release from the osmotic pump tablets was studied by fitting the dissolution data of all the formulation into the different models like first order kinetics, zero order and Higuchi. In order to describe the kinetics of drug release from controlled release preparations various mathematical equations have been proposed. The zero order rate Eq. (1) describes the systems, where the drug release is independent of its concentration (Najib and Suleiman, 1985). The first order equation Eq. (2) describes the release from systems, where release rate is concentration dependent (Desai et al., 1966). According to Higuchi model Eq. (3), the drug release from insoluble matrix is directly proportional to square root of time and is based on Fickian diffusion (Higuchi, 1963).

$Q_t = k_0 t$ (1)

$\ln Q_t = \ln Q_0 - k_1 t$ (2)

$Q_t = k_H t^{1/2}$ (3)

Where, Q_t is the amount of drug release in time t, Q_0 is the initial amount of the drug in tablet and k_0, k_1 and k_H are release rate constants for zero order, first order and Higuchi model equations, respectively. Based on the slope and the R^2 values obtained from the above models the mechanism of drug release was decided.[12, 13]

Stability studies

The optimized formulation of Metoprolol Succinate were packed in strips of 0.04 mm thick aluminum foil laminated with poly vinyl chloride by strip packing and these packed formulations were stored in ICH certified stability chambers (Thermo labs, Mumbai) maintained at 40 ^{o}C and 75% RH for 3 months (Zone III conditions as per ICH Q_1 guidelines). The samples were withdrawn and evaluated for their hardness, content uniformity and for *in vitro* drug release.[14]

RESULT 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 osmotic agent and swelling agent and other conventional excipients to form the core compartment. The core compartment was surrounded by a membrane consisting of a semipermeable membrane - forming polymer, water-soluble additives and at least one plasticizer capable of improving film-forming properties of the polymers. The semipermeable membrane-forming polymer was 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.[15] The dissolved drug is released through the pores created after leaching of water soluble additive in the membrane. Cellulose acetate and sorbitol were used as water-insoluble polymer and water soluble additive, respectively. Dibutyl phthalate was used as plasticizer.

Evaluation of powder blend

Results were shown in Table No. 3. The results of Hausner's ratio, carr's compressibility index and angle of repose indicates good flow properties of powder blend.

Table 3: Precompression Evaluation of the Powder Blend

Formulation Code	Bulk Density (gm/cm^3)	Tapped Density (gm/cm^3)	Hausner's Ratio	Carr's Compressibility Index	Angle of Repose (º)
F1	0.59±0.01	0.70±0.01	1.19±0.01	16.11±0.90	26.72
F2	0.60 ±0.01	0.69±0.01	1.14±0.04	12.63±2.75	27.93
F3	0.60±0.01	0.71±0.01	1.17±0.01	15.07±0.73	28.58
F4	0.60±0.01	0.69±0.01	1.15±0.03	13.73±2.13	26.91
F5	0.61±0.01	0.70±0.02	1.15±0.04	13.38±2.63	27.73
F6	0.59±0.01	0.70±0.01	1.17±0.03	15.28±2.10	26.11

Drug Content and Physical Evaluation

Results were shown in Table No. 4 and Table No. 5. The assay of drug in various formulations varied between 48.94 ± 3.08 mg to 49.94 ± 2.44 mg. Core tablet weights varied between 299.70 ± 3.840 mg and 301.80 ± 4.514 mg and for coated tablets ranged from 325.40 ± 4.694 mg to 327.10 ± 4.204 mg, thickness of the core tablets was found to be in the range of 4.09 ± 0.071 mm to 4.16 ± 0.074 mm and for coated tablets ranged from 4.58 ± 0.113 mm to 4.68 ± 0.077 mm. The hardness of core tablets was found to be between 5.97 ± 0.217 and 6.044 ± 0.203 kg/cm^2 and for coated tablets ranged from 6.22 ± 0.122 to 7.98 ± 0216 kg/cm^2. While the friability of core tablets ranged between 0.0756% and 0.0986%. Thus, all the physical parameters of the compressed matrices were practically within limits.

Table 4: Post compression evaluation of the osmotic Pump Tablets before coating

Formulation code	Before Coating				
	Thickness[a]	Average Weight[b]	Hardness[c]	Friabiltiy[d]	Content uniformity[e]
F1	4.12±0.05	301.80±4.51	6.064±0.20	0.0756	49.94±2.44
F2	4.16±0.07	300.85±3.51	6.025±0.26	0.0927	48.94±3.08
F3	4.13±0.13	299.70±3.84	5.975±0.23	0.0986	49.29±2.96
F4	4.09±0.07	300.40±3.84	5.995±0.27	0.0867	49.04±1.93
F5	4.14±0.08	300.50±3.84	5.99±0.18	0.0885	48.96±2.45
F6	4.12±0.11	300.45±4.19	5.97±0.21	0.0956	49.09±3.18

a= (n=3), b= (n=20), c= (n=10), d= (n=10), e= (n=5)

Table 5: Post compression evaluation of the osmotic pump tablets after coating

Formulation Code	After Coating		
	Thickness[a]	Average Weight[b]	Hardness[c]
F1	4.68±0.07	325.40±4.69	7.36±0.18
F2	4.59±0.05	325.90±4.99	7.98±0.21
F3	4.63±0.09	326.55±4.33	6.21±0.12
F4	4.58±0.11	325.95±4.97	6.75±0.11
F5	4.61±0.05	326.80±5.05	7.05±0.30
F6	4.62±0.09	327.10±4.20	7.20±0.21

a= (n=3), b= (n=20), c= (n=10), d= (n=10), e= (n=5)

In vitro dissolution study

Effect of osmotic agent

All the core formulations were coated with coating solution-B containing 10% w/w (of cellulose acetate) of sorbitol. In the formulations F1 to F3 osmotic agent concentrations were varied and swelling agent concentration was kept constant. The *in vitro* release profiles of formulation F1 to F3 containing different amount of osmotic agents is shown in Fig. 1.

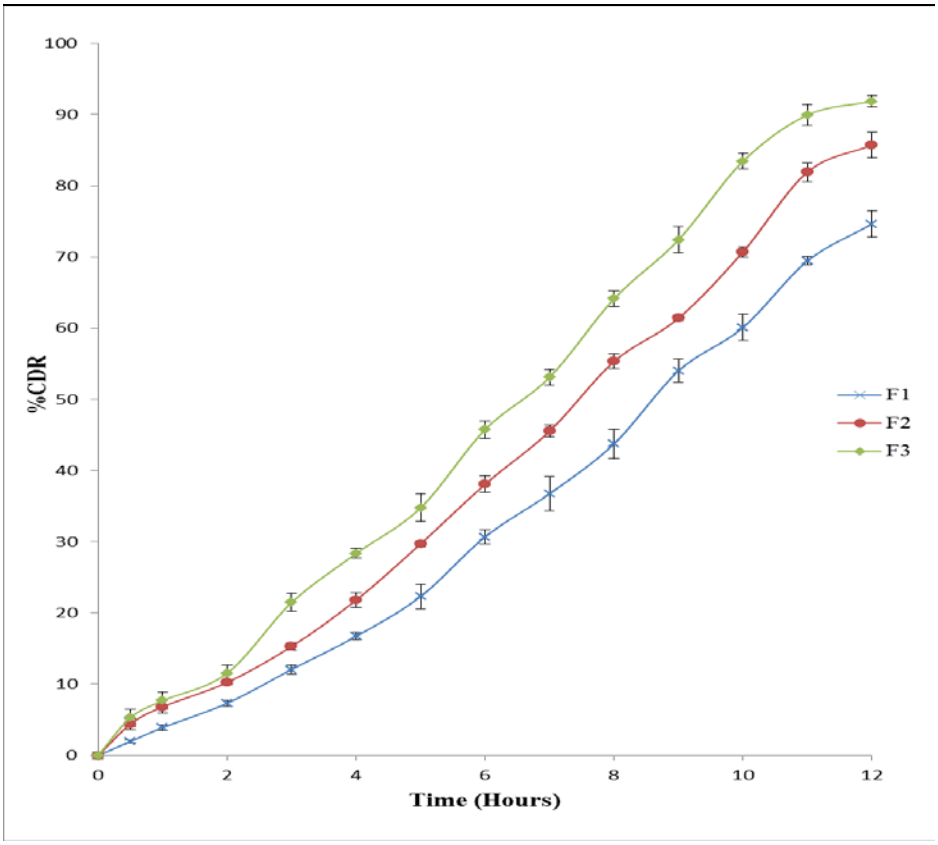

Fig. 1: *In vitro* release profile of Metoprolol succinate from formulation F1, F2 and F3 containing different concentration of osmogen.

It was clear from Fig. 1 that as concentration of osmotic agent increases release of drug from the formulation increases. This may be due to an increase in the osmotic pressure in the core tablet due to presence of different concentration of mannitol in different formulations.[16] F3 showed the highest release of 91.87 ± 0.78% as compared to F1 and F2 which showed 74.64 ± 1.89% and 85.74 ± 1.83%, respectively. Thus, it was concluded that as the concentration of mannitol increases the cumulative amount of drug release also increases.

Effect of swelling agent

The *in vitro* release profiles of formulations F4 to F6 containing different amount of swelling agent was shown in Fig. 2. From the Fig. 2, it was evident that the drug release was directly related to the concentration of swelling agent. The use of hydrophilic polymer as release retardants has attracted special attention in the field of osmotic pressure controlled drug delivery system. From the result, it was concluded that the drug release depends upon the concentration of swelling agent in the core tablets. Despite of higher solubility of Metoprolol Succinate in water, the thickening of povidone K-30 solution in the hydrated tablets containing the drug retarded the release from the system. The increased concentration of swelling agent decreased the drug release from the tablet. Initially release from all the three formulation i.e. F4 to F6 was same but as the polymer starts swelling there is retard in the release depending upon the concentration of swelling agent in the core tablet. Formulation F6 containing highest amount of swelling agent showed slow release of drug from the tablets i.e. 63.31 ± 1.58% as compared to F4 and F5 which showed release of 76.57 ± 3.49% and 68.67 ± 0.85%, respectively.

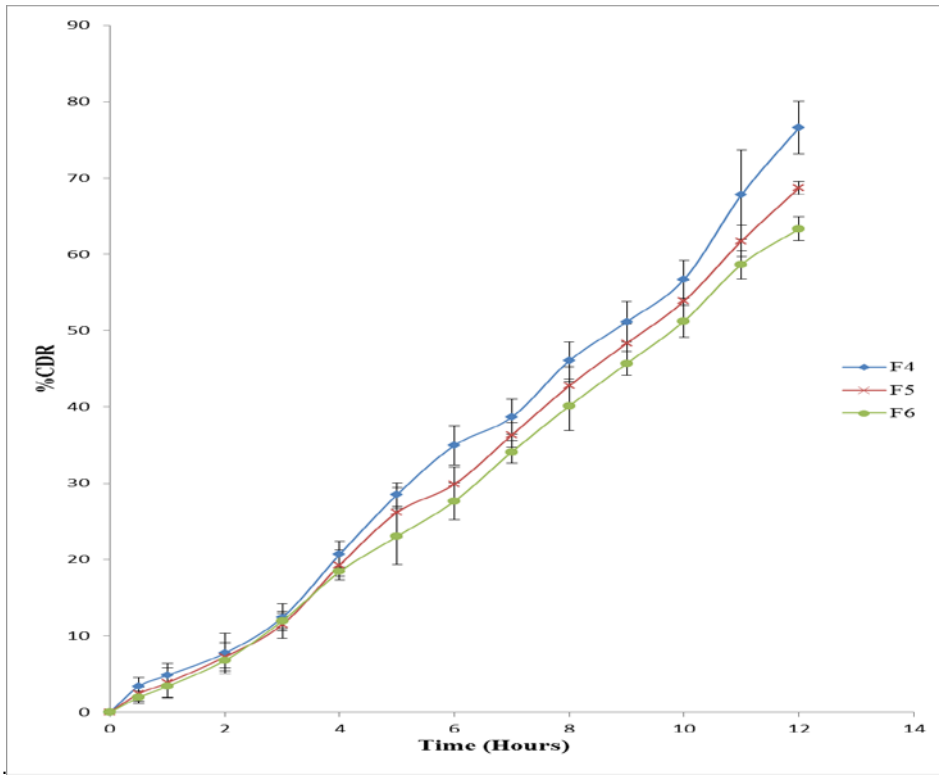

Fig. 2: *In vitro* release profile of Metoprolol succinate from formulation F4, F5 and F6 containing different concentrations of swelling polymer.

All the formulations showed release of drug more than 60% at 12 h and F3 showed the better release amongst all, hence was considered as best optimized formulation and was further evaluated for effect of various formulation variables affecting drug release from the osmotic pump tablets which are discussed as below.

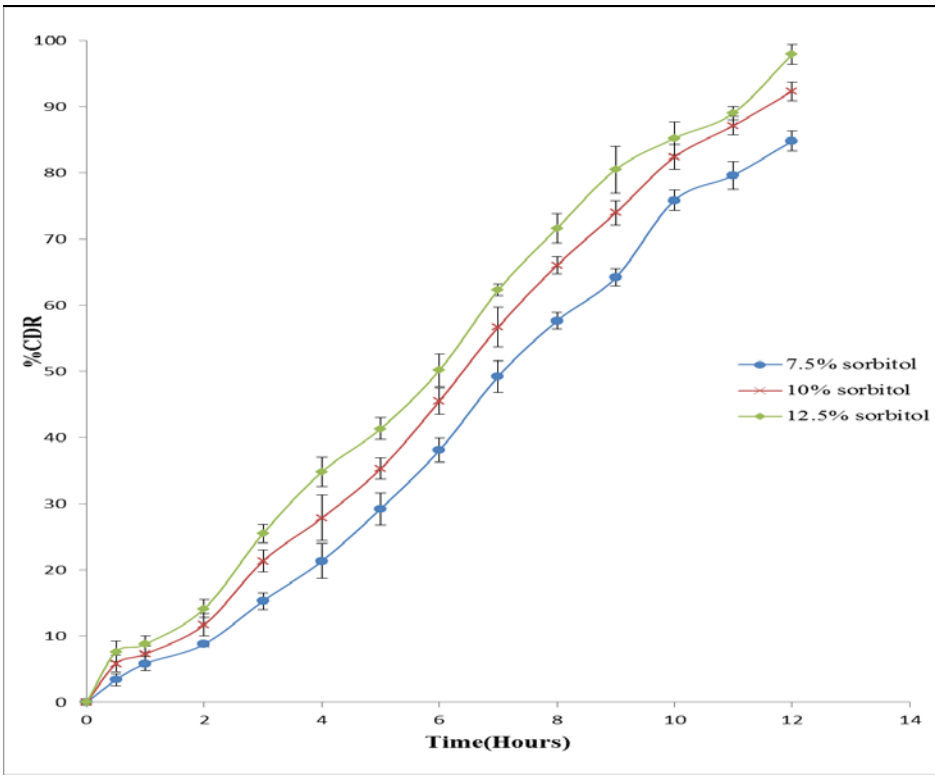

Fig. 3: *In vitro* release profiles showing the effect of concentration of pore former on Metoprolol succinate release from optimized formulation F3

Effect of pore former

To study the effect of pore forming agent, core formulations of Metoprolol Succinate F3, were coated with varying coating compositions of pore forming agent containing 7.5%, 10% and 12.5% w/w (of cellulose acetate) of sorbitol. Release profile from these formulations was as shown in Fig. 3.

From the Fig. 3, it was 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. Formulation F3 containing 7.5% sorbitol released 84.82 ± 1.52% of Metoprolol Succinate in 12 h, F3 containing 10% released 92.31±1.43% of Metoprolol Succinate. While highest release was obtained with 12.5% of sorbitol in the coating membrane with a cumulative release of 97.93±1.48% in 12 h. Drug release from controlled porosity osmotic systems takes place through pores formed *in situ* because sorbitol is water soluble additives (when in contact with the aqueous environment) thereby resulting in faster drug release. A microporous membrane coating appears to be the key factor with respect to release kinetics.

Effect of pH

The optimized formulation F3 (coat-B), was subjected to *in vitro* release studies in buffers with different pH. As shown in the Fig. 4. there was no significant difference in the release profile, demonstrating that the developed formulation shows pH-independent release. Thus, it can be expected that variations in pH of gastrointestinal tract may not affect the Metoprolol Succinate release from the core formulation.

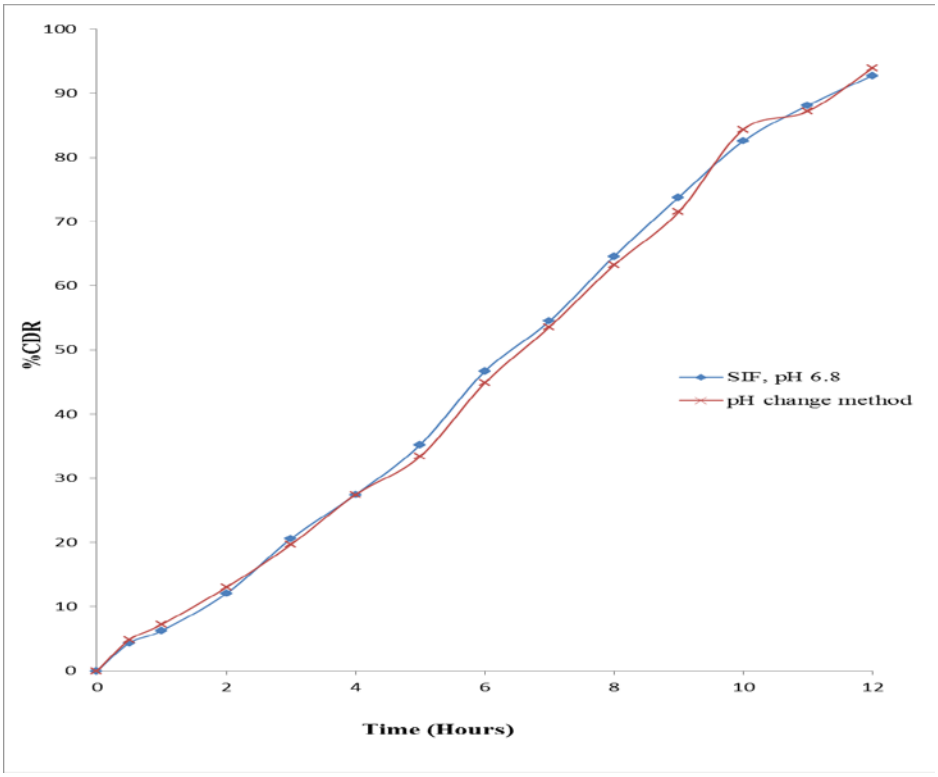

Fig. 4: *In vitro* release profiles showing the effect of pH on Metoprolol succinate release from optimized formulation F3.

Effect of agitational intensity

Drug release from osmotic pumps, need to be independent of agitational intensity of the release media. In order to verify effect of agitational intensity, the dissolution studies were conducted at three different rpm (75, 100 and 150). Formulation F3 coated with solution B was chosen for the study. Release profile was shown in Fig. 5. The cumulative percentages of drug released in 12 h were 91.36±3.49, 92.28±1.15 and 94.12±1.98%, respectively for 75, 100 and 150 rpm. A perusal to Fig. 6 showed no drastic change in release profiles, thus indicating that Metoprolol Succinate release from controlled porosity osmotic pump is independent of agitation intensity. Therefore it can be expected that the release from the developed formulations will be independent of the hydrodynamic conditions of the GIT.

Kinetics of drug release

In order to understand the mechanism of drug release from all formulations, the data was treated according to first-order (log cumulative percentage of drug remaining Vs time) along with zero-order (cumulative amount of drug released Vs time) and Higuchi model (square root of time Vs time) pattern using regression analysis. When the data was plotted according to the zero-order equation, the formulations showed a comparatively good linearity, and the regression value for zero-order equation was much higher as compared to first order and Higuchi plot, which indicated that drug release from optimized formulation, followed zero order and was independent of drug concentration [Table 6].

Table 6: Comparison of the Slope and the Regression Co-Efficient for Different Models

Formulation Code	In vitro release Regression equation			Best Fit
	Zero Order	First Order	Higuchi plot	
F1	R^2 = 0.984	R^2 = 0.457	R^2 = 0.865	Zero Order
F2	R^2 = 0.989	R^2 = 0.898	R^2 = 0.884	Zero Order
F3	R^2 = 0.993	R^2 = 0.898	R^2 = 0.907	Zero Order
F4	R^2 = 0.990	R^2 = 0.920	R^2 = 0.890	Zero Order
F5	R^2 = 0.994	R^2 = 0.953	R^2 = 0.896	Zero Order
F6	R^2 = 0.995	R^2 = 0.963	R^2 = 0.898	Zero Order

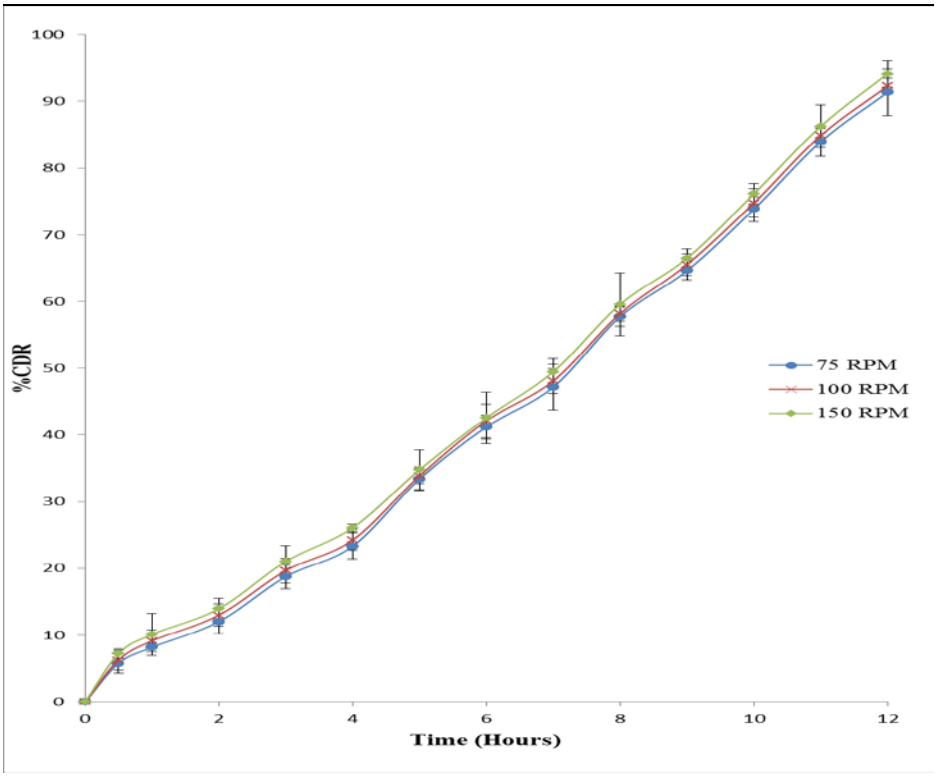

Fig. 5: *In vitro* release profiles showing the effect of agitational velocity on Metoprolol succinate release from optimized formulation F3.

Accelerated stability studies

The accelerated stability studies were carried out according to ICH guidelines. Optimized formulation F3 was packed in strips of aluminium foil laminated with PVC by strip packing and these packed formulation was stored in ICH certified stability chambers (Thermo labs, Mumbai) maintained at 40 °C and 75% RH (zone III conditions as per ICH Q_1 guidelines) for 3 months. The tablets were evaluated for the drug content, hardness and *in vitro* release.

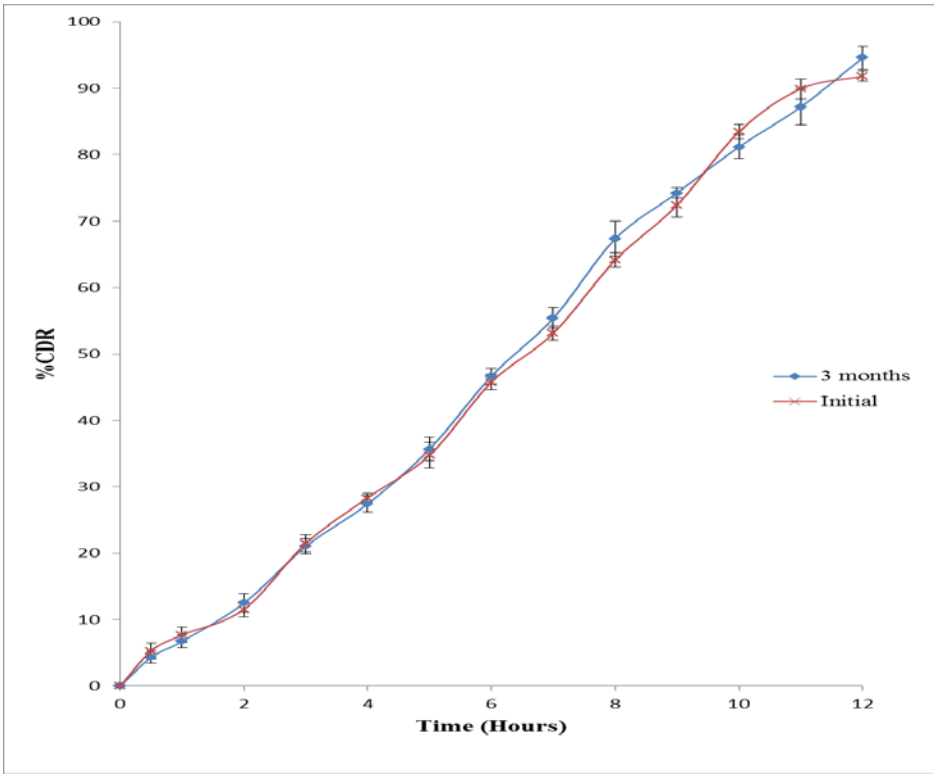

Fig. 6: *In vitro* release profile of F3 during stability studies at 40 °C and 75% RH for three months

The samples were observed for any change on coating membrane. It was observed that coating membrane was devoid of any change in colours or appearance of any kind of spot on it. It was also noted that membrane was free of any kind of microbial or fungal growth or bad odour. No change in the smoothness of the membrane was noted. The drug content of the formulation was found to 48.14 ± 3.32 mg which shows there is slight decrease in drug content but difference is insignificant. The results were tabulated in [Table 7].

The *in vitro* release of the samples after 3 months storage compared with release profile of sample at zero days, shown in [Fig 6]. The formulation F3 was found to be stable in terms of drug content and slight increase in hardness was observed. The i*n vitro* release profile of F3, initially and after 3 months was almost comparable and there is no much difference observed. Thus, the developed formulation was found to be stable for given storage conditions.

Table 7: Stability Studies Data for F3 Formulation

Parameter	Initial	After 3 months
Hardness (kg/cm^2)	6.21±0.12	7.14±0.31
Drug content (mg)	49.29±2.96	48.14±3.32
Drug release at end of 12 h	91.87±0.78	94.61±1.80

CONCLUSION

A porous osmotic pump–based drug delivery system can be designed for controlled release of highly water-soluble drug Metoprolol Succinate. It was evident from the results that the rate of drug release can be controlled through osmotic pressure of the core, swelling agent and level of pore former, with release to be fairly independent of pH and hydrodynamic conditions of the body i.e. agitational intensity. Metoprolol Succinate release from the developed formulations was inversely proportional to concentration of swelling agent in core tablet indicating that drug release depends on the amount of swelling agent in the formulation. The optimized formulation showed zero order drug release pattern. The stability studies indicated both physical and chemical integrity of the formulation during the storage period. Therefore, porous osmotic pump of Metoprolol succinate could be a safe, effective, stable, and promising preparation in the future.

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