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# Development of Controlled Porosity Osmotic Pump of Metoprolol Succinate: Design, Optimization and Characterization

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**Abstract**:

Controlled Porosity Osmotic Pump (Cpop) Drug Delivery System Is A Dosage Form Which-Provides Controlled Release Of Drug For Long Duration And Makes It One Of The Most Promising Drug Delivery Systems In The Recent Times. This Study Deals With The Development And Evaluation Of The Cpop For A Cardioselective B1-Adrenergic Blocking Agent, Metoprolol Succinate, Using Two Different Osmogens Viz. Sodium Chloride And Potassium Chloride. The Effect Of Degree Of Semipermeable Coating Essentially Consisting Of Cellulose Acetate, Polyethylene Glycol 4000 And Sorbitol As Pore Forming Agent Was Also Evaluated. In All, 18 Batches Were Prepared And Drug Release Profile Of All The Batches And Burst Strength Of Their Exhausted Shells Were Evaluated For Their Optimization. Dissolution Data Were Fitted To Various Mathematical Models To Describe Kinetics Of Drug Release And It Was Found That The Optimized System Followed Higuchi Model For Drug Release. Based On The Evaluation Parameters, Batches Consisting Of Drug: Osmogen Ratio As 1:1 With 5% Coating Was Found To Be Optimum. It Was Also Found That There Was No Effect Of Ph And Agitational Intensity. An Inverse Effect Of Osmotic Pressure Was Observed On The Drug Release. The Role Of Dextrose, Mannitol And Sucrose As Osmogens Was Also Studied And Compared In The Optimized Formulations, Which Indicated That A Direct Relationship Between The Osmotic Pressure Of The Osmogen And The Drug Release Exists. The Accelerated Stability Profiles Indicate That The Physicochemical Properties Of The Tablets Are Not Affected On Storage At 40 ± 2ºc & 75 ± 5% Rh Up To 3 Months.

**Keywords** -Controlled porosity osmotic pump, controlled release, Higuchi model, Metoprolol Succinate, osmogens, Pore forming agents

## INTRODUCTION

In the past three decades, there has been a significant advancement in the field of novel drug delivery system, of which one of the major innovations is controlled drug delivery system (1). This system overcomes the major drawbacks of the conventional drug delivery system by targeting the drug at the required site of action in a controlled and sustained pattern for a prolonged period of time (2). The other important features are reduced dose, dosage frequency, predictable release of the drug and thereby minimal toxic adverse effects (3). Thus, this novel system offers various advantages like reduction of blood level fluctuations, improved patient compliance and minimization of drug accumulation thereby reduction in local and systemic side effects (4).

A significant milestone in the novel oral drug delivery system is the development of controlled porosity osmotic pump (CPOP) oral drug delivery system. This system utilizes the principle of osmosis as the prime mechanism, for the delivery of a wide variety of soluble and insoluble drugs (5). It can ideally suit for a drug of short biological half-life (2-6h), high potency and needed for chronic therapeutic conditions (6, 7). Kisker O et al (8) have proved the use of osmotic pumps in improving the efficacy and potency of endostatin for the treatment of cancer by conducting the in-vitro and in-vivo studies. Oral osmotic drug delivery systems with their versatility and highly predictable drug release rates offer various advantages. The release of the drug is completely independent to the various physiological and hydrodynamic conditions like pH, gastric motility etc (9, 10).

Semipermeable membrane, pore forming agents and osmotic agents are the important components which can be modulated to achieve the desired drug release from this system (11). The core tablet in this system contains drug and osmogen in optimum quantity along with the other tablet excipients. Osmogens can be in the form of inorganic salts, hydrophilic polymers or sugars (12, 13). Polymers like cellulose esters or Eudragits along with a suitable plasticizer like polyethylene glycols, ethylene glycol monoacetate and diacetate, triethyl citrate or diethyl tartarate and a water soluble pore forming agent like alkaline metal salts, carbohydrates or polyols are mixed with a suitable organic solvent or their combinations like acetone, methylene chloride, ethanol, butyl alcohol, ethyl acetate, cyclohexane etc. to form a coating solution which is sprayed over the core tablets at a fixed spray rate, speed and temperature for a particular period of time to obtain a semipermeable membrane (14, 15). When this coated tablet comes in contact with an aqueous environment of the physiological system, the pore forming agent in the coating gets solubilised rendering the tablet in a microporous form. Water enters into the core of the tablet through these pores resulting in the swelling of osmogen in turn exerts pressure in the core region thereby releasing the drug from the tablet (16, 17).

Metoprolol Succinate, a cardio selective β1-adrenergic blocking agent is used for acute myocardial infarction, heart failure, angina pectoris and mild to moderate hypertension. It may also be used for many major ailments like supra-ventricular tachyarrhythmia and prophylaxis for migraine headaches. It has a relatively short elimination half-life (3-7 hours), and hence requires 2-4 times daily dosing in large number of patients which often leads to non-compliance. In conventional formulations, metoprolol succinate undergoes rapid absorption and extensive hepatic biotransformation. These limitations may be overcome by developing CPOP (18, 19). Such a formulation can thus help in reducing the dosage frequency and provides a controlled drug release with optimum therapeutic efficacy in order to improve the patient compliance (20-21). The absorption window of Metoprolol Succinate is reported through the upper part of the intestine whereas it is desirable that the drug release is seen in the major part of the gastrointestinal tract irrespective of presence of food. Drug release from CPOP has been reported to be independent of the physiological factors (22). This indicates that such formulation can provide a release throughout the gastrointestinal tract.

Few workers have attempted to develop, optimize and characterize the controlled porosity osmotic pump tablets of Metoprolol Succinate and have evaluated the effect of pH, agitation, osmogen on the drug release from these dosage forms for different periods of time (23-26). Some of the investigators have also studied the role of parameters like coating, release retardants etc. (27, 28).

It is clear from the foregoing information available in open literature that several workers have studied the CPOP based formulations of Metoprolol succinate and thereby the experimental evidence clearly shows the potential of CPOP in solving the limitations of available formulation with respect to efficiency of controlled drug release and patient compliance. However, it was felt that there is need for further strengthen the concept of CPOP tablet of Metoprolol succinate and develop inter-relationship of variables in formulations with drug release pattern in different environments. This would not only facilitate in evaluating the reproducibility and robustness of the dosage form but will also provide an opportunity to expand the studies. This paper deals with the study on formulation and optimization of CPOP tablet for Metoprolol succinate using sodium chloride and potassium chloride at different concentrations. Use of a unique diluent, MicroceLac was also introduced for the formulation of core tablets. Cellulose acetate along with PEG 4000 as plasticizer and sorbitol as pore forming agent dissolved in acetone worked out to be the best coating solution to achieve a semipermeable membrane on the core tablets. Drug release studies were carried out for 24 hours, which can possibly lower the doses and dosage frequency which minimizes the side effects. Effects of various important parameters like pH, agitational intensity and external osmotic pressure on these optimized batches were also evaluated. Study of burst strength with respect to drug release and comparative study of the major osmogens which are frequently used in the formulation of CPOP were the two important parameters which were also highlighted (29-31). These tests will simulate with in vivo conditions and provide a good indication of efficient performance of the optimized formulation. Accelerated stability studies for a period of 3 months at 40 ± 2ºC & 75 ± 5% RH were also conducted. All these factors make the study of developing and characterizing the controlled porosity osmotic pump tablets of metoprolol succinate extremely vital for a better and effective dosage form with better patient compliance and improved therapeutic efficacy.

## MATERIALS AND METHODS

### Materials

Metoprolol Succinate was received from Aarti Drugs Limited, Thane, India. The osmogens, sodium chloride and potassium chloride were received from Macron Fine Chemicals Limited, United States of America (USA) and Finar Reagents, Ahmedabad, respectively. Talc was procured from Imerys Private Limited, Paris, France. Povidone was obtained from BASF Corporation, Giesmer, Los Angeles. Magnesium stearate was procured from Ferro Corporation, Cleveland, USA. Aerosil 200 was a product of Evonik Industries, Germany. MicroceLac 100 and tablettose 80 were received by Meggle Group, Wasserburg, Germany. Microcrystalline cellulose PH 102 was obtained from FMC Biopolymers, Wallingstown. Cellulose acetate was obtained from Central Drug House Pvt. Ltd, New Delhi. Polyethylene glycol 4000 was a product from Clariant, Mumbai. Acetone was obtained from Fischer Scientific India Pvt. Ltd, Mumbai. Sorbitol, was a product of Roquette, Tokyo, Japan was used as pore forming agent. All the other excipients used were of analytical grade (32).

### Methods

#### Preparation of CPOP tablet

Core tablets were formulated using sodium chloride and potassium chloride as osmogens each at three different concentrations. Laboratory batches A, B and C contained sodium chloride and the batches D, E and F contained potassium chloride as osmogens as given in table1. Osmogens, Metoprolol Succinate, MicroceLac 100 (33) and Povidone (Kollidon 30) were accurately weighed and passed through a sieve of mesh size# 40. These ingredients were then transferred into a turbula blender (WAB (Willy A. Bachofen AG Maschinenfabrik), Mahopac, New York) of 1 litre capacity and were rotated at 40 rpm for 15 minutes. The other ingredients like colloidal silicon dioxide (Aerosil 200), talc and magnesium stearate were separately passed through sieve of mesh size# 40 and were added to lubricate the entire powder blend (34-36). Core tablets were prepared using Korsch tablet compression machine (Silverwater, Australia), using 10 mm punch, with a target tablet weight of 400mg, thickness of 5-6 mm and hardness of 9-11 kp. The hardness, weight variation and friability of the uncoated core tablets were measured using a hardness tester (Schleuniger Pharmatron, Switzerland), electronic weighing balance (Mettler Toledo, Mumbai, India) and Roche's friabiliator (Labindia, Thane, India) respectively. All were found to comply the quality target product profile (QTPP), which is to procure a tablet weight of 400mg, with hardness of 10 kp and minimal friability.

**Table 1: Details of formulation of CPOP tablets of Metoprolol Succinate**

| **Composition of Core Tablets** | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Ingredients** | **Quantity (mg/tablet)** | | | | | | | | | | | | | | | | | |
| **Core Tablets** | **A** | | **B** | | **C** | | **D** | | **E** | | **F** | | | | | | | |
| Metoprolol Succinate | 50 | | 50 | | 50 | | 50 | | 50 | | 50 | | | | | | | |
| Sodium Chloride | 25 | | 50 | | 75 | | - | | - | | - | | | | | | | |
| Potassium Chloride | - | | - | | - | | 25 | | 50 | | 75 | | | | | | | |
| MicroceLac 100 | 297 | | 272 | | 247 | | 297 | | 272 | | 247 | | | | | | | |
| Talc | 4 | | 4 | | 4 | | 4 | | 4 | | 4 | | | | | | | |
| Colloidal Silicon Dioxide (Aerosil 200) | 8 | | 8 | | 8 | | 8 | | 8 | | 8 | | | | | | | |
| Povidone (kollidon 30) | 12 | | 12 | | 12 | | 12 | | 12 | | 12 | | | | | | | |
| Magnesium stearate | 4 | | 4 | | 4 | | 4 | | 4 | | 4 | | | | | | | |
| **Total** | **400** | | **400** | | **400** | | **400** | | **400** | | **400** | | | | | | | |
| **Composition of the Coating Solution** | | | | | | | | | | | | | | | | | | |
| **Ingredients** | **Quantity (mg/100g)** | | | | | | | | | | **Quantity (%)** | | | | | | | |
| Cellulose acetate | 9 | | | | | | | | | | 9.081 | | | | | | | |
| Polyethylene Glycol 4000 | 1 | | | | | | | | | | 1.009 | | | | | | | |
| Sorbitol | 0.9 | | | | | | | | | | 0.9081 | | | | | | | |
| Water | 9 | | | | | | | | | | 9.081 | | | | | | | |
| Acetone | 81 | | | | | | | | | | 79.9209 | | | | | | | |
| **Total** | **100.9** | | | | | | | | | | **100** | | | | | | | |
| **Composition of Coated Batches** | | | | | | | | | | | | | | | | | | |
| **Coated Tablets** | **A3** | **A5** | **A7** | **B3** | **B5** | **B7** | **C3** | **C5** | **C7** | **D3** | **D5** | **D7** | **E3** | **E5** | **E7** | **F3** | **F5** | **F7** |
| **Coating (%)** | **3** | **5** | **7** | **3** | **5** | **7** | **3** | **5** | **7** | **3** | **5** | **7** | **3** | **5** | **7** | **3** | **5** | **7** |

**Procedure for coating of the core tablets:**

Each batch of core tablets were coated at three different percentage weight gains which were 3%, 5% and 7%. The coating was carried out in the coating machine (Ganscoater, Gansons, Thane, India). A batch of 800 grams tablets which included placebos and the actual core tablets were fed into a stainless steel coating pan of 1 kilogram capacity, having diameter of 28 cm and rotating at a speed of 15-16 rpm. The spray rate was set as 1.4-1.8g/min, inlet temperature as 30-40$^{o}$C and exhaust temperature as 25-32$^{o}$C. The bed temperature was maintained at 20-30$^{o}$C, atomization speed as 0.8-1kg/cm$^2$ and fan speed as 0.8-1.0 kg/cm$^2$. The pump rpm and pan rpm were maintained as 14-16. Coated tablets were dried at 40-45˚C for 12-16 h till the weight of the tablets was found to be constant (37). The details of the formulation of CPOP tablets of Metoprolol Succinate are given in table 1.

**Identification of the Drug- Metoprolol Succinate**

(a) **Melting point:** Melting point of the drug was determined by using the lab capillary method.

(b) **IR spectra**: IR spectra of drug in KBr pellets was determined at moderate scanning speed between 4000-400 cm$^{-1}$ using FTIR (Jasco FTIR 6100 TYPE A). All the powder samples were dried under vacuum prior to obtaining any spectra in order to remove the influence of residual moisture.

(c) **Standard calibration curves:** Standard calibration curves of the drug were determined in various solvents like distilled water, 0.1N Hydrochloric acid pH1.2, acetate buffer pH 4.5 and phosphate buffer pH 6.8. The straight line equation values were determined to check the nature of the standard curve and were further used for calculating the in-vitro drug release from the CPOPs during the in-vitro dissolution studies. The instrument used was a UV-1800 UV-VIS spectrophotometer (Shimadzu, Shanghai, China).

**Physical characterization of the drug- Metoprolol Succinate**

Powder characteristics like bulk density, tapped density, Carr's compressibility index and Hausner's ratio were determined using tap density tester (Labindia, Thane, India). Loss on drying was also determined using moisture analyzer (Mettler Toledo, Mumbai, India) and the particle size of the drug was determined using sieve shaker (Retsch GmbH, Germany).

**In- vitro drug release**

According to U.S. Pharmacopoeial (USP) specifications, the drug release studies for the controlled porosity osmotic pump tablets of Metoprolol Succinate were carried out using an USP Type II paddle apparatus (Labindia, Thane, India) containing 500ml phosphate buffer pH6.8, at a speed of 50 rpm, at 37 $\pm$0.5 $^{o}$C for 24 hours (38). Three tablets were taken to check and validate the in-vitro release. 5ml sample was withdrawn and filtered with Whatman filter paper and replenished with the same amount of fresh dissolution media. The samples were withdrawn at time intervals of 1, 4, 8, 20 and 24 hours and analyzed for Metoprolol Succinate content by UV spectrophotometry method at $\lambda_{max}$ of 222nm (39, 40).

**Drug release kinetics**

Dissolution data of the optimized formulation was fitted to various mathematical models in order to describe the

kinetics of drug release. Value of $R^2$ nearest to 1 was taken as the criteria for selecting the most appropriate model (41).

**Burst strength**

Burst strength is defined as the force required for rupturing the shells after dissolution studies. Burst strength of the exhausted shells (n = 3), after 24 h of dissolution, was determined to assure that the tablets would maintain their integrity in the gastrointestinal tract, thereby determine the strength of the semipermeable membrane used in the coating of the controlled porosity osmotic pump tablets (42, 43). Texture analyzer (Brookefield, Toronto, Canada) with 5 gram load cell and 20 mm acryl cylindrical probe was utilized for this purpose. Test speed of 10.00 mm/min and distance to be moved was 25 mm.

**Effect of pH on drug release**

Effect of pH (n=3) and the reliable performance of the developed formulations were studied by performing the release studies of optimized formulation batches B5 and E5 in different media at pH, 1.2, 4.5 and 6.8 which was mimicked by 0.1N hydrochloric acid, acetate buffer pH 4.5 and phosphate buffer pH 6.8, respectively. USP Type II dissolution paddle apparatus at 50 rpm and at a temperature of 37±0.5°C was used. Samples of 5ml were withdrawn at predetermined intervals and analyzed in UV Spectrophotometer at $\lambda_{max}$ 222nm (44, 45).

**Effect of agitational intensity on drug release**

The effect of agitation intensity (n=3) were studied by performing the release studies of optimized formulation batches B5 and E5. USP Type II dissolution paddle apparatus containing phosphate buffer at pH 6.8 was used at different rotational speeds of 25, 50, 75 and 100 rpm while maintaining the temperature as 37±0.5°C. Samples of 5ml were withdrawn at predetermined intervals and analyzed in UV Spectrophotometer at $\lambda_{max}$ 222nm (46, 47). Fresh buffer solutions of volume 5ml were replenished.

**Effect of osmotic pressure on drug release**

The effect of osmotic pressure (n=3) was checked by adding different amount of an osmotic agent into the dissolution media. Different concentration (0.25%, 0.5%, 1% and 1.5%) of mannitol were added in Phosphate Buffer pH 6.8 and dissolution was carried out in USP Type II paddle apparatus at 50 rpm and 37±0.5°C (48). 5ml of samples were withdrawn at the predetermined intervals and the absorbance was checked by using UV Spectrophotometer at $\lambda_{max}$ of 222nm. This study was conducted on batches B5 and E5.

**Comparative study of the optimized batches with batches containing same amount of different osmogens**

A comparative study of the batches B5 and E5 was performed (n=3) with the batches containing the same concentration of different osmogens like mannitol, dextrose and sucrose. Drug release study was carried out using USP dissolution apparatus type II at 50 rpm and 37±0.5°C using Phosphate buffer pH 6.8 as dissolution media.

**Accelerated Stability Studies**

The optimized formulations (batches B5 and E5) were charged for the accelerated stability studies according to ICH guidelines (40 ± 2ºC and 75 ± 5% RH). The tablets were packed in high density polyethylene (HDPE) container and were stored in ICH certified stability chamber for 3 months (zone III conditions as per ICH Q1guidelines). The samples were withdrawn at the end of 3 months and evaluated for in vitro drug release (22, 49).

## RESULTS

**Identification of the drug- Metoprolol Succinate**

**(a)** The reported value of melting point of metoprolol succinate is 135-137°C (18). The experimental value of metoprolol succinate was found to be 136°C, which falls within the range of the reported value of melting point.

**(b)** **Infra red (IR) spectra:** The spectrum of metoprolol succinate was compared with standard spectrum (50). The obtained spectrum was found to have similar peak values representing wave numbers as shown in figure 1 and table 2.

**(c)** **Standard calibration curves:** The standard calibration curves of the drug was determined in four different solvents, that is, distilled water, 0.1N hydrochloric acid, acetate buffer pH 4.5 and phosphate buffer pH 6.8 (51). The regression coefficients were found to be 0.9982, 0.9998, 0.9913 and 0.996 respectively, which indicated that the calibration curves are straight line graphs.

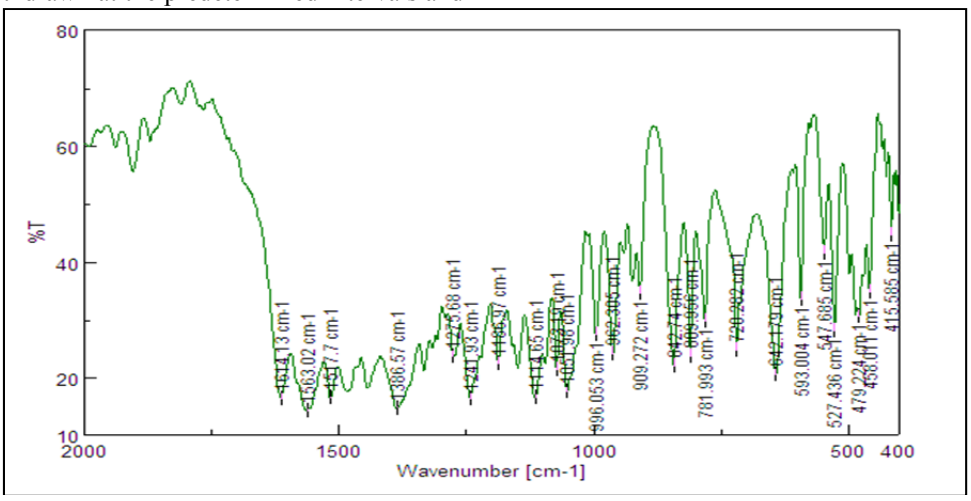


**Figure 1: FT-IR spectra of Metoprolol Succinate (Obtained)**

**Table 2: Standard and observed wavelengths of peak of FT-IR spectra of Metoprolol Succinate**

| Functional Group | Standard Wavelength ($cm^{-1}$) | Observed Wavelength ($cm^{-1}$) |
|---|---|---|
| Benzene stretching | 1618 | 1614.13 |
| N-H bending | 1583 | 1563.02 |
| C-O Stretching in C-O-C | 1110.84 | 1114.65 |
| C=O | 1245 | 1241.95 |
| C-O Stretching ($1^{o}$ Alcohol) | 1045.52 | 1051.98 |
| C-O Stretching in C=C-O-C | 1238.39 | 1241.93 |

**Physical characterization of the drug- Metoprolol Succinate**

The details of the powder characteristics like bulk density, tapped density, Carr's compressibility index and Hausner's ratio; loss on drying and particle size distribution of the drug are furnished in the table 3.

**Table 3: Physical characters of the drug: Metoprolol Succinate**

| Parameter | Value | |
|---|---|---|
| **Bulk density (g/ml)** | 0.3637±0.01 | |
| **Tapped density (g/ml)** | 0.5883±0.04 | |
| **Carr's compressibility index (%)** | 38.1818±1.08 | |
| **Hausner's ratio** | 1.6±0.03 | |
| **Particle size distribution** | | |
| **Sieves Used (#)** | **SievesSize (µ)** | **% Retained** |
| **40** | 375 | 1.08 |
| **60** | 250 | 6.52 |
| **100** | 150 | 30.43 |
| **Pan** | | 61.96 |
| **Loss on drying (50°C for 5 minutes)** | | |
| **Reported LOD (%)** | 0.14 | |
| **Observed LOD (%)** | 0.18 | |

**In- process quality control (IP-QC) tests of the uncoated tablets**

The values of hardness (n=6), weight (n=20) and friability of the different batches of the core tablets are furnished in the table 4, which comply with the desired range of values.

**Table 4: IP-QC of the uncoated core tablets**

| Batches | A | B | C | D | E | F |
|---|---|---|---|---|---|---|
| Hardness (kp) | 9.612 ±0.028 | 9.66 ±0.011 | 9.45 ±0.015 | 10.24 ±0.021 | 10.02 ±0.014 | 10.52 ±0.012 |
| Weight (mg) | 401.77 ±0.121 | 397.23 ±0.012 | 398.76 ±0.014 | 396.02 ±0.016 | 397.36 ±0.018 | 400.54 ±0.124 |
| Friability (%) | 0.08 | 0.19 | 0.18 | 0.12 | 0.14 | 0.12 |

**In-vitro drug release**

All the 18 batches were subjected to *in vitro* release study. The drug release profile of the formulation of Batch B5 and E5 were found to be the best from all the batches of sodium chloride and potassium chloride respectively. These batches provided controlled release of drug for 24 hours. The graphical representation of the drug release of batches B5 and E5 is shown in figure 2.

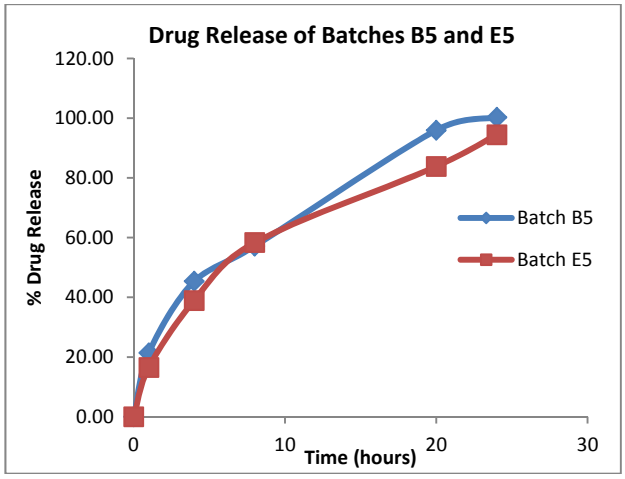


**Figure 2: Drug Release of Batches B5 and E5**

**Drug release kinetics**

The dissolution data of B5 and E5 was found to fit well into Higuchi model (Table 5) as the value of $R^2$ was nearest to 1 in Higuchi model followed by zero order model as compared to the other models. A similar release was observed in the study performed by Elbary A., Tadros MI., Eldin AA., on controlled porosity osmotic pump tablets of Etodolac (41).

**Table 5: Details for Drug Release Kinetics**

| Batches | Models | | | | |
|---|---|---|---|---|---|
| | Zero order | First order | Higuchi | Hixon-Crowell | Kosmeyer-Peppas |
| | $R^2$ Square value | | | | |
| **A3** | 0.8784 | 0.3649 | 0.8865 | 0.8841 | 0.5251 |
| **A5** | 0.8834 | 0.4321 | 0.9395 | 0.8878 | 0.6082 |
| **A7** | 0.8917 | 0.5066 | 0.9608 | 0.9035 | 0.7111 |
| **B3** | 0.9055 | 0.4565 | 0.9882 | 0.9789 | 0.6139 |
| **B5** | 0.9112 | 0.4894 | 0.9968 | 0.9667 | 0.6393 |
| **B7** | 0.9021 | 0.5533 | 0.9806 | 0.9814 | 0.7071 |
| **C3** | 0.7981 | 0.3033 | 0.8173 | 0.7195 | 0.4901 |
| **C5** | 0.8697 | 0.4561 | 0.9294 | 0.9259 | 0.6493 |
| **C7** | 0.8912 | 0.4866 | 0.9498 | 0.9446 | 0.6818 |
| **D3** | 0.8831 | 0.3991 | 0.9193 | 0.8156 | 0.5645 |
| **D5** | 0.8593 | 0.5201 | 0.9759 | 0.9202 | 0.7126 |
| **D7** | 0.8218 | 0.4686 | 0.9014 | 0.7725 | 0.6861 |
| **E3** | 0.8717 | 0.3748 | 0.9080 | 0.8685 | 0.5334 |
| **E5** | 0.8807 | 0.4594 | 0.9361 | 0.9043 | 0.6551 |
| **E7** | 0.8309 | 0.5415 | 0.8850 | 0.8452 | 0.8254 |
| **F3** | 0.8536 | 0.4238 | 0.9274 | 0.9168 | 0.6079 |
| **F5** | 0.8821 | 0.4357 | 0.9432 | 0.9165 | 0.6164 |
| **F7** | 0.8741 | 0.4872 | 0.9482 | 0.9257 | 0.6931 |

**Burst strength**

The stages showing the physical changes in the CPOP tablet during the dissolution process in shown in the figure 3. It is evident that the intact tablet becomes spherical during dissolution and the same tablet collapses as all the ingredients ooze out leaving behind only the exhausted shells. The burst strength of the exhausted shells and the amount of drug release of the different batches of tablets which were formulated are furnished in the table 6. Figures 4 and 5 represent the graph showing the same result.

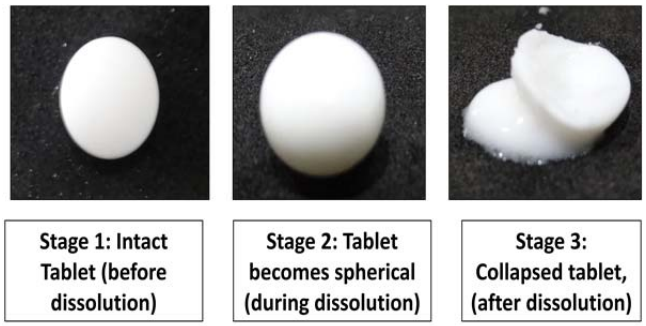


**Figure 3: Stages showing the physical changes in the CPOP tablet during the dissolution process**

**Table 6: Details of the burst strength of all the batches**

| Batch | Peak load (grams) | % Drug release |
|---|---|---|
| A1 | 522 | 90.34 |
| A2 | 690 | 88.54 |
| A3 | 972 | 75.62 |
| B1 | 416 | 101.95 |
| B2 | 565 | 100.30 |
| B3 | 825 | 88.87 |
| C1 | 326 | 102.65 |
| C2 | 453 | 97.58 |
| C3 | 786 | 96.08 |
| D1 | 712 | 74.77 |
| D2 | 985 | 70.37 |
| D3 | 1257 | 57.64 |
| E1 | 620 | 94.67 |
| E2 | 863 | 94.46 |
| E3 | 1126 | 88.18 |
| F1 | 492 | 96.74 |
| F2 | 727 | 94.93 |
| F3 | 986 | 93.03 |

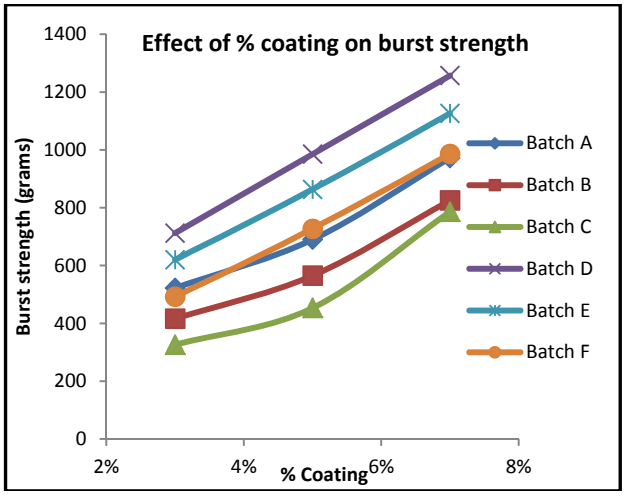


**Figure 4: Effect of % coating on burst strength**

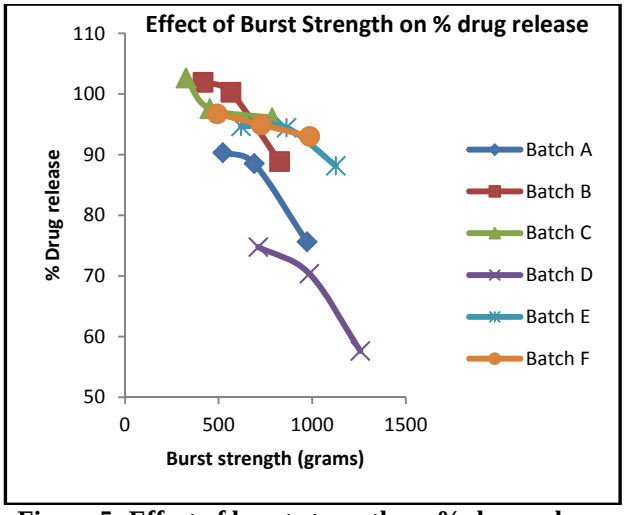


**Figure 5: Effect of burst strength on % drug release**

**Effect of pH on drug release on batch B5 and E5**

Batch B5 and Batch E5 were evaluated at different pH range and it was found that there was no difference in drug release as the pH was changed as shown in the figures 6 and 7.

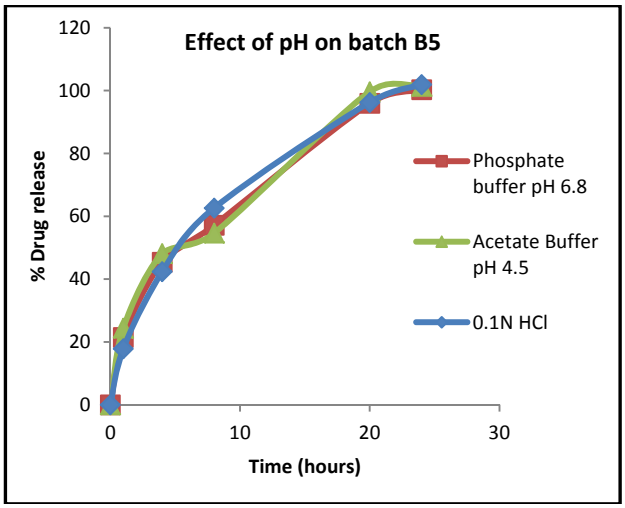


**Figure 6: Effect of pH on batch B5**

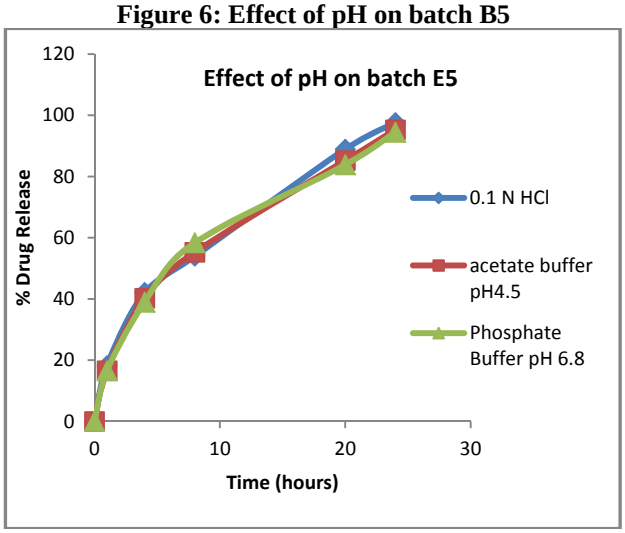


**Figure 7: Effect of pH on batch E5**

**Effect of agitational intensity on batch B5 and E5**

Effect of the agitational intensity on batch B5 and E5 was studied and it was found that no significant difference was there in the drug release when the agitational intensity was changed from 25 rpm to 150 rpm. This unchanged effect is shown in figure 8 and 9.

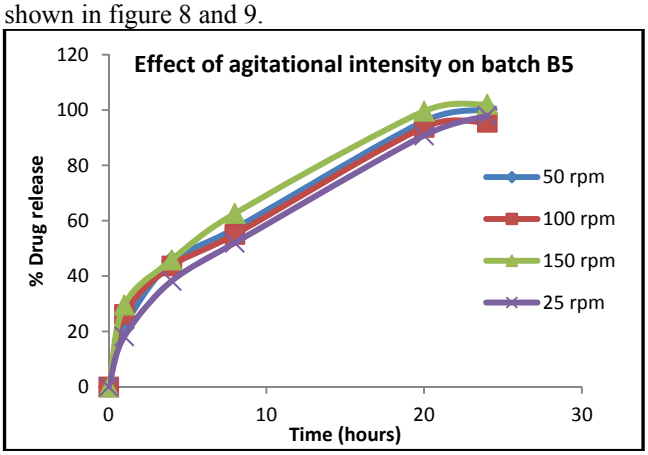


**Figure 8: Effect of agitational intensity on batch B5**

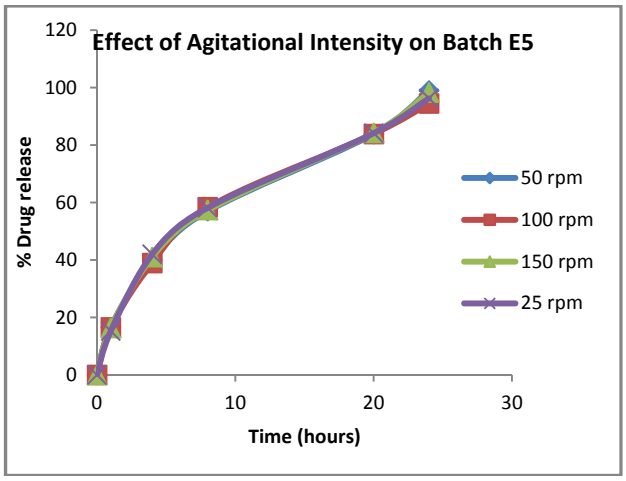


**Figure 9: Effect of agitational intensity on batch E5**

**Effect of osmotic pressure on Batch B5 and E5**

Effect of the osmotic pressure on batch B5 and E5 was studied and it was found that as the concentration of osmogen in the dissolution media is increased, the amount of drug release is decreased as shown in the figure 10 and 11.

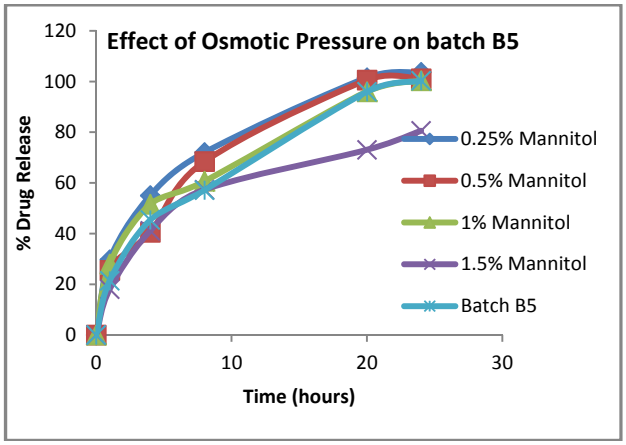


**Figure 10: Effect of osmotic pressure on batch B5**

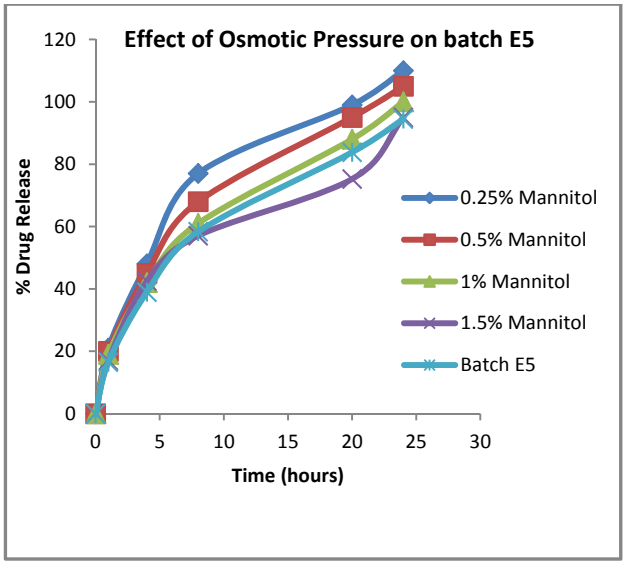


**Figure 11: Effect of osmotic pressure on batch E5**

**Comparative study of the optimized batches with batches containing same amount of different osmogens**

The osmotic pressures of the different osmogens like sodium chloride, potassium chloride, sucrose, dextrose and mannitol are 356, 245, 150, 82 and 38 atmospheres respectively. Figure 12 shows the comparison of the batches containing different osmogens on their drug release efficiency with respect to time and it was observed that the rate of drug release was directly proportional to the osmotic pressure of the osmogens.

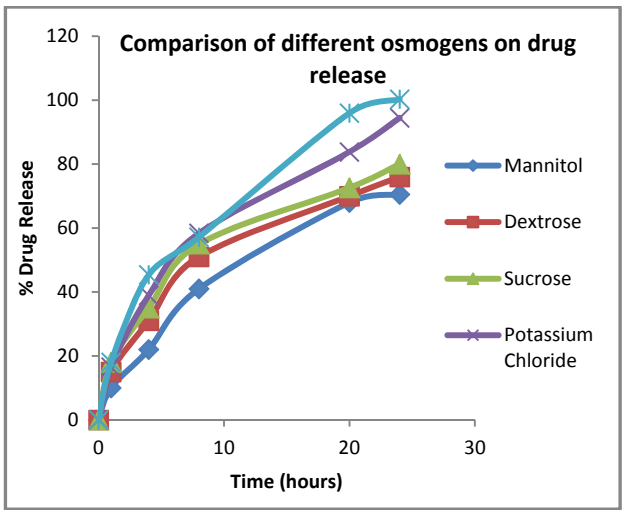


**Figure 12: Comparison of different osmogens on drug release**

**Accelerated Stability studies**

Accelerated stability study was carried out at 40±2°C/75±5% RH for 3 months on optimized formulae (B5 and E5) and it was found that there was no significant difference in in-vitro drug release before and after stability study. No fracture of coat from any tablet of optimized batches was noticed during and after stability study. The graphs representing stability in terms of *in vitro* release are shown in Figure 13 and 14.

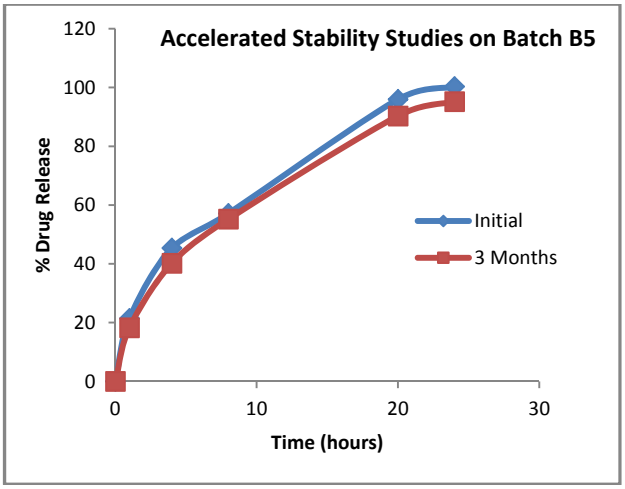


**Figure 13: Accelerated Stability Studies on Batch B5**

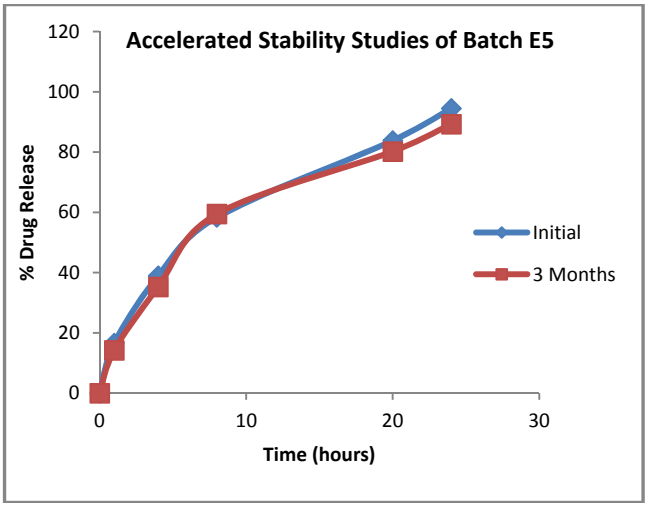


**Figure 14: Accelerated Stability Studies on Batch E5**

## DISCUSSION

In order to identify the drug and determine its purity, melting point, FT-IR spectra and standard calibration curves were ascertained. The experimental values of melting point (18) and peak values of FT-IR spectra (50) representing wave numbers identified the drug as Metoprolol Succinate and confirmed its level of purity, when compared with its theoretical values. A similar study relating FT-IR spectra of the drug was also conducted by Sharma F et al (22) and Kapoor D et al (34) to confirm the purity and for the identification of the active ingredients which were Metoprolol Succinate and Valsartan respectively. Standard calibration curves were determined in four different solvents which included distilled water, 0.1N hydrochloric acid, acetate buffer pH 4.5 and phosphate buffer pH 6.8 as a preliminary study (51). The straight line graphs and equations so obtained were further utilized to carry out the in-vitro drug release study of the formulation. 0.1N hydrochloric acid, acetate buffer pH 4.5 and phosphate buffer pH 6.8 mimics the condition of stomach, small intestines and large intestines of the human body respectively. Also, the standard calibration curves and the straight line graphs of the drug prove that the drug is in a pure form.

Powder characteristics of Metoprolol Succinate which includes bulk density, tapped density, Carr's compressibility index and Hausner's ratio were determined. The obtained experimental values were compared with the standard values as given in the US Pharmacopeia monograph (52, 53) which confirmed that the drug had a very poor flow property and required a suitable glidants and lubricants in optimum quantities.

Further, particle size distribution was also carried out which proved that the drug is extremely fine (54) as more than 61% of the drug passed through 150 µ sieve. This required suitable excipients in optimum quantities. MicroceLac 100 (55, 56) is a co-processed excipient comprising of 75% alpha- lactose monohydrate and 25% microcrystalline cellulose which exhibit the synergistic effects of both of these naturally derived tablet diluents and ensures to improve flowability and compactability in the direct compression method of manufacturing the tablets. This tablet diluent was found to be the best of all the other diluents evaluated. This use of this unique excipient was also studied by Dey NS et al (57) where fast dissolving tablets of paracetamol were formulated. The drug being extremely fine with irregular particle size distribution and poor flow properties was difficult to be designed and formulated. Hence, tablet excipients like MicroceLac 100 were used for the formulation and excellent flow properties for the direct compression of these tablets were devised and evaluated. Similarly, other excipients suitable for the development of core CPOP tablets by direct compression were selected, optimized and used.

Core tablets containing sodium chloride and potassium chloride as osmogens were prepared and optimized and the physical parameters like hardness, friability and tablet weight of the core CPOP tablets were determined which fall in the range of 9.985 $\pm$ 0.535 kp, 398.895 $\pm$ 2.875 mg and 0.10 $\pm$ 0.02% respectively so as to meet up the quality target product profile. It was found that all the parameters comply within the range of the acceptable values (58), thus making it suitable for acceptability in commercial use. An important limitation of the use of sodium chloride is that it may augment the condition of hypertension, however, this limitation is not observed in case of potassium chloride, proving it to be a better candidate among these two osmogens.

The effect of factors like type of pH and agitational intensity were studied on the in vitro drug release of the developed CPOP tablets, which are independent of the physiochemical factors like pH and agitational intensity (28). Similar results were obtained in the investigations carried out by Modi S et al (59), Patel H et al (60) and Mehta TA et al (49) where similar results were obtained when experiments were conducted on the drugs like Milnacipran, Glimepiride and Nicardipine hydrochloride respectively. They found that the amount and pattern of drug release from the CPOP in the human GIT is independent of the presence of food and the therapeutic window of the drug. In contrast to this behavior of the controlled porosity osmotic pump tablets, the conventional drug delivery systems which work on the phenomenon of matrix or erosion show their dependency of drug release on

the pH of the site and presence of food which is due to the drug release mechanisms followed by their dosage forms (61-63).

A direct relationship between the internal osmotic pressure of the CPOP and the drug release is seen. This indicates that as the concentration of the osmogen inside the core of the CPOP tablets increases, the rate of drug release is also increased proportionately. Similar results were obtained by Gao C et al (64) and Pan et al (65) by the controlled porosity osmotic pump tablets of salvianolic acid and Budesonide respectively. On the contrary, if the osmotic pressure, due to some reason, is higher in the external environment, the drug release will reduce and vice- versa. This was observed by Hou et al (66) and Pan et al (67) in CPOPs of theophylline and Dilteazem hydrochloride respectively.

A comparative study of the osmotic agents was also performed, where it was found that among the five osmogens used, mannitol had the least osmolarity and sodium chloride had the highest osmolarity, as expected. This can be explained by describing osmolarity as a colligative property which is based only on the number of particles and their dissociation constants. The more the molecule gets dissociated as ions, the number of particles of the solute in the solvent will increase thereby which the osmolarity increases. The similar phenomenon can be observed when sodium chloride and mannitol are used as osmogen. Sodium chloride dissociates the most while mannitol dissociates the lowest as a result of which the number of particles of the solute will be high for sodium chloride and low for mannitol thereby providing the highest and lowest osmolarity respectively (68).

The burst strength of the exhausted shells was found to be directly affected by the weight gain due to coating and inversely related to the amount of pore forming agents incorporated in the coating. This means that if the burst strength is high, the coating membrane is thick due to high weight gain, hence the force required to break the exhausted shells will be high. Also, the pore forming agents incorporated are more which facilitates the generation of pores on the coating membrane and thereby allow the content of the core tablet to get released (36, 47). It was also shown the burst strength has an inverse relation to the drug release. The higher the burst strength, the more will be the thickness of the coating membrane, which essentially shows that the drug will have to cross many layers of membrane to get released, thereby reducing the drug release (69). From the foregoing discussion, it can be clearly understood that optimization of concentration of osmogen, pore forming agents and the coating layer thickness is critical for an efficient drug release from CPOP formulations. The optimized formulations of this study comprising 5% coating, 50 mg osmogen and 0.9% pore forming agent in a 400mg tablet also proves the same by providing efficient zero order drug release for 24 hours (70, 71) and hence can be effectively utilized.

The system follows Higuchi model which describes that the mechanism of diffusion was based on the water penetration principle. This suggests that drug diffusion through pores created by the dissolution of sorbitol is the predominant pathway. Drug release from CPOP systems is influenced by microenvironmental osmotic pressure created by the dissolution of osmotic agents after water imbibition across the coating membrane and the diffusion through pores created by the dissolution of pore formers incorporated in the coating membrane (41, 48). Vyas SP et al (35) developed the controlled porosity osmotic pump tablets of Diltieazem hydrochloride which followed the Hixon-Crowell cube root model which suggests that the mechanism of release follow non-fickian diffusion. Dasankoppa FS et al (38) developed the CPOPs of Ketorolac which followed Kormeyers Peppas kinetic model which follows the fickian diffusion of the controlled release mechanism.

The accelerated stability study revealed that the optimized batches were stable after 3 months of storage in 40 ± 2ºC and 75 ± 5% RH conditions. Evidences show that the developed formulations provide advantages of lesser number of steps in the manufacturing procedure and are free from laser drilling which can be seen in the other types of osmotic pumps, thereby making it economical (25). It can also be deduced that controlled porosity osmotic pump is a suitable dosage form which can provide a zero order controlled release of potential drug candidates for a period of 24 hours.

## CONCLUSIONS

Formulation n characterization and drug release characteristics of Controlled porosity osmotic pump tablets of metoprolol succinate were studied. Firstly, the core tablets were formulated and optimized by overcoming the problems of poor flowability and extreme fineness of the drug which fell in the desired range of IP-QC tests. On the basis of the drug dissolution profiles and the burst strength of the exhausted shells, two batches containing sodium chloride and potassium chloride each, having drug to osmogen ration 1:1 and coating as 5%, were found to be optimized batches. The effect of coating on the burst strength of the exhausted shells was determined. Also, their effect on the drug release was ascertained. Effect of different parameters like pH, agitational intensity and osmogen were studied on both these batches. A comparison of the various osmotic agents like mannitol, sucrose, dextrose, potassium chloride and sodium chloride was studied and it was concluded that the batch carrying sodium chloride in drug: osmogen ratio of 1:1 with 5% semipermeable membrane coating is the optimal formulation as it follows the Higuchi model which shows zero order drug release for 24 hrs. The batches were found to be stable under accelerated stability conditions as per ICH guidelines.

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