IJPPR
INTERNATIONAL JOURNAL OF PHARMACY & PHARMACEUTICAL RESEARCH
An official Publication of Human Journals
ISSN 2349-7203
HUMAN

Human Journals
**Research Article**
September 2023 Vol.:28, Issue:2


# Formulation and Evaluation of Controlled Pore Forming Osmostic Tablets of Metoprolol Tartrate

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**Submitted:** 18 August 2023
**Accepted:** 20 September 2023
**Published:** 30 September 2023



**Keywords:** Controlled pore osmotic pump, Metoprolol tartrate, Hydroxy propyl cellulose, Avicel 200, cellulose acetate, β-selective adrenergic antagonist.

**ABSTRACT**

The aim of the present work was to prepare and evaluate an osmotic controlled drug delivery system of metoprolol tartrate that can provide continuous drug release for a period of 12 hours. Prior to compression, the prepared granules were evaluated for flow and compression characteristics. Prepared osmotic drug delivery system was evaluated for *in vitro* drug release study. The excipients used in this study did not alter the physicochemical properties of the drug, as tested by FTIR. The prepared osmotic tablets showed good mechanical properties (hardness and friability) as well as good *in vitro* dissolution profile showing the release of constant drug for 12 hours. A stability study was carried out for an optimized batch (F4) for period of 3 months in $40^{O}$C/75% RH condition. The results of stability study indicating insignificant statistical difference before and after storage of formulation in 3 months period.

## INTRODUCTION

Controlled drug delivery system has taken a central stage in pharmaceutical research and development which enhance tolerability and patient compliance.

Oral route is one of the most extensively used routes of drug administration, because of its obvious advantages of ease of administration, improved patient compliance and convenience of administration. The drug having high solubility and relatively short half-life are suggested for an extended-release formulation.

Controlled pore osmotic tablet consist of drug and osmogene in the core and the tablet is surrounded by a semipermeable membrane containing leachable pore forming agent which in contact with an aqueous environment dissolve and result in formulation of microporous membrane. The membrane after the formation of pores becomes permeable for both water and solutes.

Osmotic tablets are special type of controlled release drug dosage form, which are insensitive to various physiological factors that results from food intake, gastric pH and patient-to-patient variability. The delivery strategy and release profile for this type of system can be customised to suit in various APIs with a wide range of thermodynamic properties. Due to these unique features, an osmotically controlled system has witnessed increasing interest and the number of marketed products has doubled in the past decades.

The drug used for the formulation was metoprolol tartrate, which is a β-selective adrenergic antagonist used in the treatment of various cardiovascular diseases like myocardial infraction, heart failure, angina pectoris and mild hypertension. It has a short half-life of 3-7 hr, hence requires frequent dosing of medicament. This will lead to patient non-compliance and also absorption window is reported on upper part of intestine, this limitation can be overcome by developing a controlled pore osmotic drug delivery system.

## MATERIALS

The active medicament Metoprolol tartrate was purchased from Balaji pharmaceutical, Mumbai. Excipients used for the formulation are; Fructose, MCC, Lactose, Talc, Magnesium stearate, Hydroxy propyl cellulose, Stearic acid, Avicel 200.

Talc was purchased from Nice Chemical PVT Ltd, Kochi, Magnesium stearate used as glidant which was purchased from Moly chem, Mumbai. Sorbitol used as pore former

purchased from Nice chemical PVT Ltd, Kochi. Direct compressible vehicle, MCC (Avicel 200) and Cellulose acetate used as semi-permeable membrane, which was purchased from Yarrow chem products, Mumbai.

## METHODS

### Formulation of core tablets:

**Table 1: Formulation chart of core tablets of CPOP F1-F4.**

| SL.NO | INGREDIENTS | F1 | F2 | F3 | F4 |
|---|---|---|---|---|---|
| 1 | Drug [Metoprolol tartrate] (mg) | 50 | 50 | 50 | 50 |
| 2 | Mannitol (mg) | 50 | 100 | * | * |
| 3 | Fructose (mg) | * | * | 50 | 100 |
| 4 | Avicel 200 (mg) | 145 | 145 | 145 | 145 |
| 5 | Magnesium stearate (mg) | 2.5 | 2.5 | 2.5 | 2.5 |
| 6 | Talc (mg) | 2.5 | 2.5 | 2.5 | 2.5 |
| | **TOTAL WEIGHT OF TABLETS** | 250 | 250 | 250 | 250 |
| 7 | Cellulose Acetate | 4 % | 4 % | 4 % | 4 % |
| 8 | DBP | 5% | 5% | 5% | 5% |
| 9 | Sorbitol | 20% | 20% | 20% | 20% |
| 10 | Solvent | q.s | q.s | q.s | q.s |

The core tablet of Metoprolol tartrate was prepared by taking the weighed quantities of the drug (Metoprolol tartrate) and excipients like Avicel 200, Mannitol, fructose, talc and magnesium stearate. The tablets were prepared by direct compression technique. The weighed quantities of ingredients were compressed by using a rotary tablet compression machine.

### Coating of core tablets:

The coating solutions of cellulose acetate in methanol and dichloromethane containing different ratios of pore former sorbitol were prepared for the semipermeable membrane coating. Dibutyl phthalate is used as a plasticizer, which enhance the physical and mechanical stability of semipermeable cellulose acetate coating membrane.

The prepared tablets of metoprolol tartrate were coated by using pan coating machine with an operational condition of, rotation speed 40 rpm, spray gun nozzle diameter of 1mm, at a spray rate of 3ml/min to a drying temperature of $40^{O}C$. After the coating process, the tablets were dried at $50^{O}C$ to remove residual solvent.

**Pre-formulation studies:**

The pre-formulation study is an approach for the generation of pharmaceutical formulation which utilizes knowledge and area application by correlating the physicochemical properties of various chemical entities.

**Solubility study:**

The solubility of the drug Metoprolol tartrate was determined by adding a small increment of the powdered drug in to 10ml of solvent (ethanol, acetone, distilled water and buffer pH 6.4) in a test tube with vigorous shaking. The solubility was determined by visual inspection of clarity of the solvent.

**Melting point determination:**

The melting point of Metoprolol tartrate was determined by capillary method using digital auto-melting point apparatus. A small quantity of Metoprolol tartrate was taken in a glass capillary tube that is previously sealed at one end. Then the capillary tube was inserted into the melting point apparatus and the temperature at which the drug began to melt. The temperature measured using a thermometer that was already immersed into the liquid paraffin present in the apparatus. The practical value was compared with the theoretical value.

**Standard curve for Metoprolol tartrate:**

100mg of Metoprolol tartrate was accurately weighed and dissolved in 100ml of distilled water to prepare stock solution-I. 10ml of stock solution-I was taken and diluted to 100ml with the same solvent to prepare stock solution-II. The aliquot amount of stock solution-II was further diluted with distilled water to get 10-60µg/ml concentration of drug solution. Then the absorbance was measured in an UV spectrophotometer at 273nm against distilled water as blank. The graph was plotted for absorbance Vs. concentration.

**Compatibility study using FTIR**

In formulations, the interaction between active pharmaceutical ingredient and excipient in solid state can cause changes in stability, solubility, dissolution rate and bioavailability of drugs. The drug and KBr was compressed in the ratio of 1:1 and with a pressure of to prepare pellet disc for analysis. The infra-red spectroscopy was conducted by using hydroxyl propyl cellulose and the spectrum was recorded in the region of 4000 to 400 $cm^{-1}$. The interaction between the drug-excipient was observed from IR-spectrum studies by observing any shift in peaks of the drug in the spectrum of the physical mixture of the drug.

**Evaluation of precompression parameters**

**Angle of repose**

The angle of repose is a parameter commonly used to determine the flow property of solid powder. The flow properties of each powder may change due to their interparticle forces. The flow property of the powders greatly influences the uniformity of drug content in the formulation.

Here fixed funnel method is used to determine the angle of repose, where the funnel tip height is fixed as 5cm, above plane paper kept on a flat horizontal surface. The angle of repose was determined by calculating the ratio of base radius ‘r’ and height of the pile ‘h’ in the given following equation.

$$\tan \Theta = h/r$$

$$\Theta = \tan^{-1} h/r$$

Where, Θ = angle of repose

h = height of the pile

r = radius of the pile.

**Table 2: Relationship between angle of repose and flowability.**

| **Angle of repose (Θ)** | **Flowability** |
|---|---|
| 25-30 | Excellent |
| 31-35 | Good |
| 36-40 | Fair |
| 41-45 | Passable |
| 46-55 | Poor |
| 56-65 | Very poor |
| >65 | Very very poor |

**Determination of bulk density and tapped density**

The bulk density of a powder is determined by measuring the volume of a known mass powder sample. The powder sample was transferred into a graduated measuring cylinder, initial untapped volume was measured and calculated according to the formula. The bulk density was calculated by the formula;

$$\text{Bulk density } (\rho b) = \frac{\text{Total weight of granules}}{\text{Total volume of granules.}}$$

**Tapped density**

The tapped density of the powder mixture was determined by the tapping cylinder method. the measuring cylinder contains the powder sample was mechanically tapped approximately 100 times using bulk bulk-density apparatus. The tapped volume was measured and tapped density was calculated by using the formula;

$$\text{Tapped density } (\rho t) = \frac{\text{Total weight of powder}}{\text{Total volume of tapped powder.}}$$

**Carr's compressibility index**

Compressibility index is used to evaluate the flowability of pre-compressed powder by comparing the bulk density and tapped density of the powder mixture. It is also called Carr's index. The percentage compressibility index can be calculated by using the formula;

$$\% \text{ compressibility index} = \frac{\text{Tapped density} - \text{Bulk density}}{\text{Tapped density}} \times 100$$

**Table 3: Correlation between % compressibility and flowability.**

| Carr's compressibility index | Flow Characteristics |
|---|---|
| <10 | Excellent |
| 11-15 | Good |
| 16-20 | Fair |
| 21-25 | Passable |
| 26-31 | Poor |
| 32-37 | Very poor |
| >38 | Very very poor |

**Hausner's ratio**

The Hausner's ratio is a number that is correlated to the flowability of a powder or granular material. It provides an indication of the degree of densification which could result from the vibration of feed hopper interparticle interaction and settling property can be measured by Hausner's ratio.

$$\text{Hausner's ratio} = \frac{\text{Tapped density}}{\text{Bulk density}}$$

**Table 4: Hausner's ratio as an indication of powder flow.**

| Hausner's ratio | Flow Characteristics |
|---|---|
| 1.00-1.11 | Excellent |
| 1.12-1.18 | Good |
| 1.19-1.25 | Fair |
| 1.26-1.34 | Passable |
| 1.35-1.45 | Poor |
| 1.46-1.59 | Very poor |
| >1.60 | Very very poor |

**Evaluation of post-compression parameters**

The post-compression parameter of controlled pore osmotic tablet include diameter, thickness, weight variation, hardness, friability, drug content uniformity, *in vitro* dissolution study to ensure the quality control of formulated tablets.

**Weight variation test**

The weight variation test is performed by taking twenty tablets from each batch and individually weighing them by using an electronic balance. The average weight of formulations was calculated and percentage weight variation is determined by the formulae;

$$\% \text{ weight variation} = (W1-W2) \text{ X } 100/W1$$

Where, W1-Average weight of tablets.

W2 – Individual weight of tablets.

**Table 5: Weight variation limit of tablets as per IP.**

| **The average weight of the tablet** | **Limit % deviation** |
|---|---|
| 80mg or less | 10% |
| More than 80mg but less than 250mg | 7.5% |
| 250mg or more | 5% |

**Hardness**

The hardness test for tablets was performed in order to measure the physical strength of the tablet during handling. A hardness test was performed by taking 10 tablets from each batch and analysed by using a Monsanto hardness tester.

**Thickness and diameter of tablets**

The thickness and diameter of prepared tablets were measured by using a calibrated vernier calliper. The randomly selected 10 tablets from each batch of formulation were individually measured and reported.

**Friability test**

The friability refers to the ability of the compressed tablet to avoid fracture and breaking during transportation. The friability is defined as the percentage of weight loss by the tablets due to mechanical action during the test. The 10 tablets were randomly selected from a batch, weighed and loaded into the drum of tablet friablator. The friablator was operated at a speed of 25 RPM for 10 minutes. At the end of the operation, all the tablets were collected and weighed again. The percentage loss of weight was determined by the formula;

% Friability = [(initial weight-final weight) / initial weight] X100

**Uniform drug content**

10 tablets were randomly selected and average weight was calculated. Then all 10 tablets in a mortar. The amount of powder equivalent to 100mg was taken and transferred in to a 100ml volumetric flask. Add 50 ml of 0.1 N hydrochloric acid and sonicate for 20 min. then the volume made up to the mark. The solution was filtered. The filtrate was diluted suitably using 0.1N Hydrochloric acid and the uniform drug content was determined by UV spectrophotometer at 273 nm against blank. The drug content should not be less than 90% ant more than 110% of labelled value.

***In vitro* disintegration study**

The disintegration test measures the time required under a given set of conditions for a group of tablets to disintegrate into particles which will pass through a 10mesh screen. The disintegration test apparatus IP was set up according to its operation manual. The test parameters of 37±2$^{O}$C temperature and time set up to 60 minutes. One paralegal tablet is introduced into each tube, add the disk into each tube and start operation.

***In vitro* dissolution study**

A dissolution test apparatus (USP type II) was used to carry out dissolution studies of all formulation batches (F1-F4). 900ml of dissolution media contain 0.1N HCl, pH 1.2 and phosphate buffer pH 6.8 for 12 hours at 50 rpm at 37±0. 5$^{O}$C. At different time intervals (0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12hr) 2ml of sample solution were withdrawn and filtered. Then 1ml of filtered sample solution was diluted up to 10ml with same dissolution media. It is then analysed for drug content by using UV-Visible spectrophotometer at 273 nm. Before that 2ml sample was replaced in the vessel after each withdrawal to maintain sink condition. From the

*in vitro* dissolution studies percentage drug release was calculated then the percentage drug release was plotted against the time to study the release pattern of the drug.

**Drug release kinetics**

The *in vitro* release data of formulated tablets were fitted to various models (zero order, first order, Higuchi, Hixoson-Crowell and Korsmeyer-peppas model). The best fit models with higher correlation coefficient were analysed from the data.

**Stability studies**

The optimized formulation was subjected for stability study for a period of 3 months in a stability chamber which is maintained at 40±2$^{O}$C/75±5% relative humidity. After every month tablet samples were analysed for physical appearance, hardness, drug uniform content and *in vitro* release.

**RESULTS AND DISCUSSION**

**Pre-formulation studies:**

**Solubility study:**

The solubility study of Metoprolol Tartrate was performed with various solvents which is shown in table-6.

**Table 6: Solubility study of Metoprolol tartrate.**

| **Solvent** | **Observation** |
|---|---|
| Ethanol | Freely soluble |
| Acetone | Slightly soluble |
| Distilled water | Very soluble |
| Buffer pH 6.4 | Soluble |

**Melting point determination:**

The normal melting point range of Metoprolol tartrate was 121-124$^{O}$C. By the determination of the melting point of Metoprolol tartrate, the value observed was 123±0.5$^{O}$C.

**Table 7: Melting point study of Metoprolol tartrate.**

| Drug | Melting point range | Melting point obtained |
|---|---|---|
| Metoprolol Tartrate | 121-124$^{O}$C | 123±0.5$^{O}$C |

Mean ± SEM, n=3

**Preparation of standard stock solution:**

Standard drug solution of Metoprolol tartrate was prepared by dissolving 10mg pure Metoprolol Tartarate in phosphate buffer 6.8 and transferred into 100ml volumetric flask to obtain 10µg/ml of stock solution from which desired concentrations 5, 10, 15, 20, 25 µg/ml of solutions were prepared.

**Determination of λmax:**

A 10 µg/ml solution of Metoprolol tartrate was prepared and scanned in UV range of 200-400nm and the spectrum was obtained. The λmax was found to be at 273 nm wave length where absorbance was maximum.

**Preparation of calibration curve:**

The standard stock solution was suitably diluted with phosphate buffer 6.8 to obtain concentrations ranging from 5-25 µg/ml. The absorbance of these solutions was measured at 273nm using UV. The calibration curve was plotted as concentration versus absorbance over the range of 5-25 µg/mL.

**Table 8: Peak detection of Metoprolol tartrate.**

| λ (nm) | Absorbance |
|---|---|
| 399.00 | 0.007 |
| 364.40 | 0.020 |
| 341.20 | 0.025 |
| 339.60 | 0.027 |
| 305.90 | 0.047 |
| 273.30 | 0.122 |

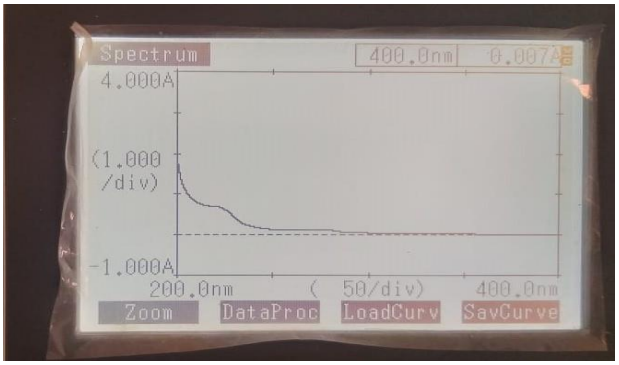


**Figure 1: Peak detection of Metoprolol tartrate by UV spectrophotometry**.

**Table 9: Calibration curve of Metoprolol tartrate at 273nm.**

| Sl. No | Concentration | Absorbance |
|---|---|---|
| 1 | 0 | 0 |
| 2 | 5 | 0.106±0.001 |
| 3 | 10 | 0.210±0.003 |
| 4 | 15 | 0.352±0.003 |
| 5 | 20 | 0.486±0.006 |
| 6 | 25 | 0.576±0.006 |

Mean ± SEM, n=3

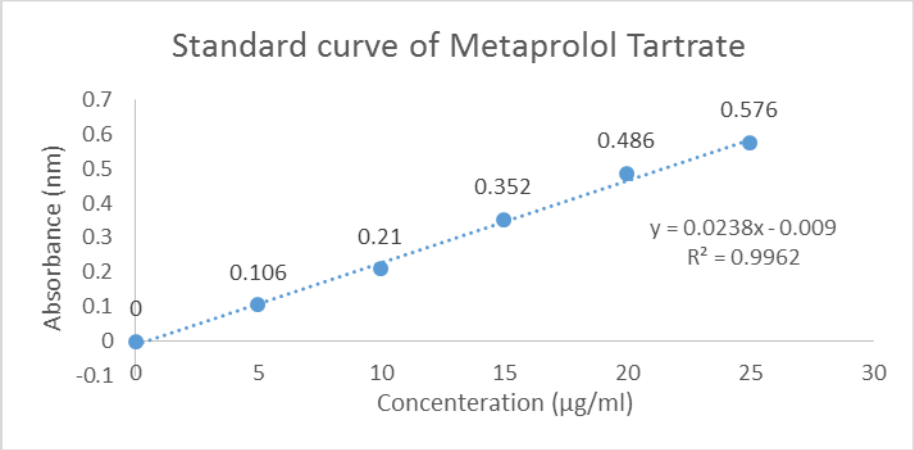


**Figure 2: Calibration curve of Metoprolol tartrate at 273nm.**

**Compatibility study:**

The FT-IR spectrum of Metoprolol tartrate shows the characteristic functional groups of this organic molecule. The hydrogen-bonded O-H band is a broad peak between 3000 to 3600 cm-$^{1}$. An alkane chain is evidenced by several sp3C-H bands between 2840 to 3000 cm-$^{1}$. An aromatic character in the sample is evidenced by several bands. Two strong C=C stretch bands at 1513 and 1591-1610 cm-$^{1}$. The phenyl alkyl ether character of the sample is evidenced by two strong bands at 1244 and 1110 cm-$^{1}$ due to the two kinds of C-O bonds. Since the pharmaceutical compound is carboxylate salt, strong bands are observed at 1395 cm-$^{1}$ due to asymmetric or symmetric stretching of this carboxylate. Comparing the results of FTIR spectrums of both pure drug as well as powder mixture lead to a conclusion that the drug and excipients are compatible for the formulation.

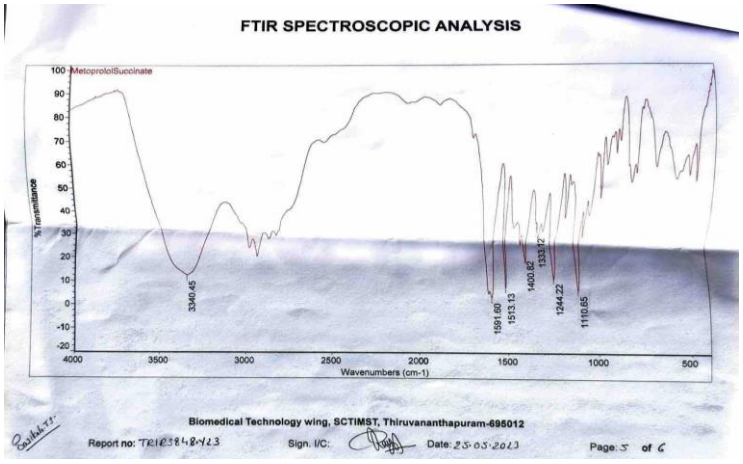


**Figure-3: FTIR spectrum of Metoprolol tartrate.**

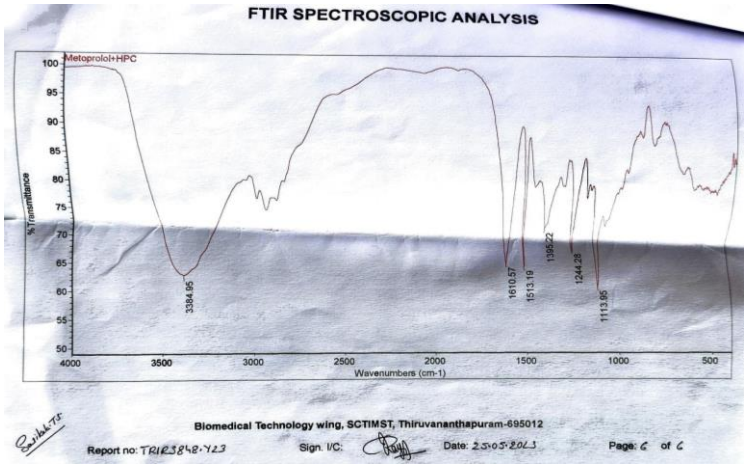


**Figure-4: FTIR spectrum of Metoprolol and excipients.**

**Micrometric properties:**

**Table 10: Micrometric properties of formulation F1-F4.**

| Formulation | Bulk density (g/ml) | Tapped density (g/ml) | Compressibility index (%) | Hausner's ratio | Angle of repose (Ɵ) |
|---|---|---|---|---|---|
| F1 | 1.20±0.02 | 1.33±0.01 | 10.35±1.37 | 1.18±0.13 | 29.07±0.96 |
| F2 | 1.17±0.01 | 1.37±0.04 | 14.39±1.59 | 1.18±0.15 | 32.12±0.66 |
| F3 | 1.11±0.1 | 1.36±0.02 | 17.82±2.4 | 1.16±0.17 | 29.55±1.40 |
| F4 | 1.12±0.02 | 1.38±0.03 | 18.61±2.81 | 1.19±0.18 | 29.83±1.36 |

Mean ± SEM, n=3.

The bulk density of the prepared powder blend found quite a higher value ranges from 1.11±0.1 to 1.20±0.02 g/ml, which shows its granular character. The tapped density of prepared powder blend ranges from 1.33±0.01 to 1.38±0.03 g⁄ml. The Hausner's ratio of formulations F1 to F4 was found to be between 1.16±0.17 to 1.19±0.18, which indicate less internal friction between powder particles results in good free flowing properties. The compressibility index ranges from 10.35±1.37 to 18.61±2.81. The results show good compression and flow property. The angle of repose for the formulations F1 to F4 was found to be in the ranges of 29.07±0.96º to 32.12±0.66º, indicating good flow property.

**Evaluation of post compression parameters:**

**Table-11: Post compression parameters of formulation F1-F4.**

| Formulation | Diameter (mm) | Thickness (mm) | Uniformity of weight (g) | Hardness (kg/Cm$^2$) | Friability (%) | Drug content (%w/w) |
|---|---|---|---|---|---|---|
| F1 | 0.8±0.005 | 0.51±0.02 | 0.224±0.002 | 2.34±0.05 | 0.89±0.32 | 98.4±0.55 |
| F2 | 0.8±0.009 | 0.51±0.01 | 0.225±0.005 | 2.06±0.14 | 0.85±0.25 | 99.73±0.83 |
| F3 | 0.79±0.14 | 0.52±0.01 | 0.217±0.009 | 2.14±0.15 | 0.79±0.21 | 100.63±1.04 |
| F4 | 0.79±0.008 | 0.52±0.00 | 0.229±0.006 | 2.01±0.15 | 0.86±0.21 | 100.96±.90 |

Mean ± SEM, n=3.

The formulated Metoprolol tartrate tablet shows almost uniform diameter and thickness in all formulations (F1-F4) is an indication of the uniform size of tablet.

The uniformity of tablets' weight was almost within the standard limit. So, all formulations passed the test of weight variation.

***In vitro* drug release study of Metoprolol tartrate CPOP tablet:**

**Table-12: *In vitro* drug release study of Metoprolol tartrate tablet F1-F4.**

| Time | F1 | F2 | F3 | F4 |
|---|---|---|---|---|
| **0** | 0 | 0 | 0 | 0 |
| **1** | 1.3 | 2.3 | 2.7 | 2.2 |
| **2** | 9.5 | 9.3 | 8.9 | 7.6 |
| **3** | 11.8 | 10.3 | 14.5 | 18.7 |
| **4** | 19.6 | 23 | 20.3 | 25.6 |
| **5** | 25.6 | 34 | 29.8 | 34.7 |
| **6** | 31.7 | 42 | 46.2 | 46.8 |
| **7** | 45.8 | 56 | 54.6 | 57.4 |
| **8** | 52.3 | 67 | 65.2 | 68.4 |
| **9** | 68.2 | 75 | 76.4 | 76.3 |
| **10** | 76.5 | 84 | 89.2 | 83.4 |
| **11** | 86.3 | 94 | 94.3 | 89.6 |
| **12** | 92.5 | 98 | 97.5 | 99.1 |

All the formulations F1-F4 were subjected to *in vitro* release study. The formulation F4 containing a 1:2 (drug: osmogene) ratio shows a better result of 99.1% drug release at 12hr. By comparing the drug release results of various osmogen, the formulation F4 with fructose gives a better result than formulations with mannitol.

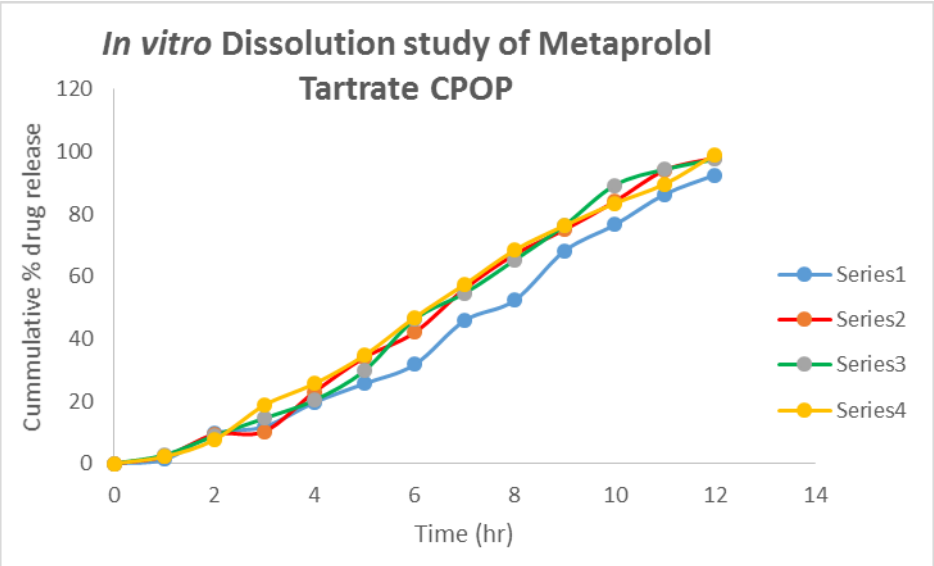


**Figure-5: *In vitro* drug release study of Metoprolol tartrate CPOP tablet**.

**Release kinetics:**

**Table-13: Release kinetics of optimized formulation Metoprolol tartrate CPOP.**

| Formulation Code | RELEASE KINETICS | | | | |
|---|---|---|---|---|---|
| | Zero order | First order | Higuchi | Peppas | |
| | | | | $R^2$ | n |
| F1 | 0.974 | 0.854 | 0.831 | 0.973 | 0.566 |
| F2 | 0.985 | 0.847 | 0.861 | 0.968 | 0.572 |
| F3 | 0.982 | 0.851 | 0.856 | 0.967 | 0.585 |
| F4 | 0.992 | 0.817 | 0.886 | 0.965 | 1.689 |

The dissolution profile of all the formulations F1-F4 were fitted to various kinetic models like zero order, first order, Hixson-Crowell, Korsmeyer and Peppas to ascertain the release pattern and mechanism. The results reveals that all the formulation F1-F4 follows zero zero-order dissolution release pattern.

**Stability studies.**

**Table-14: Stability study data of optimized formulation Metoprolol tartrate CPOP.**

| Parameters | Before stability study | stability study after 1 month | Stability study after 2 months | Stability study after 3 months |
|---|---|---|---|---|
| Physical Change | white colour, odourless | white colour, odourless | white colour, odourless | white colour, odourless |
| Hardness(kg/$Cm^2$) | 2.10±0.2 | 2.34±0.4 | 2.45±0.3 | 2.52±0.6 |
| % Drug content | 100.91±0.81 | 100.1±0.64 | 99.81±0.74 | 99.37±0.81 |
| *In Vitro* dissolution (%) | 99.12 | 98.67 | 98.11 | 97.98 |

Mean ± SEM, n=3

The optimized formulation F4 was subjected to 3-month accelerated study under the conditions of 40±2$^{O}$C at 75±5% RH as per ICH guidelines. The drug release profile, % drug content, hardness and physical changes were monitored for 3 months. The result of the accelerated stability study (**Table**) revealed no significant change in the parameters. Therefore, the formulation F4 was considered to be stable during it shelf-life period.

## CONCLUSION:

It was concluded that the Metoprolol tartrate osmotic drug delivery system can be formulated and optimized with a better release profile for a prolonged period of time up to 12 hr. It could decrease the frequency of dose administration and improve patient compliance. The optimized formulation F4 was found to be stable after 3 months of storage under accelerated stability conditions. Further, *in vivo* studies are required to correlate *in vitro* release data.

## ACKNOWLEDGEMENT:

The authors are thankful to Dr. Ganesh Sanker S, Assistant Professor, and Mrs. Lekshmi M. S. Panicker, Assistant Professor, Mar Dioscorus College of Pharmacy, Sreekaryam, Thiruvananthapuram. We also are grateful to Mar Dioscrous College of Pharmacy, Sreekaryam, and Thiruvananthapuram where we worked.

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