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DEVELOPMENT AND EVALUATION OF OSMOTICALLY CONTROLLED ORAL DRUG DELIVERY SYSTEM

S.K Ghate, Dr. D.M.Sakarkar.
[1]*IBSS College of Pharmacy Malkapur.*
[2]*Sudhakarrao Naik Institute of Pharmacy Pusad.*

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ABSTRACT

Conventional drug delivery systems have slight control over their drug release and almost no control over the effective concentration at the target site. This kind of dosing pattern may result in constantly changing, unpredictable plasma concentrations. Drugs can be delivered in a controlled pattern over a long period of time by the controlled or modified release drug delivery systems. They include dosage forms for oral and transdermal administration as well as injectable and implantable systems. For most of drugs, oral route remains as the most acceptable route of administration. Certain molecules may have low oral bioavailability because of solubility or permeability limitations. Development of an extended release dosage form also requires reasonable absorption throughout the gastro-intestinal tract (GIT). Among the available techniques to improve the bioavailability of these drugs fabrication of osmotic drug delivery system is the most appropriate one. Osmotic drug delivery systems release the drug with the zero order kinetics which does not depend on the initial concentration and the physiological factors of GIT. This review brings out new technologies, fabrication and recent clinical research in osmotic drug delivery. Osmotically controlled drug delivery systems use osmotic pressure for controlled delivery of active agent(s). Drug delivery from these systems, to a large extent, is independent of the physiological factors of the gastrointestinal tract. Because of their unique advantages over other types of dosage forms, osmotic pumps form a class of their own among the various drug delivery technologies, and a variety of products based on this technology are available on the market.

Corresponding author
S. K Ghate
IBSS College of Pharmacy Malkapur.

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INTRODUCTION

Many conventional drug delivery systems have been designed by various researchers to modulate the release a drug over an extended period of time and release (1). The rate and extent of drug absorption from conventional formulations may vary greatly depending on the factors such as physico-chemical properties of the drug, presence of excipients, physiological factors such as presence or absence of food, pH of the gastro-intestinal tract (GI) and so on (2). However, drug release from oral controlled release dosage forms may be affected by GI motility and presence of food in the GI tract (3). Drugs can be delivered in a controlled pattern over a long period of time by the process of osmosis. Drug delivery from this system is not influenced by the different physiological factors within the gut lumen and the release characteristics can be pre-dicted easily from the known properties of the drug and the dosage form (4). Osmosis can be defined as the spontaneous movement of a solvent from a solution of lower solute concentration to a solution of higher solute concentration through an ideal semipermeable membrane, which is permeable only to the solvent but impermeable to the solute. The pressure applied to higher concentration side to inhibit solvent flow is called the osmotic pressure. The first osmotic effect was reported by Abbe Nollet in 1748. Later in 1877, Pfeffer performed an experiment using semi-permeable membrane to separate sugar solution from pure water. He showed that the osmotic pressure of the sugar solution is directly proportional to the solution concentration and the absolute temperature. In 1886, Vant Hoff identified an underlying proportionality between osmotic pressure, concentration and temperature. He revealed that osmotic pressure is proportional to concentration and temperature and the relationship can be described by following equation.

$$\pi = n2\ RT$$

Where, π = osmotic coefficient
n2 = molar concentration of solute in the solution
R = gas constant
T = Absolute temperature

Osmotic pressure is a colligative property, which depends on concentration of solute that contributes to osmotic pressure. Solutions of different concentrations having the same solute and solvent system exhibit an osmotic pressure proportional to their concentrations. Thus a constant osmotic pressure, and thereby a constant influx of water can be achieved by an osmotic delivery system that results in a constant zero order release rate of drug (5).

BASIC COMPONENTS OF OSMOTIC SYSTEMS

Drug

Metoprolol succinate Which have short biological half-life and which is used for prolonged treatment are ideal candidate for osmotic systems.

Semipermeable membrane

An important part of the osmotic drug delivery system is the semipermeable membrane housing. Therefore, the polymeric membrane selection is key to the osmotic delivery formulation. The membrane should possess certain characteristics, such as impermeability to the passage of drug and other ingredients present in the compartments. The membrane should be inert and maintain its dimensional integrity to provide a constant osmotic driving force during drug delivery (6).

Osmotic agent

Osmotic agents maintain a concentration gradient across the membrane. They also generate a driving force for the uptake of water and assist in maintaining drug uniformity in the hydrated formulation. Osmotic components usually are ionic compounds consisting of either inorganic salts or hydrophilic polymers. Osmotic agents can be any salt such as sodium chloride, potassium chloride, or sulfates of sodium or potassium and lithium. Additionally, sugars such as glucose, sorbitol, mannitol or inorganic salts of carbohydrates can act osmotic agents.

Coating solvent

Solvents suitable for making polymeric solution that is used for manufacturing the wall of the osmotic device include inert inorganic and organic solvents that do not adversely harm the core, wall and other materials. The typical solvents include methylene chloride, acetone, methanol, ethanol, isopropyl alcohol, butyl alcohol, ethyl acetate, cyclohexane, carbon tetrachloride, water etc. The mixtures of solvents such as acetone-methanol (80:20), acetone-ethanol (80:20), acetone-water (90:10), methylene chloride-methanol (79:21), methylene chloride-methanol-water (75:22:3) etc. can be used (7).

Plasticizers

Different types and amount of plasticizers used in coating membrane also have a significant importance in the formulation of osmotic systems. They can change visco-elastic behavior of polymers and these changes may affect the permeability of the polymeric films (8). Some of the plasticizers used are as below:

- Polyethylene glycols
- Ethylene glycol monoacetate; and diacetate- for low permeability
- Tri ethyl citrate

Pore forming agent

These agents are particularly used in the pumps developed for poorly water soluble drug and in the development of controlled porosity or multiparticulate osmotic pumps. These poreforming agents cause the formation of microporous membrane. The microporous wall may be formed in situ by a pore-former by its leaching during the operation of the system. The pore formers can be inorganic or organic and solid or liquid in nature. For example, alkaline metal salts such as sodium chloride, sodium bromide, potassium chloride, potassium sulphate, potassium phosphate etc., alkaline earth metals such as calcium chloride and calcium nitrate, carbohydrates such as sucrose, glucose, fructose, mannose, lactose, sorbitol, mannitol and, diols and polyols such as polyhydric alcohols and polyvinyl pyrrolidone can be used as pore forming agents.

Coating solvent

Solvents suitable for making polymeric solution that is used for manufacturing the wall of the osmotic device include inert inorganic and organic solvents that do not adversely harm the core, wall and other materials. The typical solvents include methylene chloride, acetone, methanol, ethanol, isopropyl alcohal, butyl alcohal, ethyl acetate, cyclohexane, carbon tetrachloride, water etc. The mixtures of solvents such as acetone-methanol (80:20), acetone-ethanol (80:20), acetone-water (90:10), methylene chloride-methanol (79:21), methylene chloride-methanol-water (75:22:3) etc. can be used (9).

Advantages of osmotic drug delivery system

1. The delivery rate of zero-order is achievable with osmotic systems.
2. The release from osmotic systems is minimally affected by the presence of food in gastrointestinal tract.
3. A high degree of in vivo- in vitro correlation (IVIVC) is obtained in osmotic systems.
4. For oral osmotic systems, drug release is independent of gastric pH and hydro-dynamic conditions.

Limitations of osmotic drug delivery system

1. Special equipment is required for making an orifice in the system.
2. Residence time of the system in the body varies with the gastric motility and food intake.
3. It may cause irritation or ulcer due to release of saturated solution of drug.

Examples of commonly used osmogents

Table no.1.

Compound mixture	Osmotic pressure
Mannitol-Lactose	130
Mannitol-Fructose	415
Potassium Chloride	245
Mannitol	38
Sodium Chloride	356

TYPES

Elementary osmotic pump (EOP)

The was introduced in 1970s to deliver drug at zero order rates for prolonged periods, and is minimally affected by environmental factors such as pH or motility. The tablet consists of an osmotic core containing the drug surrounded by a semipermeable membrane laser drilled with delivery orifice. Following ingestion, water in absorbed into system dissolving the drug, and the resulting drug solution is delivered at the same rate as the water entering the tablet. The disadvantages of the elementary pump are that it is only suitable for the delivery of water soluble drugs (10,11).

Push–Pull Osmotic Pump (PPOP)

Push pull osmotic pump is a modified elementary osmotic pump through, which it is possible to deliver both poorly water-soluble and highly water soluble drugs at a constant rate. The push–pull osmotic tablet consists of two layers, one containing the drug and the other an osmotic agent and expandable agent. A semipermeable membrane that regulates water influx into both layers surrounds the system. While the push–pull osmotic tablet operates successfully in delivering water-insoluble drugs, it has a disadvantage that the complicated laser drilling technology should be employed to drill the orifice next to the drug compartment (12).

Osmotic bursting osmotic pump

This system is similar to an EOP expect delivery orifice is absent and size may be smaller. When it is placed in an aqueous environment, water is imbibed and hydraulic pressure is built up inside until the wall rupture and the content are released to the environment. Varying the thickness as well as the area the semipermeable membrane can control release of drug. This system is useful to provide pulsated release (13).

OROS-CT

OROS-CT (Alza corporation) is used as a once or twice a day formulation for targeted delivery of drugs to the colon. The OROS-CT can be a single osmotic agent or it can be comprised of as many as five to six push pull osmotic unit filled in a hard gelatin capsule. After coming in contact with the gastric fluids, gelatin capsule dissolved and the enteric coating prevents entry of fluids from stomach to the system as the system enters into the small intestine the enteric coating dissolves and water is imbibed into the core thereby causing the push compartment to swell. At the same time flowable gel is formed in the drug compartment, which is pushed out of the orifice at a rate, which is precisely controlled, by the rate of water transport across the semi permeable membrane. Incorporation of the cyclodextrin-drug complex has also been used as an approach for delivery of poorly water soluble drugs from the osmotic systems. Ex. Sulfobutylether-Bcyclodextrin sodium salt serves as a solubilizer and osmotic agent (1).

MATERIALS AND METHODS

Materials

Metoprolol succinate is obtained from CTX Lifescience Pvt. Ltd Surat , Gujarat, Cellulose acetate Eastman chemical INTL,USA, Tablettose obtained from Signet Pharmaceutical Pvt. Ltd, Mumbai Mannitol, Magnesium stearate obtained from Loba Chemie, Pvt. Ltd, Mumbai, NaCl obtained from Reasearch lab, Mumbai, Talc, Methanol GR obtained from Merck India, Acetone Thomas Baker (Chemicals) Ltd, Mumbai, India.

Methods

Preparation of Osmotic Pump Tablets of Metoprolol succinate

Preparation of the Core Tablets

The controlled release matrix tablets of Metoprolol succinate was prepared by direct compression method. Table No. 2 shows the composition of each matrix formulation. The formulation of each controlled release matrix tablets of Metoprolol succinate is composed of Mannitol and NaCl as a osmogents in various concentrations. The other excipients used were Tablettose, Magnesium stearate, Aerosil & talc. The weight of tablet was adjusted to 300mg and each tablet contained 47.5 mg of batches (F1-F3) were Metoprolol succinate prepared. All the excipient as per given in weighing record was dispensed and sifted through 40 mesh. Drug, Tablettose 100,osmotic agent was mixed and blended in polybag for 10 min, magnesium stearate and colloidal silicon dioxide were added to blend again for 5 min in polybag, and tablets were compressed with 8 mm round concave punch to produce the desired tablets.

Table no. 2.

Batches	API	Tablettose (mg)	Mannitol (mg)	NaCl (mg)	Aerosil (mg)	Mg. Stearate (mg)	Talc (mg)	Tablet weight (mg)
F1	47.5	152.1	50	50	0.1	0.2	0.1	300
F2	47.5	202.1		50	0.1	0.2	0.1	300
F3	47.5	202.1	50	-	0.1	0.2	0.1	300

Fig. 1 Prepared core tablet.

Evaluation uncoated/core tablet.

Hardness

Although hardness test is not an official, tablet should have sufficient handling during packing and transportation. Hardness of tablet was measured using Monsanto hardness tester. It is the pressure required to fracture diametrically placed tablets by applying the force. The hardness of 3 tablets, from each batch was determined and mean hardness was taken into account, which was expressed in Kg/cm^2

Weight Variation Test

20 tablets were weighed individually, average weight was calculated and individual tablet weight was compared to the average USP weight variation test.

Friability

Friability test was performed to assess the effect of friction and shocks, which may often cause tablet to chip, cap or break. Roche Friabilator was used for the purpose. Compressed tablets should not more than 1% of their weight.(14,15) The percentage friability was measured using the formula,

$$\% F = \{1-(Wo/W)\} \times 100$$

Where,
% F = friability in percentage
Wo= Initial weight of tablet
W= weight of tablets after revolution

Thickness

The thickness of the tablet was measured using Vernier caliper. Thickness of three tablets from each batch was measured and mean was calculated.(14,15)

Preparation of coating solution

Table no.3.

Ingradients	Quantity in gram
Cellulose acetate	5
Triacetine	1.2
Methyl orange	0.1
Acetone	80
Methanol	20

Excipients as per given in Table No-3 was dispensed cellulose acetate and triacetin were mixed in solvent with continues stirring with mechanical stirrer at 500 rpm stirred the solution for 45 min. upto complete clear solution forms.

Coating of the tablet

Coating was done by using conventional coating machine, 1 liter coating pan used for coating of the tablet. Rotation speed of the pan was 25 rpm and solution spray on tablets using spray gun from distance of 15 cm and tablets were dried by using hot air dryer.

Fig.2 Coated tablet.

Drilling of the tablet

Coated tablet was drilled by using mechanical micro drill machine by using 0.1 mm and 0.2 mm, 0.7 mm beats.

Fig. 3 Mechanical Micro drill Machine.

***In-vitro* Dissolution Stdy of Coated Tablet**

The *In-vitro* dissolution test for press coated tablets were performed in triplicate using an eight-station USP type Π (paddle) apparatus (Electro lab) at 37°C ± 0.5°C and 50 rpm speed in 500 ml each pH 6.8 phosphate buffer for rest of time were used as dissolution media. Aliquots of 5 ml dissolution fluid were removed at specified time intervals of one hour and an equivalent amount of fresh dissolution fluid equilibrated at the same temperature was replaced. Aliquots were filtered through Whatman filter paper, suitably diluted using dissolution medium and analyzed for the amount of Metoprolol succinate released by a spectrophotometer (UV1700, Shimadzu, Japan) at a wavelength 225.0 nm respectively. The amounts of drug present in the samples were calculated with the help of appropriate calibration curve constructed from reference standard. Cumulative percentage drug release was calculated.(16)

Kinetics of drug release

Zero-order model

If drug release from controlled release formulation is stable in fluid at the absorption site, has similar absorption sites and it absorbed rapidly and completely after its release then, its rate of appearance in plasma will be governed by its rate of release from the controlled release formulation. Thus, when the drug release follows zero-order kinetics, absorption will also be a zero-order process and concentration of drug in plasma at any given time can be given by equation (17):

$$C = \frac{F\,K_o\,(1-e^{-ket})}{K_E\,V_d}$$

Results and discussion 1.Characterization of Metoprolol succinate

Organoleptic Characterization and Melting Point Determination Metoprolol succinate.

Table no.4.

Test	Observation
Nature	Crystalline
Colour	White
Odor	Odorless
Taste	Bitter
Melting point	136-137^{0}C

Solubility Analysis

Table No. 5: Solubility profile of Metoprolol succinate.

Sr No.	Solvent	Solubility
1	Water	Freely Soluble
2	Methanol	Soluble
3	Ethanol	Slightly Soluble
4	Isopropyl Alcohol	Slightly Soluble

Micromeritic Characterization of Drug

Table No. 6 : Micromeritic characterization of Metoprolol succinate.

Sr No.	Parameters	Result
1	Loose bulk density	0.35 gm /cm^2
2	Tapped density	0.35 gm /cm^2
3	Carr's index	15.37 %
4	Hausner's ratio	1.18
5	Angle of repose	31^0

On the basis of Micromeretic properties it was confirmed that the drug Metoprolol succinate possessed sufficient flowability to be used for direct compression.

Spectroscopic Studies

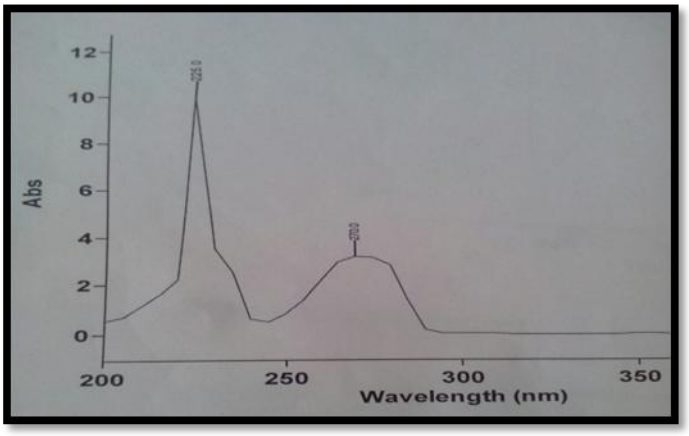

Fig.4 UV Spectroscopy.

Fig.4 shows (Determination of λ_{max}) UV-Light absorption spectrum of Metoprolol succinate in 6.8 pH Phosphate buffer

FTIR spectra of Metoprolol succinate.

FTIR spectra

Dry sample of drug and potassium bromide was mixed uniformly and filled into the die cavity of sample holder and an IR spectrum was recorded using diffuse reflectance FTIR spectrophotometer (Agilent cary 630).

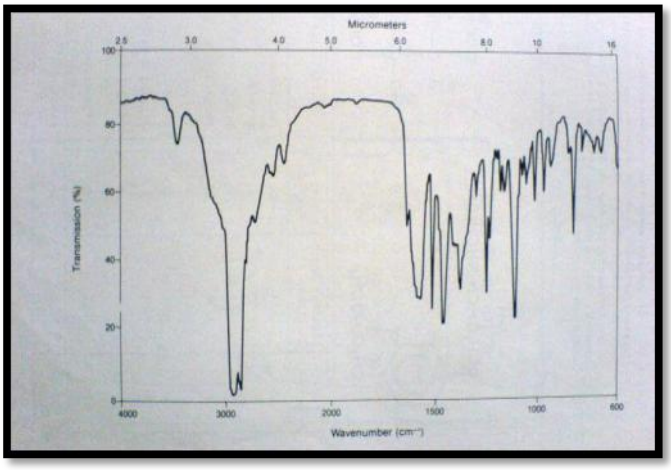

Fig. 5: FTIR Spectra Metoprolol succinate.

Preparation of pH 6.8 phosphate buffer

Phosphate buffer pH 6.8 was prepared by using 28.80gm of disodium hydrogen phosphate and 11.45 gm of potassium hydrogen phosphate in sufficient water to produce 1000 ml.

Calibration curve of Metoprolol succinate in pH 6.8 phosphate buffer

Various drug concentrations (2-18µg/ml) in intestinal fluid were prepared and the absorbance was measured at 225nm. The results are shown in Table 8 and Fig 7.

Fig.5 Calibration curve of Metoprolol succinate in water.

Metoprolol succinate was analysed by using UV-visible Spectrophotometer and using distilled water at solution at 225 nm with different concentration of solution. (as shown in fig no.6)

Table no.7.

Sr No.	Concentration (µg/ml)	Absorbance
1	0	0
2	2	0.0348
3	4	0.087
4	6	0.1256
5	8	0.1695
6	10	0.2102
7	12	0.2512

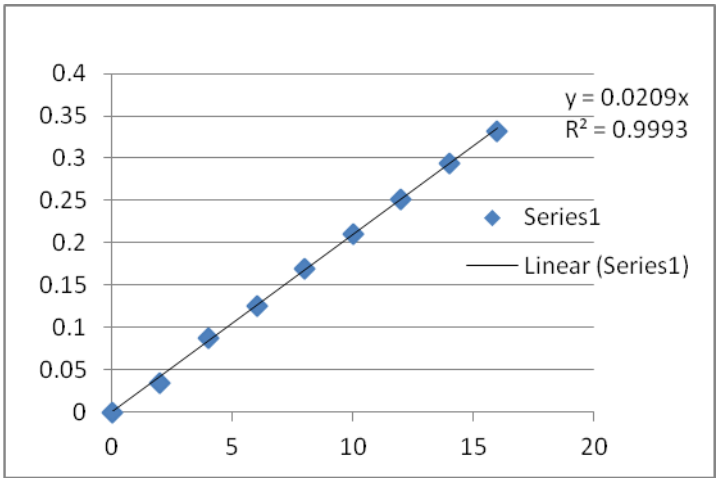

Fig. 6 UV Spectroscopy.

Table no.8.

Sr No.	Concentration (µg/ml)	Absorbance
1	0	0
2	2	0.0321
3	4	0.0645
4	6	0.0992
5	8	0.1278
6	10	0.1602
7	12	0.1945

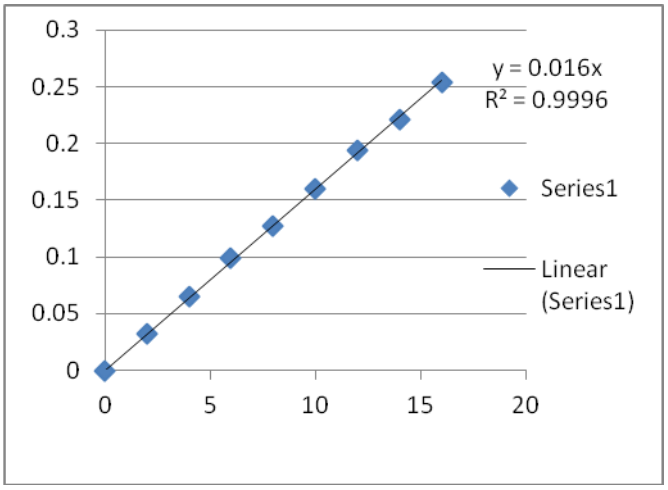

Fig. 7 UV Spectroscopy (Determination of λ_{max}).

Evaluation of prepared powder blend of Metoprolol succinate

Angle of repose

The results of angle of repose of all the formulations were found to be in range of $27^0$26'±0.01 to $29^0$64'±0.02 indicating excellent flow property and this was further supported by lower compressibility index values. Thus it can be concluded that the granules for all the batches possessed good flow characteristics.

Bulk density

It has been stated that the bulk density values less than 1.2g/cm^2 indicate good packing and values greater than 1.5g/cm^2 indicate poor packing. The loose bulk density and tapped bulk density values for all the formulation varied in range 0.43±0.01g/cm^3 to 0.46±0.02g/cm^3 respectively. The values obtained lies within the acceptable range. These results may further influence property such as compressibility and tablet dissolution.

Compressibility index

The percent compressibility of granules was determined by Carr's index. The percent compressibility for all formulation lies within the range of 8.41±0.01 % to 11.35±0.02 % indicates acceptable flow property.

Hardness

Tablet hardness was determined by using Monsanto hardness tester. Hardness of three tablets of each tablet was determined. Hardness values of the formulation ranged from 4.2 to 4.5kg/cm^2, which indicate good strength of tablet.

Friability

Tablet friability was determined by Roche friabilator and weight loss was calculated and represented in the terms of percent friability. Friability values of all the formulation were less than 1%, indicating good strength of tablet.

Weight variation

In weight variation test, the Pharmacopoeial limit for percent of deviation for tablets weight was less than 324 mg is not more than 2.5 %.The average percent deviation of all tablets was found to be within the limit and hence all formulation passes the weight variation test.

Thickness

Examination of tablets from each batch showed flat circular shape with no cracks having white colour. The thickness of tablets was determined using Vernier caliper. The thickness of tablets ranged from 4.65±0.01 to 4.67±0.08. All formulations showed uniform thickness.

Drug content

The drug content was found to be 98.19 to 99.32 %

***In-vitro* drug release studies**

The dissolution rate was studied using 500 ml of pH 6.8 phosphate buffer for 1hrs, 4hr, 8hrs, 20hrs using USP dissolution apparatus type I. The theoretical release profile calculation is important to evaluate the formulation with respect to release rates and to ascertain whether it releases the drug in predetermine manner.

Table No. 9 *In-vitro* dissolution data of F1, F2, and F3 formulation.

Time (Hrs)	Cumulative percent drug release		
	F1	F2	F3
0	0	0	0
1	3	8	7
4	20	30	27
8	35	50	45
20	70	85	78

All the values are represents as Mean ± S. D. (standard deviation) (n=3).

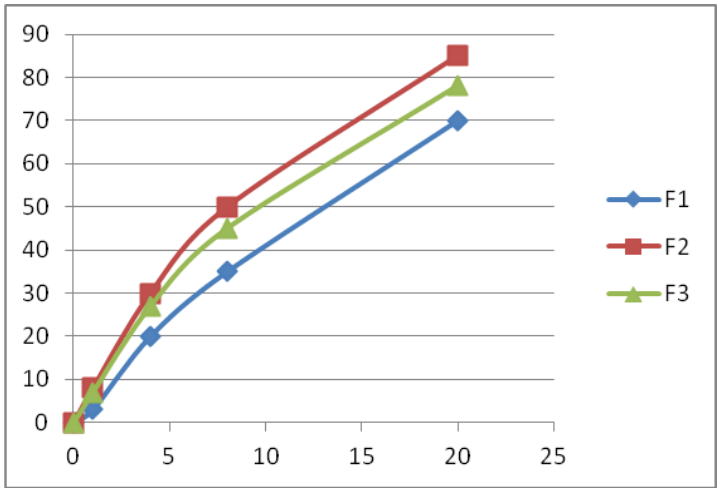

Figure: 8 In-*vitro* dissolution profile of F1, F2 and F3 formulation.

Table No.10 In-*vitro* dissolution data of F2I, F2II, and F2III formulation.

Time (hrs)	Cumulative percent drug release		
0	0	0	0
1	2	8	12
4	20	30	37
8	46	50	64
20	67	85	97

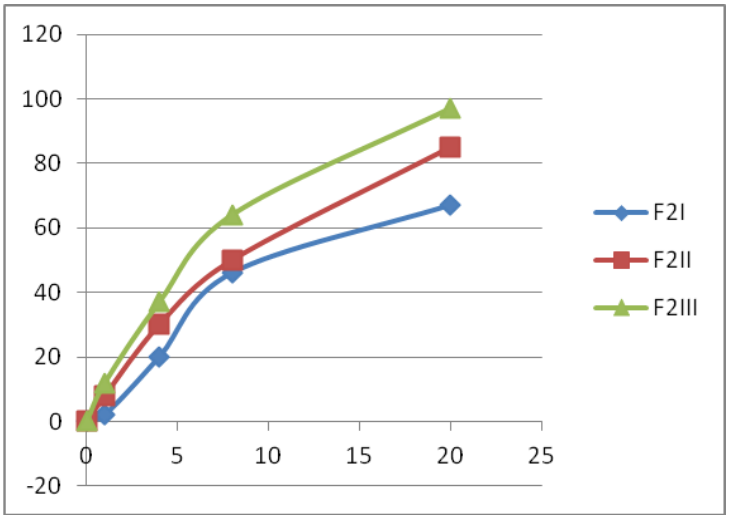

Fig No.9 *In-vitro* dissolution profile of F2I, F2II, and F2III formulation.

All the formulations were subjected to *in-vitro* dissolution studies and results are shown in table no.9 and Fig No.8.The results reveal that release profiles of Metoprolol succinate tablets containing varying proportion of Mannitol and NaCl i.e. batch F1, F2 & F3 showed drug release as given in table No. 9 in 6.8 pH phosphate buffer, drug release is slow which may be due to osmotic pressure generate inside the tablet. The drug release occurs when solvent penetrates through dry matrix, then dissolution and diffusion of drug through the resultant orifice causing release of drug through orifice. This shows that concentration of osmotic agent controls the drug release and size of the orifice.

In-vitro release studies of all the formulations were also compared and evaluate. The results showed that the drug release profile of formulation F2 resembles formulation drug release as per the USP monograph of metoprolol succinate. Hence formulation F2 containing Mannitol and sodium chloride in the concentration of 1:1 ratio was considered as optimized formulation and used for further study.

Optimized formulation was again evaluated by using the different size of orifice 0.1mm, 0.3 mm, 0.7 mm., On the observation of the release of the drug from tablet vary with the size of orifice.

All the formulations were subjected to *in-vitro* dissolution studies and results are shown in table no.9,10 and Figure no.8,9. The results reveal that release profiles of Metoprolol succinate tablets containing varying proportion of osmotic agent and orifice size i.e. batch F1, F2, F3, F2I, F2II, and F2III. Drug release from the tablet was constant with time which follows Zero order, which may be due to osmotic pressure inside the tablet due to osmotic agent. The drug release occurs when solvent penetrates through orifice, gelation of polymer and then dissolution and diffusion of drug through the resultant layer causing hydration of osmotic agent. This shows that as the concentration of mannitol and NaCl effect on the rate of drug release.

CONCLUSION

It can be concluded from the present study and results obtained that the osmotic pump for release of Metoprolol succinate can be developed as a once daily dosage form. (O. D.) Zero order release rate can be obtained by using cellulose acetate as a polymer and triacetine as a plasticizer.

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