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RESEARCH ARTICLE

Formulate and Evaluate an Osmotic Drug Delivery System of Propranolol Hydrochloride Drug by the Pores Formed *in situ* and by Avoiding Laser Drilling of Tablets and Risk of Orifice Blocking

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ABSTRACT

The present investigation embodies the development of micro porous osmotic pump of B.C.S class-1 molecule mainly with an objective to deliver a prolong time or to maintain controlled release of drug for an extended duration. Core of osmotic tablet was prepared by direct compression using drug, osmogen, release retardant, and on rotary compression machine. Core tablets were coated using cellulose acetate as semi permeable membrane and PEG 400 as pore former dissolved in 9:1acetone: watermixture. Totally six formulations were prepared. All tablets were evaluated for physical parameters such as weight variation, hardness, friability, thickness, and *in vitro* drug release. Trails F1, F2 were formulated by using sodium acetate as osmogen with 80 mg, 120 mg, and these are coated as for procedure and the study the effect of osmogen concentration on drug release was studied and osmogen concentration was optimized. 120 mg sodium acetate, that is, 80 mg per tablet showed controlled release for 10 h and hence taken as optimized but it does not attains flow properties and assay valve. Trails F3, F4 were formulated using potassium chloride as osmogen with 80 mg, 120 mg and these are coated as for procedure and the study the effect of osmogen concentration on drug release was studied and osmogen concentration was optimized. 120 mg potassium chloride, that is, 80 mg per tablet showed controlled release for 8 h and hence taken as optimized but it does not attain longer time. Trails F5, F6 were formulated by using mannitol as osmogen with 80 mg, 120 mg and these are coated as for procedure and the study the effect of osmogen concentration on drug release was studied and osmogen concentration was optimized. 120 mg mannitol, that is, 80 mg per tablet showed controlled release for 12 h and hence taken as optimized.

Keywords: Osmotic, Propranolol hydrochloride Drug, Orifice blocking

INTRODUCTION

The pharmaceutical field over the past decade has faced continuing challenges in bringing new drug entity to market. In addition, the cost of developing new drug entity keeps rising and today stands at more than US$ 800M per new drug entity. Drug delivery research continues to find new therapies for the prevention and treatment of existing and new diseases. Hence, a valuable role is played by drug delivery system (DDS) by providing optimized products for existing drugs in terms of either enhanced or improved presentation of drug to the systemic circulation.[1,2]

Treatment of an acute disease or a chronic illness has been mostly accomplished by delivery of drugs to patients using various pharmaceutical dosage forms. Traditionally, the oral drug delivery has been most widely utilized route of administration among all the routes that have been explored for the systemic delivery of drugs. Conventional oral DDS are known to provide an immediate release of drug, in which one cannot control the release of the drug and cannot maintain effective concentration at the target site

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for longer period of time. The oral bioavailability of some drug by conventional drug delivery is very low due to presence of food, in stabilization at pH of the gastrointestinal (GI) tract, degradation by enzymes of GI fluid, change in GI motility, and so forth.[3,4]

Controlled-release DDS[5-13]

Controlled-release systems also offer a sustained-release profile but, in contrast to sustained-release forms, controlled-release systems are designed to lead to predictably constant plasma concentrations, independently of the biological environment of the application site.[14-21] This means that they are actually controlling the drug concentration in the body, not just the release of the drug from the dosage form, as is the case in a sustained-release system. Another difference between sustained- and controlled-release dosage forms is that the former are basically restricted to oral dosage forms while controlled-release systems are used in a variety of administration routes, including transdermal, oral, and vaginal administration.

Controlled release of drugs from a dosage form may be achieved by the use of so-called therapeutic systems. These are DDS in which the drug is released in a predetermined pattern over a fixed period of time. The release kinetics is usually zero-order. In contrast to sustained-release systems, the dose in the therapeutic systems is of less importance than the release rate from the therapeutic system. Ideally the release rate from the dosage form should be the rate-determining step for the absorption of the drug and in fact for the drug concentration in the plasma and target site. However, controlled-release systems are not necessarily target-specific, which means that they do not "exclusively" deliver the drug to the target organ. This may be achieved by so-called targeted delivery systems which aim to exploit the characteristics of the drug carrier and the drug target to control the biodistribution of the drug. The graph is plotted against idealized plasma concentration versus time profile of a controlled-release dosage form.

Activation-modulated DDS[22-27]

In this group of controlled release DDS, the release of drug molecules from the delivery system is activated by some physical, chemical, or biochemical process and/or by energy supplied externally. The rate of drug release is then controlled by regulating the process applied or energy input.

Classification: By physical means

1. Osmotic pressure activated DDS:
2. Hydrodynamic pressure - Activated DDS
3. Vapor pressure – Activated DDS
4. Mechanically – Activated DDS
5. Magnetically Activated – DDS
6. Sonophoresis - Activated DDS
7. Iontophoresis - Activated DDS
8. Hydration - Activated DDS.

Classification By: Chemical means

1. pH-Activated DDS
2. Ion-Activated DDS
3. Hydrolysis-Activated DDS.

Classification by: Biochemical means

1. Enzyme - Activated DDS
2. Feedback Regulated DDS
3. Bioerosion - Regulated DDS.

Osmotically controlled DDSs

Osmotic devices are most promising strategy-based systems for controlled drug delivery [Tables 1 and 2].[28-30] Osmosis can be defined as the net movement of water across a selectively permeable membrane driven by a difference in osmotic pressure across the membrane.[31,32] It is driven by a difference in solute concentrations across the membrane that allows passage of water, but rejects most solute molecules or ions. Osmosis is exploited for development of ideal controlled DDS. Osmotic pressure created by osmogen is used as driving force for these systems to release the drug in controlled manner.[30]

These systems can be used for both route of administration, that is, oral and implantation. Osmotic pump offers many advantages over other controlled DDSs, that is, they are easy to formulate and simple in operation, improved patient compliance with reduced dosing frequency and

more consistence, and prolonged therapeutic effect with uniform blood concentration. Moreover, they are inexpensive and their production scale up is easy.[33,34]

Formulation and evalution of Osmotic controlled DDS

The following are the materials used in formulation of osmotically controlled DDS.

1. Semipermeable membrane
2. Hydrophilic and hydrophobic polymers[35-41]
3. Wicking agents
4. Solubilizing agents
5. Osmogens.[42-45]

Evaluation parameters for anti-hypertensive drugs

Pre-compression parameters

As per standard procedures, the pre-formulation studies including compressibility index, Hausner's ratio and angle of repose was performed for the powder.

Post-compression parameters

1. Weight variation test
   To study weight variation, 20 tablets of each formulation were weighed using an electronic balance and the test was performed according to the official method.
2. Hardness
   For each formulation, the hardness of six tablets was determined using the Monsanto hardness tester.
3. Thickness
   The thickness of the tablets was determined using a Screw gauge.
4. Friability
   A sample of six tablets was taken and was carefully dedusted before testing. The tablets were accurately weighed and placed in the drum of the Roche Friabilator. The drum was rotated for 100 times at 25 rpm and the tablets were removed, dedusted and accurately weighed. Friability of tablets was calculated using following equation.

$f = (1\text{-}W0/W) \times 100$

Wo = Initial weight, W = Final weight.

5. Drug content
   Ten tablets were powdered in a mortar. An accurately weighed quantity of powdered tablets (100 mg) was extracted with 0.1N HCl (pH 1.2 buffer) and the solution was filtered through 0.45 µ membranes. Each extract was suitably diluted and analyzed spectrophotometrically at 275 nm.
6. Buoyancy studies
   The *in vitro* floating behavior (buoyancy) of the tablets was determined by floating lag Time. The tablets were placed in 100 ml beaker containing 0.1 N HCl (pH 1.2). The floating lag time (time taken by the tablet to reach the surface) and total floating time (floating duration of the tablet) were determined.
7. *In vitro* drug release studies
   The release rate of drug from floating and osmotically controlled tablets was determined using USP type II apparatus. The dissolution test was performed in triplicate, using 900 ml of 0.1N HCl, at 37± 0.5°C at 50 rpm for 24 h. A 5 ml sample was withdrawn from the dissolution apparatus at specified time points and the samples were replaced with fresh dissolution medium. The samples were filtered through a 0.45-µm membrane filter and diluted if necessary. absorbance's of these solutions were measured at 275 nm using U.V Visible spectrophotometer. Cumulative drug release was calculated using the equation ($y = 0.0238x + 0.000246$) generated from Beer Lambert's calibration curve in the linearity range of 5–50 µg/ml.
8. Curve fitting analysis
   To study the drug release kinetics, the data obtained from *in vitro* drug release studies were plotted in various kinetic models such as a zero-order, first-order, Higuchi, and peppas equations.
9. Stability studies
   The optimized formulation was subjected to stability studies at 40±20°C and 75±5% RH for a period of 3 months. After each month, tablet was analyzed for drug content and *in vitro* drug release along with other physical parameters

10. Osmotic pressure measurements
    Osmotic pressure of the solution inside the potassium chloride tablet was measured at 37°C using a vapor pressure osmometer.
11. Helium pycnometry
    The true densities of the tablets were measured using a helium pycnometer.

Table 1: Type of Acids with Osmogens

Type	Osmogens
Water-soluble salts of inorganic acids	Magnesium chloride(or)sulfate, lithium sodium (or) potassium chloride, lithium sodium (or) potassium sulfate, sodium (or) potassium hydrogen phosphate
Water-soluble salts of organic acids	Sodium and potassium acetate, magnesium succinate, sodium benzoate, sodium citrate, sodium ascorbate
carbohydrates	Arabinose, ribose, xylose, glucose, fructose, galactose, mannose, sucrose, maltose, lactose, raffinose
Water soluble amino acids	Glycine, leucine, alanine, methionine
Organic polymeric osmogents	Sodium CMC, HPMC, crosslinked pvp, polyethyleneoxide, carbopols, polyacrylamides, hydroxyl ethyl methyl cellulose

Table 2: List of various osmogens with their osmotic pressure

Osmogens	Osmotic pressure
Adipic acid	8
Fumaric acid	10
Lactose	23
Sodium phosphate monobasic, H_2O	28
Sodium phosphate dibasic,$12H_2O$	31
Sodium phosphate dibasic,$7H_2O$	31
Sodium phosphate tribasic,$12H_2O$	36
Mannitol	38
Potassium sulfate	39
Tartaric acid	67
Citric acid	69
Dextrose	82
Sorbitol	84
Xylitol	104
Potassium phosphate	105
Melanic acid	117
Mannitol-lactose	130
Sucrose	150
Mannitol - sucrose	170
Potassium chloride	245
Lactose – sucrose	250
Fructose	355
Sodium chloride	356

Evaluation of core and coated tablets of elementary osmotic pump

1. Weight variation
   The weight variation test was carried out for 20 randomly selected tablets (core and coated) from each batch and weighed them individually. The average weight was calculated and compared with the individual tablet weights with the average tablet weight.
2. Hardness of core tablets
   Tablet hardness is defined as the load required crushing or fracturing a tablet placed on its edge. It is also termed as tablet crushing strength. In this study Pfizer hardness tester was used. The diametrical crushing strength test was observed for ten tablets from each formulation.
3. Percentage friability of core tablets
   Percentage friability of core tablet was determined using Roche friabilator. 20 tablets from each formulation were weighed and tested at a speed of 25 rpm for 4 min. After removing dusts, tablets were re-weighed. The percentage friability was determined using following formula: % Friability = Loss of weight of tablet/Initial weight ×100
4. Thickness of core and coated tablets
   Thickness of 20 core and coated tablets from every batch of formulation was measured using a screw gauge and standard deviation was calculated.
5. Diameter of core and coated tablets
   Diameter of 20 core and coated tablets from each batch was measured using screw gauge and standard deviation was also calculated.
6. Morphological study of coated membrane
   The surface morphology of the optimized tablet semi permeable coating film was studied by scanning electron microscope before and after dissolution test. The film samples were fixed on a brass stub using double-side adhesive tape. The stubs were then coated with gold to a thickness of about 300 Å using a sputter coater. These samples were than randomly scanned and photomicrographs were taken.
7. Orifice diameter
   The average orifice diameter of the osmotic pump tablets (n = 20) was determined

microscopically using optical microscope fitted with a pre-calibrated ocular scale.

MATERIALS AND METHODS

Equipment used [Table 3]

Table 3: List of equipment used in study and their manufacturers

S. NO	Equipment	Manufacturer
1	Electronic balance	Eagle
2	Mechanical sieve shaker	Jayant scientific IND
3	Rotary compression machine	Rimek, karnavathi
4	Tap density tester	Kshitij innovations
5	Disintegration tester	Kshitij innovations
6	Vernier caliper	Mansanto
7	Hardness tester	Mansanto
8	friabilator	campbell
9	Dissolution apparatus USP2	LABINDIA
10	Conventional coating pan	Kshitij innovations
11	Hot air oven	fortune
12	Stability testing equipment	Remi elektrotechnic limited
13	Magnetic stirrer	Kshitij innovations
15	U.V spectrophotometer	Labindia model-uv3092

Chemical used [Table 4]

Table 4: List of chemicals used in study and their manufacturers

S. No	Chemicals	Manufacturer
1	Propranolol hydrochloride	Yarrow Chem Products, Mumbai
2	Mannitol	Qualigens Fine Chemicals, Mumbai
3	Sodium acetate	Qualigens Fine Chemicals, Mumbai
4	Potassium chloride	Fisher Scientific India Pvt ltd, Mumbai
5	Micro crystalline cellulose	Lobal Chemime, Mumbai
6	Poly vinyl pyrollindine k30	Hi media Laboratories Pvt Ltd, Mumbai
7	Iso propyl alcohol	Merck Specialited pvt Ltd, Mumbai
8	Talc	Karnataka Fine Chemicals, Mumbai
9	Magnesium streate	Karnataka Fine Chemicals, Mumbai
10	Cellulose acetate	Oxford Laboratory, Mumbai
11	Poly ethylene gycol 4000	Lobal Chemime, Mumbai
12	Acetone	Fisher Scientific India pvt Ltd, Mumbai
13	Castor oil	
14	Distilled water	

Drug profile [Figures 1 and 2]

Propranolol

- **Description**
  This is a widely used non-cardioselective beta-adrenergic antagonist. Propranolol is used in the treatment or prevention of many disorders including acute myocardial infarction, arrhythmias, angina pectoris, hypertension, hypertensive emergencies, hyperthyroidism, migraine, pheochromocytoma, menopause, and anxiety.
- **Structure**

Weight average: 259.3434
Monoisotopic: 259.157228921
Chemical Formula: $C_{16}H_{21}NO_2$
IUPAC Name: [2-hydroxy-3-(naphthalen-1-yloxy)propyl](propan-2-yl)amine

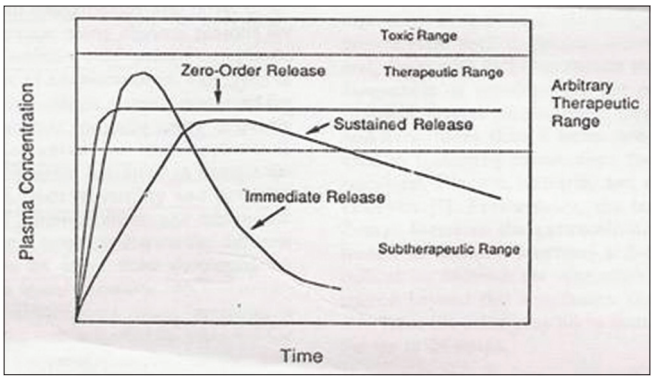

Figure 1: Controlled drug delivery system classification[31,32]

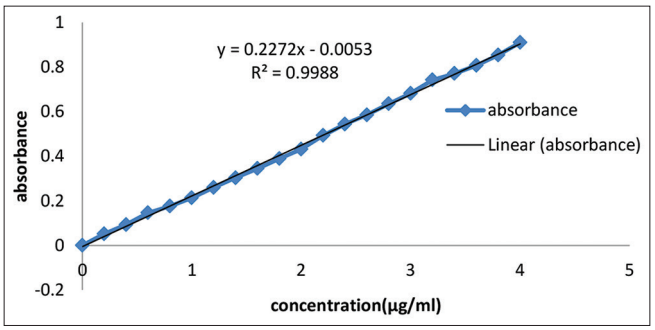

Figure 2 : Calibration curve for propranolol hydrochloride

- Pharmacology
  Nonselective, beta-adrenergic receptor blocking agent, primarily affecting the CV system (e.g. decreased heart rate, decreased cardiac contractility, and decreased BP) and lungs (promotes bronchospasm).
- Pharmacokinetics

A. Absorption
   Well absorbed from the GI tract. Extent of absorption is <90%. Bioavailability is approximately 25% (immediate-release). Food enhances bioavailability for immediate-release and increases T_{max} from 11.5 to 15.4 h for InnoPran XL. T_{max} is 1 to 4 h (immediate-release) and 6 h (ER).
B. Distribution
   Protein binding is 90%. Readily enters the CNS. Crosses the placenta; distributed into breast-milk.
C. Metabolism
   Significant first-pass hepatic metabolism through three primary routes and produces four major metabolites.
D. Elimination
   Urine is <1% excreted unchanged. Plasma half-life is 3 to 6 h (immediate-release) and about 10 h (ER). Most metabolites appear in the urine

Indications and usage

Oral

Angina pectoris caused by coronary atherosclerosis (excluding InnoPran XL); cardiac arrhythmias (excluding ER); essential tremor (excluding ER); hypertension; hypertrophic subaortic stenosis (excluding InnoPran XL); migraine prophylaxis (excluding InnoPran XL); MI (excluding ER); and pheochromocytoma (excluding ER).

- IV
- Cardiac arrhythmias.

Contraindications

Hypersensitivity to propranolol; greater than first-degree heart block; sinus bradycardia; cardiogenic shock; and bronchial asthma.

Storage/stability

Store at 68° to 77°F. Protect from light, freezing, moisture, or excessive heat.

Drug interactions

ACE inhibitors (e.g., captopril).
Increased risk of hypotension, especially in patients with acute MI; bronchial hyperactivity may be increased.

- Alcohol
  Pharmacologic and therapeutic effects are difficult to predict. Reported increased plasma concentrations, and increased and decreased clearance of propranolol.
- Aluminum salts (e.g., aluminum carbonate and aluminum hydroxide)
  Greatly reduces GI absorption of propranolol.
- Antiarrhythmic agents (e.g., amiodarone, propafenone, and quinidine)
  Inhibition of propranolol metabolism may increase pharmacologic and toxic effects. Amiodarone has additive negative chronotropic properties to those of Propranolol.
- Barbiturates (e.g., pentobarbital, phenobarbital, and primidone), levothyroxine, phenytoin, and rifampin
  May result in decreased effects of propranolol.
- Bile acid sequestrants (e.g., cholestyramine and colestipol)
  GI absorption of propranolol may be decreased.
- Calcium channel blockers (e.g. diltiazem, nicardipine, nifedipine, and verapamil), flecainide, haloperidol, phenothiazines (e.g. chlorpromazine and thioridazine), selective 5-HT 1 receptor antagonists (e.g. rizatriptan and zolmitriptan), and sulfonylureas (e.g. chlorpropamide and tolbutamide)
  Increased serum levels and effects of both drugs.
- Cigarette smoking
  Increases clearance of propranolol by as much as 100%. Cimetidine, ciprofloxacin, diphenhydramine, fluconazole, hydralazine, imipramine, isoniazid, methimazole, propafenone, propylthiouracil, ritonavir, SSRIs (e.g., fluoxetine, fluvoxamine, and paroxetine), teniposide, terbinafine, and zileuton increased effects of propranolol.

- Clonidine
  Attenuation or reversal of antihypertensive effect; potentially life-threatening increases in BP, especially on withdrawal.
- Diazepam
  Inhibition of diazepam metabolism.
- Digoxin
  Progressive bradycardia may occur.
- Dobutamine, isoproterenol
  May reverse effects of propranolol.
- Epinephrine
  Initial hypertensive episode followed by bradycardia.
- Ergot derivatives (e.g., dihydroergotamine and ergotamine)
  Peripheral ischemia, manifested by cold extremities and possible gangrene.
- HMG-CoA reductase inhibitors (e.g. lovastatin and pravastatin)
  Plasma concentrations may be increased.
- Insulin
  Prolonged hypoglycemia with masking of symptoms.
- Lidocaine (IV)
  Increased lidocaine levels, leading to toxicity.
- MAOIs, tricyclic antidepressants
  Coadministration may exacerbate the hypotensive effects of MAOIs.
- NSAIDs (e.g. ibuprofen, indomethacin, and naproxen), salicylates (e.g. aspirin)
  Some agents may impair antihypertensive effect.
- Prazosin
  Increased orthostatic hypotension.
- Reserpine
  Hypotension, marked bradycardia, vertigo, syncopal attacks, and orthostatic hypotension may result from excessive reduction of resting sympathetic nervous activity caused by reserpine-induced catecholamine depletion.
- Sympathomimetics (e.g. albuterol and formoterol)
  Pharmacologic effects may be antagonized by propranolol resulting in bronchospasm.
- Theophylline
  Reduced elimination of theophylline; propranolol concentrations may be increased.
- Warfarin
  The anticoagulant effect of warfarin may be increased.

Food interactions

- Avoid alcohol
- Avoid natural licorice
- Take with food.

Procedure and evaluation

Design of trials

The main objective of this formulation development was to design an osmotic DDS acting as a controlled release DDS [Table 5]. In this formulation, osmogen and release retardant were used to obtain suitable formulation. The drug should be released for a prolonged period of time to achieve a zero-order release. Prepared osmotic tablet combination of gives drug release for up to 12 h by combination of matrix and osmotic mechanism.

Table 5: Series of concentrations and their absorbance's

S. No	Concentration (µg/ml)	Absorbance
1.	0	0
2.	2	0.052
3.	4	0.093
4	6	0.146
5.	8	0.176
6.	10	0.213
7.	12	0.26
8.	14	0.303
9.	16	0.345
10	18	0.389
11.	20	0.432
12.	22	0.493
13.	24	0.544
14.	26	0.585
15.	28	0.635
16.	30	0.682
17.	32	0.742
18.	34	0.771
19.	36	0.807
20.	38	0.854
21.	40	0.91

Design [Table 6]

F1, F2, F3, F4, F5, and F6 were designed to optimize the concentrations of sodium acetate, potassium chloride, mannitol and to study the effect of sodium acetate, potassium chloride, and mannitol.

Preparation of core tablets

Osmotic tablets were prepared by wet granulation method according to composition given in table. All the ingredients and drug were accurately weighed and mixed in motor with a pestle for 10 min to get uniform mix. The drug blend was granulated with sufficient quantity of pvpk30 which was dissolved in isopropylalcohol. The powder mass was dried at 60 c in hot air oven for 6 h and pass through sieve no:20. The dried granules were mixed with magnesium stearate and talc for 3 min. The blended powder was then compressed by single station rotary tablet compression machine.

Coating of core tablets

Coating solution (4%w/v) was prepared by mixing required quantity of cellulose acetate (semi-permeable membrane forming agent), PEG400 (pore forming agent), and castor oil (20%v/w of total solid CA) (plasticizer) in acetone as specified in table and stirred on magnetic stirrer to get homogenous coating solution. Then, the tablets were coated using small size coating pan made up of stainless steel with rotation speed of 25 rpm and 55°C temperature of hot air then the tablets were kept in oven at 40°C for about 24 h and weight to calculate the percentage gain. These tablets were coated repeatedly until the required weight gain was achieved.

Evaluation parameters

Pre-compression parameters

As per standard procedures, the pre-formulation studies including compressibility index, Hausner's ratio, and angle of repose was performed for the powder.

Bulk density

Loose bulk density and taped bulk density were calculated by the following formulae

a. LBD = Weight of the powder/Volume of the packing

Table 6: Optimization of the concentrations of sodium acetate, potassium chloride, mannitol and to study the effect of sodium acetate, potassium chloride, and mannitol

S. No	Ingredients	F1	F2	F3	F4	F5	F6
Core of the tablet							
1.	Propranolol	80 mg	80 mg	80 mg	80 mg	80 mg	80 mg
2.	Sodium acetate	80 mg	120 mg	-	-	-	-
3.	Potassium chloride	-	-	80 mg	120 mg	-	-
4.	Mannitol	-	-	-	-	80 mg	120 mg
5.	Microcrystalline cellulose	210 mg	170 mg	210 mg	170 mg	210 mg	170 mg
6.	Pvpk30	20 mg	20 mg	20 mg	20 mg	20 mg	20 mg
7.	Talc	4 mg	4 mg	4 mg	4 mg	4 mg	4 mg
8.	Magnesium streate	6 mg	6 mg	6 mg	6 mg	6 mg	6 mg
9.	Isopropylalcohol	q.s	q.s	q.s	q.s	q.s	q.s
	Total	400 mg	400 mg	400 mg	400 mg	400 mg	400mg
Coating solution							
10.	Cellulose acetate	400 mg	400 mg	400 mg	400 mg	400 mg	400 mg
11.	PEG400	20 ml	20 ml	20 ml	20 ml	20 ml	20 ml
12.	Castor oil	10 ml	10 ml	10 ml	10 ml	10 ml	10 ml
13.	Acetone	40 ml	40 ml	40 ml	40 ml	40 ml	40 ml
14.	Water	30 ml	30 ml	30 ml	30 ml	30 ml	30 ml
	Total	420 mg	420 mg	420 mg	420 mg	420 mg	420 mg

b. TBD = Weight of the powder/Tapped volume of the packing
c. Carr's Compressibility Index:
% Carr's Index can be calculated using the following formula
Carr's Index (%) = ×100
d. Hausner's ratio
Hausner ratio is an indirect index of ease of measuring the powder flow. It is calculated by the following formula
Hausner's ratio = (Tapped density)/(Bulk density)
e. Angle of repose
Angle of repose (θ) can be calculated from the following formula
Where tanθ=h/r
h=height of pile and r=radius of the base of pile

Post-compression parameters

1. Weight variation test
To study weight variation, 20 tablets of each formulation were weighed using an electronic balance and the test was performed according to the official method for both uncoated and coated tablets.
2. Hardness
For each formulation, the hardness of six tablets was determined using the Monsanto hardness tester.
3. Thickness
The thickness of the tablets was determined using a Screw gauge for uncoated and coated tablets.
4. Friability
A sample of six tablets was taken and was carefully dedusted before testing. The tablets were accurately weighed and placed in the drum of the Roche Friabilator. The drum was rotated for 100 times at 25 rpm and the tablets were removed, dedusted, and accurately weighed. Friability of tablets was calculated using following equation.
f = (1-W0/W) × 100
Wo = initial weight, W = final weight.
5. Drug content
Ten tablets were powdered in a mortar. An accurately weighed quantity of powdered tablets (80 mg) was extracted with pH 6.8 buffer and the solution was filtered through 0.45 µ membranes. Each extract was suitably diluted and analyzed spectrophotometrically at 289 nm.
6. *In vitro* drug release studies
The release rate of drug from osmotically controlled tablets was determined using USP type II apparatus. The dissolution test was performed in triplicate, using 900 ml of ph6.8 buffer, at 37± 0.5°C at 50 rpm for 12 h. A 5 ml sample was withdrawn from the dissolution apparatus at specified time points and the samples were replaced with fresh dissolution medium. The samples were filtered through a 0.45-µm membrane filter and diluted if necessary. Absorbance's of these solutions were measured at 289 nm using U.V visible spectrophotometer. Cumulative drug release was calculated using the equation (y = 0.0238x + 0.000246) generated from Beer Lambert's calibration curve in the linearity range of 5–50µg/ml.
7. Curve fitting analysis
To study the drug release kinetics, the data obtained from *in vitro* drug release studies were plotted in various kinetic models such as a zero-order, first-order, Higuchi, and peppas equations.
a. Zero-order kinetics
To study the zero-order release kinetics, the release data were fitted into the following equation.
DQ/dt=K0
Where Q is amount of drug release
K0 is zero-order release rate constant t is release time the graph is plotted percentage cumulative release versus time
b. First-order kinetics
To study the first-order release kinetics, the release data were fitted into the following equation.
DQ/dt=K1Q
Where Q is amount of drug release
K1 is zero-order release rate constant t is release time the graph is plotted percentage log% cumulative release versus time
c. Higuchi release model
To study of Higuchi release model the release kinetics, the release data were fitted into the following equation.

Q=KHt1/2

Where Q is fraction of drug release

KH is release rate constant t is release time the graph is plotted percentage cumulative release versus square root of time

d. Korsmeyer–Peppas release

To study Korsmeyer–peppas release kinetics, the release data were fitted into the following equation.

Mt/Minfi=kHp tn

Where Mt/Minfi is amount of drug release

KHP is release rate constant t is release time n is the diffusion exponent related to mechanism of drug release the graph is plotted percentage cumulative release versus log time

8. Stability studies

The optimized formulation was subjected to stability studies at 40±20°C and 75±5% RH for a period of 3 months. After each month, tablet was analyzed for drug content and *in vitro* drug release along with other physical parameters.

RESULTS AND DISCUSSION

Pre-compression parameters

a. Solubility

Solubility of propranolol hydrochloride is slightly soluble in water and can easily soluble in 0.1N Hydrochloride, ph 6.8 phosphate buffer, ph 7.4 phosphate buffer.

b. Drug excipient compatibility studies

c. Standard curve of propranolol hydrochloride

CONCLUSION

API belongs to the category of antihypertensive which is used for hypertensives. In the present study, attempts were made to formulate and evaluate API in extended release dosage form using osmotic drug delivery. Preformulation studies were conducted using drug: excipients and the results showed that the excipient were compatible with drug. Formulation characteristics such as blend characteristics, tablet weight, hardness, and friability were found to be satisfactory. Formulations are evaluated for drug release in USP type 2 apparatus (paddle) with stationary baskets in ph 6.8 buffer. Target zero-order release was achieved with trial F6 in which 120 mg mannitol was present as osmogens and coated with 80: 20SPM: PORE FORMER RATIO (15% TO 20%wtgain). Cellulose acetate tends to keep up the best suited reservoir coating material in controlling the release system. Finally, it was concluded that these trials will provide a novel approach for formulating Propranolol hydrochloride.

REFERENCES

1. Prescott LF. The need for improved drug delivery in clinical practice. In: Novel Drug Delivery and Its Therapeutic application. West Susset, UK: John Wiley and Sons; 1989. p. 1-11.
2. Verma RK, Garg S. Current status of drug delivery technologies and future directions. Pharm Technol 2001;25:1-14.
3. Reddy PD, Swarnalatha D. Recent advances in novel drug delivery systems. Int J PharmTech Res 2010;2:2025-7.
4. Rastogi SK, Vaya N, Mishra B. Osmotic pump: A novel concept in rate controlled oral drug delivery. Eastern Pharm 1995;38:79-82.
5. Eckenhoff B, Theeuwes F, Urquhart J. Osmotically actuated dosage forms for rate-controlled drug delivery. Pharm Technol 1981;5:35-44.
6. Thombre AG, Appel LE, Chidlaw MB, Daugherity PD, Dumont F, Evans LA, *et al*. Osmotic drug delivery using swellable-core technology. J Control Release 2004;94:75-89.
7. Kaushal AM, Garg S. An update on osmotic drug delivery patents. Pharm Technol 2003;2003:38-44.
8. Li X, Jasti BR. Osmotic controlled drug delivery systems. In: Design of Controlled Release of Drug Delivery Systems. United States: McGraw Hill; 2006. p. 203-29.
9. Rose S, Nelson JF. A continuous long-term injector. Aust J Exp Biol Med Sci 1955;33:415-9.
10. Higuchi T, Leeper HM. Osmotic Disperser. US Patent No. 3732865. California: JUSTIA; 1973.
11. Higuchi T, Leeper HM. Improved Osmotic Dispenser Employing Magnesium Sulfate and Magnesium Chloride, US Patent No. 3760804. California: JUSTIA; 1973.
12. Higuchi T. Osmotic Dispenser with Collapsible Supply Container, US Patent No. 3, 760,805. California: JUSTIA; 1973.
13. Higuchi T, Leeper HM. Osmotic Dispenser with Means for Dispensing Active Agent Responsive to Osmotic Gradient, US Patent No. 3995631. California: JUSTIA; 1976.
14. Theeuwes F, Yum SI. Principles of the design and operation of generic osmotic pumps for the delivery of semisolid or liquid drug formulations. Ann Biomed Eng 1976;4:343-53.

15. Theeuwes F. Osmotic System for Delivering Selected Beneficial Agents Having Varying Degrees of Solubility, US Patent No. 4111201. California: JUSTIA; 1978.
16. Cortese R, Theeuwes F. Osmotic Device with Hydrogel Driving Member, US Patent No. 4, 327,725. California: JUSTIA; 1982.
17. Wong PS, Barclay B, Deters JC, Theeuwes F. Osmotic Device with Dual Thermodynamic Activity, US Patent 4612008. California: JUSTIA; 1986.
18. Ghosh T, Ghosh A. Drug delivery through osmotic systems-an overview. J Appl Pharm Sci 2011;2:38-49.
19. Ouyang D, Nie S, Li W, Guo H, Liu H, Pan W. Design and evaluation of compound metformin/glipizide elementary osmotic pump tablets. J Pharm Pharmacol 2005;57:817-20.
20. Theeuwes F. Elementary osmotic pump. J Pharm Sci 1975;64:1987-91.
21. Haslam JL, Rork GS. Controlled Porosity Osmotic Pump, U.S. Patent No. 4880631. California: JUSTIA; 1989.
22. Liu L, Ku J, Khang G, Lee B, Rhee JM, Lee HB. Nifedipine controlled delivery by sandwiched osmotic tablet system. J Control Release 2000;68:145-56.
23. Kumaravelrajan R, Narayanan N, Suba V. Development and evaluation of controlled porosity osmotic pump for Nifedipine and Metoprolol combination. Lipids Health Dis 2011;10:51.
24. Zentner GM, Rork GS, Himmelstein KJ. The controlled porosity osmotic pump. J Control Release 1985;1:269-82.
25. Dong L, Shafi K, Wan J, Wong P. A Novel Osmotic Delivery System: L-OROS Soft Cap. Paris, France: Proceedings of the International Symposium on controlled Release of Bioactive Materials; 2000.
26. Gupta S, Singh RP, Sharma R, Kalyanwat R, Lokwani P. Osmotic pumps: A review. Pharm Glob 2011;6:36.
27. Ajay Babu C, Prasada Rao M, Vijaya Ratna J. Controlled-porosity osmotic pump tablets-an overview. J Pharm Res Health Care 2010;2:114-26.
28. Jerzewski R, Chien Y. Treatise on Controlled Drug Delivery: Fundamentals, Optimization, Application. United States: Marcel Dekker; 1992. p. 225-53.
29. Rao BS, Kumar NR, Madhuri K, Narayan PS, Murthy KV. Osmotic drug delivery systems. Eastern Pharm 2001;521:21-8.
30. Verma RK, Krishna DM, Garg S. Formulation aspects in the development of osmotically controlled oral drug delivery systems. J Control Release 2002;79:7-27.
31. Chien YW, Jain NK. Reference novel drug delivery system. In: Controlled and Novel Drug Delivery. New York: Marcel Dekkar, Inc., CBS Publishers and Distributors; 2013. p. 17-36, 57-111.
32. Available from: http://www.pharmainfo.net.
33. Santus G, Baker RW. Osmotic drug delivery: A review of the patent literature. J Control Release 1995;35:1-21.
34. Verma RK, Garg S. Development and evaluation of osmotically controlled oral drug delivery system of glipizide. Eur J Pharm Biopharm 2004;57:513-25.
35. Kumaravelrajan R, Narayanan N, Suba V, Bhaskar K. Simultaneous delivery of Nifedipine and Metoprolol tartarate using sandwiched osmotic pump tablet system. Int J Pharm 2010;399:60-70.
36. Lindstedt B, Ragnarsson G, Hjartstam J. Osmotic pumping as a release mechanism for membrane-coated drug formulations. Int J Pharm 1989;56:261-8.
37. Seminoff LA, Zentner GM. Cellulosic Coating, US Patent 5,126,146. California: JUSTIA; 1992.
38. Jensen JL, Appel LE, Clair JH, Zentner GM. Variables that affect the mechanism of drug release from osmotic pumps coated with acrylate/methacrylate copolymer latexes. J Pharm Sci 1995;84:530-3.
39. Dong L, Shafi K, Wan J, Wong PA. Novel Osmotic Delivery System: L-OROS Soft Cap. Paris, France: Proceedings of the International Symposium on controlled Release of Bioactive Materials; 2000.
40. Parmar NS, Vyas SK. Advances in Controlled and Novel Drug Delivery. New York: CBS; 2008.
41. Rudnic EM, Burnside BA, Flanner HH, Patent 6,110,498. California: JUSTIA; 2000.
42. Jerzewski RL, Chien YW. Osmotic drug delivery. In: Kydonieus A, editor. Treatise on Controlled Drug Delivery: Fundamentals, Optimization, Application. New York, USA: Marcel Dekker; 1992. p. 225-53.
43. Guo JH. Effects of plasticizers on water permeation and mechanical properties of cellulose acetate: Antiplasticization in slightly plasticized polymer. Drug Dev Ind Pharm 1993;19:1541-55.
44. Bindschaedler C, Gurny R, Doelker E. Mechanically strong films produced from cellulose acetate latexes. J Pharm Pharmacol 1987;39:335-8.
45. Guo JH. An investigation into the formation of plasticizer channels in plasticized polymer films. Drug Dev Ind Pharm 1994;20:1883-93.