Review Article

Controlled Porosity Osmotic Pump (Cpop)-An Advanced Delivery System For Cardio Selective β1 Blockers

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ABSTRACT
Conventional drug delivery systems have little control over their drug release and unpredictable plasma concentrations.Controlled drug delivery systems offer spatial control over the drug release.Osmotic pumps are most promising for controlled drug delivery, thus can be used for both oral and implantation. Controlled porosity osmotic pump(CPOP) tablets were designed to release the drug in controlled manner upto 12 hours. Mostly it is used to treat various chronic diseases like hypertension,heart diseases, diabetes and asthma.CPOP is based on the principle of osmosis which provides better release of drug that is independent of pH and agitation intensity. The controlled porosity osmotic pump tablet is spray coated or coated with semi permeable membrane(SPM) containing leachable pore forming agents. The drug release through pores which are formed in SPM. The release rate from these systems is dependent on coating thickness,solubility of drug in tablet core and osmotic pressure difference across membrane. It is also effective in multi drug therapy of hypertension by delivering both drugs in controlled manner.

Keywords: Controlled porosity osmotic pump(CPOP),controlled osmotic drug delivery.

INTRODUCTION

Hypertension is a common cause of cardiovascular disorder and is essentially associated with abnormal lipid and altered glucose metabolism .thus management of cardiovascular disease in particular hypertension becomes important to improve health care system. About 2.5million deaths in India in 1990 which have doubled by the year 2015, where hypertension alone contributes 57% of all stroke death and 24% of all coronary heart disease. The beta blockers are used individually or a combination therapy to treat hypertension. The development of oral osmotic systems has a strong market potential and is evident from the marketed products and number of patents granted in last few years. CPOP is simple and it is not necessary to consider complicated side drilling, compared to other osmotic pump systems less excipients is required. The coating composition of CPOP includes pore forming agents which generates pores in contact with aqueous media.it was observed that most of the core content releases through pores at constant rate where the release mechanism primarily is osmotic with simple diffusion playing a minor role. A zero order delivery pattern was designed to produce plasma levels within the desired range. Controlled release drug delivery systems provide desired concentration of drug at absorption site allowing maintenance of plasma concentrations within the therapeutic range and reducing the dosing frequency. The main goal of controlled drug delivery systems is to improve the effectiveness of drug therapies.

BASIC COMPONENTS OF OSMOTICSYSTEMS

The followingare thematerials used in formulation of osmotically regulated system.

1. **Semipermeable Membrane**
   Since the membrane in osmoticsystems issemipermeableinnature,anypolymer thatispermeabletowaterbutimpermeabletosolutecan

beselected.Celluloseacetateisacommonlyemployed semipermeable polymer for thepreparation of osmotic pumps. It isavailablein differentacetylcontentgrades.Particularly,acetylcontentof32%and38%is widelyused.Acetyl content isdescribedbythedegreeofsubstitution (DS), that is, the averagenumber of hydroxyl groups on the anhydroglucoseunit ofthe polymer replacedby substitutinggroup.Some ofthepolymersthatcanbeused forabovepurposeincludecelluloseesterssuchascellulose acetate, cellulosediacetate, cellulosetriacetate, cellulose propionate, celluloseacetatebutyrate,andcelluloseethers likeethylcellulose.Apartfromcellulose derivatives, someotherpolymerssuchasagaracetate,amylosetriacetate, betaglucanacetate,poly(vinylmethyl) ether copolymers, poly(orthoesters), poly acetalsand selectivelypermeable poly(glycolicacid),poly(lacticacid)derivatives, andEudrag- itscanbeusedas semipermeablefilm-formingmaterials. Thepermeability istheimportantcriteriaforthe selectionofsemipermeablepolymers.

2. Hydrophilic and Hydrophobic Polymers

These polymers are used in the formulation development of osmotic systems for making drug containing matrix core. The highly water soluble compounds can be coentrapped in hydrophobic matrices and moderately water soluble compounds can be coentrapped in hydrophilic matrices to obtain more con- trolled release. Generally, mixtures of both hydrophilic and hydrophobic polymers have been used in the development of osmotic pumps of water-soluble drugs. The selection is based on the solubility of the drug as well as the amount and rate of drug to be released from the pump. The polymers are of either swellable or nonswellable nature. Mostly, swellable polymers are used for the pumps containing moderately water-soluble drugs. Since they increase the hydrostatic pressure inside the pump due to their swelling nature, the nonswellable polymers are used in case of highly water-soluble drugs. Ionic hydrogels such as sodium carboxymethyl cellulose are preferably used because of their osmogenic nature. More precise controlled release of drugs can be achieved by incorporating these polymers into the formulations. Hydrophilic polymers such as hydroxy ethyl cellulose, carboxy methylcellulose, hydroxy propyl methyl- cellulose, high-molecular-weight poly(vinyl pyrrolidone), and hydrophobic polymers such as ethyl cellulose and wax materials can be used for this purpose.

3. Wicking Agents

A wicking agent is defined as a material with the ability to draw water into the porous network of a delivery device. The wicking agents are those agents which help to increase the contact surface area of the drug with the incoming aqueous fluid. The use of the wicking agent helps to enhance the rate of drug released from the orifice of the drug. A wicking agent is of either swellable or nonswellable nature [32]. They are characterized by having the ability to undergo physisorption with water. Physisorption is a form of absorption in which the solvent molecules can loosely adhere to surfaces of the wicking agent via Van der Waals interactions between the surface of the wicking agent and the adsorbed molecule. The function of the wicking agent is to carry water to surfaces inside the core of the tablet, thereby creating channels or a network of increased surface area. The examples are colloidal silicon dioxide, PVP and Sodium lauryl sulfate.

4. Solubilizing Agents

For osmotic drug delivery system, highly water-soluble drugs would demonstrate a high release rate that would be of zero order. Thus, many drugs with low intrinsic water solubility are poor candidates for osmotic delivery. How everitis possible to modulate the solubility of drugs within the core. Addition of solubilising agents into the core tablet dramatically increases the drug solubility.

Non swellable solubilising agents are classified into three groups,

(i)Agentsthat inhibit crystalformation ofthedrugs orotherwiseactbycomplexationwiththe drugs (e.g.,PVP,poly(ethylene glycol)(PEG8000) and*β*- cyclodextrin),

(ii)Amicelle-formingsurfactantwithhighHLB value, particularlynon-ionicsurfactants (e.g.,Tween20,60, and80,polyoxyethyleneorpolyethylenecontaining surfactants and other long-chain anionic surfactants such as SLS)

(iii)Citrate esters (e.g.,alkyl estersparticularly triethyl citrate) and their combinations with anionic surfactants. The combinations of complexing agents such as polyvinylpyrrolidone (PVP)and poly(ethylene glycol)with anionic surfactants such as SLS are mostly preferred.

5. Osmogens

Osmogens are essential ingredient of the osmotic formulations. Upon penetration of biological fluid into the osmotic pump through semipermeable membrane, osmogens are dissolved in the biological fluid, which creates osmotic pressure build up inside the pump and pushes medicament outside the pump through delivery orifice. They include inorganic salts and carbohydrates. Mostly, potassium chloride, sodium chloride, and mannitol used as osmogens. Generally combinations of osmogens are used to achieve optimum osmotic pressure inside the system.

6. Surfactants

Surfactants are particularly useful when added to wall-forming material. They produce an integral composite that is useful for making the wall of the device operative. The surfactants act by regulating the surface energy of materials to improve their blending into the composite and maintain their integrity in the environment of use during the drug release period. Typical surfactants such as poly oxyethylenatedglycerylrecinoleate, polyoxyethylenated castor oil having ethylene oxide, glyceryllaurates, and glycerol (sorbitonoleate, stearate, or laurate) are incorporated into the formulation.

7. Coating Solvents

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 and other materials. The typical solvents include methylene chloride, acetone, methanol, ethanol, isopropyl alcohol, butyl alcohol, ethyl acetate, cyclohexane, carbon tetrachloride, and water. 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) can be used.

8. Plasticizers

In pharmaceutical coatings, plasticizers, or low molecular weight diluents are added to modify the physical properties and improve film-forming characteristics of polymers. Plasticizers can change visco elastic behaviour of polymers significantly. Plasticizers can turn a hard and brittle polymer into a softer, more pliable material, and possibly make it more resistant to mechanical stress. Plasticizers lower the temperature of the second order-phase transition of the wall or the elastic modules of the wall and also increase the workability, flexibility, and permeability of the coating solvents. Generally from 0.001 to 50 parts of a plasticizer or a mixture of plasticizers are incorporated into 100 parts of costing materials. PEG-600, PEG-200, triacetin (TA), dibutylsebacate, ethylene glycol monoacetate, ethylene glycol diacetate, triethyl phosphate, and diethyl tartrate used as plasticizer in formulation of semipermeable membrane.

9. Pore-Forming Agents

Theseagentsareparticularlyused inthepumpsdevelopedforpoorlywater-solubledrugs and inthedevelopmentofcontrolledporosityormultiparticulateosmoticpumps.These pore-formingagentscause the formationofmicroporousmembrane.Themicroporouswall maybeformed insitubyapore-former byitsleaching duringtheoperationofthesystem.Thepore-formerscan be inorganic or organic and solid or liquidin nature. Forexample,alkaline metalsaltssuchassodiumchloride, sodiumbromide,potassiumchloride, potassiumsulphate, potassiumphosphate, and soforth,alkalineearthmetals suchascalciumchlorideandcalciumnitrate,carbohydrates suchassucrose, glucose,fructose,mannose, lactose,sorbitol, andmannitol, anddiolsandpolyolssuchaspolyhydric alcohols,polyethyleneglycols, and polyvinylpyrrolidonecanbeusedaspore-forming agents.Triethylcitrate (TEC)andtriacetin(TA)arealsousedtocreateporeinthe membrane.Membranepermeabilitytothedrugis further increasedadditionofHPMC orsucrose.

Advantages

a) T hecontrolledporosityosmoticpumpcanbe followingzero orderkineticsandthusbetter controloverthedrug'sinvivoperformanceis possible.
b) Thedrugreleaseisindependentofthegastric pHandhydrodynamicconditions.
c) Thedelivery rateofdrugfromthesesystemsis highlypredictableandcanbeprogrammed by modulatingtheterms.
d) Drug release from the controlled porosity osmotic pump exhibits significant in vitro-in vivocorrelation[IVIVC]withinspecificlimits.

e) Noneedof drilling.
f) Therationale forthisapproachisthatthe presenceofwaterinGITisrelativelyconstant, atleastintermsoftheamountrequired for activationandcontrollingosmoticallybase technologies.
g) Productionscale-upis easy.

Disadvantages

a) Retrievaloftherapyisnotpossibleinthecase ofunexpectedadverseevents.
b) Drug release from the osmotic systems is affected to some extent by the presence of food.
c) If the coating process isnotwellcontrolled thereisarisk offilmdefects, whichresults in dosedumping.

OSMOSIS

Process of movement of the solvent from the lower concentration of solution to the higher concentration of the solution through the semipermiable membrane. Osmosis is the process that can control the drug delivery system. Osmotic pressure created due to imbibitions of fluid from external environment into the dosage form regulates the delivery of drug from osmotic device. Rate of drug delivery from osmotic pump is directly proportional to the osmotic pressure developed due to imbibitions of fluids by osmogen. Osmotic pressure is a colligative property of a solution in which the magnitude of osmotic pressure of the solution is independent on the number of discrete entities of solute present in the solution. Hence the release rate of drugs from osmotic dispensing devices is dependent on the solubility and molecular weight and activity coefficient of the solute (osmogent).

Principles of Osmosis

Thefirstreportofanosmotic effectdatesto Abbenollet(1748).But Pfefferobtainedthe first quantitativemeasurement in1877.InPfefferexperimentamembrane permeable towaterbut impermeable tosugarisusedtoseparateasugar solution from pure water.A flow of water then takesplaceintothesugarsolution thatcannot be halteduntilapressure πisappliedtothesugar solution.Pfeffershowedthatthispressure, the osmoticpressure πofthesugarsolutionisdirectly proportional tothesolutionconcentrationandthe absolutetemperature. Withinfewyears,VantHoff hadshowntheanalogy betweentheseresultsand idealgaslawsbytheexpression

$$\pi = \Phi c r t$$

WhereΦistheosmoticcoefficientofthesolution,c is the molar concentration of sugar in the solution,r is the gasconstant,t is the absolute temperature.

Osmoticpressure forconcentratedsolutionof soluble solutes commonly used in controlled release formulation are extremely high ranging from8atmforAdipic acidupto500atmfora lactose-fructose mixture,astheirosmoticpressure can produce high water flow across semi permeablemembrane. Theosmoticwaterflow througha membraneisgivenbythe equation,

$$dv\backslash dt = AQ\Delta\pi\backslash L$$

Where dv\dtiswater flowacross themembraneof areaA,thicknessL,andthepermeabilityQincm2, Δπistheosmotic pressuredifferencebetween the twosolutionsoneithersideofthemembrane.This equationisstrictlyforcompletely permselective membrane thatismembrane permeable towater butcompletelyimpermeabletoosmoticagent.

Drug release mechanism

Whencontrolled porosity osmotic pump is in aqueous environment the water soluble channellingagent get dissolve and formsa pore in coat.Thewater entersthrough semipermeable membraneandformsasolutionof drug which getreleasethrough pores. Rate of waterinletisdependingontypeandconcentration ofosmoticagent andthe drugreleaseisdependon hydrostaticpressurecreatedbyinlet waterandsize andnumberofpores.

Basic component of controlled porosity osmotic pump

Drug

Basic criteriaforselectionofdrug

i. It should have short biological half-lifeand which is used for prolongedtreatment are ideal candidate for osmotic systems.
ii. It should be water soluble.
iii. It should be potent.

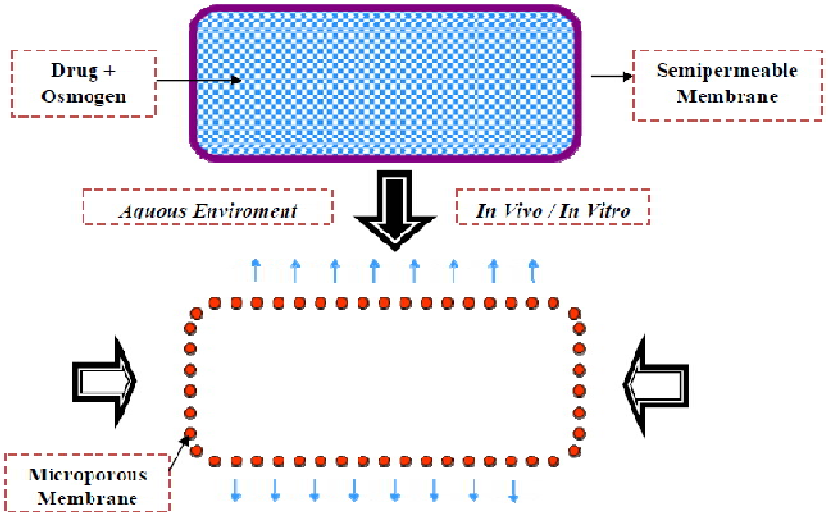

Fig. 1: Drug release mechanism of controlled porosity osmotic pump

Classification of Osmotic Drug Delivery System

I. Implantable
II. The Rose and Nelson Pump
III. Higuchi Leeper Pump
IV. Higuchi Theuwes pump
V. Implantable Mini osmotic pump

B.OralosmoticPump

VI. Singlechamberosmoticpump:Elementary osmoticpump
VII. Multi chamber osmotic pump: Pushpullosmotic pump,Osmotic pumpwithnon-expandingsecondchamber.
VIII. Specifictypes:Controlled porosity osmotic pump,Osmoticburstingosmotic pump, LiquidOROS,Delayed Delivery Osmotic device,Telescopic capsule,OROSCT(colon targeting),sandwiched oraltherapeutic system,osmoticpumpforinsoluble drugs, MonolithicosmoticsystemandOSMAT.

HISTORICAL ASPECTSOFOSMOTIC PUMPS

About 75 years after discovery of the osmosis principle, itwasfirstusedinthedesignofdrug deliverysystems. RoseandNelson,the Australianscientists,wereinitiatorsof osmoticdrug delivery. In1955,theydeveloped animplantable pump,whichconsisted ofthreechambers:adrug chamber, asaltchambercontains excesssolidsalt, andawaterchamber. Thedrugandwaterchambers areseparatedby rigidsemipermeablemembrane. Thedifference inosmoticpressureacrossthe membranemoveswaterfromthe waterchamber intothesaltchamber. Thevolumeofthesalt chamber increases because of thiswater flow, whichdistendsthelatexdiaphragm separatingthe saltanddrugchambers,therebypumpingdrugout ofthedevice.Thedesignandmechanism ofthis pumpiscomparable tomodernpush-pullosmotic pump.Themajordisadvantageofthispumpwas thewaterchamber, whichmustbecharged before use ofthe pump.The pumpingrate ofthis push-pull pumpisgivenby theequation.

$$dM/dt=dV/dtxc$$

Ingeneral,this equation, withorwithoutsome modifications, appliestoallothertypeofosmotic systems.

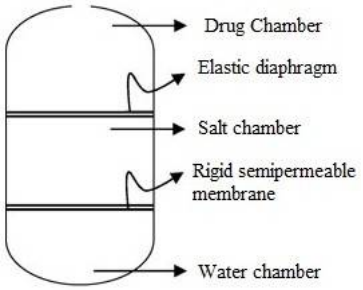

Fig. 2: Rose- Nelson Pump

Severalsimplifications inRose-Nelsonpumpwere madebyAlzaCorporation inearly1970s.The Higuchi-Leeper pumpismodifiedversionofRose- Nelsonpump.Ithasnowaterchamber andthe deviceisactivated bywaterimbibedfromthe surroundingenvironment.The pump is activated whenitisswallowedorimplantedinthebody.This pumpconsistsofarigidhousing, andthe semipermeable membraneissupportedona perforated frame.Ithasasaltchambercontaining a fluidsolution withexcesssolidsalt.Recent modification in Higuchi-Leeper pump accommodated pulsatile drugdelivery. The pulsatilereleasewasachievedbytheproductionof a critical pressure atwhich the delivery orifice opensandreleasesthedrug.

FurthersimplifiedvariantofRose-Nelsonpump wasdeveloped byHiguchiandTheeuwes. This pumpcomprisesarigid,ratecontrolling outer semipermeablemembranesurroundingasolidlayer ofsaltcoatedontheinside byanelasticdiaphragm andontheoutsidebythemembrane.Inuse,water isosmoticallydrawnbythesaltchamber, forcing drugfromthedrugchamber.

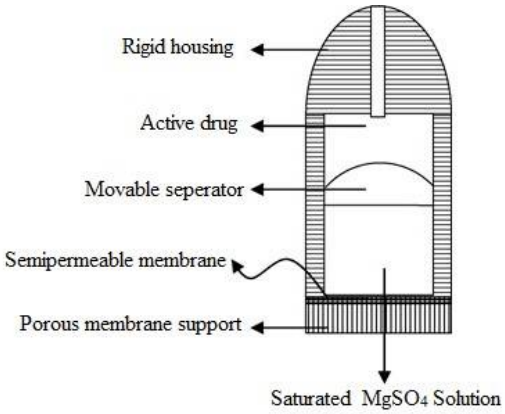

Fig. 3: Higuchi-Leeper Pump

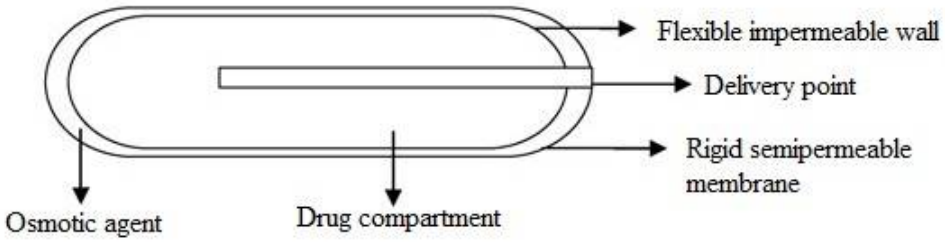

Fig. 4:Theeuwesminiature osmotic pump

In 1975, the major leap in osmotic delivery occurred astheelementary osmoticpumpfororal delivery of drugs was introduced. The pump consistsof anosmoticcorecontainingthe drug, surrounded byasemipermeablemembranewitha deliveryorifice.Whenthispumpisexposed to water,thecoreimbibeswaterosmotically ata controlledrate,determined bythemembrane permeabilitytowaterandbytheosmoticpressure ofthecoreformulation. Asthemembraneisnon-

expandable, theincreaseinvolumecausedbythe imbibitionsofwaterleadstothedevelopment of hydrostatic pressureinsidethetablet.Thispressure isrelievedbytheflowofsaturatedsolution outof thedevicethroughthedeliveryorifice.This process continues ataconstantrateuntiltheentiresolid agentinsidethetablethasbeendissolvedandonlya solutionfilledcoatingmembrane isleft.This residualdissolvedagentcontinuestobedeliveredat adecliningrateuntiltheosmoticpressureinside andoutsidethetabletisequal.Normally, theEOP delivers60-80%ofitscontentsataconstantrate, andthereisashortlagtimeof30-60 minasthe system hydratesbeforezeroorderdeliveryfromthe EOP is obtained.

TYPES OF OSMOTIC PUMPS

Based on their design andthestateofactive ingredient, osmoticdeliverysystemscanbe classifiedasfollows

1.Osmotic delivery systems for solids

a.TypeI

Singlecompartment. Inthisdesign,the drugandtheosmoticagentarelocated inthesame compartment andaresurroundedbythe semipermeable membrane(SPM).Boththecore componentsaredissolvedbywater,whichenters thecoreviaosmosis. Alimitation isthedilutionof drugsolutionwiththeosmoticsolution, which affects therelease rateofthedrugfromthesystem. Additionally,water-incompatibleorwater-insoluble drugscannotbedelivered effectivelyfromasingle-compartmentconfiguration.

b.TypeII

Multiplecompartments. Inthisdesign, drugisseparatedfromtheosmoticcompartmentby anoptionalflexiblefilm,whichisdisplaced bythe increasedpressureinthesurrounding osmotic compartment, which,inturn,displacesthedrug solution or suspension. The type II system inherentlyhasgreaterutilitythantypeIsystemsand candeliverdrugsatadesiredrateindependent of theirsolubilities inwater.Onemainadvantageof thesesystemsistheirabilitytodeliverdrugsthat areincompatiblewithcommonlyusedelectrolytes orosmoticagents.

2.Osmotic delivery systems for liquids

Activeingredientsin liquidformaredifficultto deliverfromcontrolledreleaseplatformsbecause theytendtoleakintheirnative form.Therefore, liquidactiveagentstypicallyareenclosed inasoft gelatincapsule,whichissurrounded byanosmotic layerthat,inturn,iscoatedwithasemipermeable membrane.Whenthesystemtakesupwaterfrom itssurroundings, theosmoticlayersqueezesthe innermostdrugreservoir.The increasinginternal pressuredisplaces theliquidfromthesystem via rupturingsoftgelatincapsule.

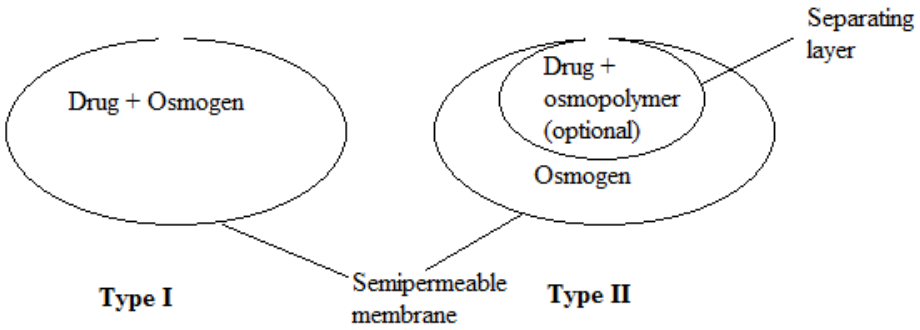

Fig. 5: Classification of osmotic delivery systems: types I and II

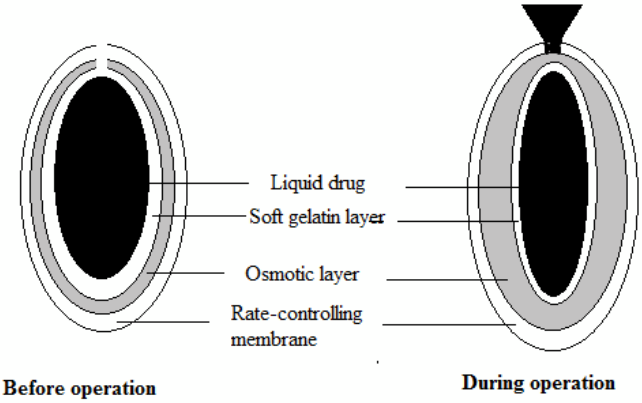

Fig. 6: Osmotic delivery system for delivery of a liquid active agent

Elementary osmotic pump (EOP)

Thewasintroducedin1970stodeliverdrugatzero orderratesforprolongedperiods,andisminimally affectedbyenvironmental factorssuchaspHor motility.Thetabletconsists ofanosmoticcore containing the drug surrounded by a semi- permeablemembranelaser drilled with delivery orifice.Followingingestion,waterinabsorbedinto systemdissolving the drug, and the resulting drug solutionisdelivered atthesamerateasthewater entering the tablet. The disadvantages of the elementary pump are that it is only suitable for the delivery of water soluble drugs.

Push–PullOsmoticPump(PPOP)

Thetwo-layerpush–pull osmotictabletsystem appearedin1980s.Pushpullosmoticpumpisamodifiedelementaryosmoticpumpthrough,which itispossibletodeliverbothpoorlywater-soluble andhighlywatersolubledrugsataconstantrate. 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 orificenext to the drug compartment.

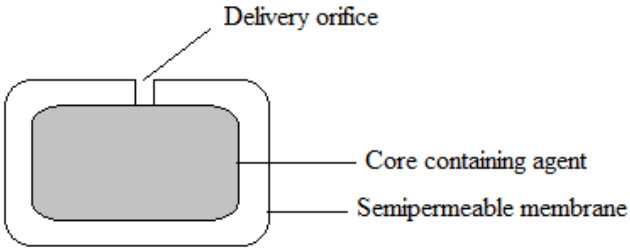

Fig. 7: Elementary osmotic pump

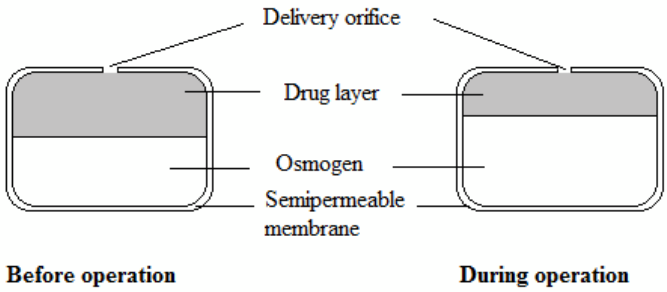

Fig. 8: Push pull osmotic pump

Controlled Porosity Osmotic Pump

Acontrolledporosityosmoticpump-based drug delivery system Unlike the elementary osmotic pump(EOP)whichconsistsof an osmoticcorewith thedrugsurroundedbyasemipermeablemembrane drilledwithadeliveryorifice,controlledporosityof themembraneisaccomplished bytheuseof differentchannelling agentsinthecoating.The CPOPcontainswatersolubleadditives incoating membrane, whichaftercomingincontactwith water; dissolveresultinginanin-situ formationofa microporous membrane. Then the resulting membraneissubstantially permeabletobothwater anddissolvedsolutesandthemechanism ofdrug releasefromthesesystemswasfoundtobeprimarily osmotic,withsimplediffusion playingaminorrole.

Drugdeliveryfrom asymmetric membrane capsuleisprincipally controlled bytheosmotic pressureofthecoreformation. In-situformed deliveryorificeintheasymmetricmembrane in mainlyresponsible forthesolubilizationinthecore fora drugwithpoorwatersolubility.

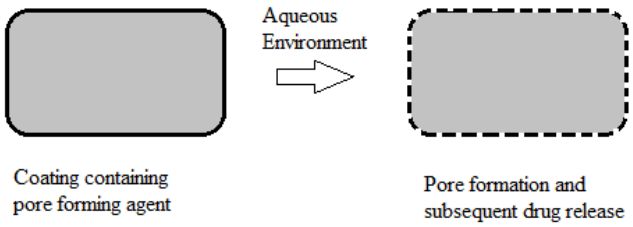

Fig. 9: Controlled porosity osmotic pump

Osmotic bursting osmotic pump

Thissystem issimilarto an EOP expect delivery orificeisabsentandsizemay besmaller. Whenitisplacedinanaqueousenvironment,water isimbibed andhydraulic pressure isbuiltupinsideuntilthe wall rupture and the content are releasedtothe environment.Varyingthethicknessaswellasthe area the semipermeablemembranecancontrol releaseofdrug.Thissystem isusefultoprovide pulsatedrelease.

Telescopic capsule for delayed release

Thisdeviceconsistsoftwochambers, thefirst contains thedrugandanexitport,andthesecond contains anosmoticengine.Alayerofwaxlike materialseparatesthetwosections.To assemblethe deliverydevice, thedesiredactiveagentisplaced intooneofthesectionsbymanualorautomatedfill mechanism. The bilayertablet with the osmotic engine isplaced intoacompletedcappartofthe capsulewiththeconvex osmoticlayerpointed into theclosed endofthecapandthebarrierintothe closed endofthecapandthebarrier layerexposed towardsthecapopening. Theopenendofthefilled vesselisfittedinsidetheopenendofthecap,and thetwopiecesarecompressedtogetheruntilthe cap,osmoticbilayer tabletandvesselfittogether tightly. Asfluidisimbibed thehousing ofthe dispensing device,theosmoticengineexpandand exertspressureontheslidableconnected firstand secondwallsections. Duringthedelayperiodthe volumeofreservoircontainingtheactiveagentis keptconstant, therefore anegligible pressure gradientexistsbetweentheenvironment ofuseand interiorofthereservoir. Asaresult,thenetflowof environmentalfluiddrivenbythepressureenterthe reservoirisminimalandconsequently noagentis deliveredfortheperiod.

OROS-CT

OROS-CT (Alzacorporation) isusedasaonceor twice a day formulationfor targeteddeliveryof drugstothecolon. TheOROS-CT canbeasingle osmoticagentoritcanbecomprisedofasmanyas fivetosixpushpullosmoticunitfilledinahard gelatincapsule.

Aftercomingincontactwiththegastricfluids, gelatincapsuledissolvedand the entericcoating preventsentryoffluidsfromstomachtothesystem asthesystementersintothesmallintestinethe entericcoatingdissolvesandwaterisimbibedinto thecoretherebycausingthepushcompartmentto swell.Atthesametimeflowablegelisformedin thedrugcompartment,whichispushedoutofthe orificeatarate,whichispreciselycontrolled,by the rate of water transport across the semi permeable membrane. Incorporation of the cyclodextrin-drugcomplexhasalsobeenusedasan approachfordeliveryofpoorlywatersolubledrugs fromtheosmoticsystems.Ex.Sulfobutylether-B-cyclodextrinsodiumsaltservesasasolubilizerand osmoticagent.

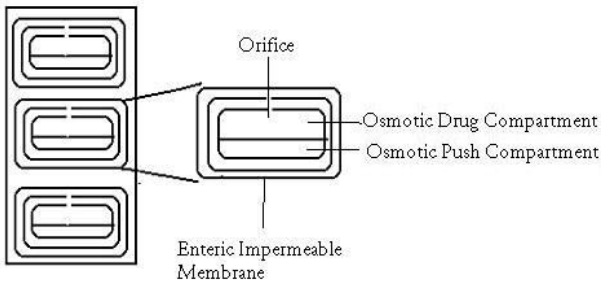

Fig. 10: OROS-CT

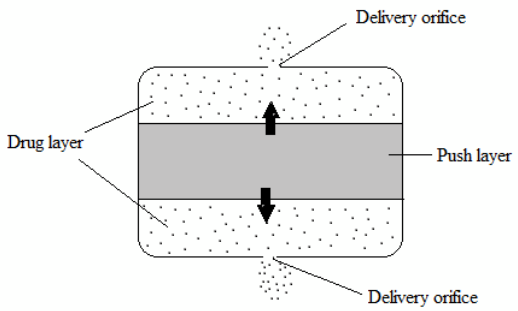

Fig. 11: Sandwiched osmotic tab

Sandwiched Osmotic Tablets(SOTS)

Inthisatabletcorecomposed ofpolymeric push layersandwichedbetweentwodrug layerswithtwo delivery orifices. Whenplacedintheaqueous environmentthemiddlepushlayercontainingthe swellingagentswellsandthedrugisreleasedfrom thetwoorificessituatedonopposite sidesofthe tablet and thus SOTS can be suitable for drugs prone tocause localirritationofthegastricmucosa.

Longitudinally compressed tablet (LCT) multilayer formulation

TheLCTmultilayerformulation istheadvanced design.Aswiththepush-pullsystemitconsistsof anosmoticpushlayer andcanbeconfiguredto containseveraldruglayers. Theopinionofmultiple drug layers provides increased flexibility and controloverthepatternofreleaseofmedication fromthe system,asopposedtothe singlelayer used inthepush-pull system,whichcandeliveradrug onlyinazeroorderfashion.Forexample, twodrug layerscouldbeformulated withdifferentdrug concentration toprovidemodulationintherelease rate profile. As with the push-pull formulation, waterisabsorbed throughtheexposed semipermeable tabletshell,expandingthepush compartment andreleasingthedrugprimarily throughthefirstcompartment throughthelaser drilledorificeat a predeterminedcontrolledrate. Aftermostofthedrug release beginsfrom the secondcompartmentatadifferentrate.Varyingthe relative viscosity and hydrophilicity of thedrug layercomponentscancontroltheamountofmixing between themultipledruglayers.Thisallowseven greater flexibilitytoachievethetargetrelease profile.

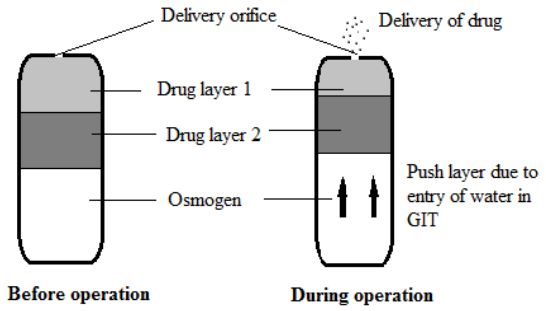

Fig. 12: Multilayer osmotic pump

The LCT multilayerformulation canalsobe formulatedwithdifferentdrugsindifferentlayers toprovidecombination therapy. Similar to the push-pull system,drugdeliverybytheLCT multilayerformulation canbeunaffectedbygastric pH, gut motility and the presence of food, dependingon where in the GI tract the drug is released.

Pulsatile delivery system

Pulsatilesystemsaregainingalotof interestas they deliverthedrugat therightsite of actionat theright timeandintherightamount,thusproviding spatial andtemporaldeliveryandincreasing patient compliance.Thesesystemsaredesignedaccording tothecircadianrhythmofthebody.Theprinciple rationale fortheuseofpulsatile releaseisforthe drugswhereaconstant drugrelease,i.e.,azero-orderreleaseisnotdesired. Thereleaseofthedrug as apulseafteralagtime hasto be designedin such a way that a complete and rapid drug release followsthe lag time.This type of tablet system consistofcorecoatedwithtwolayerofswelling andrupturablecoatingshereintheyusedspraydried lactoseandmicrocrystalline celluloseindrugcore and thencorewascoatedwithswellingpolymer croscarmellose sodium and an outer rupturable layerofethylcellulose.

Pulsatilesystemscanbeclassified intosingle- andmultiple-unit systems.Single-unitsystemsare formulated either as capsule-based or osmosis- basedsystems.Single-unit systemsaredesignedby coatingthesystemeitherwitheroding/solubleor rupturablecoating.Inmultiple-unit systems, however, the pulsatile release is induced by changing membrane permeability or by coating witharupturablemembrane.

KEY PARAMETERS THAT INFLUENCE THEDESIGNOFOSMOTIC CONTROLLED DRUG DELIVERYSYSTEMS

1. Orifice size

Toachieveanoptimalzero-order deliveryprofile, the cross-sectional area of the orifice must be smaller than a maximum size to minimize drug deliverybydiffusion throughtheorifice. Furthermore,the area mustbe sufficientlylarge, aboveaminimum sizetominimizehydrostatic pressurebuildupinthesystem.Otherwise, the hydrostatic pressurecandeformthemembraneand affectthezero-order deliveryrate.Therefore, the cross-sectional areaoftheorificeshouldbe maintainedbetweenthe minimumandmaximum values.

Methods tocreatea delivery orificein the osmotictabletcoatingare:

- Mechanicaldrill
- Laser drill: This technology is well established for producing sub-millimeter sizeholeintablets.Normally, CO2laser beam(withoutputwavelengthof10.6μ)is used fordrilling purpose, which offers excellent reliability characteristics at low costs.
- Indentationthatisnotcoveredduringthe coatingprocess:Indentationismadein coretabletsbyusing modified punches having needleonupper punch. This indentation isnotcoveredduringcoating process which actsasa path fordrug releaseinosmoticsystem.
- Use of leachable substances in the semipermeable coating : e.g. controlled porosity osmotic pump.

2. Solubility

Thereleaseratedependsonthesolubility ofthe soluteinsidethedrugdeliverysystem.Therefore, drugs should have sufficient solubility to be delivered byosmoticdelivery.Inthecaseoflow-solubilitycompounds, severalalternatestrategies maybeemployed.Broadly,theapproaches canbe dividedintotwocategories. First,swellable polymers canbeaddedthatresultinthedeliveryof poorlysolubledrugsintheform ofasuspension.Second, thedrugsolubilitycanbemodified employing different methods such as co compression of the drug with other excipients, whichimprove thesolubility.Forexample, cyclodextrincanbeincludedintheformulationto enhancedrugsolubility.Additionally, alternativesaltformsofthedrugcanbeemployed tomodulatesolubilitytoareasonable level.Inone case,thesolubilityofoxprenolol isdecreasedby preparing itssuccinate saltsothatareduced saturationconcentrationismaintained.

3. Osmotic pressure

Theosmoticpressure πdirectlyaffectstherelease rate. To achieve a zero-orderrelease rate,itis essentialtokeepπconstantbymaintaining a saturatedsolutesolution. Manytimes,theosmotic pressuregenerated bythesaturateddrugsolution may not be sufficient to achieve therequired drivingforce.Inthiscase,otherosmoticagentsare addedthatenhance osmoticpressure. Forexample, additionofbicarbonate saltnotonlyprovidesthe necessaryosmoticgradient butalsoprevents cloggingoftheorificebyprecipitated drugby producinganeffervescent actioninacidicmedia.

Table 1: Osmotic pressures of saturated solution of commonly used osmogents

Compounds of mixture	Osmotic pressure (atm)
Lactose-Fructose	500
Dextrose-Fructose	450
Sucrose-Fructose	430
Mannitol-Fructose	415
Sodiumchloride	356
Fructose	335
Lactose-Sucrose	250
Potassiumchloride	245

CONTROLLED POROSITY OSMOTIC PUMP- IN DETAIL

Thecontrolled-porosity osmoticpumptablet conceptwas developedasan oral drugdelivery systembyZentneretal. Thecontrolled-porosity osmoticpumptabletisaspray-coated orcoated tabletwithasemipermeable membrane(SPM) containingleachable poreforming agents.Theydo nothaveanyaperture torelease thedrugs;drug releaseisachieved through thepores,whichare formedinthesemipermeablewallinsituduring theoperation. Inthissystem,thedrug,after dissolutioninside the core, is released from the osmoticpumptabletbyhydrostatic pressureand diffusionthroughporescreened bythedissolution of pore formers incorporatedin the membrane. Thehydrostaticpressureis createdeitherbyan osmoticagent orbythedrug itselforbyatablet component, afterwaterisimbibedacrossthe semipermeable membrane.Thereleaseratefrom thesetypesofsystemsisdependentonthecoating thickness,levelofleachablecomponents inthe coating,solubilityofthedruginthetabletcore, andosmotic pressure differenceacrossthe membrane butisindependent ofthe pH and agitationofthe releasemedia.

Factors affecting the release of drug through controlled porosity osmotic pump

1. Drug: Osmotic agent ratio

As concentration of osmoticagentinthetablet corehasincreases therateofdrugreleaseisalso increases. Itisduetotheincreaseinosmotic pressure on increasing the concentration of osmotic agent. Asdifferent osmotic agentpossessthedifferent osmotic pressure thereleaseofdrug troughdrug deliverysystemisdepend onthetype of osmotic agent.

2. Level of coating thickness

Drugrelease from thesystemisinversely proportional tothelevelofcoatingthickness.As thicknessofcoatingincreases thedrugrelease get decreases.

3. Porosity of coating membrane

As porosity of coatingmembranegetsincreases the rate of drug release is increases. The porosity of coating membrane is depending on the type and concentration of channelling agent.

Table 2: Specification of Controlled Porosity Osmotic Pump

Subject	Specification
Plasticizers and flux Regulating agents	0 to50, preferably0.001to50partsper100partsof wallmaterial
Surfactants	0 to40, preferably0.001to40partsper100partsofwallmaterial
Wallthickness	1 to1000,preferably20to500m
MicroporousnaturePoreformingadditives	5 to95%poresbetween10ato100mdiameter0.1to60%,preferably0.1to50%,by weight,basedonthe totalweightof additiveandpolymer
Coreloading(size)	0.05mgto5gormore(includedosageformsforHumansandanimals)
Osmoticpressuredevelopedbyasolutionof core	8 to500atmtypically,withcommonlyencounteredwatersolubledrugsandexcipients
Coresolubility	To get continuous,uniformreleaseof 90%or greaterofheinitiallyloadedcoremasssolubility,S,tothecore massdensity,that is S/,mustbe0.1or lower.Typically itoccurswhen10%ofthe initiallyloadedcoremass saturatesavolumeof externalfluidequaltothetotal volumeofthe initialcoremass.

Table 3: Research on Controlled Porosity Osmotic Pump

Author	Drug	Osmoticagent	Semipermeable membrane	Channelling agent
Pritam*et.al.*	Venlafaxine-Hydrochloride	Sodiumchloride	Celluloseacetate	PEG-400 and HPMCK4M
Chong-kaiGaoetal	Salvianolic acid	Sodiumchloride	Celluloseacetate	PEG-400 andDiethyphthalate
PatelParthetal	PropranololHydrochloride	Sodiumchloride	Celluloseacetate	PEG-400
HarnishPateletal	Glimepiride	Sodiumchloride	Celluloseacetate	PEG-400

Table 4: Recent patents on Controlled Porosity Osmotic Pump

Title, Inventors, Year	PatentNo.
Salvianolicacidcontrolledporosityosmoticpumptabletsand methodofpreparingthesame.Gao*et al*.2008.	CN200810027661
Novelswellableporousosmoticpumpdrugdeliverysystem.Pritam*et al*.2009.	IN2007MU01469 A 20090619.
Controlledporosityosmoticpumptablet ofhighpermeabledrugsandthe preparationmethodthereof.Wang*etal*.2009.	EP2085078
Porouscontrolled-onsetcontrolled-releasetabletofdilthiazemhydrochlorideandits preparationmethod.Jiang*etal*.2010.	CN101766581 A20100707.
Controlledporousosmoticpumptabletsofhighpermeabledrugsandthepreparationprocessthereof.Wange*tal*.2010.	US20100291208
Surgerycontrolledreleasetherapeuticdeviceorsystemimplanteddynamicdeviceor system.Eric*et al*.2011.	US20110184389

Table 5: Marketed formulation of controlled porosity osmotic pump

Brand Name	API	Strength (mg)	Market Status(US)
Tiamate	Diltiazem Malate	120,180, 240	Discontinued
Teczem	EnalaprilDiltiazem	280	Discontinued
Acu System C	Vitamine C	NA	Prescription

EVALUATION OF OSMOTIC TABLET

Evaluation of powder

1. Weight of powder
2. Bulk density
3. Tapped density
4. Carrs index
5. Angle of repose

Evaluation of osmotic tablet

1. Hardness
2. Thickness
3. Friability
4. Weight uniformity
5. Drug content
6. In vitro dissolution study

- Effect of osmotic pressure
- Effect of pH on drug release
- Stability study
- Curve fitting analysis
- Zero order release kinetics
- First order release kinetics

- **Burst strength**

Burst strength of the exhausted shells after dissolution was determined to assure that the tablets would maintain their integrity in the gastrointestinal tract (git). Burst strength was determined as the

force required to break or rupture the shells after dissolution studies. The texture analyzer was used for this purpose.

- **Effect of pH**

In order to study the effect of pH to assure a reliable performance of the developed formulations independent of pH release studies were conducted in media of different pH, simulated gastric fluid(SGF)pH 1.2 ,simulated intestinal fluids (SIF) pH 6. And pH change method (release media was SGF for first 2 hours followed by SIF for remaining period). The sample is withdrawn (10 ml) at pre-determined interval and analysed after filtration through filter. The cumulative drug release of various pH was plotted and compared.

- **Effect of agitational intensity**

In order to study the effect of agitational intensity of the release media release studies were carried out in dissolution apparatus at various rotational speeds .samples were withdrawn at pre-determined intervals and analysed after filtration and percentage cumulative drug release was compared and plotted.

- **Osmotic pressure measurement**

In order to confirm the mechanism of drug release studies were conducted in media of different osmotic pressure.to increase the osmotic pressure of release media sodium chloride was added in SIF and osmotic pressure was measured in osmometer.

- **Curve fitting analysis**

To describe the kinetics of drug release from controlled release preparations various mathematical equations have been proposed. Release data obtained was applied to different release models in order to establish the drug release mechanism and kinetics. Best goodness offit test (R^2) was taken as criteria for selecting most appropriate model.

CONCLUSION

It can be concluded that β1 cardio selective blockers can be formulated by CPOP with good release profiles for prolonged period of time up to 13 hours which can decrease the frequency of dose administration, prevent nocturnal attack and improves patient compliance. Further in vivo studies are required to correlate with in vitro release data.

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