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Review Article

Formulation aspects in development of controlled porosity osmotic pump tablet

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ABSTRACT

The development of oral controlled release system has been a challenge to formulation scientist due to their inability to restrain and localize the system at targeted areas of the gastrointestinal tract. Various physical and chemical approaches have been applied to produce a well characterized dosage form that controls drug input into the body within the specifications of the desired release profile. This is generally accomplished by attempting to obtain "zero-order" release from the dosage form, i.e., the rate of drug release is independent of the drug concentration. Controlled porosity osmotic pump tablet; which is an extension of elementary osmotic tablet, utilizes the principle of osmotic pressure for the delivery of drugs and avoids the expensive laser drilling for creation of delivery orifice on the tablet coat. They do not have any aperture to release the drugs; drug release is achieved through the pores, which are formed in the semi permeable wall in situ during the operation. The advantages of controlled porosity osmotic pump tablet are mainly driven by the capacity to deliver drugs in a sustained manner, independent of the drug chemical properties, patient's physiological factors or concomitant food intake. However, access to this technology has been restricted by the crowded patent landscape and manufacturing challenges. The present review highlights the principle of osmosis, formulation variables, factors affecting drug release, recent researches, marketed products and the evaluation parameters of controlled porosity osmotic pump tablet.

Keywords: Osmotic pump, Osmotic pressure, Pore forming agent, Osmogen, Wicking agent

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Introduction

Oral drug delivery is the most widely utilized route of administration among all the routes that have been explored for systemic delivery of drugs via pharmaceutical products of different dosage form. Oral route is considered most natural, convenient and safe due to its ease of administration, patient acceptance, and cost effective manufacturing process. Pharmaceutical products designed for oral delivery are mainly immediate release type or conventional drug delivery systems, which are designed for immediate release of drug for rapid absorption.[1,2]

These immediate release dosage forms have some limitations such as:

1) Drugs with short half life require frequent administration, which increases chances of missing dose of drug leading to poor patient compliance.

2) A typical peak-valley plasma conc. time profile is obtained which makes attainment of steady state condition difficult.

3) The unavoidable fluctuations in the drug concentration may lead to under medication or over medication as the C_{max} values fall or rise beyond the therapeutic range.

The fluctuating drug levels may lead to precipitation of adverse effects especially of a drug with small therapeutic index, whenever over medication occurs.

In long-term therapy for the treatment of chronic disease conditions, conventional formulations are required to be administered in multiple doses and therefore have several disadvantages.[3] Controlled release (CR) tablet formulations are preferred for such therapy because they offer better patient compliance, maintain uniform drug levels, reduce dose and side effects, and increase the safety margin for high-potency drugs.[4,5] Many innovative methods have been developed for obtaining controlled drug release as shown in Figure 1.[6-9] From the practical view point, controlled porosity osmotic pump tablet is one of the best approaches for developing controlled release dosage form.

Osmotically controlled drug delivery system osmotic devices are the most reliable controlled drug delivery system and can be employed as oral drug delivery systems. Osmotic pressure is used as the driving force for these type of systems to release the drug in a controlled manner. Controlled porosity osmotic pump tablet as shown in Figure 2 is a spray coated or coated tablet with a semipermeable membrane containing leachable pore forming agents. They do not have any aperture to release the drugs; drug release is achieved through the pores, which are formed in the semipermeable membrane in situ during the operation. In this system, the drug, after dissolution inside the core, is released from the osmotic pump tablet by the hydrostatic pressure and diffusion through pores created by the dissolution of pore formers incorporated in the membrane. The hydrostatic pressure is created either by an osmotic agent or by the drug itself or by the tablet component, after water is imbibed across the semipermeable membrane.[10,11]

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.[12] Osmosis is one of the fundamental phenomena in biology enabling for instance cells and plants to adjust water balance. An osmotic flow is generated when two solutions of different solute concentrations are separated by a semi-permeable membrane rejecting the solute on the one hand but allowing passage of the solvent molecules on the other hand, as illustrated in Figure 3A. The osmotic flow across the semi-permeable membrane is directed to compensate differences in solute concentrations. This leads to a flow of solvent from the region of low solute concentration (high chemical potential) to the region of higher solute concentration (low chemical potential).

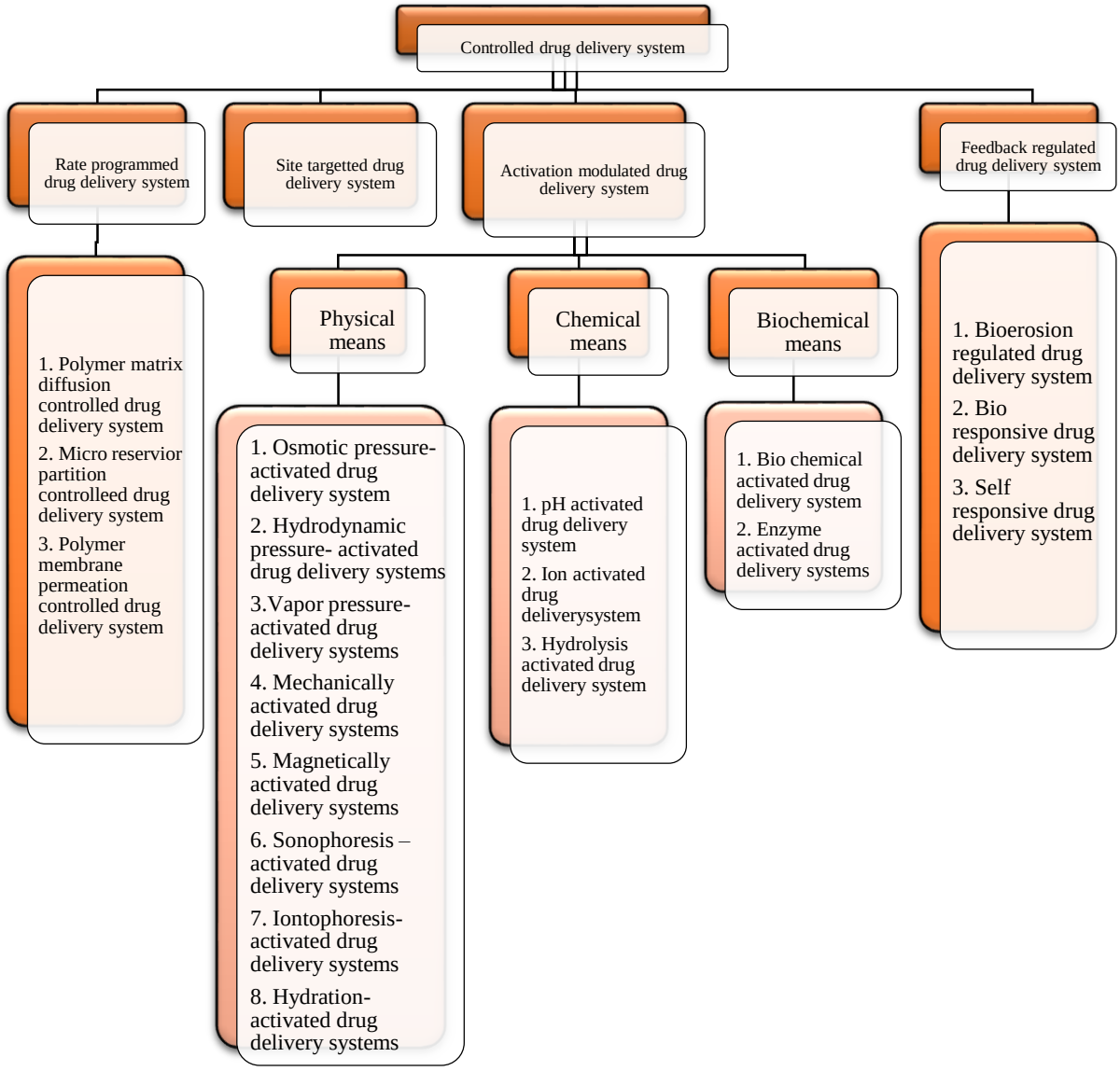

Figure 1: Classification of controlled drug delivery system.

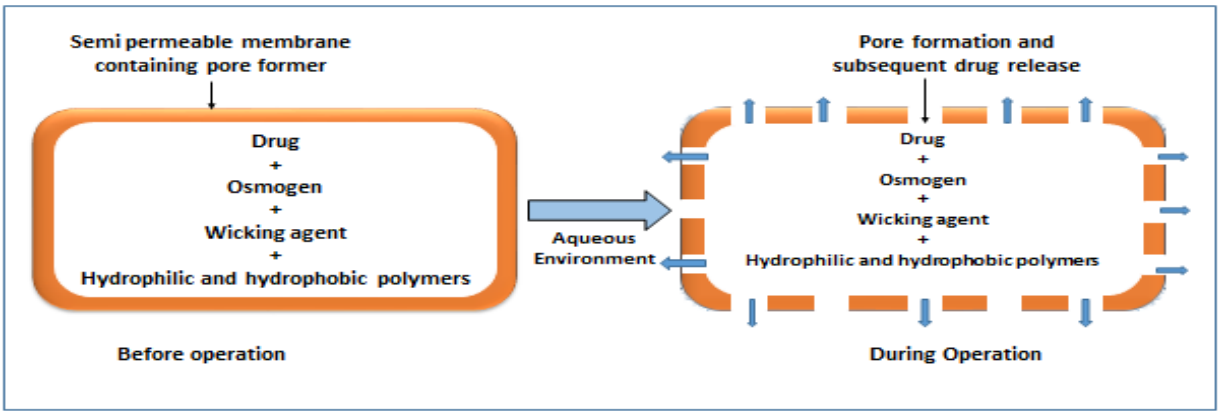

Figure 2: Drug release mechanism of controlled porosity osmotic pump tablet.

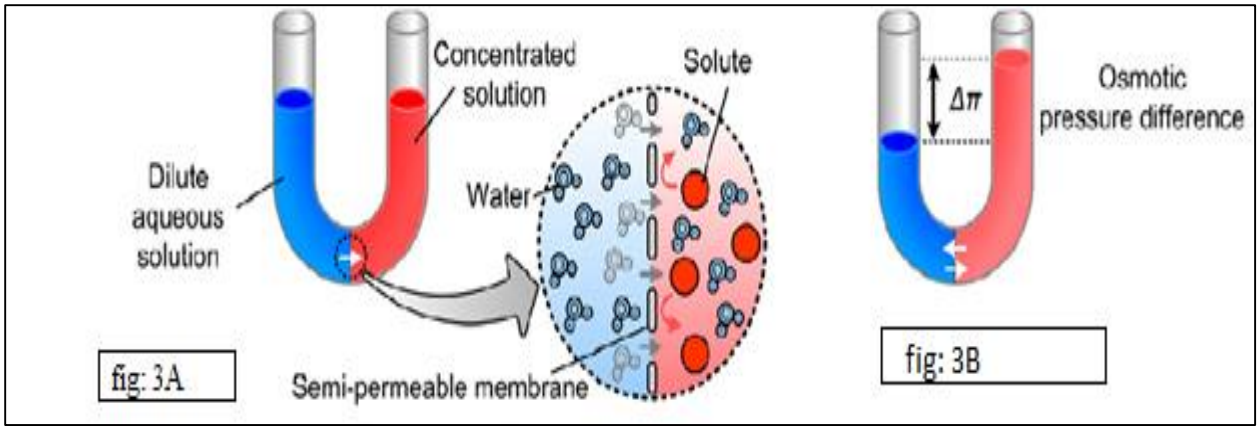

Figure 3: Principle of osmosis.

As a consequence it results in a hydrostatic pressure difference across the semi-permeable membrane causing in turn an oppositely directed flow of solvent as illustrated in Figure 3B. In equilibrium, the flow due to the hydrostatic pressure difference balances the osmotic flow. The pressure difference required to generate this balancing flow is equivalent to the difference of the osmotic pressures of the two solutions.[13] The pressure applied to the higher-concentration side to inhibit solvent flow is called the osmotic pressure.[12]

The osmotic water flow through a membrane is given by the equation

$$dv\backslash dt = A\ Q\ \Delta\ \pi\backslash\ L$$

Where,
dv\dt = water flow across the membrane of area A in cm^2,
L = thickness,
Q = permeability,
$\Delta\ \pi$ = the osmotic pressure difference between the two solutions on either side of the membrane.

This equation is strictly for completely perm selective membrane that is membrane permeable to water but completely impermeable to osmotic agent.[14]

Advantages[7,14-19]

- Zero order kinetics and thus better control over the drug's *in vivo* performance is possible.
- Drug release is independent of the gastric pH and hydrodynamic conditions, which is mainly attributed to the unique properties of the SPM employed in the coating of osmotic formulations.
- The release rate of osmotic systems is highly predictable and can be programmed by modulating the release control parameters.
- They typically give a zero order release profile after an initial lag.
- Drug delivery may be delayed or pulsed, if desired.
- They are well characterized and understood.
- The release mechanisms are not dependent on drug.
- A high degree of *in-vitro* and *in-vivo* correlation (*ivivc*) is obtained in osmotic systems.
- The rationale for this approach is that the presence of water in gastro intestinal tract is relatively constant, at least in terms of the amount required for activation and controlling osmotically base technologies.
- Higher release rates are possible with osmotic systems compared with conventional diffusion controlled drug delivery systems.
- Frequency of dosing is reduced and patient compliance is improved.
- The release from osmotic systems is minimally affected by the presence of food in gastrointestinal tract.

- This is extremely valuable for patients with chronic illnesses which require the plasma concentrations of a drug to be within its therapeutic range to avoid breakthrough symptoms, for example, overnight management of pain in terminally ill patients.

Disadvantages[18-24]

- Drug release from the osmotic systems is affected to some extent by the presence of food.
- Retrieval of therapy is not possible in the case of unexpected adverse events.
- Residence time of the system in the body varies with the gastric motility and food intake.
- It may cause irritation or ulcer due to release of saturated solution of drug.
- Integrity & consistency are difficult.
- If the coating process is not well controlled there is a risk of film effects, which results in dose dumping.
- Rapid development of tolerance.
- Expensive specialized equipment and inert ingredients may be required for osmotic pump tablet formulations.

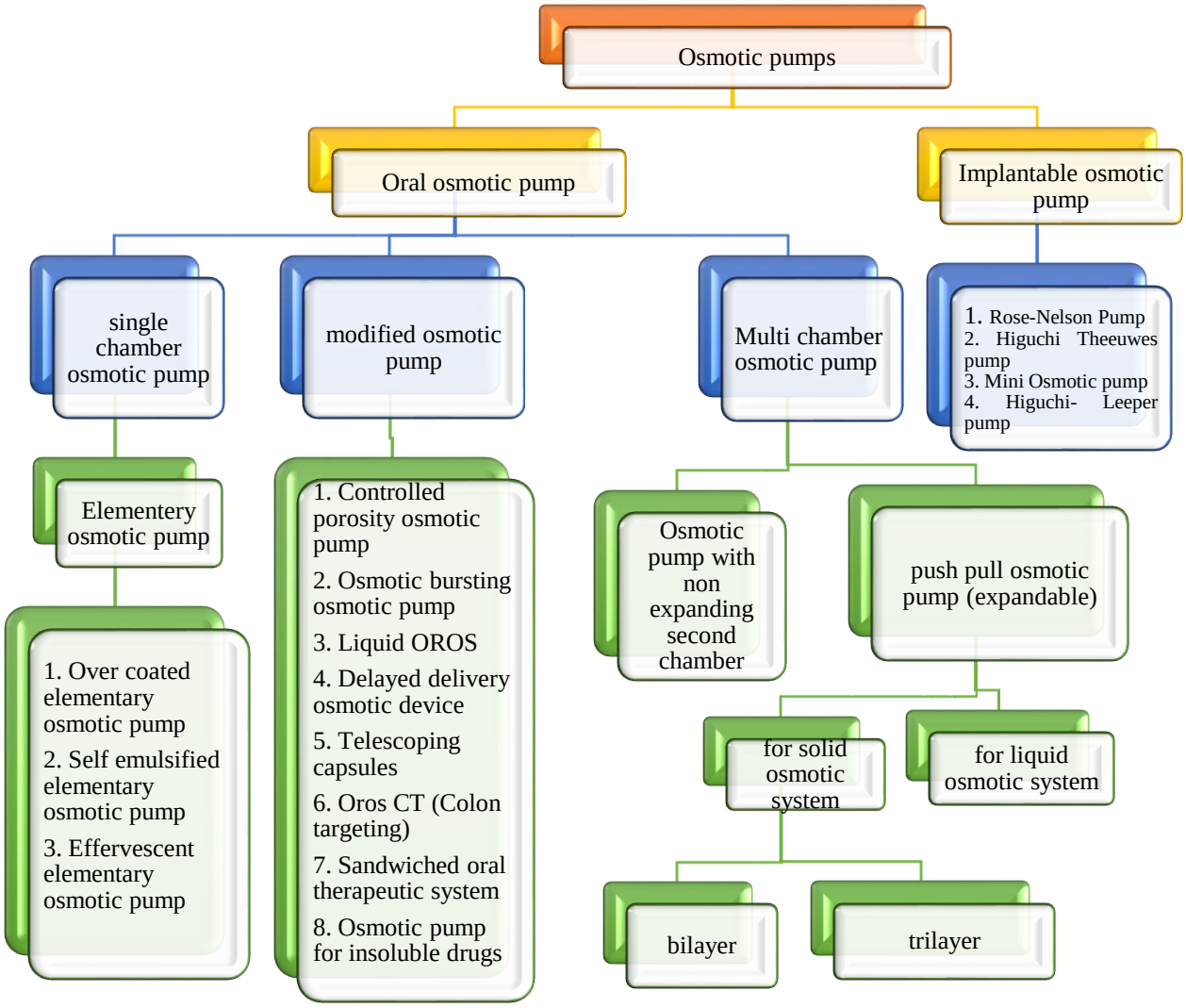

Figure 4: Classification of osmotic drug delivery system.

Classification of osmotic drug delivery system

The types of osmotic drug delivery system are shown in Figure 4.[14,15, 23, 25-27]

Basic components of controlled porosity osmotic pump tablet

Drug

Highly potent drugs required for prolonged treatment of disease (e.g. Nifedipine, Verapamil, glipizide) with shorter biological half-life (2-6 Hrs.) are ideal candidates for osmotic delivery.[8,28]

Osmotic agent

Osmogens are essential ingredient of the osmotic formulations. They maintain an osmotic gradient across the membrane. Upon penetration of biological fluid into the osmotic pump through semipermeable membrane, osmogens are dissolved in the biological fluid, which creates osmotic pressure buildup inside the pump and pushes medicament outside the pump through delivery orifice. They also generate a driving force for uptake of water and assist in maintain drug uniformity in the hydrated formulation. A water soluble drug may act as an osmogen. 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. When the solubility of drug is low then the drug will show zero order release but at a slow rate. To enhance the release rate osmotic agent is added in the formulation.[6,14,15,20] The osmogen category and examples are given Table 1.[7,13,20,21,25,29,30]

Flux regulator

Flux regulating agents (either flux enhancing agent or flux decreasing agent) are incorporated in the wall forming material to regulate the permeability of the fluid across the membrane. They also increase the flexibility and porosity of the lamina. These agents can be preselected to increase or decrease the liquid flux.[9,14]

Flux enhancing agent: Hydrophilic substances such as poly ethylene glycols (300 to 6000 Da), polyhydric alcohols such as poly alkylene glycols and low molecular weight glycols such as poly propylene, poly butylenes and poly amylene, etc tend to enhance the flux.[9]

Table 1: Classification of osmogens.

Category	Examples
Water soluble salts of inorganic acids	Magnesium chloride, Magnesium sulphate, Sodium chloride, Potassium chloride, Lithium chloride, Sodium sulphate, Potassium sulphate, Lithium sulphate, Sodium phosphate tribasic.12H_2O, Sodium phosphate dibasic.7H_2O, Sodium phosphate dibasic.12H_2O, Sodium phosphate dibasic anhydrous, Sodium phosphate monobasic.H_2O, Potassium hydrogen phosphate, Sodium bicarbonate, Potassium phosphate
Water soluble salts of organic acids	Sodium acetate, Potassium acetate, Sodium benzoate, Sodium citrate, Sodium ascorbate, Magnesium succinate
Carbohydrates	Arabinose, Ribose, Sucrose , Fructose, Mannose, Glucose, Galactose, Lactose, Raffinose, Xylose, Maltose, Dextrose, Mannitol, Sorbitol, Xylitol
Weak acids	Citric acid, Tartaric acid, Fumaric acid, Adipic acid, Melanic acid
Water soluble amino acids	Glycine, Leucine, Methionine, Alanine
Organic polymeric osmogents	Sodium carboxy methyl cellulose, Hydroxyl propyl methyl cellulose, Hydroxyl ethyl methyl cellulose, Cross linked PVP, Polyethylene oxide, Carbopols, Polyamides

Flux decreasing agent: Hydrophobic materials such as phthalates substituted with an alkyl or alkoxy (e.g., diethyl phthalate or dimethoxy ethyl phthalate) tend to decrease the flux.[14, 31]

Insoluble salts or insoluble oxides, which are substantially water-impermeable materials, also can be used for this purpose.[20, 31]

The amount of flux regulator added to material generally is an amount sufficient to produce the desired permeability and it will vary according to the lamina forming materials. Usually, from 0.001 parts to 50 parts or high weight fraction of flux regulators can be used.[9,31]

Wicking agent

The wicking agents are those agents which help to increase the contact surface area of the drug with the incoming aqueous fluid ability due to their ability to draw water into the porous network of a delivery device thereby creating channels or a network of an increased surface area.[29,32] 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. Some materials can both wick water and swell, others can function as wicking agents only. They are characterized by having the ability to undergo physical absorption with water. Physical absorption 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.[31,33] Materials like colloidal silicon dioxide, kaolin, titanium dioxide, fumed silicon dioxide, alumina, niacinamide, sodium lauryl sulfate, low molecular weight polyvinyl pyrrolidone, m-pyrol, bentoninte, magnesium aluminium silicate, polyester, polyethylene etc. may be used as wicking agents. For bioactive agents with low solubility in water, the wicking agent aids in the delivery of partially solubilized bioactive agent through the passageway in the semipermeable coating.[14,15]

Pore-forming agents (channeling agent)

These agents are particularly used in the pumps developed for poorly water-soluble drugs and in the development of controlled porosity or multi particulate osmotic pumps.[12,20] When the dissolution medium comes into contact with the semipermeable membrane it dissolves the channeling agent and forms pores on the semipermeable barrier. Then the dissolution fluid enters the osmotic system and releases the drug in a controlled manner over a long period of time by the process of osmosis.[8,10] 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. Various types of pore formers are listed in Table 2.

Table 2: Classification of channeling agents.

Category	Examples
Alkaline metal salts	sodium chloride, sodium bromide, potassium chloride, potassium sulphate, potassium phosphate
Alkaline earth metals	calcium chloride, calcium nitrate
Carbohydrates	sucrose, glucose, fructose, mannose, lactose, sorbitol, pentaerythritol and mannitol
Diols and polyols	polyhydric alcohols, polyethylene glycols and polyvinyl pyrrolidone
Phthalate derivatives	diethylphthalate, dibutyl phthalate
Protiens	bovine serum albumin (BSA)
Others	dimethyl sulfone, nicotinamide, Triethyl citrate (TEC) and triacetin (TA)

The pore-formers should be non-toxic, and on their removal, channels should be formed. The channels become a transport path for fluid. These erodible or leachable materials produce one or more passageways with different geometrical shapes. The pores may also be formed in the wall prior to the operation of the system by gas formation within curing polymer solutions, resulting in voids and pores in the final form of the membrane. The pores may also be formed in the walls by the volatilization of components in the polymer solution or by chemical reactions in the polymer solution leading to evolution of gases prior to application or during application of the solution to the core tablets resulting in the creation of the polymer foams serving as the porous wall from where the drug release can take place.[32,33]

Hydrophilic and hydrophobic polymers

Along with API polymers are used in formulation of matrix core of osmotic pump. Polymers are chosen according to the nature of the drug to be used. These polymers are used in the formulation development of osmotic systems for making drug containing matrix core.[31] 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 controlled 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.[15] Uniform rate of swelling of these polymers ensures that the drug is released at a relatively constant rate. Also, the pressure produced during swelling does not lead to rupture of the system.[32] Ionic hydrogels such as sodium carboxy methyl cellulose are preferably used because of their osmogenic nature.[9] Hydrophilic polymers such as hydroxy ethyl cellulose, carboxy methyl cellulose, hydroxy propyl methylcellulose, high-molecular-weight poly (vinyl pyrrolidone), and hydrophobic polymers such as ethyl cellulose and wax materials can be used for this purpose.[15]

Coating solvents

The primary function of solvent system is to dissolve or disperse the polymer and other additive and convey them to substrate surface. Various inorganic and organic solvents compatible with the core and other materials are suitable for making polymeric solution that is used for manufacturing the wall of the osmotic device. 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.[6,34]

The ideal solvent system should have following properties.

- It should easily and completely dissolve the polymer.
- It should easily disperse other coating components into solvent system.
- It should not give extremely viscous solution with Small concentration of polymer (2-10%) because it create process problem.
- It should be inert, odorless, colorless, tasteless, inexpensive, nontoxic and non-irritant.
- It should have rapid drying rate.

Plasticizer

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 viscoelastic behavior 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 into100 parts of costing materials. PEG-600, PEG-200, triacetin (TA), dibutyl sebacate, ethylene glycol mono acetate, ethylene glycol diacetate, triethyl phosphate, and diethyl tartrate used as plasticizer in formulation of semipermeable membrane.[7,12,20-23,32,34]

Semipermeable membrane

A semipermeable membrane, also termed a selectively-permeable membrane, a partially permeable membrane or a differentially permeable membrane, is a membrane that allows

certain molecules or ions to pass through it by diffusion and occasionally specialized "facilitated diffusion". An example of a semi-permeable membrane is the lipid bilayer, on which is based the plasma membrane that surrounds all biological cells. Many natural and synthetic materials thicker than a membrane are also semipermeable. One example of this is the thin film on the inside of an egg.[30]

Since the membrane in osmotic systems is semipermeable in nature, any polymer that is permeable to water but impermeable to solute can be selected.[29] Various types of polymers are used to build the semipermeable coat, the selection of which depends on the solubility of the drug as well as amount and rate of drug to be released from the pump.[21] Cellulose acetate is a commonly employed semipermeable polymer for the preparation of osmotic pumps. It is available in different acetyl content grades. Particularly, acetyl content of 32% and 38% is widely used. Acetyl content is described by the degree of substitution (DS), that is, the average number of hydroxyl groups on the anhydro glucose unit of the polymer replaced by substituting group. Some of the polymers that can be used for above purpose include cellulose esters such as cellulose acetate, cellulose diacetate, cellulose triacetate, cellulose propionate, cellulose acetate butyrate, and cellulose ethers like ethyl cellulose. Apart from cellulose derivatives, some other polymers such as agar acetate, amylose triacetate, betaglucan acetate, poly (vinyl methyl) ether copolymers, poly (orthoesters), poly acetals and selectively permeable poly (glycolic acid), poly (lactic acid) derivatives, and Eudragits can be used as semipermeable film-forming materials. The permeability is the important criteria for the selection of semipermeable polymers.[6,29,31]

The semipermeable membrane must meet some performance criteria as listed below:[10, 23]

a) The material must possess sufficient wet strength (10^{-5} Psi) and wet modules (10^{-5} Psi) so as to retain its dimensional integrity during the operational lifetime of the device.

b) The membrane must exhibit sufficient water permeability so as to attain water flux rates (dv/dt) in the desired range. The water vapour transmission rates can be used to estimate water flux rates.

c) The reflection coefficient (σ) or “leakiness” of the osmotic agents should approach the limiting value of unity. But polymer membranes must be more permeable to water.

d) The membrane should be biocompatible.

e) The membrane should also be rigid and non-swelling.

f) The membrane should be sufficient thick to withstand the pressure within the device.

g) The semipermeable membrane should be a stable both to the outer inner environment of the device.

The Specification for controlled-porosity osmotic pump tablet are given in Table 3.[8,16] whereas the specification for core of controlled-porosity osmotic pump tablet are given in Table 4.[8,16]

Table 3: Specification for controlled-porosity osmotic pump tablet.

Sr. No.	Formulation component	Specification
1	Plasticizers and flux Regulating agents	0 to 50, preferably 0.001 to 50 parts per 100 parts of wall material.
2	Surfactants	0 to 40, preferably 0.001to 40 parts per 100 parts of wall material.
3	Wall thickness	1 to 1000, preferably 20 to 500 m.
4	Microporous nature Pore forming additives	5 to 95% pores between 10a to 100 m diameter 0.1 to 60%, preferably 0.1 to 50%, by weight, based on the total weight of additive and polymer.

Table 4: Specification for core of controlled-porosity osmotic pump tablet.

Property	Specifications
Core loading (size)	0.05 mg to 5 g or more (include dosage forms for Humans and animals).
Osmotic pressure developed by a solution of core	8 to 500atm typically, with commonly encountered water soluble drugs and excipients.
Core solubility	To get continuous, uniform release of 90% or greater of the initially loaded core mass solubility, S, to the core mass density, that is S/, must be 0.1 or lower. Typically it occurs when10% of the initially loaded core mass saturates a volume of external fluid equal to the total volume of the initial core mass.

Factors affecting drug release rate from controlled porosity osmotic pump tablets

Drug solubility

The solubility of the active agent within the device not only dictates the feasibility of making an osmotic system, but also determines the release rate and the percentage of the drug delivered in the desired zero-order fashion.[35] Since the kinetics of osmotic drug release is directly related to solubility of drug within the core, drugs having intermediate water solubility are suitable candidates for controlled porosity osmotic pump to get the optimized drug release.[14,17,20] Assuming a tablet core of pure drug, the fraction of core released with zero-order kinetics is given by equation.

$F(z) = 1 - S/\rho$ ……..Equation (1)

Where,

F (z) = fraction released by zero-order kinetics
S = drug's solubility (g/cm^3)
ρ = density (g/cm^3) of the core tablet.

Drugs with a density of unity and the solubility of ≤0.05 g/cm^3 would be released with ≥95% zero-order kinetics, according to Equation (1). At the same time, highly water-soluble drugs (≥0.3 g/cm^3) would demonstrate a high release rate that would be zero-order for a small percentage of the initial drug load. On other hand, Zero order release rate would be slow according to the equation (2) because of the small osmotic pressure and drug solubility.[7]

$dm/dt = A/h\ K\pi C$ ……Equation (2)

where,

dm/dt = Solute delivery rate
πc = Osmotic pressure of G.I. Fluid
A= Effective Surface area.
h = Thickness of the semi permeable membrane
K=constant

Thus, the intrinsic water solubility of many drugs might prohibit them from incorporation into an osmotic pump. Candidate drugs for osmotic delivery have water solubility in the range 50–300 mg/ml. However, for the drugs appearing to be poor candidate for osmotic delivery, effective release patterns may be obtained by modifying their solubility within the core.[7,12,27,28, 32,33]

Solubility-modifying approaches

Use of swellable polymers: The formulation mainly consists of a compartment, containing the drug, swelling agents, and osmagents, coated with a rate controlling membrane. Hydrophilic polymers such as vinyl pyrrolidone/ vinyl acetate copolymer, polyethylene oxide, ethylene oxide homopolymer have uniform swelling rate which causes drug release at relatively constant rate. Also, the pressure produced during swelling does not lead to rupture of system.[14,32,35]

Use of wicking agents: These agents may enhance the contact surface area of the poorly water soluble drug with the incoming aqueous fluids. Thus, the drug is released predominantly in a soluble form through the pores of the semi permeable membrane. E.g. Colloidal silicon dioxide, polyvinyl pyrrolidone, sodium lauryl sulfate, etc. Ensotrol® technology uses the same

principle to deliver drugs via osmotic mechanism.[32,36]

Use of effervescent mixtures: Addition of effervescent couple like citric acid and sodium bicarbonate generates carbon dioxide which creates pressures in the osmotic system and ultimately dispenses the drug in the suspension form from the pores of the semi permeable membrane.[32,37]

Use of cyclodextrin derivatives: Cyclodextrin derivatives improve apparent drug solubility and dissolution through inclusion complexation or solid dispersion, by acting as hydrophilic carriers for drug with inadequate molecular characteristic for complexation, or as tablet dissolution enhancer for drug with high dose, with which use of a drug/cyclodextrin complex is difficult, eg, paracetamol. The same phenomenon can also be used for the osmotic systems.[17] Cyclodextrin derivatives like sulfobutyl ether-β-cyclodextrin sodium salt, [(SBE)-$_{7m}$-β–CD] and hydroxypropyl-β-cyclodextrin (HP-β-CD) are commonly used complexing agent.[39,40] (SBE)- 7m -β-CD can act both as a solubilizer and osmotic agent.[40]

Resin modulation approach: Ion-exchange resin methods are commonly used to modify the solubility of drugs. Release of a highly water-soluble drug, diltiazem hydrochloride from a CPOP was modulated effectively using positively charged anion-exchange resin, poly (4-vinyl pyridine). Pentaerythritol was used as osmotic agent and citric and adipic acids were added to maintain a low core pH to assure that both the drug and resin carry a positive charge. The solubility of diltiazem hydrochloride was reduced for an extended period and pH-independent zero-order release was obtained.[41]

Use of encapsulated excipients: Solubility modifying hydrophilic diluents such as PEG, PVP, dextrose, etc. are used to coat the surface of hydrophobic drug particles and render them hydrophilic.[17] The solubility of glipizide was improved by incorporating solubility modifying encapsulated meglumine in the form of mini tablet leading to its prolonged release from the device.[42]

Co-compression of drug with excipients: Different excipients can be used to modulate the solubility of APIs with different mechanisms like saturation solubility, pH dependent solubility. Examples of such excipients are organic acids, buffering agent, etc.[14] solubility of diltiazem hydrochloride was reduced by incorporating sodium chloride into the core tablet and the subsequent tablet was coated with the rate controlling membrane to prolong the drug release.[43]

Use of metastable polymorphs: metastable polymorph is more soluble than the stable polymorph of a drug that exhibit polymorphism eg. B form of chloramphenicol palmitate is more water soluble than A and C forms.[17]

Micronization: process such as spray drying or air attrition method reduces the size of the solid drug particles to 1 to 10 microns having improved water solubility.[17]

Use of crystal habit modifiers: Different crystal form of the drug may have different solubility, so the excipient which may change crystal habit of the drug can be used to modulate solubility of poorly soluble drugs.[27] The crystal habit-modifying agent is necessary only when the active agent exists in more than one crystal form and when the desired form of administration is not the most stable form. Under these conditions, crystal modification and the resulting changes in solubility can be achieved. Even in such a case, the crystal habit-modifying agent is only necessary when the resultant property change is sufficiently large. The property that best indicates the need for a crystal habit modifying agent is solubility.[35] One such example is solubility of slightly soluble drug, carbamazepine was increased using combination of hydroxyl methyl cellulose and hydroxyethyl cellulose as crystal habit modifier and formulated as osmotic tablet using other excipients, which showed zero order release.[44]

Use of alternative salt form: Salts have improved solubility and dissolution characteristics in comparison to the original drug. Alkali metal salts of acidic drugs like penicillin and strong acid salts of basic drugs like atropine are more water soluble than the

parent drug.[17] It was found that succinate salt of metoprolol was too soluble to maintain a saturated solution and hence zero order delivery for the anticipated delivery life of dosage form. Subsequently tartarate salt was found to have optimum solubility, and osmotic pump was formulated with this salt form that provided extended release up to 15 h.[45,46]

Use of lyotropic crystals: Use of lyotropic liquid crystals (also known as amphipathic compounds), enhances the solubility of poorly water soluble drugs to assist osmotic delivery. The lyotropic liquid crystals are non-polymeric compounds, generally in the molecular weight range of 200–1500 which form mesophases and swell in presence of water. Compounds that can be used as lyotropic liquid crystals include natural phosphatides such as phosphatidyl-choline (lecithin), phosphatidyl ethanolamine, phosphatidyl serine, phosphatidyl glycerol, and the like.[47,48]

Osmotic pressure:

Osmotic pressure gradient between inside the compartment and the external environment determines the release rate of drug, since rate of drug release from an Osmotic system is directly proportional to osmotic pressure of the tablet core.[20, 24] In order to achieve a zero-order release rate, it is essential to keep constant osmotic pressure by maintaining a saturated drug solution inside the core. Many times, the osmotic pressure generated by the saturated drug solution may not be sufficient to achieve the required driving force. In this case, other osmotic agents are added that enhance osmotic pressure.[33,49] Thus, by varying the type and concentration of osmogen, osmotic pressure and hence drug release gets varied.[24] The list of commonly used osmogents and corresponding osmotic pressure is given in Table 5.[7,13,20,21,29,30]

The osmotic agent should possess the following properties:

a. Having high osmotic pressure.
b. Do not degrade very quickly.
c. Do not interfere with the membrane or enclosed wall.
d. Do not interfere with action of the active drug molecule or the environment into which it is ultimately released.[7]

Table 5: List of commonly used osmogents and corresponding osmotic pressure.

Sr. No.	Name of osmogent	Osmotic pressure
1	Sodium chloride	356
2	Potassium chloride	245
3	Sodium phosphate tribasic.12H_2O	36
4	Potassium sulphate	39
5	Sodium phosphate dibasic.7H_2O	31
6	Sodium phosphate dibasic.12H_2O	31
7	Sodium phosphate dibasic anhydrous	29
8	Sodium phosphate monobasic. H_2O	28
9	Potassium phosphate	105
10	Sucrose	150
11	Fructose	355
12	Lactose	23
13	Dextrose	82
14	Mannitol	38
15	Sorbitol	84
16	Xylitol	104
17	Citric acid	69
18	Tartaric acid	67
19	Fumaric acid	10
20	Adipic acid	8
21	Melanic acid	117

Table 6: list of combination of osmogents and corresponding osmotic pressure.

Sr. No.	Combination of osmogents	Osmotic pressure
1	Lactose-fructose	500
2	Dextrose-fructose	450
3	Sucrose-fructose	430
4	Mannitol-fructose	415
5	Lactose-sucrose	250
6	Lactose-dextrose	225
7	Mannitol-dextrose	225
8	Dextrose-sucrose	190
9	Mannitol-sucrose	170
10	Mannitol-lactose	130

The list of combination of osmogents and corresponding osmotic pressure are given in Table 6.[7,13, 20,21,25,29,30]

Use of wicking agent:

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 help to enhance the rate of drug released from the orifice of the drug.[7] Thus, the drug is released predominantly in a soluble form through the delivery orifice in the membrane. The examples are colloidal silicon dioxide, PVP & Sodium lauryl sulphate.[32]

Characteristics of semipermeable membrane: Some of the membrane variables that are important in the design of oral osmotic system are:

Type and nature of polymer: Any polymer permeable to water but impermeable to solute can be selected. Drug release from osmotic system is largely independent of pH and agitational intensity of GIT. This is because of its selective water permeable membrane and effective isolation of dissolution process of drug core from the gut environment. The *in-vivo* release rate of the system is therefore independent of its position in the GIT. Examples of the polymers are Cellulose Ester, Cellulose Triacetate, Cellulose Propionate, Cellulose Acetate Butyrate, Ester, Ethyl Cellulose and Eudragits.[7]

Cellulose acetate (CA) has been widely used to form rate-controlling membranes for osmotic systems. CA films are insoluble, yet semipermeable to allow water to pass through the tablet coating. The water permeability of CA membrane is relatively high and can be easily adjusted by varying the degree of acetylation. As the acetyl content in the CA increases, the CA film permeability decreases, and solvent resistance increases. The permeability of these films can be further increased by the addition of hydrophilic flux enhancers. Incorporation of plasticizer in CA coating formulation generally lowers the glass transition temperature, increases the polymer-chain mobility, enhances the flexibility, and affects the permeability of the film.

Ethyl cellulose is also widely used in the formation of membranes for oral osmotic systems. However, the water permeability of pure ethyl cellulose membrane is very low that may result in slow release of drugs. Therefore, drug release with ethyl cellulose coated osmotic systems can be enhanced by incorporation of water-soluble additives. Incorporation of HPMC in the ethyl cellulose coating composition improves the permeability of ethyl cellulose membranes.[32]

Among above Cellulose Acetate Butyrate is most commonly used due to its,

1. High water permeability.
2. Permeability can be adjusted by varying the degree of acetylation of polymer and also by increasing plasticizer concentration.
3. Flux enhancer and Superior drying property to thermolabile drugs.
4. Superior drying property so advantageous to thermolabile drugs.[7]

Membrane thickness: Thickness of the membrane has a significant effect on the drug release from osmotic system, which is inversely proportional to each other.[12, 32]

Type and amount of plasticizer: 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 viscoelastic behavior of polymers significantly. In particular, plasticizers can turn a hard and brittle polymer into a softer, more pliable material, and possibly make it more resistant to mechanical stress. These changes also affect the permeability of polymer films.[7,12,28]

Research on controlled porosity osmotic pump (CPOP): Recent researches carried on controlled porosity osmotic pump tablet are described in Table 7.[50-59] Marketed formulation of CPOP are given in Table 8.[19,60]

Table 7: Recent researches on controlled porosity osmotic pump tablet.

Sr. No.	Author	Drug	Solubility enhancer	Osmotic agent	Channeling agent	Semipermeable membrane
1	Jadav M M et al.	Zaltoprofen	Hydroxy Propyl-β-Cyclodextrin	sodium bicarbo-nate and sodium chloride	PEG 400 and Sorbitol	Cellulose acetate
2	Dasankoppa F S et al.	Ketorolac tromethamine		dextrose monohydrate	PVP K30	Ethyl cellulose
3	Kazi M S et al	Ketoprofen		Dextrose and fructose	PEG 4000	Cellulose acetate
4	Maheswari U A et al.	Lornoxicam		Mannitol	PEG 400 Sorbitol	Cellulose acetate
5	Sambath L et al.	Lovastatin	soluplus and PEG 1500	Sodium chloride	Triethyl citrate PEG 400	Cellulose acetate
6	Kaushal A et al.	Acyclovir		Potassium chloride	Sorbitol	Cellulose acetate
7	Derakhshandeh K et al.	Buspiron		Sodium chloride	PEG 400	Cellulose acetate
8	Doshi R D et al.	Verapamil		Mannitol	PEG 400	Cellulose acetate
9	Mohammad Ali et al	prednisolone	Beta cyclodextrin	mannitol	Sorbitol and triacetin	Cellulose acetate
10	Rajagopalkumaravelrajan et al	Nifedipine and Metoprolol	Hydroxy Propyl-β-Cyclodextrin	Dicalcium phosphate	PVP (K-30) Hydroxy propyl methyl cellulose PEG 400	Cellulose acetate

Table 8: Marketed formulation of CPOP.

Sr. No.	Brand name	API	Strength (mg)	Half life (Hrs.)	Developer/marketer	Status/approval (market)	Market status (US)
1	Tiamate	Diltiazem Malate	120, 180, 240	3 – 4.5	Merck/Aventis	1996 (US)	Discontinued
2	Teczem	Enalapril Diltiazem	2805	11	Merck/Aventis	1996 (US, WO)	Discontinued
3	Acu System C	Vitamin C	n.p	3 – 5	Alza	1986 (US)	Prescription

Evaluation of controlled-porosity osmotic pump tablet: [12-15,20,21,25]

Oral osmotic drug delivery systems can be evaluated for following**:**

Visual inspection: Visual inspection of the film for smoothness, uniformity of coating, edge coverage and luster.

Coating uniformity: The uniformity of coating among the tablets can be estimated by determining the weight, thickness and diameter of the tablet before and after the coating.

Coat weight and thickness: The coat weight and thickness can be determined from depleted devices following careful washing and drying of the film, using standard analytical balance and screw gauge, respectively.

In-vitro drug release: The in-vitro delivery rate of drugs from osmotic systems can be determined using diverse methodologies including vertically reciprocating shaker, conventional USP dissolution apparatus I and II, flow-through apparatus, etc. The dissolution medium is generally distilled water or simulated gastric fluid (for first 2 h) and intestinal fluids (for subsequent hours) have been used.

Effect of pH on drug release

An osmotically controlled release system delivers its contents independently of external variables. To check this, dissolution media with different pH is used.

Effect of agitation intensity on drug release

In order to study the effect of agitational intensity of the release media, release studies is carried out in dissolution apparatus at various rotational speeds.

Effect of osmotic pressure on drug release

To study the effect of osmotic pressure on drug release, osmotic tablets are formulated with variety of osmogens or combination of osmogens with varied concentration having varied osmotic pressure and dissolution study is carried out using diverse methodologies, including vertically reciprocating shaker, conventional USP dissolution apparatus I and II, flow-through apparatus, etc. The rate of drug release is directly proportional to the osmotic pressure of the tablet.

Effect of amount of pore former on drug release

To study the effect of pore former on drug release, core osmotic tablets are coated with variety of pore former or combination of them with varied concentration and dissolution study is carried out using diverse methodologies, including vertically reciprocating shaker, conventional USP dissolution apparatus I and II, flow-through apparatus, etc. As the concentration of pore former increases, the rate of drug release also increases.

Effect of coating thickness on drug release

To study the effect of coating thickness on drug release, core osmotic tablets are coated with variety of polymers with varied concentration and dissolution study is carried out using diverse methodologies, including vertically reciprocating shaker, conventional USP dissolution apparatus I and II, flow-through apparatus, etc. The rate of drug release is inversely proportional to the coating thickness of the osmotic tablet.

In-vivo evaluation

As the environment in the intestinal tract of the dog is quite similar to that of the human beings in terms of pH and motility. Dogs have been widely used for *in-vivo* delivery for measurement of drug(s) from oral osmotic drug delivery systems and also to establish in-vitro /in-vivo correlation (IVIVC). *In-vivo* evaluation can also be performed in healthy human volunteers. Various pharmacokinetic parameters (C_{max}, T_{max}, AUC and MRT) and relative bioavailability are calculated.

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