A COMPLETE CONCLUSION OF OSMOTIC DRUG DELIVERY SYSTEM TO DATE

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ABSTRACT

The main objective of this scientific review is to create current awareness about controlled drug delivery system which follow zero order kinetics and which provide better results in the treatment tolerance as well as patient compliance. Osmotic drug delivery system has been classified in under controlled drug delivery system is based on the principle of osmosis when these system exposed to water low level of water soluble polymer is leached from polymeric material i.e., semi permeable membrane and drug release in controlled or sustained manner over extended period of time. In osmotic drug delivery system there are myriad ways of osmotic pumps are available which majorly composed of osmotically active drug core which surrounded by rate controlling membrane.

Keywords: Controlled drug delivery system, Osmotic drug delivery system, Zero order kinetics, Compliance, Osmosis, Polymeric material

INTRODUCTION TO OSMOTIC DRUG DELIVERY SYSTEM

Osmotic drug delivery system is an advanced controlled drug delivery system or control oral drug delivery system in the form of rigid tablet with a semi permeable membrane and one or more small laser drilled holes in it. As the drug passes in the body water get absorbed through semi permeable membrane by osmosis and osmotic pressure is used to push the active drug through opening tablet. Osmotic drug delivery system release drug with zero order kinetics which does not depend on initial concentration and as well as on physiological factors of gastrointestinal tract. In the osmotic drug delivery system dose of the drug and dose interval are optimized to maintain the concentration of within its therapeutic window and minimize toxic effects. Osmotic products provide benefits over conventional formulations by greater effectiveness in the treatment of chronic condition reduce side effects and enhance patient compliance due to the simplification of dosage schedule. The release of drug can be modulated by different ways but most of controlled release drug prepare by matrix, reservoir or osmotic principle. The osmotic system utilizes the principles of osmotic pressure for delivery of drugs in both routes oral as well as parenteral.

PRINCIPLE OF OSMOTIC DRUG DELIVERY SYSTEM

Principle of osmotic drug delivery system is based up on osmosis and osmotic pressure. Osmosis refers to the process of movement of solvent molecule from lower concentration to higher concentration across the semi permeable membrane. Osmotic pressure is the colligative property
of solution in which the magnitude of osmotic pressure of the solution is independent on number of discrete entities of solute present in solution. Osmotic pressure created due to inhibitions of fluid from external environment in to dosage form regulates the delivery of drug from osmotic device. Rate of drug delivery from osmotic pressure is directly proportional to osmotic pressure developed due to inhibition of fluid by osmogens. Osmotic drug delivery system uses osmotic pressure for controlled delivery of drugs by using osmogens (up to 16 hours). Osmolality is the number of osmosis per kilogram of water. Osmolarity is the number of osmoles per liter of solution. So osmotic solution is one where two solutions are separated by perfect semi permeable membrane where core contain water soluble osmotically active agent and blend with water soluble or insoluble drug, additives and coating has been carried out which function as semi permeable membrane. Barrier is only permeable to water initial penetration of water dissolves the critical part of core, resulting in development of an osmotic pressure difference across membrane. The devices deliver a saturated volume equal to volume of water uptake through membrane. Initial lag time (per hour) by which delivery rate increases to its maximum value, drug release is zero order. The relation between osmotic pressure(n) and concentration of non electrolyte is given for dilute solution which may be assumed to exhibit ideal behavior by van’t hoff’s equation:

\[ n_v = n^2RT \]

\( v \) = volume of solution  
\( n^2 \) = number of moles of solute  
\( T \) = thermodynamic temperature  
\( R \) = gas constant

**HISTORY OF OSMOTIC DRUG DELIVERY SYSTEM** [12,16,19-22]

<table>
<thead>
<tr>
<th>YEAR</th>
<th>COMMENTS / INVENTIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>1748</td>
<td>First report of osmosis.</td>
</tr>
<tr>
<td>1877</td>
<td>Quantitative measurement of osmotic pressure.</td>
</tr>
<tr>
<td>1955</td>
<td>First osmotic pump by rose and nelson.</td>
</tr>
</tbody>
</table>
| 1973 | - Higuchi leeper introduced a new version of rose and nelson pump with certain modification.  
- osmotically powered agent dispense device with filling means. |
| 1975 | Major milestones in the field of osmotic drug delivery system introduced first oral osmotic pump i.e., elementary osmotic pump. |
| 1976 | Patent granted on design of oral osmotic pump. |
| 1981 | Effervescent activity based system introduced. |
| 1982 | - Volume amplifier devices introduced.  
- Patent issues for an osmotic system which consist of layer of fluid swellable hydrogel. |
| 1984 | First report on combination therapy by push pull osmotic pump. |
| 1985 | Controlled pump osmotic pump developed. |
| 1986 | Patent issue claim a delivery for controlled administration of drug to ruminants. |
| 1989 | Developed push pull osmotic pump for nifedipine by Pfizer. |
| 1999 | Patent to osmotic dosage form for liquid drug delivery. |
| 1999 | Asymmetric membrane capsule introduced. |
| 2000 | DUROS leuprolide implants that is, verdure approved as first implantable osmotic pump for human by USFDA. |
| 2001 | Patent granted for dosage form comprising liquid drug formulation that can self emulsify to enhance the solubility, dissolution and bioavailability of drug. |
| 2003 | First report osmotic floating system. |
| 1994 | Pulsatile delivery based on expandable orifice. |
FORMULATION AND DEVELOPMENT OF OSMOTIC DRUG DELIVERY SYSTEM [24-28]

BASIC COMPONENTS FOR OSMOTIC PUMP

a) Drug
b) Osmotic agents (osmogens)
c) Semi permeable membrane
d) Pore forming agent
e) Flux regulator
f) Wicking agents
g) Coating solvents
h) Plasticizers
i) Hydrophilic and hydrophobic agents
j) Solublizing agents

Osmotic pump essentially contain a drug and semi permeable membrane. The semi permeable membrane usually contain plasticizer and in some case surfactants and also pore forming agents.

a) DRUGS:[24]
Criteria for selection of drug:-

» Highly potent.
» Short biological half life (2-6 hours).
» Required for prolong treatment.

Roger A.Rajewaki et al(1999) studied the membrane controlling factors responsible for the drug release from controlled porosity osmotic pump tablet that utilizes sulfobutyl ether cyclodextrin 7M—CD, both as Solublizing agent and osmotic agent.

b) OSMOTIC AGENTS:[25,26,27]
Osmotic agents maintain concentration gradient across membrane. Generate driving force for uptake of water maintain drug uniformity, these are ionic compounds consist of either inorganic salts or hydrophilic polymers. Sodium chloride, potassium chloride, sulfates of sodium, glucose, sorbital, sucrose inorganic salts of carbohydrates can act as osmotic agents. The osmotic pressure can provide high water flow across semi permeable membrane osmotic water flow across a membrane osmotic water flow across a membrane given by equation:-

\[ \frac{Dv}{dt} = AQ \]

» \( \frac{dv}{dt} \) = rate of water flow across the membrane
» \( A \) = area
» \( l \) = thickness
» \( Q \) = permeability

Wright etal (1992) studied on osmotic controlled release bilayer tablet for water soluble drugs. In their devices, the drug compartment containing drug and an osmopolymer, a lower weight CMC
(as thryxotrophic transport means) was placed together side by side with osmotic compartment which had a higher molecular weight CMC as osmotic agent preferably with another osmotically active compound. Both low and high molecular weight CMC in device cooperated to exhibit a high level of hydrodynamic and osmotic activity adequate for control delivery of drug overtime with minimum (3.7%) residual drugs left in device. Some of compounds and mixture of compounds are as follows with their osmotic pressure in the following table:-

<table>
<thead>
<tr>
<th>S.No</th>
<th>Compounds</th>
<th>Osmotic pressure</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Dextrose-fructose</td>
<td>450</td>
</tr>
<tr>
<td>2.</td>
<td>Dextrose-sucrose</td>
<td>190</td>
</tr>
<tr>
<td>3.</td>
<td>Dextrose</td>
<td>82</td>
</tr>
<tr>
<td>4.</td>
<td>Fructose</td>
<td>335</td>
</tr>
<tr>
<td>5.</td>
<td>Lactose-fructose</td>
<td>500</td>
</tr>
<tr>
<td>6.</td>
<td>Lactose- sucrose</td>
<td>250</td>
</tr>
<tr>
<td>7.</td>
<td>Manitol fructose</td>
<td>415</td>
</tr>
<tr>
<td>8.</td>
<td>Manitol –dextrose</td>
<td>225</td>
</tr>
<tr>
<td>9.</td>
<td>Manitol-sucrose</td>
<td>170</td>
</tr>
<tr>
<td>10.</td>
<td>Manitol-lactose</td>
<td>130</td>
</tr>
<tr>
<td>11.</td>
<td>Potassium chloride</td>
<td>245</td>
</tr>
<tr>
<td>12.</td>
<td>Potassium sulphate</td>
<td>39</td>
</tr>
<tr>
<td>13.</td>
<td>Sucrose-fructose</td>
<td>430</td>
</tr>
<tr>
<td>14.</td>
<td>Sodium chloride</td>
<td>356</td>
</tr>
<tr>
<td>15.</td>
<td>Sucrose</td>
<td>150</td>
</tr>
<tr>
<td>16.</td>
<td>Sodium phosphate tri basic12H2O</td>
<td>36</td>
</tr>
<tr>
<td>17.</td>
<td>Sodium phosphate di basic7H2O anhydrous</td>
<td>29</td>
</tr>
<tr>
<td>18.</td>
<td>Sodium phosphate monobasic H2O</td>
<td>28</td>
</tr>
<tr>
<td>19.</td>
<td>Sodium phosphate dibasic</td>
<td>31</td>
</tr>
<tr>
<td>20.</td>
<td>Sodium phosphate dibasic 12H2</td>
<td>31</td>
</tr>
</tbody>
</table>

c) **SEMI-PERMEABLE MEMBRANE:**[27,28]
   The membrane should be stable to both outside and inside environment of the device. The membrane must be rigid which could be able to retain its integrity for the operational life time of device. Membrane must be biocompatible. Example: cellulose acetate, cellulose acetate butyrate, cellulose.

d) **PORE FORMING AGENTS:**[29-31]
   These are the agents which are particularly used in the pumps developed for poorly water soluble drug and in the development of controlled porosity or multi particulate osmotic pumps. When the dissolution medium comes in to the contact with the semi permeable membrane it dissolves the channeling agents and form pores on semi permeable barrier. Then the dissolution fluid enters the osmotic system and release the drug in a controlled manner over a long period of time by osmosis. Examples: Polyethylene glycol1450, Manitol, Bovine serum albumin, di-ethyl phthalate, dibutylphlate and sorbitol.

e) **FLUX REGULATORS:**[11,32]
   Flux regulators also known to be as flux enhancing agents or flux decreasing agents are added to wall forming material. They also increases the flexibility and porosity of lamina. Polyhydric alcohol and lower molecular weight glycols as polypropylene, poly butylenes etc use as flux
regulator. Usually from 0.001 parts to 50 parts or high weight fraction of flux regulator can be used.

f) WICKING AGENTS:[33]
Wicking agents are defined as material with the ability to draw water in to the porous network of delivery system devices. They may be either swellable as well as non swellable nature. Physiosorption is a form of absorption in which the solvent molecules can loosely adhere to surface of wicking agent with Vaderwall’s interactions between surface of wicking agent and adsorbed molecule. Function of wicking agents are to carry water to surface inside the core of tablet, which helps in creating channels or a network of increased surface area. Example: - colloidal silicon dioxide, kaolin, titanium dioxide, alumina, sodium lauryl sulphate etc.

g) COATING SOLVENTS:-[25]
Solvents are defined as polymeric solution used in the manufacturing of the walls of osmotic devices includes inert inorganic and organic solvents that do not adversely harm the core wall and other material. For example methylene chloride, acetone, methanol, ethanol, isopropyl alcohol, butylalcohol, ethylalcohol etc.
Solvent or mixture of solvents can also be used are as follows:-

<table>
<thead>
<tr>
<th>S.NO</th>
<th>SOLVENTS(MIXTURE)</th>
<th>RATIO</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Acetone : Methanol</td>
<td>80:20</td>
</tr>
<tr>
<td>2</td>
<td>Acetone : ethanol</td>
<td>80:20</td>
</tr>
<tr>
<td>3</td>
<td>Acetone : water</td>
<td>90:10</td>
</tr>
<tr>
<td>4</td>
<td>Methylene chloride : methanol</td>
<td>79:21</td>
</tr>
</tbody>
</table>

h) PLASTICIZERS:[34-36]
Plasticizers help in increasing membrane permeability which modify the physical properties and improve film forming characteristics of polymers. Plasticizers change the hard and brittle polymer in to soft and more flexible material which results in more resistant to mechanical stress. Examples: Polyethylene glycol 600, polyethylene glycol-200, triacetin, dibutylsebacate, ethylene glycol mono acetate, tri ethyl phosphate, diethyl tartrate, etc. used as plasticizers in the formulations of semi permeable membrane.

i) HYDROPHILIC AND HYDROPHOBIC POLYMERS:[34,47]
Use in the formulation and development of osmotic system for making drug containing matrix core. Mixture of hydrophilic and hydrophobic polymers has been used in development of osmotic pump of water soluble drugs. Hydrophilic polymers are as follows: Hydroxyl Ethyl Cellulose, Car boxy methyl cellulose, hydroxyl propyl methyl cellulose, high molecular weight poly vinyl pyrrolidone etc. Hydrophobic polymer ethyl cellulose, wax material used for this purpose.

j) SOLUBLIZING AGENTS AND SURFACTANTS:[38]
Highly water soluble drugs demonstrate a high release rate that would be of zero order. Many drugs with low intrinsic water solubility are poor candidates for osmotic delivery. Addition of Solublizing agents in to core tablet increases the drug stability.
Non swellable Solublizing agents are as follows: agents that inhibit the crystal formation poly vinyl chloride, poly ethylene glycol, poly ethylene glycol 8000, cyclodextrin. A micelle forming surfactant with high HLB value particularly non ionic surfactant. Examples: tween-20, tween-60, tween 80 poly oxy ethylene. Etc.

Citrate esters alkyl esters particularly tri ethyl citrate and their combinations with ionic surfactants. The combinations of complexing agents are PVP, PEG and ionic surfactants as SLS are used.

**CLASSIFICATION OF OSMOTIC DEVICES:**[^11^15^16^39^66] Osmotic devices are classified on the basis of implantable and orally

A. IMPLANTABLE OSMOTIC DEVICES:
   (a). Rose and nelson osmotic device.
   (b). Higuchi theeveves osmotic device.
   (c). Mini osmotic device.
   (d). Higuchi Leeper osmotic device.
   (e). Alzet osmotic device.

B. ORAL OSMOTIC DEVICES:
   (a). Single chamber osmotic device:- Elementary osmotic device.
   (b). multi chamber osmotic device:-
      (i). Non expandable multi chamber osmotic device and
      (ii). Expandable multi chamber osmotic device.
   (c). For solid osmotic system:-
      (i). Bilayer osmotic devices.
      (ii). Trilayer osmotic devices.
   (d). For liquid osmotic system:-
      (i). Push pull osmotic device.

C. CONTROL POROSITY OSMOTIC DEVICE.

D. MODIFIED OSMOTIC DEVICE:
   (a). Osmotic device for modulated soluble drugs.
   (b). Osmotic device for modulated insoluble drugs.

E. MULTI-PARTICULATE DELAY RELEASE SYSTEM:
   (a). OROS-CT osmotic device.
   (b). Telescopic capsule for delay release.
   (c). Sandwich osmotic device.
   (d). Monolithic osmotic device.

F. SOME ADVANCE TYPE OF OSMOTIC DEVICES:
   (a). Osmat.
   (b). Osmotic bursting osmotic device.
   (c). Longitudinally compressed tablet multilayer formulation.
   (d). Lipid osmotic device.
   (e). Pulsatile drug delivery system.
   (f). Miscellaneous devices.
A. IMPLANTABLE OSMOTIC DEVICES:-

(a) ROSE AND NELSON OSMOTIC DEVICE:[39]

This is the most important type of implantable osmotic devices. This osmotic device comprises of three chambers: a drug chamber with orifice, salt chamber with elastic diaphragm containing excess solid salt, and water chamber. A semi-permeable membrane separates the drug and water chambers. The difference in osmotic pressure across the membrane moves water from the water chamber into the salt chamber. The volume of the chamber increases due to this water flow, and the drug chamber releases its drug content.

(b) HIGUCHI THEEUWES DEVICE:[40-41]

In the Higuchi Theeuwes device, the rigid housing is dispensed with, and the membrane acts as the outer casing of the pump. The membrane is quite sturdy and is strong enough to withstand the pumping pressure developed inside the device. The device is loaded with the desired drug. It is placed in an aqueous environment, and the release of the drug follows the time course set by the salt use in the salt chamber and the permeability of the outer membrane casing. With the help of solid salt, the carrier drug is released out of the device.

(c) HIGUCHI LEEPER DEVICE:[40-41]

It is a modified device of the Rose and Nelson osmotic device. It has no water chamber and is activated by water imbibed from the environment. The device is activated when it is swallowed or implanted in the body. The pump is composed of a rigid housing and a semi-permeable membrane supported on a perforated frame. It has a salt chamber containing a fluid solution with excess solid salt. Recent modifications in this device include the accommodation of pulsatile drug delivery. It is achieved by critical pressure at which delivery orifice opens and releases drug under pressure, and then the pressure reduces to cause orifice closing, and the cycle repeats to provide drug delivery in a pulsatile fashion. The orifice should be small enough to substantially close when the threshold level of osmotic pressure is not present.

(d) MINI OSMOTIC DEVICES:[42]

Implantable mini osmotic device composed of three concentric layers: the drug reservoir, osmotic sleeves, and rate controlling semi-permeable membrane. A flow moderator is inserted into the body of the osmotic device. The innermost compartment of the drug reservoir is surrounded by osmotic sleeve, a cylinder containing a higher concentration of osmotic agent. The osmotic sleeve is covered by a semi-permeable membrane when the system is placed in an aqueous environment.
water enters the sleeve through semi permeable membrane, compresses the flexible drug reservoir and displaces the drug solution through flow modulator. These devices are available with variety of delivery rates between 0.25-10 ml/hr and delivery duration between one day to four weeks.

(e) **ALZET OSMOTIC DEVICES:**[43]
Alzet device operates because of an osmotic pressure difference between a compartment within the device called salt sleeve and tissue environment in which the device is implanted. Highly Osmolality of salt sleeve cause water flux in to the pump through semi permeable membrane which form outer surface of pump.

As the water enters the salt sleeve, it compresses the flexible reservoir, displacing the test solution from device at controlled predetermined rate. Because of compressed reservoir cannot be refilled, the devices are designed for single use only.

B. **ORAL OSMOTIC PUMPS**: [16,44]

(a) **SINGLE CHAMBER OSMOTIC DEVICE:**
(b) **ELEMENTARY OSMOTIC DEVICE:**
It was introduced in 1970’s to deliver drug at zero order rates for prolonged period. Tablet consists of osmotic core containing drug surrounded by semi permeable membrane laser drilled with delivery orifice. Following ingestion water in absorbed in to system dissolving the drug, and resulting drug solution is delivered at same rate as water entering tablet. It is only suitable for water soluble drug. The pump initially releases the drug at a rate given by equation:-

\[
\frac{dm}{dt} = \frac{dv}{dt} \cdot cs.
\]

\( dv/dt \) depicts the water flow in to the tablet.
Cs is the solubility of agent inside tablet.

![Figure 3](image1.png)  ![Figure 4](image2.png)  ![Figure 5](image3.png)

**FIGURE: 3, 4 & 5 ELEMENTARY OSMOTIC DEVICE, LIQUID OSMOTIC DEVICE & PUSH AND PULL OSMOTIC DEVICE**

(REFERENCE:44,46)

(b) **MULTI CHAMBER OSMOTIC DEVICE:**[45-46]

(c) **PUSH AND PULL OSMOTIC DEVICE:**
It is modified approach of elementary osmotic device it is possible to deliver both poorly water soluble and highly water soluble drugs at constant rate. It is resembles a standard bilayer coated tablet one layer (depict as upper layer) contain drug in formulation of polymeric osmotic agent and other tablet excipients. This osmotic agent has ability to form a suspension of drug in situ. When this tablet later imbibes water the other layer contains osmotic and coloring agents,
polymer and tablet excipients. These layers are formed and bonded together by tablet compression to form single bilayer core. The tablet core then coated with semi permeable membrane. After the coating applied, a small hole is drilled through the membrane by a laser or mechanical drill of the drug layer side of tablet. When the system is placed in aqueous environment water is attracted in to the tablet by an osmotic agent in with the layers. The osmotic attraction in the drug layer pull water in to the compartment to form in situ a suspension of drug. Osmotic agent in non drug layer simultaneously attract water in to the compartment, causing it to expand volumetrically and the expansion of non drug layer push the drug suspension out of orifice and is also known as expandable osmotic device.

OSMTIC DEVICE WITH NON EXPANDING SECOND CHAMBER:[47-48] 
This non expanding seconding chamber is a device divide in to two sub groups; depend on the function of second chamber. In one category of this device, the second chamber is used to dilute the drug solution leaving devices. It is useful because in some cases if the drug leaves the oral osmotic devices as at unsaturated solution, irritation of gastrointestinal tract is risk. The problem that leads to withdrawal of osmosin, the device consists of normal drug containing porous tablet from which drug is released as saturated solution. However before the drug can escape from device it must pass through a second chamber. Water is also drawn osmotically in to the chamber either because of second chamber contains, water soluble diluents such as sodium chloride. This type of devices consist of two rigid chambers, first chamber contains a biologically inert osmotic agent as sugar or simple salt like sodium chloride. Water is also drawn osmotically in to the chamber either because of second chamber contain drug. Water is drawn in to both chamber through surrounding semi permeable membrane. The solution of osmotic agent formed in the first chamber then passes through the connecting hole to the drug chamber where it mixes with drug solution before exiting through micro porous membrane that form a part of wall surround the chamber Device could be used to deliver relatively insoluble drugs.

FIGURE 6 & 7 NON EXPANDABLE ELEMENTARY OSMOTIC PUMP TABLET & CONTROLLED POROSITY AND CONTROLLED BURSTING OSMOTIC DEVICES (REFERENCE: 48, 50)

C. CONTROLLED POROSITY OSMOTIC DEVICE:[49-51]
The device can be made with single or multi compartment dosage form in either form the delivery system comprises a core with the drug surround by semi permeable membrane which has an asymmetric structure. When exposed to water, low level of water soluble additives (examples: urea, sorbitol, nicotinamide etc) are leached from polymer materials that were permeable to water yet remain insoluble. Then resulting sponge like structure formed the controlled porosity walls of interest and was substantially permeable to with water and dissolve drug agent.
D. MODIFIED OSMOTIC DEVICE: [52-53]

(a) FOR MODERATELY SOLUBLE DRUG:
Semi permeable membrane must be 200-300 microns thick to withstand the pressure generated within the device this thick membrane lower water permeation rate which is not desirable for moderately soluble drug. It is corrected by using coating material with high water permeability example: addition of plasticizers and water soluble additives to cellulose acetate membrane this increases the membrane permeability up to ten fold. Composite structured semi permeable membrane is used for moderately soluble drugs. First layer is made up of thick micro porous film that provide the strength required to withstand the internal pressure, while second layer is composed of this semi permeable membrane that produce the osmotic flux. The supported layer is formed by cellulose acetate coating containing 40-60% of pore forming agents as sorbitol.

(b) OSMOTIC DEVICES FOR INSOLUBLE DRUG:
Osmotic agents are coated with an elastic semi permeable membrane film in fluid bed coated and this particle then mixed with insoluble drugs and compressed to form tablet which is coated with semi permeable membrane and orifice is created in membrane.

After coming in contact with aqueous environment, water is drawn through two membranes, osmotic agent particle which swells and hydrostatically pushes the insoluble drug via the orifice.

E. MULTIPARTICULATE DELAYED RELEASE SYSTEM: [54-58]

Drug containing pellets with or without osmotic agents are coated with semi permeable membrane which on contact with aqueous environment results in penetration of water in core and form a saturated solution of soluble component. Osmotic pressure difference result in rapid expansion of membrane, leads to formation of pores. For the controlled release drug is located at first orifice and for fast release drug layer located adjacent to second orifice. Push layer is located in between controlled and fast release layer.

(a) TELESCOPIC CAPSULE FOR DELAY RELEASE: [55-56]
It consist of two chambers first contain the drug and exit port second contain an osmotic engine. A layer o-wax like material separates these two sections. To assemble delivery system, the desired active agent is placed in to one of the section by manual or automated fill mechanism. The bilayer tablet with osmotic engine is placed in to completed cap part of capsule with convex osmotic layer pointed in to the closed end of cap and the barrier layer exposed towards the cap opening. The open end of filled vessel is fitted inside open end of cap and two pieces are compressed together until the cap, osmotic bilayer tablet and vessel fit together tightly. As fluid is imbibed the housing of dispensed device, the osmotic engine expand and exerts pressure on
the slidable connected first and second wall section. During the delayed period the volume of reservoir containing the active agent is kept constant therefore a negligible pressure gradient exists between environment the use and interior of reservoir. As the result the net flow of environmental fluid driven by pressure enters the reservoir is minimal and consequently no agent is delivered for a period.

(b) OROS-CT: OROS (Alza Corporation) is used as once or twice a day formulation for targeted delivery of drug to colon. OROS-CT can be single osmotic agent or it can be comprised of as many as five to six push pull osmotic unit filled in a hard gelatin capsule. After coming in contact with gastric fluids gelatin capsule dissolves and enteric coating prevents entry of fluids from stomach to system as system enters in to small intestine the enteric coating dissolves and water is imbibed in core thereby causing the push compartment to swell. At the same time flowable gel is formed in the drug compartment which pushes out of orifice at rate, which is precisely controlled by rate of water transport across semi permeable membrane. In corporation of cyclodextrin drug complex has also used for delivery of poorly water soluble drugs from the osmotic system. Example: Sulfobutyl ether- B-cyclodextrin sodium salts serve as solublizer and osmotic agent.

(c) SANDWICHED OSMOTIC TABLET: In this type of tablet core of tablet composed of polymeric push layer sandwiched between two drug layers with two delivery orifices. When placed in aqueous environment the middle push layer containing swelling agent swells and drug is released from two orifices situated on opposite sides of tablet and sandwiched osmotic device can be utilized for drug prone to cause local irritation for gastric mucosa.
(d) MONOLITHIC OSMOTIC DEVICE: 
It constitute a simple dispersion of water soluble agent in polymer matrix, when system come in contact with aqueous environment water imbibitions by the active agents take place rupturing the polymer matrix capsule surrounding drug thus liberating it to outside environment. Initially this process occurs at outer environment of polymer matrix, but gradually proceeds toward the interior of matrix in a serial fashion. However this system fails if more then 20-30 volumes/later of active agents are incorporated in to devices as above this level, significant contribution from the simple leaching of substance take place.

F. ADVANCED TYPES OF OSMOTIC DEVICES:

(a) OSMAT: 
It is novel osmotically driven matrix system, which utilizes the hydrophilic polymers to swell, and gel in aqueous medium for semi permeable membrane insitu release from such a matrix system contain an osmogens and it could be modulated by osmosis phenomenon. It combine both matrix osmotic characteristics resulting in quantum improvement in drug delivery from swellable matrix system. OSMAT produces control drug release with adequate delivery rates in agitation independent membrane. Thus OSMAT represent simple, versatile, and easy to fabricate osmotically driven controlled drug delivery system based on low cost technology.

(b) OSMOTIC BURSTING OSMOTIC DEVICES: 
In This system it is similar to elementary osmotic device except delivery orifice is absent and size may be smaller. When it is placed in aqueous medium water is imbibed and hydraulic pressure is built up until the wall rupture and the convent are released to environment. Varying thickness as well as area the semi permeable membrane can control release of drug. This system is useful to provide pulsatile release.

(c) LONGITUDNALLY COMPRESSED TABLET MULTILAYER FORMULATION: 
The longitudinally compressed tablet multilayer formulation can also be formulated with different drug in different layers to provide combination therapy. It is unaffected by gastric ph, gut motility, presence of food depend on where in the gastro intestinal tract the drug is released.
LIPID OSMOTIC DEVICE:
The pump concern an osmotic agent for dispensing beneficial active agent that has poor solubility in water. The core of the system comprises a beneficially amount of substantially water insoluble agent, which is lipid soluble or lipid wettable a sufficient amount of water insoluble lipid carrier, which is liquid at temperature of use to dissolve or suspend the drug and agent to ensure the release of lipid carrier of drug from device. The water insoluble wall is micro porous and is wetted by lipid carrier. The device is prepared by dissolving the drug of interest in lipid vehicle.

The osmogens sodium chloride is dispersed in the melted liquid and the quenched cool to form a lump that are broken and made in to tablet. The micro porous is coated at moderate flow of unheated ambient.

PULSATILE DRUG DELIVERY SYSTEM:
These systems are designed according to circadian rhythm of body. The principle rationale for the use of pulsatile release is for the drugs where a constant drug release i.e., zeros order release is not desired. The release of drug as pulse after a lag time has to be designed in such a way that a complete and rapid drug release follows lag time.

The types of tablet system consist of core coated with two layer of swelling and rupturable coating here in they used spray dried lactose and microcrystalline cellulose in drug core was coated with swelling polymer croscarmellose sodium and an outer rupturable layer of ethyl cellulose. Pulsatile system can be classified in to single and multiple unit system. Single unit systems are formulated either as capsule based or osmosis based system. These are designed by coating the system either with erodible or soluble or rupturable coating. In multiple unit system, however the pulsatile release is induced by changing membrane permeability or by coating with rupturable membrane.

MISCELLANEOUS TYPES OF OSMOTIC DEVICE:
Patent 6352721(2002) assigned to osmotic corporation (tortola, british virgin island) report a combined diffusion osmotic device drug delivery system. The device has centrally located expandable core that is completely surrounded by active substances containing layer, which is completely surrounded by membrane. The core consists of an expandable hydrophilic polymer and an optional osmogens. The composition is completely surrounded the core comprises an active substances, an osmogens and osmopolymer the membrane is micro porous in nature and may have a delivery orifice. The device is capable of delivering insoluble, slightly soluble and very soluble drug to environment.
FORMULATION OF OSMOTIC DRUG DELIVERY SYSTEM:[67-68]
One method is to utilize an osmotic mechanism to provide pre programmed controlled drug delivery system to gastro intestinal tract. This technology is comprises a polymer membrane with one or more laser drilled holes surrounding a core containing the drug or drugs, with or without osmotic or other agents. Second method is oral technology use a multiple dose system containing a large number of micro particles on the order of 5000 to 40000 micro particles per capsule or tablet depending in the specific formulation. Microparticles operate as a miniature delivery system, releasing the drug at an adjustable rate and over an extended period of time by means of osmotic pressure. Third technology was to developed as simple monolithic matrix system. These approaches use conventional tableting technologies to form swellable erodible matrix tablets, caplets or capsules that can potentially yield first order drug release profiles up to 24 hours. In addition, any combination of soluble, highly soluble, insoluble low drug dose, high drug load, combination can be easily formulated with these technologies.

NEW APPROACHES TO OSMOTIC DRUG DELIVERY SYSTEM[69-71]

A. OSMODEX TECHNOLOGY:
Osmodex family of proprietary technology combines laser drilled tablet technology with variety of single active and multiple active drug delivery systems. Osmodex system simplifies dosing in patient compliance. Osmodex technologies can be divided in to following categories of applications:

(a) . OSMODEX INSOLUBLE DELIVERY FOR INSOLUBLE DRUG:
This platform provides flexible delivery option for insoluble drugs. It can accommodates first order, zero order or delay release options while assuring full release over targeted time frame this technology has been used to solve multiple challenging insoluble drug delivery problems. Examples: osmolica, nifedipine extended release tablets.

(b) . OSMODEX SUSTAINED RELEASE DRUG DELIVERY FOR SOLUBLE DRUGS:
This platform technology can be used to resolve delivery challenges of soluble low bioavailability drugs or drugs required targeted delivery. It is a combination of immediate release and controlled release of either one or two drugs. This innovative approach allows an immediate release profile to be safety and uniformly combined with programmed release according to pharmacokinetics and pharmacodynamic need of product (allegra D224 HR tablet).

(c) . OSMODEX DOUBLE CONTROLLED RELEASE COMBINATION:
This dual controlled release platform allow delivery of two drugs from single osmotic tablet where each drug release pattern can be independently tailored to desired release profile.

(d) OSMODEX TRIPLE COMBINATION TABLET:
This delivery system incorporates compressed drug layers around an osmotic core. This combination provides the benefits of immediate release and controlled release delivery, along with unique benefits of an osmotic controlled release rates in same tablet.

B. DUROS TECHNOLOGY:
DUROS pharmaceutical system is miniature osmotic implant that deliver drug for 3 months to 1 year with precise zero order delivery kinetics. The technology is suited for potent drugs and can deliver up to 500mg of drug from a single implant with a 1 cc drug reservoir. Formulation technology has been developed that maximizes drug pay load, stabilizes drug chemically and physically for extended period at body temperature and involve use of aqueous and non aqueous vehicles.

Advanced application of DUROS technology are in clinical and preclinical testing and include the chronogesic system, delivering sufentanil systematically for chronic pain. DUROS system was advantageous for their biocompatibility and suitability for implant use. The drug contacting materials are also screened for compatibility with drug. Radiation sterilization may be utilized to sterilize the final drug product. If the drug formulation cannot withstand sterilizing doses of radiation then a DUROS subassembly is radiation sterilized and drug formulation is added in final aseptic operation.

C. ADVANCED APPLICATION OF DUROS TECHNOLOGY:
Chronogesic pain is defined as pain lasting 6 months or longer, problem associated with chronic diseases, including cancer and neurological and skeletal disorders.

Chronogesic is implanted in the inside of upper arm using specially designed sterile implanter. Implanter is trocarlike device that facilitates precise, efficient sub cutaneous placements of chronogesic implant.

D. TARGETED DRUG DELIVERY WITH CATHERIZED OSMOTIC DEVICE:
Catheters of different designs can be attached to exit port of an osmotic device for targeted drug delivery. A number of organs and tissues have been evaluated as targeted sites in various animal models using ALZET osmotic device which have been the device of choice in numerous scientific research activities involving laboratory animals. Catheters should be flexible, compatible with targeted tissues organs and non reactive with and non absorptive toward drug solution. The most commonly used material for catheters include silicone elastomers and polyolefin polymers as low density polythene. Pharmacological agents for targeted delivery include very small molecular weight drug as well as peptides and proteins. The most commonly catheter material for site specific drug delivery using ALZET with a catheter has been low density polythene tubing. Poly ethylene tubing-(PE60).
E. SPECIFIC DRUG DELIVERY USING SUCROS WITH A PRECISION MINIATURE CATHETER:
To deliver drug to specific target site DURECT is developing proprietary miniaturized catheter technology that can be attached to DUROS system to direct the flow of drug directly to the target organ or tissues. The precision, miniature size and performance characteristics of DUROS system will allow for continuous site specific delivery to a variety of precised locations within the body.

DELIVERY OF ANTI-NEOPLASTIC AGENTS IN TO THE BRAIN STEM[73]
Local or site specific delivery of chemotherapeutic agents increases drug concentration at the tumor target, decreases systemic exposure and toxicities and increases the duration of exposure of tumor to drug. Experimental and clinical studies have demonstrated statistically significant increases in survival associated with local therapy or brain tumors. Drug delivered via controlled release biodegradable matrices and infusion pumps. The brain stem continuously monitors and regulates cardiovascular, respiratory and other autonomic functions and hence attempt to target chemotherapy directly in to this brain area has always been met with extreme caution, one approach being tested to maximize the effectiveness of chemotherapeutic agents in this sensitive brain region is insertion of catheter in to pons of brain stem for intratumoral chemotherapy.

OSMOTIC DRUG DELIVERY IN COLON[74]
ENTRIC COATED AND COLON TARGETED OSMOTIC DOSAGE FORMS:
Patent 5536507(1996) assigned to Bristal-myerssquibb (new York) describes a colon targeted drug delivery system that is based on an osmotic mechanism. The three compartment pharmaceutical formulation delivers more than 80% of pharmacologically active substance to large intestine. The first compartment includes drug, micro crystalline cellulose, a ph sensitive polymer (carbomer or sodium salt of carbomer) and osmotic agent. The second compartment is delayed release coating that includes a water insoluble polymer and plasticizers. The third compartment is enteric coating which prevent drug release coating, which is activated only up on the disruption of enteric coating does not allow any drug release in small intestine.

FACTORS AFFETING OSMOTIC DRUG DELIVERY SYSTEM[75-93]
(i). SOLUBILITY:
Active pharmaceutical ingredients for osmotic delivery should have water solubility in the desired range to get optimize drug release. By modulating the solubility of these drugs within the core effective release pattern may be obtain for the drug which might otherwise appear to be poor condition for osmotic delivery.

- Use of swellable polymers:- vinyl acetate copolymer polyethylene oxide have uniform swelling rate which cause drug release at constant rate.
- Use of wicking agents:- these may enhance the surface area of drug with incoming aqueous fluids examples:- colloidal silicon dioxide, sodium lauryl sulfate, etc. msonotrol technology uses same principle to deliver drug via osmotic mechanism.
- Use of effervescent mixtures:- mixture of citric acid and sodium bicarbonate which creates pressure in osmotic system and ultimately controls release rate.
- Use of cyclodextrin derivatives: they are known to increase solubility of poorly soluble and used in osmotic system.
- Use of alternative salt form: changes in salt form of may changes solubility.
- Use of encapsulated excipients: solubility modifies excipients use in form of mini tablet coated with rate controlling membrane.
- Resin modulated approach: ion exchange resins modulated methods are commonly used to modify the solubility of activated pharmaceutical ingredients some of the resins as poly(4-vinyl pyridine)pentaerythritol citric and adipic acids.
- Use of crystal habit modifiers: different crystals form drug may have different solubility so the excipients which may change crystals habit of drug can be used to modulate solubility. Co-compression of drug with excipients can be used to modulate solubility of activated pharmaceutical ingredients with different mechanism like solubility examples of such excipients are organic acid, buffering agents etc.

(ii). OSMOTIC PRESSURE:
Osmotic pressure directly affects the release rate. To achieve a zero order release rate it is essential to keep osmotic pressure constant by maintaining a saturated solute solution. Many times the osmotic pressure generated by saturated drug solution may not be sufficient to achieve the required driving force. In this case, osmotic agents are added to enhance the osmotic pressure. Examples addition of bicarbonate salt not only provide necessary osmotic gradient but also prevent clogging of orifice by precipitated drug by producing an effervescent action in acidic medium.

(iii). ORIFICE SIZE:
To achieve an optimal zero order delivery profile the cross sectional area of orifice must be smaller than maximum size to minimize drug delivery by diffusion through orifice.

Laser Drill: it is helpful in producing sub millimeter size hole in tablets. Normally carbon di oxide laser beam (without wavelength of 10.6microns) is used for drilling purpose. It offers excellent reliability characteristics at low costs. In the simple words, the tablets in which holes are to be formed are charged into the hopper. The tablet drop by gravity into the slots of the rotating feed wheel and are carried at a predetermined velocity to the passage way forming station. At the passageway forming station, each tablet is tracked by an optical tracking system.

Indentation that is not covered during the coating process: indentation is made in core tablet by using modified punches having needle on upper punch. This indentation is not covered during coating process which act as a path for drug release in osmotic system.

Use of leachable substances in the semi permeable coating: incorporation of water-soluble additives in the membrane wall is the most widely reported method for the formation of pores in CPOP take place. These water-soluble additives dissolve on the coming in contact with water, leaving behind pores in the membrane through which drug release take place.
System with passageway formed in situ: the system consist of a tablet core of the drug along with water swellable polymer and osmotic agents, which is surrounding by rate controlling membrane. In contact with aqueous environment, water is imbibed osmotically at a controlled rate and water swellable polymer expands as the osmotic agent dissolves and increases the osmotic pressure inside the tablet. This result in a rate controlled slight expansion of the partially hydrate core. The expansion of core cause a small opening to form at the edge of the tablet (weakest point of membrane) from where the formulation is released.

(iv). SEMI PERMEABLE 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. The polymers have been discussed earlier.

» Membrane thickness: thickness of the membrane has a marked affect on the drug release from osmotic system which is inversely proportional to each other.

» Type and amount of plasticizers: in pharmaceutical coatings, plasticizers or low molecular weight diluents are added to modify the physical properties.

PREFERMENTS: [94-95]
The following preferment are contributed by osmotic drug delivery system

Delivery rate of zero order is achievable with osmotic system.

Delivery may be delayed or pulsed, if desired.

Higher release rate are possible with osmotic system compared with conventional diffusion controlled delivery system.

The release rate of osmotic system is highly predictable.

For oral osmotic system, drug release is independent to gastric pH and hydrodynamic condition.

The release from osmotic system is minimally affected by presence of food in gastrointestinal tract.

A high degree of in-vivo in-vitro correlation is obtained in osmotic system.

Improve patient compliance with reduced frequency.

IMPREFERMENTS: [96-97]
The following impreferments of osmotic drug delivery system are as

Dose dumping.

Rapid development of tolerance.

Retrieval therapy is not possible in the case of unexpected adverse event.

Special equipment is required for making an orifice in the system.

May cause ulcers due to release of saturated solution of drug.
These are the different drugs which are used in osmotic drug delivery system in the treatment of diabetes, hypertension, common cold, flus, chest pain (angina), various types of infections and allergies. Some of the drugs are used to widen the blood vessels. Useful in high blood pressure treatment. Use in hyperglycemia etc.

**EVALUATION OF OSMOTIC DRUG DELIVERY SYSTEM [100,101,102,103]**

Oral osmotic drug delivery system can be evaluated using the following parameters: - Visual appearance: visual inspection of the film can be done 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: it can be determined from depleted devices following careful washing and drying of the film, using standard analytical balance and screw guage, respectively. Orifice diameter: the mean orifice diameter of osmotic pump tablet can be determined microscopically using pre calibrated ocular micrometer.

**IN-VITRO EVALUATION:**- The conventional USP and basket type apparatus have been used for the in-vitro release of drugs from oral osmotic system. USP described the use of commercial standard dissolution apparatus and commercial applied analytic standard dissolutions apparatus. The dissolution medium is generally distilled water as well as simulated gastric fluid (for 2-4 hr) and intestinal fluids have been used. The standard specifications which are followed for oral controlled drug delivery system are equivalent applicable for oral osmotic pumps.

**IN-VIVO EVALUATION:**- The in-vivo evaluation of oral osmotic system has been carried out mostly in dogs and also monkeys. As the environment in the intestinal tract of the dogs is quite similar to that of the human beings in terms of pH and motility, dogs have been widely used for in-vivo delivery rate measurement of drugs from oral osmotic drug delivery systems and to established in-vitro, in-vivo correlation. In-vivo evaluation can be performed in healthy human...
volunteers. Various pharmacokinetics parameters (Cmax, Tmax, AUC, and MRT) and relative bioavailability are calculated.

**SCIENTIFIC STUDY:**

Vicent Malaterre et al. studied on the release mechanism underlying the drug delivery from push-pull osmotic pumps. The main aim of this study was to understand which factors have an effect on the drug delivery for modeling the drug release and to develop a mathematical model predictive of the drug release kinetics. The influence of the drug property was tested on the two model drugs, isradipine, chlorphenaramine which are respectively practically insoluble and freely soluble. Results show that, regardless of the drug properties which do not significantly affect the drug delivery, the release kinetics is mainly controlled by four factors:

- The PEG proportion in the membrane
- The tablet surface area
- The osmotic agent proportion and the drug layer polymer grade.

Hai Bang Lee et.al(2002) studied the sandwiched osmotic tablet system A sandwiched osmotic tablet core surrounded by a cellulose acetate membrane with two orifices on the surface of both sides was successfully prepared for the purpose of delivering nifedipine. The appropriate orifice size was observed in the range of 0.50-1.41 mm. it was also found that the drug release rate of SOTS could be increased by incorporating hydrophilic plasticizers in the membrane, where as it could be decreased by incorporating a hydrophobic plasticizer.

Sapna et. Al (2003) developed a controlled porosity osmotic pump based drug delivery system which consist of an osmotic core with the drug surrounded by a semi permeable membrane drilled with a delivery orifice, controlled porosity of the membrane is accomplished by the use of different channeling agents in the coating . The usual dose of pseudoephedrine was chosen as a model drug with an aim to develop a controlled release system for a period of 12 h. Sodium bicarbonate was used as the osmogens. The effect of the different ratios of drug osmogen on the in-vitro released was studied. Cellulose acetate was used as the semi permeable membrane. Different channeling agents tried was diethyl phthalate, dibutyl phthalate, dibutyl-sebacate, and poly-ethylene glycol 400. It was found that the drug release rate increased with the amount of osmogen due to the increased water uptake hence increased driving force for the drug release. This could be retarded by the by the proper choice of channeling agents in order to achieve the desired zero order release profile. Also the lag time seen with tablets coated using diethyl phthalate as channeling agent was reduced by using hydrophilic plasticizers like poly ethylene glycol 400 in combination with di ethyl phthalate. This system was found to deliver pseudoephedrine at zero order rates for 12 hr. the effect of pH on drug released was also studied.

Pratim k. chaudhary et.al (2007) developed an asymmetric membrane capsule of cellulose acetate for osmotic delivery of flurbiprofen and influence of osmogens and Solublizing agent on in – vitro drug release were evaluated. Scanning electron microscopy of the membrane confirmed its porous dense asymmetric nature. Dye test revealed in situ pore formation .the in-vitro release
study showed that as the proportion of osmogens and Solublizing agent was increased the released rate also increased. A good correlation was observed between the zero-order rate constant and the amount of the osmogens and Solublizing agent used.

**Longxiu Liu et.al (2008)** developed the bilayer-core osmotic tablet for nifedipine which does not require laser drilling to form the drug delivery orifice. The bilayer core consist of two layers (a) push layer and (b) drug layer and was made with modified upper tablet punch, which produce an indentation at the center of the drug layer surface. Sodium chloride was used as osmotic agent, polyvinyl pyrrolidone as suspending agent and croscaremellose sodium as expanding agent. The indented core tablet was coated by ethyl cellulose as semi permeable membrane containing polyethylene glycol 400 for controlling the membrane permeability. It was found that the optimal OPT was able to deliver nifedipine by an approximately zero order process up to 24 hours independent to both release media and agitation rate. AK Philip et.al (2008) developed an asymmetric membrane capsular system, formed in situ for poorly water soluble drug, ketoprofen and evaluated it by both in-vitro methods for osmotic and controlled release of the drug. Membrane characterization by scanning electron microscopy showed an outer dense region with less pores and an inner porous region for the prepared asymmetric membrane.

**Mahalaxmi. R et.al (2009)** developed the extended release controlled released porosity osmotic pump formulation of drug model drug glipizide using a wicking agent and Solublizing agent.

The effect of different formulations variables like level of wicking agent, Solublizing agent, level of pore former and membrane weight gain on in vitro release were studied.

Drug release was found to be affected by the level of wicking agent and Solublizing agent in the core.

Glipizide release from controlled porosity osmotic pump was directly proportional to the level of pore former and inversely proportional to the membrane weight gain.

**Promod kumar etal (2009)** developed elementary osmotic pump of highly water soluble drug tramadol hydrochloride. Target release profile was selected and different variables were optimized to achieve the same. Formulations variables like levels of swellable polymers (10-21.87%) and plasticizer (0-20%) w/w of polymer and coat thickness of semi permeable membrane were found to affect the drug release from the developed formulations. TRH release was directly proportional to the level of plasticizer and osmotic pressure generated by osmotic agent but inversely proportional to the level of swellable polymer within the core and coat thickness of SPM. Burst strength of the exhausted shells increased with increase in coat thickness but decrease with increase in level of plasticizers.

**Mothilal M et al (2010)** developed an osmotic controlled drug delivery system formulations of metoprolol succinate were prepared using different concentrations of Manitol, by wet granulation
The tablet were coated by dip coating with cellulose acetate. Stainless steel drilled pins were used to make an orifice on the tablets. Orifice diameter was examined using scanning electron microscopy. With increase in osmogens content and bore size, rate of drug release were found to be increasing an osmogens and bore size to give a zero order release was identified.

CONCLUSION
Osmotic drug delivery system has come a long way since the discovery of the first osmotic device. Present day osmotic delivery system devices not only seek to deliver a variety of agents (i.e., high, moderate, or low solubility and liquid formulations) but are also capable of modulating drug release. Thus a delayed, pulsatile or pH triggered release is possible with these systems. Modification implemented over time and many more possibilities for this system indicate that in spite of being used for drug delivery for nearly 30 years, osmotic drug delivery holds promise for the future too also without any doubt.

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