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REVIEW ARTICLE

ASYMMETRIC MEMBRANE CAPSULES (AMCS): A NOVEL DRUG DELIVERY SYSTEM

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ABSTRACT

Osmotic drug delivery system is oral controlled release systems based on the osmosis phenomenon. A new technology developed for osmotic delivery of drug is asymmetric membrane capsule (AMC). AMCs are the similar to the gelatin capsule but this is an osmotic system with in-situ pore formation that can be used for the controlled delivery of drugs, consist of a drug containing core surrounded by a membrane which has an asymmetric structure that is it has a relatively thin dense region supported on a thicker, porous region. AMC composed of asymmetric membranes, polymers, solvents, pore forming agents, osmotic agents, solubilizing agents etc. and prepared by simple method that is Phase Inversion. Advantage over the other oral drug delivery is that AMC provides a sustained release for the drugs with poor and high water solubility, unaffected from gastric pH and so show less bioavailability fluctuations.

KEY WORDS: osmosis, Asymmetric membrane capsule, in-situ formation, controlled release, Phase inversion.

INTRODUCTION

In recent advances, development of Novel Drug Delivery Systems (NDDS) has become a part of scientific research. NDDS are the important area of pharmaceutical research and development. The focus in NDDS includes design of NDDS for new drugs on one hand and on the other NDDS for established drugs to enhance commercial viability (Verma and Garg, 2001). This is due several advantages these are to improved patient convenience and compliance, reduction in fluctuation in steady state plasma level so decrease intensity of local or systematic side effects and increase safety margin of high potency drugs. In controlled release (CR) systems, there is maximum utilization of drug enabling reduction in total amount of dose administered and possibility of delivering drugs having short biological half-life (Prescott, 1989). Various designs are available to control or modulate the drug release from a dosage forms. Majority of oral CR dosage forms fall in the category of matrix, reservoir or osmotic systems. Conventional matrix or reservoir type formulations exhibits problem of bioavailability fluctuations due to gastric pH variations. Moreover, the release of drugs from these systems is affected by the hydrodynamic conditions of the body.

Osmotically Controlled Drug Delivery Systems (OCDDS) It is one of the most promising drug delivery technologies that use osmotic pressure as a driving force for controlled delivery of active agents (Verma *et al* 2000). Drug release from OCDDS is independent of pH and hydrodynamic conditions of the body because of the semi permeable nature of the rate-controlling membrane and the design of deliver orifice used in osmotic systems, so a high degree of in vitro/in vivo correlation is achieved. It is also possible to obtain higher release rates through

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these systems than through other diffusion-based systems. They are also known as GITS (gastro-intestinal therapeutic system) (Verma *et al* 2002) and today, different types of osmotic pumps, of various drugs, are available in the market to fulfill patient's need and requirement (Gupta *et al* 2014).

Osmotic devices are considered as a promising strategy for the controlled delivery of drugs. Since its elementary inception in 1970, osmotic delivery devices have been sequentially developed to eliminate their limitations. This led to the introduction of an asymmetric membrane concept that relies on drug delivery by an osmotic driving force (Chouhan and Suman, 2011).

Asymmetry of the membrane refers to vertically non-similar regions—the outer surface has a smooth, thin, dense, and nonporous region to resist mass transfer, while the inner region is rough, thicker, and porous to provide support and mechanical strength to the outer region. Incorporation of pore former (a water-soluble excipient) in the coating composition of the membrane results in *in-situ* and *ex-situ* pore formation when the asymmetric membrane comes in contact with aqueous media. Thus, the asymmetric membrane capsule (AMC) can be considered as a versatile device for the delivery of the drug.

Osmotic Drug Delivery from Asymmetric Membrane capsule

The asymmetric membrane capsule is also an example of a single core osmotic delivery system consisting of a drug containing core surrounded by an asymmetric membrane. Asymmetric membrane capsules (AMC) were introduced in 1999 for osmotic delivery of drugs and it is an example of a single core osmotic delivery system, consisting of a drug-containing core surrounded by an asymmetric with a non disintegrating polymer (Cellulose Acetate, Ethyl cellulose etc.) (Thombre *et al* 1999a,b,c).Further, they can be suitably optimized by varying the parameters like concentration of pore former, polymer, osmotic agents and solubility enhancers to cater the specific needs of a particular formulation. The concept can be utilized to deliver a number of drugs belonging to different pharmacological categories.

Research inputs from in the successful development of AMCs of drugs with varying water solubility, namely Ketoprofen, Flurbiprofen, Promethazine Hydrochloride, Phenyl epinephrine Hydrochloride and Triprolidine Hydrochloride thus proving the efficacy of the system for both poorly water-soluble and highly water-soluble drugs.

The basic design of AMC is similar to the hard gelatin capsule, but it shows in-situ pore formation in the shell. These systems do not require laser drilling like osmotic tablets. Their use can be done for delivery of both water soluble and insoluble drugs by using appropriate osmogen (Verma *et al* 2002). Asymmetric membrane capsule consists of a cap and a body as shown in Figure 1, which fit to each other similarly like in hard gelatin capsules. The shell of this type of capsule is usually composed of water insoluble polymer like cellulose acetate, ethyl cellulose, cellulose acetate butyrate or their mixture. The shell of the asymmetric membrane capsule does not dissolve quickly as like in the conventional capsule where the shell dissolves at a faster rate and thus AMC releases the drug on the basis of osmosis process, depending upon the core composition (Herbig *et al* 1995).

The asymmetric membrane osmotic dosage form differ from other osmotic dosage form in the aspect that there is a higher rate of water influx in this type of system due to the micro porous nature of the asymmetric membrane. It generally promotes the delivery of a drug having lower osmotic pressure and solubility (Lin and Ho, 2003). For a drug having low solubility there is necessity of high water influx, which can be easily achieved with the asymmetric membrane by proper choice and concentration of the pore forming agent. For increasing the solubility of

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poorly water soluble drug inside the core, it can be enclosed with osmotic agent or solubilizing agent so that it can be delivered osmotically (Zentner *et al* 1985).

Unlike other osmotic systems where a delivery orifice is required in the semi permeable membrane for delivery of the drug, the asymmetric membrane provides a distinct advantage of in-situ pore formation. The in-situ pore formation takes place due to leaching of the water-soluble additives incorporated in the asymmetric membrane. The leaching of water-soluble additives takes place when such a system comes in contact with the aqueous medium, resulting in formation of a micro porous membrane, through which the drug is osmotically delivered. This membrane is permeable to both water and dissolved solute and economically viable. Drug release from this system is generally independent of pH and other physiological factors.

Apart from possessing features of conventional oral osmotic systems such as independence of drug release from Gastric conditions, a high degree of *In Vitro-In Vivo* Correlation (IVIVC), higher drug release rates etc.

Advantages of Asymmetric Membrane Capsules (AMC)

(Lalit *et al* 2012)

- They are easy to formulate and there is no requirement of special manufacturing devices like laser drilling machines in case of osmotic tablets.
- AMCs do not require laser drilling because of in situ pore formation and are fabricated using conventional Pharmaceutical process equipments without additional manufacturing complexities, thus simple, economical and time saving.
- They improve the patient compliance with reduced dosing frequency and prolong therapeutic effect of drug.
- In this type of the rate of delivery of drug is independent of delivery orifice within particular size limits.
- The transport of water through asymmetric membrane is faster than that through a dense membrane of comparable thickness. Due to this fact they can be employed for delivery of poor water soluble drug. This is because for delivery of poor water soluble drugs high rate of water influx is required.
- The AMC can be employed to screen several drug excipients composition. This is because a small number of AMC can be filled with test formulation manually and can be studied for their drug release. Due to this, feasibility of prolonged release of drug can be estimated within short periods of time with small quantities of bulk drugs.
- The release rate of osmotic systems is highly predictable and can be programmed by modulating the release control parameters.
- The release from osmotic systems is minimally affected by the presence of food in gastrointestinal tract.
- The system requires small number and small quantities of excipients to be incorporated within the core. Since a small number of capsules can be manually filled with test formulations and tested for their drug release rate, the AMCs offers a convenient means to screen several drug excipients compositions. Thus, the feasibility of prolonged release can be determined in a relatively short time with small quantities of bulk drug. This is a major advantage in an industrial setting when dealing with early drug candidates.

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- Selection of two formulations being compressed and compression are critical factors in case of push – pull and sandwiched osmotic tablets while excipients incorporation in AMCs is simply mixing and filling.
- The surrounding membrane has an asymmetric structure, as shown in Figure 2, i.e., it has a relatively thin, dense region supported on a thicker, porous region (Chouhan and Suman, 2011).
- Elementary osmotic pump is limited to drugs with moderate to high solubilities but AMCs because of high water flux and permeability allows greater flexibility in incorporating drugs with lower solubility and in designing of formulations with faster release rates in contrast to other oral osmotic systems (Gaurve and Gupta, 2009; Choudhury *et al* 2007).
- Skin layer porosity is easily controlled with selection of pore former type and its concentration and thus optimization of orifice size do not require mathematical calculations as in case of other oral osmotic systems (Chouhan and Suman,2011).

Disadvantages of Asymmetric Membrane Capsules (AMCs) (Shahi *et al*, 2015)

- Poor systemic availability.
- If the membrane break possibility of Dose dumping.
- Rapid development of tolerance.
- Difficulty in retrieval of therapy.
- It may cause irritation due to release of saturated solution of drug.
- Special equipment is required for making an orifice in the system.

Mechanism of Drug Release from AMC

The basic mechanism of drug release from asymmetric membrane capsule (AMC) is osmosis. "Osmosis refers to the movement of solvent from lower concentration of solute towards higher concentration of solute across a semi permeable membrane" (Lalit *et al* 2012).

Drug release takes place through controlled porosity pores formed in situ by leaching. Once the system comes in contact with aqueous environment, water soluble additives present in the membrane dissolves, resulting in, in-situ sponge like micro porous membrane of controlled porosity formed, as shown in Figure 3, which is permeable to both water and dissolved drug agents and osmotic pumping system results (Parmar *et al* 2001; Najib N and Suleiman M, 1985).

As water diffuses into the core, the volume of the imbibed water creates a hydrostatic pressure difference across the membrane, which forces the solution out through the pores in the coating. Here the volume of drug solution delivered will be roughly equal to the volume of water imbibed within a given time interval. This delivers constant dosage form volume.

Therefore, the rate of drug delivery will be constant as long as osmotic pressure gradient across the membrane, membrane permeability and concentration of drug in the expelled solution remains constant.

However osmosis is not the only mechanism involved in the release of the drug. The capsule shell does not dissolve instantly to release the drug; instead drug is released over a prolonged duration by diffusion through the walls and via osmotic pumping through pores (Thombre *et al* 1999).

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Peffer in 1877 gave quantitative measurement of osmotic effect. He postulated that in a sugar solution, osmotic pressure of the sugar solution is directly proportional to the solution concentration and absolute temperature.

Vant Hoff established the analogy between the Peffer result and the ideal gas law by following expression:

$$\pi = nRT \ldots\ldots (1)$$

Where n represents the molar concentration of sugar (or solute) in the solution,
R depicts the gas constant and T indicates the absolute temperature.

Another method of obtaining a good a good approximation of osmotic pressure is by utilizing the expression:

$$\pi = RT \ln ({}^{Po}/_{p})/v \ldots\ldots\ldots (2)$$

Where Porepresents the vapour pressure of the pure solvent,
P is the vapor pressure of the solution, and
v is the molar volume of the solvents.

If the osmotic pressure of solution is high then it is responsible for high water flow through semi permeable membrane.

The rate of water flow dictated by osmotic pressure can be given by the expression:

$$\frac{dv}{dt} = \frac{A\theta\Delta\pi}{l} \ldots\ldots\ldots (3)$$

Where $\frac{dv}{dt}$ represents the water flow across the asymmetric membrane of area 'A',
Thickness 'l' with permeability 'θ',
$\Delta\pi$ Show the difference in osmotic pressure between the two solutions on either side of membrane.

The zero order release rate of drug during initial portion of the release profile is given by:

$$\frac{dM}{dt} = dV/dt \times S \ldots\ldots\ldots (4)$$

Where $\frac{dM}{dt}$ is release rate, dV/dt is given by equation (3) and
'S' is concentration of the component in fluid being pumped out.

If the capsule contains only one component, the osmotic pressure difference is caused by a saturated solution of the component on one side of capsule wall and sink condition (assumed) is caused on the other side of the capsule wall.

Also assuming ideality, the expression for $\Delta\pi$ can be written as.

$$\Delta\pi = MRT = S/M.RT \ldots\ldots (5)$$

Where 'R' is universal gas constant, 'T' is absolute temperature,
'M' is molecular weight, and
'S' is saturation solubility of the single component (drug).

Substituting for $\Delta\pi$ into equation (3) and substituting the resultant expression for dV/dt into equation (4), following expression is obtained:

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$$dM/dt = (A\O RT/l).S^2/M \quad \ldots\ldots\ldots(6)$$

Equation (4) indicate that a plot, release rate verses (S^2/M) should be linear with a slope given by expression in parentheses. Based upon equation (6), permeability (Ø) of capsule member ane can be calculated. However osmosis is not only the mechanism of drug release from asymmetric membrane.

Drug can be released over a prolonged period of time via diffusion through membrane or via osmotic pumping through pores.

Thus total amount of drug released from asymmetric membrane in per unit time, $(dM/dt)_t$ is given by:

$$(dM/dt)_t = (dM/dt) + (dM/dt)_d \ldots\ldots\ldots (7)$$

Where, (dM/dt) – is the amount of drug released by osmotic mechanism and $(dM/dt)_d$ – is the amount of drug released by diffusion mechanism.

However osmosis is not the only mechanism involved in the release of the drug. The capsule shell does not dissolve instantly to release the drug; instead drug is released over a prolonged duration by diffusion through the walls and via osmotic pumping through pores.

Diffusion's contribution is derived from the fact that asymmetric membrane is not truly semi-permeable. So it is possible that can also be released from pores by diffusion mainly through pores of coating. It is given by following expression:

$$(dM/dt)_d = (P_dAS)/l \ldots\ldots\ldots (8)$$

Where P_d is dissolved drug permeability in the membrane.

So combining equations (6), (7) and (8),

The total drug release by AMC is given by following expression (Lalit *et al* 2012; McClelland *et al*, 1993):

$$(dM/dt)_t = (A\O RT/l).S^2/M + (P_dAS)/l \ldots\ldots\ldots (9)$$

***Factors Influencing the Design of Osmotic Controlled Drug Delivery Systems* through AMC**

Drug Solubility (Saroj *et al* 2014)

For the osmotic system, solubility of drug is one of the most important parameters affecting drug release kinetics from osmotic pumps. The kinetics of osmotic drug release is directly related to the drug solubility within the drug core.

Candidate drugs for osmotic delivery have water solubility in the range 50–300 mg/ml.

Some of the approaches that have been used to modulate drug solubility within the membrane include:

- Co-compression of the drug with excipients, which modulate the drug's solubility within the core.
- Use of various cyclodextrin derivatives to solubilize poorly water soluble drug- Amalgamations of the cyclodextrins drug complex have also been used as an approach for delivery of poorly water-soluble drugs from the osmotic system.
- Use of alternative salt form- that may has optimum water solubility.
- Use of encapsulated excipients- Thombre and coworkers described a capsule device covered with asymmetric membranes to deliver drug having reduced water solubility, as shown in Figure 4. In the example solubility of poor water soluble drug that is glipizide was enhanced by amalgamation of encapsulated excipients (pH controlling excipients) inside the capsule device (Thombre *et al* 1999).

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- Use of lyotropic crystals- Make use of lyotropic liquid crystals, to help osmotic delivery of weakly water soluble drugs, is also reported in literature. The lyotropic liquid crystals are non polymeric compound, usually in the molecular weight in the range of 200–1500. Also identified as amphipathic compounds, these forms are mesophase and swell in the presence of water (Curatolo, 1992).
- Use of Swellable Polymers- Swellable polymers can be utilized for osmotic drug delivery having reduced aqueous solubility. Drug is delivered from the delivery orifice in the form of extremely fine dispersion prepared for dissolution and absorption.
  Examples using these approaches are reported in US patent number 4,992,278 for carbamazepine, theophylline, nifedipine and acetylsalicylic acid (Khanna, 1991).
- Use of wicking agents- Addition of wicking agents in osmotic formulations has also been reported as an approached for weakly water soluble drugs. A wicking agent is dispersed during the composition that increased the contact surface area drug with the received aqueous fluids.
- Resin Modulation Approach- (McClelland *et al* 1991)
- Use of Effervescent Mixtures- Use of effervescent mixture can be one more approach to deliver weakly water soluble drugs from asymmetric membrane dosage form. Following administration, the effervescent combination containing the drug is delivered below pressure throughout the delivery orifice in the membrane. This technique of enhancing release of weakly water soluble drug is reported in US patent number 4,036,228 (Theeuwes, 1977).

Osmotic pressure

The next release-controlling factor that must be optimized is the osmotic pressure gradient between inside the compartment and the external environment. Osmotic agent creates a very high osmotic pressure gradient inside the system and increases release rate of drug. These osmotic pressures can produce high water flows across semi permeable membranes (Saroj *et al* 2014).

Membrane Types and Characteristics:

The selection of a rate controlling membrane is a vital aspect in the formulation development of oral osmotic system. Drug release from osmotic systems is independent of the agitation intensity and pH of the Gastro-Intestinal tract (GIT) to a large level. This is as of selectively water porous membrane and efficient isolation of dissolution method from the gut environment (Sancheti *et al* 2014).

***Type and Nature of Polymer*:**

As the membranes in osmotic systems are semi permeable in nature, some polymers that are permeable to the water but impermeable to the solute can be chosen. Cellulose acetate [CA] has been extensively used to form rate controlling membranes for osmotic systems (Sancheti *et al* 2014).

***Membrane thickness*:**

Thickness of the membrane has a reflective outcome on the drug release from osmotic system (Sancheti *et al* 2014).

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Basic composition of AMC

A. Composition of Asymmetric membrane

B. Composition of core of AMC

Composition of Asymmetric membrane

The main component of AMC is asymmetric membrane. It regulates the osmotic behavior of the system. Some important characteristics of asymmetric membrane are:

- Stability of the membrane towards the internal environment and external environment of the capsule should be high (Parmar *et al* 2001).
- The membrane should show semi-permeable behavior and should have enough permeability for water to create osmotic pressure inside the system (Philip and Pataki, 2009).
- The thickness of the membrane should be appropriate. If thickness of membrane is too low then it shows high release rate of the drug but do not withstands with internal pressure of the system. Similarly if the thickness of membrane is high then it shows less release rate but it gets resisted to the internal pressure of the system (Thombre *et al* 1999b).

Asymmetric membrane is made up using polymers, pore forming agents and solvents.

Polymer for asymmetric membrane

Polymers mainly used for preparation of asymmetric membrane are water insoluble in nature. So they do not get dissolved easily before the release of drug. Usually cellulose derivatives are used for purpose. These include cellulose acetate (CA), Ethyl cellulose (EC), and Cellulose acetate butyrate (CAB). Mixture of these polymers can be also used in order to achieve a membrane of desired permeability and strength. (Lalit *et al* 2012)

Ideal properties:

- Stable to outer and inner environment, biocompatible, sufficiently rigid and semi permeable. Membrane must have sufficient water permeability so as to provide high water fluxes but not too high that causes membrane bursting.
- It should have sufficient thickness, membrane thickness has an inverse effect on release a, compromise should be made for "thickness" as thinner membranes shows an increase in the release but do not withstand the pressure within the device, a thicker membrane although is able to resist the pressure but shows a constrained release because of increased diffusion path for the drug to traverse before being released.
- It should have sufficient wet strength and wet modulus so as to retain its dimensional integrity during operational lifetime of the device.
- The reflection coefficient, “leakiness” of the membrane to osmotic agent should approach to limiting value of 1.

Asymmetric membrane

The membrane should be stable to both outside and inside environments of the device. The membrane must be sufficiently rigid so as to retain its dimensional integrity during the operational lifetime of the device. The membrane should also be relatively impermeable to the contents of dispenser so that osmogent is not lost by diffusion across the membrane. Finally, the membrane must be biocompatible. Some good examples for

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polymeric materials that form membranes are cellulose esters like cellulose acetate, cellulose acetate butyrate, cellulose triacetate, ethyl cellulose and Eudragit.

Ideal properties of Asymmetric semi permeable membrane

(Gupta *et al* 2014; Philip AK *et al* 2008; Chouhan and Suman, 2012)

- The material must possess sufficient wet strength (105 psi) and wet modules so as to retain its dimensional integrity during the operational lifetime of device.
- The membrane must exhibit sufficient water permeability so as to attain water flux rates (dv/dt) in the desired range. The water vapor transmission rate can be used to estimate water flux rate.
- The reflection co-efficient or "leakiness" of the osmotic agent should approach the limiting value of unity. But polymer membrane must be more permeable to water.
- The membrane should also be biocompatible.
- Rigid and non-swelling.
- Should be sufficient thick to withstand the pressure within the capsule.
- The semi-permeable membrane should be stable both to the outer and inner environment of the capsule.

Solvents

Solvents suitable for making polymeric solution that is used for manufacturing the wall of the asymmetric capsules include inert inorganic and organic solvents that do not adversely harm the core, wall and other materials.

The ideal properties of solvents:

- 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 odorless, colorless, tasteless, inexpensive, nontoxic and non-irritant.
- It should have rapid drying rate.
- Volatile solvents are used for making the solution of polymer and pore former, in order to make drying step easier and faster.

Solvent used commonly is acetone. It is not used alone but employed in combination with co-solvents as shown in Table 1, like ethanol, water, isopropyl alcohol, butyl alcohol.

The typical solvents include Methylene Chloride, Acetone, Methanol, Ethanol, Isopropyl Alcohol, Butyl Alcohol, Ethyl Acetate, Cyclohexane, Carbon Tetrachloride, Water etc (Lalit *et al* 2012; Chouhan and Suman, 2011).

Pore forming agents or Channeling agent or leachable pore forming agents

Pore forming agents are the water-soluble components which play an important role in the controlled drug delivery systems and main component of AMC, as these are used to control the porosity of the asymmetric membrane, thereby omitting the need of costly and precision based laser-drilling technique to make micro pores for the release of drug. They are usually poor solvent or non-solvent for the polymer that are used in preparation of asymmetric membrane.

When the dissolution medium comes into contact with the semi permeable membrane it dissolves the channeling agent and forms pores on the semi permeable barrier. Then the

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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. This water soluble additives leach from the membrane after coming in contact with aqueous body fluids and thus multiple micro pores are formed in membrane.

Examples of pore forming agents are Glycerol, Sorbitol, Polyglycolic Acid (PGA), Polylactic Acid (PLA), Polyethylene Glycol 1450, Mannitol, Bovine Serum Albumin (BSA), Diethyl phthalate, Dibutylphthalate etc (McClelland *et al* 1991; Thombre *et al* 1999).

Composition of core of AMC

Drug or Active Pharmaceutical Ingredients

Selection of drug is important for its formulation into asymmetric membrane capsule (AMC). Drug having following characteristics are suitable for formulation into AMC (Zentner, 1991; Sharma *et al* 2008):

- It should have short half-life (2 to 6 hours).
- Prolonged release of drug should be desired.
- It should be potent in nature.
- Solubility of drug should not be very high or very low.

Osmotic agent

These are also known as Osmogens or Osmogents and are used to create osmotic pressure inside the system. Polymeric osmogents are mainly used in the fabrication of osmotically controlled drug delivery systems and other modified devices for controlled release of relatively insoluble drugs. 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.

The osmotic water flow across a membrane is given by the equation,

$$\frac{dv}{dt} = \frac{AQ\Delta\Pi}{l}$$

Where $\frac{dv}{dt}$, is the rate of water flow across the membrane of area A and thickness l (Gupta *et al* 2014).

Osmotic agent creates a very high osmotic pressure gradient inside the system and increases release rate of drug (Lalit *et al* 2012). These osmotic pressures can produce high water flows across semi permeable membranes. Osmotic pressures for concentrated solution of soluble solutes commonly used in controlled release formulations are extremely high, ranging from 30 atm for sodium phosphate up to 500 atm for a lactose-fructose mixture as shown in Table 2 (Gupta *et al* 2014).

Types of osmotic agents

- Inorganic water-soluble osmogents
  Magnesium sulphate, Sodium chloride, Sodium sulphate, Potassium chloride, Sodium Bicarbonate.
- Organic polymer osmogents
  Sodium Carboxy Methylcellulose, Methylcellulose, Hydroxy propyl methylcellulose, Hydroxy ethyl methylcellulose, Polyethylene oxide, Polyvinyl pyrollidone.

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Solubilizing agent

These are agents which increase the solubility of drug in the core. They create such type of pH in the system after coming in contact with body fluids; at which drug becomes highly soluble thereby enhance the solubility of drug. Examples of these agents are fumaric acid, tartaric acid, citric acid, sorbic acid, etc (Chouhan and Suman, 2012).

Non-swellable solubilizing agents are classified into three groups (Shahi *et al* 2015)

- Agents that inhibit crystal formation of the drugs or otherwise act by complexation with the drugs.
  (e.g., PVP, PEG 8000 and β-cyclodextrins)
- A micelle-forming surfactant with high HLB value, particularly nonionic surfactants.
  (e.g., Tween 20, 60, and 80, polyoxyethylene or polyethylene containing surfactants and other long-chain anionic surfactants such as SLS)
- Citrate esters (e.g., alkyl esters particularly triethyl citrate) and their combinations with anionic surfactants. The combinations of complexing agents such as polyvinyl pyrrolidone (PVP) and poly ethylene glycol with anionic surfactants such as SLS are mostly preferred.

Solubility suppressants

These are the substances that reduce the solubility of drugs. Highly soluble drug will show high release rate that would be of zero order for only small percentage of initial drug load so there is necessity to decrease the solubility of the drug for prolonged zero order release. So addition of solubility suppressant is required in such case. For example dextrose acts as solubility suppressant for Paracetamol (McClelland *et al* 1993).

METHODS OF PREPARATION:

The basic principle of the manufacturing process of asymmetric membrane capsule is Phase Inversion. The asymmetric membrane capsule was prepared by a Phase inversion process in which the membrane structure was precipitated on a stainless steel mold pin by dipping the mold pin a coating solution followed by quenching in an aqueous solution (Gupta *et al* 2009; Patel *et al* 2012).

In this is the technique in which polymer solution get changed from solution form to a structured, continuous polymeric phase (Thakor *et al* 2010).

AMCs can be manufactured by two methods, namely Wet method and Dry method.

1. ***Wet Method***

   It is the preferred process in which the coating solution, a multi- component polymer-solvent-non solvent (pore former) is precipitated on stainless steel mold pins dimensioned to form capsule body and cap followed by Quenching in a quench bath consisting of a solvent in which polymer is not soluble but original polymer solvent system is soluble. The quench bath extracts the solvent (s) from the coated film, resulting in precipitation of the polymer in the form of a structured membrane on the mold pins (Mcclelland *et al* 1991). The shells are removed from quench bath after 15 minute, dried, stripped and trimmed. The ratio of solvents/non solvents is so selected that on evaporation phase inversion was immediately started, as shown in Figure 5 (Thombre *et al* 1999).

   This process involves three basic steps:

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***Step-1*:** It involves dipping of mould pins for the body and cap, into polymeric solution containing pore forming agent and dried briefly. Then the mould pins are dipped into the quenching solution for 10 minutes.

***Step-2*:** In this step mould pins are withdrawn from quenching solution and allowed to dry for 10 seconds. The capsule shells (cap and body) are formed on moulds. The shells are then stripped off from the mould, trimmed to size and kept in desiccators until use.

***Step-3*:** After this the drug is filled into the body manually along with osmogen. Then cap and body are sealed by using a sealing solution. Further characterization of capsule is done (Sharma *et al* 2008).

2. ***Dry Method***

It also utilizes the same coating solution precipitation as in wet process but here the solvent is allowed to evaporate completely. It requires that solvent(s) evaporate more rapidly than pore former (McClelland *et al* 1993). After filling the body of the capsule, manually with core contents, cap is placed over and finally sealed with a sealing solution consisting of polymeric solution without pore former (Thombre *et al* 1999).

CHARACTERISATION OF AMCs:

Asymmetric membrane capsules are evaluated in similar parameters as that of the hard gelatin capsules and some additional evaluation parameter are also given below as:

1. ***Morphology of Asymmetric Membrane***

Morphology of asymmetric membrane is studied using scanning electron microscopy (SEM) and transmission electron microscopy (TEM). Usually 300x, 700x and 1000x magnification of SEM is used to study porosity and structure of asymmetric membrane (Philip *et al* 2008).

2. ***Osmotic Release Study***

This study is carried out by using dye test. In this test capsule prepared are usually filled with water soluble dye like amaranth, mixture of dye with osmogent like sodium chloride or solubilizing agent like Sodium Lauryl Sulphate. Then the capsules are suspended separately in 50 ml of water and 50 ml of sodium chloride solution (10% *w/v*). Then capsules are studied visually for release of any colored dye. Release of coloring dye indicates its osmotic expulsion from core of capsule (Rastogi *et al* 1995).

3. ***In-Vitro Drug Release***

In-vitro drug release study or the dissolution studies of AMC containing drug and different type and portion of osmogents and pore forming agents were carried by using USP type II dissolution test apparatus in simulated gastric fluid (SGF) is used as dissolution media usually. The capsules were placed in dissolution vessel containing 900 ml phosphate buffer (pH 7.2) with 0.5% *w/v* SLS maintained at 37 ± 0.5°C and stirred at 50 RPM. Samples (10 ml) were collected periodically (0.5, 1, 1.5, 2, 4, 6, 8, 12, 18, 24 h) and replaced with fresh dissolution medium. The percent drug release from different formulation was determined spectrophotometrically (Choudhury *et al* 2007; Teraiya *et al* 2012; Kaur *et al* 2013).

4. ***Physical evaluation of asymmetric membrane capsules***

Physical evaluation of AMC include following tests-

- ***Weight variation***

Twenty capsules were weighed individually. The average weight was calculated and was compared with the weight of each capsule (Kaur *et al* 2013).

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- ***Thickness***
  Twenty capsules were randomly selected from each batch and individually measured the thickness of the wall and the effective surface area of the asymmetric membrane capsules using the digital micrometer. The average weight and standard deviation of 20 capsules was calculated (Kaur *et al* 2013).
- ***Void volume determination***
  (Kaur *et al* 2013)
  The void volume of each of the asymmetric membrane as the function of the pore forming agents present at different levels was determined. The weight of the empty capsule (W_o) was obtained. The weighed capsule was put into a vial filled with distilled water and left overnight to effect complete quenching of the pore forming agent present in the wall of the capsule shell. It was made sure that the capsule was completely immersed in the water. The capsule was taken out of the vial, wiped with tissue paper and immediately weighed (W_w). The capsule was then placed into an oven at 50ºC; it was periodically weighed until a constant weight was obtained (W_d).
  The volume of the pore forming agent (V_p) present in the capsule wall was measured by-
  $$\frac{Wo - Wd}{\rho}$$
  Where, ρ = density of pore forming agent used.
  The total volume of water (V_w) present in the dry film was measured by-
  $$\frac{Ww - Wd}{1}$$
  (Density of water =1 g/cm^3).
  The void volume of the polymer per unit weight of polymer was determined by-
  $$\frac{Vw - Vp}{Wd}$$

- ***Tensile strength***
  A small strip of the membrane of the capsule was cut on a glass plate with a sharp blade so it had a smooth margin. One end of the membrane was fixed between adhesive tapes to give support to the membrane when placed in the film holder. Another end of the membrane was fixed between the adhesive tape with a small pin sandwiched between them to keep the strip straight ht while stretching. A small hole was made in the adhesive tape near the pin where hook was inserted. A thread was tied to this hook, passed over the pulley and a small pin attached at the other end to hold this weight. A small pointer was attached to thread, which travelled over the graph paper affixed on the wooden plate.
  To determine the tensile strength weights were gradually added to the pan increase the pulley force till the membrane was broken. The weight required to break the membrane was noted as the break force (Kaur *et al* 2013).
  Tensile strength was calculated by using formula:
  $$\%\,Tensile\ Strength = \left[\frac{Break\ Force}{a\ X\ b}\right]\left[1 + \frac{\Delta L}{L}\right]$$

Conformation of in situ pore formation

The in-situ pore formation in asymmetric membrane capsules should take place due to the virtue of leaching of the pore forming agent present in the asymmetric membrane into the release medium. To confirm this phenomenon in the prepared system dye-test was

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conducted. The asymmetric membrane capsule with different concentrations of pore forming agent were filled with a highly water soluble amaranth dye (20 mg). The dye was filled in each of the capsule body manually and the cap was snugly fitted to the capsule body and finally sealed with a sealing solution of cellulose acetate only (14% *w/v*), to ensure that no release takes place from the seal. The capsules filled with dye were placed in 50 ml distilled water and observed for release of dye through the membrane. To demonstrate that the prepared system follows the osmotic principle to release its encapsulated contents, the capsules filled with amaranth dye were placed in a release medium of higher osmotic pressure (50 ml 10% *w/v* sodium chloride solution) and the capsules were visually observed for the release of dye (Kaur *et al* 2013).

APPLICATIONS AND EXECUTION OF AMCS

Drug release from asymmetric membrane capsule is independent of GIT pH, hydrodynamic condition of GIT, so it can be minimize the bioavailability fluctuation of drug given through oral route. So it can be employed as effective oral sustained release delivery systems. AMCs provide a sustained oral osmotic drug delivery system for the drugs with poor and high water solubility, unaffected from gastric pH, hydrodynamic conditions of GIT and thus eradicating bioavailability fluctuations. Therefore, the major areas of application of AMCs are

- Antibiotics,
- NSAIDs,
- Antihypertensive,
- Ant tubercular,
- Drugs to Treat Cardiac Disorders,
- H2 Receptor Antagonists (Chouhan and Suman 2011).

Many ***NSAIDs*** show shorter half life and GIT irritant effect, so these are potential candidate for AMCs. Phillip in 2006 developed AMCs of Flurbiprofen. He utilized ethyl cellulose (EC, 50 cps) as polymer and mannitol as osmogen. He employed citric acid to increase the solubility of drug inside the core (Philip and Pathak, 2006).

Chauhan *et al* in 2007 prepared AMCs of flurbiprofen using cellulose acetate polymer and glycerol as pore forming agent. Sodium Chloride and mannitol were used as osmogen in combination. Sodium lauryl sulphate (SLS) was used as solubilizing agent. They found that the drug release rate was higher with solubilizing agent SLS as compared to system filled with osmogent (Sodium chloride and Mannitol). They ultimately concluded that SLS, besides imparting solubilization effect, also acts as an osmogen in dissolved form (Choudhury *et al* 2007).

Further AMCs of EC via dry process were developed by Anil K. Philip et al. [2007] for controlled delivery of Ketoprofen (KT) with addition of NaCl in the core, and via wet process for controlled delivery of Flurbiprofen (FL) [2008] and established the use of AMCs as a means for delivery of GI irritant drugs in a controlled through fickian diffusion (Philip and Pathak, 2008).

Philip and Pathak in 2008 prepared in-situ formed phase transited AMC of Ketoprofen and studied level an in-vitro in-vivo correlation. Polymer used was ethyl cellulose (EC), sodium chloride was used as osmogen and citric acid was employed as solubilizing agent (Philip and Pathak, 2008).

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Cardiovascular Drug can also be potent candidates for AMCs. In 1999, Thombre *et al* developed AMC of Doxazosin using cellulose acetate polymer and compared in vitro/ in vivo performance of drug. They used tri-ethyl citrate as solubilising agent. They prepare AMC of drug using different ratios of tri-ethyl citrate and glycerin (Thombre *et al* 1999).
Wang et al in 2005 developed AMC for drug combination Nifedipine and Felodipine. They used polymer cellulose acetate (CA) for shell formation. They studied effect of hydroxyl propyl methylcellulose (HPMC) and Sodium lauryl sulphate (SLS) on drug release from the system when they were employed in the core of formulation. They concluded that SLS plays an important role in the system as an osmotic agent and also acts as a micelle solubilizer for both Felodipine and Nifedipine. They found that it shows a synergistic effect of SLS with addition of thickening agent HPMC (50 cps) to improve the release rate and release percentage for Nifedipine (Wang *et al* 2005).
Kumar and Gupta in 2009 prepared AMC of Carvedilol by using cellulose acetate (CA) polymer and glycerin as pore forming agent. They found that drug release rate increases with the increase in amount of osmogent or solubilizing agent and it is independent of different environmental media and stirring rate. This system was found to deliver the drug at zero order release rate (Gaurve and Gupta, 2009).
Kapoor *et al* in 2011 developed AMC of Valsartan using cellulose acetate polymer, PEG-6000 (Polyethylene glycol) and SLS (sodium lauryl sulphate) as solubilizing agent. Potassium chloride (KCl) was employed as osmogen. They found that release of drug was increased with increase in amount of PEG-6000, KCl, SLS added to the core of formulation (Kapoor *et al* 2011).

Anti-Epileptic Drug having short half life can also be good candidates for AMCs. Kenneth et al prepared Carbamazepine AMC in 2010. The polymer employed was cellulose acetate and PEG (Polyethylene glycol). They utilized sodium chloride as osmogen and studied release in simulated intestinal fluid. They employed high density polyethylene (HDPE) mould for the production of capsule shell with locking ridges. They concluded that when sodium chloride was used along with the sodium lauryl sulphate (SLS) in the core of capsule it shows high release of drug in biorelevant pH range (Kenneth *et al* 2010).

Anti Diabetic Drug like glipizide can be also formulated in the form AMCs. Thombre et al in 1999 developed AMC of Glipizide using cellulose acetate polymer and fructose as osmogen. They encapsulated various buffering system inside the capsule shell and studied release rate at different pH. They concluded that osmotic release of drug from AMC is dependent on its solubility (Thombre *et al* 1999c).

Anti Tubercular Drug's AMCs was developed by Vyas *et al* in 2004. They generally modify AMC by converting it into dense semi permeable membrane (DSM) capsule and modified asymmetric system (MAS) respectively. They used combination of Rifampicin and Isoniazid drugs. Cellulose acetate was used as membrane polymer, polyethylene glycol was used as pore forming agent. In the core of formulation sodium chloride and tartaric acid were used as osmogen and solubilizing agent respectively. They found that AMC are suitable for the rifampicin release but not for isoniazid due to its higher aqueous solubility. So the dense semi permeable systems (DSM) were developed to overcome this problem. Considering the results they developed modified asymmetric system (MAS) which provided better simultaneous sustained release profile of both drugs with sufficient initial burst release. In MAS the

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hydrophilic polymer was used with the drug in the core of AMC to cause initial burst release of drug (Vyas *et al* 2004).

Prabhakaran D. *et al* 2004 developed modified AMCs of CA with 20% glycerol for sustained simultaneous administration of Rifampicin (RI) and Isoniazid (IS) by filling RI in upper part and IS mixed with HPMC in lower part (Prabhakaran *et al* 2004).

Asymmetric membrane in membrane capsule (AMMC or two membrane system) of Cefadroxil (Cephalosporin Antibiotic) was developed by Philip *et al* in 2008. The polymers employed were ethyl cellulose (inner membrane) and cellulose acetate phthalate (outer membrane). Sodium Chloride was used as osmogen. They found that the developed system was able to delay the release of drug for first two hours in the gastric medium and then controlled release in the intestinal medium for an extended period of time of 12 hours. They also concluded that drug release was independent of agitation intensity and the defect of release membrane. So this AMMC could be utilized for both osmotic delivery and as delayed release formulation for poorly water-soluble drugs (Philip *et al* 2008).

H2 antagonists used for the treatment of GI ulcers or gastro-esophageal reflux disease should have gastro retentive properties. In 2010 Guan *et al* developed a gastro retentive asymmetric membrane capsule of Famotidine which is a H2--Receptor Antagonist. Cellulose acetate was used as polymer for asymmetric membrane. Polyethylene oxide (PEO) was used as floating agent in preparation (Guan *et al* 2010).

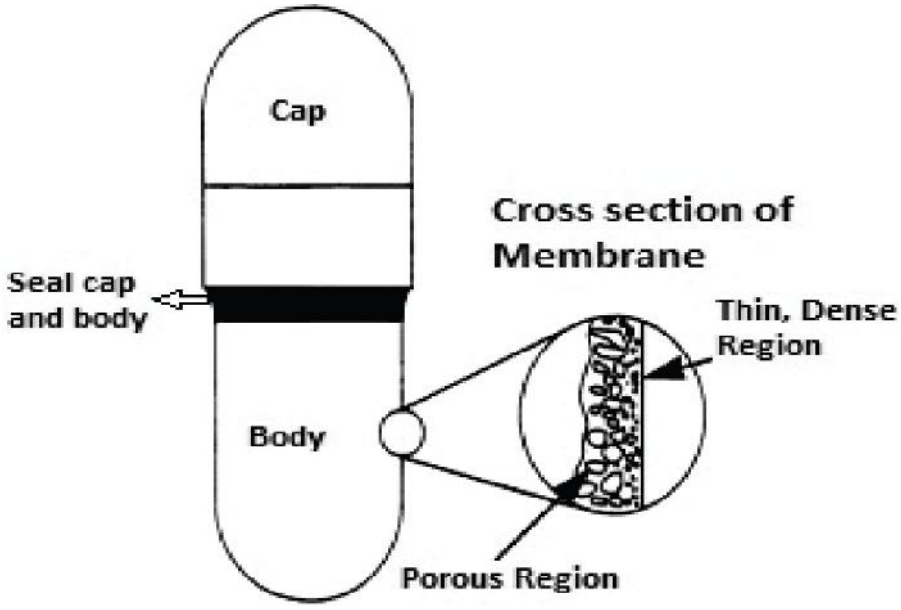

Figure 1: Asymmetric membrane capsules.

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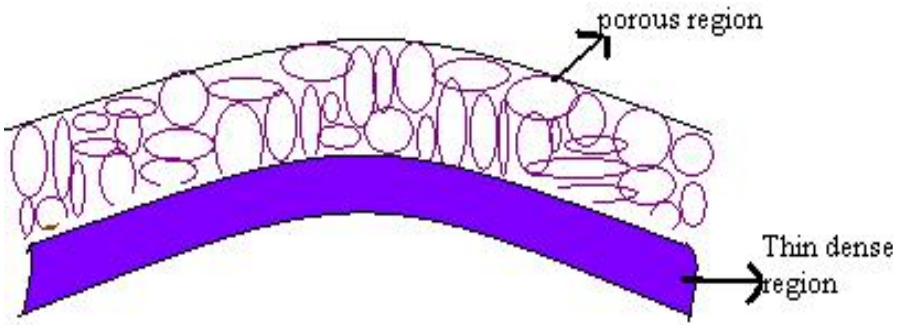

Figure 2: Cross section of asymmetric membrane showing dense region supported over porous region.

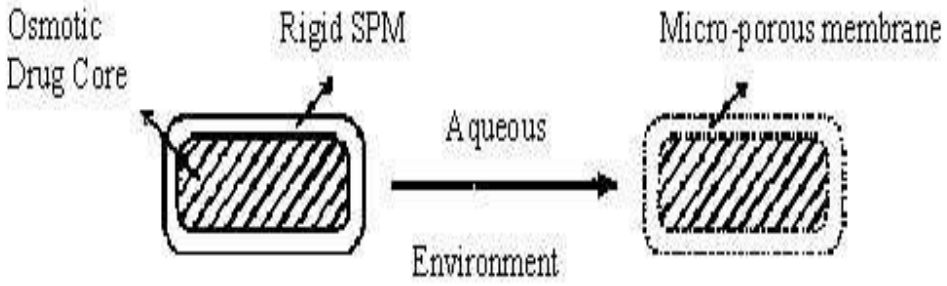

Figure 3: In Situ Pore Formation

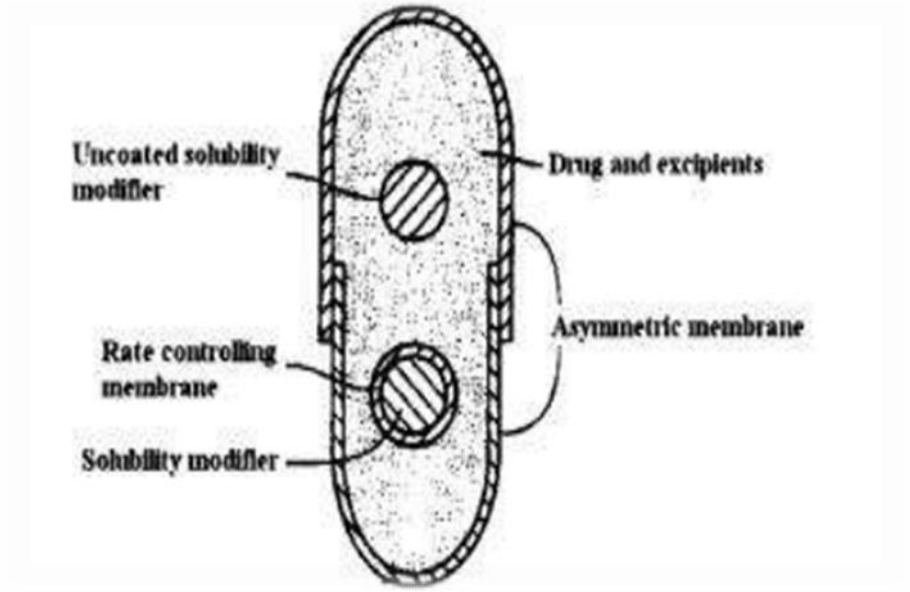

Figure 4: AMC drug delivery system having encapsulated excipients.

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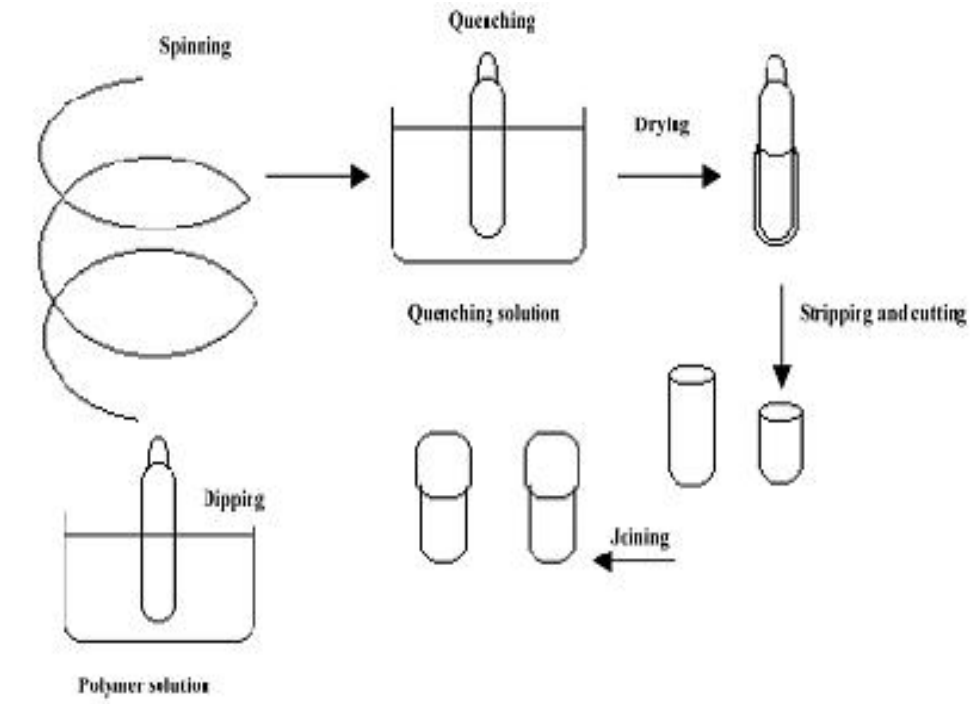

Figure 5: Process for manufacturing of asymmetric membrane capsules.

Table 1- Volume of solvent systems

Mixture of solvents	Volume
Acetone-Ethanol	80:20
Acetone-water	90:10
Methylene Chloride-methanol	79:21
Methylene Chloride-Methanol-Water	75:22:3
Acetone-Methanol	80:20

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Table 2: Osmotic Pressure of Saturated Solution of Commonly Used Osmogents.

Compound or Mixture	Osmotic Pressure (atm)
Lactose-Fructose	500
Dextrose-Fructose	450
Sucrose- Fructose	430
Mannitol- Fructose	415
Sodium Chloride	356
Fructose	335
Lactose-Sucrose	250
Potassium Chloride	245
Lactose-Dextrose	225
Mannitol-Dextrose	225
Dextrose-Sucrose	190
Mannitol-Sucrose	170
Sucrose	150
Mannitol-Lactose	130
Dextrose	82
Potassium Sulfate	39
Mannitol	38
Sodium PhosphateTribasic.12H20	36
Sodium Phosphate Dibasic.7H20	31
Sodium Phosphate Dibasic.12H20	31
Sodium Phosphate Dibasic Anhydrous	29
Sodium Phosphate Monobasic.H20	28

CONCLUSION

The Osmotic Controlled Drug Delivery System is a part of NDDS and costly type of drug delivery system but it tends to provide a good rate of drug release which tends to increase its acceptance in the pharmaceutical field. Drug delivery using principles of osmotic pressure is a

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versatile technology and AMCs further extends the scope. AMC is a characteristic type of osmotic drug delivery device that is employed for delivery to deliver poorly soluble drugs at a controlled rate for extended periods of time of various classes of drugs such as NSAIDs, Antibiotics, Antituberculars, Antihypertensive, Ant diabetics, Drugs to treat Gastro-Intestinal Disorders, Analgesics, GI irritant drugs etc.. The main advantage of this system is its cheap nature, ease of manufacturing by Phase Inversion method. AMCs also show broad area for the oral delivery of the drugs.

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