

ASYMMETRIC MEMBRANE CAPSULE (AMC): AN USEFUL OSMOTIC DRUG DELIVERY SYSTEM

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ABSTRACT

Osmotic drug delivery mechanism is well known in the field of oral controlled release systems. The release of drug from the osmotic drug delivery devices is based on the phenomenon of osmosis. An useful technology developed for osmotic delivery of drug is asymmetric membrane capsule (AMC), which is an economic and effective drug delivery device as compared to other existing technique of osmotic drug delivery like osmotic tablets. It can be prepared by a simple process known as Phase Inversion. Osmotic delivery system show less bioavailability fluctuation as compared to oral conventional controlled release (CR) systems because it releases drug independent of gastrointestinal (GI) physiological factors. Asymmetric membrane is prepared by using water insoluble polymer like ethyl cellulose (EC), cellulose acetate (CA), cellulose acetate butyrate (CAB). In this system role of osmogen is important to release the drug from it. Both water soluble or insoluble drugs can be delivered using AMC. Various categories of drug that can be formulated in AMC are NSAIDS, cardiovascular drugs, anti-diabetic drugs, antibiotics etc. This article presents an overview of AMC as an effective dosage form for oral osmotic controlled drug delivery of various categories of drugs.

Keywords: Asymmetric membrane capsule (AMC), Osmosis, Phase inversion, Osmogen.

INTRODUCTION

Popularity of oral controlled release system is increasing day by day. But various conventional controlled release (CR) systems such as matrix or reservoir type may show bioavailability fluctuation because of change in gastric pH and hydrodynamic condition of body. Osmotic systems show drug release independent to gastric physiological factor as the release of drug from this type of system is guided by osmosis, which itself is independent of pH of environment. Osmotic drug delivery systems can be of various designs like implants, tablets etc^{1,11}.

Major mile-stone in the field of oral osmotic drug delivery was achieved by Theeuwes and co-workers of Alza company USA in 1974². They gave a tablet design composed of compressed tablet core surrounded by a semipermeable membrane with a single orifice so called as elementary osmotic pump (EOP)³. First two drug formulated in EOP were indomethacin (OSMOSIN[®]) and phenylpropanolamine (ACUTRIM[™]). Asymmetric membrane capsules (AMC) were introduced in 1999 for osmotic delivery of drugs^{4,5}.

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 osmogen⁶.

Asymmetric membrane capsule consists of a cap and a body, 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 composition⁷.

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 solubility⁸. 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 poorly water soluble drug inside the core, it can be enclosed with osmotic agent or solubilising agent so that it can be delivered osmotically⁹.

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 delivered¹⁰. 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 factors¹¹. Advantages of asymmetric membrane capsules (AMC), over other controlled drug delivery systems are given below:

1. They are easy to formulate and there is no requirement of special manufacturing devices like laser drilling machines in case of osmotic tablets.
2. They improve the patient compliance with reduced dosing frequency and prolong therapeutic effect of drug¹².
3. In this type of osmotic system the rate of delivery of drug is independent of delivery orifice within particular size limits¹³.
4. 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 poorly water soluble drug. This is because for delivery of poorly water soluble drugs high rate of water influx is required.
5. 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.
6. The capsules are made of components which have a long history in pharmaceutical excipients. Therefore test formulation made using AMC can be administered to an appropriate animal to test the performance of formulation, without the need of additional toxicological studies of excipients. Thus proposed pharmacological concepts can be easily validated using this delivery system^{14,28}.

Figure 1 shows various region of asymmetric membrane capsule shell.

Mechanism of drug release from Asymmetric Membrane Capsules (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. Peffer in 1877 gave quantitative measurement of osmotic effect. He postulated that in a sugar solution, osmotic pressure (π) 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:

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

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 approximation of osmotic pressure is by utilizing the expression:

$$\pi = RT \ln (P_o/P)/v \dots\dots (2)$$

Where P_o represents the vapour pressure of the pure solvent, P is the vapour pressure of the solution, and v is the molar volume of the solvent.

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:

$$dV/dt = A\theta\Delta\pi/l \dots\dots (3)$$

Where dV/dt represents the water flow across the asymmetric membrane of area 'A' and thickness 'l' with permeability ' θ ', $\Delta\pi$ depicts the difference in osmotic pressure between the two solutions on either side of membrane^{13,14}.

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

$$dM/dt = dV/dt.S \dots\dots (4)$$

Where 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.

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

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:

$$dM/dt = (A\theta RT/l).S^2/M \dots\dots (6)$$

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 (θ) of capsule membrane can be calculated⁸. 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 is $(dM/dt)_t$ is given by:

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

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

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:

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

Where P_d is dissolved drug permeability in the membrane^{15,16,28}.

So combining eqn. (6), (7), (8), total drug release by AMC is given by following expression:

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

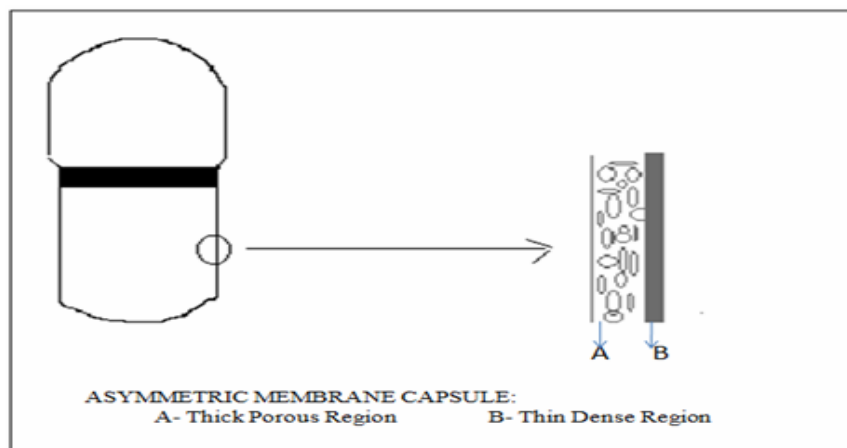


Fig. 1: Various region of Asymmetric membrane capsule shell

Formulation of Asymmetric Membrane Capsule (AMC)

A. Composition of Asymmetric membrane

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

1) Stability of the membrane towards the internal environment and external environment of the capsule should be high¹⁷.

2) The membrane should show semi-permeable behaviour and should have enough permeability for water to create osmotic pressure inside the system¹⁸.

3) The thickness of the membrane should be appropriate¹⁹. 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 system²⁰.

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

a. 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^{9,10}. 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 strength²¹.

b. Solvents

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 like ethanol, water, isopropyl alcohol, butyl alcohol^{7,21}.

c. Pore forming agents

Pore forming agents are 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 drug²². They are usually poor solvent or non-solvent for the polymer that are used in preparation of asymmetric membrane. These water soluble additives leach from the membrane after coming in contact with aqueous body fluids and thus multiple micropores are formed in membrane. Examples of pore forming agents are Glycerol, sorbitol, polyethylene glycol (PEG), polyglycolic acid (PGA), Polylactic acid (PLA)²³.

B. Composition of core of AMC

a. Drug

Selection of drug is important for its formulation into asymmetric membrane capsule (AMC). Drug having following characteristics are suitable for formulation into AMC:

1. It should have short half-life
2. Prolonged release of drug should be desired.
3. It should be potent in nature.
4. Solubility of drug should not be very high or very low²⁴.

b. Osmotic agent

These are also known as osmogens or osmogents and are used to create osmotic pressure inside the system. 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. Osmotic agent creates a very high osmotic pressure gradient inside the system and increases release rate of drug²⁵. Osmotic agents may be inorganic water-soluble salts like sodium chloride, potassium chloride, and sodium phosphate etc. They can be polymer like sodium carboxy methyl cellulose (SCMC), hydroxy propyl methyl cellulose (HPMC) or surfactant like sodium lauryl sulphate (SLS). Carbohydrates like sucrose, mannitol, fructose, lactose can also be used as osmotic agents.^{13,14,26}

c. Solubilizing agent

These are agents which increase the solubility of drug in the core²⁷. 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 drug²¹. Examples of these agents are fumaric acid, tartaric acid, citric acid etc^{13,21,27}.

d. 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 act as solubility suppressant for paracetamol²⁸.

Manufacturing method of Asymmetric Membrane Capsule (AMC)

The basic principle guiding the manufacturing process of asymmetric membrane capsule is Phase Inversion¹⁶. This is the technique in which polymer solution get changed from solution form to a structured, continuous polymeric phase²³. AMC can be manufactured by two methods, namely wet method and dry method:

a. Wet method

This process involves three basic steps:

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 dessicator 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^{11,24}. Figure 2 represents steps of manufacturing of asymmetric membrane capsule shell.

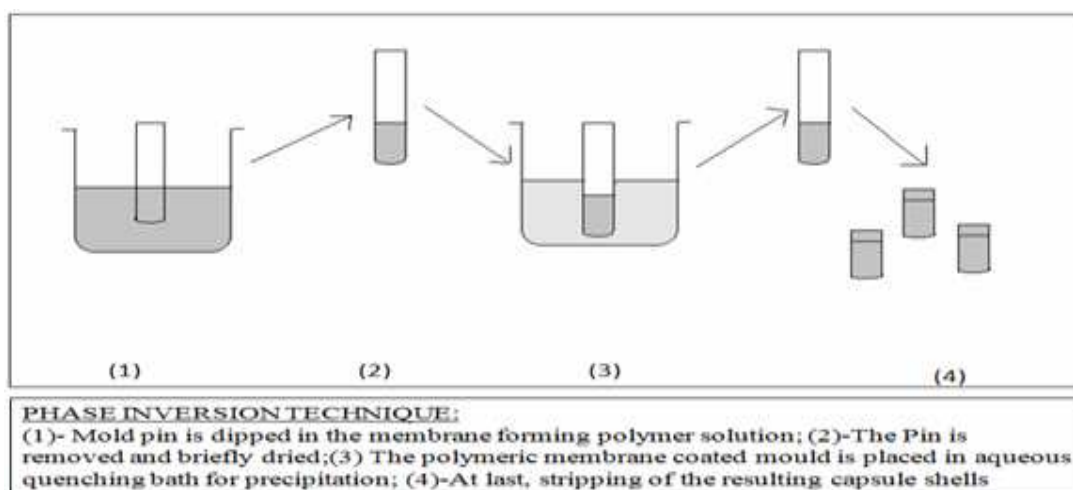


Fig. 2: Manufacturing steps of asymmetric membrane capsule shell

b. Dry method

This process is similar to the wet process but in this method complete evaporation of solvent is necessary. In this process solvent evaporates more rapidly as that of pore former²⁸.

Evaluation of Asymmetric Membrane Capsules (AMC)

Asymmetric membrane capsules are evaluated in similar fashion as that of hard gelatin capsules but some additional evaluation parameter are also required for AMC. These are given below as:

a. 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 membrane²⁹.

b. 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 osmogen (like sodium chloride) or solubilizing agent (like sodium lauryl sulphate). Then the capsules are suspended separately in 50ml of water and 50ml of sodium chloride solution (10% w/v). Then capsules are studied visually for release of any coloured dye. Release of colouring dye indicates its osmotic expulsion from core of capsule²⁵.

c. In-vitro drug release

in-vitro drug release study is carried out by using USP dissolution apparatus II. simulated gastric fluid (SGF) is used as dissolution media usually. Sample withdrawn from dissolution media are then analysed through validated analytical technique. Drug release should follow zero order kinetics³⁰.

Application of Asymmetric Membrane Capsules (AMC)

As we know that 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. Main categories of drug that can be given through AMC are cardiovascular drugs, NSAIDs, antibiotics, antidiabetic, anti mycobacterium drugs.

Many NSAIDs show shorter half life and GIT irritant effect, so these are potential candidate for AMCs. 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 osmogen (sodium chloride and mannitol). They considered that this may be due to solubilization effect of SLS causing increase in the solubility of drug, increasing osmotic pressure of drug itself, increasing amount of drug released from the system. They ultimately concluded that SLS, besides imparting solubilization effect, also acts as an osmogen in dissolved form³¹. Phillip in 2008 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. He concluded that formulations without citric acid were not able to achieve therapeutic concentration within first hour, probably owing to the lower solubility of drug in the acidic medium. The incorporation of citric acid in formulation provides an increased pH of stagnant diffusion layer around the drug particle. This stagnant diffusion layer is usually at higher pH than the bulk of dissolution medium. Because higher pH favours the dissolution of weakly acidic drug, solubility of drug in the stagnant diffusion layer gets increased at a higher pH, therefore causing high release from formulation as compared to other formulation without citric acid³². Philip and Pathak in 2008 prepared *in-situ* formed phase transited AMC of ketoprofen and studied level A *in-vitro in-vivo* correlation. Polymer used was ethyl cellulose (EC), sodium chloride was used as osmogen and citric acid was employed as solubilising agent. *In-vivo* studies were carried out

by using rabbits. Various pharmacokinetic parameters used to established correlation were C_{max} (Peak concentration), T_{max} (time to reach peak concentration), $t_{1/2}$ (elimination half life), K_a (first order absorption rate constant) etc. They found that the prepared AMC not only shows level A correlation but also shows controlled release via osmotic pumping. Level A correlation meant that by using *in-vitro* release profile of ketoprofen *in-situ* formed phase transited AMC, one can also predict their *in-vivo* performance¹⁹.

Cardiovascular drug can also be potent candidates for AMCs. 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 hydroxypropyl 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 micellar 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 nifedipine¹⁶. Kumar and Gupta in 2009 prepared AMC of carvedilol using cellulose acetate (CA) polymer and glycerine as pore forming agent. They studied release pattern of formulation using different ratios of the osmogen (mannitol) and solubilizing agent (sodium lauryl sulphate, SLS) and found that drug release rate increases with the increase in amount of osmogen or solubilising agent and it is independent of different environmental media and stirring rate. Carvedilol release rate was, directly proportional to the level of pore former, glycerine, in the membrane. This system was found to deliver the drug at zero order release rate³³. In 1999, Thombre *et al* developed AMC of doxazosin using cellulose acetate polymer and compared *in vitro/ in vivo* performance of drug. They used triethyl citrate as solubilising agent. They prepare AMC of drug using different ratios of triethylcitrate and glycerine. Then they compared *in-vitro* activity of drug with *in-vivo* by using beagle dogs as experimental animal models. They studied that *in-vitro* drug release was upto 6 hours. But *in-vivo* release rate was slower as that of *in-vitro* release rate. They concluded that difference between *in vitro* or *in vivo* activity may be due to the release of fumaric acid buffer from capsule over a period of time that was shorter than the drug release duration. After fumaric acid is depleted from the capsule, the diffusive component of drug release may become more dominant. This explanation is consistent with the *in-vivo* profile which shows decreasing release rate after the delivery of 60% of drug loading³⁴. Kapoor *et al* in 2011 developed AMC of valsartan using cellulose acetate polymer, PEG-6000 (Polyethyleneglycol) 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. Result of SEM studies verify the formation of pores in the asymmetric membrane after coming in contact with the aqueous media. They substituted *in-vitro* drug release values in different kinetic models. Ultimately they found that the drug release follow zero order kinetics³⁵.

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 found that the dissolution rate of capsule was independent of pH in biorelevant range (2 to 6.8). 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 range³⁶.

Antidiabetic drugs 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. Thus, the substances with poor aqueous solubility are released at very low rates. They postulated that this limitation for a drug like glipizide which has a pH dependent solubility,

can be overcome by using a solubility modifying excipients in the core of capsule. In order to avoid depletion of excipients from the core before complete drug release, the excipients can be encapsulated in the rate controlling membrane. They found that by controlling the ratio of encapsulated to free excipient in AMC core, drug release can be achieved to meet the desired target³⁷.

AMC for antitubercular drugs was developed by Vyas *et al* in 2004. They generally modify AMC by converting it into dense semipermeable 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 dense semipermeable systems (DSM) were developed to overcome this problem. They prepared two dense semipermeable membrane system DSM 1 and DSM 2. DSM 1 provided better controlled release of rifampicin, however it lacks initial burst release of rifampicin. DSM 2 provided better controlled release of isoniazid, which was filled in lower part of capsule. The system also failed to produce initial burst release. 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 hydrophilic polymer was used with the drug in the core of AMC to cause initial burst release of drug³⁸.

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 agitational 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 drugs³⁰.

In 2009 Guan *et al* developed a gastroretentive 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. They carried out *in-vivo* studies by using beagle dogs as experimental animal and marketed famotidine tablet as reference preparation for comparison. They noted that the optimized formulation shows complete drug delivery and zero order release rate during floating on medium. The results of pharmacokinetic studies clearly indicates that there is controlled and sustained release of famotidine from gastro-retentive AMC. This system can prolong the drug action, and minimize the frequency of drug administration and lower the average peak plasma concentration. They also found that relative bioavailability of prepared system was 1.065 in comparison to the marketed preparation owing to floating ability of the system³⁹.

CONCLUSION

Osmotically driven controlled drug delivery system shows very high therapeutic potential. AMC is a characteristic type of osmotic drug delivery device that is employed for delivery of various classes of drugs. The main advantage of this system is its cheap nature, ease of manufacturing. It does not require laser drilling as required in osmotic tablets. AMC can be employed for the delivery of drugs having low solubility by using osmogen/solubilising agent in the core. It can also be converted into gastro-retentive form by using appropriate floating agent in the core. So we can say that AMC may be effective in treating the diseases for which potent drugs and prolonged therapy is required.

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