CHAPTER 2

LITERATURE REVIEW

2.0 LITERATURE REVIEW

The influence of feeding and temporal patterns on GI transit is of great relevance in attempting to optimize drug absorption because the physiology of the digestive process is not suitable for the competent absorption of many of the modern therapeutic entities to administer. There is a short lag phase before the mixing movements in the lower part of the stomach and the pyloric antrum which increase in upper part. There is a sharp contrast between the activity in the top and bottom parts of the stomach. In the small intestine, contact time with the epithelium where absorption is possible is limited, and a small-intestinal transit time of 3.5–4.5 h in healthy volunteers. The Holy Grail of drug delivery would be to discover a mechanism that extended the period of contact with this area of the gastrointestinal tract. Various approaches are there, although a universal solution is not evident, and extend GI residence not proven fruitful. Transit through the lower part of gut is approximated at about 24 hours still in reality the ascending colonic environment has sufficient fluid which facilitate dissolution. The anatomy of the distal colon, with its thick muscular walls, supports a predominant activity. Studies with single administrations of pellets or Pulsincap devices recommended that this area is difficult to reach because the second half of the transverse colon and the descending colon function only as a channel but absorptive.

The time of dosing is an important factor in maximizing colonic contact, particularly in the ascending colon. Morning dosing without fasting is a common practice in clinical trials. It is well accepted that early-morning dosing, a non disintegrating unit clears the stomach in 1–2 h and has a small-intestinal transit time of 3–4 h. Thus, after noon the unit will be expected to reach the ileocecal junction or may have just entered the colon. Colonic transit through the proximal colon of intact objects such as capsules is usually 5–7 h. For a non-disintegrating oral formulation, dosed in the morning, the unit will have arrived at the hepatic flexure by 7–8 pm. The drug gets absorbed in the colon, the maximum time window for absorption is 6–8 h following morning dosing with a monolith. Transit of a dispersed particulate phase through the proximal colon is longer, about 12 h. The maximum time window for absorption in this case is approximately 12–15 hours.

If a delayed release formulation is taken in the afternoon, it will have progressed through to the ascending colon by the time the patient goes to bed. Propulsive movements in the large bowel during the night are relative stagnant and units remain in the ascending colon. Potentially, this can increase the time of contact to 11–13 h even for a slowly dissolving

matrix. On rising, the change in posture stimulates mass movements, experienced by the subject as an urge to defecate, and contents move from the right to the left side of the colon. For poorly soluble substances, the reserve time is an important determinant of bioavailability. Moving away from the current practice of dosing sustained- release formulations in the mornings might allow a reduction in the dosing frequency and increased efficacy of colon-targeted drugs, and would be especially suitable for formulations used to prevent acute disease episodes at night and in the early morning.

The specificity of most drug actions suggests a bond formation between the drug and some cellular constituent, generally referred to as a receptor. Drug receptor interactions may initiate responses by altering the permeability of membranes, by interfering with carrier mechanisms, by modifying templates, or by acting on enzymes. Current trends in fundamental research on drug effects focus on transport of ions and the binding and release of endogenous mediators, with much

Work being done in isolated systems. Agonistic or antagonistic effects demonstrated in the test tube can, however, be completely different when we start to evaluate the action of the drug in the human body. Various physiological factors must be considered to achieve beneficial and therapeutic effects from a drug. The goal is not only to have an effect on ''a man's heart'' but on the entire organism.

Two major functions of the small intestine are, a) efficient absorption of nutrients, fluids, electrolytes, and drugs, and b) the simultaneous exclusion of potentially antigenic or toxic inflammatory substances. The overall ability of the intestinal epithelium to provide a barrier to the absorption of these potentially harmful compounds is often referred to as selective permeability.

The oral administration of many drugs and drug candidates is prevented by their poor absorption through the intestine. Several highly potent polypeptides and protein drugs belong to this group of compounds, and it is of considerable interest to improve the understanding of this barrier to enable and optimize oral administration of such substances.

The oral route of administration is preferred for many drugs categories; ease of administration and patient compliance are the main reasons. Estimating oral bioavailability in

humans for the selection of the best development molecule is a considerable challenge to the pharmaceutical industry. Several promising in vitro models became available for the study of the absorption potential of new compounds. Systemic bioavailability is influenced by a variety of factors (Table 1), with poor solubility, poor permeation, intestinal and liver metabolism, and P-glycoprotein (P-gp)-mediated efflux being among the most common detrimental influences on drug absorption. Physicochemical properties of a drug and their influence on the overall bioavailability are major area of interest. These properties can have a particularly important effect on the absorption. The main uptake mechanism through mucosal membranes is by passive diffusion, using the transcellular pathway. However, several alternative processes needs to be considered. These processes may not be independent and take place in parallel. Membrane diffusion by the transcellular and paracellular pathways is a physicochemical process; therefore, physicochemical properties are believed to have an important influence on these membrane transport. Physicochemical properties can be a helpful guide in the selection of compounds that will have sufficient oral absorption in humans and therapeutic effects.

In vitro–in vivo correlations (IVIVC) are important because bioequivalence of changes in drug products can be approved by in vitro. The generic drug products approval decision will be solely on the basis of in vitro data if an IVIVC established. To establish IVIVC it is necessary that the chosen in vitro method can reflect the in vivo plasma profile. A precise knowledge of the in vivo situation is a key to an in-vivo in-vitro correlation (IVIVC and drug solubility, dissolution, and gastrointestinal permeability as the fundamental parameters for correlating the in vitro with the in vivo data. On the in vivo side, we have to consider that, in addition to the permeability; the motility can also impinge on the availability of the drug. The average passage time of this dosage form was about 1 day to 30 h, shows that the transit time in the major absorption site, the small intestine is less than one-sixth of the total residence time in the GI tract. In the colon, the absorption as well as enzymatic and bacterial decomposition of drugs varies compared with the small intestine. Presently, for the low-solubility, high-permeability drugs that commonly come from drug discovery, we expect an IVIVC if the in vitro dissolution rate is similar to the in vivo dissolution rate. Here in vitro dissolution and in vivo dissolution are important parameters unless the dose is very high. In contrast with poorly soluble drugs and controlled-release dosage forms, the gastric-emptying and small-intestine–transit time will not influence the fraction dose absorbed of highly soluble, highly permeable drugs because those drugs will normally be absorbed within the

gut passage. For these compounds, the gastric emptying will alter T_{max} and probably also C_{max}, and, if this occurs, it is unlikely that a satisfactory IVIVC can be achieved.

IVIVC can be expected if the dissolution rate of a drug is slower than gastric emptying particularly for class II and IV drugs. Due to variable gastric emptying regulates the absorption rate of a class I drug and the permeability limits the uptake of class III drug.
The choice of dissolution test for an IR dosage form can be facilitated by BCS classification considerations. Compounds with good solubility (Class 1 & 3) the medium and method should be kept simple. For low solubility drug with and good permeability (class 2) the choice of test will depend on the objective to be met. For the development of IVIVCs, the new biorelevant media appear to offer significant advantages over the traditional compendial media in terms of being able to forecast the in vivo dissolution behaviour. In the majority of cases, *USP* paddle are the method of choice for the dissolution test, with medium volume chosen according to the intended administration conditions (fasted or fed) and the site where the drug will most likely dissolve in the GI tract. No data predicts supports correlating rotational speed and in vivo hydrodynamics conditions. Normally, rotational speeds of 50–100 rpm yields data that can be successfully used to develop IVIVCs. Slow release of the drug from the dosage form, unstable drug in the GI tract, lack of permeability of the GI mucosa to the drug, and metabolism due to first pass effect of drug in the gut wall or liver. In principle, dissolution tests can be used to predict the in vivo performance of the dosage form when release of the drug is the limiting factor in the absorption process. There are two classic cases in which release is limiting to absorption: controlled-release (CR) dosage forms and immediate-release (IR) dosage forms containing drugs that are poorly soluble. The biopharmaceutics Classification Scheme is useful as a guide to determine whether an IVIVC can be expected for an immediate release product. Figure 1- 2 depicts Oral absorption process in Gastro-intestinal track.

Extended-release formulations are created to ensure a limited, controlled release of the drug dissolution rate. Only the amount of released drug is available for solubilisation and permeation through the gut wall.

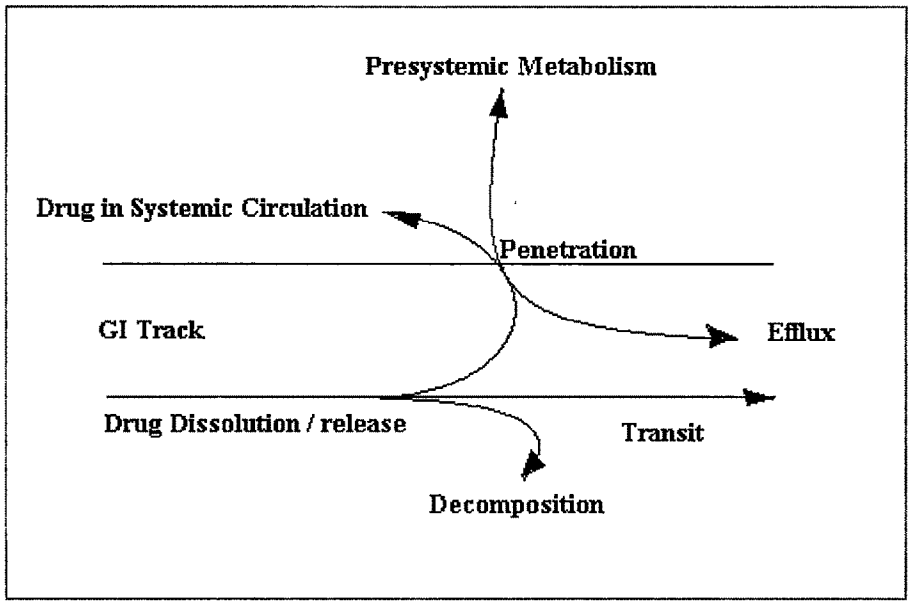

Figure 1 - 2 Oral absorption process in Gastro-intestinal tract

In vitro dissolution is a tool in development of solid dosage forms provided that in vivo predictive results are obtained. To fulfil this requirement, physicochemical and pharmacokinetic properties of the substances, as well as the function of the dosage form and physiological factors, must be taken into consideration in design of dissolution tests and in predictions of in vivo performance based on in vitro data.

Extended release Drug Delivery System

Extended release (ER) dosage forms have been extensively used because of their significantly improved efficacy clinically and better patient acceptability. Among the various controlled release (CR) drug delivery systems available in market, oral controlled release systems hold the major market share because of their obvious advantages of ease of administration and better patient compliance. A number of design options are available to control or modulate the drug release from an oral dosage form. Majority of oral CR dosage forms falls in the following categories,

- Matrix systems
- Reservoir systems and

- Osmotic systems.

2.1 Matrix Systems

In matrix systems, the drug is embedded in a polymer matrix and the release takes place by partitioning of drug into the polymer matrix and the release medium. In contrast, reservoir systems have a drug core surrounded/ coated by a rate controlling membrane. However, factors like pH, presence of food, and other physiological factors may affect drug release from conventional CR systems (matrix and reservoir). Osmotic systems utilize the principles of osmotic pressure for the delivery of drugs. Drug release from these systems is independent of pH and other physiological parameters to a large extent and it is possible to modulate the release characteristics by optimizing the properties of drug and system. Osmotic pumps are well known for delivering drug at a zero order rate.

Hydrophilic matrix tablets are the frequently developed ER dosage forms for oral use. Hydrophilic matrices do not disintegrate and are formulated for drug to release over a pre-defined period of time following exposure to water on oral administration. The goal for n oral extended release matrix is reduction in dosing frequency compared to a conventional dosage form. Preparation of matrix tablets that may involve direct compression of a blend of a drug with release retarding polymers and other excipients is most direct approach for extended release delivery of drugs for oral administration. Various polymeric materials have been explored as release retarding agents in hydrophilic matrix systems. There are different oral matrix formulations such as inert matrices and wax or hydrophobic matrices are available, formulation and design of hydrophilic matrices is important to understand due to better shelf life. Wax or lipid matrices are prepared by adding the drug and excipients to the molten fat or wax, congealing, granulating, and compressing into matrix cores. Substances that produce these matrices include carnauba wax, fatty alcohol, GPS, stearyl alcohol, beeswax, aluminium mono-stearate, and GMS. The mechanism of drug release from wax matrix may be diffusion of drug through liquid-filled pores. On the other hand, there are erodible through digestion in totality lipid-based (Wax) matrix systems that control the release of drug through combination of diffusion and erosion. Inert matrices using polymers such as ethylcellulose, methylacrylate, methylmethacrylate, polyvinyl chloride, and polyvinyl acetate are prepared through wet granulation and compression into matrices. Drug release from these matrices is by simple diffusion through water-filled pores.

The ingredients of a hydrophilic matrix HM can be either directly compressed or granulated to aid flow and compression or improve content uniformity. On exposure to water, in the hydrophilic matrix polymer on or near surface of the matrix hydrates & form a gel like layer. The gel layer controls water ingestion into the matrix and controls the mechanism of drug release. Therefore, the mechanism of drug release from HM systems is a combination of hydration and swelling of the formulation, drug dissolution, drug diffusion, and erosion of surface polymers. Polymers used in the manufacture of hydrophilic matrices alone or in combinations include Cellulose Derivatives and Non-cellulose Derivatives. Cellulose derivatives are methylcellulose (MC), hydroxypropylmethylcellulose (hypromellose, HPMC), sodium carboxymethylcellulose (Na CMC), and hydroxypropylcellulose (HPC) and Non-cellulose Derivatives are carbomers, sodium alginate, xanthan gum, guar gum and carrageenan. The choice of the polymer used in the matrix formulation depends on the chemistry of the drug, desired release profile. Hypromellose is available commercially from Dow Chemical Company under the trade name METHOCEL. It is available in different chemistries depending on the degree of hydroxypropoxyl and methoxyl group substitutions. Hypromellose 2910, USP (METHOCEL E) and (METHOCEL K) hypromellose 2208, USP are most widely used in extended release formulations and are distributed worldwide by Colorcon Inc. The USP classification code is based on the substitution type with first two digits representing mean percent methoxyl substitution and the last two digits representing the mean percent hydroxypropyl substitution. Hypromellose is the most commonly used polymer for the preparation of hydrophilic matrix systems. Hypromellose quickly forms uniform gel that protects the matrix from disintegration, formation of a strong, viscous gel layer which controls release. In addition, HPMC has a long history of application in marketed products with wide global regulatory acceptance. As described above, HPMC polymers may differ in their degree of methoxyl or hydroxypropoxyl substitution and/or degree of polymerization. Varying the ratios of methoxyl and hydroxypropoxyl substitution and molecular weights influences properties of formulation like organic solubility, thermal gelation temperature of their aqueous solutions, swelling, flow properties, compressibility and compactability, diffusion behaviour, and drug release properties. Figure 2 – 2 depicts schematic representation of hydrating swellable hydrophilic matrix formulation.

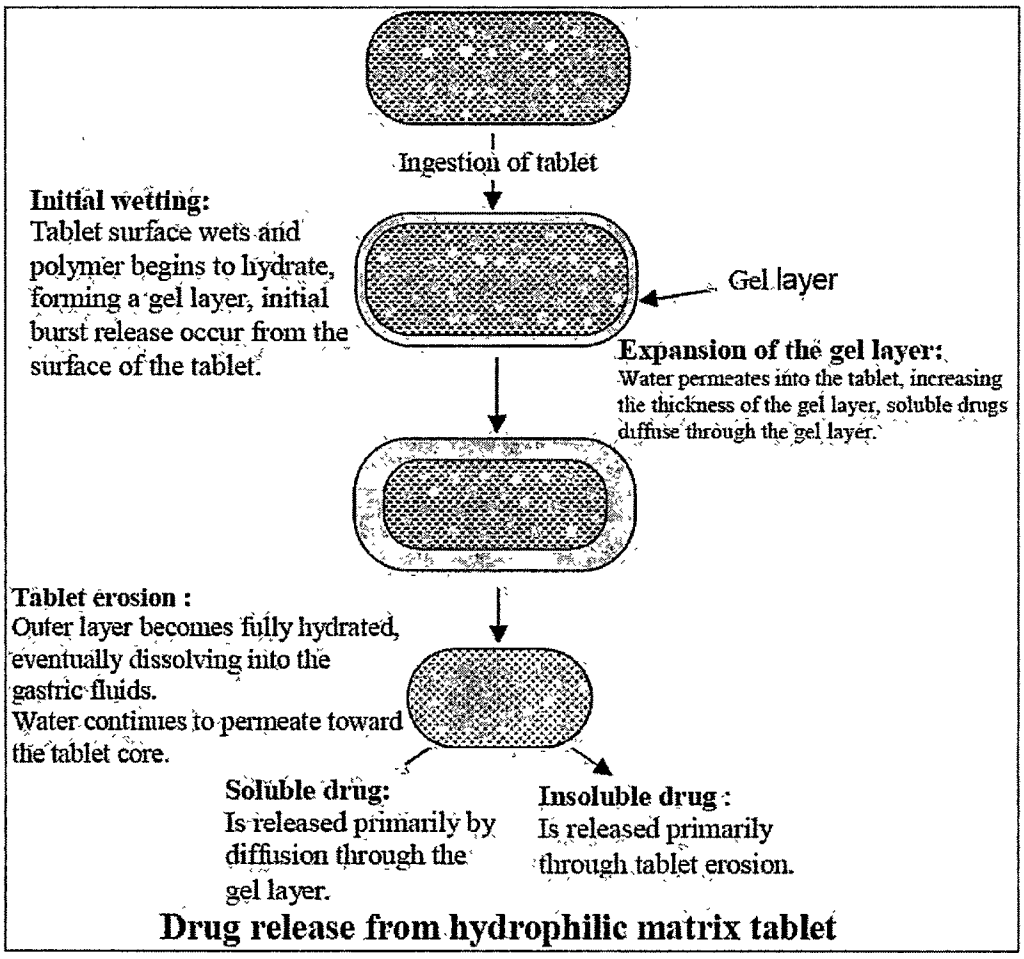

Figure 2 - 2 Schematic representation of hydrating swellable hydrophilic matrix tablet

Extended drug release from HM systems is achieved through rapid hydration of the polymer on the outer tablet surface to form a gelatinous layer. Very fast formation of a gelatinous layer is essential to retain structural integrity, prevent water ingress to the interior of the matrix, and inhibit immediate disintegration of formulation. Once gel layer is formed which is protective in nature, that controls the water movement in the gel layer and further imbibitions of water into the formulation. Logically, hydrophilic polymers are of small particle size range and so ensuring rapid and consistent hydration of the polymer. Immediately once the outer gel layer hydrates fully, the polymer starts disentangles from the surface, which is continuously replaced with the hydrated polymer from within the core to control drug release. Hydroxypropylmethylcellulose (HPMC) used in many successful controlled release systems, mainly due to generally recognized as safe (GRAS) status and biodegradable behaviour. Compatibility is proven with several drugs, high drug loading is possible using it and can be easily incorporated to form matrix tablets by through established

manufacturing techniques like direct blending or granulation. Wide range of viscosity grades of HPMC are available allows the developer to modify the release of drugs from HPMC matrix tablets according to therapeutic requirement. Increasing the HPMC concentration in the tablet or using higher viscosity grades increases the strength of the gel layer and retards the penetration of water into the dry glassy core Outcome, decrease in release of both water-soluble and water-insoluble drugs. Modification of drug release from HPMC matrix tablets has been attained by modifying the polymer concentration and by using different viscosity grades of HPMC. HPMC and polyethylene oxide are well known for their rapid hydration and gel formation. The release of drug from a hydrophilic matrix system relies on swelling of the matrix, dissolution of the drug, and diffusion and erosion properties of the gel layer. The solubility and dose of the drug, type and quantity of fillers, and the polymer influence the mechanism of drug release. Mechanism and rate of drug release from hydrophilic matrices depend not only on the type and level of the polymer, choice of filler, and size of the matrix, but also on the physic-chemical properties of the drug substance. Researchers have used quantitative structure–property relationship (QSPR) methods for prediction of mechanism and rate of drug release from HPMC matrices.

The microenvironment pH control may enhance solubility or stability of the formulated drug in the matrix and within the gel layer of a hydrated system. Compression coating (tablet in tablet) technology containing hydrophilic polymers has been applied to generate lag time followed by either fast release or slow release. Mini-matrix is examples of application of hydrophilic matrices in multiparticulate formulations. Various technologies have been investigated to modulate drug release from hydrophilic matrices. Use of polymer blends may provide an alternative approach to modulate drug release compared to conventional single polymer matrices. Matrices containing Polyethylene Oxide (MW from 600,000 to 7,000,000), polymer concentrations, and carbopol combinations also made, polymer concentrations and molecular weight, had a significant impact on drug release rate and profile. Matrices containing polymer blends of HPMC, Carbopol, are also available. It is postulated that there may be strong hydrogen bonding between the carboxyl groups of Carbopol and hydroxyl groups of HPMC leading to stronger interactions between the two polymers and therefore slower drug release than a matrix with a single polymer. Blends of HPMC and polyvinyl pyrrolidone (PVP) in a hydrophilic matrix shows a biphasic release of caffeine as a water-soluble model drug. The initial release is controlled by HPMC, but because of faster release of drug from the matrix, the PVP becomes rich progressively. The

breakup of the HPMC gel by enriched PVP resulted in a bimodal release profile with faster release at the terminal phase. The breakup happens at different time points depending on the PVP level in the matrix.

Blending of polyvinyl acetate phthalate (PVAP), an enteric polymer, HPMC, and Carbopol also studied as release retardant. Changing the ratio of the polymers in the blend, it was possible to modulate the drug release profile. Use of polymer blends at lower concentrations, providing the desired release profiles and maintaining formulation robustness, would be a suitable approach for drugs with higher dose. The retardation of drug release has been attributed to the synergistic interactions between PVA, Carbopol, and HPMC leading to formation of a stronger gel layer and slower diffusion and erosion rates.

Formulation of drugs with pH-dependent solubility in hydrophilic matrices may be helpful to release profiles that alter with variation in the pH of the media. In most situations, a desirable release profile should be pH independent to withstand the physiological pH changes in the gastrointestinal tract. Buffers and polymers are added in the formulation that maintains pH within the gel structure of hydrophilic matrix. The majority of the frequently used low molecular weight pH modifiers tend to diffuse out of the hydrated matrix faster than the drug and maintaining the desired pH over the entire duration of release can be a challenge. The effectiveness of different types of acids, fumaric acid, citric acid, succinic acid, and ascorbic acid, to maintain a microenvironment pH for the duration of release is studied. Even sodium hydroxide and melamine are studied. pH modifier leaches out of the matrix system immediately, ionic polymers that contribute to microenvironment pH are used and due to their high molecular weight they stay within the gel structure until eroded from the surface of the matrix.

Minitablets having a diameter around 2 to 3 mm can be encapsulated or compressed into larger tablets. Mini-tabs are advantageous because of reduced inter- and intra-subject variability, formulation flexibility, and appropriate dosage forms for drug delivery for lower age group. Miniaturises (2.5mm in diameter and 12 mg in weight) have been evaluated for biphasic drug release (fast/slow) HPMCK100M and EC can be used as release retardant matrix formers. Miniaturises (3mm in diameter and 2mm in height) using polymer blends of Polyethylene Oxide and polyethylene glycol (PEG) and ethylcellulose containing metoprolol

tartrate have been are also used. The minimatrices can be made through hot melt extrusion to get 24 h drug release profiles.

Hydrophilic matrix systems are widely considered, simple, robust, and versatile extended release technology. Different chemistries and viscosity grades of hydrophilic polymers and more specifically different grades of HPMC, allow this technology for ER formulations of drugs with wide range of solubility and dose strengths. Various approaches have been used to modulate drug release for having predicted pharmacological profiles. HPMC matrix can be used as a platform for blending other polymers to provide flexibility in formulation for achieving desired formulation characteristics. Ionic, nonionic, and insoluble polymers have been used in HPMC matrices as blends or as film or compression coating to successfully modulate the release profile of various drugs. The addition of ionic polymers may not only modify the drug release profile but also allow micro-environmental pH control of the gel layer, which may enhance solubility or stability of drugs.

The use of polymer blends for controlled drug delivery systems can offer major advantages, including: (i) Fabrication of desired drug release, mechanical properties and drug release mechanisms, (ii) improved matrix formation and on storage stability, and (iii) the possibility to develop novel strategies for site specific drug delivery within the gastro intestinal tract (e.g., colon targeting).

Multiple factors affect drug release from hydrophilic polymeric matrix

1. Drug
- Molecular weight
- Solubility
- Drug particle size
- Drug Dose
2. Polymer
- Molecular weight
- Polymer Particle Size
- Type of polymer
- Polymer blend
- Substitute of the polymer side chain

- Radius of gyration
- Ionic strength of medium
- Percentage of the polymer
- Intrinsic viscosity
- Dissolution medium
- Dose-dumping effect
- Temperature

3. Formulation

- Amount of water penetrating the matrix
- Characteristics of the tablet : Geometry, other drug, excipients
- Micro environmental pH
- Ait trapped in the matrix
- Resistance of matrix to breakage
- Manufacturing process

HPMC concentrations as low as 10% (w/w) can be used to modulate drug release from matrix tablets, polymer percolation threshold for robust HPMC matrix tablets is a good idea. The percolation threshold for any component (A) in a binary system (e.g. A–B) is defined as the concentration at which "individual isolated clusters" of this component (A) change to "an infinite cluster". In HPMC matrix tablet formulation, below and above this percolation threshold sudden changes in matrix integrity and/or dug release mechanism can be observed. It has been reported that the HPMC concentration has an effect on the robustness of formulation, and should be more than 30% (w/w) in matrix tablets to eliminate the effect of small variations in manufacturing method or raw material. Even viscosity deviation within the same viscosity grade and polymer chemistry in raw materials can drastically contributes drug release from erosion based HPMC (100 cP) matrix tablets. HPMC percolation threshold for controlled release application was found to be between 30 and 35% (w/w) for HPMC (100 cP) in HPMC–mannitol matrix tablets. Robust tablet performance above percolation threshold is observed, whereas disintegration was observed below this polymer concentration under stressed conditions. The low viscosity HPMC grades (50 cP and 100 cP) in combination with water-soluble generates consistent erosion controlled systems for water-insoluble drugs. Recommendations on minimum HPMC concentration for robust matrix tablets are supported by in-vitro observations. However, mostly the results obtained from in-

vitro studies cannot be directly correlated to the in-vivo environment due to in-consistency in the physiological conditions of the GI tract experienced by controlled release formulations. Evaluation of erosion and disintegration properties of tablet of this type in in-vivo, with HPMC content at 20 and 40% (w/w), representing values above and below the proposed percolation threshold is key parameter.

2.1.1 Mechanism of Drug Release from Hydrophilic Matrices

Controlled drug release from hydrophilic matrix systems is achieved through rapid hydration of the polymer (e.g., HPMC) on the outer tablet surface to form a gelatinous layer. This rapid formation of a gelatinous layer is important for retaining structural & functional behaviour, prevent water to the interior of the matrix, and inhibit disintegration of the tablet. Once the protective gel layer is created, it controls the water progress in the gel layer and further entrance into the tablet. Therefore, hydrophilic polymers are usually supplied in small particle size (CR Grade) range to ensure rapid and consistent hydration of the polymer. As the outer gel layer fully hydrates, the polymer disentangles from the surface, which is continuously replaced with the hydrated polymer from within the core to control drug release. HPMC and polyethylene oxide are well known for their rapid hydration and gel formation. The release of drug from a hydrophilic matrix system relies on swelling of the matrix, dissolution of the drug, and diffusion and erosion properties of the gel layer. The solubility and dose of the drug, type and quantity of fillers, and the polymer influence the mechanism of drug release. The release behaviour from an insoluble inert matrix can be mathematically expressed by the following equation:

$$\frac{dM}{dh} = C_0 dh - \left(\frac{C_s}{2}\right) \quad \text{.....(1)}$$

Where, dM is the change in the amount of drug release per unit area and dh denotes the change in the thickness of the zone of matrix of the drug that has depleted. C0 and Cs are the total amount of drug in a unit volume of matrix and saturated concentration of the drug within the matrix, respectively. According to diffusion theory, dM is proportional to the diffusion coefficient (Dm) and Cs; therefore,

$$dM = \left(\frac{C_m C_s}{h}\right) dt \quad \text{.....(2)}$$

Combination and integration of Equations 1 and 2 lead to

$$M = [CsDm(2Co - Cs)t]^{0.5} \quad \text{....(3)}$$

When the amount of drug is in excess of the saturated concentration, Equation 3 can be refined to Eq (4)

$M = (2C_sD_mt)^{0.5}$.....(4)

This equation (4) is known as the Higuchi equation and initially was valid only for planar matrix systems, and later it was modified to consider different geometrical shapes and matrix characteristics including porous structures. It is important to keep in mind that the classical Higuchi equation was derived under pseudo-steady-state assumptions and cannot be applied to real controlled release systems. The final equation shows that if a system is predominantly diffusion controlled, then it is expected that a plot of the drug release against square root of time will result in a straight line. For the purpose of data treatment, the Higuchi equation can be simply written as Eq (5)

$M = kt^{0.5}$.....(5)

where M is the portion of drug released at time t and k is a constant. If the predominant mechanism of drug release from this type of matrix is diffusion controlled, then the drug release can be controlled by varying the factors such as porosity, tortuosity, initial concentration of drug in the matrix, solubility of the drug, and polymer system forming the matrix. Since a hydrophilic matrix structure in an aqueous medium undergoes dynamic alterations due to the polymer hydration and swelling, drug dissolution, diffusion, and erosion, mathematical models describing drug release from these systems are complex. But for simplicity a series of transport phenomena involved in drug release have been reported. Figure 3 -2 summarizes a schematic representation of three situations described in the literature: the swelling, the erosion, and the diffusion.

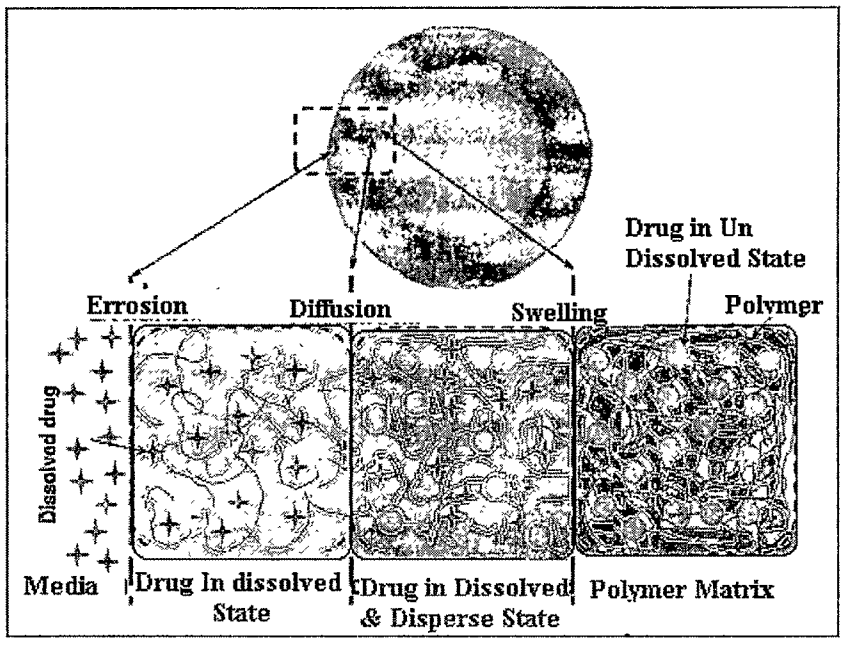

Figure 3- 2 Schematic representation of three situations swelling ,erosion and diffusion

Each situation indicates a change in physical condition from the adjoining front. The swelling separates the rubbery region (gel layer) from the glassy region (dry core) and has absorbed enough water to allow macromolecular mobility and swelling of polymer. Diffusion that separates the areas of undissolved drug from the area of dissolved drug is located between the swelling and erosion. Finally, the erosion is the border between the unstirred gel layer and the well-stirred medium separating the matrix from the bulk solution. A large number of mathematical models have been developed to describe drug release profiles from matrices. The simple and more widely used model is the one derived Eq (6)

$M_t/M_a = kt^n$.....(6)

Where Mt/Ma is the fraction of drug released, k is the diffusion rate constant, t is the release time, and n is the release exponent indicative of the mechanism of drug release. The equation was modified by Ford et al. to account for any lag time l or initial burst release of the drug:

$M_t t/M_a = k(t-1)^n$.....(7)

It is clear from Equations 6 and 7 that when the exponent n takes a value of 1.0, the drug release rate is independent of time. This case corresponds to zero-order release kinetics (also known as case II transport). Here, the polymer relaxation and erosion are the rate-controlling steps. When n¼0.5, Fickian diffusion is the rate-controlling step (case I transport). Values of

n between 0.5 and 1 indicate the contribution of both the diffusion process and polymer relaxation in controlling the release kinetics (non-Fickian, anomalous, or first-order release). It should be noted that the two extreme values of n ¼, 0.5 or 1 are valid only for slab geometry. For cylindrical tablets, these values range from 0.45<n<0.89 for Fickian, anomalous, or case II transport. In order to describe relaxation transport, Peppas and Sahlin modified Equation 7 to account for relaxation transport: Eq (8)

$Q = k_1 t^n + k_2 t^{2n}$ .....(8)

where k_1 and k_2 were Fickian diffusion constant and relaxation mechanism constant, respectively. If the surface area of the system is fixed, which is unlikely, the value of n should be 0.5 and the above equation is transformed to Eq (9):

$Q = k_1 t^{0.5} + k_2 t$ .....(9)

The first term of the equation represents the diffusion phenomenon while the second term accounts for polymer erosion.

2.2 Osmotic Systems

Since pharmaceutical agents can be delivered in a controlled pattern over a long period by osmotic pressure, past two decades have witnessed increasing interest in the development of osmotic systems.

2.2.1 Principle of osmosis

Osmosis is defined as a process in which the solvent molecules move through a semipermeable membrane from a pure solvent to a solution or from a dilute solution to a concentrated solution. Abbe Nollet first reported osmotic effect in 1748, but Pfeffer pioneered the field by quantification of osmotic effect. He measured the pressure in 1877 by utilizing a membrane, which was selectively permeable to water but impermeable to sugar (Fig. 4 -2). A semi-permeable membrane separated sugar solution from pure water allowing entry of water. He observed a movement of water in to the sugar solution that stopped when a pressure (π) applied to the sugar solution, and hence postulated that this pressure, the osmotic pressure (π) of the sugar solution directly proportional to the concentration of solution and absolute temperature.

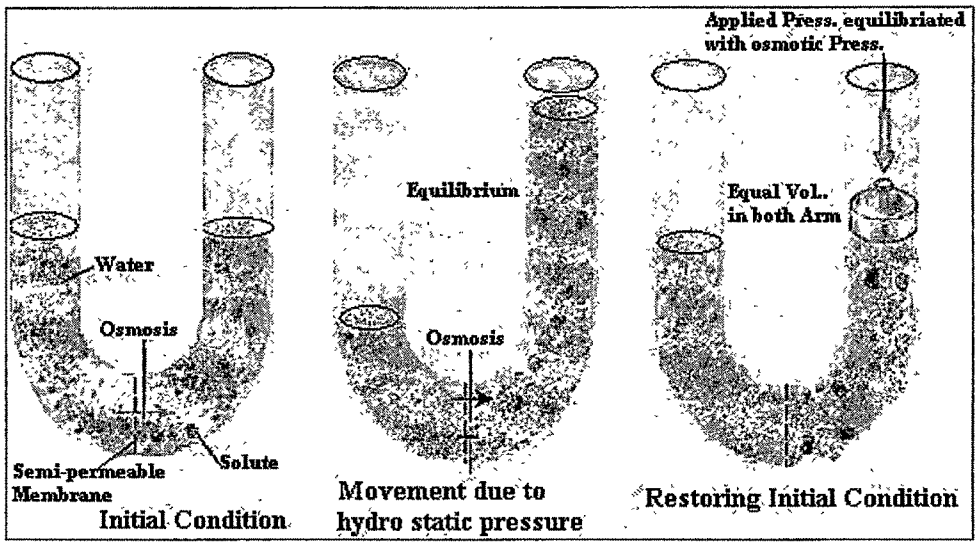

Figure 4 - 2 Osmotic movement and the osmotic equilibrium and osmotic pressure

Van't Hoff established the analogy between the Pfeffer results and the ideal gas laws by the expression, Eq (10)

$\pi V = nRT$ .....(10)

Where,

π - osmotic pressure in atmosphere

V - volume of solutions in liters

n - number of moles of solutes

R - gas constant equal to 0.082 liter atm/mole

T - absolute temperature.

Osmotic pressure can be obtained to a good approximation vapour pressure measurements by using the expression.

$\pi = RT/V \ln (P_0/P)$ .....(11)

Where,

P_0 is the vapour pressure of pure solvent

P is the vapour pressure of the solution

V is the molar volume of the solvent

The osmotic water flow across the membrane is given by,

$d_v/d_t = A\theta\Delta\pi/l$.....(12)

Where,

d_v/d_t - water flow across the membrane area A and thickness l, whose permeability is θ.

$\Delta\pi$ - osmotic pressure difference between the two solutions on either side of the membrane. Osmosis is the phenomenon that makes controlled drug delivery a truth. Osmotic pressure created due to imbibition of fluid from external environment regulates the delivery of drug from the osmotic device. There are various factors that guide of drug delivery like nature of semi-permeable membrane, diameter of delivery orifice, surface area of semipermeable membrane, nature and concentration of osmogen etc.

Pharmaceutical solutes used in osmotic pumps and the osmotic pressures of these saturated solutions are presented in Table 1 - 2 .

Compound	Osmotic pressure (atm)	Compound Mixture 50: 50	Osmotic pressure (atm)
Sodium chloride	356	Lactose- fructose	500
Fructose	355	Dextrose- fructose	450
Potassium chloride	245	Sucrose- fructose	430
Sucrose	150	Mannitol- fructose	415
Dextrose	82	Lactose- sucrose	250
Potassium sulphate	39	Lactose- dextrose	225
Mannitol	138	Mannitol- dextrose	225
Sodium phosphate tribasic	36	Dextrose- sucrose	190
Sodium phosphate dibasic	31	Mannitol- sucrose	170
Sodium phosphate monobasic	28	Mannitol- lactose	130

Table 1 - 2 Osmotic Pressures of Saturated Solutions of Commonly Used Pharmaceutical Solutes

Advantages of osmotic drug delivery systems

Osmotic drug delivery systems for oral and parenteral use offer distinct and practical advantages over other means of delivery.

- Constant (Zero Order) delivery rate is achieved with osmotic systems as shown by in vitro and in vivo experiments.
- Delivery may be delayed or pulsed, as per requirements.
- Drug release is independent of gastric pH and hydrodynamic conditions for orals.
- Fast release is possible with osmotic systems compared with conventional diffusion-controlled drug delivery systems.
- The release rate of osmotic systems is predictable and can be preprogrammed by modulating the release control parameters.
- A high degree of in vivo-in vitro correlation (IVIVC) is obtained in osmotic system.
- The release from osmotic systems is minimally affected by the presence of food in the gastrointestinal tract (GIT).

2.2.2 Types of Osmotic Pump System

2.2.2.1 Asymmetric Membranes

Use of asymmetric membranes in osmotic drug delivery that consist of very thin, dense skin structure supported by a thicker, porous structural layer is also described in the literature. These membranes have high flux characteristics and thus, higher release rates for poorly water-soluble drugs can be obtained. Moreover, the permeability of the membranes to water can be easily adjusted by controlling the membrane structure and porosity. The asymmetric membranes can be applied to tablets, capsules, or multi-particulate formulations.

Herbig and co workers in 1995 developed a new type of membrane coating for osmotic drug delivery which offers significant advantage over the membrane coatings used in conventional osmotic tablets. These new coatings have an asymmetric structure, similar to asymmetric membranes made for reverse osmosis or ultra filtration, in that the coating consists of a porous substrate with a thin outer skin. These asymmetric membrane coatings can be used to make osmotic drug delivery formulations with several unique characteristics. High water fluxes can be achieved, facilitating osmotic delivery of drugs with low solubility and making higher release rates possible. The permeability of the coating to water can be adjusted by controlling the membrane structure, allowing altering release kinetics without any change in coating material or coating thickness. In addition

the porosity of the film can be controlled, minimizing the time lag before drug delivery begins and allowing the drug to be released from a large number of delivery ports. This type of coating has also been applied to capsule and multi particulate formulations.

Lin and Ho formulated asymmetric membrane coated capsules with in-situ formation of delivery orifice. The capsule wall membrane was produced by phase inversion process in which an asymmetric membrane was formed on stainless steel mold pins by dipping the mold pins into a coating solution containing a polymeric material followed by dipping into a quenching solution. Permeability across the asymmetric membrane of the capsule was determined for drugs with water solubility in a moderate to high range. Poorly soluble drug could not generate enough osmotic pressure to activate drug release. Solubilization either by the addition of solubility enhancer, SLS, or by a solid dispersion with HPMC could increase the solubility of nifedipine to a sufficient extent to activate drug release. Synergistic action of both HPMC and SLS increased the solubility of nifedipine resulting in release from the system.

Osmotic pumps and solubility of drugs

Osmotic pumps are well known for delivering drugs at a constant rate. Formulation of both highly water soluble and highly water insoluble drugs are not suitable candidates for osmotic drug delivery. The kinetics of osmotic drug release is directly related to the solubility of the drug within the core. Assuming a tablet core of pure drug, the fraction of core released with zero-order kinetics is given by the following equation (Eq.13),

$$F(z) = 1 - S\rho \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots (13)$$

Where $F(z)$ is the fraction released by zero-order kinetics, S is the drug's solubility (g/ cm^3), and ρ is the density (g / cm^3) of the core tablet. Drugs with a solubility of ≤ 0.05 g/ cm^3 would be released with $\geq 95\%$ zero-order kinetics. Hence a solubiliser for the drug can be included in the core formulation in case of water insoluble drugs. It is also possible that the drug is very highly soluble and the water flux is too great to provide sustained release. In this case, the core can include a component that suppresses the solubility of the active agent.

Some of the approaches used to deliver drugs having extremes of solubility in the literature:

Co-compression of drug with excipients:

Incorporation of excipients that modulate the solubility of drug within the core can be one approach to control the release of drugs from the osmotic systems. McClelland et al. and Zentner et al. reported CPOP of a highly water-soluble drug, diltiazem hydrochloride (solubility more than 590 mg/ml at 37.7°C). Because of very high water-solubility, the majority of the drug fraction was released predominantly at a first-order rather than the desired zero-order rate. The solubility of diltiazem hydrochloride was reduced to 155 mg/ml by incorporation of sodium chloride (at 1 M concentration) into the core tablet formulation. The modification resulted in more than 75% of the drug to be released by zero-order kinetics over a 14–16-h period.

Controlled porosity solubility modulated osmotic pumps for delivery of drugs having low water solubility are described in US Patents. The composition described consists of controlled release solubility modulating agents, which are either surfactants (e.g. sodium dodecyl sulfate) or complexing agents (e.g. sodium salicylate). In order to prolong the availability of these excipients within the device, they were either surrounded by a rate controlling membrane or dispersed in a matrix. In the examples, tablet cores of two different drugs, namely, simvastatin and lovastatin, along with the solubility modulating agents were prepared and coated with a microporous membrane. The release of drug from the systems was controlled for an extended period of 4–24 h.

Prabakaran with his co worker formulated elementary osmotic pump for diltiazem hydrochloride. The drug candidate selected shows higher aqueous solubility, and hence is an unfit candidate for the formulation of elementary osmotic pumps. To control the solubility of the drug in the core various hydrophilic polymers (HPMC & NaCMC) were incorporated and the otherwise fast dissolving core was altered to release the drug for the prolonged period. Ingredients of the system were optimized for parameters like drug polymer ratio and amount of osmogent, for the desired release pattern. The coated tablets were drilled mechanically in the centre of each pump. The aperture diameter and coating thickness were measured microscopically using empty shells obtained after complete dissolution of the contents. Different dissolution models were applied to drug release data in order to establish release mechanism and kinetics. Criteria for selecting the most appropriate model were based on best goodness of fit and smallest sum of squared residuals.

Use of encapsulated excipients

Thombre and co-workers described a capsule device coated with asymmetric membranes to deliver drugs having poor water-solubility. In the examples, solubility of a poorly water-soluble drug, glipizide, was improved by incorporation of encapsulated excipients (pH-controlling excipients) within the capsule device. The solubility modifier (meglumine), in the form of mini-tablets, was coated with a rate controlling membrane to prolong its availability within the core. Thus, the solubility of glipizide was improved leading to its prolonged release from the device.

Use of swellable polymers

Swellable polymers can be utilized for osmotic delivery of drugs having poor aqueous solubility. Examples using this approach are reported in US Patent by Khanna for carbamazepine, theophylline, acetylsalicylic acid, and nifedipine. The formulation mainly consists of a compartment, containing the drug, swelling agents, and osmogents, coated with a rate controlling membrane. Vinylpyrrolidone / vinyl acetate copolymer (Kollidon VA 64, BASF) and polyethylene oxide (MW: 53 10 , Polyox -coagulant, Union Carbide) were used as swelling agents. Uniform rate of swelling of these polymers ensures that the drug is released at a relatively constant rate. Also, the pressure produced during swelling does not lead to rupture of the system.

Sastry and his co worker prepared and evaluated an optimized, osmotically controlled formulation of atenolol. Preparation involved the fabrication of biconvex, bilayered tablets containing drug, an osmotic agent and other additives. Studies on the screening of several variables have revealed that orifice size, coating level and the amount of carbopol have pronounced effects on the in vitro release kinetics of atenolol. For formulation optimization a three factor, three level Box-Behnken design was employed with independent variables of orifice size, coating level and the amount of carbopol. The response variables was cumulative per cent of atenolol released with constrains of time for certain percentage release. Preparation of optimized formulations showed a good correlation between predicted and observed values

Use of effervescent mixtures

Use of effervescent mixture, can be another approach to deliver poorly water-soluble drugs from osmotic dosage forms. After administration, the effervescent mixture containing the drug is delivered under pressure through the delivery orifice in the membrane. This method

of enhancing release of poorly water-soluble drug is reported in US Patent assigned to Theeuwes. In one of the examples, citric acid and sodium bicarbonate were used as the effervescent couple for the delivery of acetyl salicylic acid. The formulation imbibes aqueous fluids across the membrane causing the couple to generate an effervescent solution that dispenses the drug in a suspension form.

Use of Cyclodextrin derivatives

Incorporation of the cyclodextrin–drug complex has also been used as an approach for delivery of poorly water-soluble drugs from the osmotic systems. A CPOP has been described for testosterone (having a solubility of 0.039 mg/ml at 37 °C), solubility of which was improved to 76.5 mg/ml through complexation with sulfobutyl ether-β-cyclo dextrin sodium salt. In a comparative study with hydroxypropyl-β-cyclodextrin (HP-β-CD) and a sugar mixture, it was found that testosterone release from the device in the presence of sulfobutyl ether-β-cyclo dextrin sodium salt was mainly due to osmotic pumping while for HP-β-CD, the major contribution was due to diffusion. In case of the sugar mixture, the drug was poorly released due to the absence of solubilizer. Similar results were obtained with prednisolone and chlorpromazine. It was reported that sulfobutyl ether-β-cyclo dextrin sodium salt could serve both as a solubilizer and osmotic agent.

Okimoto defined membrane controlling factors responsible for drug release from a controlled porosity osmotic pump tablet that utilizes a sulfobutyl ether-β-cyclodextrin, as both a solubilizing and osmotic agent. Chlorpromazine was used as a model drug. The core tablets were coated with cellulose acetate solutions varying the amount and size of micronized lactose, the amount of triethyl citrate and composition ratio of dichloromethane to ethanol. The membrane surface area of the coated tablet was measured with multi point analysis by the gas absorption method. The release rate of drug from osmotic pumps increased with increasing amounts of micronized lactose and decreasing amount of TEC and lactose particle size in the membrane. Also, release rates from the formulations using mixtures of varying ratios of dichloromethane to ethanol were almost identical.

Modulation of resin

Release of a highly water-soluble drug, diltiazem hydrochloride from a CPOP was modulated effectively using positively charged anion-exchange resin, poly (4-vinyl pyridine) Zentner and co-workers. Pentaerythritol was used as osmotic agent and citric and adipic acids were added to maintain a low core pH to assure that both the drug and resin

carry a positive charge. The solubility of diltiazem hydrochloride was reduced for an extended period and pH-independent zero-order release was obtained.

Using alternative salt form

For an ionic drug, an alternative salt form can also be used as reported for metoprolol and oxprenolol. Hydrochloride salt used in commercial formulations of oxprenolol was found to have high water solubility (70% w/v) making it difficult to achieve extended zero-order delivery from osmotic systems. The authors replaced it by the less soluble succinate salt. In case of metoprolol, they used fumarate salt form as drug and osmotic driving agent, instead of tartrate salt. These salt forms were found to have optimum solubility and provided extended release up to 24 h.

Using crystal habit modifiers

If the drug exists in more than one crystal form, each having different aqueous solubility, it is beneficial to include a crystal modifying agents. One such example is reported in US Patent inventor Koparkar and Shah, 1994, wherein a slightly soluble drug, carbamazepine, along with crystal modifying agents (combination of hydroxymethyl cellulose and hydroxyethyl cellulose) and other excipients was formulated in the form of osmotic pumps that were able to provide approximately zero-order release for the desired period of time.

Use of lyotropic crystals

Use of lyotropic liquid crystals, to assist osmotic delivery of poorly water soluble drugs, is also reported in the literature (Curatolo, 1989 and 1992). The lyotropic liquid crystals are non-polymeric compounds, generally in the molecular weight range of 200–1500. Also known as amphipathic compounds, these form mesophases and swell in presence of water. Compounds that can be used as lyotropic liquid crystals include natural phosphatides such as phosphatidyl- choline (lecithin), phosphatidyl ethanolamine, phosphatidylserine, phosphatidylglycerol, and the like. Few examples using this approach are mentioned in US Patent no. 5,108,756 and 5,030,452. In these examples, Alcolec lecithin (American Lecithin Co., Atlanta, GA) and mixture of soybean phospholipids was utilized for osmotic delivery of two insoluble drugs, namely, glipizide and prazosin. The inventors claimed that the extended drug release up to 24 h was achieved.

Use of wicking agents

Inclusion of wicking agents in the osmotic formulations has also been reported as an approach for poorly water-soluble drugs. A wicking agent is dispersed throughout the composition that enhances the contact surface area of drug with the incoming aqueous

fluids. Thus, the drug is released predominantly in a soluble form through the delivery orifice in the membrane. The authors delivered nifedipine using this approach and some of the reported wicking agents are colloidal silicon dioxide, PVP, sodium lauryl sulfate, etc.

2.2.2.2 Elementary osmotic pump (EOP)

The concept of osmotic delivery through elementary osmotic pump (EOP) was first introduced by Theeuwes . The EOP consists of an osmotic core with the drug, surrounded by a semipermeable membrane with a delivery orifice. Figure 5 -2 shows schematic diagram of elementary osmotic pump (EOP), which in its simplest design, consists of an osmotic core (containing drug with or without an osmogent) coated with a semipermeable membrane.

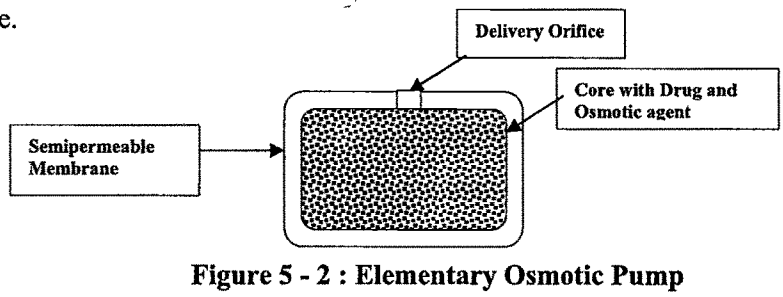

Figure 5 - 2 : Elementary Osmotic Pump

The device in fact represents a coated tablet with a hole and may be ultimate simplification of the original Rose-Nelson pump, when this coated tablet is exposed to an aqueous environment the osmotic pressure of the soluble drug inside the tablet draws water through the semipermeable coating resulting in the formation of a saturated aqueous solution inside the device. The membrane is non-extensible and the increase in volume due to imbibition of water raises the hydrostatic pressure inside the tablet, eventually leading to flow of saturated solution of active agent out of the device through small orifice.

The dosage form, after coming in contact with the aqueous fluids, imbibes water at a rate determined by the fluid permeability of the membrane and osmotic pressure of core formulation. This osmotic imbibition of water results in formation of a saturated solution of drug within the core, which is dispensed at a controlled rate from the delivery orifice in the membrane. Though 60–80% of drug is released at a constant rate from EOP, a lag time of 30–60 min is observed in most of the cases as the system hydrates before zero-order delivery from the system begins. These systems are suitable for delivery of drugs having moderate water solubility.

Solubility of drug in water plays a critical role in functioning of osmotic pump. Typically the solubility of drug delivered by these pumps are at least 10 to 15% w/w, example of drugs with this property are sodium indomethacin, potassium chloride, metoprolol and acetazolamide

Elementary osmotic pump for Indomethacin is reported in detail in a literature (Theeuwes 1982) that explains the determination of theoretical release rate of Indomethacin elementary osmotic pumps. Using that concept, delivery of any agent in solution form from the elementary osmotic pump can be achieved at a rate proportional to the solubility of the agent inside the system (Sd) and the osmotic pressure of the formulation inside the system (π_t). Given a tablet size with surface area (A), and given the membrane permeability and thickness, the desired rate can be obtained by incorporating into the core formulation substances that affect either Sd or π_t. Such a formulation can be called as the composite core.

Delivery of potent agents may require the incorporation of formulating agents to permit fabrication of a system of acceptable size (these agents are also added during the formulation of conventional tablets). If these agents are water soluble, system performance can be predicted from the knowledge of certain parameters and the theoretical considerations. The zero order release rate of drug, $(dm_d/dt)_z$, from such a system, assuming a negligible osmotic pressure of the environmental fluid, is then given by,

$$Z = \left(\frac{dm_d}{dt}\right)_z = K \frac{A}{h} \pi_t \quad \text{.....(13)}$$

Where,

K - osmotic permeability coefficient of the membrane,

A - membrane area and h is the membrane thickness. The zero order rate will persist from time t=0 to $t=t_z$, at which time the solids, drug and osmotic agent have gone into solution. The non-zero order rate will decline parabolically as a function of time.

The above equation provides a convenient way of calculating the membrane permeability (k) for a set of systems with the same release rate. Alternatively for systems with different membrane thickness and release rates, the slope of the line of the release rate versus the inverse of the membrane thickness provides a means of calculating the membrane

permeability. Consequently, the release rate can be expressed as a function of membrane weight (w), since this weight is related to membrane thickness.

$w = \rho_m Ah$. .....(14)

Where ρ_m is the membrane density, and by substituting above equation to the first equation,

$$Zd = K \frac{A^2}{w} \rho_m \pi_t S_d \text{.....(15)}$$

The membrane permeability, therefore, can be obtained from the slope of the line Z_d versus 1/w.

The final equation indicates the parameters to which the average zero order release rate will be sensitive. These parameters are, membrane permeability (k), tablet core surface are (A), membrane weight (W), density (ρ_m), total osmotic pressure (π_t) and drug solubility (S_d). When a composite composition is chosen, π_t and S_d become fixed for the zero-order release period. The fixed composition also determines the total surface area (A) of the tablet core. When the membrane is chosen and applied reproducibility, values for K and π_m are fixed. Therefore, when testing is conducted at a constant temperature, the average zero order release rate should be a function of the weight of the membrane applied.

Alza is the leading pharmaceutical concern which developed the elementary osmotic pump under the trade name OROS®, for oral controlled release. The first elementary osmotic pump that hit international market was Osmosin® (controlled release Indomethacin).

PRODUCTS INCORPORATING ALZA'S OROS® TECHNOLOGY INCLUDE

- Alpress™ LP (prazosin) once-daily extended-release tablet sold in France for the treatment of hypertension.
- Cardura® XL (doxazosin mesylate) sold in Germany for the treatment of hypertension.
- Concerta® (methylphenidate hydrochloride) CII once-daily extended-release tablet for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) in patients age six and older.
- Covera-HS® (verapamil) a Controlled Onset Extended Release (COER-24™) system for the management of hypertension and angina pectoris.

- Ditropan XL® (oxybutynin chloride) extended-release tablet for the once-a-day treatment of overactive bladder characterized by symptoms of urge urinary incontinence, urgency and frequency.
- DynaCirc CR® (isradipine) once-daily, extended-release tablet for the treatment of hypertension.
- Efidac 24® (chlorpheniramine) over-the-counter, extended-release tablet providing 24-hour relief from allergy symptoms and nasal congestion.
- Glucotrol XL® (glipizide) extended-release tablet used as an adjunct to diet for the control of hyperglycemia in patients with non-insulin-dependent diabetes.
- Sudafed® 24 Hour (pseudoephedrine) over-the-counter nasal decongestant for 24-hour relief of colds, sinusitis, hay fever and other respiratory allergies.
- Procardia XL® (nifedipine) extended-release tablet for the treatment of angina and hypertension.
- Volmax® (albuterol) extended-release tablet for relief of bronchospasm in patients with reversible obstructive airway disease.

In the OROS tablets, semipermeable membrane coating of the device must be 200-300 microns thick to withstand the pressure generated within the device. These thick coverings however, lower the water permeation rate, particularly for moderately water-soluble drugs. In general it could be predicted that these thick coating devices are suitable for highly water-soluble drugs. The delivery rate attained with moderately soluble drugs is generally low, even with the most water permeable membrane also. The above problem can be resolved by utilizing a coating material having very high water permeability, such as addition of plasticizers and a water-soluble additive to the cellulose acetate membranes which increased the permeability of latter up to tenfold. (Theeuwes and Ayer, 1978).

The second approach of Theeuwes involves the multi layer composite coating around the tablet (Figure 6 - 2). The first layer is made up of thick microporous film that provides the strength required to withstand the internal pressure, while second layer is composed of thin semi permeable membrane that produces the osmotic flux. The support layer is formed by including the coating of the tablets with a layer of cellulose acetate containing 40 to 60% of pore forming agent such as sorbitol.

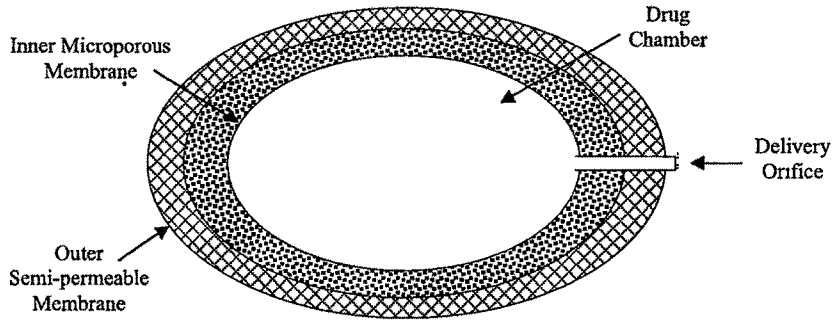

Figure 6 - 2 Composite membrane coating to deliver moderately soluble drugs

Another modification includes the addition of a carbonate or bicarbonate salt to the drug chamber, which eventually leads to effervescence when exposed to water due to formation of carbon dioxide at stomach pH.

The simple elementary osmotic pump suffers from the disadvantage that it can only deliver relatively soluble drugs, which are capable of developing an osmotic pressure greater than physiological fluids. Incorporation of water-soluble compound into the tablet formulation such as, sodium chloride, sucrose, fructose or other common tableting aids can be used, which serves as osmotic attractants and overcomes this limitation.

Several coated tablet have been reported by Zentner et al, 1985 in which the drug escapes, following leaching of water soluble components, such as lactose or polyethylene glycol from the coating material. Once the tablet has been swallowed, water-soluble component dissolves in external fluid, resulting in initiation of pumping system.

Shokri et al., 2008 designed a new type of elementary osmotic pump (EOP) tablet for efficient delivery of poorly water-soluble/practically insoluble drugs. The drug release

profile from osmotic devices showed that the type of polymer in the core formulation could markedly affect the drug release. The results also demonstrated that aperture size is a critical parameter and should be optimized for each swellable EOP system. This study also revealed that optimization of semipermeable membrane thickness is very important for approaching zero order kinetics.

2.2.2.3 Push–pull osmotic pump (PPOP)

Push–pull osmotic pump (PPOP) can be used for delivery of drugs having extremes of water solubility. As shown in Figure 7 - 2, it is a bilayer tablet coated with a semipermeable membrane. Drug along with osmogen is present in the upper compartment whereas lower compartment consists of polymeric osmotic agents Swanson et al., 1987, Wong et al., 1986. The drug compartment is connected to the outside environment via a delivery orifice. After coming in contact with the aqueous environment, polymeric osmotic layer swells and pushes the drug layer, thereby delivering the drug in the form of a fine dispersion via the orifice by Grundy in 1996.

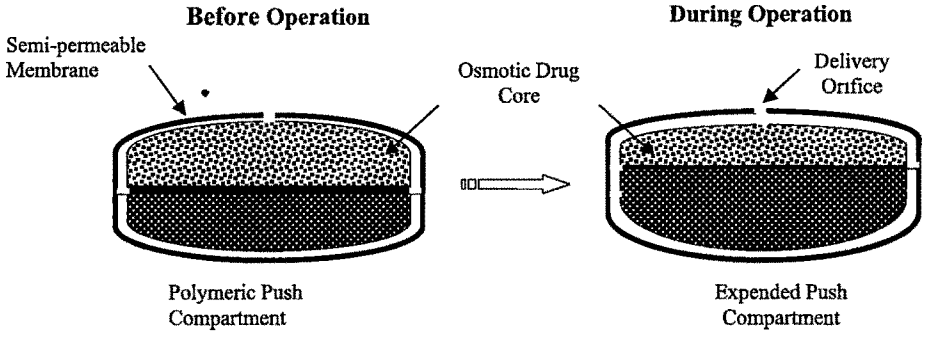

Figure 7 - 2 Drug delivery process from two-chamber osmotic tablet

Pumps with two chambers separated by an elastic or movable barrier are particularly interesting and valuable because they allow delivery of drugs with limited solubility. This class of osmotic pump can further be classified into two groups, one with internal film that moves from a rest to an expanded state leading to change in volume of chamber. The second group has fixed volume chamber communicating through opening provided in between.

Swanson et al. (1987) formulated a dosage form based on the gastrointestinal therapeutic system (GITS) push pull osmotic pump configuration in three strengths with different drug delivery rates(mg/hour) per dose (mg), as 1.7/30, 3.4/60, and 5.1/90. The delivery rates of drug from these systems are controlled by drug loading, composition of osmotic components, membrane properties, and dimensions. The release rates were independent of pH in the range from gastric pH 1.2 to intestinal pH 7.5. *In vitro* release studies were carried out at different stirring rates (50, 100, 150 rpm). The release rates are independent of stirring rate and therefore unlikely to be influenced by motility in the gastrointestinal tract. The in-vivo release tests in dogs were found to be equal to the release rate in-vitro. Nifedipine GITS dosage forms were administered to human subjects, absorption rates, calculated from resulting plasma concentrations, indicate that the cumulative amount of drug absorbed in humans over 24 hours is proportional to the amounts of drug delivered in-vitro. Plasma concentrations are therefore predictable and remain relatively constant for 24 hour dosing interval. Weight of drug layer, weight of push layer, membrane thickness, and membrane permeability along with the delivery rates was reported. Comparison of in-vitro and in-vivo cumulative amount released was shown.

Among the successful approaches incorporation of finely dispersed drug in hydrogel present a most valuable alternative. Many of the useful hydrogel polymers are ionic materials such as sodium carboxy methylcellulose, which contains ionizable groups, which provide most of the osmotic pressure required to draw water through the semipermeable membrane. These polymers possess dual property of being compressed in dry conditions and become fluid gels, which are easily extrudable through the small delivery hole in hydrated conditions. A number of modifications are available for this type of system such as delayed push–pull system (as used in Covera HS, extended release formulation for verapamil), multi-layer push–pull system (for pulsatile or delayed drug delivery), and push–stick system (for delivery of insoluble drugs requiring high loading, with an optional delayed, patterned, or pulsatile release profile)

2.2.2.4 Controlled porosity osmotic pumps (CPOP)

CPOP contain water-soluble additives in the coating membrane, which after coming in contact with water, dissolve resulting in an in situ formation of a microporous membrane (Fig. 8). The resulting membrane is substantially permeable to both water and dissolved

solutes and the mechanism of drug release from these systems was found to be primarily

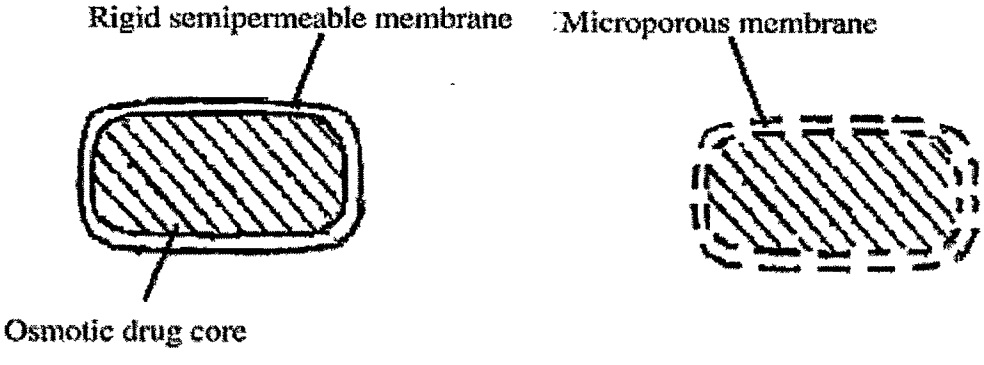

Figure 8 - 2 Cross- sectional diagram of L–OROS delivery system before and during operation

osmotic, with simple diffusion playing a minor role by Zentner et al., 1985.

Zentner et al., (1985a) developed a controlled porosity osmotic pump of cyclobenzaprine hydrochloride. The coating solution applied to the core was Cellulose Acetate-398-30: sorbitol : polyethylene glycol 400 (10 : 7.5 : 1 by parts) dissolved in dichloromethane:methanol:water.

Verma et al., (2003) developed extended release formulations of isosorbide mononitrate based on osmotic technology. Formulation variables like type (PVP, PEG 4000 & HPMC) and level of pore former, per cent weight gain were found to affect the drug release from the developed formulations. Drug release was inversely proportional to the membrane weight but directly related to the initial level of pore former in the membrane. Burst strength of the exhausted shells was inversely proportional to the level of pore former, but directly affected by the membrane weight. The release from the developed formulations was independent of pH and agitation intensity, but depended on the osmotic pressure of the release media. Results of SEM studies showed the formation of pores in the membrane from where the drug release occurred.

Gondaliya and Pundarikakshudu in 2003 developed a controlled porosity osmotic pump of diltiazem hydrochloride. *In vitro* dissolution studies of tablets were conducted in osmotically active media. The external osmotic pressure was maintained at higher levels than the osmotic pressure generated inside the tablet. The drug release rate was tested in a

2.4% (by weight) magnesium sulfate solution (6 atm pressure) and water (0 atm pressure). An *in vitro* release rate was found to be 2.2 mg/h in a magnesium sulfate solution, although in water it was found 10.6 mg/h. In the magnesium sulfate solution, the drug release rate was mainly attributed only to diffusion through the membrane, although in water, the drug release rate was mainly attributed to diffusion and osmosis. High *in vitro* drug release was mainly attributed to osmotic pressure generated inside the osmotic tablets. In an osmotically active medium, the osmosis phenomenon is stopped. These results were further confirmed by performing in *vitro* drug release study by changing the medium instead of the method. An *in vitro* drug release study was conducted for 0- 4 h in water (0 atm pressure) followed by 4- 8 h in a 2.4% (by weight) magnesium sulfate solution (~6 atm pressure) followed by 8- 12 h in water. The results showed a significant difference in the release rate in different media. From these results, one may conclude that the drug release from the tablets was mainly caused by diffusion in an osmotically active medium. *In vitro* release was carried out in a USP type II dissolution test apparatus at 100 rpm. Operating condition was 900 ml of distilled water at 37°C. Coating membrane was composed of cellulose acetate as film forming polymer, glycerol as pore forming agent and dibutylpthalate as a plasticizer. An equal portion of isopropyl alcohol and acetone was used as a coating solvent.

Verma and Garg developed controlled porosity osmotic pump of glipizide. To assure a reliable performance of this formulation independent of pH, release studies were conducted according to pH change method. The release media was simulated gastric fluid (SGF, pH 1.2) for first 2 h, acetate buffer (pH 4.5) for next 2 h, followed by SIF (pH 6.8) for the remaining period of 24 h. In order to study the effect of agitational intensity of the release media, release studies of the formulation were carried out in dissolution apparatus at various rotational speeds using USP-I dissolution apparatus (rotating basket) at 50, 100, and 150 rpm. In another experiment, stirred and stagnant conditions were induced in a single run using USP-I apparatus. The rotational speed was kept at 100 rpm (stirred conditions), which was stopped intermittently to induce the stagnant conditions. The protocol used was stirred conditions for first 3 h (0–3 h), stagnant conditions for next 2 h (3–5 h), stirred condition for next 3 h (5–8 h), and stagnant condition for next 2 h (8–10 h). In order to confirm the mechanism of drug release, release studies of the formulation were conducted in media of different osmotic pressure. To increase the osmotic pressure of the release media, sodium chloride (osmotically effective solute) was added in SIF and the pH

was adjusted to 6.8 ± 0.05. Release studies were carried out in 1000 ml of media using USP-I dissolution apparatus (100 rpm). Release from the formulation was inversely proportional to the osmotic pressure of the release media, conforming osmotic pumping to be the major mechanism of drug release.

Reported in-vitro evaluation of osmotic system in literature

Rani et al., in 2003 developed an elementary osmotic pump for diclofenac sodium. To study the effect of pH, dissolution was carried out in USP II apparatus in different release media (pH 7.4, pH 6.8, and distilled water) maintained at 37 + 0.2 °C and 100 rpm which resulted in a non-significant difference in release. To study the effect of agitation intensity, in vitro studies were performed at 50 rpm, 100 rpm, and under static conditions. Under static conditions, samples were taken at different times after uniform mixing of the media. Studies under stirred and static conditions exhibited no significant difference in the rate and extent of release. In vitro studies were done using a USP 24 dissolution apparatus II at 100 rpm.

Zentner developed a controlled porosity osmotic pump of potassium chloride. To study the effect of pH of release media on drug release, release study was conducted in deionized water and various other aqueous receptor media at 37 °C. Experiments at pH 5, 7.4, and 8 were conducted in 0.07 M Sorensen's phosphate buffer. Studies at pH 1 were in 0.1 N hydrochloric acid. Wherever required, pH adjusted media were made iso-osmotic to normal saline by adding sodium chloride. The following patterns of stirring were employed in the release studies, 100 rpm continuously and 100 rpm interrupted with a 2 hour period of no stirring at the midpoint of the steady state release profiles. The effects of receptor media osmotic pressure on potassium chloride release were studied in 1.64, 3.42, 7.06, and 11.63 molar aqueous solutions of urea at 25 °C. Coating solution composed of cellulose acetate, sorbitol and PEG 400 as film forming polymer, pore forming agent, and plasticizer, respectively. Solvent was a quaternary mixture of dichloromethane, methanol, water, and polyethylene glycol 400 mixed 150: 100: 10: 1 by weight respectively, as dictated by the solubility of the solid components that were incorporated.

Makhija and Vavia in 2003 developed a controlled porosity osmotic pump of pseudoephedrine. As a proof of an osmotically controlled release system, (delivers its contents independent of external variables) the *in vitro* release studies were conducted in buffers of different pH, i.e., pH 1.2 buffer, pH 4.5 phosphate buffer and pH 7.2 phosphate buffer as well as in distilled water. The system exhibits a media independent release. Thus, the fluid in different parts of the GI tract will scarcely affect drug release from the osmotic system. The *in vitro* release from the coated tablets was studied using USP dissolution apparatus type I at 100 rpm. The dissolution medium used was 500 ml of phosphate buffer of pH 7.2. The tablets were coated with cellulose acetate as semipermeable film forming polymer containing different channeling agent viz. diethylphthalate, dibutylpthalate, dibutylsebacate, and polyethylene glycol 400. Talc and titanium dioxide were used as antiadherant and opacifier respectively. Acetone: isopropyl alcohol (80:20) was used as a coating solvent.

Verma and Garg 2004 developed controlled porosity osmotic pump of glipizide. The *in vitro* release was carried out in a USP type 1 dissolution apparatus at 100 rpm. Dissolution medium was simulated intestinal fluid (SIF, pH 6.8, 1000 ml) maintained at 37 $\pm$ 0.5°C. Coating membranes was consisting of cellulose acetate as film forming polymer. PVP was used as a water-soluble component. PEG 400 and triacetin were used as a water-soluble and water insoluble plasticizer respectively. Dichloromethane:methanol (3:1) were used as a coating solvent.

Garg et. al., in 2007 studied the effect of formulation parameters on the release characteristics of propranolol from asymmetric membrane coated tablets. A zero order release of propranolol was obtained from the coated tablets of propranolol. The release was independent of the pH and the rate of agitation of the dissolution medium ($p > 0.05$). Asymmetric membranes could be successfully utilized in the controlled delivery of highly water soluble drugs like propranolol and by modifying preparation parameters like polymer concentration, pore former concentration and temperature of the precipitation bath, desired release rates can be obtained.

RESEARCH ENVISAGED The aim of present research was to design and optimize the Extended release drug delivery systems for water soluble drug Butorphanol Tartrate and low water soluble drug Lornoxicam.

- Controlled Porosity Osmotic System (CPOP) – Butorphanol tartrate
- Extended release matrix Tablet (ER) - Lornoxicam

CPOP

The aim of the current study was to design a controlled porosity osmotic system (CPOP) see figure 9 – 2 based drug delivery system for controlled release of highly water soluble drug, Butorphanol Tartrate.

The current study is also focused on the effect of concentration of pore formers, Sorbitol, and PEG-400. Controlled porosity osmotic pumps (CPOP), contain water-soluble additives in the coating membrane, which after coming in contact with water, dissolve resulting in an in situ formation of a microporous membrane. The resulting membrane is substantially permeable to both water and dissolved solutes and the mechanism of drug release from these systems was found to be primarily osmotic, with simple diffusion playing a minor role .

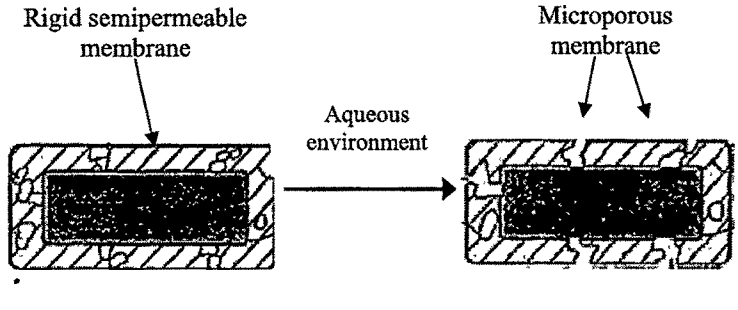

Figure 9– 2 Release mechanism from a CPOP

The mechanisms by which drug release is controlled in CPOP are dependent on many variables. One of the principles of drug release would be osmotic pressure. It is possible that one can modulate the release profile of the water soluble, sparingly soluble and poorly soluble active agents.

Matrix

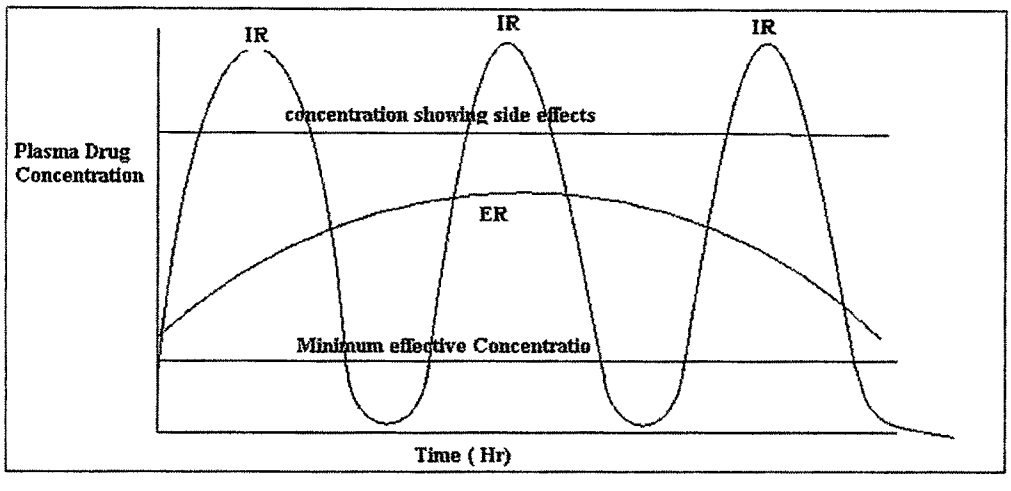

Figure 10 - 2 Simulation of ER plasma concentration versus time profile based on IR formulation PK

The release of drug in vivo can be analyzed by de-convolution of the plasma concentrations from the CR formulations with release profiles. A common approach for de-convolution is to use an orally administered immediate release formulation as a reference, which then allows one to calculate a unit impulse function from IR Formulation to obtain the input rate for the CR dosage form. Once the in vivo release profiles of the CR dosage forms are obtained, correlation of in vivo release profiles & corresponding in vitro release profiles can be established as point-to-point Level A correlation.

PK simulation employing PK principles to predict CR dosage form is an important element of CR feasibility assessment. Simulation of CR oral dosage forms requires altering the dose and release rate in an attempt to maintain selected plasma concentrations within a desired dosing interval. Initial CR formulation development, PK simulation is performed to assess if a specific drug is a candidate for CR formulation and whether it is possible to alter the release rate and dose to achieve that goal. So, plasma concentrations following administration of various CR dosage forms can be simulated if the PK data from an IR dosage form are available Figure 10 - 2.

However, simulation is conducted by employing PK principle & it encompasses biopharmaceutic properties of the drug, for example, solubility and permeability, and allows modelling of drug input rates, small and large intestinal transit time variations, and position-dependent absorption rates. The drug colonic absorption potential can be revealed

from the simulation. By inputting the in vitro dissolution profile and drug PK parameters, projected performance of a CR formulation represented by a simulated plasma concentration profile can be illustrated. If information on colonic permeability or absorption is not available, simulations can be carried out assuming low, medium, and high colonic absorption to predict the performance.

In totality, the projected performance of a CR formulation (single-dose or steady state PK) can be simulated. Simulation is conducted based on the physicochemical, biopharmaceutic, and/or PK properties of the drug. The results of simulations reveal the projected performance of a CR formulation and indicate the dose range and release rates that are reasonable to meet the clinical target.

PLAN OF WORK

1. Preformulation studies of

i. Butorphanol tartrate

ii. Lornoxicam

2. Controlled Porosity Osmotic System (CPOP)

i. Prediction of extended release profile from immediate release profile.

ii. Target drug release profile

iii. Selection of formulation

iv. Optimization of core and coating components

v. *In-vitro* drug release

vi. *Characterization studies*

3. Hydrophilic Matrix System

vii. Target drug release profile

viii. Selection of formulation

ix. Optimization of core components

x. *In-vitro* drug release

xi. *Characterization studies*

4. Performance evaluation of optimized formulations

i. Effect of pH

ii. Effect of agitational intensity

iii. Effect of osmotic pressure

iv. Scanning electron microscopy

6. *In vivo* studies

7. Stability studies

8. Compilation, analysis and interpretation of results

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