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REVIEW ARTICLE

HYDROPHILIC MATRIX TABLETS AS ORAL CONTROLLED DRUG DELIVERY SYSTEMS IN 20TH CENTURY: A REVIEW

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Abstract

Matrix systems are easy to formulate compared to other controlled release dosage forms. The manufacture of matrix tablets involves the direct compression of blend of drug, retardant material and additives to form a tablet in which drug is embedded in a matrix core of the retardant. Alternatively, retardant-drug blends may be granulated prior to compression. Of the three classes of retardant material used to formulate matrix tablets, polymers that form hydrophilic matrices are attracting the attention of pharmaceutical technologists. These polymers include Methyl cellulose (MC), Hydroxy ethyl cellulose (HEC), Hydroxy popyl methyl cellulose (HPMC), Sodium carboxy methyl cellulose (NaCMC), carbomers, chitosan, plant gums etc. The hydrophilic matrix-formers alone or in combination with other excipients form gels in situ on coming in contact with biological fluids which control the drug release. The present review gives a detailed account on the factors to be considered in the design of hydrophilic matrix systems, formulation of hydrophilic matrix tablets, in vitro and in vivo evaluation methods and advances in the design of hydrophilic matrix tablets. This review further focuses on the development of oral controlled drug delivery systems using hydrophilic matrix carriers in 20th century.

Introduction:-

Considerable attention has been focussed on the development of controlled release drug delivery systems which are capable of delivering a drug at some predetermined rate either systemically or locally for a specified period of time. The primary objectives of controlled drug delivery are to ensure safety and to improve efficacy of drugs as well as patient compliance. For controlled release dosage forms, the oral route of administration has by far received the most attention because there is more flexibility in dosage form design for oral route than other routes. It is relatively safe route of administration, and patient acceptance is quite high.

Among the various methods used to control the release of drugs from a pharmaceutical dosage form, the matrix system is the most frequently applied; it is a release system for delay and control of the release of a drug that is dissolved or dispersed in a resistant support to disintegration[1]. The formulation of the drugs in gelatinous capsules or, more frequently, in tablets, using hydrophilic polymers with high gelling capacities as base excipients, is of particular interest in the field of controlled release. Their safe forms justify the focus on hydrophilic matrix tablets in recent years and their inherent advantages of the entire controlled release dosage over other systems are as follows:

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1. With proper control of the manufacturing process, reproducible release profiles are possible. The variability associated with them is lower than that obtained with coated release forms[2,3].
2. There is an immediate release of a small amount of the drug but there is no risk of dumping a large part of the dose[4].
3. They have large capacity to incorporate drugs, which allow them to release large doses.
4. The preparation processes are very simple. The matrix tablets can be made by direct compression or through conventional dry or wet granulation methods[2,5].
5. Availability of inexpensive excipients approved by drug control administration[5].

Factors influencing the design of oral hydrophilic matrix tablets:

Design and development of hydrophilic matrix tablets for oral controlled drug delivery involves the optimization of the dosage form characteristics relative to GI environment. There are a variety of both physicochemical and biological factors that come into play in the design of oral hydrophilic matrix systems. The physico-chemical properties of the drug include aqueous solubility, pK_a, partition coefficient, drug stability, molecular size and diffusivity, and protein binding. The biological factors include the pharmacokinetics of the drug such as absorption, distribution, metabolism and elimination. The dose size, side effects and safety considerations are the other factors of importance.

Physicochemical properties

Aqueous solubility and pK_a:

Two of the most important physicochemical properties of a drug that influence its absorptive behaviour are its aqueous solubility and if it is a weak acid or base, its pK_a. These properties play an influential role in the performance of sustained release systems. The aqueous solubility of a drug influences its dissolution rate, which in turn establishes its concentration in solution and hence the driving force for diffusion across membranes. The parameter, pK_a, allows to determine the un-ionized form of a drug and, together with the partition coefficient, helps in predicting the absorption.

Partition coefficient:

A major criterion in evaluation of the ability of a drug to penetrate the lipid membranes of GI tract is its apparent oil/water partition coefficient. There is an optimum partition coefficient for a drug at which it most effectively permeates membranes and thus shows the greatest activity.

Drug stability:

With oral dosage forms the loss of drug occurs through acid hydrolysis or metabolism in the GI tract. For drugs that are unstable in the stomach, the most appropriate sustaining unit would be one that releases its contents only in the intestine. The reverse is the case for those drugs that are unstable in the environment of the intestine. However, most sustained release systems currently in use release their contents over the entire length of the GI tract. Thus, drugs with significant stability problems in any particular area of the GI tract are less suitable for formulation into sustained release systems that deliver their contents uniformly over the length of the GI tract.

Protein binding:

Protein binding characteristics of a drug can play a significant role in its therapeutic effect, regardless of the type of dosage form. Extensive binding to plasma proteins will be evidenced by a long half-life of elimination for the drug and such drugs generally do not require a sustained release dosage form. However, drugs that exhibit a high degree of binding to plasma proteins might also bind to biopolymers in the GI tract, which could have an influence on sustained drug delivery. The presence of a hydrophobic moiety on the drug molecule also increases its binding potential.

Molecular size and diffusivity:

In addition to diffusion through the biological membranes, drugs in many sustained release systems must diffuse through a polymeric membrane or matrix that is used to control their release kinetics. The ability of a drug to diffuse through polymeric membranes is a function of its diffusivity. An important influence upon the value of the diffusivity in polymers is the molecular size of the diffusing species. High molecular weight drugs or polymeric drugs should be expected to display very slow release kinetics in sustained release devices utilizing diffusion through polymeric membranes or matrices as the releasing mechanism. Drugs with molecular weights greater than 500-700 have a lower diffusion coefficient that make their use in controlled release dosage forms difficult[6].

Biological Factors

Absorption:

The rate, extent and uniformity of drug absorption are important when considering its formulation into a sustained release system. Since the rate-limiting step in drug delivery from a sustained release system is the release from the dosage form rather than absorption, a rapid rate of absorption of the drug relative to its release is essential if the system is to be successful[6]. It is difficult to formulate slowly absorbed drugs into sustained release systems.

Distribution:

The distribution of a drug into vascular and extra-vascular spaces in the body is an important factor in its overall elimination kinetics. This in-turn influences the formulation of that drug into a sustained release system, primarily by restricting the magnitude of the release rate and the dose size that can be employed. Two parameters that are used to describe the distribution characteristics of a drug are its apparent volume of distribution and the ratio of drug concentration in tissue to that in plasma at steady state, the so called, T/P ratio.

Metabolism:

The metabolic conversion of a drug to another chemical form can usually be considered in the design of a sustained release system for that drug. As long as the location, rate and extent of metabolism are known, and the rate constants for the processes are not too large, successful sustained release products can be developed. There are two factor associated with the metabolism of some drugs that present problems for their use in sustained release systems. One such factor is the ability of the drug to induce or inhibit enzyme synthesis; this may result in a fluctuating drug blood level, the other is fluctuating drug blood level, due to intestinal or hepatic first-pass effect.

Elimination half-life:

A drug with a short half-life requires frequent dosing and this makes it a desirable candidate for a sustained release formulation. On the other hand, a drug with a long half-life is dosed at greater time intervals and thus there is less need for a sustained release system. In general, drug with half-life less than 2 h is not a candidate for sustained drug delivery since it demands unacceptably large release rates and large doses. At the other extreme a drug with a half-life of greater than 8 h should also probably not be used: in most instances, formulation of such a drug into a sustained release system is unnecessary.

Side effects and safety considerations:

For some drugs, the incidence of the side effects, in addition to toxicity is related to their plasma concentration. A sustained release system can, at times, minimize side effects for a particular drug by controlling its plasma concentration and utilizing less total drug over the time course of therapy. The most widely used measure of the margin of safety of a drug is its Therapeutic Index (TI). In general, the larger the value of TI, the safer the drug. Drugs with very small values of TI are usually poor candidates for formulation into sustained release products.

Dose Size:

Since a sustained release system is designed to alleviate repetitive dosing, it will naturally contain a greater amount of drug than the corresponding conventional form. The typical administered dose of a drug in the conventional dosage form will give some indication of the total amount needed in the sustained release preparation. For the oral route the volume of the product is limited by patient acceptance.

Formulation Of Hydrophilic Matrix Tablets:

To formulate a successful hydrophilic matrix system, one must select a polymer that wets and hydrates to form a gelatinous layer fast enough to protect the interior of the table from dissolving and disintegrating during the initial wetting and hydration phase. If polymer is hydrated too slow, gastric fluids may penetrate to tablet core, dissolve the drug and allow it to diffuse out prematurely. Another result of inadequate polymer hydration speed can be premature dissolving of the excipient in the matrix. This can cause tablet to disintegrate. Thus, the successful formulation of a hydrophilic matrix tablet depends not only on the physico-chemical properties and pharmacokinetics of the drug, but also depends on several other factors as detailed below.

Selection of the polymer:

Various factors governing the selection of polymers for matrix system include type of polymers, particle size of polymer, substituent group on polymer and degree of cross linking, mode of addition of polymers, viscosity of polymer, degree of swelling, method of polymerisation, and hydrogel porosity. It also involves a careful

consideration on the possible interaction of the polymer with the drug and other additives. The polymers used in the preparation of hydrophilic matrices are divided into three broad groups:

Cellulose derivatives:
Methyl cellulose (MC) 400 and 4000 cps; hydroxyl ethyl cellulose (HEC); hydroxyl propyl methyl cellulose (HPMC) 25, 100, 4,000 and 15,000 cps; and sodium carboxy methyl cellulose (NaCMC).

Non-cellulose natural or semi-synthetic polymers:
Agar-Agar; carob gum; alginates; molasses; polysaccharides of mannose and galactose; chitosan; and modified starches.

Polymers of acrylic acid:
Carbomers such as carbopol 934p, carbopol 971p, carbopol 974p. Of all the above polymers, cellulose ethers are perhaps the most often used. HPMC (Methocel^{R}) is most widely used in the design of matrix tablets and other types of controlled release pharmaceutical dosage forms[7]. The variety of HPMC depends on viscosity and proportion between its substituents. The characteristics features of HPMC are non-toxicity, capacity to incorporate drugs, manufacture of matrix tablets by direct compression without previous granulation, and non-pH dependence[8-11].

Polymer hydration is important to study the hydration/swelling process for the maximum number of polymers and polymeric combinations. The more important steps in polymer dissolution include absorption/adsorption of water in more accessible places, rupture of polymer-polymer linking with the simultaneous forming of water-polymer linking, separation of polymeric chains, swelling, and finally dispersion of polymeric chain in dissolution medium.

The Methocel K polymer, because of its low content in methoxyl groups, hydrates quickly which justifies its application in controlled release kinetics[12]. Several studies on HPMC matrix hydration were conducted by Alderman[5], Karrali and Catalano[13] and Rajabi-siahboomi et al[14, 15]. The results obtained by Rajabi-siahboomi et al showed that larger-sized fractions of HPMC hydrated more rapidly than smaller fractions, which contraindicated the results of Alderman[5]. On the other hand, it was demonstrated that this factor is only important when the matrix has a low HPMC content[16]. Again, the data contraindicated the supposition of Alderman[5] that coarser fractions hydrate more slowly; after 60 min, however, both samples imbibed the same amount of water. The first minutes of hydration are the most important, because they correspond to the time when the protective gel coat is formed around matrices containing HPMC[17].

In accordance with Joshi and Wilson[18], the water influences the stability, rheological behaviour, and transport properties of many polymers. It was verified that misoprostol stability in HPMC matrices is affected by the polymer-water interaction[13]. In areas with low relative humidity, the increase of content in water and HPMC plastification leads to growing of degradation rate of misoprostol.

The swelling of HPMC can be one of the parameters that influence and control the drug release, because it exhibits an inverse relationship between the HPMC constant rate swelling and constant rate dissolution by Higuchi's equation[19]. In a matrix, the presence of a drug promotes the alteration of the pathway as the water binds to the cellulose ether[20,21]. The thermal analysis shows a variation promoted by water distribution in HPMC gels, in the presence of propranolol hydrochloride[22].

The composition of polymer is another important factor that determines its selection in the design of hydrophilic matrix tablets. In case of cellulose ethers, several reactions are possible. As hydroxyl groups, they can be reacted covalently with many species, both mono- and poly-functional, in order to stabilize and insolubilize their structure. The intermolecular reactions include: formation of acetals with monofunctional aldehydes, formation of hemiacetals or acetals with dialdehydes, formation of ether or methylene links with reagents containing methylol groups, and formation of ether links with epoxides, ethylene imine derivatives, solfones and labile chlorine compounds. Under very dilute solutions, some of these reactions may proceed intramolecularily[23].

Dahl et al[24] evaluated the influence of methoxyl/hydroxyl propyl ratio in HPMC on the drug release rate. It was observed that in matrices obtained by granulation, the drug dissolution rate was directly proportional to hydroxyl propyl content, and good results were obtained when HPMC had a content greater than 7.5%. The modifications

observed by alteration of particle size, proportion of methoxyl/hydroxyl propyl substituents, and relative humidity of the HPMC powders were evaluated, and it was concluded that the two last studied fractions have significant effect[25].

The polymer viscosity plays an important role in the formulation of hydrophilic matrix tablets. With cellulose ether polymers, viscosity is used as an indication of matrix weight[26]. Increasing the molecular weight or viscosity of the polymer in a matrix formulation increases the gel layer viscosity and thus slows drug dissolution. Also, the greater the viscosity of the gel, the more resistant the gel is to dilution and erosion, thus controlling the drug dissolution[5,27]. In accordance with Avan and Brossard[28], the viscosity of the gelling agent slows or speeds the initial process of hydration (without altering the release rate). Vazquez et al[29] demonstrated that the decreasing of the matrix viscosity makes the drug diffusion easier.

The possibility of polymer interaction with the drug is another important factor that determines the selection of the polymer. Studies applying differential scanning calorimetry (DSC) and dissolution tests showed that diclofenac sodium substantially reduces the thermal gelation of HPMC, and that the matrices cannot actuate[30,31]. The thermal analyte of cellulose ether polymers demonstrated that the drug-polymer interaction occurs at hydrated gel layer around the matrix tablet and is partially responsible for the drug release modulation[32].

The additives incorporated in the hydrophilic matrix tablets are likely to interact with the polymer. Thus, the polymer/additive interaction is an important factor that influences the selection of the polymer. The obtainment of technologically acceptable formulations requires, in addition to the drug and the gelling agent, the presence of other excipients, in particular, diluents and lubricants whose presence can markedly affect release. The role accomplished by the incorporation of additives has been studied. It is important to note that the presence of tensioactive agents in HPMC matrices leads to the decrease of the drug release with the influence of pH medium (because the alteration of ionic state of drug or tensioactive agent can change this behaviour). The mechanism for the decrease of drug release is the ionic interaction between drug and tensioactive agent. It leads to the formation of a complex having low solubility, as is verified by the HPMC matrix erosion mechanism[33]. Ford et al[34] evaluated the incorporation of additives on drug release rate. Studies by the same authors[35] noted the influence of anionic tensioactive agents on the release of propranolol hydrochloride from HPMC matrices, and concluded that the drug release occurred more slowly.

Abrahamsson et al[36] demonstrated that the choice of solubilizer must be carefully evaluated because of the possibility of interactions between the solubilizer and the release rate controlling excipients of the dosage form. Another work was performed by Lapidus and Lordi[37], applying diluents (soluble or insoluble) to verify that their addition in large amounts, leads to a different drug release rate. Ponumsuk et al[38] evaluated the lactose influence and concluded that this additive does not affect the swelling mechanism, but generally interferes with the drug, which was confirmed by Gao et al[39]. Mandal[40] evaluated the influence of binders on indomethacin release rate from HPMC matrices and verified that these additives change the degree of swelling and the ease with which HPMC constitutes the gelatinous layer, increasing the drug release when the amount of water is increased (derived from drug granulation). The interactions occurring within a hydrophilic matrix can be quite complicated as demonstrated by several described studies. However, each mechanism can be explained and anticipated in the formulation of the matrix through an understanding of polymeric properties.

Polymer/drug proportion:

The proportion of polymer is generally used as a control variable in drug delivery rate. In case of water-soluble drugs, this proportion is calculated from Higuchi's equation[41]. With slightly soluble drugs, that proportion is dependent on gel consistency, since it is affected by gel proportion[2,42,38]. Shah et al[43] advocated the application of the mechanism proposed by Korsmeyer et al[44] to optimize the drug release profiles, previously selecting the concentration of HPMC.

Size, shape and hardness of the tablet:

When the hydrophilic matrix tablets are exposed to the biological fluid, the drug release takes place through the surface of the matrix system. Thus, the release rates obtained with the hydrophilic matrix tablets depend on the size and shape of the tablet. Metoprolol tartrate sustained release tablets were manufactured in 2.8, 7.0 and 10.0 mm diameters[45]. While a sustained release is possible from the 7 and 10 mm diameter tablets formulated on the basis of HPC and NaCMC mixtures, tablets with 2.8 mm diameter do not allow for an adequate control of metoprolol tartrate

release during the gastrointestinal passage. Active ingredient release in the range of up to 80% release and the tablet surface area above a minimum of approximately 300 mm^2 are correlated in a linear manner.

Formulation Excipients:
The excipients used in the preparation of hydrophilic matrix tablets also play an important role in modifying the drug release rate. The release rate of morphine HCl was found increased with the incorporation of lactose in the HPMC matrix tablet[46]. This could be from the high solubility of lactose and its subsequent effect on the matrix tortuosity factor, as lactose dissolves it diffuses outwardly and decreases the tortuosity of the diffusion path of morphine hydrochloride. Various viscosity grades of HPMC matrix tablets containing water-soluble and water-insoluble diluents were studied for the release of propranolol hydrochloride[47]. In vitro release was significantly affected by varying the diluents and their concentrations. Non-Fickian diffusion with first order release kinetics was obtained in all the matrices.

The influence of diluents on the in vitro release characteristics and in vivo efficacy of theophylline from different matrix tablets was studied[48]. Formulations were produced using various concentrations of HPMC in the matrix with calcium phosphate dibasic dehydrate and lactose as the diluents. The formulation containing 20% HPMC and lactose showed a sustained release profile and pharmacodynamics comparable to that of a commercially available sustained release tablet. Matrix tablets of etofylline using HPMC K4M, K15M and K100M polymers were prepared and evaluated for controlled release[49]. The addition of water-soluble and water-insoluble adjuvants was found to modify the release rate.

The influence of tablet excipients such as microcrystalline cellulose (Avicel PH-102), calcium phosphate dibasic dehydrate and lactose on the release pattern of the model drug nafronyl oxalate and the technical characteristics of matrix tablets were investigated using xanthan gum and guar gum as matrix formers[50]. Release rate, crushing strength, friability and weight variation was determined as response parameters, and mathematical models were fitted to the data. An increase in the amount of calcium phosphate dibasic caused lower release rate and increased weight variation. An increase in the content of lactose showed lower strength and increased friability, whereas an increase in the amount of microcrystalline cellulose had the opposite effect.

In Vitro Evaluation:
The formulation of hydrophilic matrix tablets is optimized based on the in vitro drug release studies and the subsequent stability studies. The objective and methodology of these studies are explained below.

In vitro drug release studies:
Drug release testing is required for all modified release dosage forms to predict the desired therapeutic effect. The dissolution medium preferably is de-aerated water or, if substantiated by the solubility characteristics of the drug or the formulation, buffered aqueous solutions (typically pH 4 to 8) or dilute acid (0.001 N to 0.1 N hydrochloric acid) may be used. The usual volume of medium is 500 to 1000 mL, with the use of greater volumes (upto 2000 mL) allowed for drugs having limited solubility. The quantity of medium used should be not less than 3 times that required for forming a saturated solution of the drug substance. The significance of de-aeration of the medium should be determined. The addition of solutes such as surfactants and electrolytes to aid in solubilisation of the drug must be balanced against the loss of the discriminatory power of the test. The use of hydro-alcoholic media is generally not favoured. The use of such media should be supported by a documented in vitro-in vivo correlation.

The choice of apparatus should be based on knowledge of the formulation design and actual dosage form performance in the in vitro test system. Since dissolution apparatus tend to become less discriminating when operated at faster speeds, lower stirring speeds should be evaluated and an appropriate speed chosen in accordance with the test data. The most common operating speeds are 100 rpm for apparatus 1 (basket), and 50 rpm for apparatus 2 (paddle) for evaluating solid oral dosage forms. A 40-mesh screen is used in almost all baskets, but other mesh sizes may be used when the need is documented by supporting data. Apparatus 1 (basket) or apparatus 2 (paddle) may be more useful at higher rotation frequencies (e.g., the paddle at 100 rpm). Apparatus 4 (flow cell) may offer advantages for modified release dosage forms that contain active ingredients having very limited solubility. Apparatus 7 (reciprocating disk) has been shown to have application to non-disintegrating oral modified release dosage forms.

Stability studies:
The purpose of the stability testing is to provide evidence on how the quality of a drug substance or drug product varies with time under the influence of a variety of environmental factors such as temperature, humidity, and light. This study enables recommended storage conditions, retest periods, and shelf lives to be established.

The design for the stability program for the finished product should be based on the knowledge of the behavior and properties of the drug substance and the experience gained from clinical formulation studies and from the stability studies on the drug substance. The length of the studies and the storage conditions should be sufficient to cover storage, shipment, and subsequent use. Heat sensitive drug products should be stored under an alternative lower temperature condition, which will eventually become the designated long-term storage temperature. The designated long term testing conditions will be reflected in the labelling and expiration date. Storage under conditions of high relative humidity applies particularly to solid dosage forms. Accelerated and long term storage conditions and minimum times are as shown in Table No.1.

Table No. 1:- Conditions for stability testing.

Procedure	Conditions		Minimum time period at submission
	Temperature(°C)	Relative Humidity(%)	
Long term testing	25 ± 2	60 ± 5	12 months
Accelerated testing	40 ± 2	75 ± 5	6 months

Where "significant change" occurs due to accelerated testing, additional testing at an intermediate condition, e.g., 30 ± 2°C/60 ± 5% RH should be conducted. "Significant change" at the accelerated condition is defined as:

1. A 5% potency loss from the initial assay value of a batch
2. Any specified degradant exceeding its specification limit
3. The product exceeding its pH limits
4. Dissolution exceeding the specification limits for 12 capsules or tablets
5. Failure to meet specifications for appearance and physical parameters

Should significant change occur at 40°C/75% RH, then a minimum of 6 months data from an ongoing one year study at 30°C/60% RH should be obtained; the same significant change criteria shall then apply. The long-term testing will be continued for a sufficient time beyond 12 months to cover shelf life at appropriate test periods. Then further accumulated data should also be obtained.

The effects of storage humidity on the properties of HPMC based hydrophilic matrix tablets were investigated[51]. Hydrochorothiazide tablets prepared with HPMC of different thickening capacities were stored for 6 months (a) at a relative humidity corresponding to the pre-storage equilibrium moisture content of the HPMC, or (b) at a higher relative humidity. Only tablets stored at the higher humidity showed significant changes in properties, indicating that the observed changes were due to water uptake. All changes were completed within one month of storage. Drug release properties were unaffected, even after 6 months. Effectively identical results were obtained regardless of whether the HPMC variety used had a nominal viscosity of 4,000 cP or 100,000 cP.

Drug Release Kinetics
Theoretically, the controlled drug delivery systems are expected to release a constant amount of drug for a long time, i.e., the drug should be released from the formulation at a zero order rate. When the cumulative amount of drug released in the in vitro drug release studies at different time intervals are plotted, it gives a straight line, the slope of which gives the zero order release rate. However, due to several factors involved in the formulation and preparation, most of the oral hydrophilic matrix systems do not provide a perfect zero order release. Alternatively, the amount of drug to be released from the hydrophilic matrix tablets in the in vitro drug release studies is plotted against the time to yield a straight line, the slope of which gives the first order release rate constant. The hydrophilic matrix tablets are expected to provide a controlled delivery whether the release pattern follows either a zero order or first order kinetics. Depending on the correlation coefficients obtained for each of the above release kinetics, one could predict whether the in vitro drug release from the hydrophilic matrix tablets follows a first order kinetics or zero order kinetics.

Drug Release Mechanism

One of the proposed mechanisms for drug release from hydrophilic matrices implies water penetration in the matrix (with drug dissolution on the surface, causing its immediate release), hydration and swelling of the polymer (with its expansion), diffusion of the dissolved drug, and erosion of gelatinous polymer layer. In accordance with the results of Alderman[5] , the quick formation of gelatinous viscous layer resulting from hydration is considered to be the first essential step for obtention of delivery/release of drug from HPMC matrices (a corroborated phenomenon by Pham and Lee[11]). Papadimitriou et al [52] have verified that drug release from HPMC matrices is affected by swelling method. This phenomenon was evidenced when studies with HPMC matrices were performed exhibiting impermeable coatings on one or both matrix faces and allowing the observation of preferential swelling directions[53]. It was thus demonstrated that the release rate from the matrix decreases with the increase of coating surface. However, the release rate by exposed area stays unalterable and the drug is releases at constant rate by exposed surface, albeit with different kinetics[54].

Drug release from a matrix is controlled by diffusion through the polymeric matrix obeying Fick's law. Each hydrophilic matrix system has a drug release mechanism that is dependent on the pH, the drug, and its own polymeric support. Higuchi's model[55] had successive improvements in the following years, namely, with homogeneous and heterogenous solid matrices[41]. Similarly, Lapidus and Lordi[56] have further modified Higuchi's model, defining the cases where the drugs are soluble or insoluble in water. Developments that followed were presented by Bamba et al[57,58], in which the penetration rate of water was a limitation.

It is important to refer to the model developed by Korsmeyer et al[44] which were verified by Peppas and Franson[59], Peppas[60], peppas and Sahlin[61]. This model relates the drug fractional release with potency time:

$$M_t/ M_\infty = kt^n \quad \text{----- (1)}$$

$$\log [M_t/ M_\infty] = \log k + n \times \log t \quad \text{----- (2)}$$

Where "M_t/ M_∞" is the fractional release of the drug, "t" denotes the release time, "k" represents a constant incorporating structural and geometric characteristics of the release device, and "n" is the time exponent indicative of the release mechanism. If one plots the logarithm of the fractional release versus the logarithm of time, the slope of the graph gives the value of "n". The geometrical pharmaceutical dosage form is important[62,63], especially in this release model where the diffusional exponent has several values in accordance with the geometrical form[2,64]. An analysis of the diffusional drug release using Korsmeyer et al[44] is shown in Table 2. This classification has been successfully used by Ford et al[65] to characterize the release of a number of different drugs from HPMC matrices.

Table No. 2:- Analysis of diffusional drug release from hydrophilic matrix tablets.

Diffusional Exponent (n)	Drug release mechanism
0.5	Fickian diffusion
0.5<n<1.0	Non-Fickian diffusion
1.0	Case II transport
>1.0	Super case II transport

In Vivo Evaluation[66]

In evaluating hydrophilic matrix tablets, a fundamental issue is the type of studies that should be performed to give reasonable assurance of safety and efficacy. While providing important information concerning the release characteristics of the drug from the dosage form, at present in vitro studies are most useful for such purposes as monitoring drug product stability and manufacturing process control. The assessment of safety and efficacy of a hydrophilic matrix tablets is best achieved through observing in vivo pharmacodynamics or pharmacokinetics. Moreover, when there is a well-defined predictive relationship between the plasma concentrations of the drug or active metabolites and the clinical response (therapeutic and adverse), it may be possible to use plasma drug concentration data alone as a basis for the approval of hydrophilic matrix tablets.

The types of pharmacokinetic studies that should be conducted are a function of how much is known about the active drug entity, its clinical pharmacokinetic and biopharmaceutic properties, and whether pharmacokinetic studies are intended to be the sole basis for product approval. As a minimum, (1) a single-dose crossover study for each strength of hydrophilic matrix tablets and (2) a multiple-dose , steady-state study using the highest strength of hydrophilic matrix tablets are required to characterize the product. Some appropriate single-dose crossover and multiple-dose steady-state are described below.

Case A type of study:
Case A type of study applies to the original oral hydrophilic matrix tablet of an active drug entity already marketed in immediate-release form and for which extensive pharmacodynamic/pharmacokinetic data exist.

A single dose crossover study should include the following treatments: the hydrophilic matrix tablets administered under fasting conditions; a dosage form that is rapidly available administered under fasting conditions; and the hydrophilic matrix tablets administered at the same time with a high-fat meal (or any type of meal that has potential for causing maximum perturbation). The study involving food effects should include provision for control of the fluid intake (e.g., 200 to 250 mL) and temperature (e.g., ambient) at the time of drug administration. The dosage form should be administered within 5 minutes after completion of the meal. If there are no significant differences in the rate or extent of bioavailability (AUC, C_{max} and T_{max}) as a function of the meal, then additional food effect studies are not necessary.

If significant differences in bioavailability are found, it is necessary to define how food affects the hydrophilic matrix tablets, as well as how the food-drug effect relates to time. The purpose of these studies is twofold: first, to determine whether there is a need for labelling instructions describing special conditions for administration with respect to meals and second, to provide information concerning the pattern of absorption of the hydrophilic matrix tablets. This will aid in the development of an appropriate in vitro dissolution test. For dosage forms that exhibit high variability, replicate studies are recommended.

Multiple-dose, Steady-state studies
When data demonstrating linear pharmacokinetics exist for an immediate-release dosage form (**Study I)**, a **steady-state study** should be conducted with the hydrophilic matrix tablets at one dose rate using an immediate-release dosage form as a control. At least three trough-plasma drug concentration (C_{min}) determinations should be made to ascertain that steady-state conditions have been achieved. Plasma-drug concentration determinations, over at least one dosing interval of the hydrophilic matrix tablets, should be made in each phase of the crossover study.

It may be preferable to measure concentrations over an entire day in each phase.

The presence or absence of circadian variation should be verified. The hydrophilic matrix tablets should produce an AUC that is equivalent to the immediate release dosage form. The degree of fluctuation for the hydrophilic matrix tablets should be the same as or less than, that for the immediate release dosage form given by the approved regimen. Appropriate concentration measurements should include unchanged drug and major active metabolites.

Where comparisons of the pharmacokinetic properties of an immediate release dosage form at different doses are not available, or where the data show non-linearity (**study II**), **steady-state crossover studies** comparing effects of the hydrophilic matrix tablets with those of the immediate release dosage form should be conducted at two different dose rates: one at the low end of the recommended dosing range and the second at the high end of the dosing range. In each case, the hydrophilic matrix tablets must meet the criteria described in Study I with respect to AUC and fluctuations in plasma drug concentrations. If there are significant differences between the hydrophilic matrix tablets and the immediate release dosage form at either the low or the high dosing rate, these data alone are not adequate to characterize the product.

Data can be misleading when obtained from subjects with atypical drug disposition or physiologic characteristics, relative to the target population. Therefore, subject selection should be randomized or from an appropriate target population. If the hydrophilic matrix tablet is for use in a specific sub-population (e.g., for children), it should be tested in that population. Regardless of whether a drug exhibits linear or nonlinear pharmacokinetics, the basis for characterization is equivalence of AUC and other relative degree of fluctuation of concentrations of the modified release and immediate release dosage forms.

Steady-state studies in selected patient population groups or drug interaction studies may also be necessary, depending upon the therapeutic use of the drug and the types of individuals for whom the hydrophilic matrix tablets will be recommended. For drugs having narrow therapeutic indices, it may be necessary to perform more extensive plasma concentration measurements to determine the potential for unusual drug-release patterns in certain sub-populations. In such studies, it is advisable to perform more than one AUC measurement per patient to assess variability with both the modified release and the immediate release dosage forms.

Case C type of study:
This type of study applies to a generic equivalent of an approved hydrophilic matrix tablets. A generic equivalent of an approved hydrophilic matrix tablets should be bioequivalent to the standard hydrophilic matrix tablets in its rate and extent of availability (AUC, C_{max}, C_{min} and degree of fluctuation) in cross over single dose and steady-state studies. For an oral, hydrophilic matrix tablets, the food studies described under case A type of studies should also be performed.

In Vitro-In Vivo Correlations
The term in vitro-in vivo correlation refers to the establishment of a rational relationship between a biological property, or a parameter derived from a biological property produced by a dosage form, and a physicochemical property or characteristic of the same dosage form. With the proliferation of modified-release products, it becomes necessary to examine the concept of in vitro-in vivo correlation in greater depth. Unlike immediate-release dosage forms, hydrophilic matrix tablets cannot be characterized using a single-time point dissolution test. Furthermore, with a modified-release product a patient is to experience a specific plasma level curve covering a finite time period, usually 12 to 24 hours. There must be some in vitro means of assuring that each batch of the same product will perform identically in vivo. An in vitro-in vivo correlation would satisfy this need.

There are at least three correlation techniques (deconvolution, statistical moment, and single point) available to the pharmaceutical scientist for developing in vitro-in vivo correlation of modified-release products. Of the three correlation levels, Level A correlation is the highest category of correlation representing a point-to-point relationship between in vitro dissolution and the in vivo input rate (in vivo dissolution) of the drug from the dosage form. In such a correlation, the in vitro dissolution and in vivo input rate curves are either directly superimposable or may be made to be superimposable by the use of a constant offset value. The mathematical description for both curves is the same. Such a procedure is most applicable to modified-release systems that demonstrate an in vitro release rate that is essentially independent of the typical dissolution media. With this correlative procedure, a product's in vitro dissolution curve is compared to its in vivo input curve (the curve produced by deconvolution of the plasma level data). This may be done by the use of mass balance model-dependent techniques, such as the Wagner-Nelson procedure or the Loo-Riegelman method, or by model-independent, mathematical deconvolution.

Level B correlation utilizes the principles of statistical moment analysis. The mean in vitro dissolution time is compared to either the mean residence time or the mean in vivo dissolution time. Level B utilizes all of the in vitro and in vivo data but is not considered to be a point-to-point correlation. This is because it does not reflect the actual in vivo plasma level curve, since there are a number of different in vivo curves that will produce similar mean residence time values.

Level C relates one dissolution time point ($t_{50\%}$, $t_{90\%}$, etc.) to one pharmacokinetic parameter such as AUC, C_{max}, or T_{max}. It represents a single point correlation. It does not reflect the complete shape of the plasma level, which is the critical factor that defines the performance of hydrophilic matrix tablets. Since this type of correlation is not predictive of actual in vivo product performance, it is not used in practice for evaluating hydrophilic matrix tablets.

Establishment of Dissolution Specification Ranges
It is relatively easy to establish a multipoint dissolution specification for a hydrophilic matrix tablet. The dissolution behavior of the bio-batch may be used to define the amount to be released at each time point. The difficulty arises in the variation to be allowed around each time point. In the case of Level A correlation, this may be done in two ways, both of which utilize the in vitro-in vivo correlation: convolution and deconvolution.

Convolution:
Reasonable upper and lower dissolution values are selected for each time point established from the bio-batch. Historically, dissolution specifications have been selected by using the average dissolution of the development batches, with a range of ± 2.5 to 3 standard deviations. It is now expected that the average dissolution values are approximately the same as those of the bio-batch. The dissolution curves defined by the upper and lower extremes are convoluted to project the anticipated plasma level curves that would result from administration of these formulations to the same panel to which the bio-batch was administered. If the resulting plasma level data fall within the 95% confidence intervals obtained in the definitive BA-BE study, these ranges can be considered to be acceptable. An alternative acceptance approach that has been suggested is that when the therapeutic window for a drug has been defined, one may establish an upper and lower limit if the convolution results fall within the

therapeutic window, even if they fall outside the confidence interval. If they fall outside the intervals, a more limited range must be established. This should be continued until the predicted values meet the desired ranges.

Deconvolution:
An acceptable set of plasma-level data is established both for a batch of material demonstrating a more rapid release and for one demonstrating a slower release than that of the bio-batch. These may be selected by using the extremes of the 95% confidence intervals or ± 1 standard deviation of the mean plasma level. These curves are then deconvoluted, and the resulting input rate curve is used to establish the upper and lower dissolution specifications at each time point. In the case of Level B and C correlation, batches of product must be made at the proposed upper and lower limits of the dissolution range, and it must be demonstrated that these batches are acceptable by performing a BA-BE study.

A review on the development of the hydrophilic matrix tablets with various carriers
The design of hydrophilic matrix tablets involves the incorporation of a suitable hydrophilic polymer in a particular proportion along with the drug in the tablet. Most of these polymers are cellulose derivatives such as methyl cellulose (MC), hydroxyl ethyl cellulose (HEC), hydroxyl propyl methyl cellulose (HPMC) and sodium carboxy methyl cellulose (NaCMC). Many of the reports involving the development of hydrophilic matrix tablets utilised HPMC as the carrier. However, in the recent times, a good number of studies are being carried on the utility of non-cellulose natural or semi-synthetic polymers as carriers in the design of hydrophilic matrices. Another interesting feature is the utility of a blend of carriers to obtain the required dissolution profile from the hydrophilic matrix systems. The most important reports on the use of both the cellulose and non-cellulose carriers with respect to each of the polymer alone or in combination with other carriers as hydrophilic matrices is cited below.

HPMC:
In oral products, hydroxyl propyl methyl cellulose is primarily used as a tablet binder, in film coating and as an extended release tablet matrix. Concentrations of between 2 – 5 % w/w may be used as a binder in either wet or dry granulation processes. High viscosity grades may be used to retard the release of water-soluble drugs from a matrix. Depending upon the viscosity grade, concentrations between 2-10% w/w are used as film-forming solutions to film-coat tablets. The drug release from the HPMC-based matrices involves the simultaneous absorption of water and desorption of drug release via diffusion and/or erosion controlled mechanisms, depending on the drug solubility type and viscosity of HPMC. This carrier is widely used in pharmaceutical industries because it offers several advantages: simple manufacturing process; cost effective; essentially pH-independent; applicable for a wide range physico-chemical properties of drugs; and available in various types and grades providing a flexibility in modifying the drug release profiles.

Sustained release hydrophilic matrix tablets containing 200 mg of carbamazepine and HPMC (50%) of different viscosity grades, Methocel K 100LV, Methocel K4M, or Methocel K 100M, were prepared, and the influence of HPMC on the crystalline properties of carbamazepine in the gel layer of the hydrated sustained action tablets was studied by Katzhendler et al[67]. The results suggest that HPMC inhibit the transformation of carbamazepine to carbamazepine dehydrate in the gel layer, participates in its crystallization process, and induces amorphism of carbamazepine crystals.

The development of model extended release matrix tablet formulations for metoprolol tartrate (100 mg) sufficiently sensitive to manufacturing variables to serve as the scientific basis for regulatory policy development on scale-up and post approval changes for modified release dosage forms is described by Nellore et al[68]; several grades and levels of HPMC (Methocel K4M; Methocel K15 M; Methocel K100M; Methocel K100LV), fillers and binders were studied as well as 3 granulation processes. Fluid bed granulations were made using various binders and appeared to be satisfactory in terms of flow and tableting performance. At a fixed polymer level, drug release from the higher viscosity grades was slower as compared to the lower viscosity grades. In addition, release from lower viscosity grades was found to be more sensitive to polymer level changes. Increase in polymer level from 10-40% and/or filler change from lactose to calcium phosphate dibasic resulted in about 25-30% decrease in the amount of metoprolol release after 12 h. Results of the study led to the choice of Methocel K100LV as the hydrophilic matrix polymer and fluid bed granulation as the process of choice for further evaluation of critical and non-critical formulation and processing variables.

Hydrophilic matrix tablets for extended oral delivery of zileuton were prepared by wet granulation using low and medium viscosity grades of HPMC. The in vitro drug release from all formulations followed zero-order kinetics and was independent of compression force. In general, the release rate decreased with increasing drug load and higher polymer concentration or viscosity. High shear granulation also resulted in lower release rate. The hydrophilic matrix system effectively controlled the in vitro release of zileuton. It was concluded that matrix tablets with desired release rates could be prepared by adjusting various formulation and processing parameters[69].

Kabanda et al[70] developed a hydrophilic matrix tablet containing 300 mg of propylthiouracil and HPMC K15M, K4M or K100LV and evaluated for in vitro dissolution and in vivo bioavailability in 8 healthy volunteers. The amount dissolved at 8 h from K15M, K4M and K100LV tablets was 40, 51 and 100% respectively. The relative bioavailability was 50, 51 and 87% for the K4M, K15M and K100LV tablets respectively. Gao et al[71] investigated the concentration dependence of drug diffusion coefficients to predict the relative drug release rate in extended release tablets that vary in formulation composition. Extended release adinazolam mesylate tablets and 2 strengths (0.5 mg and 3 mg) of extended release alprazolam tablets were manufactured with variable amounts of HPMC and lactose, and their diffusion rates were evaluated and compared to a mathematical model. Reasonable correlation was obtained between the experimental drug release rate ratios and the predicted drug release rate ratios for the adinazolam. The lower dose alprazolam and extended release alprazolam 0.5 mg tablets exhibited primarily a diffusion controlled release mechanism, while the extended release alprazolam 3 mg tablets deviated from pure diffusion release.

The release of isoniazid, anhydrous caffeine, theophylline, salicylic acid and indomethacin from HPMC matrices was found to follow first order kinetics[72]. The release rate of the drug was influenced by the solubility of the drug, and by the viscosity and the content of HPMC. As the drug solubility increased, the drug release rate also increased and conversely, as the viscosity and / or the content of HPMC increased, the drug release rate decreased. The effect of HPMC on the mechanism of soluble drug release from hydrophilic matrix tablets using captopril and albuterol sulphate as model drugs was investigated[73]. The results confirmed that the drugs were released by non-Fickian diffusion mechanisms. A minimum of 30% HPMC was found to provide controlled delivery of soluble drugs. The different contents of HPMC in the matrices only affected Higuchi release patterns of soluble drugs after about 80% of total drug was released, but did not change the release mechanism.

The HPMC matrix tablet of rantidine hydrochloride was compressed by wet method. The amount and viscosity of HPMC, compressing pressure, tablet size and additives affected the drug release from matrix tablets[74]. The results showed that the release behaviour of tablets followed Higuchi kinetics. A HPMC matrix tablets containing melatonin was formulated as a function of its viscosity, drug loading, type and amount of disintegrant, lubricant and glidant, and aqueous polymeric coating level and was compared with two commercial products[75]. As the HPMC polymer viscosity increased, the release rate had a tendency to decrease. As the drug loadings increased, the release rate slightly decreased. When crospovidone, sodium starch glycollate and croscarmellose sodium, except microcrystalline cellulose, were incorporated in the HPMC matrix tablet, the release rate was markedly increased. There was no significant difference in release profiles when a mixture of lubricants and glidants, except for magnesium stearate alone, was incorporated into low and high-viscosity grade HPMC matrix tablets. As the coating level increased, the release rate gradually decreased, giving an increased lag time.

HPMC matrix tablets containing a poorly soluble drug such as nimodipine were prepared by wet method, and the effect of the viscosity, amount of methoxy and hydroxyl propyl content and particle size of HPMC, additives and pH of release medium on the nimodipine release from the matrix tablets was observed[76]. The matrix tablets release followed approximating to zero order kinetics and the effect of HPMC viscosity, content, particle size and pH of release medium on nimodipine release was significant. The addition of lactose could increase the release rate, and microcrystalline cellulose and sodium lauryl sulphate in the test range affected insignificantly.

HPMC matrix tablets containing pseudoephedrine HCl were manufactured by direct compression technology and investigated the effects of the controlling factors on drug release from a swellable hydrophilic delivery system[77]. It was found that the release rate of the drug decreased with increasing the polymer molecular weight and the polymer content in tablets and was independent of compaction pressure and pH of dissolution fluids. With increasing the concentration of the sodium lauryl sulphate within the matrix, drug release rate decreased.

The sustained release water-insoluble tablets of atenolol were prepared by using the releasing mechanism of the HPMC matrix systems to decrease the fluctuation of plasma concentration and possible side effects of atenolol[78]. The releasing behavior of the tablets followed the Higuchi kinetics, and the Higuchi releasing rate constant (R) was affected by the viscosity of vehicle, the HPMC addition, pH, rotation speed of the basket and the different release methods.

The effect of some formulation variables on the release rate of oxazepam from HPMC has been investigated[79]. The principal factors affecting this parameter were the content and molecular weight of HPMC, and the drug particle size, pH modified the oxazepam solubility; however, the liberation mechanism was not affected. The oxazepam release mechanism from these matrices has been examined. Values of the diffusional exponent 'n' were in the range of 0.61-0.74, indicating that the release of drug was controlled by both diffusion and erosion. When the tablets contained 30% HPMC K100 and the oxazepam particle size was 0.210-0.250 mm, near zero-order kinetics was obtained (n=0.85), indicating that erosion plays an important role in the oxazepam liberation.

Four formulations of controlled release tablets containing 850 mg of metformin hydrochloride were prepared using different amounts of HPMC and stearic acid and the preparations were submitted to dissolution assays[80]. The results showed that the drug delivery was affected by the adjuvants employed, but not by pH variation.

Sodium CMC:
Carboxymethylcellulose sodium is widely used in oral and topical pharmaceutical formulations primarily for its viscosity-increasing properties. Viscous aqueous solutions are used to suspend powders intended for either topical application or oral and parenteral administration. Sodium CMC may also be used as a tablet binder and disintegrant, and to stabilize emulsions. Higher concentrations, usually 4-6% of the medium-viscosity grade is used to produce gels which can be used as the base for applications and pastes.

Three viscosity grades of sodium carboxy methyl cellulose (NaCMC), namely NaCMC (Blanose 7H 4XF), NaCMC (Courlose P 800), NaCMC (Courlose P 350) and HPMC were investigated for their ability to provide a sustained release of propranolol hydrochloride from matrices[81]. The rank order of release rate, in the absence of HPMC, was NaCMC (Blanose)<NaCMC P 800<NaCMC P 350 for matrices containing 95-285 mg NaCMC, and was dependent on their viscosity grades. The effects of changing the ratio of HPMC to NaCMC(Blanose) and the drug/total polymer ratio were examined. The release rates decreased as the proportion of NaCMC in the matrices increased, Zero-order release of propranolol hydrochloride was obtained from matrices containing 285 mg 3:1 NaCMC (Blanose)/HPMC.

Xanthan gum:
Xanthan gum is widely used in oral and topical pharmaceutical formulations, cosmetics, and foods as a suspending and stabilizing agent. It is nontoxic, compatible with most other pharmaceutical ingredients and has good stability and viscosity properties over a wide pH and temperature range. Although primarily used as a suspending agent xanthan gum has also been studied to prepare sustained release matrix tablets.

Matrix tablets containing xanthan gum (XG) as the carrier for controlled delivery using caffeine as a model drug were prepared, the effects of direct and wet granulation, gum concentration, binders, pH, ionic strength, rotation speed and surfactant were examined by Talukdar et al[82]. In aqueous medium, release rate kinetics was almost zero order and in the presence of ions, drug release followed zero and /or square root of time kinetics. Release kinetics was independent of the preparation method and compression force. It was concluded that xanthan gum may be used for the preparation of hydrophilic matrix tablets.

The oral absorption of theophylline anhydrous from two sustained release formulations prepared using the hydrogels, xanthan gum or sodium alginate was investigated in beagle dogs[83]. Both dissolution tests and in vivo studies indicated that the xanthan gum tablet released drug at a constant rate and performed as pH independent zero order controlled release formulation. The matrix tablet containing sodium alginate showed faster release rates in acid medium.

The swelling and drug release behaviour of xanthan gum matrix tablets using three drugs having different properties i.e., caffeine as a soluble neutral drug, indomethacin as an insoluble acidic drug and the sodium salt of indomethacin as a soluble acidic drug were studied in the form of matrix tablets[84]. The mean drug dissolution time and swelling

rate were calculated from dissolution and swelling experiment respectively, and were used as responses for comparison under different experimental conditions. The dependence of drug release on the swelling of the polymer matrix and on the type of the drugs added was established. The ionic strength and buffer concentrations mainly influenced the former. The latter was affected by the solubility of the drug. The mechanism of matrix swelling followed Fickian diffusion whereas drug release from this polymer matrix confirmed non-Fickian diffusion.

Controlled release frusemide matrix tablets were prepared using different polymers, namely: XG, HPMC 4000 and NaCMC at different concentrations[85]. The prepared tablets were subjected to in vitro release studies as well as medium penetration and wet/dry weight determinations to elucidate the overall mechanism of drug release from the matrix tablets. The release rate studies showed that the most drug sustainment was obtained from tablets prepared with 10% of XG, when compared with those prepared with 20% of HPMC 4000, or 60% of NaCMC. The results of medium penetration and wet/dry weight determinations indicated that the highest liquid uptake, medium infiltration and erosion were obtained with NaCMC tablets.

Pectin:
Matrix formulations consisting of pectin with quinidine sulphate, metoclopramide HCl, chlorpheniramine maleate or diclofenac sodium in tablet form by direct compression of physical mixtures and of wet granulation, solvent deposition or coprecipitation systems were evaluated for their possible sustained release properties[86]. For all drugs tested, the dissolution rate was considerably less for tablets prepared with pectin than that of drug alone, and the rate of dissolution was inversely related to the concentration of pectin.

Chitosan:
The drug release behaviour was studied using the chitosan-g-PVA copolymer matrix containing prednisolone in a drug delivery system under various conditions[87]. The relationship between the amount of the drug released and the square root of time was linear. From this the drug release behaviour through the chitosan-g-PVA copolymer matrix is shown to be consistent with Higuchi's diffusion model. The drug release apparent constant (K_H) was slightly decreased at pH 1.2, but increased at pH 7.4 and 10 according to the increasing PVA grafting percent. Also, the value of K_H decreased by heat treatment and crosslinking. The drug release behaviour of the chitosan-g-PVA copolymer matrix could be controlled by the PVA grafting percent, heat treatment, or crosslinking and was also less affected by the pH values than was the chitosan matrix.

Adusumilli et al[88] synthesized, isolated, purified and identified chitosan citrate complexes of several viscosity grades and evaluated the ability of these complexes in sustaining drug release from matrix tablets using a 2 factor 3 level full factorial design with theophylline as the model drug.

The release characteristics of tablets containing matrices of sodium alginate, chitosan and their mixture using propafenone hydrochloride as a model drug[89] were investigated. The matrices containing a mixture of sodium alginate and chitosan were found to provide controlled drug delivery.

The utility of chitosan as an excipient suitable for producing a prolonged release hydrophilic matrix was investigated[90]. Two matrix systems one with chitosan (Q) and the other with the mixture chitosan-alginic acid (alginate) (Q/A), were prepared. The formulation (Q/A) produced a more prolonged drug release than formulation (Q). Formulation B (Q20%), C (Q30%) and D (Q/A10%) showed a Fickian diffusion controlled drug release mechanism. Formulation E (Q/A20%) and F(Q/A30%) showed a non-Fickian diffusion.

The release of glibenclamide from various matrix tablets containing various proportions of chitosan was studied in the form of a matrix tablet[91]. The in vitro and in vivo evaluation showed that matrix tablets containing 6% of chitosan showed controlled drug release with reference to conventional glibenclamide tablet.

Carbomers:
Carbomers are used mainly in liquid or semisolid pharmaceutical formulations as suspending or viscosity-increasing agents. Carbomer grades with a low residual benzene content, such as Carbomer 934P or 974P, may additionally be used in oral preparations, in suspensions, tablets, or sustained release tablet formulations. In tablet formulations, carbomers are used as a binder in either direct compression or wet granulation processes.

Drug release from controlled release matrix tablets of 200 mg of ibuprofen prepared with different concentrations of carbomer 934P (Carbopol 934P) or a mixture of carbomer 934P and carbomer 971P (Carbopol 971P) (1:0.1) was studied[92]. The influence of co-excipients such as lactose, microcrystalline cellulose, starch, magnesium stearate and talc on the release of ibuprofen from matrix tablets prepared with carbomer 934P were studied in phosphate buffer at 37°C. The results showed that the release of ibuprofen from matrix tablets prepared with carbomer 934P was dependent on polymer concentration. Drug release from tablets prepared with a mixture of carbomer 934P and carbomer 971P versus that from tablets prepared with carbomer 934P was more linear at much lower polymer concentrations. All the co-excipients substantially enhanced the release of ibuprofen. The release of ibuprofen from the matrix tablets was described by diffusion and swelling controlled mechanisms.

The potential of carbomer 974P as a carrier in hydrophilic matrix tablets containing ibuprofen was assesed[93]. The influence of matrix concentration and several co-excipients on ibuprofen release rate was also investigated. The in vitro dissolution test showed that drug release from all the formulations containing carbomer 974P was considerably prolonged in a concentration dependent manner. Increasing the amount of carbomer 974P in tablets resulted in a reduction in the drug release rate and a linearization of the drug release curve. All co-excipients enhanced the ibuprofen release rate. Salbutamol sulfate and the carbomer were blended and directly compressed into tablets and in vitro drug release studies were performed[94]. The carbomer by forming a matrix, retarded the release of drug significantly.

Hydrogels are hydrophilic polymers that swell to an equilibrium volume in the presence of water but preserve their shape. The dynamic swelling behaviour of poly(acrylic acid-co-acrylamide) copolymers, at 37°C, was investigated[95]. The release mechanism was non-Fickian. Diffusion coefficients according to Ficks law as a function of concentration of N, N'-methylenebisacrylamide and results on the effects of crosslinked on the release of theophylline were reported.

Carrageenan:

The use of 2 types of K-carrageenan (Gelcarin GP 812 and Gelcarin GP 911) and 1-type of I- carrageenan (Gelcarin GP 379) as potential controlled drug delivery of theophylline was explored[96]. The drug release was dependent on the ability of the carrageenan to form elastic gels and to swell. The theophylline release depended on the extent of swelling.

Guar gum/modified guar gum:

Guar gum (GG) tablet formulations were prepared and evaluated using diltiazem as model drug[97]. Varying the lot of guar gum as well as using guar from different suppliers had little effect on diltiazem dissolution. Also, dissolution of diltiazem from guar gum tablets was essentially independent of stir speed under normal conditions. The stability of guar-based formulations under stressed conditions was also established. All four formulations gave similar plasma concentrations over time in the healthy volunteers.

Hydrolysed guar gum (HGG) hydrophilic matrix for controlled release tablets containing phenyl propanolamine hydrochloride (PPA) as a model drug[98]. The swelling characteristics and dissolution profile from GG/HGG matrices were studied and compared with that from HPMC(K4M). The results suggested controlled hydrolysis produce GG with improved interaction coefficient and dissolution profile. When evaluated for their performance in male healthy male volunteers, the HGG matrix tablets showed comparable results with that of HPMC matrix tablets. A reaction product of guar gum and succinic acid was used for developing modified release tablets of diclofenac sodium[99]. The drug release was best explained by zero-order model.

Modified guar gum was used as a matrixing agent to develop sustained release tablets of diltiazem hydrochloride[100]. Modified guar gum was a combination of guar gum and lactic, citric, or tartaric acid. The lactic acid modified guar gum exhibited improved swelling characteristics at pH 1.2 and 7.0 as compared to that of the untreated guar gum. The kinetics of drug release was explained as per the Korsemeyer and Peppas model. The drug release kinetics for guar gum and methylated guar gum matrices and factors affecting their in vitro release are reported, including the effect of the composition of matrices and the method of tablet preparation, using chlorpheniramine maleate as a model drug[101]. It was concluded that the degree of methylation, composition of matrix, and the method of preparation of matrix tablets are important parameters that influence the formation of an obstructive barrier layer around the tablet and subsequent erosion of gel matrix.

HPMC/ NaCMC/ MC:
A blend of cellulose polymers was evaluated as carriers for controlled delivery of ketorolac tromethamine[102]. When only one polymer (HPMC or NaCMC) was used, the release profiles were of first order or siamoidal in nature respectively. By mixing the drug with an optimum amount of the non-ionic (HPMC or MC) and anionic (NaCMC) polymers, excellent release profiles close to zero order were obtained. The effect of polymer viscosity on the release of salbutamol sulphate from hydrophilic matrices using differing viscosity grades of HPMC and NaCMC alone or blended in various proportions was studied[103]. It was concluded that the release of salbutamol from matrices is dependent on rheological properties of the polymers.

HPMC/ Xanthan gum:
The performance of HPMC and XG as hydrophilic matrix forming agents in respect of compaction characteristics and in vitro drug release behaviour was assessed[104]. The overall compaction characteristics are found to be quite similar to each other and typical of polymer behaviour. But the flow characteristics are different, i.e., XG is more readily flowable than HPMC. The observed difference in drug release profiles between these two potential excipients are explored and explained by the difference in their hydrophilicity and subsequent hydration properties.

HPMC/Carrageenan:
A mixture of carrageenan and HPMC (Methocel K4M) was used as a carrier in the form of a hydrophilic matrix tablet containing chlorpheniramine maleate to obtain pH independent release profiles of the drug[105]. The results confirmed the suitability of carrageenan/ HPMC mixtures for obtaining linear release of chlorpheniramine from hydrophilic matrices.

HPMC/ EC:
Tablets of dextromethorphan hydrobromide were prepared with HPMC, ethyl cellulose (EC) and lactose as sustained release excipients and in vitro dissolving characteristics of the tablets were studied[106]. The results suggested that the releasing rage of sustained release tablets of dextromethorphan hydrobromide could be changed as the amounts of diluents agents or blocking agents were changed.

HPMC/ EC/ Guar gum:
Bhall et al[107] also reported controlled release matrix tablets of Ketoprofen with various release retardants. Ethyl cellulose, guar gum and methocel combination could provide tablets with suitable characteristics and appropriate drug release profile.

Xanthan gum/ n-octenyl succinate starch:
The bioavailability after oral administration of two sustained release ibuprofen formulations using xanthan gum or a 1:1 blend of xanthan gum/ n-octenyl succinate starch (CL490) as hydrophilic matrix has been investigated in healthy human volunteers[108]. In comparison with the conventional suspension, the oral bioavailability was 86.83 ± 25.80% (n=6) and 75.50 ± 17.18% (n=6) for the tablets made with xanthan gum and with a combination of xanthan gum and CL490 (ratio1/1) respectively. The combination of xanthan gum and n-octenyl succinate starch could offer some advantages in the formulation of sustained release hydrophilic matrix tablets.

Advances in the Design Of Hydrophilic Matrix Tablets
Multi layer Matrix Tablets (Geomatrix Systems):
In this novel technology one or both faces of matrix tablets are coated so that water cannot penetrate between the protected surfaces. The delivery system comprises of a core of defined geometrical form containing the drug and polymer substance which swells on contact with aqueous environment and also has gelling properties and some excipients. A barrier is applied to the core to partially cover its surface. The barrier contains hydrophilic polymer substances, plasticizers and possibly other substances with adjuvant function.

The release of the drug can be manipulated by varying the formulation of the different barrier layers and varying the geometry of the device. Using specific barrier formulations it is possible to achieve accurate control over the release of drugs of different solubility. For highly soluble drugs swellable barriers are suitable whereas for sparingly soluble drugs erodible barriers are suitable.

Geomatrix is based on the idea that the restriction of the matrix area exposed to the dissolution medium may lead to a dual control in the system performance- (a) matrix hydration rate and consequent swelling are lowered, (b) the

surface through which the drug can be delivered is reduced. These effects, possibly more effective in the initial phase of the dissolution process and less pronounced as swelling proceeds lead to a linearization of release profile.

The drug release mechanism from the geomatrix tablets involves the following sequence. In the initial phase, barriers applied to the core are able to delay the interaction of the core with the dissolution medium by reducing the surface available for drug release and by limiting the solvent penetration rate. Thus, in this system the burst effect can be controlled and the area available for drug release can be maintained at a relatively constant level during the swelling/ erosion processes. During dissolution, barrier layers are progressively eroded and the surface available for the drug release increases. In this way the decrease of the delivery rate due to an increase of the diffusion path length is compensated by the concurrent increase of the area for drug release. After this main release phase, in the last portion of the dissolution process water can finally reach the core, even under the coating and the matrix can freely swell or dissolve.

Specific Dissolution Profiles with multilayered matrix tablets (Geomatrix tablets):
The multilayer design allows for the production of various tablet designs. Drug charged layers possessing different release properties can achieve specific dissolution profiles such as delayed, pulsatile or biphasic delivery systems.

Biphasic drug delivery system:
The application of an immediate release layer to the Geomatrix system can produce the rapid onset of plasma levels followed by an extended release phase at a constant rate, e.g. Ratiopharm Uno^{R} (Manufactured by M/s. Ratiopharm, Germany) is a Geomatrix tablet containing diclofenac sodium (25 mg for quick release + 125 mg for slow release).

Programmable drug release:
This type of programmable drug release is required for the therapy of those diseases that depend on circadian rhythms. In such a case, Geomatrix system consists of core formulations coated by compression with different barrier layers. Coating prevents drug release from the core until the polymeric shell is completely eroded or swollen. This delay in the start of release is not influenced by the core composition and depends only on the shell formulation. Moreover, except for time lag, the release kinetics of the core is not significantly influenced by erodible barrier.

Sigmoidal release profile:
Depending on the in vivo performance of the drug, it may be necessary to produce delivery systems able to release the drug with a sigmoidal release profile. For this reason, a new tablet design was developed to obtain a slow delivery of drug at the beginning of dissolution process and a faster release rate in the subsequent phase. This could be particularly suitable to treat the morbid symptoms obeying circadian rhythms. Tablet in this case has a thin, lenticular form and consists of two barriers serving the purpose of preventing release of drug from protected surfaces for a programmable range of time.

The advantages of Geomatrix tablets are (i) possibility to avoid completely the “dose dumping” phenomenon, (ii) possibility to administer the dosage form for the treatment of all morbid symptoms of circadian rhythms and for which it is convenient that the drug release begins after a determined range of time from administration (iii) can be produced industrially using already available technology and methods, (iv) allows better control of drug release rates, and (v) with little modification in the matrix tablet it is possible to achieve zero order drug release profiles.

The HPMC matrix tablets containing 150 mg theophylline anhydrous distributed between the matrix coating and the centralized core in ratios of 4/1, 2/1 and 1/1 and release profiles were studied in vitro[109]. Bimodal release was achieved, but the intensity of each release phase depended on the drug content of the core and matrix coating.

Multilayered hydrophilic matrix tablets as constant drug release devices and their effectiveness, reproducibility and technological properties were studied in vitro[110].

The system allowed the release performance of the matrix to modulate in a wide range of variation. A preparative shifting of release kinetics toward constant drug release was achieved by increasing the extent of the surface area coated with the barrier. The barriers appear to be more effective in the control of drug release from swellable matrices.

Mini matrix tablets containing ibuprofen were prepared by wet granulation method[111]. The hydrophilic matrix was formed with either xanthan gum, karaya gum or HPMC together with other additives. Multiple unit dosage forms were subsequently obtained encapsulating the mini matrix tablets into hard gelatine capsules.

Limitations:

The limitations of the hydrophilic matrix tablets are as follows.

1. The presence of relatively large proportion of polymers is likely to increase the possibility of drug-polymer interaction.
2. Though they involve the least manufacturing variables, the influence of manufacturing variables should be studied with respect to the reproducibility of release profiles in the in vitro and in vivo conditions.
3. The release of the drug from the surface of the matrix tablet (burst effect) may be undesirable with certain classes of drugs. However, this could be avoided by using an appropriate design such as a Geomatrix system.
4. The "dose dumping" phenomenon is possible.
5. With the conventional hydrophilic matrix tablets, the pulsatile drug delivery is not possible. However, a proper design of multilayered matrix tablets overcomes this limitation.
6. A perfect zero order release is not possible with conventional hydrophilic matrix tablets.

Conclusion:-

Hydrophilic matrix tablets are gaining importance in the design of oral sustained action dosage forms because of their ease of preparation, low processing variables, use of the existing technology, availability of a wide range of hydrophilic polymers and ability to design tablets with the required dissolution profiles. Of the hydrophilic polymers so far studied for oral sustained drug delivery, hydroxyl propyl methyl cellulose (HPMC) appears to be the most promising and is widely used commercially in the design of sustained action dosage forms. However, in the recent times, a number of other hydrophilic polymers are being investigated as carriers for sustained drug delivery. These include chitosan, plant gums, xanthan gum, modified gums etc. The burst effect is possible with hydrophilic matrix tablets containing highly water soluble drugs. The multilayered matrix tablets are attracting the attention of the pharmaceutical technologist in providing a programmed drug delivery using the conventional methods and facilities. The limitations of these hydrophilic matrix tablets include the incorporation of a relatively large proportion of polymers as release retarding materials that may interact with the active moiety. More studies are required to establish the required dissolution ranges with respect to time during the in vitro drug release studies. The reproducibility of the dissolution profiles both in the in vitro and in vivo on storage needs to be established.

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