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REVIEW ARTICLE

FLOATING DRUG DELIVERY SYSTEMS: RATIONALE FOR DRUG SELECTION.

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Abstract

In recent years scientific and technological advancements have been made in the research and development of rate-controlled oral drug delivery systems by overcoming physiological adversities, such as short gastric residence times (GRT) and unpredictable gastric emptying time (GET). Several approaches are currently utilized in the prolongation of the GRT. In this review, the current technological developments of FDDS including their drug of choice to be formulated and future potential for oral controlled drug delivery are discussed. The main motto of writing this review article is to compile the information regarding the criteria of drug selection for the floating drug delivery system. In this present review various attempt was made for the discussion of the nature of drug to be selected while formulating floating drug delivery system. Numerous properties of the drug and their mechanism of reaction with polymers was compiled for this study. The various properties of drug such as Biopharmaceutical classification system, Solubility in acidic medium, Partition coefficient, Dissociation constant, Half life, Hepatic clearance, Absorption window, First pass metabolism, Acidic stability, Hydrolysis, Crystallinity of drug, Hydrates form of drug, Irritancy of drug, GI motility, Non Emetic are taken into consideration . With contrast to the various properties of drug molecule, their utilization in the floating drug delivery system is point of concern. The various properties and nature of drug tends to produce an eventual and effective drug delivery system, so that one can understand the basic information for formulating floating drug delivery system.

Introduction:-

The basic rationale of controlled release drug delivery system is to optimize the biopharmaceutical, pharmacokinetic and pharmacodynamic properties of a drug administered by the most suitable route to achieve its maximum utility, to control condition within shortest possible time by using smallest quantity of drug. It also provides constant drug level in the blood with reduced dosing frequency and reduced side-effects, thus increasing patient compliance and decreasing adverse drug effects[1]. In this present review, an attempt was made to discuss the different types of physicochemical as well as preformulary criteria for selection of drug before making attempt for formulating floating microsphere. Considerable research has been made for the development of various types of floating drug

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delivery system for the beneficial of human being. But still lack of various factors influencing floating drug delivery system are dominant. This causes serious problem in formulating floating drug delivery system. Many research has been carried out to increase the gastric residence time by formulating floating drug delivery system but without understanding the rationale of drug of choice, it is difficult to formulate the dosage form into floating drug delivery system. Poor absorption of many drugs in the lower gastrointestinal (GI) tract necessitates controlled release dosage forms to be maintained in the upper GI tract, particularly the stomach and upper small intestine[7]. Over two decades ago, many types of gastric retained drug delivery systems were tested to overcome the limited regions and time for drug absorption in the GI tract . Gastric retentive drug delivery systems involves the mechanism of inherent physiology, dosage forms that rely on size , solubility of drug molecule. Various factors involves in the formulation of floating drug delivery system. FDDS is one of the important approaches to achieve gastric retention to obtain sufficient drug bioavailability. This system is desirable for drugs with an absorption window in the stomach or in the upper small intestine. This have a less density then gastric fluids and so remain buoyant in the stomach without affecting gastric emptying rate for a prolonged period and the drug is released slowly as a desired rate from the system. After release of drug, the residual system is emptied from the stomach. This results in an increased GRT and a better control of the fluctuation in plasma drug concentration. The dosage form containing pelletized product can freely disperse in the gastrointestinal tract as a subunit, thus providing the advantage by maximising drug absorption and reducing peak plasma fluctuation. Finally, potential side effects can be minimized without affecting drug bioavailability. It adds another advantage by preventing local irritation derived from high local concentrations of a drug from a single-unit dose, in certain class of drugs. Floating drug delivery system should obey following criteria for formulating it, which are as follows:

Biopharmaceutical classification system (BCS):-

The biopharmaceutical classification system (BCS) is a new concept in the field of pharmaceutical science and technology. This is a valuable tool for the formulation scientists, for the selection and design of the formulation of any drug substance. The recent developments have also enabled us to predict the solubility and permeability characteristics of the drug molecule in the early development stages so that the necessary structural changes can be made to the molecule in order to optimize the pharmacokinetic parameters. The BCS has also got a place in various guidance documents of regulatory importance. This article reviews the criteria for classifying drugs according to the BCS and discusses further potential applications of the BCS, including the developments of new drugs and controlled release product. The BCS is a scientific framework for classifying drug substances based on their aqueous solubility and intestinal permeability. When combined with the dissolution of the drug product, the BCS takes into account three major factors that govern the rate and extent of drug absorption from IR solid oral dosage forms: dissolution, solubility, and intestinal permeability. According to the BCS, drug substances are classified as follows:

Class 1: High Solubility – High Permeability
Class 2: Low Solubility – High Permeability
Class 3: High Solubility – Low Permeability
Class 4: Low Solubility – Low Permeability

The basic importance of BCS is to understand the physical properties of drug molecule before formulating into dosage form. The candidates molecule should have high solubility as well as high permeability for development of floating drug delivery system. Once the solubility and permeability characteristics of a drug are known, the formulation scientist can then, based on BCS, easily decide which drug delivery technology will best help in getting the optimum pharmacokinetic characteristics. The major challenge in the development of drug delivery systems for a class I drug is to achieve a targeted release profile associated with the particular pharmacokinetic and pharmacodynamic properties. Formulation approaches include both the control of release rate and physiochemical Properties. The systems that are developed for class II drugs are based on the micronization, lyophilization, addition of surfactants, formulation as emulsions and microemulsion systems, use of complexing agents like cyclodextrins, and so. Class III drugs are required for technologies that address the fundamental limitations of absolute or regional perm The class IV drugs present a major challenenges in the formulation of novel drug delivery system. Thus BCS classification gives basic knowledge of the drug substance which is to be formulated in the floating drug delivery system.

p*Ka* Value:-

Many potential candidate drugs are weak acids or bases, therefore, one of the most pertinent determinations carried out prior to development is the p*K*a or ionization constant. Strong acids, e.g., HCl, are ionized at all pH values,

whereas the ionization of weak acids is dependent on pH. It is useful to know the extent to which the molecule is ionized at a certain pH, since properties such as solubility, stability, drug absorption and activity are affected by this parameter. The basic theory of the ionization constant is based on the utilities of proton acceptor and proton donor. Fundamental to our appreciation of the determination of this parameter, however, it plays important role in determining the acidity of the drug. The pKa value helps to understand the solubility and absorption of the molecule with a range of value. The pKa value of a substance should be more than 7.5 to show better molecule for floating drug delivery system. If it is in the range of 2.5- 7.5, then also it is treated as good molecule for formulating floating system. The higher the pKa value, the substance is weak acid and vice versa. Similarly the lower the pKa value, the substance is strong acid. So for floating drug delivery system, the molecule should be weak acid so that number of unionized ion is more. If a compound is poorly soluble in water, the p*K*a may be difficult to measure. One way around this problem is to measure the apparent p*K*a of the compound in solvent and water mixtures.

The Partition and Distribution Coefficients:-

The relationship between chemical structure, lipophilicity and its disposition *in vivo* has been matter of concern for formulating floating drug delivery system. It has been shown that many biological phenomena can be correlated with this parameter, such that "quantitative structure activity relationships" (QSARs) may be deduced. These include solubility, absorption potential, membrane permeability, plasma protein binding, volume of distribution and renal and hepatic clearance. The lipophilicity of an organic compound is usually described in terms of a partition coefficient, log *P*, which can be influenced by the concentration of the unionized compound, at equilibrium, between organic and aqueous phases. The role of log *P* in absorption processes occurring after oral administration has been shown effective. Generally, compounds with log *P* values between 1 and 3 show good absorption, whereas those with log *P*s greater than 6 or less than 3 often have poor transport characteristics. Highly non-polar molecules have a preference to reside in the lipophilic regions of membranes, and very polar compounds show poor bioavailability because of their inability to penetrate membrane barriers. Thus, there is a parabolic relationship between log *P* and transport, i.e., candidate drugs that exhibit a balance between these two properties will probably show the best oral bioavailability.

Initial solubility:-

The solubility of a candidate drug may be the critical factor determining its usefulness, since aqueous solubility dictates the amount of compound that will dissolve and, therefore, the amount available for absorption. If a compound has a low aqueous solubility, it may be subject to dissolution rate-limited absorption within the gastro-intestional (GI) residence time. Recently, the importance of solubility, in biopharmaceutical terms, has been highlighted by its use in the biopharmaceutics classification system (BCS) described by Amidon et al. (1995). In this system, compounds are defined in terms of combinations of their solubility and permeability, e.g., high solubility, high permeability or low solubility, high permeability. High solubility is defined as the highest dose strength that is soluble in 250 mL or less of aqueous media across the physiological pH range. Poorly soluble drugs can be defined as those with an aqueous solubility of less than 100 _g/mL. If a drug is poorly soluble, then it will only slowly dissolve, perhaps leading to incomplete absorption (Hörter and Dressman 1997). The importance of solubility (and permeability) in drug discovery and development arenas has also been discussed by Lipinski et al. (1997). If solubility of a compound is accompanied by degradation, the quotation of a solubility figure is problematic. In this case, it is preferable to quote a solubility figure but with the caveat that a specified amount of degradation was found. Obviously, large amounts of degradation will render the solubility value meaningless. A technique to estimate the water solubility of a number of water unstable prodrugs of 5-fluorouracil has been reported by Beall et al. (1993) It is desirable to predict the influence of drug dissolution on oral absorption based on measurements of dissolution or solubility, both before the selection of a candidate drug, in order to obtain a drug molecule with acceptable properties, and in the preformulation phase, to determine the need for solubility-enhancing formulation principles. The primary variable for judgements of *in vivo* absorption is the dissolution rate rather than the solubility. Drug dissolution will limit the bioavailability when the dissolution rate is too slow to provide complete dissolution in the part of the intestine where it can be absorbed. In addition, the drug concentration in the intestinal fluids will be far below the saturation solubility, under the assumption that "sink conditions" in the GI tract will be obtained due to absorption of the drug. However, most often, solubility data are more readily available than dissolution rates for a drug candidate, especially in early phases when the amount of drug available does not allow for accurate dissolution rate determinations. Predictions of *in vivo* effects on absorption caused by poor dissolution must thus often be made on the basis of solubility data rather than dissolution rate. This can theoretically be justified by the direct proportionality between dissolution rate and solubility under "sink conditions" according to equation 1. A list of proposed criteria to be used to avoid a reduction in absorption caused by poor dissolution is given in Table 4.2.

These criteria are discussed in further detail in this chapter. A solubility in water of _ 10 mg/mL in pH range 1–7 has been proposed as an acceptable limit to avoid absorption problems, while another suggestion is that drugs with water solubilities _0.1 mg/mL often lead to dissolution limitations to absorption (Kaplan 1972; Hörter and Dressman 1997). It should be noted that these limits may be conservative, especially in the context of screening and selection for candidate drugs. For example, a drug with much lower solubility, such as metformin have more problem to formulate as FDDS

Initial stability:-

Knowledge about the chemical and physical stability of a candidate drug in the solid and liquid state is extremely important in drug development for a number of reasons. In the longer term, the stability of the formulation will dictate the shelf life of the marketed product, however, to achieve this formulation, careful preformulation work will have characterized the compound such that a rational choice of conditions and excipients is available to the formulation team. Candidate drugs being evaluated for development are often one of a series of related compounds that may have similar chemical properties, i.e., similar paths of degradation may be deduced. However, this rarely tells us the *rate* at which they will decompose, which is of more importance in pharmaceutical development terms. To elucidate their stability with respect to temperature, pH, light and oxygen, a number of experiments need to be performed. The major objectives of the preformulation team are, therefore, to identify conditions to which the compound is sensitive and to identify degradation profiles under these conditions. The major routes of drug degradation in solution are via hydrolysis, oxidation or photochemical means. Conners et al. (1986) have dealt very well with the physical chemistry involved in the kinetic analysis of degradation of pharmaceuticals. Size and shape of dosage unit also affect the gastric emptying. Garg and Sharma reported that tetrahedron- and ring-shaped devices have a better gastric residence time as compared with other shapes. The diameter of the dosage unit is also equally important as a formulation parameter. Dosage forms having a diameter of more than 7.5 mm show a better gastric residence time compared with one having 9.9 mm.

Half – life of Drug:-

Half life of drug is very influential factor for the floating drug delivery system. Half life of the drug contribute assistance to find out the drug elimination rate, by which we can conclude the de-activity of the drug. It is generally associated with the drug decomposition in the plasma membrane. The elimination of drugs from the body and the different modes of dealing with this process on a quantitative scale are discussed. The concepts of half-life and clearance are briefly reviewed. It is shown that with the term "half-life" the investigator focuses upon the elimination of the drug from the whole of the body. With the term "clearance" the interest is focused on the drug-clearing organs or on the effectiveness of these organs in eliminating the drug from the blood stream. As a consequence of this situation, the half-life is the truly useful parameter for the physician since it enables him to establish appropriate drug administration schedules for his patients. Clearance values, on the other hand, are chiefly of use to the pharmacokineticist in establishing the kinetic profile of a new drug. Among the pharmacokinetic concepts, the elimination half-life is most frequently used to describe the fate of a drug in the organism. The fact is often neglected, that the half-life depends on various physiological processes (organ clearances, distribution, occasionally absorption or binding to macromolecules). In many situations, the half-life has little to do with the duration of the effect which may depend on effective concentrations, equilibration delays at site of action, indirect response mechanisms, tolerance, or appearance of active metabolites. Finally, the half-life represents an ambiguous criterion for the choice of drugs: short (or long) half-life can be considered either advantageous or disadvantageous, according to endpoints selected. One of the main reasons that this is useful is that to use it for rational prescribing or in understanding the time course of adverse events does not require complicated mathematics. Basically, the half-life of a drug is that time required for the body to eliminate or biotransform half of the amount present in the body at any given point in time. This, correctly, suggests that elimination (metabolism and excretion) are the rate limiting factors (i.e. slower) than the other pharmacokinetic variables (absorption and distribution). Thus, for most drugs, the time taken for absorption and distribution may be neglected in determining dosing requirements. The drugs with which we associate and use the half-life concept are those which are cleared from the body (eliminated and/or biotransformed) by a fixed rate. This means that the amount eliminated is proportional to the amount available to be eliminated. Stated another way, the greater the drug concentration, the greater the amount cleared per unit time. Mathematically this is known as a first order process (would plot out as a straight line on semi-log paper). Most drugs are in this category. This is in contrast to the zero order process where a fixed amount of the drug is eliminated per unit time. Thus, the amount cleared is independent of the amount to be cleared. Drugs such as ASA, ethanol and phenytoin are primary examples in this category. These drugs present quite a different problem to the physician. With these, the only way to speed the elimination process is to go to dialysis. In clinical research, the half-life is

needed and used to determine how long after the dosing of the test agent that one is required to take blood samples so that the area under the time course curve (AUC) represents the true time course of the drug. Drugs whose effects or efficacy or actions outlast their plasma concentration form a very significant group and introduce the term "efficacy half-life". This is defined as that time it would take for a drug to lose half of its effectiveness or efficacy. This is obviously more difficult to measure and less precise than a plasma concentration making it difficult to determine with accuracy. Non-the-less, the concept is valid. What usually happens is that it is noticed that a dug with a relatively short half-life is still able to produce an effect long after it is supposedly eliminated (which would be 5 times the plasma half-life). It is presumed that the drug is acting intracellularly and either remains partly bound to the receptor long after most of the extracellular drug has been eliminated or the drug is a "hit-and -run" type which alters a receptor such that the effect remains long after the drug is gone. The reason it is important to always be on the lookout for this phenomenon is that it is far easier for patients to take a drug once or twice a day than three of four times a day.

Hydrolysis:-

Hydrolysis is considered to be the major cause of deterioration of drug, especially for those in aqueous solution. It may be because of the reaction of a compound with water, and one may distinguish between ionic and molecular forms of hydrolysis. Many pharmaceuticals contain ester or amide functional groups, which undergo hydrolysis in solution. The hydrolysis of an ester in to a mixture of an acid and alcohol essentially involves the rupture of a covalent linkage between a carbon atom and an oxygen atom. Although some of this hydrolyses can be effected in pure water, in majority cases, the presence of catalyst is needed to promote the reaction. These catalysts are invariably substances of a polar nature, such as mineral acids, alkali or certain enzymes, all of which are capable of supplying hydrogen or hydroxyl ions to the reaction mixture. The alkaline hydrolysis of an ester does not differ essentially from an acids-catalyzed hydrolysis, except that it is irreversible, and therefore quantitative, because the resultant acid is at once neutralized. On the other hand, the acids-catalyzed hydrolysis of esters is reversible and may be made essentially complete in either direction by an excess of water or alcohol. The magnitude of rate of hydrolytic reaction catalyzed by (H^+) and (OH^-) can vary considerably with pH. Hydrogen ion catalysis predominates at lower pH range, whereas hydroxyl ion catalysis operates at higher pH range. At the intermediate pH range, the rate constants in this pH range are usually less than those at higher or lower pH values. To determine the influence of pH on the degradative reaction, the decomposition is measured at several hydrogen ion concentrations.

First pass metabolism:-

Metabolism is vital criteria of a drug to be formulated as floating drug delivery system. It is both breakdown as well as building up process of the drug in hepatocyte cell of the liver. While formulating the floating drug delivery system, one should have depth knowledge about the drug which undergoes first pass metabolism in the liver cell or not. First-pass elimination takes place when a drug is metabolised between its site of administration and the site of sampling for measurement of drug concentration. Clinically, first-pass metabolism is important when the fraction of the dose administered that escapes metabolism is small and variable. The liver is usually assumed to be the major site of first-pass metabolism of a drug administered orally, but other potential sites are the gastrointestinal tract, blood, vascular endothelium, lungs, and the arm from which venous samples are taken. Bioavailability, is often used as a measure of the extent of first-pass metabolism. When several sites of first-pass metabolism are in series, the bioavailability is the product of the fractions of drug entering the tissue that escape loss at each site. The extent of first-pass metabolism in the liver and intestinal wall depends on a number of physiological factors. The major factors are enzyme activity, plasma protein and blood cell binding, and gastrointestinal motility. Models that describe the dependence of bioavailability on changes in these physiological variables have been developed for drugs subject to first-pass metabolism only in the liver. Discrimination between the 2 models may be performed under linear conditions in which all pharmacokinetic parameters are independent of concentration and time. The predictions of the models are similar when bioavailability is large but differ dramatically when bioavailability is small. The 'parallel tube' model always predicts a much greater change in bioavailability than the 'well-stirred' model for a given change in drug-metabolising enzyme activity, blood flow, or fraction of drug unbound. Many clinically important drugs undergo considerable first-pass metabolism after an oral dose. One major therapeutic implication of extensive first-pass metabolism is that much larger oral doses than intravenous doses are required to achieve equivalent plasma concentrations. For some drugs, extensive first-pass metabolism precludes their use as oral agents. Bioavailability of orally administered drugs can be influenced by a number of factors including release from the formulation, dissolution, stability in the gastrointestinal (GI) environment, permeability through the gut wall and first-pass gut wall and hepatic metabolism. Although there are various enzymes in the gut wall which may

contribute to gut first pass metabolism, Cytochrome P450 (CYP) 3A has been shown to play a major role. The efflux transporter P-glycoprotein (P-gp; MDR1/ABCB1) is the most extensively studied drug efflux transporter in the gut and might have a significant role in the regulation of GI absorption. Although not every CYP3A substrate will have a high extent of gut wall first-pass extraction, being a substrate for the enzyme increases the likelihood of a higher first-pass extraction. Similarly, being a P-gp substrate does not necessarily pose a problem with the gut wall absorption however it may reduce bioavailability in some cases (e.g. when drug has low passive permeability). An on-going debate has focused on the issue of the interplay between CYP3A and P-gp such that high affinity to P-gp increases the exposure of drug to CYP3A through repeated cycling via passive diffusion and active efflux, decreasing the fraction of drug that escapes first pass gut metabolism (F(G)). The presence of P-gp in the gut wall and the high affinity of some CYP3A substrates to this transporter are postulated to reduce the potential for saturating the enzymes, thus increasing gut wall first-pass metabolism for compounds which otherwise would have saturated CYP3A. Such inferences are based on assumptions in the modelling of oral drug absorption. These models should be as mechanistic as possible and tractable using available in vitro and in vivo information. In accordance with the Biopharmaceutics Classification System (BCS) within one of the most physiological models of oral drug absorption currently available, respectively ADME.

Absorption window:-

The oral route is considered as the most promising route of drug delivery. Effective oral drug delivery may depend upon the factors such as gastric emptying process, gastrointestinal transit time of dosage form, drug release from the dosage form and site of absorption of drugs. Most of the oral dosage forms possess several physiological limitations such as variable gastrointestinal transit, because of variable gastric emptying leading to non-uniform absorption profiles, incomplete drug release and shorter residence time of the dosage form in the stomach. This leads to incomplete absorption of drugs having absorption window especially in the upper part of the small intestine, as once the drug passes down the absorption site, the remaining quantity goes unabsorbed. The gastric emptying of dosage forms in humans is affected by several factors because of which wide inter- and intra-subject variations are observed 1 . Since many drugs are well absorbed in the upper part of the gastrointestinal tract, such high variability may lead to non-uniform absorption and makes the bioavailability unpredictable. Hence a beneficial delivery system would be one which possesses the ability to control and prolong the gastric emptying time and can deliver drugs in higher concentrations to the absorption site (i.e. upper part of the small intestine).The identification of new diseases and the resistance shown towards the existing drugs called for the introduction of new therapeutic molecules. In response, a large number of chemical entities have been introduced, of which some have absorption all over the gastrointestinal tract (GIT), some have absorption windows (i.e. absorption sites, especially the upper part of the small intestine) and some drugs have poor solubility in intestinal media. The drugs belonging to the second and third categories, and the drugs which are required for local action in the stomach, require a specialized delivery system. All the above requirements can be met and effective delivery of the drugs to the absorption window, for local action and for the treatment of gastric disorders such as gastro-esophageal reflux, can be achieved by floating drug delivery systems (FDDS). To date, a number of FDDS involving various technologies, carrying their own advantages and limitations were developed such as, single and multiple unit hydro dynamically balanced systems (HBS), single and multiple unit gas generating systems, hollow microspheres and raft forming systems. The hydrodynamic balanced system (HBS) also called Floating drug delivery system (FDDS) is an oral dosage form (capsule or tablet) designed to prolong the residence time of the dosage form within the GIT. It is a formulation of a drug with gel forming hydrocolloids meant to remain buoyant in the stomach contents. Drug dissolution and release from the dosage form retained in the stomach fluids occur at the pH of the stomach under fairly controlled conditions Floating systems are one of the important categories of drug delivery systems with gastric retentive behavior. Drugs that could take advantage of gastric retention include: furosemide, cyclosporine, allopurinol ciprofloxacin and metformin. Drugs whose solubility is less in the higher pH of the small intestine than the stomach (e.g. chlordiazepoxide and cinnarizine, the drugs prone for degradation in the intestinal pH (e.g. captopril), and the drugs for local action in the stomach (e.g. misoprostol) can be delivered in the form of dosage forms with gastric retention. Antibiotics, catecholamines, sedative, analgesics, anticonvulsants, muscle relaxants, antihypertensive and vitamins can be administered in HBS dosage form.

Conclusion:-

Recently many drugs have been formulated as floating drug delivery systems with an objective of controlled release and restricting the region of drug release to stomach. The principle of buoyant preparation offers a simple and practical approach to achieve increased gastric residence time for the dosage form and sustained drug release. The

currently designed floating drug delivery have not efficient drug criteria on the basis of gastric emptying and buoyancy principles, appear to be a very much effective approach to the modulation of controlled oral drug delivery. The most important criteria which has to be looked into for the productions of a floating drug delivery system is that the density of the dosage form should be less than that of gastric fluid. And hence, it can be concluded that these dosage forms. The drug of choice should have naroow absorption window, GI motility, Non emetic property and should not be irritant to the stomach. These following criteria satisfies to formulate floating drug delivery system . And hence, it can be concluded that these dosage forms serve the best in the treatment of diseases related to the various organs and for extracting a prolonged action from a drug with a short half life.

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