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Nanotechnology Based Approaches For Enhancements of Bioavailability of Sustain Release Formulation

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ABSTRACT

In recent years drug bioavailability has become a subject of matter not only in drug development, additionally within the early stages of drug discovery. Bioavaibility is the major and important pharmacokinetic property of drug. This property of drug is used to describe the fraction of an administered dose of unchanged drug which can reaches to the systemic circulation. When a drug is administered intravenously, its bioavailability is 100%.and if the drug is administered through other routes like oral, its bioavailability decreases because of the incomplete absorption or first pass metabolism. So there is a need in the enhancement of the bioavaibility of sustained release dosage form.This is a consequence of the finding that the majority of candidate drugs that were unsuccessful in clinical trials did so because of problems with absorption, distribution, metabolism, excretion (ADME) and toxicology. Efforts are being created within the Pharmaceutical industry to improve success rates by taking into account the ADME and toxicology aspects in drug discovery. The efficacy of a drug further depends on the ability of the dosage to deliver the active drug to the site of action and at a rate and amount which is sufficient to show the desired pharmacological response. This property is also known as bioavaibility or biologic avaibility.

Keywords: Bioavailability, Pharmacokinetic, Sustained release, ADME.

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Introduction

Bioavaibility is one of the most important factors. This factor is used to achieve the optimal concentration of drug in systemic circulation. When a drug has a poor bioavaibility then it shows poor solubility, slow dissolution rate, poor stability of drug and extensive first pass metabolism.[1] Over the past thirty years, because the expense and complication concerned in new entities have hyperbolic with concomitant recognition of the medical aid benefits of controlled drug delivery, bigger attention has been centered on development of sustained or controlled drug delivery system. [1]Goal of designing sustained release delivery systems is to increase the effectiveness of drug by localization at the site of the action, to reduce frequency of dosing or for providing uniform drug delivery.[2] The ideal drug delivery systems has require two things which would be first it would be a single dose, the duration of treatment whether it is for days or week, as with infection, or for the life time of the patient, as in hypertension or diabetes. It should deliver the active entity directly to the site of the action by minimizing side effects.[5] Bioavailability refers to the relative amount of drug from the administered dosage form which enters into the systemic circulation and the rate at which the drug appears in systemic circulation.[3]

Oral sustained release products give us an advantage over conventional dosage forms which can optimize biopharmaceutics and pharmacokinetic property of drug when it is incorporated in Nanoparticulate system. Pharmacokinetic property includes bioavaibility of drug.[4]It includes any drug delivery system achieves release of drug over an extended period of time, which not timedependent. Hydrophilic polymer matrix is widely used for formulation of Sustained dosage form. The role of ideal drug delivery system is to provide proper amount of drug at regular time interval and attarget site of action to maintain therapeutic effect of drug in blood plasma[4]

Bioavailability will be typically documented by a systemic exposure profile obtained by measuring drug concentration in the systemic circulation over time. The systemic exposure profile determined during clinical trials in the early drug

development can serve as a benchmark for subsequent bioequivalence studies. Bioequivalence studies should be conducted for the comparison of two medicinal products containing the same active substance. Two products marketed by totally different licensees, containing same active ingredients, must be shown to be therapeutically equivalent to one another in order to be considered interchangeable. Several test methods are available to assess equivalence[5]

From time to time varied authors have proposed different types of drug release mechanisms from matrices. It has been planned that drug release from matrices usually implies water penetration in the matrix, hydration, swelling, diffusion of the dissolved drug (polymer hydro fusion), and/or the erosion of the gelatinous layer. Several Kinetics models are relating to the drug release from matrices. They are selected from the most important mathematical model**s**, are described over here. However, it is worth mention that the release mechanism of a drug would depend upon the dosage from selected, pH, nature of the drug and, which type of polymer used.[6]

Rational of sustained drug delivery:

The basic principle for sustained drug delivery is to improve the pharmacokinetics and pharmacodynamics of pharmacological active moieties by using Nanoparticulate system.Formulation of sustained drug delivery minimizes dosing frequency and sustained release provides availability of a drug at action site throughout the treatment to improve clinical efficiency of a drug molecule.[7]

Advantages of sustained release dosage form: [7]

- SR dosage form improves potency in treatment optimized medical care and a lot of uniform blood concentration.
- It reduces in fluctuation of drug level and because of that more uniform pharmacological response, cure of control of condition more promptly, less reduction in drug activity with chronic use.
- Method by which sustained unharness is achieved, will improve the bioavailability of some medication.
- Encapsulation for chemical compound systems required is appropriate for unharness sustained.
- It can be protected by encapsulation in polymer systems suitable for sustained release.
- It also improves patient compliance, less frequent dosing, reduced night-time dosing and reduced patient care time.
- The importance of patient compliance in flourishing drug medical care is well recognized.
- It has been found that there is an inverse relationship between the quantity of dosages as per the day and therefore the compliance rate.
- Although the initial unit cost of sustained release products is usually greater than that of conventional dosage forms because of the special nature of these products, the average cost of treatment over an extended period of time is less.
- Due to economy it may also result a decrease in nursing time and hospitalization time.
- Improvement in bioavailability of some drugs because of spatial control.

Disadvantages of sustained release dosage form: [7]

- It gives delay onset of drug action.
- It has a chance of dose dumping within the case of a poor formulation strategy.
- III.It has increased potential of first pass metabolism
- Possibility of less accurate dose adjustment in some cases.
- Cost per unit dose is higher when compared with conventional doses.

Challenges in sustained drug delivery:

Biocompatibility Cost of formulation, preparation and processing fate of polymer additives, Fate of controlled release system if not biodegradable. e.g., plasticizers, stabilizers, antioxidants.[4]Although the oral drug delivery is effective for drug with epithelial permeabilityand high solubility, systematic oral administration of poorly water soluble drug is a challengeand high solubility. Presently, most of the new chemical entities are lipophilic and have poor solubility On the basis of biopharmaceutical classification system, a number of new therapeutic entities are characterized under BCS class II (high permeability and low solubility) or BCS class IV(low permeability and low solubility).[8]The oral bioavailability of some drugs is also affected by their poor gastrointestinal permeability. To reach to the certain level oftherapeutic action, these drugs have to be given at a high dose. Moreover, chemical barriers presented by the gastrointestinal tract also affect oral administration.[8]Bioavailability is one of the essential tools in sustainedbecause it should be thought about when calculating dosages for non-intravenous routes of administration. It is known as absolute or relative bioavailability.[9]

Bioavailability:

Absolute bioavailability: Compares the bioavailability of the same drug following intravenous administration with the bioavailability of the active drug in systemic circulation following non-intravenous administration. The comparison must be dose normalized; the amount absorbed is corrected by dividing on the corresponding dose administered.[10]this is the dose corrected AUC intravenousdivided by area under curve no intravenous. Therefore, a drug given by the intravenous route will have an absolute bioavailability of one while drugs given by other routes usually have man absolute bioavailability of less than one. If we compare the bioavailability of two ingredients, it is called comparative bioavailability.[11]

Relative bioavailability: The term relative bioavailability denotes to a comparison of two or more dosage forms in terms of their relative rate and extent of absorption. If an intravenous injection is employed as the reference dose, then can determine the complete bioavailability of the test dosage form. Two dosage forms which don't differ in their extent and rate of absorption are termed bioequivalent. Bioequivalence determinations is made bypharmaceutical alternatives which can be defined as drug products that contain the identical therapeutic moiety or its precursor, but it is not necessarily in the same amount or as the same salt.Every single product meets the identical compound and alternative applicable standard of identity, strength, quality, purity as well as efficiency, content uniformity, and dissolution rates.[12]

Factors influencing bioavailability:

The factors affecting the release and bioavailability of contaminants present in sediments through thenatural and anthropogenic disturbance, events are analyzed and our current state of understanding of those processes studied. Available data are focused on the distribution of contaminants within undisturbed sediment, these affinities to the various solid-phase fractions and the interaction of contaminants between sediment and pore water. Sediment disturbance can lead to change in chemical properties of sediment which stimulates mobilization of contaminants. Research shows that changes in redox potential and pH can increase speed for desorption, partitioning, bacterial degradation and the oxidation,when these processes are sediment- and compound-specific. With the affection of the affinity of contaminants to sediments and disturbance events will have a big impact on the bioavailability. Few research have examined this development and it is clear from that there are gaps in our understanding in a number of key areas where the assessing the release of contaminants from sediments is done. The fate of contaminants in undisturbed sediments and those which are not subjected to major disturbances, the kinetic processes which regulate metal release through the changes in redox potential, from sediments through the repeat procedure of suspension, the bioavailability of organic and the processes affecting contaminant release.[12]

Techniques for improving bioavailability:

1. Enhancement of solubility and dissolution rate
2. Modification of partition coefficient
3. Avoidance of hepatic first pass metabolism
4. Avoidance of degradation in gastrointestinal tract
5. Novel Drug Delivery system.

Enhancement of solubility and dissolution rate:

Physical Modification:

Particle size reduction:

Particle size reduction increases the effective surface area which results in enhancement of solubility and dissolution velocity of the drug. Micronization and nanonization these techniques are used to improve dissolution rates of drugs which further improve the oral bioavailability of same. Micronization of drugs is done by milling techniques using jet mill, colloid mills etc. [10]

Eg. Farinha Aet. Alhas found important increase which is in the oral bioavailability of micronized Megestrol acetate from in vivo study. To overcome these limitations of micronizationalternative approach used is nanonization. Nanonizationresults in formation of nanosuspension. Nanosuspension is a micron dispersion of pure particles of drug stabilized by surfactants. It increases dissolution rate due to larger surface area exposed to gastrointestinal fluid.[10]

E.g. Jia L. et al has found that this formulation enhances rat oral bioavailability of the poorly soluble thiadiazole derivative.

pH adjustment:

It is well documented that the influence of the changes in pH within the gastrointestinal tract upon the bioavailability of pharmaceuticals. The absorption of drug is largely dependent upon diffusion, which varies with pH of the individual regions within the gastrointestinal tract, the pKa of the drug and permeability, which are not only moderated by the surface area of the region in which it is released, but also the regional pH effects upon drug ionization. By applying a pH change, poorly water soluble drugs with parts of the molecule that can be protonated (base) or deprotonated (acid) may potentially be dissolved in water. While the importance of critical parameters like salt selection and pH adjustment has been stressed on pre-formulation, the use of pH altering excipients within drug delivery systems is also of significant utility. pH adjustment can in principle be used for both oral and parenteral administration.[13]

Chemical modification:

Change in pH of system:

When organic solutes which are ionizable then changing the pH of system is simplest and most effective which will increases the aqueous solubility, with the help of proper conditions the solubility of an ionizable drug increases by adjusting the pH of the solution,which further improve the oral bioavaibility.[14]

Salt formation:

Salt formation is very common and effective method for increase in the solubility and dissolution rates of acidic drugs and basic drugs. It is main parameters to changes in solubility and permeability of the molecule, which can further improve bioavailability. The use of salt forms is a technique for enhancement of dissolution rates. Alkaloidal base is very less soluble in water but when the pH of medium is reduced by adding the acid the solubility of the base is increases as the pH continues to be reduced. The solubility of very less soluble acid which increases as when the pH is increased by adding alkali. This is the reason of salt formation.[14]

Formulation Based Approaches:

a) Co-crystallization:

Co-crystals are alternative option for salt formation for neutral compounds or for those which have weakly ionizable groups to modify the chemical and physical properties of an active pharmaceutical ingredient without making covalent bonds. It is also referred as molecular complexes. This will help to improve the bioavaibility.[14]

b) Co-solvency:

Weak electrolytes have poor water solubility which is improved by changing the polarity of the solvent which is done generally by the adding water miscible solvent which the has good solubility. It is prominent that the addition of an organic co solvent can change the solubility of drugs. This process is known as co solvency and the solvents are known as co solvents. This improves the oral bioavaibility of that drug. [14]

c) Solid dispersion:

Solid dispersion is the system made up of one or more active ingredients which are dispersed in inert carrier in a solid state. SD are classified as follows: first generation as crystalline carriers such as urea, second generation amorphous carriers which are generally polymers and third generation carriers with surface activity properties. Generallyit contains surfactant or a mixture of surfactants. They are prepared by the fusion method, solvent method and fusion solvent-method. Eutectic mixtures are also form of solid dispersions which are also prepared by fusion method with the help of specific solvents on the basis of a formulation strategy to improve the physical properties of

the active ingredient for the enhanced dissolution rate and solubility.[15]

1. Modification of partition coefficient:

a. Ester formation:

This denotes to improvement in oral bioavailability of poorly water-soluble drugs by chemical derivatization to a water-soluble prodrug. It utilizes esterification of a hydroxyl, amine or carboxyl group of a drug with a moiety (progroup) designed to introduce an ionizable function or reduce intermolecular interactions responsible for low solubility. The use of spacer groups to introduce derivatizable functions and/or to position ionizable progroups for unhindered hydrolysis is also described.[14]

2. Avoidance of first pass metabolism:

a. Prodrug Approach:

This approach is used to reduce the presystemic metabolism and also for chemical decomposition. The basic and important principle linked with Prodrug is to cover the functional group. Designation of prodrug is used for improving the oral and nasal bioavaibility. This is one of the best approaches for protein and peptide molecules. Ideal prodrug foe bioavaibility enhancement of these would exhibit enhanced membrane permeability with increased stability. After crossing enzymatic membrane barrier the

Prodrug undergoes enzymatic transformation to reduce the parent molecules.[16]

b. Co-administration with another drug:

If a drug has a high first-pass metabolism then one can expect an increase in its plasma concentration. When it is co-administered with another drug then it inhibits its metabolism. When administered alone lopinavir has insufficient bioavailability (25%); but when like HIV protease inhibitors, its blood levels are increased by low doses of ritonavir, a potent inhibitor of cytochrome P450.[14]

3. Avoidance of degradation in gastrointestinal tract

a. Avoidance of degradation in stomach – Enteric coating

An enteric coatingis a barrier for oral medication which resists destructive action of the gastric fluid and then disintegrates in the intestinal tract by releasing the drug in the intestine. Reasons for enteric-coating a drug product is as follows:

- Preventing destruction of the drug by gastricenzymes or by the acidity of the gastric fluid
- Preventing nausea and vomiting caused by the drug's irritation of the gastric mucosa
- Delivering a drug that is primarily absorbed in the intestines to that site at the highest possible concentration

Enteric coating worksthrough presenting a surface which is stable at the highly acidic pH which is found in the stomach but breaks down rapidly at a less acidic pH (basic pH). For example they will not dissolve in the acidic juices of the stomach with pH ~3 but will dissolve in the higher pH which is above pH 5.5. Materials which are used for enteric coatings include fatty acids like stearic acid, hydrogenated castor oil, waxes like carnauba wax, cellulose acetate phthalate and shellac. The enteric materials are used to coat tablets, capsules andgranules.

b. Avoidance of degradation in intestine –

Many drugs are stable in the acidic environment of stomach but cannot resist the pH and enzymatic conditions of the intestine. An increase in the residence time of such drugs in stomach leads to the absorption of significant amount in stomach before it reaches the intestine.[14]

Novel Drug Delivery system

Nano suspensions, Nanoemulsions, Selfmicroemulsifying and self-nanoemulsifyingdrug delivery system, Solid lipid nanoparticles, polymeric nanoparticles,Vesicular delivery systems such as liposomes, niosomes etc.[10]Drugs who has poor solubility possess the tough scenarioin formulation by applying typical approaches as they present issues like slow onset of action, poor oral bioavailability, lack of dose proportional, failure to achieve steady state plasma concentration, and side effects. The conventional dosage forms thus may result in over- or undermedication and poor patient compliance. These challenges are also overcome by making them as novel drug delivery systems which canoffers edgessuch as reduction in dose frequency, lowering of dose size, specific targeting, increasedporosity, and improvement in oral bioavailability. Nanotechnology is a very good and promising strategy in which the development of drug delivery systems for those potent drugs whose clinical development was unsuccessfulbecause to their poor solubility, low permeability, inadequate bioavailability, and other poor biopharmaceutical properties.[17]

Novel drug delivery systems are one of the IMP methods in which they alters to beat the issues associated with the drug bioavailability. It is the rate and extent to which a drug becomes available to the target, once its administration is done. Most of the newest drugs used have poor bioavailability and are required to be administered at higher doses because only a small fraction of the administered dose is absorbed within the circulation and ready to reach the target site.[18]

1. Nano suspensions:

Nano suspensions are biphasic colloidal dispersions of drug particles in which they are stabilized by using surfactants. Nano suspensionshave particles dispersed in an aqueous vehicle with the size of particle less than 1 µm. Nano suspensions can overcome the problems related to the delivery of poorly water soluble drugs due to their Nano size particle range.[19] Nano suspensions are part of nanotechnology which consists of poorly water soluble drug without any matrix material suspended in dispersion. One of the major problems which is associated with poorly soluble drugs is the very low bioavailability of drug. The problem is more complex for drugs such asItraconazole, Simvastatin, and Carbamazepine which are weakly soluble in aqueous and no aqueous media, belonging to as classified by biopharmaceutical classification system.Formulation as Nano suspension is an attractive and promising alternative to solve these problems. This approach is most suitable for the compounds with high log P value, melting point and dose.[19]

Various methods likelyophilization also known as freezedrying;spray drying, melt granulation, and extrusion-spheronization are used for the preparation of nanosuspension. These have been applied for converting Nano suspensions to pellets or tablet-like dosage forms.[19]

Method for preparation of Nano suspension

1. Lyophilization:

Lyophilization is a process into which water is frozen and then it is removed from the sample initially by sublimation and then by desorption. this is the process of drying in which water is sublimed from the product after it is frozen. For prolonged storage a drying process applicable to manufacture of certain chemicals, pharmaceuticals and biological that are thermolabile or otherwise unstable in aqueous solutions and it is stable in the dry state. The term lyophilization describes a process to produce a product that loves the dry state. Lyophilization is performed at temperature and pressure conditions below the triple point of water, to enable sublimation of Ice.[20]

2. Spray Drying:

Spray drying includes the spraying of liquid feed formulation such as solutions, suspensions, emulsions into a hot drying medium (air, nitrogen). The droplets formed by the atomisation process are dried through solvent evaporation to form particles which are collected as a dry powder.The drying of the spray continues until the desired moisture content in the dried particles is achieved, and the product is recovered from the air. It is a unique drying process since it involves both particle formation and drying. Process parameters such as inlet and outlet temperature of the drying medium and the atomization pressure influence the physico-chemical properties of the produced powders. The characteristics of the spray dried powder can be controlled, and the powder properties can be maintained constant throughout the continuous operation. With the different designs of spray dryers available, it is possible to select a dryer layout to produce either fine or coarse particle powders, agglomerates or granulates.[21]

3. Melt Granulation:

This is the technique in which powder agglomeration is obtained through the addition of a lipid as binder that melts or softens at relatively low temperatures. In melt granulation technique it offers several advantages over the conventional wet granulation since the liquid addition and the subsequent drying phase are omitted. The main parameters which control the granulation process are listed such as impeller speed, mixing time, binder particle size, and the viscosity of the binder. A wide range of solid lipids and semisolid lipids can be applied as meltable binders.[22]

4. Melt Extrusion/Extrusion Spheronization:

Melt Extrusion has been used in the plastic, rubber, and food manufacturing industry to produce items ranging from pipes to sheets and bags. With the advent of high throughput screening, currently more than half of all plastic products including bags, sheets, and pipes are manufactured my HME and therefore various polymers have been used to melt and form different shapes for a variety of industrial and domestic applications. The technology (HME) has proven to be a robust method of producing numerous drug delivery systems and therefore it has been found to be useful in the pharmaceutical industry as well. Extrusion is the process of pumping raw materials at elevated controlled temperature and pressure through a heated barrel into a product of uniform shape and density. Breitenbach first introduced the development ofmelt extrusion process in pharmaceutical manufacturing operations[10]however, Follonier and his coworkers first examined the hot-melt technology to manufacture sustained release polymer-based pellets of various freely soluble drugs.

Advantages of use of Nano suspensions for enhancement of bioavaibility:

- Nano suspensions are cost-effective and technically simpler alternative.
- Nano suspension shows good reproducibility in case of large-scale production.
- It also increases the dissolution rate and saturation solubility.
- It gives efficient release of hydrophobic drugs [23]

2. Nanoemulsions:

Nanoemulsions are dispersions of shear-induced ruptured Nano scale droplets. It can be defined as oil-in-water emulsions with mean droplet diameters ranging from 50 to 1000nm. It is very likely that Nanoemulsions played commercially important role; since they can typically formulate with the help of less surfactant than is required for nanostructured lyotropic microemulsion phases. Nanoemulsions are kinetically stable, even for several years. The term sub–micron emulsion, mini-emulsion and ultra-fine emulsion are used as synonyms. It has to be considered that these novel Nanoemulsions again are fluid systems where the production is not easy to handle. Different techniques for the production of Nanoemulsions are High pressure homogenization in which disruptive forces are responsible for conversion of coarse emulsion into Nanoemulsions and Low energy emulsification methods, in which condensation forces are utilized for this purpose. A narrow size distribution can be obtained using Micro fluidization technique, where emulsions are forced through micro channels in the central chamber of the micro fluidizer using high pressure pump. A heterogeneous distribution of droplet size is achieved using Ultra sonication technique which uses ultrasound energy to disrupt macroscopic droplets. Lipophilic drug entrapped lipid nanoemulsions improved bioavailability of drugs by increasing drug absorption through the gastrointestinal tract.[24]

Nanoemulsions were shaped both by high energy emulsification methods or low energy emulsification methods. High energy emulsification methods engage high shear mixing, high-pressure homogenization or ultrasonication, while low energy emulsification methods used the advantage of the physicochemical properties of the system which exploits phase transitions to produce nanoemulsions. Nanoemulsion prepared with oil, surfactant and Cosurfactant are non-toxic, non-irritant and approved for humans.[3]

Advantages of use of nanoemulsions for enhancement of bioavaibility:

- Nanoemulsions eliminate variability in absorption by increasing the rate of absorption.
- Nanoemulsions are effective transport system because these have much higher surface area and free energy and also do not possess problems of inherent creaming, flocculation, coalescence and sedimentation which are commonly associated with macro emulsions.
- These show rapid and efficient permeability of the drug moiety thus there is significant increase in bioavailability.
- Since theseare formulated with surfactants which are approved for human consumption, they can be taken by enteric route.[17]

3. Self-emulsifying, Self-micro emulsifying (SMEDDS) and Self-nano emulsifying (SNEDDS) drug delivery system:

Self-Emulsifying:

The self-emulsifying drug delivery systems offers advantages in addressing the challenges of drug solubility and absorptionof drug; the next challenge stays the delivery of the drug in an acceptable dosage form. The oral dosage forms are the preferred drug administration route, and lipid formulations offer flexibility for oral dosage because they can be formulated as solutions, semisolid, and solid forms. Conventional self-emulsifying drug delivery systems are prepared in a liquid form which then can produce some disadvantages such as low stability, irreversible drugs/excipients precipitation, large volume of dose, difficulty in handling and portability, and few choices of dosage forms[12] so because of that the need for development of solid SEDDS

Solidification Technique for converting Liquid SEDDS to Solid-SEDDS

Solid SEDDSs are being developedfrom liquid/semisolid SEDDS mainly by adsorptionon solid carriers, spray drying, lyophilization; melt extrusion, and nanoparticals technology. Such powders/nanoparticles, which are then, referred to SE nanoparticles/solid dispersions, which are processed into other solid SE dosage forms.[24]

SMEDDS gives a great potential by improving the oral bioavailability of therapeutic agents. Some of the nano-emulsions such as surfactants which can inhibit the Cytochrome P450 metabolizing enzymesWherethe few lipidic components like glyceryl monooleate, long-chain triglycerides have been shown to promote the lymphatic absorption of the therapeutic agents which prevent the first pass metabolism of the drugs. The SMEDDS have been found to be useful in improving the oral bioavailability of drugs in which it undergoes degree of firstpass metabolism. The developed SMEDDS formulations improves the oral bioavailability and the relative oral bioavailability of SMEDDS compared with available tablets was 413%.[25]

SNEDDS are oil-in-water Nanoemulsions which are in the form of anhydrous isotropic mixture of surfactant, oil, and drugs. When these introduced into aqueous phase with gentle agitation get transformed into nanoemulsions. The digestive motility of gastrointestinal tract gives agitation for formation of nanoemulsions. The SNEDDS givesaids associated with nanoemulsions such asincrease in oral bioavailability and increase inporosity of drug, improved chemical/enzymatic stability, and ease of fabrication.[25]

Advantages of use of Self-nanoemulsifying for enhancement of bioavaibility: [17]

- Self-nanoemulsifying DDS gives protection for sensitive drug substance
- Ithas a selective targeting for drugs toward specific absorption window in GIT.
- It gives controlled drug delivery profiles.
- It used inenhancement in oral bioavailability which enables the reduction in dose.
- It reduced variability like food effects
- It has more regular temporal profiles of drug absorption

4. Solid lipid nanoparticle:

SLNs are aqueous dispersions of solid lipids which has a size ranges between 50 to 1000 nm. A clear advantage and bold advantage of solid lipidnanoparticle is the fact in which lipid matrix is made from physiologically tolerated lipid components, which decreases the potential for acute and chronic toxicity. SLNs involvethe advantages for polymeric nanoparticles and liposomes. They are melt-emulsified nanoparticles which are depends on type of lipids used at room temperature. SLNs were prepared by many techniques. This technique mainly involves high pressure homogenization and microemulsiontechnique. To manufacture SLNs hot high pressure homogenization above melting point of lipid and subsequent crystallization is recommended but for thermo labile drugs cold high pressure homogenization exists. Other production methods for SLN are the precipitation. These mainly differ from ultrasound, normally in particle size distribution. One of the major advantages of SLNs over other systems is the reduction in acute and chronic toxicity due to the presence of physiologically tolerated lipid components. SLN is a promising strategy in bioavailability enhancement. SLNs give benefits like biocompatibility, nontoxicity and stability against coalescence. Solid lipid nanoparticles can be also be applied for delivery of hydrophilic and for hydrophobic drug[20]

Lipids have been used as an alternative carrier for polymeric nanoparticles, particularly for lipophilic pharmaceuticals and lipid nanoparticles are known as solid lipid nanoparticles (SLNs). SLNs introduced in 1991 represent an alternative and suitable system to traditional colloidal carriers such as emulsions, liposomes and polymeric micro and nanoparticles. The system consists of spherical solid lipid particles in the nanometer ranges, which are dispersed in water or in aqueous surfactant solution. SLN are made of solid hydrophobic core having a monolayer of phospholipids coating. The hydrophobic chains of phospholipids incorporated in the fat matrix and have the potential to carry lipophilic or hydrophilic drugs or diagnostics[25]

Advantages of use of solid lipid nanoparticle for enhancement of bioavaibility:

- SLN have adhesive properties which make them adhere to gut wall and then releases the drug exactly where it should be absorbed.
- These improve the bioavailability of drugs with the help ofdecreasing first pass metabolism.
- SLNconsists of high biocompatibility and controlled release
- They do not have any problems with multiple route of administration like oral, intravenous, pulmonary and transdermal administration.[17]

4.1 Nanoparticles:

The word nanoparticlesderived from nanostructures particulate with variable shape but with at least one dimension in Nano scale, which should be lower than 100 nanometers.These drug delivery technologies offers many advantages like increased bioavailability, extended drug half-life and reduced off-target toxicities. The new generation of therapeutic nanoparticle is a multifunctional combination of an active drug compound with selective targeted moieties. In many cases imaging agents which permit localization by standard x-ray, magnetic resonance or positron emission tomography technologies. Mesoporous silica nanoparticles areused in controlled delivery of

hydrophilic or hydrophobic active agents. Later advances in the MSNs surface properties like surface functionalization and PEGylation rendered them as a promising drug delivery vehicle for cancer treatment.Polymer systems offers immense flexibility in customization and optimization of nanocarrier to efficiently deliver new therapeutics and provide an integral step in aiding their progression to clinical practice.[13]

The term nanoparticles name of combination forNano spheres and Nano capsules. Nano spheresare matrix system in which drug is uniformly dispersed and nanocapsules are the system in which the drug is surrounded by a unique polymeric membrane.This systemic review gives the Classification, method ofpreparation, Characterization, application and health prospective.

Classification of nanoparticles

There are various approaches for classification of Nanomaterials. They are classified based on one, two and three dimensions

a. One dimension nanoparticles

This system includes thin film or manufactured surfaces which has been used for electronics, chemistry and engineering. Production of thin films sizes1 to 100nm is now common place in the field of solar cells or catalysis. These thin films are then used in different technological applicationswhich gives information about storage systems, chemical and biological sensors, fiber-optic and magneto-optic system and optical device.[22]

b. Two dimension nanoparticles

These are also known as Carbon nanotubes. They are hexagonal network of carbon atoms, 1 nm in diameter and 100 nm in length, as a layer of graphite rolled up into cylinder. CNs are of two types, single walled carbon nanotubes and multi-walled carbon nanotubes.The small dimensions of carbon nanotubes, combined with their remarkable physical, mechanical and electrical properties which make them unique material. They displays metallic conductive properties, depending on how the carbon leaf is wound on itself. The current density which can reach one billion amperes per square meter making it a superconductor. Mechanical strength of carbon nanotubes is sixty times more than the best steels. Nanotubes have a more capacity for molecular absorption and offering a three dimensional configuration. Nanotubes are chemically very stable.[22]

c. Three dimension nanoparticles

These are also known as Fullerenes. They are spherical cages consisting from 28 to 100 carbons which contain C60. They are a hollow ball made upof interconnected carbon pentagons and hexagons which resembles as asoccer ball. Fullerenes are materials of class displaying unique physical properties. They can be exposed to extreme pressure andreformed in their original shape when the pressure is released. These molecules don't combine with each other, giving them major potential for application as lubricants. They have interesting electrical properties, it has been suggested to use them in the electronic field, ranging from data storage to production of solar cells.[22].

Vesicular delivery system

Liposomes

Liposomes are vesicles made up of a hydrophobic lipid bilayer film of numerous sorts of natural cells. The medication of liposomes is inactive dissemination because of the layer and uptake of the vesicles with the help of other lipid bilayer structure. A novel class of liposomes nanoparticles has been used with labeled antibodies on their surfaces which can further gofor about homing ligands, guarantee awesome capability of acknowledging multi-reason shrewd vehicles for pin-point conveyance of a show of payloads at a Nano scale. The adjusted liposomes are a compelling approach to target heart, liver, kidney, lungs and bone. With the advancement of innovation, liposomes intervened medication conveyance will assume a more vital part in clinical environment later on. The principle inconvenience of liposome is that it is difficult to cross most customary pellicle hindrances because of their forced size.[23]

Liposomes are one of the most extensively investigated colloidal carriers which are used to improve the therapeutics of potent drugs, can be further used to control retention of entrapped drugs in the presence of biological fluids by target cells. With respect to oral administration liposomes formulation are targeted to reduce toxicity and improve bioavailability. For acid labile drugs, like Cefpodoxime entrapment by liposomes which provide a temporary protection for the drug from the hostile acidic environment of the stomach. Also they increases the intestinal permeability which is induced by the lipid components of liposomes.[19]

An outer hydrophobic environment is established with the linkage of a lipophilic moiety of the player and non-polar part lipophilic can associate depending upon their geometry and size8. Hydrophilic drugs or molecules interact with the inner aqueous phase of the vesicles. This bypass characteristic composition and construction of liposomes offer a dynamic and adaptable technology for enhancing drug solubility. These can be classified depending upon the size, the number of players and the existence of inner vesicles as multilamellar large vesicles, oligolamellar vesicles, unilamellar vesicles, small unilamellar vesicles, medium sized unilamellar vesicles, large unilamellar vesicles, giant unilamellar vesicles and multi vesicular vesicles.[23]

Advantages of use of liposomes for enhancement of bioavaibility:

- Liposomes encapsulate hydrophilic and lipophilic drugs which are then protect them from degradation.
- PEGylated liposomes have advantages such as increase bioavailability and the targeted delivery to the organs which needed most of them.
- Liposomes regulates the membrane permeability and so they do not allow the leakage of solute.[17]

Niosomes:

Niosomes are nonionic surfactant vesicles which are well recognized for drug delivery vehicles. They can also carry hydrophilic drugs by encapsulation and are quite stable.Preliminary studies specify that niosomes increases the absorption of some drugs from the gastrointestinal tract following oral ingestion. Improved oral bioavailability owing to the lipophilic nature of the niosomes formulation and the effect of the nonionic surface-active agent on the permeability of the gastrointestinal membrane. Improved portioning of the lipophilic system to the mucosa, a direct effect of the surface active agent on the barrier function of the mucosa, and prolonged localization of the drug-loaded niosomes at the site of absorption may be possible reasons for the improved bioavailability[23]

Advantages of use of niosomes for enhancement of bioavaibility:

- Niosomes are successfully using for oral administration of peptide or protein drugs like insulin to reduce the use injection as the mode of administration.
- Niosomes increases stability of entrapped drug as they are osmotically active and stable.
- These provide enhancement of skin permeation and improvement of oral bioavailability of poorly soluble drug.
- Structure of the noisome is designed by such a way that thevesicles can entrap hydrophilic and lipophilic as well as amphiphilic drug moieties.

Bilosomes:

Bilosomes are the novel, innovative drug delivery carriers which is produced by incorporating deoxycholic acid into the membrane of niosomes. Incorporation of bile in the formulation which could then stabilize the membrane against the effects of bile acids in the gastrointestinal tract where conventional vesicles such as liposomes and niosomes which can cause dissolution and undergo enzymatic degradation. These bile salts then stabilized vesicles which are known as blossoms. These show various advantages likebiocompatibility as they are produced from naturally occurring lipids. Bile salts along with lipid content increase the bioavailability of enclosed bioactive substance and act as penetration enhancers. These have been found to increase in the bioavailability of drugs as they can absorb through the small intestine into the circulation[19]

Advantages of use of Bilosomes for enhancement of bioavaibility:

- Bilosomes increases the bioavailability of bioactive substance and also act as penetration enhancers
- In this bile salts used as a penetration enhancers in the formulation which could stabilize the membrane against the effects of bile acids in GI tract[17]

Transferosomes:

These are ultra-flexiblelipid supramolecular aggregates which easily penetrate skin intact. Conventional drug carriers aren't suitable for transdermal delivery because their poor skin permeability, breaking of vesicles, leakage of drug, aggregation and fusion of vesicles. Transferosomes are the promising NDDS which are capable of transdermal delivery of low molecular weight drugs as well as high molecular weight drugs. These have at least one inner aqueous compartment which is then surrounded by a lipid bilayer and edge activatorslike sodium chelate, sodium deoxycholate, span and Tween 80. They are attached to a vesicular membrane.[8]

Transfersomes were developed in order to take the advantage of phospholipids vesicles as transdermal drug carrier. These self-optimized aggregates, with the ultra-flexible membrane, are able to deliver the drug reproducibly either into or through the skin, depending on the choice of administration or application, with high efficiency. These vesicular Transfersomes are several orders of magnitudes more elastic than the standard liposomes and thus well suited for the skin penetration. Transfersomes overcome the skin penetration difficulty by squeezing themselves along the intracellular sealing lipid of the stratum corneum. There is provision for this, because of the high vesicle deformability, which permits the entry due to the mechanical stress of surrounding, in a self-adapting manner. Flexibility of Transfersomes membrane is achieved by mixing suitable surface-active components in the proper ratios[26]

Advantages of use of Transferosomes for enhancement of bioavaibility:

- These are suitable for transdermal drug delivery which have ultra-deformable vesicles which can squeeze itself through a pore many times smaller than its size owing[17]

Dendrimers:

Dendrimers are innovative polymeric carrier attracting attention due to their advantages such as three-dimensional structure, nanometer size, narrow polydispersity index, and controlled molecular structure whichcan help for accompanied with multiple functional groups. The word Dendrimers derives from a Greek word Dendra which has a meaning of reminiscent of a tree. Dendrimers has a size ranges between 1 to 100 nm with distinct domains: first is a core which is at the center containing atom with at least 2 identical chemical functions, second one is the branches which are the units repeated in geometric progression that leads to radially concentric layers known as generations and the third terminal functional groups are at the surface which determines the properties of Dendrimers. Dendrimers were applied as a versatile drug delivery system for delivery of drugs, gene, proteins and peptides. For different pharmaceutical purposes, dendrimers have also been formed as conjugates by linking to different carriers such as liposomes, CNTs, and nanoparticles. Few applications of dendrimers include both Solubilization and gene therapy. The conjugation and encapsulation of drug with dendrimers have provided a platform for oral delivery of hydrophobic.[17]

Structure of dendrimers has a well-defined size, shape and defined molecular weight and also Dendrimers are hyper-branched, globular, monodisperse, three dimensional nanoscales synthetic Polymers. Molecular chemistry and polymer chemistry both exhibit well-defined characteristics features of Dendrites[27]

Advantages of use of dendrimersfor enhancement of bioavaibility:

- Dendrimers are highly promising platforms because of the modularity andtailoring their physicochemical and biological properties which can further helps to achieve precise targeted outcomes.

Conclusion

Drugs poor solubility, its poor bioavailability have major difficulty in administration of drug, to overcome this nanotechnology have great potential. For overcoming difficulties in the administration of drugs having poor solubility's, poor bioavailability, Nanoparticulate drug carriers provide great potential. The important characteristics of the drugs such as solubility, bioavailability and Pharmacokinetic, Pharmacodynamic properties and can be improved by nano particulate carrier systems. The nanosystems has some important advantages as biocompatibility, colloidal size, drug targeting, lowered dose size, reduced toxicity, and patient compliance. Thus, nanotechnology offers opportunity for formulation scientists to extend research and development. It can be concluded that nanocarriers offer a promising vehicle for the improvement of bioavailability of poorly soluble drug candidates.

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