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REVIEW ARTICLE

Biodegradable Polymers, Role in Enhancing Bioavailability of Drug

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ABSTRACT

Biodegradable polymer has been the subject of interest for its use as a polymeric drug carrier material in dosage form design due to its appealing properties such as biocompatibility, biodegradability, low toxicity and relatively low production cost from abundant natural sources. The greatest advantage of these degradable polymers is that they are broken down into biologically acceptable molecules that are metabolized and removed from the body via normal metabolic pathways, for example, polylactides, polyglycolides, and their copolymers—the polymers will eventually break down to lactic acid and glycolic acid, enter the Kreb's cycle, and be further broken down into carbon dioxide and water and excreted through normal processes. Many biodegradable polymers are used as binder such as acacia, gelatin, whereas some used to coat tablets such as hydroxypropyl cellulose, polyethylene glycol, povidone and sodium carboxymethyl-cellulose., and to thicken suspensions and in ophthalmic solution as a protective colloid ,to stabilize emulsions and suspensions. . Sustained-release dosage forms employ polymers as shells for microencapsulated drugs, as erodible and non-erodible matrices, as barrier membranes to regulate the release of drugs by diffusion. The biodegradable polymer used in medical devices and controlled-drug-release applications are sterilizable and capable of controlled stability or degradation in response to biological conditions. These all play a very crucial role in enhancing the bioavailability of drug. This review covers all the aspects of biodegradable polymers in enhancing bioavailability of the drug.

KEYWORDS: Biodegradable polymer, Sustain release, Guar gum, bioavailability, drug

INTRODUCTION

Biodegradable polymer is a class of biodegradable and biocompatible polymer. These are produced by biological system such as micro-organisms, plants and animals. These polymer are synthesized chemically but are derived from biological starting materials such as amino acids, sugars etc A polymer based on C-C backbone tends to resist degradation, whereas heteroatom-containing polymer confer biodegradability. Biodegradability can therefore be engineered into polymers by the judicious addition of chemical linkages such as anhydride, ester or amide bonds, among others. The usual mechanism for degradation is by hydrolysis or enzymatic cleavage of the labile heteroatom bonds resulting in a scission of the polymer backbone in recent years, there has been a marked increase in interest for biodegradable materials for their use in packaging, agriculture, medicine and other areas. As a result, many researchers are investing time into modifying traditional materials to make them more user-friendly and into designing novel polymer composites out of naturally occurring materials.

POLYESTERS 1)Poly hydroxyl-alkanoates 2) Poly lactic acid **PROTEINS** 1)Collagen/Gelatin 2)Elastin 3)Polyamino acids 4)Soy,Zein,Gluten 5)Casein	**D) LIPIDS/SURFACTANTS** 1)Waxes 2)Emulsan 3)Acetoglycerides **E) POLYPHENOLS** 1)Lignin 2) Tannin

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POLYSACCHARIDES 1)Cellulose 2)Starch 3)Pectin 4)Various gums(Guar-Gum) 5)Chitin 6)Alginate 7)Agar	**F) MISCELLANEOUS** 1)Shellac 2)Natural rubber 3) Synthetic polymer from natural fats and oils(nylon from castor oil).

Table No. 1: Biopolymer Family

POLYMERS	MONOMER	FUNCTION(S)
1.Nucleic acids	Nucleotides	Carriers of genetic Informations universally recognized in all organisms
2. Protein	Alpha-amino acids	Biological catalysts (enzymes), growthfactors, receptors, structural materials(wool, leather, silk, hair, connective tissue); hormones (insulin); toxins;antibodies
.Polysaccharides Carbohydrates)	Sugars	Structural materials in plants and some higher organisms (cellulose, chitin); energy storage materials (starch,glycogen); molecular recognition (blood types), bacterial secretions
. Polyhydroxyalkanoates	Fatty acids	Microbial energy reserve materials.
. Polyphenols	Phenols	Structural materials in plants (Iignin), soil structure (humics, peat), plant defense mechanisms (tannins)
. Polyphosphates	Phosphates	Inorganic energy storage materials
7. Polysulfates	Sulfates	Inorganic energy storage materials

Table No. 2: Biopolymers found in nature and their functions

APPLICATION OF BIODEGRADABLE POLYMER IN PHARMACEUTICALS FIELD:

Biodegradable polymers generate interest among pharmaceutical scientist as they not only enhance the bioavailability of a drug but are also biocompatible.The chemical nature of the degradation products rather than of the polymer itself, often critically influences biocompatibility. Many of these materials are designed to degrade within the body, among them are

1. Polylactides (PLA).
2. Polyglycolides (PGA).
3. Poly(lactide-co-glycolides) (PLGA).
4. Polyanhydrides.
5. Polyorthoesters

Originally, polylactides and polyglycolides were used as absorbable suture material, and microparticles made from these polymers have been used as carriers for vaccine applications, gene delivery and chemotherapeutic agents all of which play an important role in controlled drug delivery systems. Controlled drug delivery technology is concerned with the systematic release of a pharmaceutical agent to maintain a therapeutic level of the drug in the body for a sustained period of time. This may be achieved by incorporating the therapeutic agent into a degradable polymer vehicle, releasing the agent continuously as the matrix erodes. Controlled drug delivery take place when a polymer, whether natural or synthetic, is sensibly combined with a drug or other active agent in such a way that the active agent is released from the material in a predesigned manne These are useful in obtaining the slow release of water-soluble drugs, the fast release of low-solubility drugs, drug delivery to specific sites, drug delivery using nanoparticulate systems, delivery of two or more agents with the same formulation, and systems based on carriers that can dissolve or degrade and be readily eliminated. .

Biodegradable polymer Chitosan has been used in several drug delivery systems both alone and in combination with other materials. A number of polymeric nanoparticles have been synthesized and studied in the past few years as promising drug delivery systems to improve delivery efficiency and reduce side-effects of drug toxicity. Nanoscale drug systems can circumvent the rapid recognition by the immune system and deliver drugs to cells with high efficiency compared with microparticle based system. Chitosan-based materials have drawn considerable attention in view of chitosan's excellent biocompatibility, biodegradability, and reactive surface functional groups for easy surface modification. The positively charged amino groups of chitosan tend to adhere to the negatively charged cell surfaces, facilitating the penetration of chitosan nanoparticles across the cell membrane of this natural polysaccharide in modified release dosage forms for oral administration is its fast dissolution rate in the stomach. To overcome this disadvantage, chemical modifications such as co-polymerisation or derivatisation have been applied. Since chitosan is positively charged at low pH values (below its pK_a value), it spontaneously associates with negatively charged polyions in solution to form polyelectrolyte complexes. These chitosan based polyelectrolyte complexes exhibit favourable physicochemical properties with preservation of chitosan's biocompatible characteristics. These complexes are therefore good candidate excipient materials for the design of different types of dosage forms. Hydrocolloids like alginate can play a significant role in the design of a controlled-release product. At low pH hydration of alginic acid leads to the formation of a high-viscosity "acid gel." Alginate is also easily gelled in the presence of a divalent cation as the calcium ion. Dried sodium alginate beads reswell, creating a diffusion barrier decreasing the migration of small molecules (e.g., drugs). The ability of alginate to form two types of gel dependent on pH, i.e., an acid gel and an ionotropic gel, gives the polymer unique properties compared to neutral macromolecules. Alginate is likely to make an important contribution in the development of polymeric delivery system. Alginate is a non-toxic polysaccharide with favorable pH sensitive properties for intestinal delivery of protein drugs. Drug leaching during hydrogel preparation and rapid dissolution of alginate at higher pH are major limitations, as it results in very low entrapment efficiency and burst release of entrapped protein drug, once it enters the intestine. To overcome these limitations, another natural polysaccharide, guargum was included in the alginate matrix along with a cross linking agent to ensure maximum encapsulation efficiency and controlled drug release.

GUAR-GUM AS A BIODEGRADABLE POLYMER:

Guar gum is a natural nonionic polysaccharide derived from the seeds of *Cymompsis tetraganolobus* (family: Leguminaceae). Chemically, guar gum is a galactomannan type of polysaccharide having very high molecular weight. Structurally ,the polysaccharide consists of a main chain of (1-4)glycosidic-linked mannose units, on which branches of single galactose units are attached through (1-6)linkage .Guaran is a creamish amorphous powder, dispersible in cold or hot water to form a nearly clear colloidal solution. It produces very high viscosity even at low concentration (3500-6000cps in 1% solution).It is non-ionic and maintain a high viscosity over a broad

range of pH(3-9) and is compatible with a variety of inorganic and organic substances, including certain dyes and various constituents of food. It bears excellent thickening, suspending, emulsifying, stabilizing and film-forming properties. At very low concentrations, it has excellent settling (flocculation) property, and acts as a filter aid. It has strong hydrogen bonding properties due to the cis-pair of –OH group in main mannan chains. Galactose to mannose ratio of guaran is about 1:2. Guar gum has recently been highlighted as an inexpensive and flexible carrier for oral extended release drug delivery. As a hydrogel, guar gum was not found to be highly suitable for controlled release of water-soluble drugs because of their relatively fast delivery, but is useful for poorly water-soluble. The wider application of Guar gum is due to its unique features such as high swelling and water retention capacity, high viscosity properties and abundant availability.

SOLID DISPERSIONS OF DRUG:

An ideal drug delivery system should be able to deliver an adequate amount of drug, preferably for an extended period of time for its optimum therapeutic activity. Most drugs are inherently not long lasting in the body and require multiple daily dosing to achieve the desired blood concentration to produce therapeutic activity. To overcome such problem, controlled release and sustained release delivery systems are receiving considerable attention from pharmaceutical industries worldwide. A controlled release drug delivery system not only prolongs the duration of action, but also results in predictable and reproducible drug-release kinetics. In order to use Curcuminoids for cancer therapy, a controlled release system is needed in order to enhance bioavailability and to reduce effective dose. Oral bioavailability of a drug depends on its solubility and/or dissolution rate, therefore efforts to increase dissolution of drugs with limited water solubility is often needed. Solubility is one of the important parameter to achieve desired concentration of drug in systemic circulation for pharmacological response and dissolution of drug is the rate determining step for oral absorption of the poorly water soluble drugs, which can subsequently affect the in vivo absorption of drug. Therapeutic effectiveness of a drug depends upon the bioavailability and ultimately upon the solubility of drug molecules. The mechanism of solubilisation involves the breaking of inter-ionic or intermolecular bonds in the solute, the separation of the molecules of the solvent to provide space in the solvent for the solute, interaction between the solvent and the solute molecule or ion. The solubility depends on the physical form of the solid, the nature and composition of solvent medium as well as temperature and pressure of system. Improvement in the dissolution rate of the poorly soluble drugs after oral administration is one of the most crucial challenges in modern pharmaceutics. Many methods are available to improve these characteristics including salt formation, micronization and addition of solvent or surface-active agents. The salt formation, solubilization and particle size reduction have commonly been used to increase dissolution rate and thereby oral absorption and bioavailability of such drugs, there are practical limitations of these techniques. The salt formation is not feasible for neutral compounds and the synthesis of appropriate salt forms of drugs that are weakly acidic or weakly basic may often not be practical. Even when salts can be prepared, an increased dissolution rate in the gastrointestinal tract may not be achieved in many cases because of the reconversion of salts into aggregates of their respective acid or base forms. The solubilization of drugs in organic solvents or in aqueous media by the use of surfactants and cosolvents leads to liquid formulations that are usually undesirable from the viewpoints of patient acceptability and commercialization. Although particle size reduction is commonly used to increase dissolution rate. The use of very fine powders in a dosage form may also be problematic because of handling difficulties and poor wettability. Solid dispersions are one of the most successful strategies to improve drug release of poorly soluble drugs. These can be defined as molecular mixtures of poorly water soluble drugs in hydrophilic carriers, which present a drug release profile that is driven by the polymer properties. Solid dispersions appear to be a better approach to improve drug solubility than these techniques, because they are easier to produce and more applicable. The solid dispersion is based on the concept that the drug is dispersed in an inert water-soluble carrier at solid state. Several water soluble carriers such as mannitol, urea, lactose, citric acid, polyvinyl pyrrolidone and polyethylene glycols are used as carriers for solid dispersion. Solid dispersion is defined as the dispersion of one or more active ingredients in an inert hydrophilic carrier or matrix at solid state prepared by the fusion, solvent or solvent-fusion method this system allows a particle size reduction of drug to nearly a molecular level. As this system exposed to aqueous media, the carrier is dissolved and the drug is released as very fine particles for quick dissolution and absorption. Solid dispersions of curcuminoids with synthetic polymer such as PVP-K30, PEG and semi-synthetic polymers such as Eudragit, HPMC, Xylitol etc are prepared to improve its aqueous solubility and drug release rate.

BIOAVAILABILITY PROBLEMS:

The pharmacological safety and efficacy of a drug for e.g., Curcumin makes it a potential compound for treatment and prevention of a wide variety of human diseases. In spite of its efficacy and safety, Curcumin has not yet been approved as a therapeutic agent, and the relative bioavailability of Curcumin has been highlighted as a major problem for this. The reasons for reduced bioavailability of any agent within the body are low intrinsic activity, poor absorption, high rate of metabolism, inactivity of metabolic products and/or rapid elimination and clearance from the body. The first reported study to examine the uptake, distribution, and excretion of Curcumin was by Wahlstrom and Blennow in 1978 using Sprague– Dawley rats. Negligible amounts of Curcumin in blood plasma of rats after oral administration of 1 g/kg of Curcumin, showed that Curcumin was poorly absorbed from the gut. Earlier researchers had shown that after oral administration of 400 mg of Curcumin to rats, no Curcumin was found in heart blood, whereas a trace amount (less than 5μg/mL) was found in the portal blood from 15 min to 24 h after administration of Curcumin. In another study using tritium-labeled Curcumin, the same group showed detectable amounts of Curcumin in blood with doses ranging from 10 to 400 mg of Curcumin per animal. When Curcumin was given orally at a dose of 2 g/kg to rats, a maximum serum concentration of 1.35 (0.23 μg/mL was observed at time 0.83 h, whereas in humans the same dose of Curcumin resulted in either undetectable or extremely low (0.006 /0.005 μg/mL at 1 h**)** serum levels. Few Scientists also investigated the pharmacokinetic properties of Curcumin administered either orally or intraperitoneal (i.p.) in mice. With oral administration of 1.0 g/kg of Curcumin, low plasma levels of 0.13 μg/mL appeared in plasma after 15 min, while a maximum plasma level of 0.22μg/mL was obtained at 1 h; plasma concentrations then declined below the detection limit by 6 h. entirely different plasma Curcumin levels were found after I.P. administration of 0.1 g/kg. Plasma Curcumin levels peaked (2.25μg/mL) within 15 min of administration and declined rapidly within 1 h. Some studies have also shown that 10 mg/kg of Curcumin given I.V. in rats gave a maximum serum Curcumin level of 0.36 $\pm$ 0.05 μg/mL, whereas a 50-fold higher Curcumin dose administered orally gave only 0.06 $\pm$ 0.01 μg/mL maximum serum level in rat. Marczylo et al. (2007) also showed a maximum serum Curcumin concentration of 6.5 $\pm$ 4.5 nano gram reached 0.5 h after oral dosing of Curcumin. These studies clearly suggest the role of route of administration on achievable serum levels of Curcumin Uptake and distribution of Curcumin in body tissues is obviously important for its biological activity, yet only a limited number of studies have addressed this issue. Some scientists have shown that after oral administration of 400 mg of Curcumin to rats only traces of unchanged drug were found in the liver and kidney. At 30 min, 90% of Curcumin was found in the stomach and small intestine, but only 1% was present at 24 h. In a study by Pan et al.(1999) using a mouse model, a Curcumin dose of 0.1 g/kg via i.p. route showed a maximum amount of Curcumin in the intestine (117 μg/g) 1 h after dosing. Spleen, liver, and kidney showed moderate Curcumin amounts of 26.1, 26.9, and 7.5 μg/g, respectively, whereas only a trace amount (0.4 μg/g) was found in brain tissue. Various studies have evaluated the metabolism of Curcumin in rodents and in humans. Once absorbed, Curcumin is subjected to conjugations like sulfation and glucuronidation at various tissue sites. The very first biodistribution study reported the metabolism of major part of Curcumin orally administered to rats .Liver was indicated as the major organ responsible for metabolism of Curcumin. Holder et al. reported that the major billiary metabolites of curcumin are glucuronides of tetrahydrocurcumin (THC) and hexahydrocurcumin (HHC) in rats. A minor biliary metabolite was dihydroferulic acid together with traces of ferulic acid. In addition to glucuronides, sulfate conjugates were found in the urine of Curcumin treated rats. Hydrolysis of plasma samples with glucuronidase have shown that 99% of Curcumin in plasma was present as glucuronide conjugates. This study also revealed curcumin–glucuronoside, dihydrocurcumin–glucuronoside, tetrahydrocurcumin (THC)–glucuronoside, and THC are major metabolites of Curcumin Curcumin in vivo. The enzymatic hydrolysis of plasma samples showed that the predominant metabolites in plasma following oral administration were glucuronides/sulfates of Curcumin. The plasma concentrations of conjugated Curcuminoids reached a maximum 1 h after administration. The presence of conjugative enzyme activities for glucuronidation and sulfation of Curcumin in liver, kidney and intestinal mucosa suggested that orally administered Curcumin is absorbed from the alimentary tract and present in the general blood circulation after largely being metabolized to the form of glucuronide/sulfate conjugates. Most studies indicate that Curcumin glucuronides and THC are less active than Curcumin itself. There are other studies which suggest that they may actually be more active than Curcumin. For example, THC was found to show better antidiabetic and antioxidant activity than Curcumin in type 2 diabetic rats, whereas Sandur et al. established much lower anti-inflammatory and antiproliferative activities of THC compared to Curcumin. Further it was also established that the metabolism of Curcumin by reduction or conjugation

generates species with reduced ability to inhibit COX-2 expression,45 indicating lesser antiproliferative effects of Curcumin metabolites like glucuronides and THC than Curcumin. Systemic elimination or clearance of curcumin from the body is also an important factor, which determines its relative biological activity. An early study by Wahlstrom and Blennow reported that when 1 g/kg Curcumin was given orally to rats, 75% of it was excreted in the feces and negligible amounts were found in the urine. Intravenous (i.v.) and i.p. administration of Curcumin resulted in biliary excretion of drug from cannulated rats. Another study using radiolabeled Curcumin showed that when drug was administered orally to rats at a dose of 400 mg/rat, nearly 40% of Curcumin in unchanged form was found in the feces. Though no detectable amount of Curcumin was found in urine, some of the derivatives like Curcumin glucuronide and sulfates were observed. The major route of elimination of the radio labeled products was through feces; urinary excretion of the label was very low regardless of the dose.A clinical study with 15 patients and oral Curcumin doses between 36 and 180 mg of Curcumin daily for up to 4 months found neither Curcumin nor its metabolites in urine, but Curcumin was recovered from feces. The absorption and elimination half-lives of orally administered Curcumin (2 g/kg) in rats were reported to be 0.31 $\pm$0.07 and 1.7 $\pm$0.5 h, respectively. But in humans, the same dose of Curcumin did not allow the calculation of these half-life values because the serum Curcumin levels were below the detection limit at most of the time points in most of the experimental subjects A lower Curcumin dose of 1 g/kg administered orally in rats was found to have an elimination half-life value of 1.45 h,38 which is not significantly different from the half-life reported for a higher Curcumin dose and may be indicative of dose independency of Curcumin elimination half-life in rats. The elimination half-life values for i.v. (10 mg/kg) and oral (500 mg/kg) Curcumin in rats were reported to be 28.1$\pm$5.6 and 44.5 $\pm$7.5 h, respectively.

OVERCOMING BIOAVAILABILITY PROBLEM:

The absorption, biodistribution, metabolism, and elimination studies of Curcumin have, unfortunately, shown only poor absorption, rapid metabolism, and elimination of Curcumin as major reasons for poor bioavailability of this interesting polyphenolic compound. Some of the possible ways to overcome these problems. Adjuvants, which can block metabolic pathways of curcumin, are one of the major means that are being used to improve its bioavailability. Nanoparticles, liposomes, micelles, and phospholipid complexes are other promising novel formulations, which appear to provide longer circulation, better permeability, and resistance to metabolic processes.

1. ADJUVANTS:

Piperine, a known inhibitor of hepatic and intestinal glucuronidation, was combined with Curcumin and administered in rats and healthy human volunteers. In rats, 2 g/kg of Curcumin alone produced a maximum serum curcumin level of 1.35 (0.23 μg/mL at 0.83 h, whereas concomitant administration of piperine (20 mg/kg) increased the serum concentration of Curcumin for a short period; time to maximum peak level (*T*max) was significantly increased, while elimination half-life and clearance were significantly decreased resulting in an increase of bioavailability of 154%. In contrast, in humans receiving a dose of 2 g Curcumin alone, serum levels were either undetectable or very low. Concomitant administration of piperine, however, produced 2000% increase in bioavailability. Thus, the effect of piperine on bioavailability of Curcumin has been shown to be much greater in humans than in rats. Six healthy adult male human volunteers took 2 g of Curcumin with or without 5 mg of piperine (as bioperine) in this crossover design study. Three people were randomized to receive Curcumin only, while the remaining 3 received the Curcumin + piperine combination. One week following initial drug administration, volunteers were crossed over to the opposite therapies and blood samples were again obtained for evaluation. Doubling of the absorption of Curcumin was found in the presence of piperine. The effect of piperine on tissue uptake of a radio labeled fluoropropyl-substituted Curcumin was evaluated in mice. Brain uptake of Curcumin after 2 min was increased by 48% due to co-administration of piperine relative to that without piperine. The glucuronidation inhibiting effect of piperine28 and the established lesser activity of Curcumin glucorinides will indicate that inhibition of glucuronidation by piperine may be the major mechanism by which it increases the bioavailability of Curcumin.

2. NANOPARTICLES:

Recently, targeted and triggered drug delivery systems accompanied by nanoparticle technology have emerged as prominent solutions to the bioavailability of therapeutic agents. Nanoparticle-based delivery systems will probably be suitable for highly hydrophobic agents like Curcumin circumventing the pitfalls of poor aqueous solubility. However, very few studies have been published citing Curcumin nanoparticles. A recent study has reported the synthesis, physicochemical characterization and cancer related application of a polymer-based nanoparticle of

Curcumin namely "nanocurcumin" with less than 100 nm size. Nanocurcumin was found to have similar *in* V*itro* activity as that of free Curcumin in pancreatic cell lines. Like free Curcumin, nanocurcumin also inhibits activation of the transcription factor NFκB, and reduces steady state levels of pro-inflammatory cytokines like interleukins and TNF-alpha Solid lipid nanoparticles (SLNs) loaded with Curcuminoids for topical application were developed and characterized. Curcuminoid loaded SLNs having 450 nm size were found to be stable for 6 months at room temperature and gave prolonged *in* V*itro* release of Curcuminoids up to 12 h. Furthermore, the light and oxygen sensitivity of Curcuminoids was strongly reduced by incorporating Curcuminoids into this unique type of formulation. An *in Vivo* study with healthy volunteers revealed the improved efficiency of a topical application cream containing Curcuminoid loaded SLNs over that containing free Curcuminoids.

3. LIPOSOMES MICELLES, AND PHOSPHOLIPID COMPLEXES:

Liposomes are excellent drug delivery systems since they can carry both hydrophilic and hydrophobic molecules. Li et al. investigated the *in* V*itro* and *in* V*ivo* antitumor activity of liposomal Curcumin against human pancreatic carcinoma cells and demonstrated that liposomal Curcumin inhibits pancreatic carcinoma growth and, in addition, exhibits antiangiogenic effects.Ruby etal. also reported the antitumor and antioxidant activities of neutral unilamellar liposomal Curcuminoids in mice. Kanwar et al. evaluated the *in* V*itro* cellular uptake of liposomal and albumin loaded Curcumin.

Micelles and phospholipid complexes can improve the gastrointestinal absorption of natural drugs, thereby giving higher plasma levels and lower kinetic elimination resulting in improved bioavailability. The intestinal absorption of Curcumin and micellar curcumin formulation with phospholipid and bile salt was evaluated using an *in* V*itro* model consisting of everted rat intestinal sacs. This study suggested biological transformation of Curcumin during absorption. Further, the *in* V*itro* intestinal absorption of Curcumin was found to increase from 47% to 56% when the same was present in micelles Pharmacokinetic studies have also demonstrated that a polymeric micellar Curcumin gave a 60-fold higher biological half-life for Curcumin in rats compared to Curcumin solubilized in a mixture of DMA, PEG and dextrose. Phospholipid complex formulations of several natural drugs, such as silymarin and dolichol, have been found to show improved bioavailability. Liu et al., for example, showed a significant improvement in Curcumin bioavailability due to Curcumin-phospholipid complex formation. In this study, Curcumin (100 mg/kg) and Curcumin– phospholipid complex (corresponding to 100 mg/kg of Curcumin) were administered orally to Sprague–Dawley male rats. Curcumin–phospholipid complex showed a maximum plasma Curcumin level of 600 ng/mL 2.33 h after oral administration as opposed to that of free Curcumin having maximum plasma concentration of 267 ng/mL after 1.62 h of oral dosing. About a 1.5-fold increase in Curcumin half- life in rats was found in this study for the Curcumin phospholipid complex over free Curcumin. These results indicate that the Curcumin phospholipid complex can significantly increase circulating levels of presumably active Curcumin in rats. Another study showed a 3-fold increase in aqueous solubility and a better hepatoprotective effect for a Curcumin phospholipid complex compared to free Curcumin. Curcumin–phospholipid complex significantly protected the liver from carbon tetrachloride induced acute liver damage in rats by restoring enzyme levels of liver glutathione system and that of superoxide dismutase, catalase and thiobarbituric acid reactive substances.

4. DERIVATIVES AND ANALOGUES:

The chemical structure of Curcumin plays a pivotal role in its biological activity. For example, isomerization has been proved to have an influence on antioxidant activity of Curcumin. Thus, researchers hope to achieve improved biological activity of Curcumin by structural modifications. Numerous studies dealing with the enhanced biological activity of Curcumin derivatives and/or analogues can be found in the literature. A review by Mosley et al. for example, systematically describes several studies dealing with the biological activity relationships of Curcumin and its derivatives. A Curcumin analogue designated EF-24 was reported to be a lead compound displaying increased antitumor action *in* V*itro* and *in* V*ivo* in comparison to Curcumin. Another strategy to improve the biological activity of Curcumin was to chelate it with metals. The presence of two phenolic groups and one active methelene group in a Curcumin molecule makes it an excellent ligand for any chelation. Several metal chelates of Curcumin are reported to possess biological activity over that of free Curcumin. Copper complexes of Curcumin and its derivatives were found to be better antitumor agents than were the parent compounds. Studies by Sui et al. showed that the modest activity of Curcumin as an *in* V*itro* inhibitor of HIV-1and HIV-2 proteases is enhanced more than 10-fold when Curcumin is complexed with boron.

5. BIOCONJUGATES:

Bioconjugates can increase the cellular uptake and hence better bioavailability of Curcumin. For example, BCM-95 (also called Biocurcumax) Curcuminoids combined with turmeric oil (turmerons) in a specific proportion enhanced the bioavailability and showed better absorption into blood and had longer retention time compared to Curcumin.

6. IMPROVE THE SOLUBILIZATION OF POORLY SOLUBLE DRUGS (CURCUMINOIDS):

Solubility is one of the important parameter to achieve desired concentration of drug in systemic circulation for pharmacological response to be shown and dissolution of drug is the rate determining step for oral absorption of the poorly water soluble drugs, which can subsequently affect the in vivo absorption of drug. Therapeutic effectiveness of a drug depends upon the bioavailability and ultimately upon the solubility of drug molecules. The mechanism of solubilisation involves the breaking of inter-ionic or intermolecular bonds in the solute, the separation of the molecules of the solvent to provide space in the solvent for the solute, interaction between the solvent and the solute molecule or ion. The factors which affect solubility are particle size, temperature, pressure, nature of solute and solvent, molecular size, polarity and polymorphs

SOLID DISPERSION:

The solid dispersion approach to reduce particle size and therefore increase the dissolution rate
and absorption of drugs was first recognized in 19611 The term —solid dispersions refers to the dispersion of one or more active ingredients in an inert carrier in a solid state, frequently prepared by the melting (fusion) method, solvent method, or fusion solvent-method. Novel additional preparation techniques have included rapid precipitation by freeze drying18 and using supercritical fluids and spray drying. often in the presence of amorphous hydrophilic polymers and also using methods such as melt extrusion The most commonly used hydrophilic carriers for solid dispersions include polyvinylpyrrolidone, polyethylene glycols, Plasdone-S630. Many times surfactants may also used in the of solid dispersion. Surfactants like Tween-80, Docusate sodium, Myrj-52, Pluronic-F68 and Sodium Lauryl Sulphate used .The solubility of etoposide ,glyburide ,itraconazole , ampelopsin , valdecoxib, celecoxib, halofantrine can be improved by solid dispersion using suitable hydrophilic carriers. The eutectic combination of chloramphenicol/urea and sulphathiazole/ urea served as examples for the preparation of a poorly soluble drug in a highly water soluble carrier.

METHOD OF PREPARATION OF SOLID DISPERSIONS:

1. HOT MELT METHOD:

Sekiguchi and Obi used a hot melt method to prepare solid dispersion. Sulphathiazole and urea were melted together and then cooled in an ice bath. The resultant solid mass was then milled to reduce the particle size. Cooling leads to supersaturation, but due to solidification the dispersed drug becomes trapped within the carrier matrix. A molecular dispersion can be achieved or not, depends on the degree of supersaturation and rate of cooling used in the process. An important requisite for the formation of solid dispersion by the hot melt method is the miscibility of the rug and the carrier in the molten form. When there are miscibility gaps in the phase diagram, this usually leads to a product that is not molecularly dispersed. Another important requisite is the thermostability of the drug and carrier.

2. SOLVENT EVAPORATION METHOD:

Tachibana and Nakumara34 were the first to dissolve both the drug and the carrier in a common solvent and then evaporate the solvent under vacuum to produce a solid solution. This enabled them to produce a solid solution of the highly lipophilic β-carotene in the highly water soluble carrier polyvinylpyrrolidone. An important prerequisite for the manufacture of a solid dispersion using the solvent method is that both the drug and the carrier are sufficiently soluble in the solvent. The solvent can be removed by various methods like by spraydrying or by freeze-drying. Temperatures used for solvent evaporation generally lie in the range 23-65C .The solid dispersion of the 5- lipoxygenase/cyclooxygenase inhibitor ER-34122 shown improved in vitro dissolution rate compared to the crystalline drug substance which was prepared by solvent evaporation. These techniques have problems such as negative effects of the solvents on the environment and high cost of production due to extra facility for removal of solvents. Due to the toxicity potential of organic solvents employed in the solvent evaporation method, hot melt extrusion method is preferred in preparing solid solutions

3. HOT-MELT EXTRUSION:

Melt extrusion was used as a manufacturing tool in the pharmaceutical industry as early as 1971.
It has been reported that melt extrusion of miscible components results in amorphous solid solution formation, whereas extrusion of an immiscible component leads to

amorphous drug dispersed in crystalline excipient. The process has been useful in the preparation of solid dispersions in a single step.

4. MELTING –SOLVENT METHOD:

A drug is first dissolved in a suitable liquid solvent and then this solution is incorporated into the melt of polyethylene glycol, obtainable below 70C without removing the liquid solvent. The selected solvent or dissolved drug may not be miscible with the melt of the polyethylene glycol. Also polymorphic form of the drug precipitated in the solid dispersion may get affected by the liquid solvent used.

SUITABLE PROPERTIES OF A CARRIER FOR SOLID DISPERSIONS:

Following criteria should be considered during selection of carriers: (a) High water solubility – improve wet ability and enhance dissolution (b) High glass transition point – improve stability (c) Minimal water uptake (reduces Tg) (d) Soluble in common solvent with drug –solvent evaporation (e) Relatively low melting point –melting process (f) Capable of forming a solid solution with the drug-similar solubility parameters

Chemical Class	Examples
1. Acids	Citric acid, Tartaric acid, Succinic acid
2. Sugars	Dextrose, Sorbitol, Sucrose, Maltose, Galactose, Xylitol
3. Polymeric Materials	Polyvinylpyrrolidone, PEG-4000, PEG-6000, Carboxymethyl cellulose, Hydroxypropyl cellulose, Guar gum, Xanthan gum, Sodium alginate, Methyl cellulose, HPMC, Dextrin, Cyclodextrins, Galactomannan
4. Surfactants	Polyoxyethylene stearate, Poloxamer, Deoxycholic acid, Tweens and Spans, Gelucire 44/14, Vitamine E TPGS NF
5. Miscellaneous	Pentaerythritol, Urea, Urethane, Hydroxyalkyl xanthenes

Table No. 3: Carriers for Solid Dispersions

ADVANTAGES OF SOLID DISPERSIONS OVER OTHER STRATEGIES TO IMPROVE BIOAVAILABILITY OF POORLY WATER SOLUBLE DRUGS:

Improving drug bioavailability by changing their water solubility has been possible by chemical or formulation approaches. Chemical approaches to improving bioavailability without changing the active target can be achieved by salt formation or by incorporating polar or ionizable groups in the main drug structure, resulting in the formation of a pro-drug. Solid dispersions appear to be a better approach to improve drug solubility than these techniques, because they are easier to produce and more applicable. For instance, salt formation can only be used for weakly acidic or basic drugs and not for neutral. Furthermore, it is common that salt formation does not achieve better bioavailability because of its in vivo conversion into acidic or basic forms. Formulation approaches include solubilization and particle size reduction techniques, and solid dispersions, among others. Solid dispersions are more acceptable to patients than solubilization products, since they give rise to solid oral dosage forms instead of liquid as solubilization products usually do. Milling or micronizations for particle size reduction are commonly performed as approaches to improve solubility, on the basis of the increase in surface area. Solid dispersions are more efficient than these particle size reduction techniques, since the latter have a particle size reduction limit around 2–5 mm which frequently is not enough to improve considerably the drug solubility or drug release in the small intestine and, consequently, to improve the bioavailability. Moreover, solid powders with such a low particle size have poor mechanical properties, such as low flow and high adhesion, and are extremely difficult to handle.

SOLID DISPERSIONS DISADVANTAGES:

Despite extensive expertise with solid dispersions, they are not broadly used in commercial products, mainly because there is the possibility that during processing

(mechanical stress) or storage (temperature and humidity stress) the amorphous state may undergo crystallization and dissolution rate decrease with ageing. The effect of moisture on the storage stability of amorphous pharmaceuticals is also a significant concern, because it may increase drug mobility and promote drug crystallization. Moreover, most of the polymers used in solid dispersions can absorb moisture, which may result in phase separation, crystal growth or conversion from the amorphous to the crystalline state or from a metastable crystalline form to more stable structure storage. This may result in decreased solubility and dissolution rate.

COMBINATION OF SOLID DISPERSION WITH SUSTAINED RELEASE TECHNIQUES:

One approach is direct modification of character of solid dispersion by using water-insoluble or slower dissolving carriers instead of conventional hydrophilic polymers. In this technique, a selection of suitable carrier for each drug would be a critical factor. Another approach is a membrane controlled sustained release tablet containing solid dispersion. Since the release of drug from such a diffusion-controlled system is driven by the gradient of the drug concentration resulting from penetration of water.

SOME EXAMPLE OF SOLID DISPERSIONS IN MARKET:

Sporanox® (itraconazole)
Intelence® (etravirine)
Prograf® (tacrolimus)
Crestor® (rosuvastatin)
Gris-PEG® (griseofulvin)
Cesamet® (nabilone)

BASIL M. BARISH ET AL. (2010):

The oral sustained release microspheres of Cefazolin sodium were formulated by using guar gum as polymer. Cefazolin sodium microspheres were formulated by solvent evaporation technique, using Guar gum at 1:1, 1:2, 1:3, 1:4, 1:5 drug:polymer ratios, this method was most suitable as it requires no heating procedure and cefazolin sodium is a thermoliable drug, all the formulated microspheres were found to be discrete, spherical, free flowing and specific yield was obtained. Five formulations coded as F1 ,F2, F3, F4 and F5 with 1:1, 1:2, 1:3, 1:4, 1:5 drug: polymer ratio were comparatively evaluated for their better release profile. The percentage release of drug from Guar gum formulations (F1, F2, F3, F4, and F5) was 42.08, 39.38, 61.09, 61.95, and 69.66 respectively. It was concluded that on increasing the polymer ratio the release of the drug also increased.

NATTHA .K ET AL. (2009):

Solid dispersions (SD) of Curcumin :polyvinylpyrrolidone in the ratio of 1:2, 1:4, 1:5, 1:6, and 1:8 were prepared in an attempt to increase the solubility and dissolution. Solubility, dissolution, powder X-ray diffraction (XRD), differential scanning calorimetry (DSC) and Fourier transform infrared spectroscopy (FTIR) of solid dispersions, physical mixtures (PM) and Curcumin were evaluated. Both solubility and dissolution of Curcumin solid dispersions were significantly greater than those observed for physical mixtures and intact Curcumin. The powder X-ray diffractograms indicated that the amorphous Curcumin was obtained from all solid dispersions. It was found that the optimum weight ratio for Curcumin:PVP K-30 is 1:6. The 1:6 solid dispersion still in the amorphous from after storage at ambient temperature for 2 years and the dissolution profile did not significantly different from freshly prepared.

PHAECHAMUD .T ET AL. (2010):

The extract of Curcuminoids was prepared from turmeric. It composed of Curcumin 39.14%, desmethoxy-curcumin 15.47% and bisdesmethoxy-curcumin 15.90%. The solid dispersion (SD) between the curcuminoids and different carriers (PEG 4000, PEG 6000, PEG 20000, HPMC, xylitol, chitin, ac-di-sol, citric acid, sucrose and -cyclodextrin) in ratio of 1:10 was prepared by co-grinding. The dissolution of Curcuminoids from SD was performed in a dissolution medium containing 0.02%w/v tween 80. The great dissolution rate of Curcuminoids was observed in SD using xylitol as carrier. From DSC, IR and powder x-ray diffraction studies, no chemical interaction between Curcuminoids and xylitol. The increase of Curcuminoids dissolution rate from this co-grinding mixture could be explained by improving wettability of hydrophobic Curcuminoids particles. Xylitol effectively increased the dissolution of Curcuminoids from solid dispersion.

FUTURE PROSPECTS:

Biodegradable polymers can be explored more for their role in enhancing bioavailability of a drug and also they can be physically and chemically modified/derivatized to carboxymethyl and other derivatives for increasing his bioavailability of the drug. Thease can be further formulated for nano drug delivery.

REFERENCES:

1. Ain S and Parveen S."An Overview on Various Approaches used for Solubilization of Poorly Soluble Drugs". The Pharma Research, 2:84-104, 2009.

2. Arora G , Maliki K, Sharma J, Nagpal M, et al. "Preparation and Evaluation of Solid Dispersions of Modified Gum Karaya and Aceclofenac : Controlled Release Application". Der Pharmacia Sinica , 2 :142-151, 2011

3. Barish,Venkatnarayanan R "Formulation and Relative Evaluation of Cefazolin Sodium Microspheres with Guar gum in Different Ratios" .Research Journal of Pharmaceuticals, Biology and Chemical Sciences,1:536, 2010

4. Cheng L, Hsu H. "PhaseI Clinical trial of Curcumin, a chemopreventive agent in patients with high risk or premaligant lesions". Anticancer Research, 21:2895-2900, 2001

5. Craig D Q M "The mechanisms of drug release from solid dispersions in water-soluble polymers". Int. J. Pharm. 231:131–144, 2002

6. Das A,Wadhwa S and Srivastava AK "Cross-linked guargum hydrogel discs for colon
specific delivery of Ibuprofen". Formulation and Invitro evaluation.Drug Delivery, 13:139-142, 2006.

7. Davaran S, Rashidi MR, Khani A. "Synthesis of chemically cross-linked hydroxy propyl methyl cellulose hydrogels and their application in controlled release of 5-amino salicylic acid" Drug Devlivery Ind Pharm, 33: 881-887, 2007

8. Ganesan V and Jayachandran DL "Design and Evaluation of Matrix Tablets of Ambroxol Hydrochloride using Guargum". Research Journal of Pharmacy and Technology, 1:1309-1314, 2008

9. Hoare T and Kohane D. "Hydrogels in drug delivery: Progress and challenges".Polymer,49:1993-2007, 2008

10. Kumawat M,Reddy R,Moorthy S,et al . "Formulation of Sustain Release Solid Dispersions of Verapamil Hydrochloride Using Ethyl Cellulose and Eudragit RSPO". International Journal of Pharmacy and Pharmaceutical Sciences, 3:116-122, 2011

11. Modi A, Tayade P. "Enhancement of Dissolution Profile by Solid Dispersion (Kneading) Technique".AAPS PharmSciTech, 7: 68, 2006

12. Manjanna K, Kumar T, Shivakumar B Natural Polysaccharide "Hydrogels as Novel Excipients for Modified Drug Delivery Systems" International Journal of ChemTech ResearcH, 2:113-121, 2010

13. Pemiroz F,Acarturk F and Jakka S "In-vitro and In-vivo evaluation of mesalazine-guar gum matrix tablets for colonic drug delivery "Journal of Drug Targeting, 12: 105-112., 2004

14. Serajuddin A. "Solid dispersion of poorly water-soluble drugs: early promises, subsequent problems and recent breakthroughs" Journal of Pharmaceutics Science, 88:1058-1066, 1999

15. Tiwari R, Srivastava B and Rai A. "Solid Dispersions:An Overview To Modify Bioavailability of Poorly Water Soluble Drugs".International Journal of Pharm Tech Research,1:1338-1349, 2009