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Bioavailability enhancement of poorly water soluble drugs: A review

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Abstract

Solubility is the phenomenon of dissolution of solid in liquid phase to give a homogenous system and is one of the important parameter to achieve desired concentration of drug in systemic circulation for pharmacological response. Poorly water-soluble drugs after oral administration often require high doses in order to reach therapeutic plasma concentrations. The bioavailability of an orally administered drug depends on its solubility in aqueous media over different pH ranges. The insufficient dissolution rate of the drug is the limiting factor in the oral bioavailability of poorly water soluble compounds. Various techniques are used for the improvement of the aqueous solubility, dissolution rate, and bioavailability of poorly water soluble drugs include micronization, chemical modification, pH adjustment, solid dispersion, complexation, co-solvency, micellar solubilization, hydrotropy etc. The purpose of this review article is to describe the techniques of solubilization for the attainment of effective absorption with improved bioavailability.

Key-Words: Active Pharmaceutical Ingredients (APIs), co-solvent, β-cyclodextrin, solid dispersion.

Introduction

Throughout the past decade, in the development and commercialization of new pharmaceutical products, the formulation and delivery of Active Pharmaceutical Ingredients (APIs) have played a crucial role. To improve bioavailability, stability and convenience to the patient, is the major objective of formulation chemistry[1]. Bioavailability means the rate and extent to which the active substance or therapeutic moiety is absorbed from a pharmaceutical form and becomes available at the site of action[2]. The bioavailability of an orally administered drug depends on its solubility in aqueous media over the pH range of 1.0–7.5 and the rate of mass transfer across biological membranes[3]. In the oral bioavailability of poorly water soluble compounds, the insufficient dissolution rate is the limiting factor[4]. Some new technologies have been recently developed to improve wettability and aqueous solubility of APIs. These methods are based on the use of compressed gases, supercritical fluids, anti-solvent[5].

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The critical requirement for a poorly water-soluble drug for absorption to be possible from the gastrointestinal (GI) tract is, achieving a solution of drug in the GI fluid. Horter and Dressman[6] defined a poorly water-soluble drug as the one whose dissolution in the GI fluid under ordinary conditions takes a longer time than its transition through the absorption sites in the GI tract. To increase dissolution rates of drugs, salt formation, particle size reduction etc., have commonly been used but achieving desired bioavailability enhancement may not always be possible due to some practical limitations with these techniques[7]. Solid dispersion systems have shown promising results in increasing bioavailability of poorly water-soluble drugs in which the drug is dispersed in solid water-soluble matrices either molecularly or as fine particles[8,9,10] and Serajuddin et al.[11] reported that some of the manufacturing problems with solid dispersion systems may be overcome by using surface-active and self-emulsifying carriers.

Methods for solubility enhancement

Supercritical fluid technology

Supercritical fluids are fluids whose temperature and pressure are greater than their critical temperature (Tc) and critical pressure (Tp). In the supercritical fluid (SCF) process, micronization is done by the supercritical fluid which is highly compressible, and allows moderate changes in pressure to greatly alter the

density and mass transport characteristics that largely determine its solvent power. The SCF process can create nanoparticle of particles 5–2,000 nm in diameter[12, 13]. Solvent extraction-evaporation, solvent diffusion and organic phase separation are some conventional methods which require the use of organic solvents. These organic solvents are hazardous to the environment as well as to physiological systems. Supercritical fluids are environmentally safe. Therefore, to prepare biodegradable micro and nano-particles the supercritical fluid technology has been investigated as an alternative[14]. A supercritical fluid can be generally defined as a solvent at a temperature above its critical temperature, at which the fluid remains a single phase regardless of pressure[14]. The most widely used supercritical fluid is supercritical CO_2 (SC CO_2) because of its mild critical conditions (T_c = 31.1°C, P_c = 73.8 bars), non-toxicity, non-flammability, and low price.

The most common processing techniques involving supercritical fluids are

1. Supercritical anti-solvent (SAS)
2. Rapid expansion of critical solution (RESS).

A liquid solvent is required in the process of SAS to dissolve the solute to be micronized; at the process conditions, because the solute is insoluble in the supercritical fluid, the liquid solvent should be completely miscible with the supercritical fluid (SC CO_2), eg methanol. The extract of the liquid solvent by supercritical fluid leads to the instantaneous precipitation of the solute[15]. Thote and Gupta[16] reported the use of a modified SAS method for formation of hydrophilic drug dexamethasone phosphate drug nanoparticles for microencapsulation purpose by SAS method. Unlike the SAS process, in the RESS process, the solute is dissolved in a supercritical fluid (such as supercritical methanol) and then through a small nozzle the solution is rapidly expanded into a region lower pressure[14]. Thus the solvent power of supercritical fluids decreases and the solute eventually precipitates. This technique is basically solvent free, so this is a clean technique. RESS and its modified process are used for the production of polymeric nanoparticles[17]. Supercritical fluid technology technique requires specially designed equipment and is more expensive. The advantage of supercritical fluid technology technique is that, it is environmentally friendly and suitable for mass production.

Prodrug approach

Throughout the past decades prodrug approaches have been used to improve the pharmaceutical properties such as solubility, taste, odor, stability, etc. Designing of prodrug is also used to improve the physicochemical properties such as compound lipophilicity and solubility to prevail over the pharmacokinetic demerits associated with drug molecules. The chemical decomposition and presystemic metabolism is to be reduced by the use of prodrug approach. The basic principle associated with is to cover the undesired functional group(s) with another functional group, which usually are referred as promoiety. Designing prodrug for improving bioavailability is one of the lucrative approaches especially for protein and peptide molecules. Designing of cyclic prodrug using C and N terminal ends reduced the metabolic degradation caused by exopeptidase. A recent study involved synthesis of cyclic hexapeptide to improve the enzymatic stability and permeability through biological membranes[18]. It showed increased permeability of cyclic prodrug than parent molecule. Derivatization is another lucrative approach for synthesis of prodrug to improve bioavailability of drug molecules especially for peptide molecules. Derivatization could be possible in C terminal amide group, N terminal amide group and phenol group in various peptide molecules[19].

Microemulsion formulations

Microemulsion is a lipid based delivery system whose major advantages include high solubilization potential, thermodynamic stability, improved dissolution of lipophilic drugs[20] and surfactant-induced permeability enhancement[21].

Physico-chemical properties of microemulsions include transparency, optical isotropy, low viscosity and thermodynamic stability[22-24]. It can also be used for transdermal and dermal delivery of drugs as an efficient route of drug administration[25-28]. There are several mechanisms to explain the benefits of using microemulsions for the transdermal and dermal delivery of drugs[29, 30]. Large amount of a drug can be incorporated in the formulation. Due to this, the thermodynamics towards the skin is also increased which may favor its partitioning into the skin. The ingredients of microemulsion may increase the permeation rate of drug. Table 1 summarizes successfully work done on microemulsions and self-emulsifying systems for improvement of bioavailability.

Dissolution enhancement by physical modification of the drug

The solubility of a drug determines the dissolution behavior of an active pharmaceutical ingredient (API) in the formulation as well as therapeutic efficacy of the drug. Reduction of particle size, complexation, and solid dispersions of drug in suitable carriers are some commonly used physical modifications of the API. In solubility limited absorption (intrinsic solubility controlled), the formulation approach is commonly

used to enhance the solubility of the API and this approach also includes the use of surfactants in the formulation (solid dispersions), non-crystalline materials, and different salt forms of API.

Particle Size Reduction

According to the modified Noyes–Whitney equation, the rate of mass lost from the particle is given by

$$-dM/dt = DS/h (CS - CB)$$

where M is the mass of compound dissolved in time t, D is the diffusion coefficient of the compound in medium, S is surface area, h is thickness of the stagnant film layer, CS is the saturated solubility of the compound at the particle–media interface, and CB is the concentration of compound in the bulk medium.

By evaluating each term in the equation, we can conclude that dissolution rate of the drug can be enhanced with effective changes in two parameters, surface area and solubility and both are controlled and easily measurable. From a bioavailability point of view, any modification in the film thickness h or the diffusion coefficient D is either impractical or useless. The film thickness only can be decreased by increasing the stirring rate dramatically and this condition is not applicable to the in vivo environment. However, the diffusion coefficient is a function of temperature, the radius of the molecule, and the viscosity of the medium, all of which are constant under in vivo conditions.

a) Micronization

For many decades, the dissolution rate is being increased by reducing the particle size of poorly water-soluble drugs. Conventional methods of particle size reduction, such as comminution and spray drying, rely upon mechanical stress to disaggregate the active compound. Today, micronization of drugs is widely done by milling techniques using a jet mill, rotor stator, colloidal mill, and air attrition[33]. Kornblum and Hirschorn[34] evaluated two specific methods of micronization, spray drying and air attrition, which provided drug forms of different specific surface areas and particle size ranges. With the aforementioned advantages, micronization has some limitations; micronization of sparingly or poorly soluble drugs is by no means a guarantee of better dissolution and absorption.

b) Nanotechnology

Nanotechnology will be used to improve drugs having poor solubility. Nanotechnology is basically for the use of materials and structures at the nano-scale level of approximately 100 nm or less than 100 nm[35]. For many new chemical entities with very low solubility, oral bioavailability enhancement by micronization is not sufficient. Micronized product has the tendency to agglomerate, which leads to decreased effective surface area for dissolution[36]. So nanonisation is used[37]. Table 2 shows some marketed nanotechnology based approaches to improve bioavailability.

Solid Dispersions

The dispersion method allows the preparation of physically modified forms of the drug that are much more rapidly soluble in water than the pure compound. The most commonly used hydrophilic carriers for solid dispersions include polyvinyl pyrrolidone, polyethylene glycols, and plasdone-S630. Surfactants may also be used in the formation of solid dispersions. Surfactants like Tween-80, Myrj-52, and Pluronic-F68 and sodium lauryl sulfate are used. Chiou and Riegelman[39] recommended polyethylene glycol, a water-soluble polymer, as an excellent universal carrier for improving the dissolution rate and oral absorption of water-insoluble drugs. They reported that the dissolution of griseofulvin, as well as its absorption and total availability in both dog[40] and man[41], was significantly higher when the solid was dispersed in polyethylene glycol 4000, 6000, or 20,000, as compared with the traditionally micronized form of the drug. Deshpande and Agrawal[42] reported that the dissolution rates of chlorothiazide, hydrochlorothiazide, flumethiazide, and cyclopentathiazide also were increased when dispersed in polyethylene glycol 6000. Takai et al.[43] studied the quantitative relationship of the dissolution behavior of griseofulvin with the properties of the polyethylene glycol polymer used. Various newer strategies investigated by several investigators include fusion (melting), solvent evaporation, lyophilization (freeze drying), melt agglomeration, extrusion, spray drying, surfactant use, electrostatic spinning, and super critical fluid technology for solid dispersions.

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. However, the definition can now be broadened to include certain nanoparticles, microcapsules, microspheres and other dispersion of the drug in polymers prepared by using any one of the process. Sekiguchi and Obi suggested that the drug was present in a eutectic mixture in a microcrystalline state, after few years Goldberg et.al. reported that all drug in solid dispersion might not necessarily be presented in a microcrystalline state, a certain fraction of the drug might be molecular dispersion in the matrix, thereby forming a solid solution[16]. Once the solid dispersion was exposed to aqueous media & the carrier dissolved, the drug was released as very fine, colloidal particles. Because of greatly enhanced surface area obtained in this way, the dissolution rate and the bioavailability of

poorly water-soluble drugs were expected to be high[15]. The commercial use of such systems has been limited primarily because of manufacturing problems with solid dispersion systems may be overcome by using surface active and self-emulsifying carriers. The carriers are melted at elevated temperatures and the drugs are dissolved in molten carriers. Table 3 shows various materials used as carriers for preparation of solid dispersions.

Methods of preparation of solid dispersion[45]

Hot Melt Extrusion: Melt extrusion was used as a manufacturing tool in the pharmaceutical industry as early as 1971. Hot melt extrusion has in recent years gained wide acceptance as a method of choice for the preparation of solid dispersions. The hot-melt extrusion process is highly dependent on the physicochemical properties of the compounds and their miscibility in the molten state. There is a potential that the API, the polymer or both may degrade if excessively high temperature is needed in the melt extrusion process, especially when the melting point of the API is high. This report details a novel method where the API was first converted to an amorphous form by solvent evaporation and then melt-extruded with a suitable polymer at a drug load of at least 20% w/w. By this means, melt extrusion could be performed much below the melting temperature of the drug substance 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 excipients. The process has been useful in the preparation of solid dispersions in a single step[46]. The amorphous melt extrusion formulations showed higher bioavailability than formulations containing the crystalline API. There was no conversion of amorphous solid to its crystalline form during accelerated stability testing of dosage forms.

Solvent evaporation: This method works best for water insoluble drugs. The solvent evaporation method provides good encapsulation efficiency and produces amorphous form of compound, which gave better solubility and dissolution than its crystalline form. Like required quantity of drug dissolved in suitable solvent (like Methanol for nitrezepam), then added to polymer by stirring & melted into water-bath (50-60^{0}C). This mixture was kept in water-bath until solvent gets evaporated. Afterward it was cooled to room temperature & pass through sieves as per requirement[47]. This Process involves, active ingredient dissolved or dispersed in solution of the polymer in a suitable water-immiscible & volatile organic Solvent. This solution or dispersion is emulsified in an aqueous medium to form micro droplets. The organic solvent then diffuses into the aqueous phase and evaporates at the water/air interface. The micro droplets solidify and solid, free-flowing microspheres are obtained after complete organic solvent evaporation, filtration and drying. Many variables can influence the preparation and properties of microspheres[48]. Many different methods (including spray- and freeze-drying) have been used to remove organic solvents from solid dispersions. Simonelli et al. evaporated the ethanolic solvent with a steam bath and removed the residual solvent by applying reduced pressure. Chiou and Riegelman dried an ethanolic solution of griseofulvin and PEG 6000 in an oil bath at 115^{0}C until ethanol bubbles were no longer formed. The viscous mass was then solidified by cooling it in a stream of cold air[48].

Removal of organic solvents such as chloroform from large masses of material may be difficult because the solid dispersions are usually amorphous and may be viscous and waxy. Additional problems may be residual solvent, the cost of recovering the solvents and the further processing (such as pulverization and sifting) of the solidified product[48].

Co-precipitation: Co-precipitation is a recognised technique for increasing the dissolution of poorly water soluble drugs, so as to consequently improve bioavailability. Co-precipitationtechniques employ the use or solvents of an organic solvent to dissolve and intimately disperse the drug and carrier molecules as herein before described[49]. Separation of the drug and carrier from the solvent on precipitation can rely on the solubility properties of either the drug or carrier**.** The required quantity of polymer and the drug were mixed and then solvent was added to obtain clear solution. The Solution was first dried under vacuum at room temperature and kept inside incubator(37^{0}C) for 12 hrs. Finally it was passed through sieves (as per requirement) [48].

Dropping method: The dropping method facilitate the crystallization of different chemicals, is a new procedure for producing round particles from melted solid dispersions. This technique may overcome some of the difficulties inherent in the other methods.

Laboratory-scale preparation- A solid dispersion of a melted drug-carrier mixture is pipetted and then dropped onto a plate, where it solidifies into round particles (Figure 1). The size and shape of the particles can be influenced by factors such as the viscosity of the melt and the size of the pipette. Because viscosity is highly temperature dependent, it is very important to adjust the temperature so that when the melt is dropped onto the plate it solidifies to a spherical shape[45].

Complexation with β-Cyclodextrins

Complexation is the association between two or more molecules to form a nonbonded entity with a well-

defined stoichiometry. The two types of complexation that are most useful for increasing the solubility of drugs in aqueous media are stacking and inclusion. Stacking complexes are formed by the overlap of the planar regions of aromatic molecules, while inclusion complexes are formed by the insertion of the non-polar region of one molecule into the cavity of another molecule (or group of molecules). The α-, β- and γ-cyclodextrins are cyclic oligosaccharides consisting of six, seven, and eight glucose units, respectively. One of the important properties of these naturally occurring cyclodextrins is their ability to form inclusion complexes with smaller molecules that fit into the hydrophobic cavity of the cyclodextrin. The formation of inclusion complexes alters a variety of the physicochemical properties of the drug molecule such as its solubility, dissolution rate, membrane permeability, chemical reactivity, and dissociation constant. In some cases, as the concentration of cyclodextrin increases, the solubility increases initially, levels off, and then decreases. In 1963, Cohen and Lach[50, 51] were the first to report that inclusion complexes with various drugs in solution increase drug solubility and improve the dissolution rate. In 1975, Kurozumi et al.[52] made a simple freeze-dried complex of drug and β-cyclodextrin to improve the solubility and dissolution of drug. Although natural cyclodextrin, especially the β-type, has been utilized extensively to improve the dissolution rate and absorption of insoluble drug molecules, Uekama and others have reported that β-cyclodextrin has some undesirable characteristics, the most important of which are its definite cavity size and its relatively low aqueous solubility (1.8% at 25 °C) [53, 54]. Recently, chemically modified cyclodextrins have been introduced to overcome this limitation. Uekama et al.[55] demonstrated that the inclusion complex of the anti-inflammatory drug flurbiprofen with the heptakisdimethyl derivative of β-cyclodextrin was superior to the natural β-cyclodextrin. Zerrouk et al.[56] reported the aqueous solubility of glyburide was improved 40-fold when mixed with hydroxypropyl-β-cyclodextrin and 25-fold when mixed with β-cyclodextrin. Another cyclodextrin chemically modified with epichlorhydrin is extremely soluble in water and interacts with a variety of guest molecules[57, 58] like phenytoin.

Hydrotrophy

Hydrotrophy is a solubilisation process whereby addition of a large amount of second solute results in an increase in the aqueous solubility of another solute. Solute consists of alkali metal salts of various organic acids. Hydrotropic agents are ionic organic salts. Additives or salts that increase solubility in given solvent are said to “salt in” the solute and those salts that decrease solubility “salt out” the solute. Several salts with large anions or cations that are themselves very soluble in water result in “salting in” of non electrolytes called “hydrotropic salts” a phenomenon known as “hydrotropism”. Hydrotropic solutions do not show colloidal properties and involve a weak interaction between the hydrotropic agent and solute. Hydrotrophy designate the increase in solubility in water due to the presence of large amount of additives. The mechanism by which it improves solubility is more closely related to complexation involving a weak interaction between the hydrotrophic agents like sodium benzoate, sodium acetate, sodium alginate, urea and the poorly soluble drugs.[59-62]

Advantages of hydrotropic solubilization technique:

- Hydrotropy is suggested to be superior to other solubilization method, such as miscibility,
  micellar solubilization, cosolvency and salting in, because the solvent character is independent of pH, has high selectivity and does not require emulsification.
- It only requires mixing the drug with the hydrotrope in water.
- It does not require chemical modification of hydrophobic drugs, use of organic solvents, or preparation of emulsion system.

The hydrotropes are known to self-assemble in solution[63].The classification of hydrotropes on the basis of molecular structure is difficult, since a wide variety of compounds have been reported to exhibit hydrotropic behaviour. Specific examples may include ethanol, aromatic alcohols like resorcinol, pyrogallol, catechol, *a* and *b*-naphthols and salicylates, alkaloids like caffeine and nicotine, ionic surfactants like diacids, SDS (sodium dodecyl sulphate) and dodecylated oxidibenzene.[64] The aromatic hydrotropes with anionic head groups are mostly studied compounds. They are large in number because of isomerism and their effective hydrotrope action may be due to the availability of interactive piorbitals. Hydrotropes with cationic hydrophilic group are rare, e.g. salts of aromatic amines, such as procaine hydrochloride. Besides enhancing the solubilization of compounds in water, they are known to exhibit influences on surfactant aggregation leading to micelle formation, phase manifestation of multicomponent systems with reference to nanodispersions and conductance percolation, clouding of surfactants and polymers, etc. Other techniques that enhance the solubility of poorly water soluble drugs include salt formation, change in dielectric constant of solvent, Chemical modification of the drug, use of hydrates or solvates, use of Soluble

prodrug, Application of ultrasonic waves, spherical crystallization.[65]

Miscellaneous Approaches

Microemulsions: is a four-component system composed of external phase, internal phase, surfactant, and cosurfactant. The addition of surfactant, which unlike the cosurfactant, is predominately soluble in the internal phase, results in the formation of an optically clear, isotropic, thermodynamically stable emulsion. It is termed a microemulsion because the internal or dispersed phase has a droplet diameter of less than 0.1 µm. Microemulsion formation is spontaneous and does not involve the input of external energy as for coarse emulsions. The surfactant and the cosurfactant alternate each other and form a mixed film at the interface, which contributes to the stability of the microemulsion. Lawrence and Rees[66] reported microemulsion-based media as novel drug delivery systems to enhance the dissolution and bioavailability of poorly soluble and poorly bioavailable (Biopharmaceutical Classification System class IV) drugs. Nonionic surfactants, such as Tweens (polysorbates) and Labrafil (polyoxyethylated oleic glycerides), with high hydrophile–lipophile balances are often used to ensure immediate formation of oil-in-water droplets during production.

Plasma Irradiation: has been investigated as a possible technique for increasing the dissolution rate of poorly soluble drugs. Plasma is a partially ionized gas that contains an equal number of positive and negative ions and unionized neutral species such as molecules, atoms, and radicals. It is created by subjecting a gas (e.g. O_2) to a radio-frequency potential in a vacuum chamber. This leads to the production of electrons, which are accelerated by an electric field and collide with neutral molecules to produce free radicals, atoms, and ions. In an oxygen plasma, O_2 can be excited from the ground state to higher electronic levels to form O^{2+} and O^{2-}. Further dissociation reaction leads to the production of oxygen atoms and ions such as O^+ and O^-. During plasma treatment, these oxygen radicals then react with the chemical groups on the surface of an exposed sample that leads to the formation of an O^{2-} containing functional group such as hydroxyl, carbonyl, or carboxyl group. The production of these functional groups leads to an increase in wettability and thus increases the effective surface area available for dissolution, which increases the dissolution rate[67].

Liquisolid Compacts: Liquisolid compact formulation is a technique that utilizes hydrophobic drugs dissolved in nonvolatile, nontoxic, hydrophilic solvents like polyethylene glycol, glycerin, propylene glycol, or polysorbate-80 (well known as Liquid Medications) mixed with carriers like microcrystalline cellulose, lactose, or polyvinyl pyrrolidone- K30 using coating materials like silica in optimized proportions and finally compressed into a compact mass. In recent years, this technique was used to enhance the dissolution rate of carbamazepine[68], piroxicam[69], naproxen[70], famotidine[71], and prednisolone[72].

By using P-glycoprotein inhibitors: Several studies have demonstrated the possible use of P-glycoprotein inhibitors that reverse P-glycoprotein - mediated efflux in an attempt to improve the efficiency of drug transport across the epithelia, thus resulting in enhanced oral bioavailability. P-glycoprotein inhibitors may also influence absorption, distribution, metabolism and elimination of P-glycoprotein substrates in the process of modulating pharmacokinetics. Early studies on verapamil to reverse P-glycoprotein mediated resistance to vincristine and vinblastine provided the rationale for its clinical usefulness as P-glycoprotein inhibitor. In addition to this, orally administered Verapamil has been shown to increase peak plasma level, prolong elimination half-life and increase volume of distribution of doxorubicin, another P-glycoprotein substrate, after oral administration[73]. Many natural compounds from medicinal plants have demonstrated capacity to enhance the bioavailability of co-administered drugs by inhibiting efflux pumps or oxidative metabolism, and perturbing the intestinal brush border membrane. These natural compounds include quercetin, genistein, naringin, sinomenine, piperine, glycyrrhizin and nitrile glycoside[74]. Oral bioavailability of paclitaxel was increased from 4.6% to 34.4% when coadministered with P-Glycoprotein Inhibitor KR30031 (Verapamil analog) [75].

Future prospects:

Poor bioavailability is a major limitation in successful drug delivery by oral route. Lot of research work is focused on oral bioavailability enhancement of the poorly absorbed drugs. It is necessary to understand the reason behind the poor bioavailability before designing a delivery system. The positive results obtained with the use of various delivery systems or different approaches of bioavailability enhancement seem to be promising. However, the commercial development of the product demands much more research for overcoming the challenges such as scale up, cost effectiveness and instability of some of the formulations.

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Table 1: Examples of work done on microemulsions and self-emulsifying systems

Drug	Work done	Result obtained
Cefpirome and Cefodizim	Microemulsion and mixed micelle for oral administration as new drug formulations for highly hydrophilic drugs	Up to 64% absolute bioavailability of Cefpirome and Cefodizim was obtained by their combination with Microemulsion and mixed micelle[31].
Halofantrine (Hf)	Formulation design and bioavailability assessment of lipidic self-emulsifying formulations of halofantrine	The lipid-based formulations of Hf base afforded a six- to eight-fold improvement in absolute oral bioavailability relative to previous data of the solid Hf.HCl tablet formulation[32].

Table 2: Marketed Nanotechnology based approaches to improve bioavailability[38]

Company	Nanotechnology	Description
Elan	NanoCrystal	NanoCrystal drug particles (<1,000 nm) produced by wet-milling and stabilized against agglomeration through surface adsorption of stabilizers
Baxter	Nanoedge	Nanoedge technology: drug particle size reduction to nanorange by platforms including direct homogenisation, microprecipitation, lipid emulsions and other dispersed-phase technology
SkyePharma	IDD	Insoluble Drug Delivery: micro-nm particulate/droplet water-insoluble drug core stabilised by phospholipids; formulations are produced by high shear, cavitation or impaction
Eurand	Biorise	Nanocrystals/amorphous drug produced by physical breakdown of the crystal lattice and stabilised with biocompatible carriers (swellable microparticles or cyclodextrins)
BioSante	CAP	Calcium Phosphate-based nanoparticles: for improved oral bioavailability of hormones/proteins such as insulin; also as vaccine adjuvant
PharmaSol	NLC	Nanostructured Lipid Carriers: nanostructured lipid particle dispersions

	with solid contents produced by high-pressure homogenisation; lipid-drug conjugate nanoparticles provide high-loading capacity for hydrophilic drugs for oral delivery

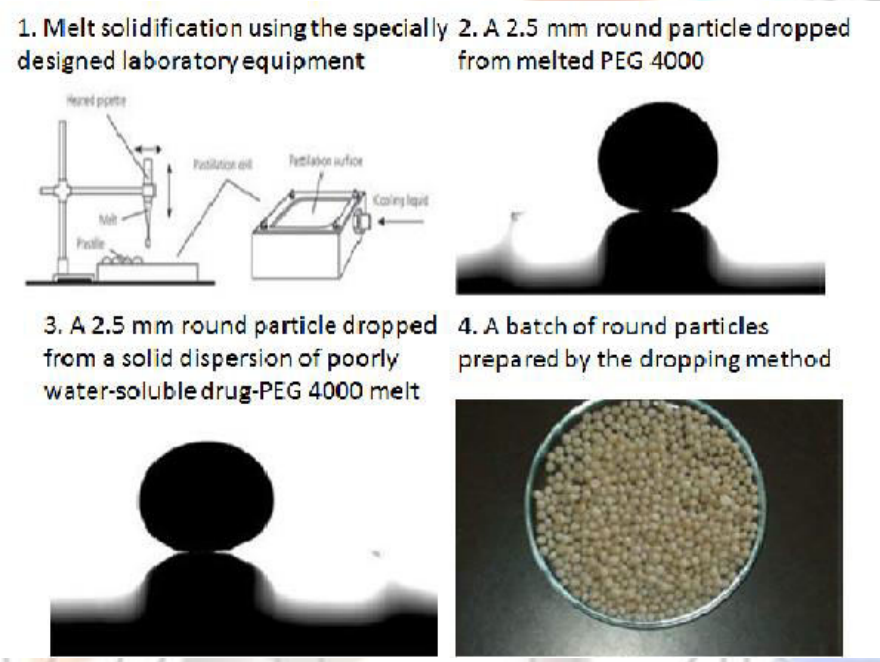

Fig. 1. Round particles made by the dropping method

Table 3: Various materials used as carriers for preparation of solid dispersions[44]

Chemical Class	Carrier
Polymeric Materials	Polyvinylpyrrolidone, PEG-4000, PEG-6000, CMC, HPC, HPMC, Guar gum, Xanthan gum, Sodium alginate, Methyl cellulose, Galactomannan
Surfactants	Poloxamers, Tweens and Spans, Deoxycholic acid, Polyoxyethylene stearate, Gelucire 44/14
Sugars	Dextrose, Sorbitol, Sucrose, Maltose, Galactose, Xylitol
Acids	Citric acid, Tartaric acid, Succinic acid
Miscellaneous	Pentaerythritol, Urea, Urethane, Hydroxyalkyl xanthenes