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Disparate practical way of doing solubility enhancement study to improve the bioavailability of poorly soluble drugs

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ABSTRACT

Bioavailability is the rate and extent to which the active ingredient or active moiety is absorbed from a drug product and becomes available at the site of action. Traditionally, nearly 40% of the new chemical entities (NCEs) identified by pharmaceutical industry screening programs have failed to be developed due to of poor water solubility, which makes their formulation difficult or even impossible to come into the regular market. Solubility is one of the important ways to achieve the desired concentration of drug in to the systemic circulation for its pharmacological response and also most of the drugs are weakly acidic and weakly basic with poorly aqueous solubility. The oral route of administration is the most preferred and widely acceptable route of delivery due to ease of ingestion for many drugs, however these drugs with slow dissolution rate and low solubility in aqueous media shows the incomplete absorption leading to low bioavailability when orally administered. Poorly aqueous soluble drugs often require high doses in order to reach therapeutic plasma concentrations of oral concentration because of which increase in the side effects for certain drugs. Pharmaceuticals falling under the Biopharmaceutics Classification System (BCS) class II and IV are the main emphasis of this review as these drugs are of low solubility. Here we discussed about traditional techniques, novel drug delivery technologies, solid dispersion techniques and vascular approaches to enhance the solubility as well as the bioavailability of low soluble drugs.

Keywords: Bioavailability; New chemical entities; Solubility; Absorption; Biopharmaceutics Classification System; drug delivery technologies.

INTRODUCTION

Solubility is the measure of its saturation to remain un-dissolved while adding solute upon the solvent. The solubility of substance fundamentally depends on the solvent used as well as on temperature and pressure [1]. Oral route of drug administration is the most common and preferred method of delivery due to its convenience and ease of ingestion, but for many of the drugs it can be hard way due to its poor solubility, hence will lead to low bioavailability. Solubility of drug substance is directly proportional to the dissolution rate as per Noyes-Whitney equation and hence solubility is an important factor for the estimation of the bioavailability. Therapeutic effectiveness of a drug depends upon the dissolution, bioavailability and ultimately upon the solubility of drug molecules. Solubility is one of the important ways to achieve desired concentration of drug in systemic circulation and hence can be defined concentration of the solute in a saturated solution at a certain temperature and in qualitative terms, and in another word can be describe as the spontaneous interaction of two or more substances to form a homogeneous molecular dispersion. Only 8% of new drugs in the world have both high solubility and permeability [2].The techniques generally applied form solubilization of drug includes micronization, chemical

modification, pH adjustment, salt form, wettability, complexation, polymorphism, solid dispersion, solvency, micellar solubilization, hydrotropy, vascular approaches etc [3]. General definition for different solubility terms are given in the table 1 [4].

Table 1: Definitions of solubility

Definition	Part of solvent required per part of solute (in ml)
Very soluble	Less than 1
Freely soluble	1 to 10
Soluble	30-Oct
Sparingly soluble	30 to 100
Slightly soluble	100 to 1000
Very slightly soluble	1000-10, 000
Practically insoluble	10,000 and more

The Biopharmaceutical Classification System (BCS) is a guide for predicting the intestinal drug absorption provided by the U.S. Food and Drug Administration. This system restricts the prediction using the parameters solubility and intestinal permeability. The intestinal permeability classification is based on a comparison to the intravenous injection [1]. Solubility is based on the highest-dose strength of an immediate release product and is considered highly soluble when the highest dose strength is soluble in 250mL or less of aqueous media over the pH range of 1 to 7.5. The volume estimate of 250mL is derived from typical bioequivalence study protocols that prescribe administration of a drug product to fasting human volunteers with a glass of water [1].

All drugs have been divided into four classes
Class I— high solubility and high permeability
Class II—low solubility and high permeability
Class III—high solubility and low permeability
Class IV—low solubility and low permeability

A per the literature survey many more review papers were available to enhance the bioavailability by using traditional, novel, solid dispersions and vascular techniques [1-8, 11, 21, 23, 24, 25, 26, 31, 32, 34,37], but unable to get all the approaches in one review. Here the aim of this review is to explain the all the possible ways in a descriptive manner at one place by gathering tremendous techniques like traditional, novel, solid dispersions as well as vascular approaches.

1.1. Bioavailability and its importance

The term Bioavailability is one of the principal pharmacokinetic properties of drugs and is used to describe the fraction of an administered dose of unchanged drug that reaches the systemic circulation. Generally the medication is administered intravenously; its bioavailability is 100%. But, when a medication is administered via other routes (such as oral, rectal, transdermal, and subcutaneous administration), its bioavailability decreases (due to incomplete absorption or first-pass metabolism). The measurement of the amount of the drug in the plasma at periodic time intervals indirectly indicates the rate and extent at which the active pharmaceutical ingredient is absorbed from the drug product and becomes available at the site of action. Bioavailability is one of the essential tools in pharmacokinetics, as it must be considered when calculating dosages for non-intravenous routes of administration. It is expressed as either absolute or relative bioavailability [5].

- Absolute bioavailability
- Relative bioavailability

1.1.1. Absolute bioavailability

Absolute bioavailability measures the availability of the active drug in systemic circulation after non-intravenous administration (i.e., after oral, rectal, transdermal, and subcutaneous administration). In order to determine absolute bioavailability of a drug, a pharmacokinetic study must be done to obtain a plasma drug concentration vs. time plot for the drug after both intravenous and non-intravenous administration. The absolute bioavailability is the dose-corrected area under curve (AUC) non-intravenous divided by AUC intravenous administration. Therefore, a drug given by the intravenous route will have an absolute bioavailability of 1 (F=1) while drugs given by other routes usually have an absolute bioavailability of less than one [5].

1.1.2. Relative bioavailability: This measures the bioavailability of a certain drug when compared with another formulation of the same drug, usually an established standard, or through administration via extra vascular routes of drug administration [5].

1.2. Reasons for studying Bioavailability

There are various reasons for studying bioavailability as follows and it will help to

i. Offer practical information on the potential health effects of contamination.
ii. Modify defaults by using site specific data.
iii. Change proposed cleanup levels and saves time as well as money to reach the accepted levels.
iv. Prioritize sites for subsequent evaluation.

1.3. Ways to measure bioavailability

There are abundant ways that are followed to estimate bioavailability. The Site specific analysis can offer vital information that can influence a risk assessment. In soil, a contaminant bioavailability can be measured in several ways such as:

i. Extraction using acids and bases
ii. Extraction using biological fluids
iii. In vitro assays using bacterial systems
iv. In vivo assays using aquatic mammals and organisms
v. Statistical estimation procedures

Measuring the bioavailability has become an integral part to estimate the new formulation development by the pharmaceutical industry.

Today there are so may reputed clinical research organizations conduct bioavailability studies to offer various useful pharmacokinetic information associated with distribution, elimination, the effects of nutrients on absorption of the drug, dose proportionality, linearity in the pharmacokinetics of the active moieties as well as inactive moieties and many more. Bioavailability information can also offer data directly about the drug substance properties prior to its entry into the systemic circulation, for instance permeability and the impact of pre-systemic enzymes and transporters. Once a product is accepted of having a sufficient bioavailability then the same product can be select for bioequivalence study comparison with the innovator drug formulation in order to get into the generic market.

1.4. Physical form of drugs

The physical form of drug substance will give adequate information for the development of new dosage form, as a result of this will decide the path that weather the drug is suitable for further formulation development and also what delivery option could be browbeaten to maximize the bioavailability. The physical form of drug can be used as transparent guide to understand the advantages and disadvantages of various formulation technologies to be used. The drug may be in solubilized form, amorphous form or crystalline form in the formulation [6].

- Solubilized form
- Amorphous form
- Crystalline form

1.4.1. Solubilized form

The solubilized form is preferred for intravenous administration. This form has the inherent advantage that drugs are already in solution form, therefore eliminating the necessity of dissolution step. But lack of long term chemical stability and risk of drug precipitation on dilution are unfavorable facts associated with this form [6].

1.4.2. Amorphous form: The amorphous form is considered when drug cannot be solubilized suitably. The use of amorphous form provides with opportunity to increase oral absorption but associated with lack of physical and chemical stability [6].

1.4.3. Crystalline form: The toughest form of drug substance, from perspective of chemical stability, which can be used to develop a dosage form of poorly water soluble drug is the crystalline form. To be orally bioavailable solid crystalline form first has to dissolve [6].

1.5. Process of solubilization

The process of solubilization involves the breaking of intermolecular or inter-ionic 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 [7, 8]. Solubilization process occurs into three steps.

Step 1, break down of solvent bond occurs and holes can be formed in-between shown in figure 1.
Step 2, when solubilization process occurs solid molecules break down because of breaking of inter molecular bonding shown in figure 2.
Step 3, about freed solid molecule is integrated in the solvent shown in figure 3.

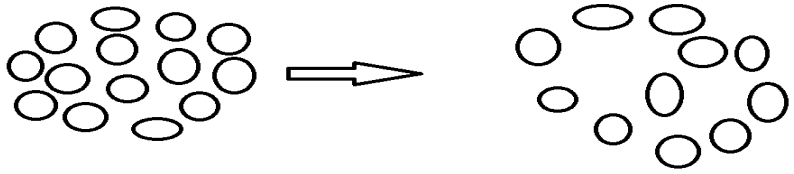


Fig. 1: Step 1-Holes opens in the solvent

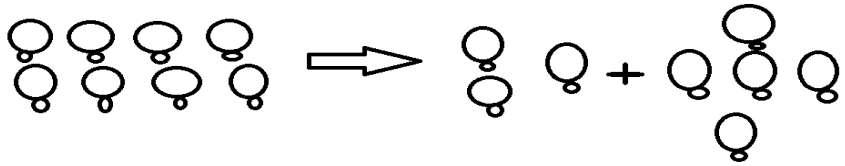


Fig. 2: Step 2-Molecules of solid breaks away from bulk form

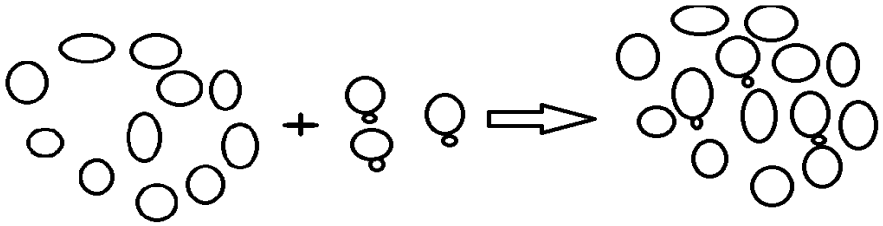


Fig. 3: Step 3-The free solid molecules were penetrated in to the gaps in the solvent

1.6. Factors affecting the solubility

The solubility depends on the nature and composition of solvent medium, the physical form of the solid as well as temperature and pressure on the system.

- Particle Size
- Temperature
- Pressure
- Nature of the solute and solvent
- Molecular size
- Polarity
- Polymorphs

1.6.1. Particle Size: The size of the solid particle influences the solubility because as a particle becomes smaller, the surface area to volume ratio increases of the particle. The larger surface area allows a greater interaction with the solvent.

$$\log (C_s / C_\infty) = (2 \sigma V / 2.303 RT\rho r)$$

where, Cs is saturated solubility, C∞ is solubility of solid consisting of large particles, V is molar volume of particles, R is gas constant, T is absolute temperature, ρ is density of solid, and r is particle radius [9].

1.6.2. Temperature: As the temperature is increased then the solution process absorbs energy and the solubility will be increased but if the solution process releases energy then the solubility will decrease with increasing temperature. A few solid solutes are less soluble in warm solutions. For examples all gases, the solubility decreases as the temperature of the solution increases [4,8].

1.6.3. Pressure: For solids and liquid solutes, no effect on solubility while changes in pressure have practically but for gaseous solutes, an increase in pressure, increases solubility and a decrease in pressure, decrease the solubility [4,8].

1.6.4. Nature of the solute and solvent: Depending on the nature of the solvent and solute, solubility will vary and the example: 1 gram of lead (II) chloride can be dissolved in 100 grams of water at room temperature while 200 grams of zinc chloride can be dissolved in the same [4,8].

1.6.5. Molecular size: The solubility of the substance is decreased when molecules have higher molecular weight and higher molecular size because larger molecules are more difficult to surround with solvent molecules in order to solvate the substance. In the case of organic compounds the amount of carbon branching will increase the solubility since more branching will reduce the size (or volume) of the molecule and make it easier to solvate the molecules with solvent [4,8].

1.6.6. Polarity: Generally like dissolves like means non-polar solute molecules will dissolve in non-polar solvents and polar solute molecules will dissolve in polar solvents. Polarity of the solute and solvent molecules will affect the solubility. The polar solute molecules have a positive and a negative end to the molecule. Due to intermolecular forces or dipole-dipole interactions, if the solvent molecule is also polar then positive ends of solvent molecules will attract negative ends of solute molecules. The other forces called london dispersion forces where the positive nuclei of the atoms of the solute molecule will attract the negative electrons of the atoms of a solvent molecule. This gives the nonpolar solvent a chance to solvate the solute molecules [8].

1.6.7. Polymorphs: The capacity for a substance to crystallize in more than one crystalline form is polymorphism [10]. A crystal is made up of atoms, ions, or molecules in a regular geometric arrangement or lattice constantly repeated in three dimensions is known as the unit cell. The shape or habit of a crystal of a given substance may vary but the angles between the faces are always constant. Melting point may vary from form to form and will eventually affect the solubility.

2. SOLUBILITY ENHANCEMENT TECHNIQUES

The solubility of a solute is the maximum quantity of solute that can dissolve in a certain quantity of solvent or quantity of solution at a specified temperature. Various techniques are available to improve the solubility of poorly soluble drugs. These techniques can be categorized in four basic approaches:

- Traditional techniques
- Newer and novel techniques
- Solid dispersion techniques
- Vesicular approaches

2.1. TRADITIONAL TECHNIQUES

- Co-solvency
- Co-crystallization
- Hydrotropy
- Micronization
- Alteration of pH of solvent
- Change in dielectric constant of solvent
- Amorphous forms
- Slat formation
- Chemical modification of drug
- Use of surfactants
- Complexation

- Use of hydrates or solvates
- Use of soluble pro-dugs
- Use of ultrasonic waves
- Functional polymer technology
- Controlled precipitation technology
- Evaporative precipitation in aqueous solution
- Use of precipitation inhibitors
- Solvent deposition
- Spherical agglomeration
- Selective adsorption on insoluble carriers

2.1.1. Co-solvency

The solubilization of drugs in co-solvents is a technique for improving the solubility of poorly soluble drug. The addition of a water-miscible or partially miscible organic solvent is a common and an effective way to increase the solubility of a non-polar drug. This process is known as co-solvency and the solvents used in combination to increase the solubility of the drugs are known as co-solvents. The co-solvent system will works by reducing the interfacial tension between the predominately aqueous solution and the hydrophobic solute. Most co-solvents have hydrogen bond donor and/or acceptor groups as well as small hydrocarbon regions. Their hydrophilic hydrogen bonding groups ensure water miscibility, while their hydrophobic hydrocarbon regions interfere with waters hydrogen bonding network, reducing the overall intermolecular attraction of water By disrupting waters self-association, co-solvents reduce waters ability to squeeze out non-polar, hydrophobic compounds. Co-solvents such as ethanol, propylene glycol, glycerin, sorbitol and polyoxyethylene glycols can be used [4].

Example: Solubility enhancement as high as 500-fold is achieved using 20% 2-pyrrolidone.

Advantages [10, 11]

- This may be paired with other solubilization techniques such as pH adjustment to increase solubility.
- High concentrations of the compound can also be dissolved compared to other methods.
- It is Simple and rapid method to formulate and produce.

Disadvantages [11]

- Here, chemical stability of the insoluble drug is worse than in the crystalline state, as with all solubilized forms.
- The toxicity and tolerability of the excipients must be closely watched. Also, for intravenous administration, uncontrolled amorphous or crystalline precipitation may occur upon dilution with aqueous media. This is due to the drug is insoluble in water and after precipitation forms the co-solvent mixture is not readily able to re-dissolve.

Application

NMP is also used to enhance drug delivery of hypericin, which is an antitumor, photodynamic, and photodiagnostic agent with have very low water solubility, into solid tumors and enhances the photodynamic therapeutic effects of hypericin on human bladder carcinoma [12].

2.1.2. Co-crystallization

The new approach available for the enhancement of drug solubility is through the application of the co-crystals, it is also referred as molecular complexes. If the solvent is an integral part of the network structure and forms at least two component crystals, then it may be termed as co-crystal. If the solvent does not participate directly in the network itself, as in open framework structures, then it is termed as clathrate (inclusion complex). A co-crystal may be defined as a crystalline material that consists of two or more molecular (and electrically neutral) species held together by non-covalent forces. Co-crystals are more stable, particularly as the co-crystallizing agents are solids at room temperature [7] .

Advantages

- Co-crystal formation may offer for the pharmaceutical industry are the opportunity of intellectual property (IP) protection and the possibility of extending the life cycles of old APIs [13].

• Co-crystals having advantages like stable crystalline form (as compared to amorphous solids) and also no need to make or break covalent bonds, theoretical capability of all types of API molecules (weakly ionizable/non-ionizable) to form co-crystals [14].

Applications

• Co-crystals were developed by using this technique for Itraconazole and Sildenafil to enhance the solubility and bioavailability [13].

• Co-crystals insulin investigation and production were studied and very useful for medics and pharmacologists [15].

2.1.3. Hydrotropy

Hydrotropy is a solubilization process whereby addition of bulky amounts of a second solute (Hydrotropic agents) results to enhance 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 results in "salting in" of non-electrolytes called "hydrotropic salts" a phenomenon known as "Hydrotropism" [10]. Concentrated aqueous hydrotropic solutions of sodium benzoate, sodium salicylate, urea, nicotinamide, sodium citrate and sodium acetate have been observed to enhance the aqueous solubilities of many poorly water soluble drugs [7].

Example: The solubility of rofecoxib was enhanced by using hydrotropes such as urea and nicotinamide [10].

Advantages [11]

• This method does not require chemical modification, preparation of emulsion system, or use of organic solvents.

• The mixing step is done only with the drug and hydrotrope in water will have high selectivity and does not involve emulsification.

Disadvantages [11]

Hydrotropes may self-assemble in solution and lose the ability to enhance drug's water solubility

Application

Hydrotropes have been used are procaine/HCl in Riboflavin®, absorbic acid in Saquinavir®, sodium salt of Ibuprofen in Ibuprofen®, sodium benzoate in Carbamazepine®, and sodium salicylate in Paracetamol [11].

2.1.4. Micronization

The particle size reduction technique enhance the solubility in terms of dissolution rate of poorly water soluble drugs due to the enormous surface that is generated due to less particle size by micronization. The process involves reducing the size of the solid drug particle to 1 to 10 microns commonly by spray drying or by use of air attrition methods such as fluid energy mill, jet mill, rotor stator colloid mill etc. is also called as "Micromilling". Micronization is not suitable for drugs having a high dose number because it does not change the saturation solubility of the drug due to the tendency of agglomeration, which leads to decreased effective surface area for dissolution [16]. Conversion of single course particle to Cluster of micro particles are shown below in figure 4.

Fig. 4: Diagram for big to small particles

2.1.5. Alteration of pH of solvent [17]

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 de-protonated (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 [8].

Advantages

- Simple to formulate and analyze.
- Simple to produce and fast track.
- Uses small quantities of compound, amenable to high throughput evaluations [8].

Disadvantages [17]

- Tolerability and toxicity may occur due the use of non-physiological and extreme pH's.
- Risk for precipitation upon dilution with aqueous media having a pH at which the compound is less soluble. Intravenously this may lead to emboli, orally it may cause variability [8].
- As with all solubilized and dissolved systems, a dissolved drug in an aqueous environment is frequently less stable chemically compared to formulations crystalline solid. The selected pH may accelerate hydrolysis or catalyze other degradation mechanisms.

Applications

- Phenytoin Injection (Epanutin® ready mixed, Pfizer) 50mg/ml with propylene glycol 40% and ethanol 10% (1.1 mmol Na+ per 5 ml ampoule) is an example of a pH adjusted formulation containing co-solvents [17].
- It was attempted to enhance dissolution of gliclazide using pH change approach [18].

2.1.6. Change in dielectric constant of solvent

Generally the addition of a co-solvent can increase solubility of hydrophobic molecules by reducing the dielectric constant of the solvent. Due to the nature of hydrogen bonding, water is a good solvent for polar molecules and has a high dielectric constant. The dielectric constant is a measure of the effect a substance on the energy needed to separate two oppositely charged bodies. The energy required to separate two oppositely charged bodies is inversely proportional to the dielectric constant of the medium [19]. Changes in dielectric constant of the medium may have a dominant effect on the solubility of the ionizable solute in which higher dielectric constant can cause more ionization of the solute and results in more solubilization [20].

Advantage

It does not require any experimental solubility data in mixed solvents [20].

Disadvantage

The disadvantage of this method is that it is applicable only for the solubility prediction of electrolytes or zwitterions in which the ionization is the dominant parameter and the phenomenon could be represented using Born model as well [20].

2.1.7. Amorphous form

In amorphous forms atoms or molecules are randomly placed and have higher thermodynamic energy than corresponding crystalline forms. Generally amorphous form having more surface area than crystalline form and eventually increase the dissolution rate.

2.1.8. Salt formation

Salt formation of poorly soluble drug candidates (weak acids and bases) has been a strategy for several decades to enhance solubility. It is an effective method in parenteral and other liquid formulations, as well as in solid dosage forms. Over 300 new chemical entities approved by the FDA during the 12 years from 1995 to 2006 for marketing,

120 were in salt forms. In addition, out of the 101 approved salts of basic drugs, 54 salts were prepared with hydrochloric acid, indicating the hydrochloride was the predominant salt form [21]. The aqueous solubility of an acidic or basic drug as a function of pH dictates whether the compound will form suitable salts [10]. The general salt formation in pictorial form mentioned in the figure 5.

The pH-solubility interrelationships says that what counter ions would be necessary to form salts, how easily the salts may dissociate into their free acid or base forms, and what their dissolution behavior would be under different GI pH conditions, and whether solubility and dissolution rate of salts would be influenced by common ion.

Several reviews have outlined general strategies and considerations for salt selection. For the salt formation drug should have ionizable groups that will assist salt formation. The criteria used to select counter ion is as follows.

- There should be minimum difference of 2-3 pKa units between the drug and the counter ion.
- Counter ion should decrease crystal lattice forces.
- It should be FDA approved or should have enough toxicological data to support the selection of the counter ion [1].

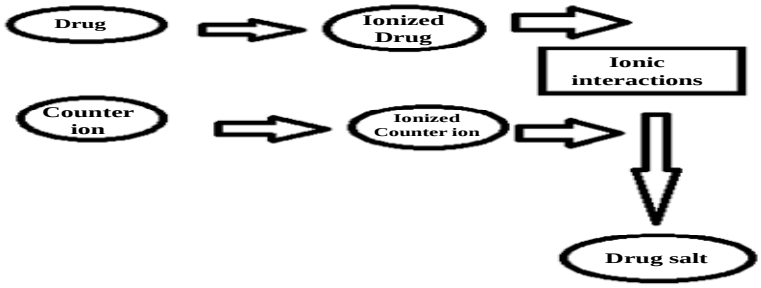


Fig 5: Systematic diagram for salt formation

Disadvantage

This technique has tremendous capability to enhance dissolution rate but it is grasped with disadvantages like approval of salts is a tedious task and also not useful for neutral molecules [22].

Application

Improvement of dissolution Rate of Gliclazide through sodium salt formation [23].

2.1.9. Chemical modification of drug

By the addition of polar groups like carboxylic acids, ketones and amines by which solubility enhanced due to increasing hydrogen bonding and the interaction with water [19].

2.1.10. Use of Surfactants

The presence of surfactants may lower the surface tension and increase the solubility of the drug within an organic solvent. Surfactants are amphiphilic in nature having a polar end (the circular head) and non-polar end (the tail). Most surfactants consist of a hydrocarbon segment connected to a polar group can be anionic, cationic, zwitterionic or nonionic. Small molecules of polar molecules can be accumulated into hydrophobic core of micelles [7]. When a surfactant such as tween-80, sodium lauryl sulphate is placed in water, it will form micelles. A non polar drug will partition into the hydrophobic core of the micelle and the polar tail will solubulize the complex. This has been illustrated improvement of wetting characteristics and micellar solubilization

Advantage

Biosurfactants are biodegradability, low toxicity, better surface and interfacial activity.

Disadvantage

Inability to scale up the production process and patent rights by using biosurfactants.

2.1.11. Complexation

Complexation is the association between two or more molecules to form a non-bonded entity with london forces, hydrogen bonding and hydrophobic interactions [7]. There are many types of complexing agents and major three are listed below.

- Staching complexation
- Inclusion complexation
- Cyclodextrin Inclusion Complexes

2.1.11.1. Staching complexation

Staching complexes are formed by the overlap of the planar regions of aromatic molecules. Nonpolar moieties tend to be squeezed out of water by the strong hydrogen bonding interactions of water and causes some molecules to minimize the contact with water by aggregation of their hydrocarbon moieties. This aggregation is favored by large planar non-polar regions in the molecule. Stached complexes can be homogeneous or mixed. The former is known as self association and latter as complexation [7].

Examples: For staching complexes are as Nicotinamide, Anthracene, Pyrene, Methylene blue, Benzoic acid, Salicylic acid, Ferulic acid, Gentisic acid, Purine, Theobromine, Caffeine, and Naphthalene etc [7].

Preparation: Considerable increase in solubility and dissolution rate of the drug has been achieved by the use of cyclodextrins. These complexes can be prepared with ß-cyclodextrin (ß-CD) and HP-ß-CD; the required quantity of ß-CD is weighed and water added to get tough consistency. To the mass, weighed quantity of the drug is added. The mixture is kneaded in a glass mortar for one hour and then completely dried in hot air oven at 60°C for 2 hours. The dried mass is sieved through proper mesh.

2.1.11.2. Inclusion complexation

Inclusion complexes are formed by the insertion of the non-polar molecule or the non-polar region of one molecule (known as guest) into the cavity of another molecule or group of molecules (known as host). The major structural requirement for inclusion complexation is a comfortable fit of the guest into the cavity of host molecule. The cavity of host molecule must be large enough to accommodate the guest and small enough to eliminate water as well, so that the total contact between the water and the non-polar regions of the host and the guest is reduced [7].

2.1.11.3. Cyclodextrin Inclusion Complexes

Cyclodextrins (CD) are bucket shaped cyclic oligosaccharides composed of 6-8 dextrose units (α, β, γ CD) respectively joined through C-C double bonds. The interior of these molecules is lipophilic and exterior of these molecules is hydrophobic. Lipophilic molecules can be incorporated into interior cavity of CD leading to better stability, high water solubility, and increased bioavailability or decreased undesirable side effects. The presence of hydroxyl groups on the external surface of the CD molecule increases the possibility of hydrogen bonding with the drug molecules resulting in the formation of non-inclusion complexes as well.

Examples: 2-hydroxy propyl- β cyclodextrin, methyl β cyclodextrin etc are widely used due to high water solubility and low toxicity.

Applications

➢ The complex of praziquantel with β CD showed significantly improved dissolution profile compared with that of pure drug, here hydrophobic CD can act as sustained release carriers for water soluble drugs.

➢ The inclusion complexes of aceclofenac with hydroxypropyl-β-cyclodextrin provided increased dissolution rates as well as improved therapeutic effect [6].

Preparation: The drug – CD complexes are prepared by freeze drying, spray drying, and co- precipitation of CD drug solution.

- Kneading Method.
- Lyophilization/Freeze-Drying Technique.
- Microwave Irradiation Method.

2.1.11.3.1. Kneading Method
Little amount of water or hydro alcoholic solution is taken with CD to convert into a paste. And the drug is added to the above paste and kneaded for a specified time. The kneaded mixture is then dried and passed through a respected sieve if required. In small scale, kneading can be achieved by using a mortar and pestle. In production scale, kneading can be done by utilizing the extruders and other machines. This is the simple and most common method used to prepare the inclusion complexes and it presents very low cost of production [1].

2.1.11.3.2. Lyophilization/Freeze-Drying Technique
In order to get a porous, amorphous powder with high degree of interaction between drug and CD, lyophilization/freeze drying technique is considered suitable. In this technique, the solvent system from the solution is eliminated through a primary freezing and subsequent drying of the solution containing both drug and CD at reduced pressure [1].

Advantage : Heat sensitive substances can be successfully made into complex form by this method.

Disadvantage: The limitations of this technique is the use of specialized equipment, time consuming process, and yield poor flowing powdered product.

2.1.11.3.3. Microwave Irradiation Method
This technique involves the microwave irradiation reaction between drug and complexing agent using a microwave oven. The drug and CD in definite molar ratio are dissolved in a mixture of water and organic solvent in a specified proportion into a round bottom flask. The mixture is reacted for short time of about one to two minutes at 60◦C in the microwave oven. After the reaction completes, sufficient amount of solvent mixture is added to the above reaction mixture to remove the residual un-complexed free drug and CD. The precipitate so obtained is separated using whatman filter paper, and dried in vacuum oven at 40◦C [1].

Advantages
- It is a shorter reaction times and higher yield of the product [1].
- Uniform heating occurs throughout the material as opposed to surface and conventional heating process.
- Desirable chemical and physical effects are produced.
- Floor space requirements are decreased.
- Better and more rapid process control is achieved
- In certain cases selective heating occurs which may significantly increase efficiency and decrease operating cost.
- High efficiency of heating,
- Reduction in unwanted side reaction (reaction Quenching),
- Improve reproducibility
- Saving of environmental heat loss.
- Reduce wastage of heating reaction vessel.

Application
Microwave assisted extraction to obtain taxanes from Taxus biomass [24].

2.1.12. Use of Hydrates or Solvates
A crystalline compound may contain either a stoichiometric or non-stoichiometric adducts, such as inclusions, involve entrapped solvent molecules within the crystal lattice. A stoichiometric adducts normally referred to as “Solvate”, and is a molecular complex that has incorporated the crystallizing solvent molecules into specific sites within the crystal lattice. When the incorporated solvent is water, the complex is called as “Hydrate”. A compound not containing any water within its crystal structure is termed “Anhydrous”. Aqueous solubilities of anhydrous forms are higher than the hydrate forms [25].

2.1.13. Use of Soluble Pro-drugs
The physicochemical properties of the drugs are improved by bio-reversible chemical modification. The most common pro-drug strategy involves the inclusion of polar or ionizable moiety into the parent compound to improve aqueous solubility. The chemical decomposition and presystemic metabolism is to be reduced by the use of pro-drug approach [2]. Designing of cyclic pro-drug using C and N terminal ends reduced the metabolic degradation caused

by exopeptidase. Derivatization is another lucrative approach for synthesis of pro-drug to improve bioavailability of drug molecules particularly for peptide molecules. Derivatization could be possible in C terminal amide group, N terminal amide group and phenol group in various peptide molecules [1].

Applications

- The pro-drug approach has been successfully used to improve the water solubility of corticosteroids, vitamins and benzodiazepines [8].
- Enhancement of rate of dissolution of allopurinol was successfully achieved by pro-drug formation [8].
- A recent study involved synthesis of cyclic hexapeptide to improve the enzymatic stability and permeability through biological membranes.

2.1.14. Ultrasonic Waves

Solubility can be improved by the use of ultrasonic vibrators. An oscillator of high frequency (100-500 KHz) is used and the device is known as "Pohlman whistle".

2.1.15. Functional Polymer Technology

Functional polymers enhance the dissolution rate of poorly soluble drugs by avoiding the lattice energy of the drug crystal, which is the main barrier to rapid dissolution in aqueous media. These polymers are ion exchange materials which contain basic or acidic groups that interact with the ionizable molecules of the surrounding medium and exchange their mobile ions of equal charge with surrounding medium reversibly and stoichiometrically. The resultant complex, known as, "Resinate", can be formulated as a suspension, dry powder or tablet. The resins are insoluble and not absorbed into the body and the drug is released from resinate on exposure to the physiological fluids.

2.1.16. Controlled Precipitation Technology

Here the drug is dissolved in a water miscible organic solvent and then dissolved into aqueous medium containing stabilizers (HPMC, cellulose ethers, gelatin). The solvent dissolves in water and causes precipitation of the drug in the form of micro-crystals. Here, the stabilizers control particle growth and enhance the dissolution rate of poorly soluble drug due to large surface area hydrophilized by the adsorbed stabilizer.

Example: Nanomorph, a patented technology by Solids for controlled crystallization of drugs.

2.1.17. Evaporative Precipitation in Aqueous Solution (EPAS)

The EPAS process utilizes rapid phase separation to nucleate and produce nanoparticles and microparticles of lipophilic drugs.

Preparation: The drug is first dissolved in a low boiling point organic solvent, and solution is pumped through a tube where it is heated under pressure to a temperature above the solvents boiling point, and then sprayed through a fine atomizing nozzle into a heated aqueous solution. Surfactants are added to the organic solution and aqueous solution to optimize particle formation and solubilization as well.

Application

The solubility of danazol was enhanced by this technique [26].

2.1.18. Use of Precipitation Inhibitors

A significant increase in free drug concentration above equilibrium solubility results in supersaturation, which can lead to drug precipitation or crystallization this process also call as anti-nucleation . This can be prevented by use of inert polymers such HPMC, PVP, PVA, PEG etc. which act as precipitation inhibitors by one or more of the following mechanisms

- Increase the viscosity of crystallization medium thereby reducing the crystallization rate of drugs.
- Provide a steric barrier to drug molecules and inhibit crystallization through specific intermolecular interaction on growing crystal surfaces.
- Adsorb onto faces of host crystals, reduce the crystal growth rate of the host and produce smaller crystals.

2.1.19. Solvent Deposition

In this technique, the poorly aqueous soluble drugs is dissolved in an organic solvent like alcohol and deposited on a inert, hydrophilic, solid matrix such as starch or microcrystalline cellulose followed by evaporation of solvent.

Advantages [27]

- This method is readily adaptable for thermolabile drugs and carriers.
- Many polymers with high melting temperatures that cannot be utilized in melt solid dispersion processes could be carriers for solvent deposited drug formulations.
- Tackiness and stickiness associated with melt or fusion method can be avoided.
- A common solvent having solubility for both hydrophobic drug and a hydrophilic carrier is not necessary

Application

The solvent deposition system of griseofulvin using disintegrants Primojel, Mobile Starch and Nymcel were punched to form tablet containing 125 mg griseofulvin [27].

2.1.20. Spherical agglomeration

It is a particle engineering technique. It is combine unite process of crystallization, agglomeration and Spheronization, which convert fine crystal in spherical shape particle. This technique is significant for improving the flow property like wettability and dissolution rate of poorly soluble drug. Amount of addition of spherical liquid, temperature and agitation speed parameter must be optimize in this technique for production of spherical crystal[10].

Advantages [10]

- Micromeritics properties of drug molecule increases.
- This method helps to improve the wettability and flow property of drug.
- This method is also useful for taste masking of some drug.

Disadvantages [10]

- Solvent selection is tedious for this method.
- Difficult to maintain process parameter.

Application

Enhanced dissolution rate of Felodipine using spherical agglomeration with Inutec SP1 by quasi emulsion solvent diffusion method [28].

2.1.21. Selective adsorption on insoluble carriers

A highly active adsorbent such as inorganic clays like Bentonite can enhance the dissolution rate of poorly water-soluble drugs such as griseofulvin, indomethacin and prednisone by maintaining the concentration gradient at its maximum.

2.2. NEWER AND NOVEL TECHNIQUES

Newer and novel drug delivery technologies developed in recent years for solubility enhancement of insoluble drugs are

- Size reduction technologies
  Nanoparticle technology
  Nanocrystal technology
  Nanosuspension technology
  Milling
  Precipitation
  High pressure homogenization
  Cryogenic technology
  Sonocrystallisation
  Plasma irradiation
  Liquisolid compacts
  Supercritical technology
  Self-Emulsification

Super critical fluid technology
- Lipid based delivery system
- Micro-emulsion Technology
- Micellar technologies
  Mixed Micelle
  Polymeric Micelle
- Porous Microparticle technology
- Floating drug delivery system

2.2.1. Nanoparticle technology

Nanotechnology will be used to improve drugs solubility by increasing the surface area. Oral bioavailability enhancement in some new chemical entities of very low solubility by micronisation is not sufficient because micronized product has the tendency of agglomeration, which leads to decreased effective surface area for dissolution and hence Nanonisation will be useful [7].

2.2.2. Nanocrystal technology

A nanocrystal is a crystalline material with dimensions measured in nanometers and the structure is mostly crystalline. The nanocrystallization is defined as a way of decreasing the drug particles to the size range of 1-1000 nanometers. Nanocrystallization is a universal method that can be applied to any drug. There are two distinct methods as follows in this technology [7].

- Bottom-up development.
- Top-down development.

In bottom-up method, nanoscale materials are chemically composed from atomic and molecular components to nanosized particles by Precipitation and Cryo-vacuum method. The top-down methods will be done by milling and high pressure homogenization down from micron sized particles.

Advantages

Nanocrystals as fast dissolution, increased kinetic saturation solubility and adhesion to biological membranes, which ultimately results in enhanced solubility and permeability [6].

Application

Novel lipid nanocrystals were developed for glibenclamide, which showed enough promise for lipid nanocrystals as an approach to enhance the dissolution and maintain stability of the model drug [29].

2.2.3. Nanosuspensions technology

Nanosuspensions have promising approach for efficient solubility enhancement of poorly water soluble drugs because of their versatile features and unique advantages often referred as hydrosols, are very finely dispersed solid particles in aqueous vehicle, size distribution of solid particles is usually < 1 nm, with average particle size range of 200-600 nm. Here, the bioavailbility is improved by increase in surface area and saturation solubility aided by particle size reduction [6, 10]. These are prepared by using high pressure homogenization, precipitation and pearl milling [10].

Preparation: The nanosuspensions are prepared by using high-shear media mills charged with milling media, water, drug, and stabilizer is rotated at a very high-shear rate under controlled temperatures for several days (at least 2–7 days). The milling medium is composed of glass, Zirconium oxide, or highly cross-linked polystyrene resin. High energy shear forces are generated as a result of the impaction of the milling media with the drug resulting into breaking of micro particulate drug to nanosizedparticles [1].

Advantages
- It improves the solubility and bioavailability of drug which gives rapid onset of action.
- Nanosuspensions formulation will increase the bioavailability of drugs with high log P.
- Dose reduction is possible.

Disadvantages
Limitations in drug loading as well as side effects due to matrix components are bypassed by nanosuspension system.

Application
Prednisolone and carbamazepine that could be considered acceptable for parenteral administratio[30].

2.2.4. Milling
2.2.4.1. Jet milling
A fluid jet mill uses the energy of the fluid (high pressure air) to attain ultra fine grinding of pharmaceutical powders and has several advantages of being a dry process, size reduction of micron-sized particles with narrow size distributions, absence of contamination and is suitable for heat sensitive drugs [16].

Application
Ibuprofen was also subjected to simultaneous micronization through continuous fluid energy milling, resulting in the improvement of dissolution rate while avoiding disadvantages of conventional micronization such as agglomeration, poor flowability, loss of expected large surface area, low bulk density and insignificant or no dissolution improvement [31].

2.2.4.2. Ball milling
A pharmaceutical ball millIng is generally a cylindrical crushing device that is used for grinding of pharmaceutical powders by rotation around a horizontal axis. The device is partially filled with the material to be ground plus the grinding medium usually ceramic balls, flint pebbles or stainless steel balls [16].

Application
Danazol showed enhanced bioavailability in beagle dogs when compared to that of aqueous suspension of conventional danazol particles [32].

Disadvantage
There will be degradation of mill surfaces and subsequent suspension contamination.

2.2.5. Precipitation
Here poorly aqueous soluble drug is dissolved in a suitable organic solvent followed by its rapid mixing with a non-solvent to effect precipitation of drug in nanosize particles. The product so prepared is also called as “Hydrosol”. Hydrosols are colloidal aqueous suspensions containing drug nanoparticles of poorly water soluble drugs for intravenous administration. In precipitation technique the drug is dissolved in a solvent where it dissolve more, which is then added to anti-solvent to precipitate the crystals in terms os nano particles. These nanocrystals can be removed from the solution by filtration and then dried in air [7].

Procedure: Here, the drug solution is mixed with a relatively high volume of water (96–98% water after mixing) in the presence of stabilizing agents such as poloxamer and modified gelatins, which act as “short term stabilizers”. After precipitation, the amorphous hydrosol is stable for approximately 60 min because of the stabilizers and the high amount of non-solvent. After this time, the drug crystallizes. Because the clouding correlates with the particle size, crystallization and particle growth can be observed by a steep increase of absorbance at a wavelength where the drug substance does not absorb. Thus, for durable stabilizing the amorphous nanosized drug, the hydrosol is immediately spray dried with excipients such as lactose or mannitol before crystallization occurs. Before use, the preparations are reconstituted with water. Hydrosols contain the drug in a particle size of approximately 200 nm and are thus suitable for parenteral application.

Advantages
The basic advantage of precipitation technique is the use of simple and low cost equipment;

Disadvantages
- Here the challenge is the addition of the growing drug crystals to avoid formation of microparticles.
- The drug needs to be soluble in at least one solvent and this solvent needs to be miscible with anti-solvent.
- This technique is not suitable for the drugs which are poorly soluble in both aqueous and non-aqueous media.

Applications

- Nanosuspension of Danazol and Naproxen improved dissolution rate and oral bioavailability by precipitation technique [1].
- Apparent increase in the rate of absorption by approximately 4-fold in naproxen by this technique [1].
- Cyclosporin, which can be formed as a hydrosol (ratio drug: gelatin-1: 20).
- Preparation of mefenamic acid and astemizole crystals by precipitation [33].

2.2.6. High pressure homogenization

In high pressure homogenization is an aqueous dispersion of the crystalline drug particles is passed with high pressure through a narrow homogenization gap with a very high velocity. Here the priciple is based on the cavitation forces within the particles are adequately high to convert the drug microparticles into nanoparticles. The particle size obtained during the homogenization process depends mainly on the nature of the drug, the pressure applied and the number of homogenization cycles as well [7].

Disadvantage

Here we require small particles initial itself and also require many cycles of homogenization [34].

Applications

- Dissolution rate and bioavailability of poorly soluble drugs such as spironolactone, budesonide, and omeprazole have been improved by reducing their particle size by high pressure homogenization [1].
- Valsartan nanosuspension (VAL-NS) was prepared using high-pressure homogenization followed by lyophilisation [35].

2.2.7. Cryogenic techniques

Cryogenic techniques have been developed to enhance the dissolution rate of drugs by creating nanostructured amorphous drug particles with high degree of porosity at very low temperature conditions. After cryogenic processing the dry powder can be obtained by various drying lyophilisation [1].

- Cryo-vacuum method
- Spray freezing into cryogenic fluids (SFL)
- Spray freezing into vapor over liquid (SFV/L)

2.2.7.1. Cryo-vacuum method

Cryo-vacuum method is to generate the drug substance nanoparticles by using liquid nitrogen.

Preparation

The active ingredient to be nanonized is first dissolved in water to attain a quasi-saturated solution. And then sudden cooling of a solvent by immersing the solution in liquid nitrogen (-196 ºC). Here, Rapid cooling causes a very fast rise in the degree of saturation based on the degree of solubility and development of ice crystals when the temperature drops below 0 ºC and also this leads to a fast nucleation of the dissolved substance at the edges of the ice crystals [7].

Advantage

- Cryo-assisted sublimation makes it possible to remove the solvent without changing the size and habit of the particles produced, so they will remain crystalline [7].
- This method yields very pure nanocrystals since there is no need to use surfactants or harmful reagents [7].

2.2.7.2. Spray freezing into cryogenic fluids (SFL)

Briggs and Maxwell invented the method of spray freezing onto cryogenic fluid. The SFL particle engineering technology has been used to produce amorphous nanostructured aggregates of drug powder with high surface area and good wettability by liquid – liquid impingement between the atomized feed solution and cryogenic liquid to provide more intense atomization into micro droplets and consequently significantly faster freezing rates leads particles are then lyophilized to obtain dry and free-flowing micronized powders [1].

Preparation: In this method, the drug and the carrier (mannitol, maltose, lactose, inositol or dextran) were dissolved in water and atomized above the surface of a boiling agitated fluorocarbon refrigerant sonication probe can be placed in the stirred refrigerant to enhance the dispersion of aqueous solution [1].

Application
It produced the rapid dissolving high potency Danazol powders by using Spray Freezing into liquid process [1].

2.2.7.3. Spray freezing into vapour over liquid (SFV/L)
Freezing of drugs solution in cryogenic fluid vapours and consequent removal of frozen solvent will produces fine drug particles with high wettability called SFV/L [1].

Operation: During SFV/L the atomized droplets typically start to freeze in the vapour phase before they contact the cryogenic liquid. As the solvent freezes, the drug becomes supersaturated in the unfrozen regions of the atomized droplet, so fine drug particles may nucleate and grow [1].

2.2.8. Sonocrystallisation
The novel move toward particle size reduction on the basis of crystallisation by using ultrasound-assisted is called sonocrystallisation.

- Melt Sono-Crystallization (MSC)

2.2.8.1. Melt Sono-Crystallization (MSC)
Melt sonocrystallization is an novel particle engineering technique to enhance dissolution of hydrophobic drugs and to study its effect on crystal properties of drug.

Preparation: Melt sonocrystallization process was developed for valdecoxib in which valdecoxib melt was poured in deionized water maintained at 60°C and at the same time subjected to ultrasonic energy. The agglomerates obtained after solidification of dispersed droplets were separated by filtration and dried at room temperature [36].

Application
It forms Valdecoxib agglomerates with number of shallow circular pits on the surface leads to increase solubility [36].

2.2.9. Plasma Irradiation
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. This is the possible technique for increasing the dissolution rate of poorly soluble drugs.

Generation of plasma: It is created by subjecting a gas (e.g. O_2) to a radio-frequency potential in a vacuum chamber and thus 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 [1].

Operation: During plasma treatment oxygen radicals produced by irradiation plasma 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 [1].

Application
Plasma irradiation was investigated as a possible technique for increasing the dissolution rate of the poorly soluble drug griseofulvin [37].

2.2.10. Liquisolid Compacts
Here, low soluble hydrophobic drugs dissolved in non-volatile, nontoxic, hydrophilic solvents like polyethylene glycol, glycerine, propylene glycol, or polysorbate-80 mixed with carriers like microcrystalline cellulose, lactose, or polyvinyl pyrrolidone- K30 along with coating materials like silica in optimized proportions and finally compressed into a compact mass [1].The increased bioavailability is due to either increased surface area of drug available for release, an increased aqueous solubility of the drug, or improved wettability of the drug particles [38].

Application
In recent years, this technique was used to enhance the dissolution rate of carbamazepine, naproxen, famotidine, and prednisolone [2].

2.2.11. Self-Emulsification
In the absence of external phase (water), the mixture of oil, surfactant, co-surfactant, one or more hydrophilic solvents and co-solvent forms a transparent isotropic solution that is known as the self-emulsifying drug delivery system (SEDDS) and is used for improving lipophilic drug dissolution and absorption. The self-emulsification process is specific to the nature of the oil/surfactant pair, surfactant concentration, oil/surfactant ratio and temperature at which self emulsification occurs.

Advantages [10]
- High drug loading efficiency
- Improvement in oral bioavailability enabling reduction in dose.
- More consistent and reproducible profile of drug absorption and blood time profile.
- Ease of manufacturing and scale up.
- Protection of drugs from the gut environment.

Disadvantages [10]
- Chemical instability of drug and surfactant in formulation.
- High surfactant concentration irritates the GIT.

Application
The oral bioavailability of progesterone was significantly enhanced in rats by forming positively charged emulsion in comparison to the corresponding negatively charged formulation.

Examples: Neoral® is composed of ethanol, corn oil- mono-, di-, triglycerides, Cremophor RH 40 and propylene glycol. It exhibits less variability and better drug uptake compared to Sandimmune®. There is a long list of water soluble, insoluble and surfactants, which can use as solubilizing excipients [1].

2.2.12. Supercritical fluid Technology
A supercritical fluid is a substance at a temperature and pressure above its critical point, where distinct liquid and gas phases do not exist. Novel nanosizing and solubilization technology whose application has increased particle size reduction via supercritical fluid (SCF) processes. Generally supercritical fluids are fluids whose temperature and pressure are greater than its critical temperature (Tc) and critical pressure (Tp). SCF processing for micronized particles are
- Rapid expansion of supercritical solutions (RESS)
- Gas anti-solvents recrystallisation (GAS)

2.2.12.1. Rapid expansion of supercritical solutions (RESS)
It 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 and 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. This modified process is used for the production of polymeric nanoparticles [1].

2.2.12.2. Gas anti-solvents recrystallisation (GAS)
A liquid solvent is required in the process of GAS 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), e.g. methanol. The extract of the liquid solvent by supercritical fluid leads to the instantaneous precipitation of the solute.

Both of which are employed by the pharmaceutical industry using carbon dioxide (CO_2) as the SCF due to its favorable processing characteristics like its low critical temperature (Tc = 31.1-C) and pressure (Pc = 73.8 bar) . The SCF process can create nanoparticle of particles 5–2,000 nm in diameter.

Advantages
Generally solvent extraction-evaporation, solvent diffusion and organic phase separation are some conventional methods which require the use of organic solvents but these organic solvents are hazardous to the environment as well as to physiological systems so, SCF are environmentally safe. Therefore, to prepare biodegradable micro and nanoparticles the supercritical fluid technology has been investigated as an alternative.

Disadvantages
Poor control over the precipitated crystal morphology, size distribution and presence of residual solvents [39].

Application
Gas Antisolvent Recrystallization of Paracetamol from acetone using compressed carbon cioxide as antisolvent [40].

2.2.13. Lipid based delivery system/Solid Lipid Nanoparticles
Solid lipid nanoparticles (SLN) are a new pharmaceutical delivery system or pharmaceutical formulation. Solid lipid nanoparticles (SLNs) are particulate systems with mean particle diameters ranging from 50-1000 nm and they are derived in oil in water emulsions by replacing liquid lipid by solid lipid. Solid lipid nanoparticles have recently materialized as a novel approach to oral and parenteral drug delivery systems. SLNs join the advantages of lipid emulsion and polymeric nanoparticle systems while overcoming the temporal and in vivo stability issues that predicament the conventional as well as polymeric nanoparticles drug delivery approaches [10].

Advantages
- Improved bioavailability, protection of sensitive drug molecules from the outer environment water, light and even controlled release characteristics were claimed by incorporation of poorly water-soluble drugs in the solid lipid matrix.
- There are number of potential advantages associated with SLNs as lipid matrix of system is made from physiologically tolerated lipids components which reduces the risk of toxicity, they can be produced on large industrial scale by high pressure homogenization, they have the capable of being stable for at least 3 years [10].

Applications
- Use of solid lipid nanoparticles as a platform for oral delivery of the nutrient mineral iron by incorporating the hydrophilic molecule ferrous sulphate (FeSO4) in a lipid matrix composed of steric acid.
- Quercitin and lovastatin Lipid-based formulations have been shown to enhance oral absorption of lipophilic drugs [10].
- Formulation of vinopocetine using lipid matrix as glyceryl monostearate by ultrasonic solvent emulsification technique and showed significant enhancement in bioavalability compared to vinopocetine solution [10].

2.2.14. Micro-emulsion Technology
The term micro-emulsion was first used by Jack H. Shulman in 1959. A micro-emulsion is a four component system composed of external phase, internal phase, surfactant and co-surfactant. It is a dispersion made of water, oil, and surfactant(s) that is an isotropic and thermodynamically stable system of two immiscible liquids stabilized by interfacial films of surface active molecules with dispersed domain diameter varying approximately from 1 to 100 nm, usually 10 to 50 nm.

Formation of Micro-emulations
These are formed by simple agitation of oil, water, surfactant and co-surfactant. The co-surfactant together with the surfactant reduces the interfacial tension to very low and even transient negative values. Here, the addition of surfactant, which is predominately soluble in the internal phase unlike the co-surfactant, results in the formation of an optically clear, isotropic, thermodynamically stable emulsion. It is termed as microemulsion because of the internal or dispersed phase is < 0.1 μ droplet diameter.

Advantages
The pre-concentrates are relatively easy to manufacture and well developed micro-emulsion preconcentrates are not normally dependent upon digestion for drug release. Therefore, optimal bioavailability and reproducibility can be also being expected without co-administration of food (i.e. the fasted state) [8].

Disadvantage
Dilution of micro-emulsions below the critical micelle concentration of the surfactants could cause precipitation of the drug [8].

Applications

- Micro-emulsions have been employed to enhance the solubility of many drugs that are practically insoluble in water, along with incorporation of proteins for oral, parenteral, as well as percutaneous/ transdermal use [8].
- Micro-emulsion applied in HIV protease inhibitor tipranavir (Aptivus® capsules, Boehringer Ingelheim GmBH) and the category defining immunosuppressant cyclosporine A, USP modified (Neoral® capsules, Novartis AG) [41].

2.2.15. Micellar Technologies
Micelle is an aggregate of surfactant molecules dispersed in a liquid colloid. A typical micelle in aqueous solution forms an aggregate with the hydrophilic "head" regions in contact with surrounding solvent, sequestering the hydrophobic single-tail regions in the micelle centre. Micelle formation can only occur above a certain solute concentration called critical micellar concentration (CMC), and at solution above temperatures called critical micellar temperature (CMT). In general, amphiphilic, ionic, anionic or ampholytic molecules, which are able to decrease the surface tension of a solvent when they arranged in micelles above a certain critical concentration and temperature. The formation of micelle is mentioned in the figure 6 and solubilization is mentioned in the figure 7.

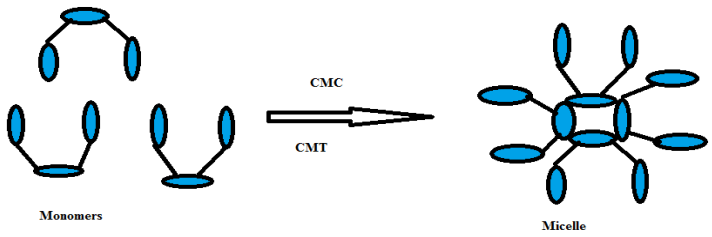


Fig 6: Schematic representation of the general structure of triblock polymer and micelle formation at CMC and CMT

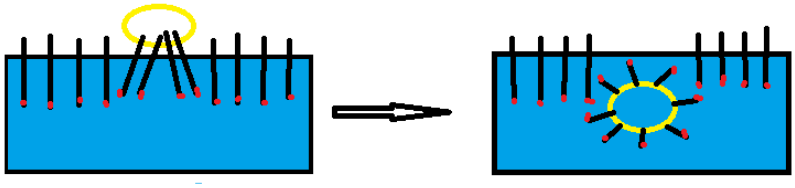


Fig 7: Schematic of micellar solubilization of fatty substance in water with the use of a dispersant

- Mixed Micelles
- Polymeric Micelles
- Porous Microparticle Technology

2.2.15.1. Mixed Micelles
Mixed micelles have a hydrophobic core in which low soluble compounds can dissolve. The addition of salt, alcohol etc. can vary the degree of penetration into the micelle (co-solubilization).

Application
Solubility enhancement for clonazepam in aqueous mixed micellar solution with proper shelf stability was achieved [42].

2.2.15.2. Polymeric Micelles
Amphiphilic polymers bring together into nano-scopic supra molecular core-shell structures, known as polymeric micelles, which are under extensive study for drug delivery. Polymeric micelles may be safe for parenteral

administration relative to existing solublizing agents, permitting an increase in the dose of potent toxic and poorly water soluble compounds.

Advantages [16]

- Polymeric micelles have several advantages as drug carriers and can incorporate several poorly soluble drugs and are considered inexpensive, safe and stable drug carriers.
- polymeric micelles is possible by preparing thermo- or pH-sensitive block co-polymers and additionally, a vector molecule such as antibody, peptide, lectin, saccharide, hormone and some low-molecular-weight compounds can be attached to the surface of micelles that helps in targeting against specific ligands at specific site of interest.

Applications

- Polymeric micelles solubilize poorly soluble drugs such as amphotericin B, propofol, paclitaxel, and photosensitizers [43].
- High bioavailability/solubilization and long-term stability of an anticancer drug paclitaxel were observed when the drug was solubilized into hydrotropic polymeric micelles by dialysis method [44].

Examples: Solubilization is depends on the polymeric micelles and here are some poly (ethylene glycol) (PEG)-phospholipid conjugates, PEG-b-poly (ester)s, and PEG-b-poly (L-amino acid)s considered for drug delivery [8].

2.2.16. Porous Microparticle Technology

The poorly water soluble drug is embedded in microparticles having a porous, water soluble, sponge like matrix. When mixed with water, the matrix dissolves, wetting the drug and leaving a suspension of rapidly dissolving drug particles.

Application

This core technology applied as HDDS™ (Hydrophobic Drug Delivery System).

2.2.17. Floating drug delivery system

Floating drug delivery system is an low-density systems that have sufficient buoyancy to float over the gastric contents and remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time and the drug is released slowly at the desired dissolution rate from the system. Effervescent and non-effervescent are two class of floating drug delivery system and can formulate either in single unit dosage form or in multiple unit dosage form.

Advantage

Administration of prolongs release floating dosage forms, tablet or capsules, will result in dissolution of the drug in the gastric fluid [45].

Disadvantage

Floating system is not feasible for those drugs that have solubility or stability problem in GIT and causes irritation to gastric mucosa [45].

Applications

- Novel approach for dissolution enhancement of ibuprofen (a weekly acidic, non-steroidal anti inflammatory drug) by preparing floating formulation in order to get dissolved in GIT for best therapeutic action [46].
- Sustained release floating capsules of nicardipine hydrochloride were developed and were evaluated in vivo [45, 47, 48].

2.3. SOLID DISPERSION SYSTEM

Chiou and Riegelman defined the term solid dispersion as “a dispersion involving the formation of eutectic mixtures of drugs with water soluble carriers by melting of their physical mixtures”. The term solid dispersion refers to a group of solid products consisting of at least two different components, generally a hydrophilic matrix and a hydrophobic drug. The matrix can be either crystalline or amorphous. The drug can be dispersed molecularly, in amorphous particles (clusters) or in crystalline particles. Based on their molecular arrangement, six different types of solid dispersions can be distinguished.

- Simple Eutectic Mixture.
- Solid Solution Continuous Solid Solution.
- Discontinuous Solid Solution.
- Substitutional Crystalline Solid Solution.
- Interstitial Crystalline Solid Solution.
- Amorphous Solid Solution.
- Glass Solution and Glass Suspension
- Drug dispersion in carriers

Hot melt method
Hot stage Extrusion
Solvent evaporation method
Melting –solvent method

Advantages [10]

- **Reduction in particle size:** Different carriers used in solid dispersion reduce particle size of drug particle which improve solubility and bioavailability.
- **Improve wettability of particle:** Solid dispersion improves wettability of particle.
- **Improve porosity:** Solid dispersions containing linear polymers produce larger and more porous particles than those containing reticular polymers and therefore, result in a higher dissolution rate and bioavailability.
- Improve dissolution which ultimately improves the solubility and bioavailability.

Disadvantages [10]

- Instability due moisture content.
- Difficulty in incorporating into formulation of dosage forms.

2.3.1. Simple Eutectic Mixture

When a mixture of A and B with composition E is cooled, A and B crystallize out simultaneously, whereas when other compositions are cooled, one of the components starts to crystallize out before the other. Solid eutectic mixtures are usually prepared by rapid cooling of a co-melt of the two compounds in order to obtain a physical mixture of very fine crystals of the two components. When a mixture with composition E, consisting of a slightly soluble drug and an inert, highly water soluble carrier, is dissolved in an aqueous medium, the carrier will dissolve rapidly, releasing very fine crystals of the drug. The large surface area of the resulting suspension should result in an enhanced dissolution rate and thereby improved bioavailability.

2.3.2. Solid Solution Continuous Solid Solution

In a continuous solid solution, the components are miscible in all proportions. Theoretically, this means that the bonding strength between the two components is stronger than the bonding strength between the molecules of each of the individual components.

2.3.3. Discontinuous Solid Solution

In the case of discontinuous solid solutions, the solubility of each of the components in the other component is limited. Below a certain temperature, the mutual solubilities of the two components start to decrease. It has been suggested by Goldberg that the term `solid solution' should only be applied when the mutual solubility of the two components exceeds 5%. Whether or not a given solid solution can be utilized as a dosage form strategy will depend not only on the mutual solubilities of the two components but also on the dose of the drug component. The upper limit for the mass of a tablet or capsule is about 1 g.

2.3.4. Substitutional Crystalline Solid Solution

Classical solid solutions have a crystalline structure, in which the solute molecules can either substitute for solvent molecules in the crystal lattice or into the interstices between the solvent molecules. Substitution is only possible when the size of the solute molecules differs by less than 15% or so from that of the solvent molecules.

2.3.5. Interstitial Crystalline Solid Solution

In interstitial solid solutions, the dissolved molecules occupy the interstitial spaces between the solvent molecules in the crystal lattice. To occupy interstitial space, the solute molecules should have a molecular diameter that is no

greater than 0.59 of the solvent molecule's molecular diameter. Furthermore, the volume of the solute molecules should be less than 20% of the solvent.

2.3.6. Amorphous Solid Solution

In an amorphous solid solution, the solute molecules are dispersed molecularly but irregularly within the amorphous solvent. Using griseofulvin in citric acid, it was the first attempt to report the formation of an amorphous solid solution to improve a drug's dissolution properties. Other carriers that were used in early studies included urea and sugars such as sucrose, dextrose and galactose. More recently, organic polymers such as polyvinylpyrrolidone (PVP), polyethylene glycol (PEG) and various cellulose derivatives have been utilized for this purpose.

2.3.7. Glass Solution and Glass Suspension

A glass solution is a homogenous, glassy system in which a solute dissolves in a glassy solvent. The glassy or vitreous state is usually obtained by an abrupt quenching of the melt. It is characterized by transparency and brittleness below the glass transition temperature (Tg). On heating, it softens progressively and continuously without a sharp melting point.

2.3.8. Drug dispersion in carriers

- Hot melt method
- Hot stage Extrusion
- Solvent evaporation method
- Melting –solvent method

The solid dispersion approach to reduce particle size and therefore increase the dissolution rate and absorption of drugs was first recognized in 1961. 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 drying and using supercritical fluids and spray drying , often in the presence of amorphous hydrophilic polymers and also using methods such as melt extrusion [7].

Examples

The most commonly used hydrophilic carriers for solid dispersions include polyvinylpyrrolidone, polyethylene glycols and Plasdone-S630. Many times surfactants may also used in the formation of solid dispersion. Surfactants like Tween-80, Docusate sodium, Myrj-52, Pluronic-F68 and Sodium Lauryl Sulphate used.

Applications

The solubility of etoposide, glyburide, itraconazole, ampelopsin, valdecoxib, celecoxib and halofantrine can be improved by solid dispersion using suitable hydrophilic carriers.

2.3.8.1. Hot melt method

Sekiguchi and Obi used a hot melt method to prepare solid dispersion.

Preparation: 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.

2.3.8.2. Hot-melt extrusion

Hot melt extrusion (HME) is the process of applying heat and pressure to melt a polymer and force it though an orifice in a continuous process. HME is a well known process, developed to produce polymer products of uniform shape and density, and its industrial application dates back to the 1930’s. It is one of the most widely applied processing technologies in the plastic, rubber and food industries and is used to prepare more than half of all plastic products including bags, films, sheets, tubes, fibers, foams, and pipes. HME has more recently been applied to the health-care industry where it is used to manufacture medical devices and to mix active pharmaceutical ingredients (APIs) with polymers to enhance the API’s bioavailability [49].

Advantages [10]

- This technique protect drug susceptible to oxidation and hydrolysis by complete elimination of oxygen as well as moisture from the mixture [1].
- Improve the solubility and bioavailability of poorly soluble compounds.
- Processing in the absence of solvents and water.
- Economical process with reduced production time, fewer processing steps, and a continuous operation.
- Uniform dispersion of fine particle occurs.
- Good stability at varying pH and moisture levels.
- Safe application in humans due to their non swellable and water insoluble nature.

Disadvantages [10]

- Not applicable to heat sensitive material.
- Limited number of available polymer.
- This method requires high energy input.
- HME are complex mixture of active drug and excipient.

2.3.8.3. Examples of general excipients used in HME

Polyethylene glycol, Polyethylene oxide, Hydroxypropyl cellulose, Hydroxypropylmethyl cellulose, Poly(dimethylamino ethyl methacrylate-co- methacrylate ester), Ammonio-comethacrylate copolymer and co-povidone [10].

Application of HME [10]

- To mask the bitter taste of an active drug.
- Formation of polymer-drug solutions/dispersions which increased drug solubility and increased drug dissolution rate.
- Formulation of controlled release dosage forms (including implants).
- Formulation of targeted release dosage forms.
- Prednisolone, Carbamazepine and Nifedipine were developed in HME to increase the solubility [50, 51].

2.3.8.4. Solvent evaporation method

Tachibana and Nakumara 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 _-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 spray-drying or by freeze-drying Temperatures used for solvent evaporation generally lie in the range 23-65 C.

Disadvantages

- Effect of 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.

Application

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.

2.3.8.5. 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 70°C without removing the liquid solvent.

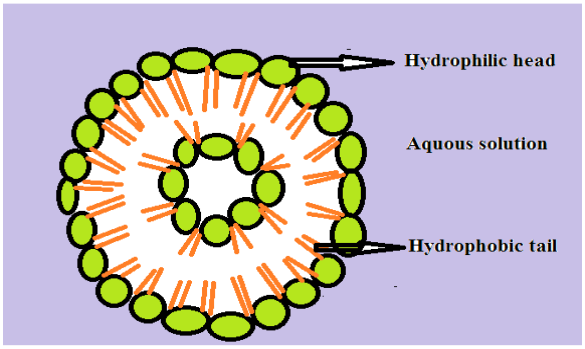
The selected solvent or dissolved drug may not be miscible with the melt of the polyethylene glycol. Also polymorphic form of the drug precipitated in the solid dispersion may get affected by the liquid solvent used. Carriers for solid dispersions as shown in table 2.

Table 2: Carriers for solid dispersions

S/No.	Chemical class	Examples
1	Acids	Citric acid and Tartaric acid
2	Sugars	Dextrose, Sucrose and Sorbitol
3	Polymeric material	Polyvinylpyrrolidone, PEG-4000 and Cellulose
4	Surfactants	Polyxyethylene Stearate, Tweens and Spans
5	Miscellaneous	Urea and Urethase

2.4. VESICULAR APPROACHES

In cell biology, a vesicle is a small structure within a cell, consisting of fluid enclosed by a lipid bilayer. Vesicles form naturally during the processes of secretion (exocytosis), uptake (phagocytosis and endocytosis) and transport of materials within the cytoplasm and shown below in the figure 8.



Fug 8: Scheme of a liposome formed by phospholipids in an aqueous solution

Recently lipid vesicles were found to be of very much use in membrane biology. These vesicles were first reported by Bingham in 1965 and thereby also called Bingham bodies. The vesicular approach basically takes into consideration the concept of micellar solubilzation. Poorly soluble compounds which fit into the micelle structure are most appropriate. These micelles soak up the lipophilic substance in their lipophilic region and subsequently no dissolution of poorly soluble compound needed before absorption as the drug is already in solubilized form[14][6].

Advantages

➢ These are easy to formulate and reproducible on large scale.
➢ It prolongs the survival of drug in systemic circulation and also delays the elimination of rapidly metabolizable drugs [6].

2.4.1. Liposomes

A liposome is a spherical vesicle having at least one lipid bilayer and can be used as a vehicle for administration of nutrients and also pharmaceutical drugs. Liposomes are microscopic, synthetic cells used as sustained-action delivery vehicles for a wide variety of drugs, vaccines, enzymes, non enzyme proteins, and genetic material and now, for some nutritional supplements as well [6, 10].

Mechanism of action

The drug is encapsulated within the liposomes, which eventually break down through natural processes and spill their contents into the bloodstream or into tissues to which they have migrated by diffusion through the walls of capillaries. The liposome encapsulation effectiveness of lipophilic drugs depends on both the physicochemical properties of the drug lipophilicity. Ready-for-use liposomes with defined particle size and instantaneous loading procedures with poorly water soluble drugs liposomes are certainly useful options to increase the solubility of poorly water soluble compounds offer a dynamic and adaptive technology for enhancing drug solubility [6].

Advantages

• Liposomes are a safe and efficient way to introduce agents into system that are difficult for some reason when taken orally, as well as agents that cannot be taken orally at all (because they are degraded by digestive juices).

- Liposomal formulations in contrast to other carrier systems are generally regarded as safe status of phospholipid constituents [6].

Disadvantages [52]
- It is very expensive preparation
- May cause the Deterioration of lipids by oxidation.
- Settlement of vesicles in suspension.
- Leakage of drug from vesicles.
- Lack of purity of crude phospholipids.

Application
Gancicyclovir liposomes were formulated and ocular bioavailability was shown to increase 1.7 fold higher than gancicyclovir solution [6].

2.4.2. Niosomes
Niosomes are a novel drug delivery system, in which the medication is encapsulated in a vesicle. The vesicle is composed of a bilayer of non-ionic surface active agents and hence the name niosomes. Structurally niosomes are similar to liposomes, in that they are also made up of a bilayer [6].

Advantages
Niosomes have recently been shown to greatly increase transdermal drug delivery and also can be used in targeted drug delivery, and thus increased study in these structures can provide new methods for drug delivery [6, 10].

Disadvantages [52]
- Shelf life of aqueous suspension limited due to aggregation, leaching or hydrolysis of entrapped drug.
- More time consumption and unstable.

Application
Niosomes of griseofulvin were prepared using different non ionic surfactants by thin film method and ether injection method. The in vivo study revealed that niosomal dispersion significantly improved the oral bioavailability of griseofulvin in albino rats after single dose [6].

2.4.3. Pharmacosomes
Pharmacosomes are colloidal, nanometric size micelles, vesicles or may be in the form of hexagonal assembly of colloidal drug dispersions attached covalently to the phospholipid. Pharmacosomes act as befitting carrier for delivery of drugs quite precisely owing to their unique properties like small size, amphiphilicity, active drug loading, high entrapment efficiency, and stability [52]. As the system is formed by linking a drug (pharmakon) to a carrier (soma), they are termed as pharmacosomes. It majorly depends on surface and bulk interactions of lipids with drug. Generally any drug conatining an active hydrogen atom (-NH2, -COOH, -OH, , etc.) can be esterifies to the lipid, with or without spacer chain that strongly result in an amphiphilic compound, which will make possible membrane, tissue, or cell wall transfer in the organism.

Advantages
- These act as controlled release of drug at the site of action as well as in reduction in cost of therapy, drug leakage and toxicity, increased bioavailability of poorly soluble drugs, and restorative effects [52].
- Advancement in the scope of this delivery system for a number of drugs used for heart diseases, protein delivery, inflammation, cancer, and along with a large number of herbal drugs. Hence, pharmacosomes open new challenges and opportunities for improved novel vesicular drug delivery system [52].

Disadvantages [52]
- Expensive technique.
- It is chemically unstable due to oxidative degradation.
- Less abundance of high purity phospholipids

Applications

- Pharmacosomes of aceclofenac were prepared using phosphatidylcholine (80%) in two different ratios in 1:1 and 2:1 by conventional solvent evaporation technique. Aceclofenac pharmacosomes showed improved dissolution profile than aceclofenac acid [14].
- Diclefenac solubility enhancement was studied by pharmacosome and found to be increased solubility from 10.5 to 22.1 μg/mL [53].

CONCLUSION

By this article it is accomplished that drug solubility and bioavailability enhancement are the most essential aspect in formulation development and also in therapeutic efficacy. Numerous techniques like Traditional, novel, solid dispersions and vascular approaches were described here in this review can lead to enhancement in drug solubility resulting in increased bioavailability as well. Choice of method for solubility enhancement depends upon drug characteristics like solubility, melting point, physical nature, chemical nature, absorption site, pharmacokinetic behavior, dosage form requirement like tablet or capsule formulation, strength, immediate, or modified release, regulatory requirements like maximum daily dose of any excipients and/or drug, approved excipients, analytical accuracy and so forth.

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