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POORLY SOLUBLE DRUGS- A CHALLENGE IN DRUG DELIVERY SYSTEM

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ABSTRACT

The therapeutic effectiveness of a drug depends upon the bioavailability and solubility. The process of solubilisation involves the breaking of inter-ionic or inter-molecular bonds in the solute, the separation of the molecules of the solvent to provide space in the solvent, interaction between the solvent and the solute. The various factors affecting solubility are particle size, temperature, pressure, nature of the solute and the solvent, molecular size, polarity, etc. It is estimated that about 40% of compounds being developed by pharmaceutical industry are poorly water soluble which serves serious challenge to the successful development of new drugs. A limiting factor to this is the inadequate dissolution rates. Thus, increasing the dissolution rate of poorly water soluble active pharmaceutical ingredients has become a major challenge and transfers them into highly bioavailable drug delivery systems by distinct measures such as chemical transformation, biopharmaceutical measures and physiological measures. Multiple technologies are available for the successful formulation of poorly soluble drugs such as controlled precipitation, ultra-rapid freezing, hydrotropic solubilisation, complexation, solid dispersion, salt formation, use of co-solvents, solubilzing agents, co-crystallization, etc. Overall, discoveries of new technologies will be useful for drugs with problems of poor solubility and bioavailability, which would allow future drugs and new entities to reach market successfully and thereby, serve mankind in a better way.

KEYWORDS: Solubilisation, Bioavailability, Solubility, Pharmaceutical Industry.

INTRODUCTION

The fact that more than 40% of newly discovered drugs have little or no water solubility presents a serious challenge to the successful development and commercialization of new drugs in the pharmaceutical industry. No matter how active or potentially active a new molecular entity (NME) is against a particular molecular target, if the NME is not available in solution at the site of action, it is not a viable development candidate. As a result, the development of many exciting NMEs is stopped. The fact that more than 40% of newly discovered drugs have little or no water solubility presents a serious challenge to the successful development and commercialization of new drugs in the before their potential is realized or confirmed because pharmaceutical companies cannot afford to conduct rigorous preclinical and clinical studies on a molecule that does not have a sufficient pharmacokinetic profile due to poor water solubility. Which of these rejected NMEs would have been the next blockbuster drug?.[1]

Aqueous solubility can also be an issue for some marketed drugs. More than 90% of drugs approved since 1995 have poor solubility, poor permeability, or both. Approximately 16% have less-than-optimal performance specifically because of poor solubility and low bioavailability. A marketed drug with poor water solubility can still show performance limitations, such as incomplete or erratic absorption, poor bioavailability, and slow onset of action. Effectiveness can vary from patient to patient, and there can be a strong effect of food on drug absorption. Finally, it may be necessary to increase the dose of a poorly soluble drug to obtain the efficacy required.

Although pharmaceutical companies have been able to overcome difficulties with very slightly soluble drugs, those with aqueous solubility of less than 0.1 mg/ml present some unique challenges. These drugs are particularly good candidates for advanced solubilization technologies developed by companies specializing in drug delivery. However, solubilization technologies and the concepts on which they are based vary widely, as do the characteristics of potential NMEs and commercial drugs. What characteristics and capabilities are important in a solubilization technology? What technologies are available? If a technology works on a milligram laboratory scale, will that success translate to kilo- and commercial-scale quantities? This article describes how a new portfolio approach to solubilization problems is providing some answers.[2]

1. CURRENT SOLUBILIZATION TECHNOLOGIES[3]

Traditional approaches to enhancing delivery of poorly water-soluble drugs include pharmaceutical salts, solvent/cosolvent solutions, wetting agents, emulsions, micronization, and solid-state modifications (polymorphs/amorphous). Expertise in applying these approaches has developed within the pharmaceutical industry throughout many years. However, recent advances in drug discovery present new challenges for the effective delivery of poorly soluble drug compounds. The application of combinatorial chemistry, molecular modeling, and high-throughput cellular screening technologies has resulted in drug compounds with properties and activities more closely resembling the natural mediators in the body, which they are designed to mimic in their action. Many of these natural mediators are hydrophobic substances and are synthesized at or near their site of action; thus, they do not have to overcome the absorption, distribution, metabolism, and excretion (ADME) issues with administered drugs. As drug compounds have become less soluble and more challenging to formulate, advanced solubilization approaches are required to help overcome these resulting ADME challenges.

Development of these techniques often requires multifunctional capabilities beyond the current breadth of expertise or capacity of many pharmaceutical companies.

More than 70 companies have developed advanced drug delivery technologies for poorly water-soluble drugs. These approaches include solid dispersions, microemulsions, self-emulsifying systems, complexation, liposomes, and the creation of nanostructured particles through particle size reduction and particle formation techniques. Table 1 summarizes the main characteristics of each of these technologies.

Table 1: Current advanced approaches to enhancing delivery of poorly water - soluble drugs.

Advanced Approaches	Concept
Solid Dispersions	Intimate mixture of drug substances and diluents, such as polyethylene glycol or polyvinylpyrrolidone. The modified drug is often in an amorphous, more soluble state. Due to the higher energy state, there is a potential for recrystallization.
Self-Emulsifying Systems	Mixture of drugs, oils, surfactants, and co solvents that form an emulsion upon administration. Phase inversion may further promote drug release. Can be administered as a solid dosage form.
Complexation	Formation of a reversible, non covalent chemical complex of a drug with a carrier compound. Cyclodextrins are the most common complexing agents used to enhance drug absorption.

Liposomes	Encapsulation of a drug in uni- or multilayered vesicles of phospholipids. Specific sites can be targeted and certain drugs can be protected from inactivation.
Particle Size Reduction (Attrition)	Increased particle surface area enhances rate of Solubilization.
Wet Milling	Particle size reduction to nano-sized particles through attrition in the presence of stabilizing agents.
Homogenization	Particle size reduction by high shear processing of an aqueous slurry of drug and stabilizing agents.
Controlled Particle Formation	Growth of drug particles with controlled morphology.
Super Fluid- Based Approach	Engineered particle growth using super-critical fluid as a solvent.
Multi-faceted Approaches	Engineered particle growth using a wide variety of solvents and stabilizers under several conditions, including precipitation, cryogenics and the use of hydrophobic media.

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. The substance to be dissolved is called as solute and the dissolving fluid in which the solute dissolve is called as solvent, which together form a solution. The process of dissolving solute into solvent is called as solution, or hydration if the solvent is water.[4]

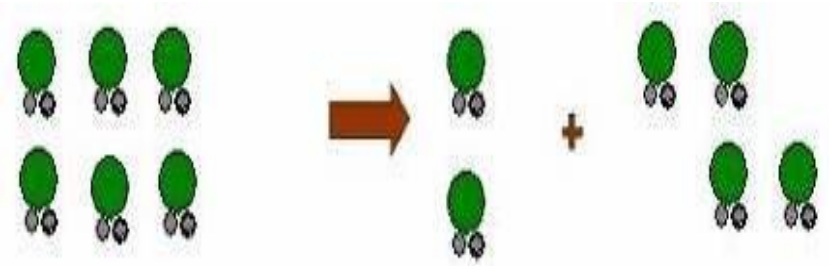
Table 2: Solubility chart

Definition	Parts of Solvent required for one part of Solute
Very Soluble	< 1
Freely Soluble	1-10
Soluble	10-30
Sparingly Soluble	30-100
Slightly Soluble	100-1000
Very Slightly Soluble	1000-10,000
Insoluble	>10,000

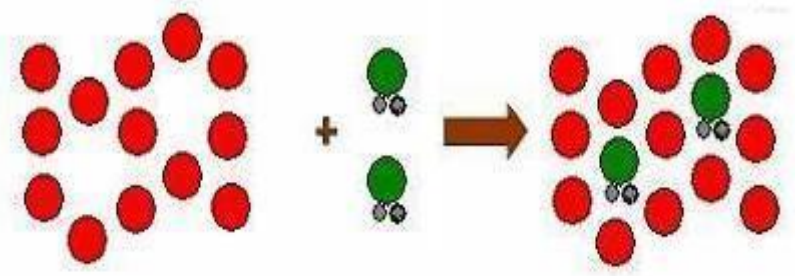
2. PROCESS OF SOLUBILISATION[5]

The process of solubilisation involves the breaking of inter-ionic or intermolecular bonds in the solute, the separation of the molecules of the solvent to provide space in the solvent for the solute, interaction between the solvent and the solute.

Step 1: Holes opens in the solvent.



Step2: Molecules of the solid breaks away from the bulk.



Step 3: The freed solid molecule is integrated into the hole in the solvent.

Figure 1: Steps involved in the process of solubilization.

3. FACTORS AFFECTING SOLUBILITY

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

1. Particle Size
2. Temperature
3. Pressure
4. Nature of the solute and solvent
5. Molecular size
6. Polarity
7. Polymorphs

4. RATE OF SOLUTION

The rate of solution is a measure of how fast substances dissolve in solvents.

Factors affecting rate of solution

1. Size of the particles
2. Temperature
3. Amount of solute already dissolved
4. Stirring.

5. Methods used to increase solubility of poorly water-soluble drugs.

5.1. Controlled Precipitation[6]

Controlled precipitation is a particle engineering technology that creates crystalline nanostructured drug particles with rapid dissolution rates. With this technology, the drug is dissolved in a suitable solvent then precipitated into an aqueous solution in the presence of crystal growth inhibitors to form drug nanoparticles. Particles prepared by controlled precipitation have the advantage of a narrower particle size distribution as compared to particle size reduction technologies, such as wet-milling.

Advantages:

- The process is fast, continuous, and scalable with conventional process equipment.
- Levels of residual solvents are low, and the excipients used are pharmaceutically acceptable.

There have been many formulations developed specifically for increasing the aqueous solubility of poorly soluble drugs.

5. 2. Ultra-Rapidfreezing[6]

Complementary to the aforementioned, ultra-rapid freezing is a novel, cryogenic technology that creates nanostructured drug particles with greatly enhanced surface area. The technology has the flexibility to produce particles of varying particle morphologies, based on control of the solvent system and process conditions.

The technology involves dissolving a drug (ketoconazole in this case) in a water-miscible or anhydrous solvent along with a stabilizer acting as a crystal growth inhibitor. The ketoconazole/stabilizer solution is then applied to a cryogenic substrate. The solvent is removed by lyophilization or atmospheric freeze-drying, resulting in highly porous, agglomerated particles. As with controlled precipitation, this process uses pharmaceutically acceptable solvents and excipients and conventional process equipment and thus is fast and scalable. An additional feature is that polymer absorption on the crystal surface upon freezing aids reduction of Ostwald ripening.

5. 3. Lip'ral Technology[7,8]

It is a clinically proven oral delivery technology for water insoluble drugs. Water insoluble drugs present significant challenges in product design and compliance, including poor bioavailability leading to high dose and/or multiple dosage units per dose. Highly variable

pharmacokinetics leading to inadequate therapy and/or safety concerns significant food effects on bioavailability leading to dosing restrictions in labeling and consequent patient compliance problems like slow or delayed absorption.

These challenges may be attributed to inadequate drug dissolution/solubilization in vivo leading to poor and inconsistent bioavailability. Lip'ral is a patented technology based on lipidic compositions which form the optimal dispersed phase in the gastrointestinal environment for improved absorption of the insoluble drug. Lip'ral represents insoluble drugs efficiently to the intestinal absorption site, thus bringing the absorption process under formulation control and making the product robust to physiological variables such as dilution, pH, and food effects. In some cases, solubilization in the dispersed phase can also improve aqueous stability allowing for improved gastrointestinal residence time of highly unstable drug molecules. Lip'ral utilizes a wide range of proprietary compositions with bioacceptable excipients. Lip'ral can be extended with Lipocine's Synchronized Solubilizer Release technology, Lip'ral-SSR, to enable controlled release of insoluble drugs and drugs with pH-sensitive solubility. Lip'ral in combination with Lipocine's solid lipid dispersion technology, Nanosplode, supports a wide variety of dosage form configurations including capsules, tablets, beads and multicomponent systems for a combination of different release/absorption profiles.

Lip'ral technologies use conventional manufacturing processes that are easy to scale-up and commercialize, thus reducing time to market. Lip'ral enables development of superior products with:

1. Improved solubilization and high drug loading capacity.
2. Improved bioavailability leading to reduced dose.
3. Faster and more consistent absorption leading to reduced variability.
4. Reduced sensitivity to food effects potentially improving patient compliance.

5.3.1 Lip'ral Synchronized Solubilizer Release (SSR)

It is a breakthrough oral controlled release technology for superior controlled therapeutics of insoluble drugs.

Conventional controlled release technologies have been designed primarily for water soluble drugs. These technologies can be inherently inefficient for delivery of water insoluble drugs due to inadequate or pH sensitive solubilization and release, and due to "absorption window"

limitations. Such limitations can result in inadequate absorption or often leading to reduced efficacy. Lip'ral Synchronized Solubilizer Release (SSR) is an extension of the Lip'ral technology platform superimposing controlled release aspects while preserving the solubilizing power and absorption improvement of Lip'ral technology. Lip'ral-SSR synchronizes the release of the insoluble drug and solubilizers and is ideally suited for drugs that require solubilization and controlled release.

Lip'ral-SSR offers

- Diverse Release Profiles: Can be modulated for extended release throughout the GI tract or for delayed, extended, pulsatile, or other forms of targeted release.
- PH-independent solubilization: Ideal for acidic and basic drugs requiring consistent absorption throughout the gastro-intestinal tract for safety or efficacy.
- Optimization: Utilizes a wide range of proprietary compositions with bioacceptable excipients specifically designed for the physicochemical properties and pharmacokinetic requirements of a particular drug.
- Dosage Form Flexibility: In combination with Lipocine's solid lipid dispersion technology, Nanosplode, supports a wide variety of form a thin dispersed system in gastro-intestinal fluids.

This system maintains the drug in a dissolved state in the physiological dosage form configurations including capsules, tablets, beads and multicomponent systems for a combination of different release profiles.

- Ease of Manufacturing: Uses conventional manufacturing processes that are easy to scale-up and commercialize, thus reducing time to market.

Lip'ral-SSR enables superior products with improved bioavailability/reduced dose.

- Reduced dosing frequency/improved patient compliance.
- Targeted absorption or chronotherapeutic release.

6. BIODIS TECHNOLOGY[9]

Physica Pharma has developed Biodis, a technology that enables to overcome solubilisation limitations to provide efficient drug absorption. Biodis technology is based on the application

of reactive lipid based carriers enabling to milieu and therefore facilitates its absorption through epitheliumcells.

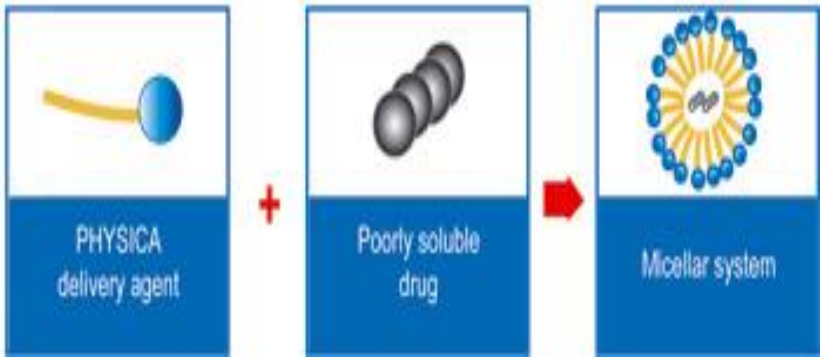


Figure 2: Biodis technology for enhancing solubilization.

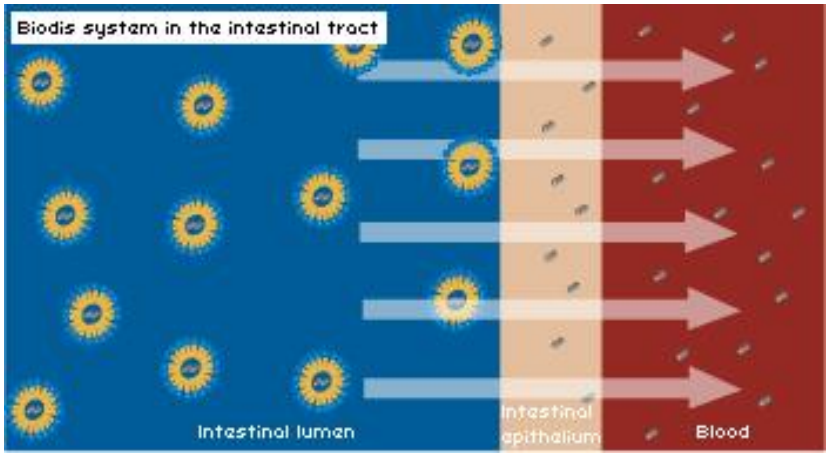


Figure 3: Biodis technology in the intestinal tract.

Physica Pharma currently works on various internal and partnered programs utilizing Biodis technology to enable the development of novel pharmaceutical products. Physica's Biodis technology was used to develop an oral formulation of, a compound with low water solubility. Physica's goal was to increase the bioavailability of the products.

7. HYDROTROPIC SOLUBILIZATION[10]

Ultraviolet absorption spectrophotometric method for the estimation of poorly water soluble drugs like nalidixic acid, norfloxacin, tinidazole, and metronidazole in pharmaceutical formulations, has been developed. Aqueous solubilities of these selected model drugs were enhanced to a great extent (5 to 98 fold) in 2.0 M sodium benzoate, and in 2.0 M niacinamide solutions. The primary objective of the present investigation was to employ these hydrotropic solutions to extract the drugs from their dosage forms, precluding the use of costlier organic solvents. The selected lmax for nalidixic acid, norfloxacin, tinidazole, and metronidazole,

were 330 nm, 324 nm, 318 nm and 320 nm, respectively. Sodium benzoate and niacinamide did not show any absorbance above 300 nm, and therefore, no interference in the estimation was seen. The results of analysis have been validated statistically, and by recovery studies. The proposed methods are new, simple, economic, accurate, safe, and precise.

Increasing the aqueous solubility of insoluble and slightly soluble drugs, is of major importance. Various techniques have been employed to enhance the aqueous solubility of poorly water-soluble drugs. Hydrotropic solubilization is one of them. The term hydrotropy has been used to designate the increase in solubility of various substances in water, due to the presence of large amounts of additives. sodium benzoate, niacinamide, sodium salicylate, sodium acetate, sodium citrate, and urea, have been employed to enhance the aqueous solubility of many poorly water soluble drugs. Various poorly water-soluble drugs were analyzed using hydrotropic solubilization phenomenon viz. cefixime, frusemide, salicylic acid, ketoprofen , tinidazole and aceclofenac.Various analytical techniques were developed employing hydrotropic solubilization phenomenon, to analyze poorly water-soluble drugs, hydrochlorothiazide, ofloxacin and aceclofenac.

Various organic solvents like methanol, chloroform, alcohol, dimethyl formamide, and benzene have been employed for the solubilization of poorly water soluble drugs for spectrophotometric estimations. Drawbacks of organic solvents include higher cost, toxicity, pollution, and error, in analysis due to volatility.

The primary objective of this study was to employ hydrotropic solubilizing agents, sodium benzoate and niacinamide for the selected model drugs to preclude the use of organic solvents. In the preliminary solubility studies, it was found that there was considerable enhancement in the aqueous solubilities of nalidixic acid, norfloxacin, tinidazole, and metronidazole, in 2.0 M sodium benzoate, and 2.0 M niacinamide solutions. Since sodium benzoate and niacinamide do not absorb above 300 nm, it was thought worthwhile to use these hydrotropic agents, to extract out the drugs having lmax above 300 nm, from their corresponding solid dosage forms.

The spectrophotometric estimations of drugs were not affected in the presence of solublizing agents, sodium benzoate and niacinamide. Recovery studies and statistical analysis were used to validate the methods.

8. Complexation[11, 12]

Complexation is the association between two or more molecules to form a nonbonded entity with a well defined stoichiometry. Complexation relies on relatively weak forces such as London forces, hydrogen bonding and hydrophobic interactions. There are many types of complexing agents and a partial list can be found in below table.

Table 3: List of Complexing Agents

Sr.No.	Types	Examples
1	Inorganic	I_B^-
2	Coordination	Hexamine cobalt(III) chloride
3	Chelates	EDTA,EGTA
4	Metal-Olefin	Ferrocene
5	Inclusion	Cyclodextrins, Choleic acid
6	Molecular Complexes	Polymers

8.1 Staching Complexation[13]

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. This causes some molecules to minimize the contact with water by aggregation of their hydrocarbon moieties. This aggregation is favored by large planar nonpolar regions in the molecule. Stached complexes can be homogeneous or mixed. The former is known as self association and latter as complexation. Some compounds that are known to form staching complexes are as follows:

Nicotinamide, Anthracene, Pyrene, Methyleneblue, Benzoic acid, Salicylic acid, Ferulic acid, Gentisic acid, Purine, Theobromine, Caffeine and Naphthalene etc.

8.2 Inclusion Complexation[13]

Inclusion complexes are formed by the insertion of the non- polar molecule or the nonpolar 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 snug fit of the guest into the cavity of host molecule. The cavity of host must be large enough to accommodate the guest and small enough to eliminate water, so that the total contact between the water and the nonpolar regions of the host and the guest is reduced.

The most commonly used host molecules are cyclodextrins. The enzymatic degradation of starch by cyclodextrin-glycosyltransferase (CGT) produces cyclic oligomers, Cyclodextrins. Cyclodextrins are non-reducing, crystalline, water soluble, cyclic, oligosaccharides.

Cyclodextrins consist of glucose monomers arranged in a donut shape ring. Three naturally occurring CDs are α Cyclodextrin, β-Cyclodextrin, and γ- Cyclodextrin. The complexation with cyclodextrins is used for enhancement of solubility. Cyclodextrin inclusion is a molecular phenomenon in which usually only one guest molecule interacts with the cavity of a cyclodextrin molecule to become entrapped and form a stable association. The internal surface of cavity is hydrophobic and external is hydrophilic, this is due to the arrangement of hydroxyl group within the molecule.

Molecules or functional groups of molecules those are less hydrophilic than water, can be included in the cyclodextrin cavity in the presence of water. In order to become complex, the "guest molecules" should fit into the cyclodextrin cavity. The cavity sizes as well as possible chemical modifications determine the affinity of cyclodextrins to the various molecules.

The kinetics of cyclodextrin inclusion complexation has been usually analyzed in terms of a one-step reaction or a consecutive two-step reaction involving intra-complex structural transformation as a second step. Cyclodextrins is to enhance aqueous solubility of drugs through inclusion complexation. It was found that cyclodextrins increased the paclitaxel solubility by 950 fold. Complex formation of rofecoxib, celecoxib, clofibrate, melarsoprol, taxol, cyclosporin A etc. with cyclodextrins improves the solubility of particular drugs.

Factors Affecting Complexation[14]

- Steric effects.
- Electronic effects.
- Effect of proximity of charge to CD cavity.
- Effect of charge density.
- Effect of charge state of CD and drug.
- Temperature, additives and cosolvent.

9. Solid Dispersion[15]

The solid dispersion approach to reduce particle size and therefore, increase the dissolution rate and absorption of drugs was first recognised 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. The most commonly used hydrophilic carriers for solid dispersions include polyvinylpyrrolidone, polyethylene glycols, 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.

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

The eutectic combination of chloramphenicol/urea and sulphathiazole/ urea served as examples for the preparation of a poorly soluble drug in a highly water soluble carrier.

9.1 Methods of Solid Dispersion.[16]

9.1.1 Hot Melt method

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

9.1.2 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 β-carotene in the highly water soluble carrier polyvinylpyrrolidone. An important prerequisite for the manufacture of a solid dispersion using the solvent method is that both the drug and the carrier are sufficiently soluble in the solvent. The solvent can be removed by various methods like by

spray-drying or by freeze-drying. Temperatures used for solvent evaporation generally lie in the range 23-65 ^{0}C.

9.1.3 Hot-melt Extrusion

Melt extrusion was used as a manufacturing tool in the pharmaceutical industry as early as 1971. It has been reported that melt extrusion of miscible components results in amorphous solid solution formation, whereas extrusion of an immiscible component leads to amorphous drug dispersed in crystalline excipient. The process has been useful in the preparation of solid dispersions in a single step.

9.1.4 Melting –solvent method

A drug is first dissolved in a suitable liquid solvent and then this solution is incorporated into the melt of polyethylene glycol, obtainable below 70^{0}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.

Table 4: Carriers for Solid Dispersions[17]

Sr. No.	Chemical Class	Examples
1	Acids	Citric acid, Tartaric acid, Succinic acid
2	Sugars	Dextrose, Sorbitol, Sucrose, Maltose, Galactose, Xylitol
3	Polymeric Materials	Polyvinylpyrrolidone PEG-4000, PEG -6000,Carboxymethylcellulose, Hydroxypropyl cellulose, Guar gum, Xanthan gum, Sodium alginate, Methyl cellulose, HPMC, Dextrin, Cyclodextrins, Galactomannan
4	Surfactants	Polyoxyethylene stearate, Tweens and Spans, Poloxamer,Deoxycholic acid, Gelucire 44/14, Vitamine E TPGS NF
5	Miscellaneous	Pentaerythritol, Urea, Urethane.

10. Salt formation[18]

For organic solutes that are ionizable, changing the pH of the system may be simplest and most effective means of increasing aqueous solubility. Under the proper conditions, the solubility of an ionizable drug can increase exponentially by adjusting the pH of the solution. A drug that can be efficiently solubilized by pH control should be either weak acid with a low pKa or a weak base with a high pKa. Similar to the lack of effect of heat on the solubility of non-polar substances, there is little effect of pH on nonionizable substances.

Nonionizable, hydrophobic substances can have improved solubility by changing the dielectric constant (a ratio of the capacitance of one material to a reference standard) of the solvent by the use of co-solvents rather than the pH of the solvent.

The use of salt forms is a well known technique to enhanced dissolution profiles. Salt formation is the most common and effective method of increasing solubility and dissolution rates of acidic and basic drugs.An alkaloid base is, generally,slightly soluble in water, but if the pH of medium is reduced by addition ofacid, and the solubility of the base is increased as the pH continues to bereduced. The reason for this increase in solubility is that the base is converted to a salt, which is relatively soluble in water (e.g. Tribasic calcium phosphate).The solubility of slightly soluble acid increased as the pH is increased by addition of alkali, the reason being that a salt is formed (e.g. Aspirin, Theophylline, Barbiturates).

11. Co-crystallization[19]

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 crystal, 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. Only three of the co-crystallizing agents are classified as generally recognised as safe (GRAS) it includes saccharin, nicotinamide and acetic acid limiting the pharmaceutical applications. Co-crystallisation between two active pharmaceutical ingredients has also been reported. This may require the use of subtherapeutic amounts of drug substances such as aspirin or acetaminophen. At least 20 have been reported to date, including caffeine and glutaric acid polymorphic co-crystals. Co-crystals can be prepared by evaporation of a heteromeric solution or by grinding the components together. Another technique for the preparation of co-crystals includes sublimation, growth from the melt, and slurry preparation. The formation of molecular complexes and co-crystals is becoming increasingly important as an alternative to salt formation, particularly for neutral compounds or those having weakly ionizable groups.

12. Cosolvency[18]

The solubilisation of drugs in co-solvents is an another technique for improving the solubility of poorly soluble drug. It is well-known that the addition of an organic co-solvent to water can dramatically change the solubility of drugs.

Weak electrolytes and non-polar molecules have poor water solubility and it can be improved by altering polarity of the solvent. This can be achieved by addition of another solvent. This process is known as co-solvency. Solvent used to increase solubility known as cosolvent. Co-solvent system works by reducing the interfacial tension between the aqueous solution and hydrophobic solute. It is also commonly referred to as solvent blending.

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, thus increasing solubility. A different perspective is that by simply making the polar water environment more non-polar like the solute, co-solvents facilitate solubilization. Solubility enhancement as high as 500-fold is achieved using 20% of 2-pyrrolidone.

13.. Hydrotrophy[18]

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 (sodium benzoate, sodium acetate, sodium alginate, and urea) and the solute.

Example: Solubilisation of Theophylline with sodium acetate and sodium alginate.

14. Solubilizing agents[18]

The solubility of poorly soluble drug can also be improved by various solubilizing materials. PEG 400 is improving the solubility of hydrochlorthiazide. Modified gum karaya (MGK), a recently developed excipient was evaluated as carrier for dissolution enhancement of poorly soluble drug, nimodipine. The aqueous solubility of the antimalarial agent halofantrine is increased by the addition of caffeine and nicotinamide.

15. Particle size reduction

Particle size reduction can be achieved by micronization and nanosuspension. Each technique utilizes different equipments for reduction of the particle size.

15.1 Micronization[20]

The solubility of drug is often intrinsically related to drug particle size. By reducing the particle size, the increased surface area improves the dissolution properties of the drug. Conventional methods of particle size reduction, such as comminution and spray drying, rely upon mechanical stress to disaggregate the active compound. The micronization is used to increased surface area for dissolution.

Micronization increases the dissolution rate of drugs through increased surface area, it does not increase equilibrium solubility. Micronization of drugs is done by milling techniques using jet mill, rotor stator colloid mills etc. Micronization is not suitable for drugs having a high dose number because it does not change the saturation solubility of the drug.

15.2 Nanosuspension[21]

Nanosuspensions are sub-micron colloidal dispersion of pure particles of drug, which are stabilized by surfactants. The advantages offered by nanosuspension is increased dissolution rate is due to larger surface area exposed, while absence which eliminates the concentration gradient fact.

CONCLUSION

A drug administered in solution form is immediately available for absorption and efficiently absorbed than the same amount of drug administered in a tablet or capsule form. Solubility is a most important parameter for the oral bioavailability of poorly soluble drugs. Dissolution of drug is the rate determining step for oral absorption of the poorly water soluble drugs, which can subsequently affect the in vivo absorption of drug. Currently only 8% of new drug candidates have both high solubility and permeability.

Because of solubility problem of many drugs the bioavailability of them gets affected and hence solubility enhancement becomes necessary. It is now possible that to increase the solubility of poorly soluble drugs with the help of various techniques as mentioned in this article.

Significant advances have been made in drug delivery technologies throughout the past 3 decades, and drug delivery at a desired release rate is now possible. Even highly sophisticated drug delivery technologies, however, often fail to produce marketable oral controlled-release dosage forms, as a result of the physiological limitations of the gastrointestinal (GI) tract and/or the utilization of non-feasible pharmaceutical components. In oral drug delivery, there are many scientific challenges that could be studied for years to come, and breakthrough technologies are required to generate novel dosage forms raising drug delivery to higher level. This article examines several aspects in oral drug delivery requiring implementation of novel ideas to improve oral drug delivery systems.

Further advances in oral controlled-release dosage forms depend on uses of novel polymers, and it would be highly desirable if the pharmaceutical industry in general finds a mechanism to support such activity as testing new polymers and classifying them with GRAS status. Companies that focus on drug delivery technologies are usually small and may not be able to afford the high cost of toxicity testing of novel polymers. Support from larger companies is required more than ever. Developing oral drug delivery systems based on novel polymers will eventually help everyone involved in the pharmaceutical industry.

The area of controlled drug delivery is an exciting and challenging area, and thanks to the many researchers involved and their collective concerted efforts, there is great promise and bright prospects for the future of healthcare.

Overall, discoveries of new techniques will be useful for drugs with problems of poor solubility and bioavailability which would allow future drugs and new entities to reach market successfully and thereby, serve mankind in a better way.

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