REVIEW ARTICLE

Different approaches toward the enhancement of Drug Solubility: A Review

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ABSTRACT

As we know that for achieving therapeutic effect in human body, drug should be bioavailable and hence it depends on solubility of drug. Recently 40% of the drugs are poorly water soluble which produce side effects such as gastric irritation, peptic ulceration etc. whereas only 8% of new drug candidates have both high solubility and permeability. For BCS class II drugs, enhancement of solubility is important parameter before formulation of dosage form. The aim of this review is to improve the solubilization and bioaviailability of poorly soluble drugs by using various approaches like physical, chemical and others modifications or techniques and included BCS classification, carriers for solubility enhancement and different techniques for solubility enhancement.

Keywords Solubility, Bioavailability, Solubility enhancement techniques, Poorly water soluble drugs.

INTRODUCTION [1, 4, 8, 9]

IUPAC defines solubility as the analytical composition of a saturated solution expressed as a proportion of a designated solute in a designated solvent.

Solubility defines as the phenomenon of dissolution of solute in solvent to give a homogenous system. Solubility is the phenomenon of dissolution of solid in liquid phase to give a homogenous system. Dissolution is defined as the transfer of molecules or ions from a solid state into solution. Solubility is defined as the analytical composition of a saturated solution expressed as a proportion of a designated solute in a designated solvent. Solubility may be stated in units of concentration, molality, mole fraction, mole ratio, and other units. Solubility is one of the important parameter to achieve desired concentration of drug in systemic circulation for showing pharmacological response. Any drug to be absorbed must be present in the form of an aqueous solution at the site of absorption. Low aqueous solubility is the major problem with formulation development of new chemical entities. Poorly waters soluble drugs often require high doses in order to reach therapeutic plasma concentrations after oral administration. Most of drugs are weakly acidic and weakly basic with poor aqueous solubility.

Table 1: Expression of Solubility [1,2,3]

Descriptive term	Part of solvent required per part of solute
Very soluble	Less than 1
Freely soluble	From 1 to 10
Soluble From	10 to 30
Sparingly soluble	From 30 to 100
Slightly soluble	From 100 to 1000
Very slightly soluble	From 1000 to 10,000
Practically insoluble	10,000 and over

The dissolution rate of a solid in a liquid may be described quantitatively by the Noyes-Whitney equation:

$$dm/dt = ka (Cs - C)$$

where,

m = mass of solute that has passed into solution in time t, dm/dt = rate of dissolution,

A =surface area of undissolved solid in contact with the solvent,

Cs =concentration of solute required to saturate the solvent at the experimental temperature,

C = solute concentration at time t and

ka = intrinsic dissolution rate or simply the dissolution rate constant.

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Biopharmaceutical Classification System

Table 2: Biopharmaceutical Classification System [3,4,5,21]

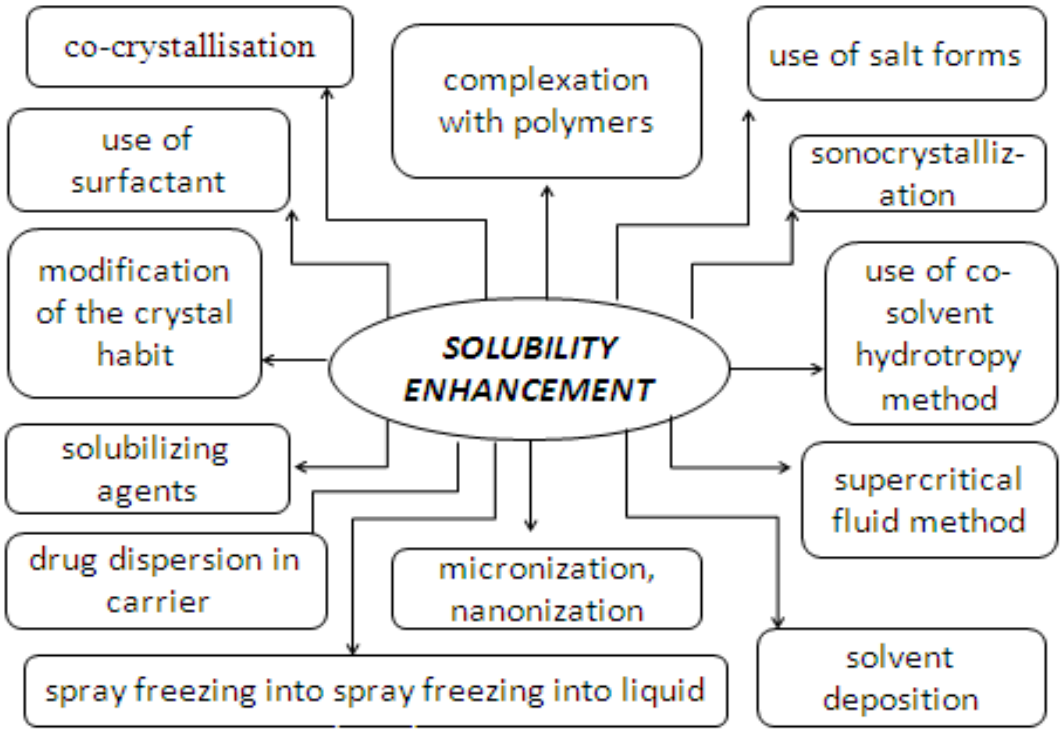
BCS CLASS	SOLUBILITY	PERMEABILITY
I	HIGH	HIGH
II	LOW	HIGH
III	HIGH	LOW
IV	LOW	LOW

Orally administered drugs on the Model list of Essential Medicines of the World Health Organization (WHO) are assigned BCS classifications on the basis of data available in the public domain. The 130 orally administered drugs on the WHO list, 61 could be classified with certainty.84% of these belong to class I (highly soluble, highly permeable), 17% to class II (poorly soluble, highly permeable), 24 (39%) to class III (highly soluble, poorly permeable) and 6 (10%) to class IV (poorly soluble, poorly permeable).

METHODS FOR SOLUBILITY ENHANCEMENT [6, 10]

- Physical Modifications: Particle size reduction, modification of the crystal habit like polymorphs, amorphous form and cocrystallization, drug dispersion in carriers like eutectic mixtures, solid dispersions, solid solutions and cryogenic techniques
- Chemical Modifications: Change of pH, use of buffer, derivatization, complexation, and salt formation.
- Miscellaneous Methods: Supercritical fluid process, use of adjuvant like surfactant, solubilizers, cosolvency, hydrotrophy, and novel excipients.

Figure.1 Techniques of Solubility Enhancement:[7, 11,12]



Micronization[12,13]

By micronization we get uniform and narrow particle size distribution. As micronization occurs, surface area increases with decreasing particle size and solubility increases and observed solubility increased with decreasing particle size in accordance with this equation.

$$\text{Log } S/S_0 = 2(€/2.303RTr)$$

Where,

S = the observed solubility,

S_0=Inherent equilibrium solubility,

€= surface Energy of particle,

R = Gas constant,

T =Absolute Temperature,

r = Radius of the particles.

Following methods can be used for achieving Micronization

1. Jet milling
2. Solid solution and eutectic mixtures
3. Micro precipitation & microcrystalization
4. Controlled crystallization
5. Supercritical fluid technology
6. Spray freezing into liquid
7. Spray freeze dry (SFD)

Micronized fenofibrate exhibited more than 10-fold (1.3% to 20%) increase in dissolution in at 30 minutes biorelevant media.[08]

Nanonization[10,27]

Drug powder is converted to nanocrystals of size 200-600nm.

Three basic technologies in use to prepare nanoparticles

a. Pearl milling

b. Homogenization in water (wet milling asin a colloid mill)

c. Homogenization in non-aqueous media or in water with water-miscible liquids.

This technology is applied to poorly soluble drugs that are insoluble in both water and oils.

Nanotechnology approaches to improve the solubility of hydrophobicDrugs

Precipitation Technique

In precipitation technique the drug is dissolved in a solvent, which is then added to non-solvent to precipitate the crystals. Nano-suspension of Danazol, Naproxen, prepared by precipitation technique to improve their dissolution rate and oral bioavailability

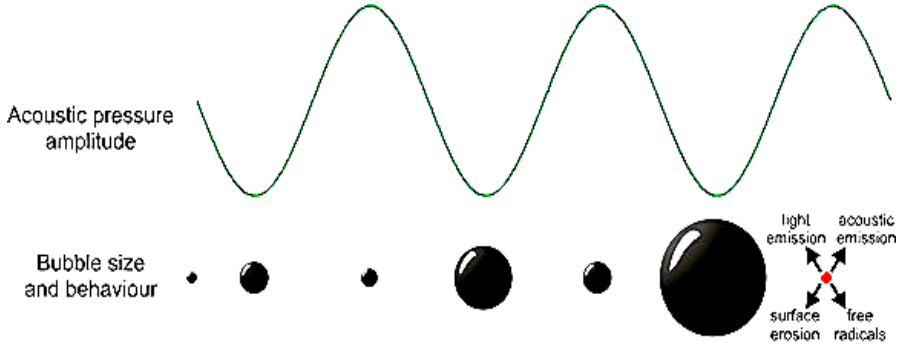
Media milling (Nanocrystals or Nanosystems)

The nanosuspensions are prepared by using high-shear media mills. The milling chamber 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. The high energy shear forces are generated as a result of the impaction of the milling media.

Sonocrystallization[14]

Application of ultrasound energy to modify the nucleation of a crystallization process is known as sonocrystallization. The energy of ultrasound fashions consecutive compression and expansion. After several cycles a bubble forms and grows then collapses. The collapse of the bubble provides energy to promote the nucleation process.

Figure 2: Sonocrystallisation



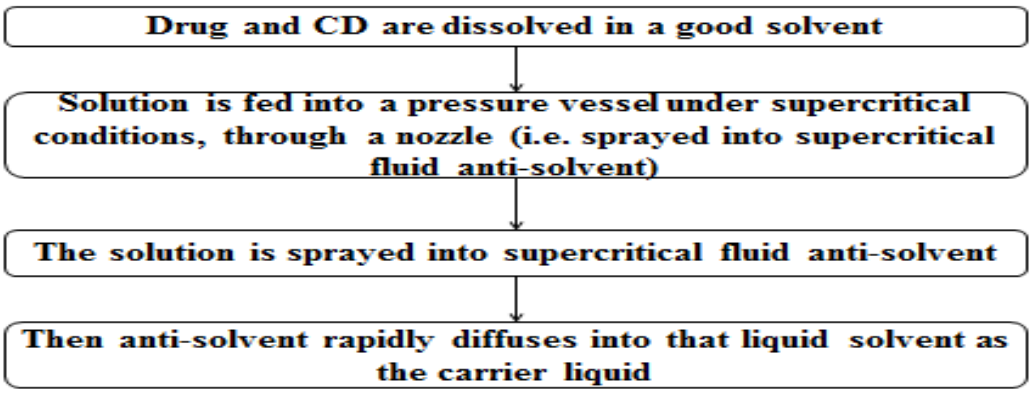
A bubble initially at rest can grow during the rarefactional half-cycles of an applied acoustic field. Through rectified diffusion, gas and vapour are transported into the bubble, until it reaches a critical size and collapses. The bubble contents are compressed rapidly, resulting in extreme local conditions and a range of secondary effects that drive processes, and may also be measured.

Supercritical Fluid Method [23-25]

Various supercritical fluid technologies used in pharmaceutical processing include:

- Supercritical antisolvent system with enhanced mass transfer (SAS-EM).
- Rapid expansion of supercritical solutions (RESS),
- Supercritical antisolvent (SAS) precipitation technique
- Particles from Gas Saturated Solutions (PGSS),
- Gas antisolvent system (SAS),
- Precipitation using compressed antisolvent (PCA) ,
- Aerosol solvent extraction system (ASES),
- Solution enhanced dispersion by supercritical fluids (SEDS),

In this technique, carbon dioxide is used as anti-solvent for the solute but as a solvent with respect to the organic solvent. The use of supercritical carbon dioxide is advantageous due to its low critical temperature and pressure .It is also non-toxic, nonflammable, in expensive and is much easier to remove from the polymeric materials when the process is complete, Supercritical particle generation processes are new and efficient route for improving bioavailability of pharmaceutically active compounds.



In addition, supercritical fluid processes were recently proposed as a new alternative method for the preparation of drug cyclodextrin complexes. Supercritical carbon dioxide is suggested as a new complexation medium due to its properties of improved mass transfer and increased solvating power. This method constitutes one of the most innovators methods to prepare the inclusion complex of drug with CD in solid state. This is a non-toxic method as it is not utilizing any organic solvent, fast process, maintenance cost is low with promising results, but it requires a quite high initial cost.

Spray freezing into liquid and Lyophilization

In the spray freezing into liquid (SFL) process, the drug and its excipients are dissolved into a solvent and injected into a cryogenic liquid such as liquid nitrogen. The droplets of the drug solution freeze at a rate sufficient to minimize crystallization and particle growth, thus forming highly porous, nanostructured particles.

Evaporative precipitation into aqueous solution (EPAS)

The EPAS process utilizes rapid phase separation to nucleate and grow nanoparticles and microparticles of lipophilic drugs. The drug is first dissolved in a low boiling point organic solvent. This solution is pumped through a tube where it is heated under pressure to a temperature above the solvent's boiling point and then sprayed through a fine atomizing nozzle into a heated aqueous solution. Surfactants are added to the organic solution and the aqueous solution to optimize particle formation and stabilization. In EPAS, the surfactant migrates to the drug-water interface during particle formation, and the hydrophilic segment is oriented towards the aqueous continuous phase. The hydrophilic stabilizer on the surface inhibits

crystallization of the growing particles and therefore facilitates dissolution rates

Co-Solvency

Cosolvent system is a mixture of miscible solvents often used to solubilize lipophilic drugs. Currently, the water-soluble organic solvents are polyethylene glycol 400 (PEG 400), ethanol, propylene glycol, and glycerin.. The water insoluble solvents include long-chain triglycerides (i.e. peanut oil, corn oil, soybean oil, sesame oil, olive oil, peppermint oil. The co-solvents are having hydrogen acceptor or donor groups with a small hydrocarbon region. The hydrophobic hydrocarbon region usually interferes with the hydrogen bonding network of water which consequently reduces the intermolecular attraction of water while the hydrophilic hydrogen bonds ensures water solubility.

Use of Surfactants

Conventionally, for solubilizing a poorly soluble substance is to reduce the interfacial tension between the surface of solute and solvent for better wetting and salvation interaction. Improvement of drug solubility by using the amphiphilic surfactants is due to lowering surface tension between drug and solvent, improvement of wetting characteristics and micellar solubilization .Surfactants like Spans, Polyglycolized glyceride, Tweens, Polyoxyethylene stearates and synthetic block copolymers like Poly (propylene oxide)-poly (ethylene oxide)- poly (propylene oxide) like Poloxamers based micelles, Poly (beta-benzyl-L-aspartate)-b-poly (ethylene oxide), Poly (caprolactone)-b-poly (ethylene oxide) etc are very successful as excipient and carrier for dissolution enhancement.

Co-grinding/ Co-micronization

Cogrinding of a poorly water-soluble drug with water-soluble polymers like hydroxyl propyl methyl cellulose (HPMC), poly vinyl alcohol (PVA) etc in the presence of small amount of water is extremely effective to improve its apparent solubility with maintenance of drug crystallinity to some extent 20. Small particles produced by milling or micronization have increased surface area and expected to have enhanced dissolution rate. However, energy added to reduce particle size results in increased Van der Waal's interactions and electrostatic attraction between particles leading to reduce effective surface area due to agglomeration thus decreasing dissolution rate.

Co-micronization of drugs by using excipients like microcrystalline cellulose can be used as an alternative to reduce or eliminate cohesive and electrostatic forces. This approach increases apparent surface area available for drug dissolution by creating an ordered mixture, thereby causing a reduction in particle-particle agglomeration or by reducing Van der Waal's interactions. Increase in true surface area of the ordered powdered mixture is expected due to the inherent surface roughness and porosity of microcrystalline cellulose-Drug mixture 21.

b. Pearl Milling: Based on pearl milling the drug microparticles are ground to nanoparticles (< 400 nm) in between the moving milling pearls. The milling efficiency is dependent on the properties of the drug, the medium and the stabilizer. Rapamune, an immune suppressant agent, is the first FDA approved nanoparticle drug using Nano-Crystals technology developed by Elan Drug Delivery. Emend is another product containing 80 or 125 mg. A prepitant formulated by this technique. In general the limitation of the pearl milling process is the introduction of contamination to the product from the grinding material, batch-to-batch variations and the risk of microbiological problems after milling in an aqueous environment.

Solid Dispersions/ Solid Solution [15-18]

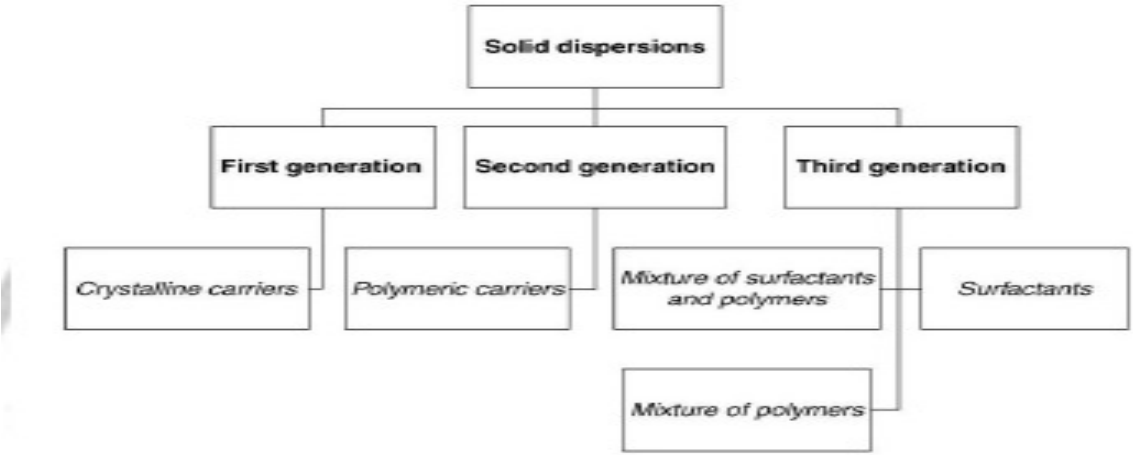
In 1971 Chiou and Riegelman defined solid dispersion as "the dispersion of one or more active ingredients in an inert carrier matrix at solid-state prepared by the melting (fusion), solvent or

melting-solvent method"). The solid dispersions may also be called solid-state dispersions, as first used by Mayersohn and Gibaldi (1966).[15] Corrigan defined the term as "product formed by converting a fluid drug-

carrier combination to the solid state".[16]In a recent review work by Dhirendra et al. adopted the definition given by Chiou and Riegelman "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" [17].The most commonly used solvents for solid dispersions includes water, methanol, ethanol, chloroform, DMSO, acetic acid.

Classification of Solid Dispersions

Figure 3: Classification of Solid Dispersions



Factors Responsible For Higher Dissolution Rates Of Solid Dispersions

(i) The formation of higher energy metastable states of the components as a function of the carrier system being used and the proportion of carriers present.

(ii) The reduction of particle size to nearly a molecular level.

(iii) Formation of amorphous forms of drug and carriers.

(iv) As the soluble carrier dissolves, the insoluble drug is exposed to dissolution medium as very fine particles leading to an increase in both surface area and solubilization for fast dissolution and absorption.

(v) The presence of carrier may also prevent aggregation of fine drug particles, thereby providing a larger surface area for dissolution. The wetting properties are also greatly increased due to the surfactant property of the polymer, resulting in decreased interfacial tension between the medium and the drug, hence higher dissolution rates. The presence ofcarrier polymers also inhibits crystal growth of the drug which facilitates faster dissolution.

(vi) Cosolvent effect on the drug by the water soluble carriers

(vii) Intermolecular hydrogen bonds between drug and carrier

Various factors affecting dissolution of drug from solid dispersion includes the method of preparation of the solid dispersion, amount and properties of the polymer carriers, drug polymer contact and drug-polymer interactions 55. Many water-soluble excipients were employed as carriers of solid solutions/dispersions. Among them, polyethylene glycols (PEG, Mw 1500-20000) were the most commonly used due to their good solubility in water and in many organic solvents, low melting points (under 65°C), ability to solubilize some compounds and improvement of compound wettability. The marketed Gris-PEG is the solid dispersion of griseofulvin in PEG 8000. The others carriers include polyvinyl pyrrolidone (PVP), polyvinyl alcohol (PVA), polyvinyl pyrrolidonepolyvinylacetate copolymer

(PVP-PVA), hydroxyl propyl methylcellulose (HPMC), hydroxyl propyl cellulose (HPC), urea, Poloxamer 407, sugars, emulsifiers (SDS, Tween 80) and organic acids (succinic acid and citric acid).

Methods of Preparation of Solid Dispersions

1. Melting Method (Fusion Method)

The melting or fusion method involves the preparation of physical mixture of a drug and a water-soluble carrier and heating it directly until it melted. The melted mixture is then solidified rapidly in an ice-bath under vigorous stirring. The final solid mass is crushed, pulverized and sieved. However many substances, either drugs or carriers, may decompose or evaporates during the fusion process which employs high temperature.

2. Melt Extrusion Method

This method is same as the melt method where polymer processing technology applied and intense mixing of drug/carrier mix is typically processed with a twin-screw extruder.The process involves embedding a drug in a polymer while shaping the composite material to form a pharmaceutical product. The drug/carrier mix is simultaneously melted, homogenized and then extruded and shaped as tablets, granules, pellets, sheets, sticks or powder. The intermediates can then be further processed into conventional tablets.

3. Solvent Evaporation Method

Another most useful method is solvent evaporation method where the first step is formation of solution containing physical mixture of the drug and carrier dissolved in a common solvent and second step involve the removal of solvent resulting the formation of solid dispersion. The product is crushed, pulverized & sieved through a suitable mesh number sieve. This enabled them to produce a solid solution of the highly lipophilic drug in the highly water soluble carrier like 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.

4. Melting Solvent Method (Melt Evaporation)

Here the solid dispersions are prepared by dissolving the drug in a suitable liquid solvent and then incorporating the solution directly into the melt of polyethylene glycol, which is then evaporated until a clear, solvent free film is left. The film is further dried to constant weight. The 5 –10% (w/w) of liquid compounds can be incorporated into polymer without significant loss of its solid property. It is possible that the selected solvent or dissolved drug may not be miscible with the melt of the polymer. Also the liquid solvent used may affect the polymorphic form of the drug, which precipitates as the solid dispersion. This technique possesses unique advantages of both the fusion and solvent evaporation methods. From a practical standpoint, it is only limited to drugs with a low therapeutic dose e.g. below 50 mg.

5. Alternative Methods:

- Physical Mixture Method: The physical mixtures were prepared by weighing the calculated amount of drug and carriers and then mixing them in a glass mortar by triturating. The resultant physical mixtures were passed through 44-mesh sieve and stored in desiccators until used for further studies.
- Co-Grinding Method: The calculated amounts of drug and carriers where weighed and mixed together with one ml of water. The damp mass obtained was passed through a 44- mesh sieve; the resultant granules were dispersed in Petri dishes and dried at 60°C under vacuum, until a constant weight was obtained. The granules obtained were stored in desiccators until used for further studies.
- Kneading method: A mixture of accurately weighed drug and carrier is wetted with solvent and kneaded thoroughly for some time in a glass mortar. The paste formed is dried and sieved.
- Advantages of Solid Dispersions
- Particles with reduced particle

- Particles with improved wettability
- Particles with higher porosity

Hot melt extrusion: (HME) [19, 22]

HME can be simply defined as the process of forming a new material (the extrudate) by forcing it through an orifice or die under controlled conditions, such as temperature, mixing, feed-rate and pressure. HME differs from simple extrusion in that, polymer, drug and excipients blends are mixed thoroughly in the molten state in this process, needing no solvents for granulation. The molten polymer serves as the thermal binder.

Hydrotrophy [19, 20]

The term hydrotropy refers to the increase in solubility insoluble or slightly soluble drugs in water by the addition 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.

Hydrotropic agents are ionic organic salts. Additives or salts that increase solubility in given solvent are said to "salt in" the solute and those salts that decrease solubility "salt out" the solute. Several salts with large anions or cations that are themselves very soluble in water result in "salting in" of non-electrolytes called "hydrotropic salts" a phenomenon known as "hydrotropism". Hydrotropic solutions do not show colloidal properties and involve a weak interaction between the hydrotropic agent and solute.

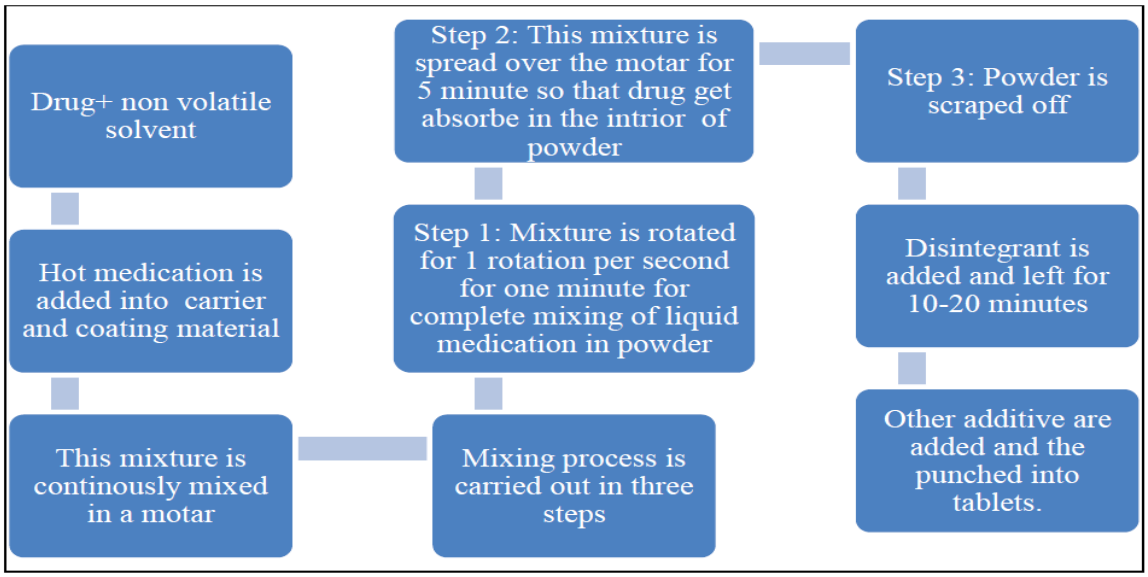
Example: Solubilisation of Theophylline with sodium acetate and sodium alginate.

Liquisolid systems [5,28,29]

Liquisolid system refers to powdered forms of liquid medications formulated by converting liquid lipophilic drugs, or drug suspensions or solutions of water insoluble solid drugs in suitable non-volatile solvent systems, into dry, non-adherent, free-flowing and readily compressible powder admixtures by blending with selected carrier and coating materials

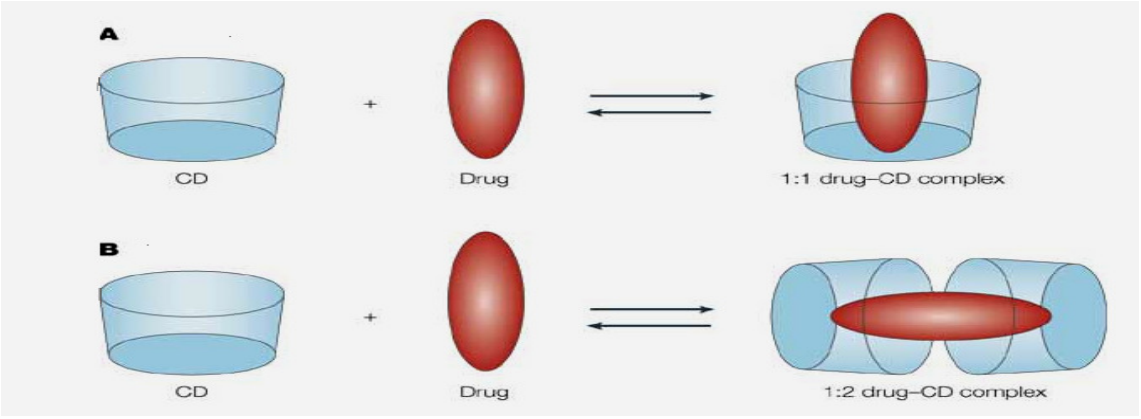
Steps involved in processing of Liquisolid system.

Figure 4: Steps in processing of Liquisolid system



Complexation

In complexation technique,the insertion of the nonpolar molecule or the nonpolar region of one molecule (known as guest) into the cavity of another molecule or group of molecules (known as host).

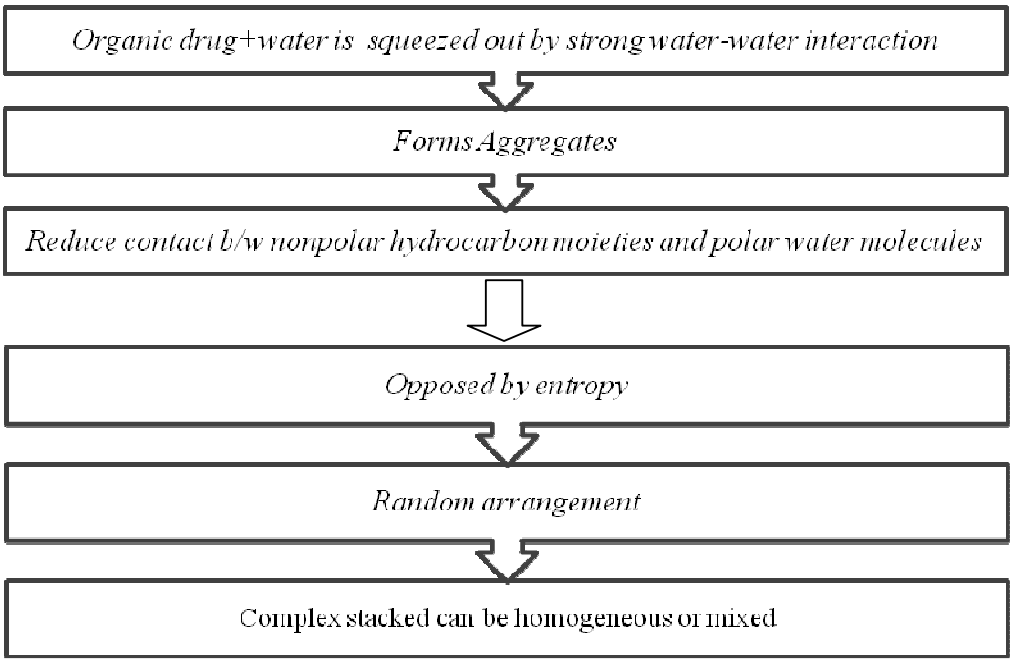


Advantages

- ❖ Good enhancement in solubility
- ❖ Use of conventional equipment.

Inclusion complexes include the use of hydrophilic polymers which on contact with the medium dissolve rapidly, resulting in the fine precipitation of the drug.

1) Self association and stacking complexation



2) Solid inclusion complexes

1. Kneading Technique: In this technique, cyclodextrin (CD) is impregnated with water and converted to paste. Drug is then added and kneaded for specified time. The kneaded mixture is then dried and passed through sieve if required.
2. Co-precipitation: Required amount of drug is added to the solution of β-CD. The system is kept under magnetic agitation with controlled process parameters and protected from the light. The formed precipitate is separated by vacuum filtration and dried at room temperature in order to avoid the loss of the structure water from the inclusion complex.
3. Neutralization:Drug is added in alkaline solution like sodium hydroxide, ammonium hydroxide. A solution of β- Cyclodextrin is then added to dissolve the joined drug. The clear solution obtained after few seconds under agitation is neutralized using HCl solution until reaching the equivalence point. At this moment, the appearance of a white precipitate could be appreciated,

corresponding to the formation of the inclusion compound. The precipitate is then filtered and dried.

4. Co-grinding:Drug and cyclodextrin are mixed and the physical mixture is introduced in a suitable mill like oscillatory mill and grinded for suitable time.
5. Spray-Drying Method:Drug is dissolved in suitable solvent and the required stoichiometric amount of carrier material like β-cyclodextrin is dissolved in water. Solutions are then mixed by sonication or other suitable method to produce a clear solution, which is then spray dried.
6. Microwave Irradiation Method
7. 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 b 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, adequate amount of solvent mixture is added to the above reaction mixture to remove the residual, uncomplexed free drug and CD. The precipitate so obtained is separated using whatman filter paper, and dried in vacuum oven at 40 °C for 48 hrs.

The forces driving complexation were attributed to

1. the exclusion of high energy water from the cavity
2. the release of ring strain particularly in the case of -CD
3. Van der Wal's interactions
4. Hydrogen and hydrophobic bindings

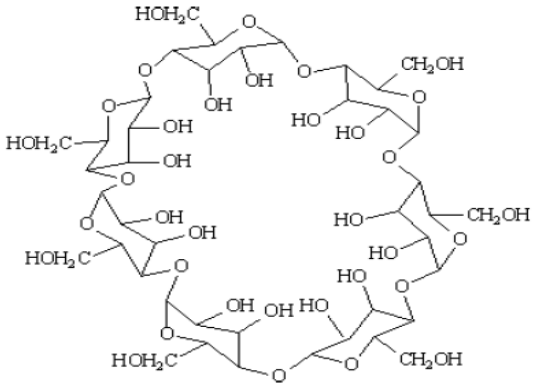
The most common complexing ligands arecyclodextrins,urea, caffeinepolyethylene glycol, N methylglucamide. Considerable increase in solubility and dissolution of the drug has been achieved by the use of cyclodextrins

Cyclodextrins

Cyclodextrins are macrocyclic torus shaped molecules formed by D-(+)-glucopyranose units. Size and shape of cyclodextrin is correlated to the type and number of (1,4) linkages between those units.,Three naturally occurring cyclodextrins are α-Cyclodextrin, β Cyclodextrin, and γ- Cyclodextrinare those with 6,7and 8of these units respectively.Cyclodextrins consist of glucose monomers arranged in a donut shape ring.

Molecular formula $(C_6H_{10}O_5)_7$

Structural formula



Cyclodextrins are sparingly soluble in water; freely soluble in hot water; slightly soluble in ethanol. The complexation with cyclodextrins is used for enhancement of solubility. The enzymatic degradation of starch by cyclodextrin-glycosyltransferase (CGT) produces cyclic oligomers, Cyclodextrins.

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.. CDs are capable of forming inclusion complexes with many drugs by taking up a whole drug molecule or some part of it into the cavity. Such molecular encapsulation will affect many of the

physicochemical properties of drugs, such as their aqueous solubility and rate of dissolution

The rate and extent of absorption of class IIand class IV compounds is highly dependent on thebioavailability which ultimately depends on solubility. . This is most widely used method to enhance water solubility and increase stability of hydrophobic drugs by using cyclodextrins.

Derivatives of cyclodextrin

RMβCD	Randomly methylated β–CD
HPβCD	Hydroxy propyl β –CD
HP γ-CD	hydroxyl propyl γ-CD
DM β-CD	2,4-dimethyl β –CD
SBE βCD	Sulfobutylether β- CD

CONCLUSION

Solubility is a challenging task for researchers and pharmaceutical scientists for the formulation and development of various dosage forms.different approaches discussed above either used in combination or individually will have A potential for the dissolution enhancement of poorly soluble drugs .Proper selection of suitable method is the key for improvement of solubility,dissolution, bioavaibility and it helps to avoid the rejection of new chemical entities due to low solubility.

REFERENCES

1. Sajid A, Chaudhary V. Solubility Enhancement Methods with Importance Of Hydrotropy. J Drug Discovery and Therapeutics. 2012; 2(6):96-101
2. Tyagi S, Patel C, Dadrwal P, MangukiaD,Sojitra I, NimbiwalBk, Sigh V, Subrahmanyamkv.Anovel Concept For Solublization And Bioavailibility Of Poorly Soluble Drugs: Hydrotropy. Int. J Pharmres. And Bio Sci.2013;2(1):372-381.
3. Alton's Pharmaceutics: The Design And Manufacturing Of Medicines, Churchill Livingstone Elsvier.3rd Edition.2007:322-538
4. Reddy B K,Karunakar A ,Biopharmaceutics Classification System:A Regulatory Approach Dissolution Technologies | February 2011.Journal Of Applied Pharmaceutical Science 01 (07); 2011: 13-203
5. Gavali S M, Pacharane S S, Sankpal S V, Jadhav K R, Kadam V J. Liquisolid Compact: a new technique for enhancement of drug dissolution. International Journal of Research In Pharmacy And Chemistry, 1(3):705-713, 2011.
6. Kapadiya N, Indrjeet S, Mehta K, Karwani G, ShruboJs. Hydrotropy: A Promising Tool For Solubility Enhancement.Int. J Drug Discovery And Resarch.2011; 3(2):26-33
7. Yogesh S. Thorat, Indrajeet D. Gonjari AndAvinash H. Hosmani.Solubility Enhancement Techniques: A Review On Conventional And Novel Approaches International Journal Of Pharmaceutical Sciences And Research.Ijpsr (2011), 2(10)
8. Chen, X, Young, T, Sarkari, M, Williams, Ro, Johnston, Kp. Preparation Of Cyclosporine A Nanoparticles By Evaporative Precipitation Into Aqueous Solution, International Journal Of Pharmaceutics. 2002; 242: 3- 14.
9. Michael, H, Stephen, T, Cathy, F. Part 1: "Oral Delivery Of Poorly Soluble Drugs Pharmaceutical Manufacturing And Packing Sourcer. Summer Samedan Ltd, 2003; 03.
10. AmitChaudhary, UpendraNagaich, NehaGulati, V. K. Sharma, R. L. Khosa. Enhancement Of Solubilization And Bioavailability Of Poorly Soluble Drugs By Physical And Chemical Modifications: Journal Of Advanced Pharmacy Education & Research.2012; 2 (1) 32-67.
11. Lachman L, Lieberman H, The Theory And Practice Of Industrial Pharmacy, Cbs Publication & Distributors Pvt. Ltd. Special Indian Edition 2009: 221.
12. Varshney, H. M., Chatterjee, A. Solubility Enhancement Of Poorly Hydrophilic Drugs By Using Different Newer Techniques: A ReviewInternational Journal Of Therapeutic Applications, Volume 6, 2012, 8 – 13
13. Patel Jn, RathodDm, Patel Na, Modasiya Mk, Techniques To Improve The Solubility Of Poorly Soluble Drugs, Int J Pharm Life Sci, 2012, 3, 2, 1459-1469.
14. Satish K. Patil, Kalpesh S. Wagh,Venkatesh B. Parik, Anup M. Akarte, Dheeraj T. Baviskar. Strategies For Solubility Enhancement Of Poorly Soluble Drugs International Journal Of Pharmaceutical Sciences

Review And Research Volume 8, Issue 2, May – June 2011; Article-013 74-80

15. Chiou W.L., Reigelman S. Pharmaceutical Applications Of Solid Dispersion Systems. J Pharm Sci. 1971; 60(9): 1281-1302.
16. Corrigan, O.I. Mechanisms Of Dissolution Of Fast Release Solid Dispersions.Drug DevInd Pharm. 1985; 11: 697–724.
17. Dhirendra K., Lewis S., Udupa N., Atin K. Solid Dispersions: A Review. Pak J Pharm Sci. 2009; 22 (2): 234-246.
18. Meera C.; Sayyad, A. B.; Sawant, S. D. Review on various techniques of solubility enhancement of poorly soluble drugs with special emphasis on solid dispersion. Singh, Journal of Pharmacy Research;2010, 3(10):2494
19. Jagtap P.S., Sanjay S. Jain, Neha D.,Jadhav K.R. Melt Extrusion Technology, Approach Of Solubility Enhancement:A Brief Review Scholars Research Library, 2012, 4 (1):42-53
20. Deepshikha Sikarra, Shukla V, Kharia A, Chatterjee D. P. Techniques For Solubility Enhancement Of PoorlySoluble Drugs: An Overview Journal Of Medical Pharmaceutical And Allied Sciences (2012) 01; 1-22
21. Brahmankar D.M, Jaiswal S.B. Biopharmaceutics and Pharmacokinetics, VallabhPrakashan, 1st Edn., 347-352, 1995.
22. Chavan S, Patel K, Shelar D, Vavia P. Preparation of Oxcarbazine Solid Dispersion by Hot Melt Extrusion for Enhanced Dissolution: Doenstream Processing to tablets. Am. J. PharmTech Res. 2013, 3(1).
23. Vikas A Saharan, VipinKukkar, Mahesh Kataria, Manoj Gera. Pratim K Choudhury. Dissolution Enhancement of Drugs. Part I: Technologies and Effect of Carriers. Int. J Health Res. 2009; 2(2): 107-124.Available at http://www.ijhr.org
24. Pawar Anil R, Choudhari Pravin D. Novel techniques for solubility, dissolution rate and bioavailability enhancement of class II and IV drugs. Asian Journal of Biomedical and Pharmaceutical Sciences.2012; 2(13): 9-14.
25. Patel VR, Agrawal YK, Nanosuspension:An Approach To Enhance Solubility Of Drugs.J.Adv Pharm. Tech.Res.20112;(2):81-87
26. Ch. Prabhakar, K. Bala Krishna. A Review on Nanosuspensions in Drug Delivery. International Journal Pharma and Bio Sciences.2011; 2(1):549-558.
27. Patel PB, Prajapati ST, Patel NR, Patel NN, Patel CN. Solid Dispersion: A Method of Improving Bioavailability and Taste Masking. Inventi Rapid: Pharm Tech. 2012; (4):1-7.
28. Patil MS, Godse SZ, Saudagar RB, Solubility enhancement by various techniques: An overview, World Journal Of Pharmacy And Pharmaceutical Sciences 2013;2(6).
29. Khalid M E, Ahmed M Samy, Mohamed I. Fetouh for mulation and evaluation of Rofecoxib Liquisolid Tabl ets. International Journal of Pharmaceutical Sciences Review and Research,2010; 3(1):135.142.
30. Chandel P, Raj K, Kapoor Ankita. Liquisolid technique: an approach for enhancement of solubility. Journal of Drug Delivery & Therapeutics, 2013; 3(4), 131-137.

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