JETIR.ORG ISSN: 2349-5162 | ESTD Year : 2014 | Monthly Issue
JOURNAL OF EMERGING TECHNOLOGIES AND INNOVATIVE RESEARCH (JETIR)
An International Scholarly Open Access, Peer-reviewed, Refereed Journal

COMPREHENSIVE REVIEW ON VARIOUS APPROACHES FOR SOLUBILITY ENHANCEMENT OF POORLY WATER SOLUBLE DRUGS

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Abstract : Solubility is the process of dissolution of solute in solvent to form homogenous system. This is the one of the very important factor to achieve desired concentration of the drug in systemic circulation for desired pharmacological response. On the basis of solubility drugs are classified into four classes of BCS classification. Solubility challenges are faced in class II and class IV of the BCS system. In the development of new drug formulation development lower aqueous solubility is the major problem. Near about 40 % new chemical entities developed in the pharmaceutical industries are insoluble in water. There are various approaches are used to enhanced solubility of poorly water soluble drugs like particle size reduction, physical and chemical modification of drugs, salt formation, use of surfactant, solid dispersion and many more. This review article represents various methods used for enhancement of solubility of poorly water soluble drugs.

Key words-solubility, dissolution, BCS classification, surfactant.

INTORDUCTION

Oral bioavailability enhancement of insoluble solvent medications is the one of biggest challenging elements to be viewed as in the medication formulation and development. There are many generally utilized strategies accessible like salt arrangement, solublization, and molecule size reduction to increase solubility, disintegration rate and accordingly oral bioavailability of such medications is expanded, yet there are functional impediments of these methods. For unbiased mixtures, salt arrangement isn't attainable and the combinations of suitable salt types of medicament that are pitifully are in acidic and essential may frequently is not reasonable. The solubility of the medicament in the natural solvent or in watery aqueous media by using different types of surfactant and various co solvent prompts fluid details that are normally undesirable according to the viewpoints of patient pleasantness and commercialization. In spite of the fact that molecule size reduced or decreased is generally used to increment of dissolution and disintegration rate , there is a down as far as possible to how much size is reduced or decreased can be accomplished by such ordinarily involved techniques as controlled crystallization crushing, and so on.[1-6]

Solubility is the process of dissolving solute; it may be a solid, liquid or gaseous substance to dissolve into suitable solvent to form homogenous solution. Solubility is totally depending on the solvent used along with atmospheric condition of temperature and pressure. The extent of solubility ranges into different classes like infinitely soluble, poorly soluble and insoluble.

Factors affecting solubility:

Molecular structure of solute

A smaller change in the molecular structure of the chemical compound can have a marked effect on its solubility in a given liquid. For example, the introduction of a hydrophilic hydroxyl group can produce a large improvement in water solubility. In addition, the conversion of a weak acid to its sodium salt leads to a much greater degree of ionic dissociation of the compound when it dissolves in water. The

overall interaction between solute and solvent is markedly increased and the solubility consequently rises. Esterification of drug will also decrease the solubility.

Te`mperature

Solubility of drug substance is depends on the temperature of solvent. In this process if heat is absorbed the solubility increased with increase in the temperature.

Nature of the solvent

The nature of the solvent can be discussed in terms of the statement 'like dissolves like', and in relation to solubility parameters. In addition, the point has been made that mixtures of solvents may be employed. Such mixtures are often used in pharmaceutical practice to obtain aqueous-based systems that contain solutes in excess of their solubility in pure water. This is achieved by using co solvents such as ethanol or propylene glycol, which are miscible with water and which act as better solvents for the solute.

Particle size of the solid:

The changes in interfacial free energy that accompany the dissolution of particles of varying sizes cause the solubility of a substance to increase with decreasing particle size. The increase in solubility with decrease in particle size ceases when the particles have a very small radius, and any further decrease in size causes a decrease in solubility.

Crystal characteristics:

Different crystalline forms of the same substance, which are known as polymorphs, consequently possess different lattice energies, and this difference is reflected by changes in other properties. The effect of polymorphism on solubility is particularly important from a pharmaceutical point of view, because it provides a means of increasing the solubility of a crystalline material and hence its rate of dissolution by using a metastable polymorph. The absence of crystalline structure that is usually associated with a so-called amorphous powder may also lead to an increase in the solubility of a drug compared to that of its crystalline form.

pH:

If the pH of a solution of either a weakly acidic drug or a salt of such drug is reduced then the proportion of unionized acid molecules in the solution increases. Precipitation may therefore occur because the solubility of the unionized species is less than that of the ionized form. Conversely, in the case of solutions of weakly basic drugs or their salts precipitation is favored by an increase in pH.

Solubilizing agent:

These are the agents which are capable of forming large aggregates or micelles in solution when their concentrations exceed certain values. In aqueous solution, the center of the segregates resembles a separate organic phase and organic solutes may be taken up by the aggregates, thus producing an apparent increase in their solubility in water. This phenomenon is known as solublization. A similar phenomenon occurs in organic solvents containing dissolved solubilizing agents, because the center of the aggregates in these systems constitutes a more polar region than the bulk of the organic solvent.

Polarity:

Polarity of the solute and solvent molecules will affect the solubility. Generally ‘like dissolves like’ means non-polar solute molecules will dissolve in non-polar solvents and polar solute [7-12]

It is generally liquid, which can be in the event of strong measurements structure like tablets, capsules when a medication is regulated orally, it should be set free from the dose structure and broke down in the GI liquids before it tends to be retained. The bioavailability of various inadequately water solvent medications are restricted using their disintegration rates. an ideal measurements regiments of the drugs treatment of any kind of sickness is the one that achieve wanted bioavailability. It might be the characterized as the rate and amount of medication retention in systemic circulation. A medication with unfortunate bioavailability may having one with the following

1. Extensive pre efficient digestion.
2. Unfortunate steadiness of the broke down drug at the below physiological pH.
3. Lacking allotment coefficient and consequently unfortunate pervasion throughout biomembrane.

There are various methods to treat the bioavailability problem.

1. The pharmaceutics method approach which includes method in the physiochemical property of the medicament without altering the compound, change or alters of plan, fabricating process,
2. The pharmacokinetic method approach in which the pharmacokinetic of the medication is modified by the change or altering its synthetic design.

3. Another method is natural method wherein change in course of medication organization might be changed, eg.From oral route to parenteral [15-17]

There are drawbacks in second methodology of substance adjustment that is of being extravagant and tedious, require reiteration of clinical review and longer time for administrative perspectives. The endeavors whether streamlining the definition, producing process, or physiochemical parameter of the medication, are basically focused on improvement of disintegration rate as it is the significant rate restricting move toward ingestion of the most medications. Unfortunate dissolvability of medication substance in which prompt slower dissolution, disintegration rate and hence to deficient bioavailability.

The dissolvability of the solute is characterizes as the as most extreme quantity and amount of the solute that can be dissolve or disintegrate in the specific amount of solvent or amount of arrangement at the predetermined specific temperature. In different words the dissolvability can likewise characterize as the capacity of the agent or any substance to shape solution with another substance[1]. The substance to be broken up is known as solute and medium in which dissolve or solute break down is called as solvates which together formed a solution. The most common way of the dissolving solute into dissolvable is called as arrangement or hydration in the event that the dissolvable is water.

There are several methodological possibilities to increase and enhancement in the dissolution and solubility rate of the poorly water soluble drugs such as Solid dispersion, cyclodextrin complexation, nanosuspension, altering the pH, etc.[4,18,19,30-35]

Approaches for enhancement of solubility

Different method is there which are used for the enhancement of solubility and dissolution rate of the drugs medicament. It is categorized into physical modification, chemical modification of the drug and some other techniques.

Physical modification-particle size reduction like micronization and nanosuspension, modification of crystal habits like polymorph, amorphous form and crystallization, drug dispersion like solid dispersion, eutrctic mixtures, solid solution etc.

Chemical modification - use of buffer, change in Ph, complex formation and salt formation.

Miscellaneous - cosolvency, hydrotrophy, use of excipients like surfactant and solubilizers.

Using surfactants [20, 21-24]

The surfactant increase dissolvability and breaking down rate essentially by propelling wetting and invasion of crumbling the fluid into the solid medicine substance. They are all around are use in obsession underneath their critical micelle conc. Value since above the CMC the prescription caught in the micelle structure fails to distribute the crumbling fluid. Nonionic surfactant model such as polysorbate are used comprehensively. Cases of medicine for which bioavailability is extended by using of surfactants in the definition consolidate steroid such as spiranolactone.

Micronization

The cycle includes limiting diminishing sizes of the of the medication particles from 1 to 10 microns. Most normal strategies are by utilization of air wearing down technique or splash drying strategy. Instances of medication whose bioavailability was expanded by this technique incorporate griseofulvin and a few steroidal and sulfa drugs.4But this strategy has a few burdens; the main impediment drawback is restricted an open door to control significant characteristics of definite particles like size, shape and morphology. [5, 25-26, 38]

Salt form use

Salts have further developed dissolvability and disintegration rate in contrast with the first medications. Antacid metals salt of acidic nature medications such as penicillin and solid corrosive salt of fundamental medications like atropine is more water dissolvable than parents drugs. The main disadvantages are that inadequately aqueous solvent medication is not appropriate for working on their dissolvability by salt arrangement technique.[6,39,27]

Change in pH of the drug medicament

The liquid dissolvability of medicament can be extended using change in the pH. An extension in the pH the deterioration rate and the dissolvability can be addition. Drugs having low pH having lower dissolvability.[28]

There are two methods for this can be achieved

1) In situ salt formation and

2) Addition of pads to the specifying for instance padded ibuprofen tablets [4,40-44]

Use of metastable polymorphs

It is the course of presence of a medication in at least two glasslike structures, every one of which has an alternate space cross section plan yet is synthetically indistinguishable. Two kinds of polymers are available [5, 45]

1) Enantiomeric polymorph 2) Monomeric polymorph

Solute-solvent complexation

The solvates of medications with natural solvents for the most part have higher water dissolvability than their separate hydrates of the first medications. A lot higher dissolvability can be achieved by freeze drying such as a solute in arrangement with a natural dissolvable with which framing a solvate.

Solvent deposition

In this approach the poor water soluble drugs like nifedepine is miscible with organic solvent such as alcohol and it is deposited on an inert, hydrophilic solid matrix such as microcrystalline cellulose or starch by process of evaporation of the solvents. [6,29,46]

Selective adsorption on insoluble carriers

An exceptionally dynamic adsorbent for example, the inorganic like bentonite can upgrade solvency and disintegration pace of inadequately water solvent medications such as Indomethacin and griseofulvin and prednisone by keeping up with the fixation slope at its greatest. Two main reason reasons proposed for this, quick arrival of medications from the outer layer of dirts are the feeble actual holding between the two adsorb ate and adsorbent, and hydration and enlarging of the mud in the watery media. [5, 30, 47]

Solid solution

Three methods by which the molecular size of the drug substance or any medication can be decreased to the submicron level are -

i) Using strong arrangement.

ii) Use of the eutectic blends and

iii) Using strong scatterings.

In view of decrease in molecule size to the atomic level, strong arrangement show more noteworthy fluid dissolvability and quicker disintegration than eutectic and strong scatterings. They are by and large ready by combination strategy by which an actual combination of a solute and dissolvable are liquefied together followed by fast cementing. Such framework, ready by combination is frequently known as melts. for example griseofulvin from such strong arrangement disintegrated 6 to multiple times quicker than unadulterated griseofulvin.

The component recommended for upgraded solvency and fast disintegration of atomic scattering are: [5, 48]

1. When double blend is presented to water, the solvent transporter disintegrate quickly leaving the insoluble medication in a condition of microcrystalline scattering of extremely fine particles and

2.When the strong arrangement ,which is supposed to be in a condition of haphazardly organized solute and dissolvable particles in the gem grid , is presented to the disintegration liquid, the solvent transporter broke down quickly leaving the insoluble medication abandoned at practically sub-atomic level .[49]

Eutectic mixture

These frameworks are ready by combination strategy. Eutectic dissolves vary from strong arrangement in that the melded soften of solute - dissolvable show total miscibility yet unimportant strong dissolvability. Exactly when the eutectic mix is introduced to water, the dissolvable carrier separated departing the prescription in a microcrystalline state which solubilizes rapidly.

- Thermo liable medications and
- Transporters, for example, corrosive that decays at liquefying point.

Drugs which neglect to solidify from the blended liquefy [50-53]

Solid dispersion

This concept was introduced by Sekiguchi and Obi, for the investigation of dissolution performance of eutectic melts of sulfonamide drug. These are ready by dissolvable or co-precipitation strategy by which both the visitor solute and the strong transporter dissolvable are broken up in a typical unpredictable fluid dissolvable like alcohols. Solid dispersion are generally prepared by solvent or co-precipitation process and hot melt method (fusion method). In the fusion method the physical mixture of the drug and water soluble carrier are heated directly until the two melts. The melted mixture is then cooled, and solidified rapidly in ice bath with rigorous stirring. The final solid mass is then crushed, pulverized and sieved which can be compressed into tablets. [8, 9] In the solvent evaporation method, the fluid dissolvable is taken out by vanishing under decreased pressure or by freeze drying which brings about undefined precipitation of visitor in a translucent transporter. The main difference between strong scattering and strong arrangement is that

the medication is encouraged out in an undefined structure in the previous rather than glasslike structure in the last option. The technique is appropriate for thermo liable substances yet has number of hindrances as follows [19-20, 54]

- Greater expense for handling
- Utilization of bigger amounts of dissolvable
- Trouble in complete evacuation of dissolvable.

Cyclodextrin encapsulation

Two subordinates of cyclodextrin beta and gamma and a few of their subordinates are one of a kind in being able to frame sub-atomic consideration complex with hydrophilic medications having low water dissolvability. These cyclodextrin particles are flexible and having hydrophobic pit of size sufficiently reasonable to oblige the lipophilic medications as visitor; the beyond the host particle is generally hydrophilic. In this way the microscopically exemplified drugs has enormously further developed solvency and disintegration rate. There are a few instances of medications with further developed bioavailability because of such a peculiarity –thiazide diuretics, barbiturates and number of NSAID. [6, 55]

Pharmaceutical nanosuspension:

it is portrayed as "finely colloid, biphasic, discrete strong medication particles in a fluid vehicle, settled via surfactants, parenteral and pneumonic organization, oral and skin use, with diminished molecule size, prompting increased dissolvability and disintegration rate and in this way improved bioavailability". This technology has been developed as promising candidates for efficient delivery of hydrophobic drugs. Various methods are used for the preparation of nanosuspension including precipitation technique, media milling, high pressure homogenization in water and non aqueous media and combination of precipitation and high pressure homogenization. [51]

Precipitation techniques

In this method drug is dissolved in the solvent which is then added to antisolvent to precipitate the crystals. Moreover this method is not applicable to drugs, which are simultaneously poorly soluble in aqueous and non aqueous media.

Media milling

In this method 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. High energy shear forces are generated as a result of the impaction of the milling media with the drug resulting into breaking of microparticulate drug to nanosized particles [28]. 6.3. High Pressure Homogenization. High-pressure homogenization has been used to prepare nanosuspension of many poorly water soluble drugs. In this method, the suspension of a drug and surfactant is forced under pressure through a nanosized aperture valve of a high pressure homogenizer. The principle of this method is based on cavitation in the aqueous phase. The cavitations forces within the particles are sufficiently high to convert the drug microparticles into nanoparticles. The concern with this method is the need for small sample particles before loading and the fact that many cycles of homogenization are required [32, 58]

Supercritical fluid Process

Once the drug particles are solubilized within SCF, they may be recrystallized at greatly reduced particle sizes. The flexibility and precision offered by SCF processes allows Micronization of drug particles within narrow ranges of particle size, often to sub-micron levels. The flexibility and precision offered by SCF processes allows micronization of drug particles within narrow ranges of particle size, often to submicron levels. Hence, it is possible to fine-tune a unique combination of properties necessary for a desired application. These unique processing capabilities of SCFs, long recognized and applied in the food industry, have recently been adapted to pharmaceutical applications. [59]

Hydrotrophy

It is a solubilisation process whereby addition of a large amount of second solute results in an increase in the aqueous solubility of another solute. Solute consists of alkali metal salts of various organic acids. Hydrotropic agents are ionic organic salts. Additives or salts that increase solubility in given solvent are said to “salt in” the solute and those salts that decrease solubility “salt out” the solute. Several salts with large anions or cations that are themselves very soluble in water result in “salting in” of non electrolytes called “hydrotropic salts” a phenomenon known as “hydrotropism”. Hydrotropic solutions do not show colloidal properties and involve a weak interaction between the hydrotropic agent and solute. Hydrotrophy designate the increase in solubility in water due to the presence of large amount of additives. The mechanism by

which it improves solubility is more closely related to complexation involving a weak interaction between the hydrotrophic agents like sodium benzoate, sodium acetate, sodium alginate, urea and the poorly soluble drugs. [60-63]

CONCLUSION

By this review article we conclude that, solubility of the drug is the most important factor that controls the formulation of the drug as well as therapeutic efficacy of the drug, hence the most critical factor in the formulation development. Dissolution of drug is the rate determining step for oral absorption of the poorly water soluble drugs and solubility is also the basic requirement for the formulation and development of different dosage form of different drugs. The various techniques described above alone or in combination can be used to enhance the solubility of the drug. Solubility can be enhanced by many techniques and number of folds increase in solubility. 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 above

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