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SOLID DISPERSION: A REVIEW

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ABSTRACT

The solubility issues complicating the delivery of the new drugs and also affect the delivery of many existing drugs. There are various techniques are available for enhancement of solubility. Solid dispersion is one of the most promising approaches for solubility enhancement. Currently only 8% of new drug candidates have both high solubility and permeability. More than 60% of potential drug products suffer from poor water solubility. In solid dispersion particle size of drug is reduced or a crystalline pure drug is converted into amorphous form and hence the solubility of drug is increased. Polymers incorporated in solid dispersion technologies are usually hydrophilic in nature and also showing compatibility with the drug to enhance the drug solubility.

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INTRODUCTION

The poor solubility and slow dissolution rate of poorly water soluble drugs in the aqueous gastrointestinal fluids often cause insufficient bioavailability especially for class-II substances according to BSC. The bioavailability may be enhanced by increasing solubility and dissolution rate of the drug in the gastro-intestinal fluid.[1] Solubility is the amount of a substance that has passed into solution when equilibrium is attained between the solution and excess (i.e., undissolved) substance at a given temperature and pressure. The BCS is a scientific framework for classifying a drug substance based on its aqueous solubility and intestinal permeability. It allows for the prediction of in vivo pharmacokinetics of oral immediate-release (IR) drug products by classifying drug compounds into four classes (Table 1) based on their solubility. [2]

Table.1 The Biopharmaceutics Classification System [2].

BCS Class	Solubility	Permeability
Class I	High	High
Class II	Low	High
Class III	High	Low
Class IV	Low	Low

The relative terms of solubility are as follows. [3].

Table 2 Relative Terms of Solubility.

Descriptive terms	Parts of solvent required for 1 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
Practically insoluble or insoluble	>10,000

SOLID DISPERSION

Definition :Solid dispersion technology is the science of dispersing one or more active ingredients in an inert matrix in the solid stage to achieve an increased dissolution rate or sustained release of drug, altered solid state properties and improved stability.[4]

A unique approach to presenting a poorly soluble drug in an extremely fine state of subdivision to the gastrointestinal fluids, is the administration of the drug in the form of a solid eutectic mixture. Such a mixture consists of a microcrystalline dispersion of the poorly soluble drug (e.g. sulphathiazole) in a matrix consisting of a physiologically inert, readily water-soluble such as urea. The water soluble solid is often referred to as the 'carrier'. Exposure of this type of solid dispersion system to the gastrointestinal fluids results in dissolution of the water soluble matrix (carrier). As the matrix dissolves it exposes the dispersed poorly soluble drug, which is in an extremely fine state of subdivision, to the aqueous gastrointestinal fluids. Hence the poorly soluble drug is presented to the aqueous fluids in a form which facilitates its dissolution rate and bioavailability. It is interesting to note that the bioavailability of sulphathiazole was found to be increased when this drug was presented in the form of a solid eutectic mixture with urea. [5]

There is widespread interest in solid dispersion because they may offer a means of facilitating the dissolution and frequently, therefore, the bioavailability of poorly soluble drugs when combined with freely soluble 'carriers' such as urea or polyethylene glycol. This increase in dissolution rate is achieved by a combination of effects, the most significant of which is reduction of particle size to an extent that cannot be readily achieved by conventional comminution approaches. Other contributing factors include increased wettability of the material, reduced aggregation and agglomeration, and a likely increase in solubility of the drug owing to the presence of the water-soluble carrier**.** [6]

TYPES OF SOLID DISPERSION

On the basis of molecular arrangement, six types of molecular dispersion can be distinguished.

1.Simple Eutectic Mixture

A simple eutectic mixture consists of two compounds that are completely miscible in the liquid state but only to a very limited extent in the solid state. The eutectic mixture of a sparingly water-soluble drug and highly water soluble carrier may be regarded thermodynamically as an intimately blended physical mixture of its two crystalline components. These components are assumed to crystallize simultaneously in small particulate sizes. The increase in specific surface area therefore, is mainly responsible for the increased rate of dissolution of poorly water soluble drug. [7]

2. Solid Solution

In a solid solution, the two components crystallize together in a homogeneous one phase system. The particle size of the drug in the solid solution is reduced to its molecular size responsible for increase in dissolution rate. On the extend of miscibility of two components, solid solution is classified as continuous and discontinuous. In continuous solid solution, the two components are miscible in the solid state in all proportions. In discontinuous solid solutions, the solubility of each of the components in the other component is limited**.** [8]

3. Glass Solution and Suspension

A glass is a homogeneous glassy system in which solute dissolves in the glassy system. A glass suspension refers to a mixture in which precipitated particles are suspended in a glassy solvent. Characterization of the glassy state is transparency and brittleness below the glass transition temperature. [8]

4. Amorphous Precipitation

Amorphous precipitation occurs when the drug precipitates as an amorphous form in the inert carrier. The high-energy state of the drug in this system generally produces much greater dissolution rates than the corresponding crystalline forms of the drug. [7]

MECHANISMS OF DRUG RELEASE FROM SOLID DISPERSION

1. Particle size reduction and reduced agglomeration

These may be usefully considered together as both are related to increases in the exposed surface area of the drug. Size reduction has been classically considered to be a result of eutectic or solid solution formation; it is worth noting that this mechanism suggests an intrinsic link between solid state structure and release. Similarly it has been suggested that the presentation of particles to the dissolution medium as physically separate entities may reduce aggregation. In addition, many of the carriers used for solid dispersions may have some wetting properties, hence it is reasonable to suggest that improved wetting may lead to reduced agglomeration and hence increased surface area. [9]

2. Increased solubility or dissolution rate of the drug

Again, many of the carriers used may increase the solubility of the drug. There has been some debate over this mechanism as solubility studies have indicated that at the concentrations used for in vitro experiments the carriers often elicit minimal solubility increases. This does, however, work on the assumption that the concentration of the carrier after complete dissolution in the water bath (e.g. 0.5 g/l) may be used as a model of the behaviour at the dissolving surface. Similarly, the carrier and drug may form a soluble complex, as is well established for cyclodextrins, although the evidence for this occurring with other carriers is weaker. Finally, changes to the physical properties of the drug such as degree of crystallinity and polymorphic form may also be considered under this category. [9]

3. Transferring the drug from crystalline to amorphous state/Formation of high energy state

Amorphous drug represent the higher energy states and can be considered as cooled liquids. They have greater aqueous solubility than crystalline forms because the energy required to transfer a molecule from crystal is greater than required for non crystalline (amorphous) solid. For example the amorphous state of novobiocin is ten times more soluble than crystalline form. [10]

4. Particles with improved wettability

A strong contribution to the enhancement of drug solubility is related to the drug wettability improvement verified in solid dispersions. It was observed that even carriers without any surface activity, such as urea improved drug wettability. Carriers with surface activity, such as cholic acid and bile salts, when used, can significantly increase the wettability properties of drugs. Moreover, carriers can influence the drug dissolution profile by direct dissolution or co-solvent effects. Recently, the inclusion of surfactants in the third generation solid dispersions reinforced the importance of this property. [11]

Advantages of Solid Dispersion [4]

- Preparation of drug-drug solid dispersions results in particles with reduced particle size and thus the surface area is improved and increased dissolution rate is, the ultimate result is improved bioavailability.
- Wettability is improved during solid dispersion production. Improved wettability results in increased solubility
- Economic method.
- Particles in solid dispersion have been found to have higher degree of porosity; the increased porosity of dispersion particles accelerates the drug release profile.
- Less time consuming process.
- In solid dispersions drugs are presented as supersaturated solution which are considered to be metastable polymorphic form. Thus presenting drug in amorphous form increase the solubility of particles.
- Increase the solubility without using physiological inert carrier.

Disadvantages of Solid Dispersion [10]

- Poor stability is the main disadvantage of solid dispersion. The amorphous state of drug may undergo crystallization.
- Ageing may decrease the dissolution rate and there may be changes in crystallinity.
- Solid dispersion may be deteriorated in presence of moisture and excessive temperature. The presence of moisture influences the crystallinity of drugs.
- Some polymers used in dispersion are hygroscopic in nature and may adsorb moisture, that can result in crystal growth or the amorphous form can get converted to crystalline state.
- Sometimes the metastable form of a drug may change to stable form. So there may be decrease in solubility and dissolution rate.

SELECTION CRITERIA OF A CARRIER FOR SOLID DISPERSION [19]

Following criteria should be considered during selection of carriers
(a) High water solubility which improve wettability and enhance dissolution.
(b) High glass transition point which improve stability.
(c) Minimal water uptake (reduces Tg).
(d) Soluble in common solvent with drug (solvent evaporation).
(e) Relatively low melting point (melting process).
(f) Capable of forming a solid solution with the drug (similar solubility parameters).
(g) Low viscosity and high swelling capacity.

CARRIERS USED FOR THE SOLUBILITY ENHANCEMENT [20]

1. SUGARS - Dextrose, Sucrose, Galactose, Sorbitol, Maltose, Xylitol, Mannitol.
2. ACIDS - Citric acid, Succinic acid.
3. POLYMERIC MATERIALS - PVP, PEG, HPMC, Methyl cellulose, Hydroxyl ethyl Cellulose, Cyclodextrins.
4. HYDROTROPS - Urea, Nicotinamide, Sodium Benzoate, Sodium Salicylate, Sodium Acetate , Sodium Alginate.
5. SURFACTANTS - Polyoxyethylene stearate, Renex, Poloxamer 188, TexaforAIP, Tweens , Spans.
6. INSOLUBLE OR ENTERIC POLYMER - HPMC Pthalate, Eudragit L100, Eudragit S100

METHODS OF PREPARATION OF SOLID DISPERSIONS

FUSION METHOD

The melting or fusion method, first proposed by Sekiguchi and Obi 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. Appropriately this has undergone many modifications in pouring the homogenous melt in the form of a thin layer onto a ferrite plate or a stainless steel plate and cooled by flowing air or water on the opposite side of the plate .In addition, a super-saturation of a solute or drug in a system an often be obtained by quenching the melt rapidly from a high temperature. Under such conditions, the solute molecule is arrested in the solvent matrix by the instantaneous solidification process. The quenching technique gives a much finer dispersion of crystallites when used for simple eutectic mixture. [12] However many substances, drugs or carriers, may decompose during the fusion process which employs high temperature. It may also cause evaporation of volatile drug or volatile carrier during the fusion process at high temperature. Some of the means to overcome these problems could be heating the physical mixture in a sealed container or melting it under vacuum or in presence of inert gas like nitrogen to prevent oxidative degradation of drug or carrier.[13] .Although frequently applied, the fusion method has serious limitations. Firstly, a major disadvantage is that the method can only be applied when drug and matrix are compatible and when they mix well at the heating temperature. When drug and matrix are incompatible two liquid phases or a suspension can be observed in the heated mixture , which results in an inhomogeneous solid dispersion. This can be prevented by using surfactants .Secondly, a problem can arise during cooling when the drug-matrix miscibility changes. In this case phase separation can occur. Indeed, it was observed that when the mixture was slowly cooled, crystalline drug occurred, whereas fast cooling yielded amorphous solid dispersions. Thirdly, degradation of the drug and or matrix can occur during heating to temperatures necessary to fuse matrix and drug. For example, to melt a sugar matrix of galactose a temperature of 169°C was required and in order to get the glassy PVP in the rubbery state a temperature of about 170°C is required. Poly ethylene glycols melt at around 70°C and are therefore often used for the preparation of solid dispersions with the fusion method [14]

HOT MELT EXTRUSION

Melt extrusion is essentially the same as the fusion method except that intense mixing of the components is induced by the extruder. When compared to melting in a vessel, the product stability and dissolution are similar (Forster et al., 2001), but melt extrusion offers the potential to shape the heated drug-matrix mixture into implants, ophthalmic inserts, or oral dosage forms like in the traditional fusion process, miscibility of drug and matrix can be a problem. Solubility parameters are investigated to predict the solid state miscibility and to select matrices suitable for melt extrusion. High shear forces resulting in high local temperatures in the extruder be a problem for heat sensitive materials. However, compared to the traditional fusion method, this technique offers the possibility of continuous production, which makes it suitable for large-scale production. Furthermore, the product is easier to handle because at the outlet of the extruder the shape can be adapted to the next processing step without grinding. [13]

SOLVENT EVAPORATION METHOD

In this method, the physical mixture of the drug and carrier is dissolved in a common solvent, which is evaporated until a clear, solvent free film is left. The film is further dried to constant weight. The main advantage of the solvent method is thermal decomposition of drugs or carriers can be prevented because of the relatively low temperatures required for the evaporation of organic solvents. However, some disadvantages are associated with this method such as

1) The higher cost of preparation.
2) The difficulty in completely removing liquid solvent.
3) The possible adverse effect of traces of the solvent on the chemical stability
4) The selection of a common volatile solvent.
5) The difficulty of reproducing crystal form**.** [11]

MELTING SOLVENT METHOD

It involves preparation of solid dispersions 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 polyethylene glycol 6000 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 polyethylene glycol. 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 stand point, it is only limited to drugs with a low therapeutic dose e.g. below 50 mg**.** [13]

SUPERCRITICAL FLUID TECHNOLGY

This technology has been introduced in the late 1980s and early 1990s, and experimental proofs of concept are abundant in the scientific literature for a plethora of model compounds from very different areas such as drugs and pharmaceutical compounds, polymers and biopolymers, explosives and energy materials, superconductors and catalyst precursor's dyes and biomolecules such as proteins and peptides. From the very beginning of supercritical fluid particle generation research, the formation of biocompatible polymer and drugloaded biopolymer micro-particles for pharmaceutical applications has been studied intensively by a number of researcher groups. CFs either as solvent: rapid expansion from supercritical solution (RESS) or antisolvent: gas antisolvent (GAS), supercritical antisolvent (SAS), solution enhanced dispersion by supercritical fluids (SEDS) and/or dispersing fluid: GAS, SEDS, particles from gas-saturated solution (PGSS). Conventional methods, i.e. Spray drying, solvent evaporation and hot melt method often result in low yield, high residual solvent content or thermal degradation of the active substance. the supercritical fluid antisolvent techniques, carbon dioxide is used as an antisolvent for the solute but as a solvent with respect to the organic solvent. Different acronyms were used by various authors to denote micronization processes: aerosol solvent extraction system (ASES), precipitation with a compressed fluid antisolvent (PCA), gas anti-solvent (GAS), solution enhanced dispersion by supercritical fluids (SEDS) and supercritical anti-solvent (SAS). The SAS process involves the spraying of the solution composed of the solute and of the organic solvent into a continuous supercritical phase flowing cocurrently use of supercritical carbon dioxide is advantageous as it is much easier to remove from the polymeric materials when the process is complete, even though a small amount of carbon dioxide remains trapped inside the polymer; it poses no danger to the patient. In addition the ability of carbon dioxide to plasticize and swell polymers can also be exploited and the process can be carried out near room temperature. Moreover, supercritical fluids are used to lower the temperature of melt dispersion process by reducing the melting temperature of dispersed active agent. The reason for this depression is the solubility of the lighter component (dense gas) in the forming phase (heavier component). [12]

KNEADING METHOD

In this method, carrier is permeated with water and transformed to paste. Drug is then added and kneaded for particular time. The kneaded mixture is then dried and passed through sieve if necessary.[15] The physical mixture of drug and carrier is triturated to thick paste utilizing small volume of solvent. The solvent used can be organic [alcohol, dichloromethane, acetone] or aqueous mixture thereof. The kneaded paste is dried in an oven and the dried mass is pulverized and subsequently stored in dessicator. This process is economical but the residual solvent may be issue. [17]

LYOPHILIZATION TECHNIQUE

Lyophilization has been thought of a molecular mixing technique where the drug and carrier are co dissolved in a common solvent, frozen and sublimed to obtain a lyophilized molecular dispersion. This technique was proposed as an alternative technique to solvent evaporation. The advantages of freeze drying is that the drug is subjected to minimal thermal stress during the formation of the solid dispersion and the risk of phase separation is minimized as soon as the solution is vitrified. An even more promising drying technique is spray-freeze drying. The solvent is sprayed into liquid nitrogen or cold dry air and the frozen droplets are subsequently lyophilized. The large surface area and direct contact with the cooling agent results in even faster vitrification, thereby decreasing the risk for phase separation to a minimum. Moreover, spray freeze drying offers the potential to customize the size of the particle to make them suitable for further processing or applications like pulmonary or nasal administration.[16]

USE OF SURFACTANT

The utility of the surfactant systems in solubilization is very important. Adsorption of surfactant on solid surface can modify their hydrophobicity, surface charge, and other key properties that govern interfacial processes such as flocculation/dispersion, floating, wetting, solubilization, detergency, and enhanced oil recovery and corrosion inhibition. Surfactants have also been reported to cause solvation/plasticization, manifesting in reduction of melting the active pharmaceutical ingredients, glass transition temperature and the combined glass transition temperature of solid dispersions. Because of these unique properties, surfactants have attracted the attention of investigators for preparation of solid dispersions.[16]

ELECTROSPINNING

Electrospinning is a process in which solid fibres are produced from a polymeric fluid stream solution or melt delivered through millimetre scale nozzle. This process involves the application of strong electrostatic field over a conductive capillary attaching to a reservoir containing a polymer solution or a melt and conductive collection screen. Upon increasing the electrostatic field upto but not exceeding a critical value, charge species accumulate on the surface of pendant drop; destabilize the hemispherical shape into a conical shape (commonly known as Taylor's cone). Beyond the critical value the charged polymer jet is ejected from the apex of cone (as a way of relieving the charge built up on the surface of pendant drop). The ejected charged jet is then carried to the collection screen via electrostatic force. The thinning down of the charged jet is limited. If the viscosity increases, the charged jet is dried. This techniques has tremendous potential for the preparation of nanofibres and controlling the release of biomedicine as it is simplest, the cheapest technique can be utilized for solid dispersions in future.[16]

FREEZE DRYING METHOD

Freeze drying consists of three successive steps: freezing , primary drying and secondary drying. A sample to be freeze dried consists of a drug, excipients and one or more solvents. High freezing rates can be achieved by using cryogenic liquid such as liquid nitrogen. Either vials containing the solution can be immersed in the cryogenic solution or the solution is sprayed directly into the cryogenic liquid. It is preferred for the preparation of solid dispersion of thermolabile materials but also has a disadvantage of being time consuming and expensive method.[17]

EVALUATION PARAMETER OF SOLID DISPERSION [8]

- Phase solubility study
- Drug content
- Powder X-ray diffraction studies
- Dissolution studies
- Interaction studies
- Stability study
- Microscopy

APPLICATIONS OF SOLID DISPERSION [21]

Apart from absorption enhancement, the solid dispersion technique may have numerous pharmaceutical applications, which should be further explored. It is possible that such a technique be used :

1. To obtain a homogeneous distribution of a small amount of drug in solid state.
2. To stabilize the unstable drug.
3. To dispense liquid or gaseous compounds in a solid dosage.
4. To formulate a fast release primary dose in a sustained released dosage form.
5. To formulate sustained release regimen of soluble drugs by using poorly soluble or insoluble carriers.
6. To reduce pre systemic inactivation of drugs like morphine and progesterone.
7. Polymorphs in a given system can be converted into isomorphous, solid solution, eutectic or molecular addition compounds.

FUTURE PROSPECTS

Despite many advantages of solid dispersion, issues related to preparation, reproducibility, formulation, scale up, and stability limited its use in commercial dosage forms for poorly water-soluble drugs. Successful development of solid dispersion systems for preclinical, clinical, and commercial use have been feasible in recent years due to the availability of surface-active and self-emulsifying carriers with relatively low melting points. The preparation of dosage forms involves the dissolving of drugs in melted carriers and the filling of the hot solutions into hard gelatin capsules. Because of the simplicity of manufacturing and scale up processes, the physicochemical properties and, as a result, the bioavailability of solid dispersions are not expected to change significantly during the scale up. For this reason, the popularity of the solid dispersion system to solve difficult bioavailability issues with respect to poorly water-soluble drugs will grow rapidly. One major focus of future research will be the identification of new surface-active and self-emulsifying carriers for solid dispersions. Only a small number of such carriers are currently available for oral use. Some carriers that are used for topical application of drug only may be qualified for oral use by conducting appropriate toxicological testing. One limitation in the development of solid dispersion systems may the inadequate drug solubility in carriers, so a wider choice of carriers will increase the success of dosage form development. Research should also be directed toward identification of vehicles or excipients that would retard or prevent crystallization of drugs from supersaturated systems. Attention must also be given to any physiological and pharmacological effects of carriers used. Many of the surface-active and self-emulsifying carriers are lipidic in nature, so potential roles of such carriers on drug absorption, especially on their inhibitory effects on CYP3-based drug metabolism and p-glycoprotein-mediated drug efflux, will require careful considerations.[18]

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Conflict of Interest

The author does not report any conflict of interest.

REFERENCES.

1. Bhanja S.B., Ellaiah P., Martha S.K.,Sahu A. and Padhy S.K. : Preparation and Evaluation of Solid Dispersions of Poorly Soluble Drug Repaglinide. Asian Journal of Biochemical and Pharmaceutical Research 2011; 1:201-221.
2. Reddy B. Basanta Kumar, and Karunakar A. : Biopharmaceutics Classification System: A Regulatory Approach. Dissolution Technologies 2011; 31-37.
3. Loyd V., Nicholas G. Popovich howard C. Ansel: Pharmaceutical dosage Forms and Drug Delivery Systems. Edition 8, 156.
4. Shaikh Siraj N. ,Khan Javeed G., Fakir Hina S., Shaikh Mohsin F., Shaikh Salman I., Shaoor Ahmad S. : Drug-Drug Solid Dispersion: A Unique Approach in Solubility Enhancement. International Journal of Pharma Research & Review 2016;5(1):19-27.
5. Aulton M.E.,: Pharmaceutics The science of Dosage Form Design. 156.
6. Patrick J.S.,:Martin's Physical Pharmacy and Pharmaceutical Sciences. Published by Lippincott Williams and Wilkins, 5th Edition, 53.
7. Remington-The Science and Practice of Pharmacy, Loppincott Williams and Wilkins, 21st Edition, 2006; 239.
8. Sareen Swati, Mathew George, Joseph Lincy,: Improvement in solubility of poor water-soluble drugs by solid dispersion. International Journal of Pharmaceutical Investigation. 2012;2(1):12-17.
9. Duncan Q.M.,:The mechanisms of drug release from solid dispersions in water-soluble polymers. International Journal of Pharmaceutics. 2002:231:131–144.
10. Kumar P.D., Arora Vandana,:Solid Dispersions: A Review. Journal of Pharmaceutical and Scientific Innovation. 2012:1(3)27-34
11. Singh Sameer, Baghel Raviraj Singh and Yadav Lalit,:A review on solid dispersion. International Journal Of Pharmacy and Life Sciences.2011:2(9):1078-1095
12. Singh Jaskirat, Walia Manpreet, Harikumar S L: Solubility Enhancement By Solid Dispersion Method: A Review. Journal of Drug Delivery & Therapeutics; 2013, 3(5), 148-155.
13. Argade P S, Magar D D, Saudagar R B, : Solid Dispersion:Solubility Enhancement Technique for Poorly Water Soluble Drugs. Journal of Advanced Pharmacy Education & Research.2013:3(4), 427-439.
14. Dhirendra K, Lewis S, Udupa N And Atin K: Solid Dispersions: A Review. Pakistan Journal Of Pharmaceutical Sciences.2009:22(2), 234-246.
15. Ladan Akbarpour Nikghalb, Singh Gurinder, Singh Gaurav and Kimia Fazaeli Kahkeshan : Solid Dispersion: Methods and Polymers to Increase the Solubility of Poorly Soluble Drugs. Journal of Applied Pharmaceutical Science. 2012:2 (10), 170-175.
16. Iswarya Sridhar, Doshi Abha, Joshi Bhagyashri, Wankhede Vandana, Doshi Jesal, :Solid Dispersions: an Approach to Enhance Solubility of poorly Water Soluble Drug. Journal of Scientific and Innovative Research. 2013; 2 (3), 685-694.
17. Pahwa Rakesh, Kataria Umang, Rana A.C., Rao Rekha, Nanda Sanju, : Solid Dispersion Technology : Recent Advancement In The Delivery of Various Phytoconstituents. International Journal of Pharmaceutical Sciences and Research. 2015;6(2), 510-520.
18. Abu T. M. Serajuddin : Solid Dispersion of Poorly Water-Soluble Drugs: Early Promises, Subsequent Problems, and Recent Breakthroughs. Journal of Pharmaceutical Sciences 1999; 88(10), 1058-1066.
19. Sapkal Sandip, Narkhede Mahesh, Babhulkar Mukesh, Mehetre Gautam, Rathi Ashish : Natural Polymers: Best Carriers For Improving Bioavailability Of Poorly Water Soluble Drugs In Solid Dispersions. Marmara Pharmaceutical Journal 2013; 65-70.

20. Gulia Ritu, chaudhary Hema, Hooda Aashima, Jain Nitin, : Solid Dispersion: A Promising And Prominently Considered Technique For Solubility Enrichment Of Poorly Soluble Drugs. International Journal Of Drug Formulation And Research 2013; 4(5), 1-11.
21. Jatinder Kaur, Geeta Aggarwal, Gurpreet Singh, A.C. Rana, : Improvement Of Drug Solubility Using Solid Dispersion. International Journal of Pharmacy and Pharmaceutical Sciences 2012; 4(2), 47-53.

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