

## An Overview on the Recent Technologies and Advances in Drug Delivery of Poorly Water-Soluble Drugs

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### Abstract:

Solubility can be defined as the amount of solute dissolved in a solvent at certain conditions to yield a single-phase system. Solubility of active pharmaceutical ingredients is considered the main parameter to get the most desired drug concentration in general circulation

in order to achieve the desired therapeutic effect. Poor aqueous solubility considered the main problem occurs in the formulation progress of new chemical entities; in addition to the standard improvement; solubility is the main dispute for formulation scientists. The drug must appear as solution at the site of absorption in order to be absorbed. Many physical or chemical modification techniques are used to improve the solubility of low aqueous soluble drugs, in addition to other techniques such as particle size reduction, crystal engineering, salt formation, solid dispersion, use of surfactant and complexation. The selection of the solubility improvement methods depends on drug characteristics, location of absorption and the features of the administered dosage form.

**Key words:** Bioavailability, chemical modification, physical modification, poorly soluble drugs.

نظرة عامة عن الطرق والتطورات الحديثة المستخدمة لتوصيل الادوية قليلة الذوبانية في الماء  
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### الخلاصة:

يمكن تعريف الذوبانية بانها كمية المادة المذابة في المذيب لتكوين مخلوط متجانس بظروف معينة تعتبر الذوبانية المادة الصيدلانية الفاعلة العامل الرئيسي المحدد لكمية الدواء الواصلة للدورة الدموية من اجل الحصول على الفعالية الدوائية المطلوبة. ان مشكلة الذوبانية القليلة هي احدى المشاكل الرئيسية التي تواجه الصيدلاني اثناء عملية التصنيع الدوائي, مما جعلها احدى اهم المواضيع الواجب دراستها ومعالجتها حيث يتوجب على الدواء ان يذوب اولا لأجل امتصاصه. ومن اجل هذا الغرض ممكن اتباع عدة طرق فيزيائية وكيميائية من اجل تحسين ذوبانية الادوية قليلة الذوبان مثل طحن وتصغير حجم الحبيبات الدوائية, هندسة شكل الحبيبات, تكوين الاملاح, تكوين المزيج الصلب بالإضافة الى استخدام المواد المقللة للشد السطحي او استخدام المعقدات. ان اختيار الطريقة المثلى تعتمد على الصفات المتعلقة بالحقن بالإضافة الى موقع الامتصاص والخصائص المتعلقة بالصيغة الدوائية.

**لكلمات المفتاحية:** التوافر الحيوي, التعديل الكيميائي, التعديل الفيزيائي, الادوية قليلة الذوبانية.

### Introduction

Solubility of drug defined as the maximum amount of solute that can be dissolved in a defined amount of solvent at a certain

temperature, this physical characteristic has a significant effect on the bioavailability and ultimately on the therapeutic efficacy of drug. There are many factors affecting drug solubility like

the nature and composition of solid in addition to the system properties like pressure and temperature <sup>[1]</sup>.

Since a significant number of drugs getting approvals have poor biopharmaceutical properties, as approximately 40% of approved drugs and nearly 90% of the developmental pipeline drugs consist of poorly soluble molecules. Generally, there are two strategies adapted by pharmaceutical companies in drug discovery to improve the aqueous solubility of drug molecule including physical and chemical modification of drug entities in addition to other miscellaneous technologies <sup>[2]</sup>.

Exploring a recent advances of insoluble drug delivery technologies will help in better therapeutic applications with improved patient compliance. On the other hand, the insoluble drug delivery technologies are being effectively utilized predominantly for commercial benefits through oral route by developing improved formulations. Therefore, further advancement in the insoluble drug delivery technologies and their exploration for new drug applications will be much more promising in coming years <sup>[3]</sup>.

#### **Factors affecting solubility:**

**Temperature:** This factor depends on the state of the solute, so in case of endothermic reactions an increase in the solution temperature can increase the solubility of the solid solute. While, if the solute was in gaseous state, its solubility decreased by increasing the temperature.

**Pressure:** Solubility increases with the application of pressure if the solute is in gaseous state while changes in pressure have no effect on solubility if the solute is in solids and liquid state.

**Particle size:** Although this factor mainly affecting the dissolution rate, an inverse relationship is observed between particle size and the surface area of drug molecule, small particle has a large surface area which allows a greater interaction with the solvent. This effect continues to a certain

limit (to 1  $\mu\text{m}$ ) at which any further reduction in the size might reduce the solubility. The effect of particle size on solubility can be describe by Eq.1

$$\log S/S^0 = 2\gamma V / 2.303RT r \dots\dots\dots \text{Eq. 1}$$

Where, S is the solubility of infinitely small particles,  $S^0$  is the solubility of large particles, V is molar volume, r is the radius of the fine particle <sup>[4]</sup>.

**Polymorphs:** It is defined as the presence of substance in more than one crystalline form have the same chemical structure but differ in physical properties such as melting point, solubility and dissolution. Generally the range of solubility differences between different polymorphs is only 2-3 folds due relatively small differences in free energy <sup>[5]</sup>.

**Polarity:** Polarity is considered as the main factor which influences drug solubility. The statement "Like dissolves like" means the polar solute dissolves in polar solvent and vice versa. The polar solute particle consists of positive and negative ends. When the solvent molecule is also polar in its nature, the negative end of polar solute will attract to positive end of the solvent molecule, this type of interactions between molecules called dipole-dipole interaction. There is another kind of force between molecules known as London dispersion forces where the positive nuclei of the atoms of the solute molecule will pull towards the negative electrons of the atoms of a solvent molecule. This gives the non-polar solvent a probability to solvate the solute molecules <sup>[6]</sup>.


#### **The need of the solubility:**

When drug administered orally its absorption affected by many factors such as drug aqueous solubility and drug permeability. The drug should be dissolved in gastric or intestinal fluids in order to pass through the membrane of GIT and reach the systemic circulation. Therefore, many

attempts were performed by the pharmaceutical researchers to enhance drug bioavailability by improving the solubility and the dissolution rate of low water-soluble drug [7]. Biopharmaceutical Classification System (BCS) based on drug

solubility, permeability and dissolution of the dosage form. According to biopharmaceutics classification system (BCS) system, drugs are classified into four groups as shown in table (1)

**Table 1: Biopharmaceutical classification system**

| BCS Class | Solubility | Permeability | Oral Dosage Form Approach   | Chances of Non-oral Dosage Form being Required                                      |
|-----------|------------|--------------|---|---|
| 1         | High       | High         | Simple solid oral dosage form   |  |
| 2         | Low        | High         | <ul style="list-style-type: none"> <li>• Techniques to increase surface area like particle size reduction, solid solution, solid dispersion</li> <li>• Solutions using solvents and/or surfactants</li> </ul> |   |
| 3         | High       | Low          | Incorporate permeability enhancers, maximize local luminal concentration  |   |
| 4         | Low        | Low          | Combine 2 and 3   |   |

Nearly all chemical entities are water insoluble lipophilic compounds, i.e. belong to Class II or Class IV compounds. For this reason, it is necessary for the pharmaceutical scientists to discover and adapt different technologies to enhance the solubility and hence the absorption and the bioavailability for such compounds [9].

**Different techniques used to enhance the solubility of poorly water-soluble drugs:**

**1. Physical modifications:**

There are various technologies to enhance the solubility by physical adaptation including:

- 1- Reduction of particle size by different methods:
  - a- Micronization by milling that is achieved by comminution
  - b- spray drying
  - c- Nanosuspension achieved generally by different techniques like homogenization and wet milling.
  - d- Sonocrystallisation
  - e- supercritical fluid process
- 2- The dispersion of drug in suitable carriers
  - a- Solid dispersions
  - b- Solid solutions
  - c- Eutectic mixtures

- 3- Cryogenic techniques
- 4- Crystal habit modification like:
  - a- Polymorphs
  - b- Pseudopolymorphs
  - c- Co-crystals
- 5- Solubilization by surfactants including:
  - a- Microemulsions
  - b- Self microemulsifying drug delivery systems
- 6- Inclusion complexation [10]

**Reduction of particle size:**

Generally, the solubility of a medication is often intrinsically related to the particle size of the medication. Therefore, reducing the particle size increases the surface area of the drug that exposed to the solvent which improves the dissolution properties of the drug. This can be achieved by:

**Micronization by milling:** This is a conventional method of particle size reduction that enhances the dissolution rate of the drug. It could be accomplished by comminution, they do so by imparting a significant amount of physical stress upon the drug which might cause degradation. Although, micronization cannot be used for drugs with high dose number because it

does not increase the saturated solubility<sup>[11]</sup>. Usually, comminution can be done by milling techniques like jet mill, rotor and stator colloid mills.

**Spray drying:** on the other hand, spray drying is a commonly used method for drying a liquid by the application of a hot gas. Typically, this hot gas is air, but it could be replaced by nitrogen gas for sensitive materials that require an oxygen-free drying such as pharmaceuticals and to evaporate solvents like ethanol. Spray drying is considered as a single step for drying and particle size reduction process which eliminates any additional steps<sup>[12]</sup>.

**Nanosuspensions:** They are a sub-micron colloidal dispersion (200-600 nm) of pure particles of drug, that stabilized by surfactants. They can be used for topical, oral, pulmonary or parenteral administration of the drug, and it is considered as promising technology for efficient delivery of hydrophobic products due to the enhancement in the dissolution rate due to creation of the larger surface area<sup>[13]</sup>. Furthermore, it offers a narrow particle size distribution range, avoiding the Ostwald ripening that occurs in the presence of concentration gradient. Although, there is one major concern in the conversion of the high-energy polymorphic form of the drug into a low energy crystalline form, which might have no therapeutic efficacy<sup>[14]</sup>. Nanosuspensions generally produced by either homogenization or wet milling. In the homogenization process the suspension is forced to pass under pressure through a valve that has nano aperture in a homogenizer, thus causing the water bubbles to collapse and cracking the drug particle. Usually three types of homogenizers are commonly used including sonicators, conventional homogenizers and high shear fluid processors. While in the wet milling procedure the drug is defragmented by milling in the presence of surfactants<sup>[15, 16]</sup>.

**Sonocrystallisation:** It involves the recrystallization of poorly soluble materials using liquid solvents and anti-solvents. Sonocrystallisation is considered as unique approach for particle size reduction on the basis of crystallisation by utilizing ultrasound power in the range of 20-100 kHz to induce nucleation and controlling the particle size distribution of the active ingredients<sup>[17]</sup>.

**Supercritical fluid (SCF) process:** It is a novel method for particle size reduction having the ability to give a narrow range nanoparticulate suspensions of particles (5-2000 nm in diameter). This technique uses a drug dissolved in a dense non condensable fluid known as supercritical fluid (usually CO<sub>2</sub>), whose temperature and pressure is greater than its critical temperature and critical pressure that allowing it to assume both liquid and gas properties. Therefore, This SCF is highly compressible at points near its critical temperature, allowing a significant change in the density and the mass transport property of that liquid upon a moderate change in its pressure causing a recrystallization of the dissolved drug with a greater reduction in its particle size<sup>[18]</sup>.

**Dispersion of drug in a suitable carrier:** This technique involves the spreading of the drug within an inert carrier system of powder, it involves three types of mixtures: **Solid dispersion:** It refers to the dispersion of one or more hydrophobic drug(s) in an inert hydrophilic carrier in a solid form<sup>[19]</sup>. It was discovered in early 1961 as an approach that enhances the dissolution of poorly soluble ingredient due to particle size reduction, increase wettability and porosity in addition to the possible conversion of the drug to the metastable form<sup>[20,21]</sup>. Table 2 summarizes the main types of the hydrophilic carriers that could be used in the formulation of solid dispersion.

Commonly, it can be prepared by three methods Hot-Melt Method (Fusion

Method), solvent evaporation and Hot-Melt Extrusion method.

**Hot-melt or fusion method:** It is a simple and economical method that was first suggested by Sekiguchi and Obi. A physical mixture of the drug along with a water-soluble polymer is heated until the two are melted, this followed by cooling rapidly in an ice bath to permit solidification with vigorous stirring. Finally, the solid mass is crushed and screened to be formulated in the suitable dosage form like a tablet. Although, there are certain points should be considered when selecting this method, like stability of both drug and polymer upon heating in addition to the miscibility of the drug in the molten carrier. Furthermore, the melting point of the binary mixture depends on the type of the polymer in addition to the weight fraction of the drug <sup>[22]</sup>.

**Solvent evaporation method:** This method can be performed by dissolving the drug and the carrier in a common solvent,

followed by solvent evaporation under vacuum. It was first discovered by Tachibana and Nakamura to overcome the problem of thermal decomposition of both drug and carrier because of the low temperature required to evaporate the solvent. However, it has some drawbacks represented by its high cost and difficulties in the complete removing of the organic solvent, in addition to other difficulties in the selection of the common solvent for both drug and carrier <sup>[23]</sup>.

**Hot-Melt Extrusion method:** This method basically the same as a traditional fusion method, but the intense mixing of the component here is performed by an extruder. It has the same difficulties like fusion method, though, it has the privilege on the traditional fusion method by offering a continuous production, making it more suitable for large-scale, moreover, it is providing easier to handle product which avoids the grinding step by manipulating the outlet of the extruder and hence the shape of the product <sup>[24]</sup>.

**Table 2: hydrophilic carriers used in solid dispersion**

| No. | Chemical class      | Examples                                   |
|-----|---------------------|--|
| 1   | Acids               | Citric acid, tartaric acid                 |
| 2   | Sugars              | Dextrose, sucrose, sorbitol                |
| 3   | Polymeric materials | PVP, PEG-4000, cellulose                   |
| 4   | Surfactants         | Polyoxyethylene stearate, tweens and spans |
| 5   | Miscellaneous       | Urea, urethase                             |

Solid solution: it is a binary system consisting from solid solute that is molecularly dispersed in a solid solvent in the form of homogeneous one phase system. Usually, it can be classified by two ways, either according to the extent of miscibility between the two excipients (continuous or discontinuous solid solutions), or according to the size of the

two materials forming the solid solution (Substitutional or interstitial solid solution) <sup>[25]</sup>.

Continuous solid solution: In this type the two components of the solid solution are completely miscible in all proportions (Fig. 1). Furthermore, the total lattice energy for the mixture is greater than that of each solid component.



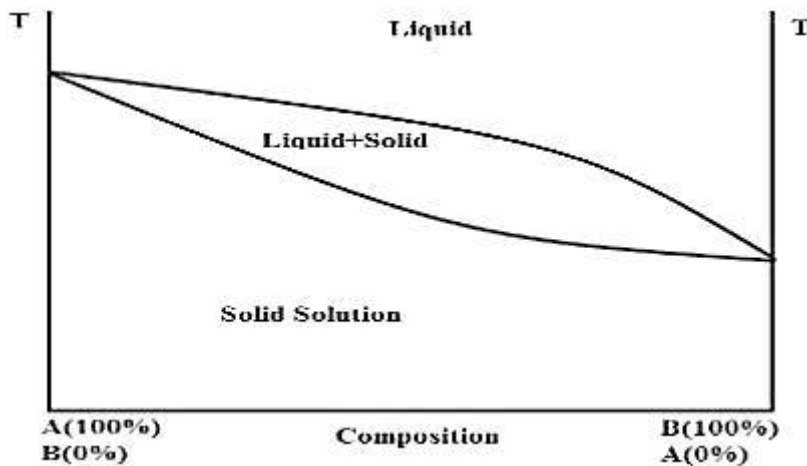


Figure 1: Illustrative representation of continuous solid solution [25]

**Discontinuous solid solution:** In contrast to the continuous solid solution, in this type there is a little solubility of the solute in the solid solvent. Figure 2 demonstrates the area of solid solution

as  $\alpha + \beta$  region that became narrower at higher temperature. Moreover, each component can dissolve the other to a certain degree above the eutectic temperature.

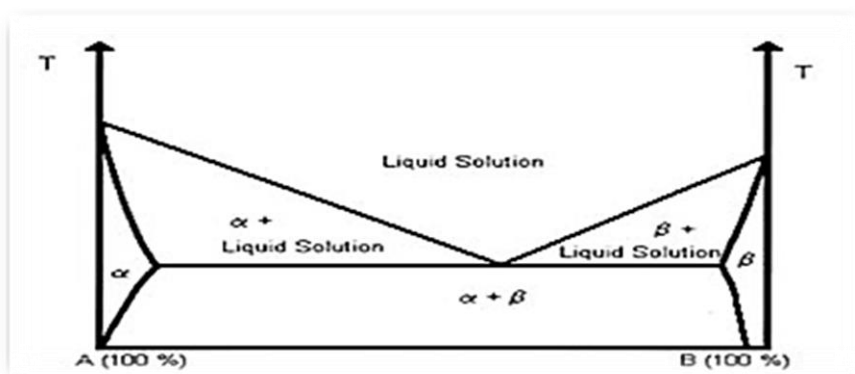


Figure 2: Illustrative representation of discontinuous solid solution [25]

**Substitutional solid solution:** In this type, the size of both solid solute and solvent should be close together, so that the solid solute could substitute the solid solvent in the crystal lattice of the solid solution and could be either continuous or discontinuous, as shown in Figure 3. Examples of this type of solid solution, Anthracene- Acenaphtalene, and ammonia- Potassium thiocyanate.

**Interstitial solid solution:** Here the size of the solute (guest) should be small enough to fit in the interstitial spaces of the solid solvent (host), and generally constitutes a discontinuous solid solution (Fig. 3). Examples of this type solid solution of digoxin, methyl testosterone, prednisolone acetate, hydrocortisone acetate in PEG-6000 matrix [26].

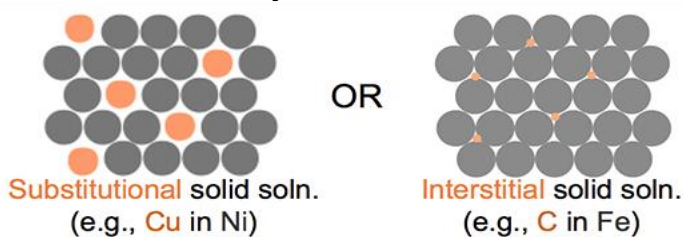
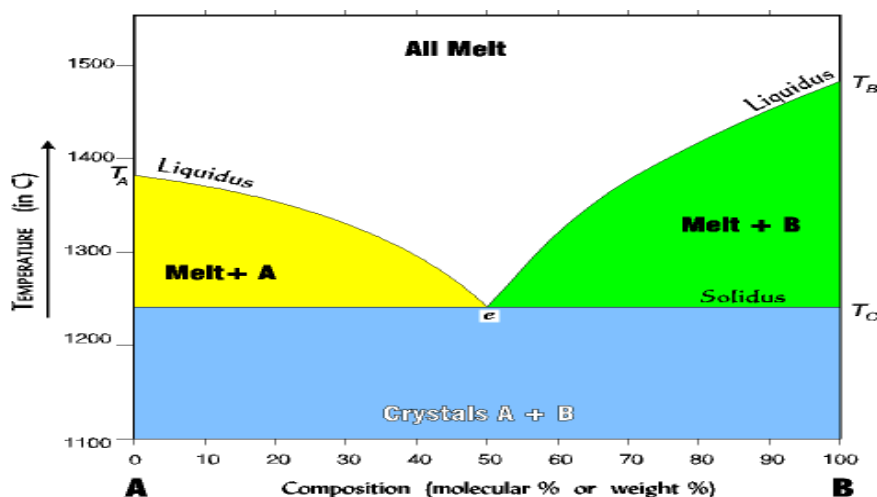


Figure 3: Illustrative representation of substitutional, and interstitial solid solution

**Eutectic mixtures:** A eutectic mixture comes from Greek “easily melted”, it is a homogeneous mixture of two compounds that melts and solidifies at single temperature that is lower than the melting point of each one alone. Figure 4 illustrates the eutectic mixture composition, where, the liquidus line separates the melt +

crystals from the all melt phase, while, the solidus line separates the all crystal phase from the melt + crystal phase. These lines were determined experimentally by melting and cooling several mixtures at different percent composition, and the point at which all phases exists together is called the eutectic point <sup>[27]</sup>.



**Figure 4: Graphical demonstration of eutectic mixture** <sup>[27]</sup>

#### **Cryogenic techniques:**

This technology enhances the rate of dissolution by producing a nano size drug with amorphous highly porous structure at a very low temperature. Different cryogenic methods were invented depending on the composition of the cryogenic liquid (N<sub>2</sub>, Ar, hydrofloroalkanes, O<sub>2</sub> or organic solvents), type of the device used for injection (rotary, capillary, pneumatic or ultrasonic nozzle) or depending on the nozzle location (above or below the liquid surface). Finally, a dry porous powder is usually obtained by different drying methods, including atmospheric freeze drying, spray freeze drying, lyophilisation and vacuum freeze drying <sup>[28]</sup>. Consequently, this technique can be classified into:

**Spray freezing into cryogenic liquids (SFL):** This method involves the direct incorporation of a liquid-liquid impaction between the cryogenic liquid and the automatized feed solution providing powerful atomization into micro droplets that result in a faster freezing rate. Then the

frozen materials lyophilized to obtain dry and free-flowing micronized powders of high porosity and wettability <sup>[29]</sup>.

**Spray freezing onto cryogenic fluids:** In this technology, an aqueous dispersion of the drug in a suitable carrier like (maltose, inositol, lactose, mannitol or dextran) was atomized above the surface of a boiling agitated freezing fluorocarbon. A sonication probe can be placed in the agitated refrigerant to enhance the dispersion of the aqueous solution within the cryogenic material <sup>[30]</sup>.

**Spray freezing into vapour over liquid (SFV/L):** Here, the drug solution is frozen in cryogenic liquid vapour followed by the removal of the frozen solvent creating a fine particle with a high porosity. The nucleation of the fine drug particle in this process actually resulted from the supersaturation of the unfrozen region in the atomized droplet, resulting from the rapid freezing of its solvent as it passes through the vapour phase before contacting the cryogenic liquid <sup>[31]</sup>.

**Ultra-rapid freezing (URF):** It is a novel cryogenic technology that creates nanostructured particles by using the solid cryogenic material. A drug solution is directly exposed to a solid surface of cryogenic substrate causing direct freezing and lyophilization (removal of the solvent) forming micronized drug powder with improved solubility. Ultra-rapid freezing in this technique prevents phase separation and crystallization of the drug leading to well mixed, amorphous drug-carrier solid dispersions, and solid solution <sup>[32]</sup>.

#### **Crystal habit modification:**

This process offers a useful method for enhancing the solubility and dissolution rate and hence, the bioavailability of the hydrophobic medications. In addition, it developed to give high purity particles with distinct particle size distribution, crystal habit, crystal form (amorphous or crystalline), surface energy and surface nature. This can be achieved by preparing crystals with different packing structures (polymorphs), the incorporation of water or solvent (hydrate or solvate), or by the addition of other component (co-crystals) in addition to the commonly known methods of recrystallization and solid dispersion <sup>[33]</sup>.

**Polymorphs:** It is the ability of the active ingredient to exist in more than one crystalline form, that possessing variant physicochemical and biological properties such as vapor pressure, melting point, shelf life, morphology, solubility, bioavailability and efficacy. Generally, it can be assumed one of two types, enantiotropic (in which one form can change into another at certain transition temperature below the melting point), or monotropic (where no transition is possible). Usually the metastable crystalline polymorph form having higher energy and solubility than stable polymorph.

Some materials are existing in amorphous form (with no internal crystal structures), such material will possess higher energy and solubility than both crystalline forms.

Therefore, we can arrange materials according to their order of solubility into, amorphous > metastable polymorph > stable polymorph <sup>[34]</sup>.

**Pseudopolymorphs (hydrates and solvates):** Crystal modification also includes the formation of hydrate or solvate to enhance the dissolution rate of poorly soluble drugs. This can be achieved by incorporation of solvent molecules within the lattice structure of the material during the crystallization process. If the solvent is water, then the resultant product called hydrate, while if any other solvent was used it called solvate. These solvate and hydrate can exist in more than one crystalline form and called pseudopolymorphs. Furthermore, they have lower energy for crystal breaking comparing to the unhydrous forms, e.g. the pentane or toluene solvate form of the antidiabetic glibenclamide possess greater solubility and dissolution rate than the non-solvated polymorph <sup>[35]</sup>.

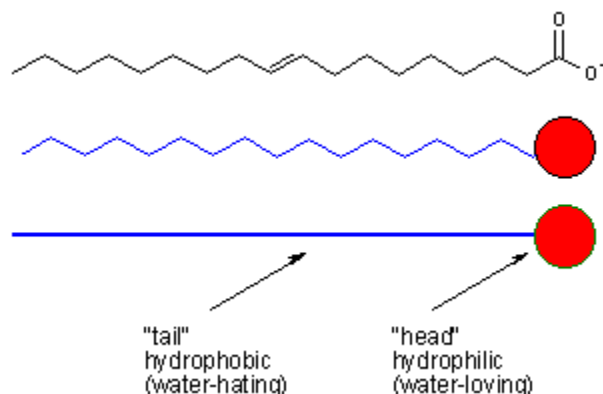
**Co-crystals:** this method opens a new way to resolve the problems of the low solubility drugs. These consist of two or more molecules arranged together, creating a new crystal form that has better properties than separate molecules. This was achieved by combining ionic or molecular drug with co-crystal former material, via slow evaporation of the drug solution containing stoichiometric amount of the co-crystal former. Though, there are other suitable methods like growth from melt, sublimation, or milling of two or more co-crystal formers in ball mill. Example of this technology is the co-crystal of carbamazepine: saccharin which has better solubility, stability, and oral absorption than each one alone <sup>[36]</sup>.

#### **Solubilization by surfactants:**

It is one of the oldest methods for improving the solubility and dissolution properties of poorly soluble drugs. Surfactants are molecules having both polar and nonpolar parts (most commonly hydrocarbons) as shown in Figure 5. It can



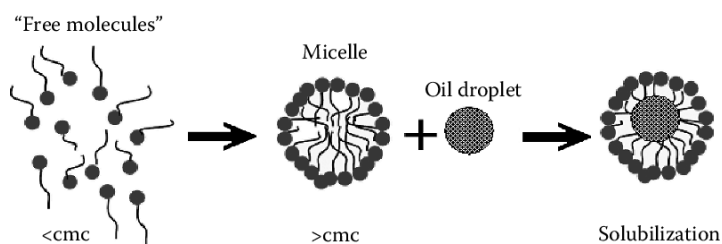
be classified depending on the type of the polar part into anionic, cationic, zwitterionic or non-ionic [37].



**Figure 5: Structure of the surfactant** [37]

The surfactants have many benefits like reducing surface tension, stabilization of suspensions and increasing the wettability of particles, Furthermore, it is also used to increase the solubility of lipophilic drugs in concentration above that its critical micelle

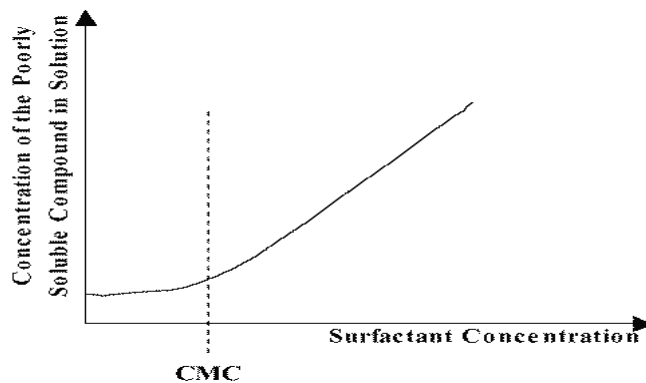
concentration (CMC) that is in the range of 0.05%-0.10% of most types, due to the entrapment of the drug in the hydrophobic core of the micelle [38] as shown in Figure 6.



**Figure 6: Solubilisation effect of the micelle** [38]

The solubilisation curve of the surfactant is illustrated in Figure 7. It clearly shows that the concentration of poorly soluble compound is constant when the surfactant present as monomer

in solution below CMC, however, above the CMC it is shown clearly that the concentration of the solute will increase linearly with increasing surfactant concentration [39].



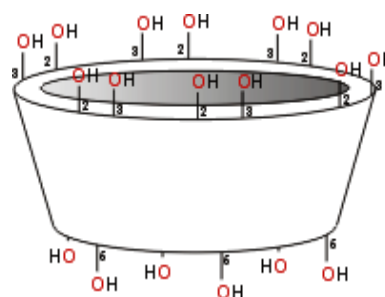
**Figure 7: Solubilisation curve of surfactant** [39]

**Microemulsions:** It is a four-component system containing internal and external phases in addition to the surfactant: co-surfactant mixture. Unlike the co-surfactant, the surfactant is usually soluble in the internal phase, which results in the formation of a transparent, clear, isotropic and thermodynamic system which can enclose both hydrophilic or lipophilic moieties in their internal phase (O/W or W/O), so acting as a potential reservoir of lipophilic or hydrophilic drugs, respectively [40,41].

**Self microemulsifying drug delivery systems (SMEDDS):** They are generally isotropic mixtures consisting of the drug with lipids and surfactant, in addition to one or more hydrophilic co-solvent or co-emulsifier, having a droplet size ranging from 10-100 nm. SMEDDS have the advantage of greater improvement in drug solubility, stability and bioavailability, with high loading capacity and little inter-subject and intra-subject variability. However, this system may have certain drawbacks represented by the chemical instability at high surfactant concentration, lack of the in-vitro assessment model, in addition to the possible precipitation of the lipid inside hard or soft gel capsules due to the migration of the volatile solvent to the capsule shell [42].

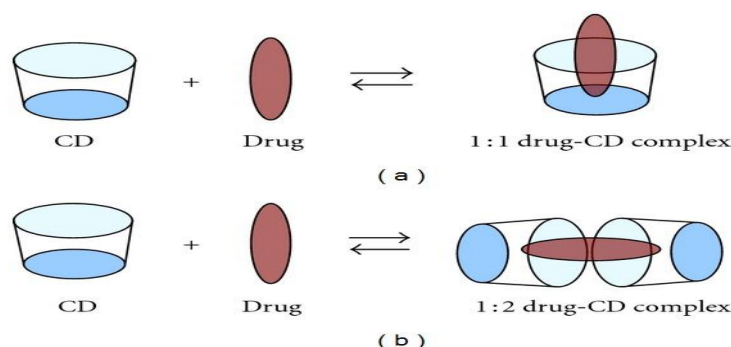
**Inclusion complexation:** This technique was one of the widely used methods for enhancing the solubility,

dissolution properties and bioavailability for the poorly soluble compounds. It is made by the insertion of the nonpolar molecule (guest molecule) in the cavity of another molecule (host molecule). Cyclodextrin (CD) is considered one of the most common examples of the host molecule. It is a cyclic oligo-saccharide consisting of glucose molecules arranged in a donut shape ring with a hydrophobic cavity and external hydrophilic surface due to the presence of OH groups (Fig. 8), usually formed from starch degradation by the effect of cyclodextrin-glycosyltransferase (CGT).



**Figure 8: The structure of cyclodextrin** [43]

Generally, there are three types of the naturally occurring CDs, including  $\alpha$ - cyclodextrin,  $\beta$ -cyclodextrin and  $\gamma$ - cyclodextrin. The major prerequisite of the inclusion complex formation is the fitting of the guest molecule in the cavity of the host molecules; therefore, the host cavity should be small enough to exclude any water and large enough to fit the guest molecule. Consequently, there are two possibilities of the drug: cyclodextrin complex; 1:1 or 1:2 (Fig. 9); depending on the structure and property of the drug molecule [43].



**Figure 9: Cyclodextrin inclusion complex** [43]

Different methods can be used for the preparation of the inclusion complexes, these include:

- ❖ **Microwave irradiation method:** This technology is considered as a novel technology for industrial scale due to its high percentage yield and shorter time of reaction. It involves the microwave irradiation reaction between the drug and the complexing agent using a microwave oven. Using a round bottle flask, a certain molar ratio of the drug and CD mixture are dissolved in a mixture of organic solvent and water in a specific ratio. This mixture allowed to react in the microwave oven at 60 °C for 1-2 minutes. Followed by the addition of a certain volume of the solvent mixture in order to eliminate the un-complexed drug or CD, and filtration in Whitman filter paper and drying at 40 °C in vacuum filter [44].

**Kneading method:** It is the most common method for the preparation of inclusion complexes due to its simplicity and low production cost. This technique involves the formation of CD paste after soaking with a little amount of aqueous or hydroalcoholic solution, followed by the addition of the drug to the previous paste and kneaded for a certain time, after that drying and screening performed to get the final product. The process of kneading can be established on a small-scale using mortar and pestle, while, in large scale, it can be achieved by extruder or any other machine [45].

**Freeze-drying or lyophilisation method:** This technique generally used for thermo-labile product in order to obtain amorphous powder with a high degree of porosity and interaction between the drug and CD. It is performed by molecular mixing of the drug and carrier in a suitable solvent, followed by subsequent drying of the solution by freezing and subsequent drying under low pressure. Although, this method has certain disadvantages like poor flow properties of the resultant product in addition to its time-

consuming nature and the requirement of special equipment [46].

**Chemical modification techniques:** these generally include different methods including:

- 1-Salt formation
- 2-Pro-drug technology
- 3-Co-solvency method

**Salt formation:**

Salt formation is considered one of the different methods used to enhance the solubility and increase the dissolution rates of weakly acidic or basic drugs by transforming the drugs to their particular salt form, e.g. clindamycin solubility elevated in a significant approach when transformed to clindamycin phosphate and the solubility is significantly elevated from 3mg/ml to 150mg/ml due to salt formation [47].

**Pro-drug technology:**

It is a procedure of drug modification where the drug moiety binds with inert delivery carrier or matrix. Sometimes the unstable nature of the active ingredients leads to the degradation of the drugs outside the body which consequently gives a lower solubility of drug. When pro-drug is administered, the covalent bond between the drug and inert delivery carrier is broken down and drug is offered in its parent form inside body or in short term it can be said that pro-drug is effective inside the body and where drug material gives its optimum pharmacological effect with best solubility. Cyclophosphamide (anti-cancer drug) is pro-drug and its active metabolite in body is 4-hydroxy cyclophosphamide [48].

**Co-solvency method:**

This method used to increase the solubility of poorly soluble drugs in water by addition of external aqueous solvent such as poly ethylene glycol (PEG-400), propylene glycol (PG) and glycerol which are used as recognized co-solvents and the process called co-solvency. Co-solvent technique works by diminish the interfacial tension between the aqueous solution and

hydrophobic solute. Nearly all co-solvents have hydrogen bond donor and/or acceptor groups in addition to small hydrocarbon regions. Their hydrophilic hydrogen-bonding groups guarantee water miscibility, while their hydrophobic hydrocarbon regions impede with waters hydrogen bonding group, lead to reduction in the on the whole intermolecular attraction of water. The solubility of etoricoxib can be enhanced by co-solvency technique using PEG 400 [49,50].

**Miscellaneous methods:**

**Liquisolid method:**

By this method liquid is possibly converted into free flowing, readily compressible and seemingly dry powder by simple blending with chosen carrier and coating material. The liquid part which can be drug suspension or drug solution in an appropriate non-volatile liquid medium can be changed into adequately flowing and compressible powders by combination

with chosen powder additives as shown in table 3. The satisfactory flowing and compressible powder form of liquid drug is liquisolid compact. The liquisolid considered as a novel and economical approach because of easy manufacturing method, the cost of manufacture low and appropriate for industry because of good flow and compact property of liquisolid formulation. When the drug dissolved in the liquid medium is included into a carrier substance which has a porous surface and directly matted fibres in its interior as cellulose, both absorption and adsorption happen; i.e. the liquid at first absorbed in the interior of the particles is retained by its internal structure, and after the saturation of this process, adsorption of the liquid onto the internal and external surfaces of the porous carrier particles occur. Then, the coating material having high adsorptive characteristics and large precise surface area gives the liquisolid system the wanted flow uniqueness [51-53].

**Table 3: Components of Liquisolid System**

| Component                  | Examples  |
|----------------------------|---|
| Non-Volatile Liquids       | Poly Ethylene Glycol 200, Poly Ethylene Glycol 300, Poly Ethylene Glycol 400, Glycerine, Propylene Glycol, fixed oils.  |
| Carrier Materials          | Microcrystalline Cellulose PH 101, Microcrystalline Cellulose PH 200, Lactose, Methyl Cellulose, Ethyl Cellulose, Starch1500, Ethocel, Eudragit RL, Eudragit RS 12, Hydroxy Propyl Methyl Cellulose K4M, Hydroxy Propyl Methyl Cellulose K100M, Xanthum Gum, Guar gum |
| Coating Materials          | Aerosil 200, Silica (Cab-O-Sil M5), Syloid 244FP, and Colloidal Silicon Dioxide   |
| Disintegrants              | Sodium Starch Glycolate (Explotab, Primogel), Croscarmellose Sodium, Cross Polyvinyl Pyrrolidine, Pregelatinized Starch   |
| Glidant                    | Talc  |
| Lubricant                  | Magnesium Stearate  |
| Release retardant material | Eudragit RS, RL, Hydroxy Propyl Methyl Cellulose K100M, K15M, K4M.  |

**Direct capsule filling method:**

This was achieved by direct filling of the liquid melt of solid dispersion inside a hard gelatin capsules avoiding by that the changes in crystalline nature that is induced by milling. Furthermore, the solidification

process of the molten dispersion upon cooling occurs inside the sealed capsule, reducing by that dusting and cross contamination during the powder filling process, in addition to a less weight

variation and content uniformity problems<sup>[54]</sup>.

#### **Electro-spinning method:**

This can be considered as the cheapest and simplest technology for producing solid dispersion in the future. It is achieved by passing a potential between 5 and 30 kV into a liquid stream of drug and polymer mixture which produces a submicron fiber when the electrical force overcomes the surface tension at the surface drug/polymer solution. For this reason, this method has a great potential for nanofibers preparation and controlling the release of biomedicines<sup>[55]</sup>.

#### **Dropping method solution:**

In this process a blank tablet was compressed using dicalcium phosphate dihydrate as a diluent with different concentrations of super disintegrants, followed by dropping of the drug solution on the tablet using a special microsyringe. This method has the advantage of avoiding solvent evaporation problems as it doesn't contain any organic solvents<sup>[56]</sup>.

#### **Functional polymer technology:**

Generally, Polymers play an important role in improving the bioavailability of drug product. For example, Eudragit derivatives are used to enhance the solubility of poorly soluble drugs like Eudragit E 30D (ethyl prop-2-enoate; methyl 2-methylprop-2-enoate) and Eudragit E (butyl 2-methylprop-2-enoate); both that can be used to enhance the felodipine and carbamazepine aqueous solubility<sup>[57]</sup>.

#### **Conclusions:**

The solubility of the drug in the GIT is the rate limiting step in the absorption of poorly soluble drugs and hence its bioavailability at its site of action. For this reason, various technologies could be implemented to achieve this goal. The selection of the proper method to increase the solubility of a specific product depends

on the properties of the given product, the dosage form requirement and the special requirements for both drug and excipients, in addition to the cost and the yield of the given process.

#### **References:**

- 1- Swarbrick J. Encyclopedia of Pharmaceutical Technology. Informa Health Care, New York. 2007.
- 2- Lipinski CA. Drug-like properties and the causes of poor solubility and poor permeability. Journal of Pharmacological & Toxicological Methods. 2000; 4(4): 235-249.
- 3- Sandeep K, Vijay KN. Insoluble drug delivery strategies: review of recent advances and business prospects. Acta Pharmaceutica Sinica B. 2015; 5(5):442-453.
- 4- Lindenberg M, Kopp S, Dressman J. Classification of orally administered drugs on the WHO model list of essential medicines according to biopharmaceutical classification system. European Journal of Pharmaceutics and Biopharmaceutics. 2004; 58: 265-278.
- 5- Sharma N, Bharkatiya M. Solubility enhancement techniques: A review. International Journal of Pharmaceutical Erudition. 2011;1(3): 40-53.
- 6- Bharti PV, Attal RV, Munde AV, Birajdar AS, Bais S. Strategies to enhance solubility and dissolution of a poorly water-soluble drug. Journal of Innovations in Pharmaceutics and Biological Sciences. 2015; 2(4): 482-494.
- 7- Patil MS, Godse SG, Saudagar RB. Solubility enhancement by various techniques: An overview. World Journal of Pharmacy and Pharmaceutical Sciences. 2013; 2(6): 4558-4572.
- 8- Chiou WL, Riegelman S. Pharmaceutical application of solid dispersion. Journal of Pharmaceutical Sciences. 1971; 60 (1):1281-1302.



- 9- Sharma PK, Chaudari PD, Badagale MM, Kulkarni KA, Barate NS. Current trends in solid dispersion techniques. *Pharmaceutical Reviews*. 2006.
- 10- Vilas PB, Vinayta RA, Anirudha VM, Arunadevi SB, Sanjay B. Strategies to enhance solubility and dissolution of a poorly water-soluble drug. *Journal of Innovations in Pharmaceuticals and Biological Sciences*. 2015; 2 (4): 482-494.
- 11- Christopher VD, Parimalakrishnan S, Jeganathan NS, Anbazhagan S. Techniques to enhance solubility of hydrophobic drugs: an overview. *Asian Journal of Pharmaceutics*. 2016; 10(2): 67-75.
- 12- Maa YF, Nguyen PA, AndyaJ D, Dasovich N, Sweent TD, Shire SJ, Hsu CC. Effect of spray drying and subsequent processing conditions on residual moisture content and physical/biochemical stability of protein inhalation powders. *Pharmaceutical Research*. 1998; 15(1): 768-775.
- 13- Muller RH, Jacobs C, Kayer O. Nanosuspensions for the formulation of poorly soluble drugs. In *Pharmaceutical Emulsion and Suspension*, edited by Nielloud F and Marti-Mestres G. Marcel Dekker, New York, NY, USA. 2000; pp. 383-407.
- 14- Ketan TS, Anuradha KG, Jignasa KS. Drug solubility: importance and enhancement techniques. *International Scholarly Research Network*. 2012; 1(1): 1-10.
- 15- Nash RA. Suspensions. In *Encyclopedia of Pharmaceutical Technology*, edited by Swarbrick J and Boylan JC. Marcel Dekker, New York, NY, USA. 2002; 2nd ed: pp. 2045-3032.
- 16- Chowdary KP and Madhavi BL. Novel drug delivery technologies for insoluble drugs. *Indian Drugs*. 2005; 42(9): 557-564.
- 17- Emara LH, Badr RM, Elbary AA. Improving the dissolution and bioavailability of nifedipine using solid dispersions and solubilizers, *Drug Development and Industrial Pharmacy*. 2002; 28(1): 795-807.
- 18- Perrut M, Jung J, Leboeuf F. Enhancement of dissolution rate of poorly soluble active ingredients by supercritical fluid processes Part II: Preparation of composite particles. *International Journal of Pharmaceutics*. 2005; 288(1): 11–16.
- 19- Jinal NP, Dharmendra MR, Nirav AP, Moin KM. Techniques to improve the solubility of poorly soluble drugs. *International Journal of Pharmacy & Life Sciences*. 2012; 3(2): 1459-1469.
- 20- Sareen S, Mathew G, Joseph L. Improvement in solubility of poor water-soluble drugs by solid dispersion. *International Journal of Pharmaceutical Investigation*. 2012; 2(1): 12-17.
- 21- Kumar SK, Sushma M, Raju PY. Dissolution enhancement of poorly soluble drugs by using complexation technique: A review. *Journal of Pharmaceutical Sciences and Research*. 2013; 5(1): 120-124.
- 22- Chiou WL, Riegelman S. Pharmaceutical applications of solid dispersion systems. *Journal of Pharmaceutical Sciences*. 1971; 60(9): 1281-1302.
- 23- Satish KP, Kalpesh SW, Venkatesh BP, Anup MA, Dheeraj TB. Strategies for solubility enhancement of poorly soluble drugs. *International Journal of Pharmaceutical Sciences Review and Research*. 2011; 8(2): 74-80.
- 24- Abdul-Fattah AM, Bhargava HN. Preparation and in vitro evaluation of solid dispersions of halofantrine. *International Journal of Pharmaceutics*. 2002; 235(2):17-33.
- 25- Kapoor B, Kaur R, Kour S, Behl H, Kour S. Solid dispersion: An evolutionary approach for solubility enhancement of poorly water-soluble

- drugs. *International Journal of Advances in Pharmaceutical Research*. 2012; 2(1): 1-6.
- 26- Mahesh IL, Milan A, Amit S, Shailesh S. Solubility Enhancement techniques for poorly soluble drugs: A review. *International Journal of Pharmaceutical Research and Development*. 2012; 4(4): 71-86.
- 27- Shargel L, Wu-Pong S, Andrew BC. *Applied Biopharmaceutics and pharmacokinetics*. McGraw-Hills Access Pharmacy, 5th ed., 2004.
- 28- Leuenberger H. Spray freeze-drying- the process of choice for low water-soluble drugs. *Journal of Nanoparticle Research*. 2002; 4(2): 111-119.
- 29- Rogers TL, Hu J, Yu Z, Johnston KP and Williams RO. A novel particle engineering technology: spray-freezing into liquid. *International Journal of Pharmaceutics*. 2002; 242(2): 93-100.
- 30- Briggs AR and Maxwell TJ. Process for preparing powder blends. US Patent no. 3721725, 1973.
- 31- Buxton IR and Peach JM. Process and apparatus for freezing a liquid medium," US Patent no. 4470202, 1984.
- 32- Purvis T, Mattucci ME, Crisp MT, Johnston KP and Williams RO. Rapidly dissolving repaglinide powders produced by the ultra-rapid freezing process. *AAPS PharmSciTech*. 2007;8(3): 58-68.
- 33- Blagden N, de Matas M, Gavan PT, and York P. Crystal engineering of active pharmaceutical ingredients to improve solubility and dissolution rates. *Advanced Drug Delivery Reviews*. 2007; 59(7): 617-630.
- 34- Raza K, Kumar P, Ratan S, Malik R, Arora S. Polymorphism: The phenomenon affecting the performance of drugs. *SOJ Pharm Sci*. 2014; 1(2):10-25.
- 35- Ritika, Harikumar SL, Aggarwal G. Formulation tactics for the delivery of poorly soluble drugs. *International Journal of Pharm Tech Research*. 2012; 4(1): 914-923.
- 36- Shan N and Zaworotko MJ. The role of cocrystals in pharmaceutical science. *Drug Discovery Today*. 2008; 13(10): 440-446.
- 37- A. Martin. *Physical Pharmacy*. Willaims and Wilkins, Baltimore, Md, USA, 4th ed., 1993.
- 38- Rangel-Yagui CD, Pessoa A, and Tavares LC. Micellar solubilisation of drugs. *Journal of Pharmacy and Pharmaceutical Sciences*. 2005; 8(2): 147-163.
- 39- Lieberman HA, Rieger MM, and Banker GS. *Pharmaceutical Dosage Forms: Disperse Systems*. New York, Marcel Decker, 2nd ed., 1996.
- 40- Yasser QA, Zainab HM, Nidhal KM. Preparation and in vitro evaluation of montelukast sodium oral nanoemulsion. *International Journal of Applied Pharmaceutics*. 2018; 10(5): 49-53.
- 41- Rawat S, Derle DV, Parve BS, Shinde PR. Self-emulsifying drug delivery system (SEDDS): A method for bioavailability enhancement. *International Journal of Pharmaceutical Chemical and Biological Sciences*. 2014; 4(2): 479-94.
- 42- Rawat S, Jain SK. Solubility enhancement of celecoxib using cyclodextrin inclusion complexes. *European Journal of Pharmaceutics and Biopharmaceutics*. 2004; 57(3): 263-267.
- 43- Wen X, Tan F, Jing Z, and Liu Z. Preparation and study of the 1:2 inclusion complex of carvedilol with  $\beta$ -cyclodextrin. *Journal of Pharmaceutical and Biomedical Analysis*. 2004; 34(3): 517-523.
- 44- Parikh RK, Mansuri NS, Gohel MC, and Soniwala MM. Dissolution enhancement of nimesulide using complexation and salt formation techniques. *Indian Drugs*. 2005; 42(3): 149-154.

- 45- Cao F, Guo J, and Ping Q. The physicochemical characteristics of freeze-dried scutellarin-cyclodextrin tetra-component complexes. *Drug Development and Industrial Pharmacy*. 2005; 31(8):747-756.
- 46- Patravale VB, Date AA, and Kulkarni RM. Nanosuspensions: a promising drug delivery strategy. *Journal of Pharmacy and Pharmacology*. 2004; 56(7): 827-840.
- 47- Vimalson D C, Parimalakrishnan S, Jeganathan N.S, Anbazhagan S. Techniques to enhance solubility of hydrophobic drugs: An overview. *Asian Journal of Pharmaceutics*. 2016; 10 (2): 67-75.
- 48- Vishweshwar P, McMahon JA, Bis JA, Zaworotko MJ. Pharmaceutical co-crystals. *Journal of Pharmaceutical Sciences*. 2006; 95(3): 499-516.
- 49- Shan N, Zaworotko MJ. The role of co-crystals in pharmaceutical science. *Drug Discovery Today*. 2008; 13(9): 440-446.
- 50- Hickey MB, Peterson ML, Scoppettuolo LA. Performance comparison of a co-crystal of carbamazepine with marketed product. *European Journal of Pharmaceutics and Biopharmaceutics*. 2007; 67(1): 112-119.
- 51- Rautio J, Kumpulainen H, Heimbach T, Oliyai R, Järvinen T, Savolainen J. Prodrugs: Design and clinical applications. *Nature Reviews Drug Discovery*. 2008; 7(1): 255-70.
- 52- Faiyaz S, Fars KA, Ibrahim A, Nazrul H. Solubility prediction of indomethacin in PEG 400+water mixtures at various temperatures. *Journal of Molecular Liquids*. 2013; 188(1): 28-32.
- 53- Chandel P, Raj k, Kapoor A. A liquisolid technique; an approach for enhancement of solubility. *Journal of drug delivery and Therapeutics*. 2013; 3(4): 131-137.
- 54- Mogal SA, Gurjar PN, Yamgar DS, Kamod AC. Solid dispersion technique for improving solubility of some poorly soluble drugs. *Der Pharmacia Lettre*. 2012; 4(2):1574-1586.
- 55- Nikghal LA, Singh G, Singh G, Kahkeshan KF. Solid dispersion: Methods and polymers to increase the solubility of poorly soluble drugs. *Journal of Applied Pharmaceutical Science*. 2012; 2(1): 170-175.
- 56- Anjum H, Sandhya P, Sultana S, Shadan SK. Enhancement of solubility of poorly soluble drug using drug solution dropping technique. *International Journal of Scientific and Research Publication*. 2014;4(3): 1-6.
- 57- akayuki M. Using polymers to enhance solubility of poorly soluble drugs. *Pharmaceutical technology*. 2009; 1(1): 25-38.