

Poorly Water Soluble Drugs: Change in Solubility for Improved Dissolution Characteristics a Review

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Abstract: The aim of this review is to study various parameters to improve the solubility and bioavailability of poorly water soluble drugs. The oral route of administration is the most preferred and widely acceptable route of delivery due to ease of ingestion for many drugs. Drugs with slow dissolution rate show the incomplete absorption leading to low bioavailability when orally administered. Various approaches such as micronization, solid dispersion, complexation, hydrodrotropy, co-solvency, use of surfactant, sonocrystallization, particle size reduction, micro emulsion, nanosuspensions, cryogenic Techniques has been used to enhance the solubility of poorly water soluble drugs. In this review authors discussed about various Techniques used to enhance absorption and bio availability of drugs and various patents available on solubility enhancement.

Key words: Bioavailability • Dissolution • Solubility Enhancement

INTRODUCTION

The oral route is the most common and preferred route for drug administration due to its convenience and ease to ingestion [1]. When drug administered orally in solid dosage form like tablet, capsule; firstly it undergo dissolution in the GI fluids before absorption. For various poorly soluble drugs bioavailability is limited by the dissolution rate. In the development of pharmaceutical dosage form, many difficulties arise due to poor water soluble drugs. Therapeutic efficacy of a drug depends upon the solubility of drug molecules. Solubility can be defined as qualitatively as well as quantitatively. Quantitatively solubility can be defined as the solute concentration in a saturated solution at a particular temperature. Whereas qualitative it can be defined as the spontaneous interaction of two substances to produces a homogenous molecular dispersion [2].

The absorption of drug from solid dosage forms generally occurs by two processes as follow:

- *In vivo* drug dissolution to produce a solution.
- Dissolved drug was transport of the across the gastrointestinal membrane [3].

In the biopharmaceutical classification system (BCS) drugs are classifying on the basis of aqueous solubility and membrane permeability. Many poor water soluble drugs come to the BCS classes of II and IV [4]. The process of drug absorption from oral route for such types of drugs is occurs via dissolution rate limiting step. So that it is important to increase dissolution of these drugs to give maximum therapeutic effect of these drugs. Before studying the many Techniques to increase dissolution it is importance to understand the dissolution process. In the dissolution process solid substance (Active Pharmaceutical Ingredients) comes into the solution. The solubility of drug is directly proportional to its dissolution rate as per Noyes- Whitney equation and hence solubility is an important parameter of a drug for determination of its absorption and dissolution rate hence its bioavailability. Parameters such as Particle size, salt form, solubility, wettability, complexation, polymorphism etc. affect the rate of dissolution and hence can be used to increase solubility of poorly water soluble drug.

The aqueous solubility of a drug is a critical factor to evaluate the oral bioavailability of orally administered poorly water soluble drugs. The modification in the dissolution profile of these lipophilic drug molecules

without changing the molecular structure can be possible by various Techniques used to enhancement of aqueous solubility of drug candidates. Some of these Techniques include particle size reduction, solid dispersion, crystal modification, lipid based system, pH modification, use of surfactant of delivery in dosage form [5]. To increase solubility of hydrophobic drugs, generally water soluble excipients such as carbohydrates, surfactant, superdisintegrants and polymers (e.g. polyvinyl pyrrolidone, polyethylene glycols, hydroxypropyl methylcellulose, mannitol etc.) are used [6, 7].

Importance of Solubility Enhancement includes [8]:

- Solubility is one of the important parameters to achieve preferred concentration of drug in Systemic circulation for achieving required pharmacological response.
- Poorly water soluble drugs frequently require high doses and need high dosage regimens in order to influence therapeutic plasma concentrations after oral administration.
- Low aqueous solubility is the main problem encountered with preparation and development of new chemical entities as well as for generic drugs.
- For orally administered drugs solubility is the one of the important rate limiting parameter to reach their desired concentration in complete circulation for pharmacological response.
- Water is the solvent of excellent for liquid pharmaceutical formulations.
- Most of the drugs like weakly acidic or weakly basic having poor aqueous solubility.
- Poorly water soluble drugs having slow drug absorption leads to insufficient and gastrointestinal mucosal toxicity and variable bioavailability.

Techniques for Solubility Enhancement:

Use of Surfactant: To increase both dissolution of drug, surfactants are used. The basic mechanism behind the action of surfactant is that the wetting is firstly promoted so that penetration of dissolution fluid in to the solid drug particles can be increased. Poorly water soluble drug had been studied which is used a series of co-solvent and surfactant. Among the various types of surfactants, ionic surfactants were preferred over others for better solubilising agents. In most cases the anionic surfactants (such as sodium dodecyl sulphate) was found

to give better results compare to cationic surfactant (such as cetyltrimethyl ammonium bromide) for solubility enhancement [9].

Complexation [10]:

Physical Mixture: In this, the drug and suitable polymer in different ratios is triturated in a mortar for approximately one hour. Then the mixture is sieved through sieve no. 80 and stored in desiccators with fused NaCl.

Kneading Method: In this method drug and suitable polymer in different ratios is mixed in a mortar and triturated with small quantity of solvent to prepare slurry. The drug is then added slowly into the slurry with constant stirring. The slurry which is prepared then air dried at 25°C for 24 hrs. The product is prepared and sieved through sieve # 80 and stored in desiccator with fused NaCl.

Co-precipitation method: In this method the active drug and suitable polymer are mixed with different molar ratios. Then it is dissolved in solvent and distilled water at a room temperature. The mixture is stirred for one hour at room temperature and the solvent will be evaporated. The precipitate obtained as a crystalline powder is pulverised and sieved through sieve # 80 and stored in desiccator.

Co-solvency: Organic solvent such as water miscible solvents is used to enhance the aqueous solubility of a water insoluble drug [11]. Water and solvents which are soluble in water form a solution called co-solvent. PEG 300, ethanol, propylene glycol are some of the solvents which are used in preparation of co-solvent mixtures. For example 5-40% concentration of solid binary system comprising polyethylene glycol 6000 has been used to enhance the solubility and dissolution of meloxicam. Many thousand times co-solvency enhances the solubility of poorly soluble compounds compared to the aqueous solubility of the drug. In the design of many different formulations, co-solvency had been highly utilized. The co-solvency mainly used in parenteral dosage forms because of the most surfactants give the irritating effects and many co-solvents show the low toxicity, due to the more ability to make co-solvents to solubilise nonpolar drugs. Low toxic co-solvents used for parenteral dosage forms are glycerine, propylene glycol, polyethylene glycol and ethanol [12].

Solid dispersion: For increasing the absorption, dissolution and therapeutic effectiveness of drugs in dosage forms, a widely used and most suitable

pharmaceutical technique is Solid dispersion. "The term SD can be defined as the distribution of one or more active ingredients (hydrophobic) in an inactive carrier or matrix (hydrophilic) at solid state. Solid dispersion mentions to a group of solid products containing of at least two different components, generally a hydrophobic drug and a hydrophilic matrix. The matrix can be either amorphous or crystalline. The drug can be isolated molecularly, in amorphous particles (clusters) or in crystalline particles. The most commonly used solvents for solid dispersions includes methanol, water, ethanol, DMSO, chloroform, acetic acid.

The most frequently used hydrophilic carriers for solid dispersions such as,

First Generation Carriers: Example: Crystalline carriers: Organic acids, Urea, Sugars.

Second Generation Carriers: Fully synthetic polymers include polyethyleneglycols (PEG) and povidone (PVP), polymethacrylates. Natural product based polymers are mainly used by cellulose derivatives, such as hydroxypropylmethylcellulose (HPMC) or hydroxypropylcellulose, ethyl cellulose or sch derivatives, such as cyclodextrins.

Third Generation Carriers: Example: Surface active self-emulsifying carriers: Tween 80, poloxamer 408 and Gelucire 44/14.

Solid dispersions can be prepared by various methods as described below:

Fusion Method (Melting Method): The fusion or melting method, first suggested by Sekiguchi and Obi includes the preparation of physical mixture of a drug and a water-soluble carrier and heating directly whenever the mixture is melted. The melted mixture is then solidified quickly in an ice-bath under stirring. The final solid mass is crumpled, pulverized and sieved. However several substances, either drugs or carriers, may decompose or evaporates through the fusion process which employs high temperature. These problems could be overcome by heating the physical mixture in a closed container or melting it under vacuum or in the presence of inert gas such as nitrogen to prevent oxidative degradation of carrier or drug [13].

Melt Extrusion Method: This method is similar as the melt method where polymer processing technology useful and intense mixing of drug/carrier mix is naturally

processed with a twin-screw extruder. The process includes embedding a drug in a polymer although shaping the composite material to form a pharmaceutical product. The drug/carrier mix is simultaneously melted, standardized and then extruded and shaped as tablets, pellets, granules, sticks, sheets or powder [14].

Solvent Evaporation Method: Solvent evaporation method is very useful method where formation of solution is the first step containing physical mixture of the carrier and drug dissolved in a common solvent. In the second step the removal of solvent resulting the solid dispersion formation. The product is crushed, pulverized and sieved through an appropriate mesh number sieve. This allowed them to produce a solid solution of the extremely lipophilic drug in the highly water soluble carrier such as polyvinylpyrrolidone. An important requirement for the manufacture of a solid dispersion using the solvent method is that both the drug and the carrier are sufficiently soluble in the solvent.

Melting Solvent Method (Melt Evaporation): Here the solid dispersions are organized by dissolving the drug in appropriate liquid solvent and then including the solution directly into the melt of polyethylene glycol, which is then evaporated until a clear, solvent free film is left. The film is dried to constant weight. The 5-10% (w/w) of liquid compounds can be combined into polymer without significant loss of its solid property. It is possible that the particular solvent or dissolved drug may not be miscible with the melt of the polymer. Liquid solvent are also used and affect the polymorphic form of the drug, which precipitates as the solid dispersion [15].

Sonocrystallization: Sonocrystallization is a new particle engineering technique to increase solubility and dissolution of hydrophobic drugs and to study its effect on crystal properties of drug. Recrystallization of poorly soluble materials using antisolvents and liquid solvents has also been employed successfully to decrease particle size by using ultrasound. Sonocrystallization employs ultrasound power characterized by a frequency range of 20-100 kHz for inducing crystallization. Most applications use ultrasound in the range 20 kHz-5 MHz. Melt sonocrystallization (MSC) is promising technique of sonocrystallization to find porous, amorphous material with high stability [16].

Supercritical Fluid Method: A supercritical fluid (SCF) can be defined as a dense non-condensable fluid, is

additional novel nanosizing and solubilisation technology, which application has been improved in recent years. A SCF process permits the micronization of drug particles within sub-micron levels. Supercritical fluids are fluids whose temperature and pressure are greater than critical pressure (T_p) and critical temperature (T_c). At near-critical temperature, SCFs are highly compressible, permitting moderate changes in pressure to greatly change the density and mass transport characteristics of a fluid that mostly determine its solvent power. Once the drug particles are solubilised within SCF, they may be recrystallised at significantly reduced particle size. Water and Carbon dioxide are the most commonly used supercritical fluids. The SCF process can create nanoparticulate suspensions of particles 5-2,000 nm in diameter. Eg. Increasing water solubility of etraconazole with water soluble polymer HPMC by using supercritical fluid processing [17].

Hydrotropy: The term hydrotropy refers to enhance in solubility of insoluble or slightly soluble drugs in water by the addition of additives. The mechanism by which it increases solubility is more closely associated to complexation involving a weak interaction between the hydrotrophic agents and the solute. Some hydrotrophic agents used are sodium benzoate, urea, sodium alginate, sodium acetate etc. In hydrotropy techniques many different class of drugs like anti-viral, antipyretic, anti-tumour, anti-inflammatory and analgesic drugs used for solubility enhancement. Hydrotropy technique is applied for solubility enhancement of riboflavin, nimesulide, nifedipine and xanthine derivatives such as caffeine and theophylline [18].

Particle Size Reduction: The solubility of drug is often essentially related to drug particle size; as a particle becomes smaller, the surface area to volume ratio increases. The larger surface area permits greater interaction with the solvent which causes an increase in solubility.

There are two methods to reduce the particle size. They are:

Conventional Methods: Conventional methods of particle size reduction, like comminution and spray drying, rely upon mechanical stress to disaggregate the active compound. Particle size reduction is thus authorizing reproducible, efficient and economic means of solubility

enhancement. However, the mechanical forces essential to comminution, such as grinding and milling often impart significant amounts of physical stress upon the drug product which may induce degradation. The thermal stress which may occur during comminution and spray drying is also a concern when processing thermo sensitive or unstable active compounds. Using traditional approaches for nearly insoluble drugs may not be able to increase the solubility up to desired level [19].

Micronization: Micronization is another conventional technique for the particle size reduction. Micronization enhance the dissolution rate of drugs through increased surface area, it does not enhance equilibrium solubility. Decreasing the particle size of these drugs, which cause enhance in surface area, improve their rate of dissolution. Micronization of drugs is done by milling techniques by rotor stator colloid mills, jet mill and so forth micronization is not appropriate for drugs having a high dose number because it does not change the saturation solubility of the drug [20, 21].

Micro Emulsion: Micro emulsion is known as a system of water, oil which is thermodynamically stable liquid solution. A micro emulsion can be divided of four component system such as internal phase, external phase, surfactant and cosurfactant, Non-ionic surfactant like labrafil and tweens with high hydrophile-lipophile balances which are used to formation of oil-in water droplets during the production. In micro emulsion technique, many equipment are used such as water bath, stirring rod, volumetric flask and homogenizer. Micro emulsion is known as the isotropic, clear pre concentrate, thermodynamically stable translucent system which is containing a mixture of oil, hydrophilic solvent and hydrophilic surfactant dissolved in a poorly water soluble drug [22].

Nano-suspension: Nano-suspension is defined as a biphasic systems which consist of nano sized drug particles stabilized by surfactants for topical and oral use or pulmonary and parenteral administration. In nano-suspension technology, promising candidate had been developed for efficient delivery of hydrophobic drugs [23]. Poorly soluble drugs that are insoluble in both oils and water was applied in nano-suspension technology. In nano-suspension the particle size distribution of the solid particles is less than one micron with the range of particle size between 200 and 600

nm. Various methods which are used for preparation of Nano-suspension such as High Pressure Homogenization in water (Dissocubes), media milling (nanocrystal), combination of Precipitation and High-Pressure Homogenization (Nanoedge) and High Pressure Homogenization in non-aqueous media (Nanopure) [24]. Various Techniques Are Used in Nano-suspension Are:

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

Media Milling (Nanocrystals and Nanosystem): By using high-shear media mills, the nanosuspensions are prepared. The milling chamber charged with water, milling media stabilizer and drug is rotated at a very high shear rate at temperatures for several days (at least 2-7 days). The milling medium which composed of Zirconium oxide or highly cross-linked polystyrene resin or glass.

Cryogenic Techniques: Cryogenic techniques are used to progress the dissolution rate of drugs by producing nanostructured amorphous drug particles with high degree of porosity at very low temperature conditions. This Cryogenic techniques can be defined by the type of injection device (capillary, ultrasonic nozzle, pneumatic and roy), location of nozzle (above or under the liquid level) and the composition of cryogenic liquid (N₂, O₂, hydro fluoro alkanes and organic solvents). After in this processing, dry powder can be found by different type of drying processes including- spray freeze drying, vacuum freeze drying, atmospheric freeze drying and lyophilisation (for removal of solvent) [25].

Patents for Solubility Enhancement:

- Wurn *et al.* [26] has invented a method to enhance solubility of an active compound by combining an active compound (having an aqueous solubility that is less than or equal to about 10 mg/mL), with an amount of methoxypolyethylene glycol which is sufficient to enhance the aqueous solubility of the active compound. Enhancement of aqueous solubility for this combination may be significantly greater than that of an active compound in combination with an equivalent amount of

polyethylene glycol. Particularly enhanced solubility is shown where a small amount of water is also included. The development may be used in a wide variety of applications, such as for pharmaceutical, antimicrobial, agricultural and personal care products.

- Sandeep *et al.* [27] has invented Dissolution enhanced controlled drug delivery system for poorly water soluble drugs by using a solid dispersion of a poorly water-soluble or insoluble drug and found enhanced dissolution in an aqueous medium. The invention further discloses a process of preparation of these controlled-release dosage forms.
- William *et al.* [28] has invented Solid pharmaceutical dispersions with enhanced bioavailability which provide Spray dried solid dispersions including a sparingly soluble drug and hydroxyl propylmethylcellulose acetate succinate (HPMCAS) provide enhanced aqueous solubility and/or bioavailability in the use environment.
- Philip *et al.* [29] has invented Methods of increasing solubility of poorly soluble compounds and methods of making and using formulations of such compounds that related to novel soluble forms of planar ring structured organic compounds such as flavonoids and their production. The invention relates to a wide variety of applications of the formulations of the invention. The subject invention contains novel soluble forms and various formulations of flavonoids. Further, the invention includes novel methods of manufacturing the flavonoid formulations.
- Mani *et al.* [30] have invented Solubility enhanced terpene glycoside(s) by inclusion complexes comprising a substantially pure terpene glycoside and at least one cyclodextrins, wherein the solubility of the inclusion complex is greater than the solubility of the substantially pure terpene glycoside alone. He also study the methods for improving the taste of an orally ingestible composition and an inclusion complex comprising at least two substantially pure terpene glycosides and at least one cyclodextrins.
- Bilgic *et al.* [31] has invented Solubility and Stability Enhancing Pharmaceutical Formulation that relates to pharmaceutical preparations comprising a combination of a therapeutic agent with solubility problem and a therapeutic agent with stability problem and the methods for the preparation and the uses.

- Suck-Hyune *et al.* [32] has invented Conductive polymers having high solubility in organic solvent and electrical conductivity and synthesizing process that related to a new process of synthesizing conductive polymers from monomers substituted with amine group. The process offers simple synthesizing steps for the conductive polymers without using other additives including stabilizers or emulsifiers. The conductive polymers synthesized according to the present invention have highly enhanced solubility in common organic solvents and electrical conductivity associated to conventional conductive polymers. Therefore, the conductive polymers synthesized according to the present process can be utilized in applications that involve high electrical conductivity, for example an electromagnetic interference shield or a transparent electrode of thin film, as well as in specific applications such as various conductive films, polymer blends, fibers, battery electrodes or conductive etch mask layer.
- Ravula Sayisiva *et al.* [33] has invented Solid lipid dispersion for aqueous solubility enhancement of poorly water soluble drugs that related to a poorly water soluble drug and a lipid material in the form of lipid solid dispersion and their use in dosage form. The said solid dispersions increase the bioavailability of active agents, are convenient to administer and are stable. The present invention also delivers a process for the preparation of these lipid solid dispersions by spray drying a dispersion of poorly water soluble drug and lipid excipients.
- Liang *et al.* [34] has prepared and invented Stabilized solubility-enhanced formulations for oral delivery including vitamins and co-factors into self-emulsifying formulas (SEF) and optionally sorbing the SEF into pores of porous solid particulates, or making supersaturated solutions (SSS) and sorbing the SSS into pores of porous solid particulates. These preparations are useful as dosage forms with oral availability.
- Bruce *et al.* [35] has invented Method to enhance aqueous solubility of poorly soluble drugs using methoxypolyethylene glycol by combining an active compound (having an aqueous solubility that is less than or equal to about 10 mg/ml), and an amount of methoxypolyethylene glycol that is sufficient to enhance the aqueous solubility of the active compound. Enhancement of aqueous solubility for this combination may be significantly greater than that of an active compound in combination with an equivalent amount of polyethylene glycol. Particularly increase solubility is shown where a small amount of water is also included. The invention may be used in a wide variety of applications, such as for pharmaceutical, antimicrobial, agricultural and personal care products.
- Isaac *et al.* [36] has invented Process for enhancing the solubility of poorly soluble drugs is enhanced by a process that utilizes a twin-screw extruder comprising (i) a feed zone containing a first liquid and powder feed stations; (ii) a grinding/mixing zone comprising a second liquid feed port located at an upstream portion of such zone; (iii) a granulation zone containing a second powder feed station situated at an upstream portion of such zone and a third liquid feed port located at a downstream portion of such zone; and (iv) a wet milling zone.
- Argaw *et al.* [37] have invented Osmotic delivery of therapeutic compounds by solubility enhancement due to inherent hydrophobicity or to saturation limitations in the core of the osmotic system which found appropriate for the osmotic delivery of glipizide and other hydrophobic drugs, but runs the spectrum to other therapeutic agents with higher aqueous solubility.
- Ramachandran *et al.* [38] have invented “novel solubility enhancer accomplished of being active in formulating safe and effective pharmaceutical preparations of partially soluble drugs.” The solubility enhancer is selected from dialkyl substituted amides of fatty acids having C₆ to C₁₆ carbon chain, preferably from N, N-dimethyl hexanamide, N, N-dimethyl octanamide, N, N-dialkyl decanamide, N, N-dialkyl dodecanamide or N, N-dialkyl hexadecanamide.
- Padmanabh *et al.* [39] has invented Osmotic delivery of therapeutic compounds. The present invention is appropriate for the osmotic delivery of glipizide and other hydrophobic drugs, but runs the spectrum to other therapeutic agents with higher aqueous solubilities, yet having a solubility limitation in an osmotic dosage unit due to high drug load.
- Davila *et al.* [40] has invented “Pharmaceutical composition for solubility enhancement of hydrophobic drugs” and found that a pharmaceutical composition containing a drug and polyethylene glycol (where the ratio of polyethylene glycol to drug by weight is from about 0.2:1 to about 10:1 and the polyethylene glycol has a melting point of at least

37°C), Exhibit rapid dissolution upon contact with physiological solvents, like water, gastrointestinal fluids or saliva.

- Wagner *et al.* [41] has invented Enhanced solubility of magnesium halides, catalysts and polymerization process using same that relates to magnesium halide compositions, catalysts made therefrom, methods of increasing the solubility of magnesium halides, methods of making magnesium halide compositions and catalysts, as well as methods of polymerization.
- Roberto *et al.* [42] has invented Enhancement of oral bioavailability of non-emulsified formulation of prodrug esters with lecithin by formulating the ester as non-emulsified formulation with lecithin; as well as a therapeutic composition of at least one antibiotic and lecithin in a non-emulsified preparation; a method of treating infections with the non-emulsified formulation and a method for making tablets by direct compression of blends of drugs with lecithin are disclosed. Non-emulsified formulations such as solids, capsules, lozenges, tablets, suspensions, elixirs and solutions and exclude liposomes, emulsion, lipid matrix systems and micro-emulsions.
- Atul *et al.* [43] has invented Dosage forms for increasing the solubility and extending the release of drugs such as topiramate and phenytoin, dosage forms and devices for enhancing controlled delivery of pharmaceutical agents by use of a drug core composition comprising a polymer carrier (e.g. polyethylene oxide) and a surfactant (e.g. poloxamer, polyoxyl stearate). The present invention provides a means of delivering high doses of poorly soluble drug in oral drug delivery systems that are convenient to swallow, for once-a-day administration.
- Richard *et al.* [44] has invented Particulate compositions for improving solubility of poorly soluble agents that found particles for oral drug delivery prepared by spray-drying a dilute solution of a poorly soluble agent. The particles include regions of poorly soluble agent wherein the dissolution rate enhancement was between about 2-fold and about 25-fold compared to the agent in bulk form.
- Alexey *et al.* [45] has invented Solubility and stability enhancement tag for structural and ligand binding studies of proteins that provides methods of stabilizing proteins in solution. The present invention offers a method of solubilizing and stabilizing a get protein in solution by making a fusion protein of the get protein with a small solubility and stability enhancing tag. The present invention also features methods of responsible the structure of a get protein using a fusion protein to stabilize the get protein in solution.
- Sylvia Rossi-Montero *et al.* [46] has invented Solubility enhancement of drugs in transdermal drug delivery systems and method for the continuous and controlled transdermal delivery of an active agent containing a pharmaceutically acceptable active agent carrier and cellulose derivative which provides a solubilizing and stabilizing effect on the active agents combined therein.
- David *et al.* [47] has invented Solubility enhancement of drugs in transdermal drug delivery systems and methods which is used a composition and for the continuous and controlled transdermal delivery of an active agent including a pharmaceutically acceptable active agent carrier and cellulose derivative which provides a stabilizing and solubilizing effect on the active agents incorporated.
- Behl *et al.* [48] has invented Method for increasing the solubility of morphine through the use of organic acid or its salts as a solubilizing agent. Particularly suitable as solubilizing agents are salts of carboxylic acids, includes gluconate, acetate, tartrate, aspartate, fumarate, citrate, lactate, malate, maleate, succinate and combinations. Pharmaceutical compositions of morphine and organic acids or its salts as solubilizing agents, found satisfactory.
- Elke *et al.* [49] has invented Methods for enhancing the solubility of substantially water-insoluble compounds, by combining such compounds with a water-soluble polymer e.g., polyalkylene oxide polymer or a cellulose ether, having a molecular weight of from about 50,000 to 7,000,000 grams per gram in an amount effective to enhance the water-solubility of the compound in an acidic environment, e.g., pH less than about 5.
- Jesus Miranda *et al.* [50] has invented Solubility parameter based on drug delivery system and method for altering drug saturation concentration that provide the method of adjusting the saturation concentration of a drug in a transdermal composition for application to the dermis, which contains mixing polymers having different solubility parameters, so as to modulate the delivery of the drug. This results in the ability to achieve a determined permeation rate of the drug into and through the dermis. In one embodiment, a dermal composition of the present invention includes a drug, an acrylate polymer and a

polysiloxane. The dermal compositions can be produced by a variety of methods known in the preparation of drug-containing adhesive preparations, including the mixing of the drug, polymers and additional ingredients in solution, followed by removal of the processing solvents. The method and composition of this invention permit selectable loading of the drug into the dermal formulation and adjustment of the delivery rate of the drug from the composition through the dermis, while maintaining acceptable tack, shear and peel adhesive properties.

- Morton *et al.* [51] has invented Enhanced solubility pharmaceutical solutions related to a solution comprising acidic, basic and/or amphoteric pharmaceutical agents for encapsulation in gelatin capsules.
- John Francis Connolly *et al.* [52] has invented a method of enhancing and controlling the solubility of lithium salts in liquid sulphur dioxide which found that the solubility of lithium salts can be enhanced and controlled by the presence of a salt which comprises a cation selected from the group consisting of metal cation complexes, organic phosphonium cations and quaternary ammonium cations.
- Girard *et al.* [53] has invented Method of enhancing solubility of halogenated hydantoins and found that the generation of total and free halogen in aqueous solutions of halogenated hydantoins is potentiated by the use of a solubility agent selected from the group consisting of magnesium oxide, barium hydroxide, sodium carbonate, 5,5-dialkyl substituted hydantoin and mixtures. The use of these solubility agents in combination with halogenated hydantoins, such as bromochloromethylethylhydantoin, is especially suitable for use as a toilet bowl cleaner.
- Josef *et al.* [54] have invented Enhanced-solubility aspartame compounds that related to a class of soluble sweetener compositions including a mixture of a depeptide sweetener and a solubilizing agent. The compositions are readily dissolved in aqueous solution.
- Jean-Claude *et al.* [55] has invented Enhancement of heteropolysaccharide solubility which was carried out by making the salts of heteropolysaccharide, the results found that the dissolution conjointly with an organic acid or anhydride having at least one pK value between 5 and 7, the calcium salt or salts of such anhydride or organic acid itself or themselves being soluble in water.

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