



## Dissolution Enhancement Technique

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### ABSTRACT

Solubility, the phenomenon of dissolution of solute in solvent to present a Homogenous system, is one of the essential parameters to gain preferred attention Of drug in systemic circulate for preferred (anticipated) pharmacological Response. Low aqueous solubility is the Principal trouble encountered with formula improvement of latest chemical Entities as well as for the widely wide-spread improvement. More than 40% Nces (new chemical entities) advanced in Pharmaceutical enterprise are nearly insoluble in water. Solubility is a first-rate Project for formula scientist. Any drug to be absorbed ought to be gift withinside The shape of answer at the web web page of absorption. Various strategies are Used for the enhancement of the solubility of poorly soluble tablets which Consist of bodily and chemical adjustments of drug and other strategies like Particle length reduction, crystal engineering, salt formation, stable dispersion, Use Of surfactant, complexation, and so forth. Selection of solubility enhancing Technique depends on drug property, webweb page of absorption, and required Dosage shape characteristics.

### I. INTRODUCTION

Solubility is the belongings of a strong, liquid, or gaseous chemical Substance referred to as solute to dissolve in a strong, liquid, or gaseous Solvent to shape a homogeneous answer of the solute in The solvent. The solubility of a substance basically relies upon at the solvent Used as well as on temperature and pressure. The volume of solubility of a Substance in a selected solvent is measured because the saturation awareness In which including extra solute does now no longer growth its Awareness in the answer [1].The solvent is commonly a liquid, which may be A natural substance or a combination of liquids. One may additionally Communicate of strong answer, however not often of answer in a gas. The Volume of

solubility stages widely, from infinitely soluble (completely Miscible) inclusive of ethanol in water, to poorly soluble, inclusive of silver Chloride in water. The time period insoluble is often carried out to poorly or Very poorly soluble compounds [2]. Solubility happens below dynamic Equilibrium, this means that that solubility outcomes from the Simultaneous and opposing approaches of dissolution and segment joining (e.g., precipitation of solids). Solubility equilibrium happens whilst the 2 Approaches continue at a consistent rate. Under positive situations Equilibrium solubility can be handed to offer a so-referred to as Supersaturated answer, that is metastable [3]. Solubility isn't always to be Stressed with the cappotential to dissolve or liquefy a substance, on account That these approaches might also additionally arise now no longer best due To dissolution however additionally due to a chemical reaction. For example, Zinc is insoluble in hydrochloric acid, however does dissolve in it through Chemically reacting into zinc chloride and hydrogen, in which zinc chloride Is soluble in hydrochloric acid. Solubility does now no longer additionally Rely on particle length or otherkinetic factors; given sufficient time, even big Debris will ultimately dissolve [4]. IUPAC defines solubility because the analytical composition of a saturated answer expressed as a percentage of a delegated solute in a delegated solvent. Solubility can be said in devices of awareness, molality, mole fraction, mole ratio, and different devices [5]. Extensive use of solubility from specific attitude has caused solubility being expressed in diverse manners. It is typically expressed as a awareness, both through mass (g of solute in step with kg of solvent, g in step with dL (one hundred mL) of solvent), molarity, molality, mole fraction, or different comparable descriptions of awareness. The most equilibrium quantity of solute that can dissolve in step with quantity of solvent is the solubility of that solute in that solvent below the targeted



situations [6]. The gain of expressing solubility on this way is its simplicity, even as the drawback is that it could strongly rely on the presence of different species within the solvent (e.g., the not unusual place ion effect). Saturated answers of ionic compounds of highly low solubility are from time to time described through solubility constants. It is a case of equilibrium process. It describes the stability between dissolved ions from the salt and undissolved salt. Similar to different equilibrium constants, temperature could have an effect on the numerical price of solubility consistent. The price of this consistent is commonly impartial of the presence of different species within the solvent. The Flory-Huggins answer concept is a theoretical version describing the solubility of polymers. The Hansen Solubility Parameters and the Hildebrand solubility parameters are empirical techniques for the prediction of solubility. It is likewise viable to expect solubility from different bodily constants which include the enthalpy of fusion. The partition coefficient (Log P) is a degree of differential solubility of a compound in a hydrophobic solvent (octanol) and a hydrophilic solvent (water). The logarithm of those two values allows Compounds to be ranked in phrases of hydrophilicity (or hydrophobicity). USP and BP classify the solubility no matter the solvent used, simply best in Phrases of quantification and feature described the standards as given The Biopharmaceutics Classification System (BCS) is a manual for predicting the intestinal drug absorption furnished via way of means of the U.S. Food and Drug Administration. This gadget restricts the prediction the usage of the parameters solubility and intestinal permeability. Solubility is primarily based totally on the very best-dose power of an instantaneous launch product. A drug is taken into consideration distinctly soluble whilst the very best dose power is soluble in 250 mL or much less of aqueous media over the pH variety of one to 7.5. The extent estimate of 250 mL is derived from usual bioequivalence have a look at protocols that prescribe management of a drug product to fasting human volunteers with a tumbler of water [9]. The intestinal permeability type is primarily based totally on a assessment to the intravenous injection. All the ones elements are distinctly important, due to the fact that 85% of the maximum excessive soluble and excessive permeable, magnificence II—low soluble and Excessive permeable, magnificence III—low soluble and excessive permeable And magnificence IV—low soluble and coffee permeable excessive permeable, magnificence III—low soluble

and excessive permeable and magnificence IV—low soluble and coffee permeable.

### IMPORTANCE OF SOLUBILITY

Oral ingestion is the maximum handy and usually hired direction of drug Shipping due to its ease of administration, excessive affected person Compliance, costeffectiveness, least sterility constraints, and versatility Within the layout of dosage shape. As a result, a few of the frequent Drug agencies are willing greater to provide bioequivalent oral drug Products [10]. However, the foremost task with the layout of oral dosage Bureaucracy lies with their bad bioavailability. The oral bioavailability relies Upon on numerous elements such as aqueous solubility, drug permeability, Dissolution price, first-byskip metabolism, presystemic metabolism, and Susceptibility to efflux mechanisms. The maximum common reasons of low Oral bioavailability are attributed to bad solubility and coffee permeability. Solubility additionally performs a first-rate function for different dosage Bureaucracy like parenteral formulations as well [11]. Solubility is one of The crucial parameters to reap preferred attention of drug in systemic flow For attaining required pharmacological response [12]. Poorly water soluble Capsules regularly require excessive doses that allows you to attain healing Plasma concentrations after oral administration. Low aqueous solubility is The foremost trouble encountered with formula improvement of recent Chemical entities in addition to frequent improvement. Any drug to be Absorbed ought to be gift within the shape of an aqueous answer on the Web website online of absorption. Water is the solvent of preference for Liquid pharmaceutical formulations. Most of the medicine are both weakly Acidic or weakly primary having bad aqueous solubility. More than 40% NCEs (new chemical entities) advanced in pharmaceutical enterprise are Nearly insoluble in water. These poorly water soluble capsules having Sluggish drug absorption ends in insufficient and variable bioavailability and Gastrointestinal mucosal toxicity. For orally administered capsules solubility Is the maximum crucial one price restricting parameter to reap their preferred attention in systemic flow for pharmacological response. Problem of solubility is a first-rate task for formula scientist [13]. The development of drug solubility thereby its oral bioavailability stays one of the maximum difficult factors of drug improvement technique specially for oral-drug shipping system. There are several strategies to be had and mentioned in literature to



beautify the solubility of poorly water-soluble capsules. The strategies are selected on the premise of sure factors inclusive of homes of drug beneathneath consideration, nature of excipients to be selected, and nature of supposed dosage shape. The bad solubility and coffee dissolution price of poorly water soluble capsules withinside the aqueous gastrointestinal fluids regularly purpose inadequate bioavailability. Especially for sophistication II (low solubility and excessive permeability) materials in keeping with the BCS, the bioavailability can also additionally be more suitable via way of means of growing the solubility and dissolution price of the drug withinside the gastro-intestinal fluids. As for BCS elegance II capsules price restricting step is drug launch from the dosage shape and solubility withinside the gastric fluid and now no longer the absorption, so growing the solubility in turn will increase the bioavailability for BCS elegance II capsules [10, 13, 14]. The poor impact of compounds with low solubility consist of bad absorption and bioavailability, inadequate solubility for IV dosing, improvement demanding situations main to growing the improvement value and time, burden shifted to affected person (common excessive-dose.

### Techniques for Solubility Enhancement

Solubility development strategies may be labeled in to bodily change, Chemical changes of the drug substance, and different strategies.

#### Physical Modifications

Particle length discount like micronization and nanosuspension, change of the Dependancy like polymorphs, amorphous shape and cocrystallization, drug Dispersion in vendors like eutectic mixtures, strong dispersions, strong answers And cryogenic strategies.

#### Chemical Modifications

Change of ph, use of buffer, derivatization, complexation, and salt formation.

#### Miscellaneous Methods

Supercritical fluid process, use of adjuvant like surfactant, solubilizers, Cosolvency, hydrotrophy, and novel excipients.

### PARTICLE SIZE REDUCTION

The solubility of drug is regularly intrinsically associated with drug particle Length; as a particle becomes smaller, the floor location to quantity ratio will Increase. The large floor location

permits greater interplay with the solvent Which reasons an boom in solubility. Conventional strategies of particle length discount, along with comminution And spray drying, rely upon mechanical strain to disaggregate the lively Compound. Particle length discount is thus allowing an efficient, reproducible, And financial approach of solubility enhancement. However, the mechanical Forces inherent to comminution, along with milling and grinding, regularly Impart sizable quantities of bodily strain upon the drug product which may also Induce degradation. The thermal strain which may also arise for the duration of Comminution and spray drying is additionally a subject while processing Thermosensitive or risky lively compounds. Using conventional strategies for Almost insoluble tablets won't be capable of beautify the solubility as much as Preferred level. Micronization is every other traditional method for the particle Length discount. Micronization will increase the dissolution fee of medicine Thru extended floor location, it does now no longer boom equilibrium Solubility. Decreasing the particle length of those tablets, which purpose boom In floor location, enhance their fee of dissolution. Micronization of medicine is Finished with the aid of using milling strategies the usage of jet mill, rotor stator Colloid turbines and so on micronization isn't always appropriate for tablets Having a excessive dose variety as it does now no longer extrade the saturation Solubility of the drug [15]. These tactics have been carried out to griseofulvin, Progesterone, spironolactone diosmin, and fenofibrate. For every drug, Micronization advanced their digestive absorption, and therefore their Bioavailability and medical efficacy. Micronized fenofibrate exhibited more Than 10-fold (1.3% to 20%) boom in dissolution in at half-hour biorelevant Media [16,17]

### SOLID DISPERSION

The idea of stable dispersions become firstly proposed through Sekiguchi And Obi, who investigated the era and dissolution overall performance of Eutectic melts of a sulfonamide The idea of stable dispersions become firstly Proposed through Sekiguchi and Obi, who Investigated the era and dissolution overall performance of eutectic melts of A sulfonamide.

#### Hot-Melt Method (Fusion Method)

The foremost benefits of this direct melting approach is its simplicity and Economy. The melting or fusion approach became first proposed through Sekiguchi and Obi to put together speedy launch stable Dispersion dosage forms. In this approach,



the bodily aggregate of a drug And a water-soluble service are heated without delay till the 2 melts. The Melted aggregate is then cooled and solidified swiftly in an ice tubtub with Rigorous stirring. The very last stable mass is then crushed, pulverized, and Sieved, which may be compressed into pills with the assist of tableting Agents. The melting factor of a binary gadget depends upon its composition, That is, the choice of the service and the burden fraction of the drug Withinside the gadget [22]. An critical considered necessary for the Formation of stable dispersion through the hot-soften approach is the Miscibility of the drug and the service withinside the molten form. Another Critical considered necessary is the thermostability of each the drug and the Service.

### Solvent Evaporation Method

Tachibana and Nakamura [23] have been the primary to dissolve each the Drug and the service in a not unusualplace solvent after which evaporate the Solvent below vacuum to supply a stable answer. This enabled them to Supply a stable answer of the exceedingly lipophilic  $\beta$ -carotene withinside The water soluble service povidone. Many investigators studied stable dispersion of meloxicam, naproxen, and nimesulide the usage of solvent evaporation approach. These findings endorse that the above-noted approach may be hired efficiently for development and balance of stable dispersions of poorly water soluble capsules [15, 17]. The foremost benefit of the solvent evaporation approach is that thermal decomposition of capsules or companies may be averted due to the low temperature required for the evaporation of natural solvents. However, the risks related to this approach are the better price of preparation, the issue in absolutely putting off the natural solvent (aregulatory perspective), the feasible unfavourable impact of the supposedly negligible quantity of the solvent at the chemical balance of the drug, the choice of a not unusualplace unstable solvent, and the issue in reproducing crystal forms [24].

### Hot-Melt Extrusion

Hot-soften extrusion is basically similar to the fusion approach besides that Extreme blending of the additives is brought on through the extruder. Just Like withinside the conventional fusion process, Miscibility of the drug and the matrix might be a hassle. High-shear forces Ensuing in high neighborhood temperature withinside the extruder is a Hassle for warmth touchy materials. However, as compared to the Conventional fusion method, this approach gives the opportunity of Continuous

production, which makes it appropriate for large-scale Production. Furthermore, the product is less difficult to deal with due to the Fact at the opening of the extruder the form may be tailored to the next Processing step with out grinding [20].

### NONSUSPENSION

Nanosuspension generation has been advanced as a promising candidate for Efficient shipping of hydrophobic capsules. This generation is carried out to Poorly soluble capsules that are insoluble in each water and oils. A Pharmaceutical nanosuspension is a biphasic system which include nano Sized drug debris stabilized through surfactants for both oral and topical use Or parenteral and pulmonary administration. The particle length distribution Of the solid Debris in nanosuspensions is typically much less than one micron with a Mean particle length ranging among two hundred and six hundred nm [25,26]. Various strategies applied for education of nanosuspensions consist of Precipitation technique, media milling, excessive-strain homogenization in Water, excessive strain homogenization in nonaqueous media, and aggregate Of Precipitation and excessive-Pressure homogenization [27,28].

### Precipitation Technique

In precipitation approach the drug is dissolved in a solvent, that's then Introduced to antisolvent to precipitate the crystals. The primary gain of Precipitation approach is the use of easy and occasional fee equipments; However the mission is the addition of the developing drug crystals to keep Away from formation of microparticles. The drawback of this precipitation Approach is that the drug desires to be soluble in at the least one solvent and This solvent desires to be Miscible with antisolvent. Moreover, precipitation approach isn't relevant to Drugs, which are concurrently poorly soluble in aqueous and nonaqueous Media [29]. Nanosuspension of Danazol and Naproxen were organized Through precipitation approach to enhance their dissolution fee and oral Bioavailability. The length discount of naproxen become additionally Associated with an obvious boom withinside the fee of absorption through about 4-fold [30, 31].

### Media Milling

The nanosuspensions are organized through the use of excessive-shear Media mills. The milling chamber charged with milling media, water, drug, And stabilizer is turned around at a totally excessive-shear feebeneathneath Managed





temperatures for numerous days (at the least 2–7 days). The Milling medium is composed of glass, Zirconium oxide, or incredibly cross-Related polystyrene resin. High energy shear forces are generated because of The impaction of the milling media with the drug ensuing into breaking of Microparticulate drug to nanosized debris [28].

### High Pressure Homogenization

High-strain homogenization has been used to put together nanosuspension Of many poorly water soluble drugs. In this approach, the suspension of a Drug and surfactant is pressured beneathneath strain thru a nanosized Aperture valve of a excessive strain homogenizer. The principle of this Approach is primarily based totally on cavitation withinside the aqueous Phase. The cavitations forces inside the debris are sufficiently excessive to Transform the drug microparticles into nanoparticles. The difficulty with this Technique is the want for small pattern debris earlier than loading and the Fact that many cycles of homogenization are required [32]. Dissolution charge and bioavailability of poorly soluble pills which includes Spironolactone, budesonide, and omeprazole were stepped forward with the Aid of using decreasing their particle length with the aid of using high strain Homogenization [33–35].

### Combined Precipitation and Homogenization

The prompted drug nanoparticles have a propensity to hold crystal increase To the dimensions of microcrystals. They want to be processed with high-Strength forces (homogenisation). They Are in absolutely amorphous, partly amorphous or absolutely crystalline Bureaucracy which create issues in long time balance in addition to in Bioavailability, so the prompted particle suspension is in the end Homogenized which maintain the particle length received after Theprecipitation step.

### LIQUISOLID METHOD

When the drug dissolved withinside the liquid car is added into a service fabric Which has a porous floor and fibers in its indoors as cellulose, each absorption And adsorption take place; i.e. the liquid first of all absorbed withinside the Indoors of the debris is captured via way of means of its inner structure, and After the saturation of this process, adsorption of the liquid onto the inner and External surfaces of the porous service debris occur. Then, the coating fabric Having excessive adsorptive homes and massive specific floor region offers the Lquisolid machine with perfect flow characteristics.

Microcrystalline and Amorphous cellulose and silica powders can be used as coating materials.[37]

## II. CONCLUSION

Dissolution of drug is the fee figuring out step for oral absorption of the poorly Water soluble tablets, that may in the end have an effect on the in vivo Absorption of drug. Because of solubility hassle of many tablets the Bioavailability of them gets affected and for this reason solubility enhancement Will become necessary. The fundamental approaches accompanied via way of Means of all of the presently available technology engaged withinside the Solubility and dissolution enhancement is to maximise the bioavailability and Healing efficacy. To conquer the solubility hassle numerous solubility Enhancement strategies are broaden these days that's business applicable. By the Use of more recent techniques which might be mentioned above it's far feasible To enhance solubility of poorly water soluble tablets.

## References

- [1]. L. Lachman, H. Lieberman, and J. L. Kanig, *The Theory And Practise of Industrial Pharmacy*, Lea & Febiger, 3rd edition, 1986.
- [2]. M. Clugston and R. Fleming, *Advanced Chemistry*, Oxford Publishing, Oxford, UK, 1st edition, 2000.
- [3]. P. B. Myrdal and S. H. Yalkowsky, —Solubilization of drugs in aqueous media,| in *Encyclopedia of Pharmaceutical Technology*, J. Swarbrick, Ed., p. 3311, Informa Health Care, New York, NY, USA,, 3rd edition, 2007.
- [4]. A. Martin, *Solubility and Distribution Phenomena*, *Physical Pharmacy and Pharmaceutical Sciences*, Lippincott Williams and Wilkins, 6th edition, 2011.
- [5]. —IUPAC gold book,|
- [6]. M. Aulton, —Dissolution and solubility,| in *Pharmaceutics: The Science of Dosage form Design*, M. E. Aulton, Ed., p. 15, Churchill Livingstone, 2nd edition, 2002. View at:
- [7]. *The United States Pharmacopeia*, USP 30-NF 25, 2007.
- [8]. *British Pharmacopoeia*, 2009.
- [9]. G. L. Amidon, H. Lennernäs, V. P. Shah, and J. R. Crison, —A theoretical basis for a biopharmaceutic drug classification: the correlation of in vitro drug product dissolution and in vivo bioavailability,| *Pharmaceutical Research*, vol. 12, no. 3, pp. 413–420, 1995.



- [10]. S. R. K. Yellela, —Pharmaceutical technologies for enhancing oral Bioavailability of poorly soluble drugs, *Journal of Bioequivalence & Bioavailability*, vol. 2, no. 2, pp. 28–36, 2010.
- [11]. K. H. Edward and D. Li, —Solubility, *in Drug Like Properties: Concept, Structure, Design and Methods, from ADME to Toxicity Optimization*, p. 56, Elsevier, 2008.
- [12]. V. R. Vemula, V. Lagishetty, and S. Lingala, —Solubility enhancement Techniques, *International Journal of Pharmaceutical Sciences Review and Research*, vol. 5, no. 1, pp. 41–51, 2010.
- [13]. D. Sharma, M. Soni, S. Kumar, and G. D. Gupta, —Solubility Enhancement—eminent role in poorly soluble drugs, *Research Journal of Pharmacy and Technology*, vol. 2, no. 2, pp. 220–224, 2009.
- [14]. A. Kumar, S. K. Sahoo, K. Padhee, P. S. Kochar, A. Sathapathy, and N. Pathak, —Review on solubility enhancement techniques for hydrophobic Drugs, *Pharmacie Globale*, vol. 3, no. 3, pp. 001–007, 2011.
- [15]. N. Blagden, M. de Matas, P. T. Gavan, and P. York, —Crystal engineering of Active pharmaceutical ingredients to improve solubility and dissolution rates, *Advanced Drug Delivery Reviews*, vol. 59, no. 7, pp. 617–630, 2007.
- [16]. M. Vogt, K. Kunath, and J. B. Dressman, —Dissolution enhancement of Fenofibrate by micronization, cogrinding and spray-drying: comparison With commercial preparations, *European Journal of Pharmaceutics and Biopharmaceutics*, vol. 68, no. 2, pp. 283–288, 2008.
- [17]. J. C. Chaumeil, —Micronization: a method of improving the bioavailability Of poorly soluble drugs, *Methods and Findings in Experimental and Clinical Pharmacology*, vol. 20, no. 3, pp. 211–215, 1998.
- [18]. K. Sekiguchi and N. Obi, —Studies on absorption of eutectic mixtures. I.A. Comparison of the behaviour of eutectic mixtures of sulphathiazole and that of Ordinary sulphathiazole in man, *Chemical and Pharmaceutical Bulletin*, vol. 9, pp. 866–872, 1961.
- [19]. P. Gupta, V. K. Kakumanu, and A. K. Bansal, —Stability and solubility of Celecoxib-PVP amorphous dispersions: a molecular perspective, *Pharmaceutical Research*, vol. 21, no. 10, pp. 1762–1769, 2004.
- [20]. A. M. Abdul-Fattah and H. N. Bhargava, —Preparation and in vitro Evaluation of solid dispersions of halofantrine, *International Journal of Pharmaceutics*, vol. 235, no. 1-2, pp. 17–33, 2002.
- [21]. S. Sinha, M. Ali, S. Baboota, A. Ahuja, A. Kumar, and J. Ali, —Solid Dispersion as an approach for bioavailability enhancement of poorly Water-soluble drug ritonavir, *AAPS PharmSciTech*, vol. 11, no. 2, pp. 518–527, 2010.
- [22]. W. L. Chiou and S. Riegelman, —Pharmaceutical applications of solid Dispersion systems, *Journal of Pharmaceutical Sciences*, vol. 60, no. 9, pp. 1281–1302, 1971.
- [23]. T. Tachibana and A. Nakamura, —A methode for preparing an aqueous Colloidal dispersion of organic materials by using water-soluble polymers: Dispersion of  $\beta$ -carotene by polyvinylpyrrolidone, *Colloid and Polymer Science*, vol. 203, no. 2, pp. 130–133, 1965.
- [24]. Nanosuspension drug delivery technology and application—nanotech—express pharma pulse.
- [25]. R. H. Muller, C. Jacobs, and O. Kayser, —Nanosuspensions for the formulation of poorly soluble drugs, *in Pharmaceutical Emulsion and Suspension*, F. Nielloud and G. Marti-Mestres, Eds., pp. 383–407, Marcel Dekker, New York, NY, USA, 2000.
- [26]. R. A. Nash, —Suspensions, *in Encyclopedia of Pharmaceutical Technology* J. Swarbrick and J. C. Boylan, Eds., vol. 3, pp. 2045–3032, Marcel Dekker, New York, NY, USA, 2nd edition, 2002.
- [27]. K. P. R. Chowdary and B. L. R. Madhavi, —Novel drug delivery technologies for insoluble drugs, *Indian Drugs*, vol. 42, no. 9, pp. 557–564, 2005.
- [28]. V. B. Patravale, A. A. Date, and R. M. Kulkarni, —Nanosuspensions: a promising drug delivery strategy, *Journal of Pharmacy and Pharmacology*, vol. 56, no. 7, pp. 827–840, 2004.
- [29]. R. H. Muller, B. H. L. Bohm, and J. Grau, —Nanosuspensions: a formulation approach for poorly soluble and poorly bioavailable drugs, *in Handbook of Pharmaceutical Controlled Release Technology*, D. Wise, Ed., pp. 345–357, 2000.
- [30]. E. Merisko-Liversidge, G. G. Liversidge, and E. R. Cooper, —Nanosizing: a formulation



- approach for poorly-water-soluble compounds,| *European Journal of Pharmaceutical Sciences*, vol. 18, no. 2, pp. 113–120, 2003.
- [31]. G. G. Liversidge and P. Conzentino, —Drug particle size reduction for decreasing gastric irritancy and enhancing absorption of naproxen in rats,| *International Journal of Pharmaceutics*, vol. 125, no. 2, pp. 309–313, 1995.
- [32]. C. M. Keck and R. H. Müller, —Drug nanocrystals of poorly soluble drugs produced by high pressure homogenisation,| *European Journal of Pharmaceutics and Biopharmaceutics*, vol. 62, no. 1, pp. 3–16, 2006.
- [33]. P. Langguth, A. Hanafy, D. Frenzel et al., —Nanosuspension formulations for low-soluble drugs: pharmacokinetic evaluation using spironolactone as model compound,| *Drug Development and Industrial Pharmacy*, vol. 31, no. 3, pp. 319–329, 2005.
- [34]. C. Jacobs and R. H. Müller, —Production and characterization of a budesonide nanosuspension for pulmonary administration,| *Pharmaceutical Research*, vol. 19, no. 2, pp. 189–194, 2002.
- [35]. J. Möschwitzer, G. Achleitner, H. Pomper, and R. H. Müller, —Development of an intravenously injectable chemically stable aqueous omeprazole formulation using nanosuspension technology,| *European Journal of Pharmaceutics and Biopharmaceutics*, vol. 58, no. 3, pp. 615–619, 2005.
- [36]. Wu, C.Y., Benet, L.S., *Pharmaceutical research*. 2005, 22(1), 23-27
- [37]. Pardhi, D., Shivhare, U., Suruse, P., Chabra, G., *Res J Pharm Dosage Forms Tech*. 2010, 2(5), 314-322.