SOLUBILITY ENHANCEMENT OF POORLY HYDROPHILIC DRUGS BY USING DIFFERENT NEWER TECHNIQUES: A REVIEW

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ABSTRACT

Therapeutic effectiveness of a drug depends upon the bioavailability and ultimately upon the solubility of drug molecules. In case of the oral administration solubility is one of the important parameter for achieving desired concentration of drug in systemic circulation for pharmacological response to be shown. Currently, 40% of the drugs are poorly water soluble which produce side effects such as gastric irritation, peptic ulceration etc. whereas only 8% of new drug candidates have shown both high solubility and permeability. Dissolution rate, absorption, distribution and excretion of a moiety depend upon its solubility characteristics. On the basis of solubility, drugs are classified into four classes of the BCS classification. Solubility challenges are faced in the Class II and Class IV of the BCS system (where dissolution becomes the rate limiting step for the absorption of drug) which comprises of newer generation of NSAIDs like Zaltoprofen, Aceclofenac, Flurbiprofen, their older congeners like Indomethacin, Ibuprofen, Ketoprofen and Diclofenac; anti-diabetics Gliclazide, Glipizide ; newer calcium channel blockers (CCBs) like Nimodipine, Felodipine. Till date various methods of ameliorating the solubility has been suggested, current write up is devoted to the novel methods introduced in recent times wiz. hydrotropy, sono crystallization, hot melt extrusion technique, steam aided granulation, floating granulation, dried nano suspensions, spherical agglomeration, liquisolid technology, cryo techniques .

Keywords: Bioavailability, Solubility enhancement, Novel methods, Dissolution Characteristics.

INTRODUCTION

According to IUPAC, solubility may be defined as "The analytical composition of a saturated solution, expressed in terms of the proportion of a designated solute in a designated solvent, is the solubility of that solute. The solubility may be expressed as a concentration, molality, mole fraction, mole ratio, etc.".[(1)]

The major problem faced during the oral administration of active agent is the bioavailability factor, which ultimately depends on the solubility of the agent. 40% of the drugs discovered are hydrophobic which produce side effects such as gastric irritation, peptic ulceration etc. whereas only 8% of new drug candidates have shown both high solubility and permeability.[(2-3)] The knowledge of solubility and permeability lineaments of the active agents led the way to the BCS (Biopharmaceutics classification system) given by Dr. Gordon Amidon, comprising of four classes of drugs (Table-1). Problematic classes include the Class II and Class IV (Fig.-1).[(4)]

Table 1: BCS classification

Class	Permeability	Solubility	Examples
I	High	High	Metoprolol
II	High	Low	Glibenclamide
III	Low	High	Cimetidine
IV	Low	Low	Hydrochlorothiazide

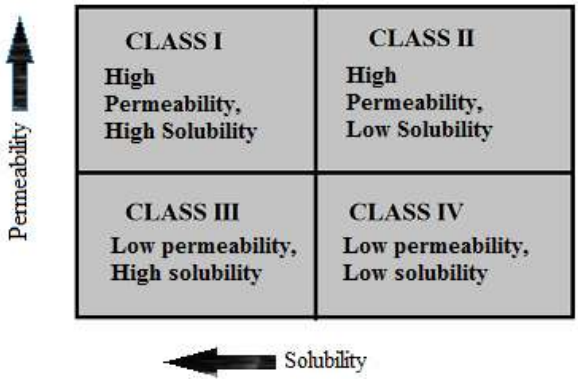

Fig.1 BCS Classification [(4)]

Lower the solubility, less it gets dissolved in the

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surrounding media, lesser it is available for therapeutic effectiveness. [5] Therefore solubility is an essential factor for drug effectiveness, independent of the route of administration. Poorly soluble drugs are often a challenging front for formulators in the industry. Conventional approaches like , use of surfactants, micronization, salt formation, pH regulation , co-solvency for augmentation of solubility have limited applicability, especially when the drugs are poorly soluble simultaneously in aqueous and in non-aqueous media. Therefore interest in finding newer methods to increase solubility and dissolution rate is growing.

METHODS OF AMELIORETING SOLUBILITY

Pharmaceutical industry has been plagued by solubility problems for years. Various methods have been devised by number of authors but with advancing introduction of the molecules day by day newer and efficient methods are required. Here in this piece of review we would take up some new methods which were introduced in last few decades.

1) Hydrotropy

Hydrotropy describes the increase in the solubility of a less soluble solute by the addition of fair concentrations of alkali metal salts of various organic acids. Hydrotropes are the compounds having both an anionic group and a hydrophobic aromatic ring or ring system. Essentially the anionic group increases the hydrophilicity and the ring system interacts with the solute to be dissolved. The term Hydrotropy was coined by *Carl Neuberg* in 1916[6] but the practical implications were introduced as late as 1976 by *Thoma and co-workers*. In 1985, *Saleh co-workers* broadened the virtue of hydrotropic compounds by including the cationic, anionic or neutral molecules having an aromatic ring structure.[7] Hydrotropic polymers were later on added to the list, *Park and co-workers*,*2003,2010*, indentified N-Picolylnicotinamide (PNA) was one of the best hydrotropes for paclitaxel; N, N-diethylnicotinamide (DENA) and N, N-dimethylbenzamide (DMBA) were also used as solubility enhancers.[8-9] *Maheshwari and co-workers* increased solubility of Paracetamol using Urea and of aceclofenac using mixed hydrotropic phenomenon using Urea and Sodium acetate.[10] Sodium acetate was used as a hydrotropic agent to increase the mass transfer coefficient of salicylic acid by *Theneshkumar and co-workers*.[11] Hydrotropy has been used by *Tambe and co-workers* for developing a chromatographical and spectrophotometrical method of estimation of Cefixime.[12] *Pandey and co-workers* used hydrotropic phenomenon of Potassium acetate for analytical estimation of ketoprofen tablet dosage form.[13](Table 2)

Table 2: Various Agents Used For Hydrotropic Solubilization of Drugs [10-15]

Drug	Additive used to exhibit Hydrotropism
Cefadroxil	Potassium acetate, potassium citrate, sodium acetate, urea
Paracetamol, Diclofenac Sodium	Sodium Acetate,Urea
Theophylline	Sodium salicylate
Nifedepine	Sodium salicylate
Ketoprofen	Urea, sodium Citrate

2) Hot Melt Extrusion (HME) Technique

Hot melt extrusion process has been used since 1930 in plastic industry [14]. Extrusion can be simply defined as the process of forming a new material (the extrudate) by forcing it through an orifice or die under controlled conditions, such as temperature, mixing, feed-rate and pressure. HME technique is utilized in the formulation development of poorly water-soluble because of the enhanced dissolution properties, absorption and therapeutic efficacy.[16-17] Advantages of this technique include no requirement of solvent, polymers itself act as binders. (Table-3)

Table 3 Hot Melt Extrusion Technique and its Applications [18-23]

Drug	Polymer
Ibuprofen	**Ethyl cellulose**
Nifedipine	**Poly (oxy) ethylene glycol**
Nimodipine	**HPMC, PVA, Eudragit**
Itraconazole	**HPMC**

3) Steam Aided Granulation

Steam granulation technique was invented by *Karl Hammer* in the year 1982; this method entails an introduction of stream of steam into a bed of particles which are to be granulated.[24] *Rodriguez and co-workers, 2001*, prepared Diclofenac–Polyethylene glycol 4000 accelerated-release granules which showed enhanced dissolution properties than pure drug and physical mixture.[25] *Albertini and co-workers, 2002-03,* developed improved release piroxicam granules using

different excipients like, β-lactose and Polyvinylpyrrolidone of two grades (PVP K-12 and PVP K-90) having better dissolution characteristics. Steam has better penetrability than water and also leaves a thin layer of water on the particles which can be easily aloofed afterwards.[26-27]

4) Floating Granulation

Patel and co-workers, 2010, developed a novel technique called floating granules for enhancement of the solubility of poorly soluble drugs by extending the mean gastric residence time. Ibuprofen and Furosemide are poorly water soluble drugs having good permeability in the stomach but lower in intestine. So they should spend more time in the stomach but gastric emptying time being 30 min-2 hrs is insufficient for complete absorption. Ibuprofen granules were made by simply fusing with Gelucire 44/14 which showed a 3 hrs. residence time with 100% drug release. Furosemide granules with Hydroxylpropyl β- cyclodextrin were prepared by three methods such as kneading method, physical mixture and solvent evaporation method which dissolved completely in 30 mins.[28-29]

5) Dried Nano Suspensions

Nanosuspension are sub nanosized colloidal dispersion stabilized by the use of surface active agents. Pharmaceutical nanosuspensions are defined as dispersion of finely divided drug particles in a vehicle for all the routes of administration. The particle sizes varies from 200-600 nm.[30-31] Dried nanosuspensions are prepared by spray freeze drying or lyophillization. *Eerdenbrugh and co-workers, 2008,* displayed the enhanced dissolution properties of D-α-tocopherol polyethylene glycol stabilized nanosuspensions of indomethacin, loviride, phenytoin.[32] *Chaubal and Popsecu,2008,* studied the efficiency of this technique. [33] *Yang and co-workers, 2011,* enhanced the dissolution profile of Itraconazole using HPMC as stabilizers.[34]

6) Spherical Agglomeration

Spherical agglomeration is a process which is combined unit process of crystallization, Agglomeration and Spheronization. The resultant crystals can be designated as spherical agglomerates. Due to the their spherical shape, the particle characterization properties such as flowability and compressibility of the obtained crystals are more, which makes it more viable for direct tableting or coating without any further processing (size separation etc.). In this process aggregates of crystals are formed by liquid bridges. The agglomerates are formed by agitating the crystals in a liquid suspension in presence of binding agent. The binding liquid should be immiscible in the suspending medium but capable of joining the particles which are processed. This technique is used to increase solubility, dissolution and hence bioavailability of hydrophobic drugs.[35] *Dixit and co-workers,2010-11,* increased the solubility of Mefenamic acid and Indomethacin using this technique.[36-37]

7) Lquisolid Technology

Liquisolid technique is used to prepare compacts or compressible forms of liquid dosage form like that solutions or suspension of hydrophobic active agents. Basic principle implies

Table 4 Summary of Techniques

Technique	Active Principle	Polymer	Ref.
Hot melt Extrusion	Ibuprofen	Ethyl cellulose	20
	Nifedipine	Poly (oxy) ethylene glycol	21
	Itraconazole	HPMC	22
	Nimodipine	HPMC, PVA, Eudragit	23
Floating Granulation	Furosemide	Gelucire	28
	Ibuprofen	Hydroxylpropyl β- cyclodextrin	29
Liquisolid Technique	Piroxicam	Microcrystalline cellulose	40
	Indomethacin	Propylene glycol, Microcrystalline cellulose	41
	Carbamazepine	PEG, HPMC, PVP	42
	Glyburide	Propylene glycol, Microcrystalline cellulose	43
Ultra cryo milling	Phenytoin	PVP	49
Sono crystallization	Flurbiprofen	-	52
	Valdecoxib	Paraffin oil	53
	Progesterone	-	54

conversion of liquid form in to a dried powdered form which has free flow, non adhesive properties by mixing it with a suitable carrier and a coating agent.[38-39]Researchers such as *Spiras and co-workers,1999, and Javadzadeh and co-workers,2005-06,* used various grades of cellulose, starch and sorbitol as carrier material; Silica and its modified grades as coating materials; propylene glycols, polysorbates, glycerin and fixed oils as solvents. Advantages of this technique includes greater bioavailability, increased dissolution properties, working cost is less than capsular dosage form as compacts are later on compressed into tablets, sustained release dosage forms have been developed using this technique.[40-42]. *Singh and co-workers, 2012,* formulated liquisolid tablets of Glyburide using PVP and microcrystalline cellulose for improved dissolution characteristics than direct compressed tablets.[43]

characteristics of Carbamazepni and Danazol ; later on applied to Bovine serum albumin.[46-47] Atmospheric Spray freeze drying by *Wang and co-workers,2006,* in 2006 also showed the properties of solubility enhancement.[48] *Niwa, T., and coworkers, 2012,* used a novel method of ultra-cryo millimg and co-grinding technique to produce nanoparticles of Phenytoin with improved dissolution profile, in this technique liquid nitrogen jet was used for grinding Phenytoin and PVP to produce finer , uniform shape and size particles.[49]

9) Sono Crystallization

Application of ultrasound energy to modify the nucleation of a crystallization process is known as sono crystallization. The energy of ultrasound fashions consecutive compression and expansion. After several cycles a bubble forms and grows then collapses. The collapse of the bubble provides

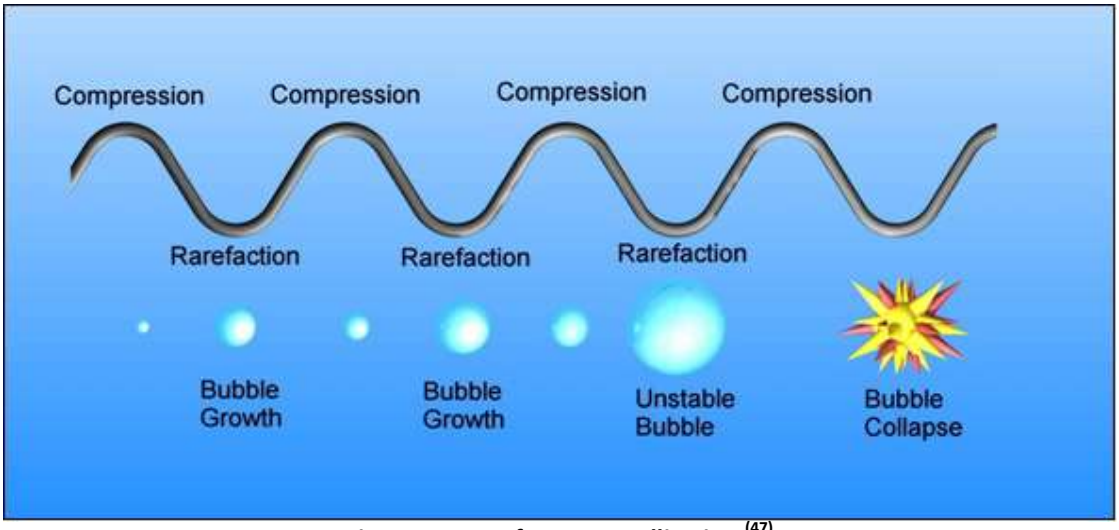

Fig. 2 Process of Sonocrystallization [47]

8) Cryo Techniques

Cryo techniques include Spray freezing drying(SFD), thin film freezing(TFF) and spray freezing into liquid(SFL), which gives rise to amorphous nanostructured aggregates having higher dissolution rates.[43] Spray freeze drying invented by *Erik Thuse, Lewis F, Ginnete And Robert R. Derby* in the year 1964, is a combination of atomization and lyophillisation. It entails spraying of a solution containing the required drug of interest into liquified gase like N_2, O_2, Argon etc. the droplets generated by spraying gets condensed into porous spherical particles.[45] Spray freezing into liquid is similar to SFD where the drug solution is sprayed below the liquefied gases to produce particles which are lyophilized later on. *Williams and co-workers, 2002, 2004* used spray freezing into liquid to enhance the dissolution

energy to promote the nucleation process. (Figure 2) This results in a highly repeatable and predictable crystallization process. Applying Ultrasound to crystallization results in:

- Nucleation at the lowest level of supersaturation where the crystallization overcomes the tendency of the compound to re-dissolve in the solution
- Narrowing of the metastable zone width
- Narrow particle size distribution
- Decrease in the level of cooling necessary to achieve crystallization
- Highly repeatable and predictable crystallization
- Polymorph control

Crystallization consists of two major events:

Nucleation: Solute molecules gather into clusters and reach a critical size to constitute nuclei.

Crystal growth: Subsequent growth of the nuclei.

The ultrasound energy creates sequential compression then expansion. Over several cycles a bubble forms and grows then collapses. The collapse of the bubble provides energy to encourage the nucleation process at the earliest possible point in time. This results in highly repeatable and predictable crystallization.[50] Two of the methods used in industrial level are Ultrasound Mediated Amorphous to Crystalline Transition (UMAX®) and Dispersive Crystallization with Ultrasound (DISCUS®) for the development of inhalational drug delivery.[51] *Kamel,2008,* enhanced the dissolution characteristics of Flurbiprofen using melt sonocrystallization technique [52], *Chaudhari and co-workers,2009,* studied the process on Valdecoxib[53] and *Paradkar and co-workers,2010,* analyzed the various polymeric form of Progesterone.[54]

CONCLUSION

Various technologies have been introduced for the enhancement of solubility of poorly hydrophilic drugs. The basic approaches involve the interaction of a hydrophillic molecule with a poorly soluble drug to give rise a phenomena of increased solubility, which in turn increase the bioavailability and intrinsic activity (pharmacological activity). Older methods had the problem of irregular shape or size, larger particle sizes which to lead to irregular dissolution characteristics or toxicity problems as in case of surfactants. Novel methods have shown the properties of uniform shape and size which when either used in combination or individually will have a potential for the dissolution enhancement of the newer chemical entities to be introduced in the future.

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