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Important Approaches of Current Novel Solubility Enhancement Techniques

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ABSTRACT

Drug therapeutic effectiveness depends upon the drug molecules solubility and the bioavailability of drug molecules. After oral administration of drug to give pharmacological response, solubility is crucial parameter for obtaining desired concentration of drug molecule in systemic circulation. In current scenario about 40% of the newly developed drug molecules is poorly water soluble. With rate of dissolution and pharmacokinetic parameters like, absorption, distribution and excretion of drug molecules depend upon its solubility. Depending upon solubility and permeability, drugs are classified into four basic classes of the biopharmaceutical classification system (BCS) classification. The problem of poor solubility are faced in the Class II and Class IV of the biopharmaceutical classification system which comprises of novel generation of most all category of drugs like NSAIDs like Zaltoprofen,; anti-diabetics Gliclazide; newer calcium channel blockers like Nimodipine,. Till date various methods of ameliorating the solubility has been discovered and utilized successfully to enhance the solubility. This review highlights briefly on information about important approaches of novel solubility enhancement techniques.

Keywords: Solubility enhancement, Cryo-technology, Sono-crstallization

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INTRODUCTION

The maximum amount of the solute, which is in equilibrium with the solid solute at a given temperature, pressure and pH is called as solubility[1]. Also solubility defined for the solute as the analytical composition of a saturated solution, expressed in terms of the proportion of solute in solvent. The solubility may be expressed by various units such as a molarity, concentration, normality, molality, mole fraction, etc[2]. Dr. Gordon Amidon gives four main classes for drug molecules designed as Biopharmaceutics classification system (BCS) based on solubility and permeability of the active drug molecule as Class-I High solubility & High permeability (Eg: Metoprolol, etc.), Class-II Low solubility & High permeability (Eg: Glibenclamide, ezetimide, etc), Class-III High solubility & Low permeability (Eg: Cimetidine, etc.) and Class-IV Low solubility & Low permeability (Eg: Bifonazole,s etc.)[3]. The main obstacle observed during the developing dosage form for administration by oral route of newly invented therapeutically active agent is the optimum bioavailability of drug, which ultimately depends on the solubility as well permeability of the therapeutically active agent. About 40% of the newly discovered drug molecules are hydrophobic in nature which shows less bioavailability as well as local side effects in gastrointestinal tract like irritation of gastric mucosa, etc [4-5]. For reducing these obstacles in developing the dosage forms for oral administration it is necessary so show good solubility, so drug is easily available for absorption. Therefore solubility of therapeutically active agent is one of most important factor for drug effectiveness as well as for development of oral dosage form with optimum bioavailability. Conventional solubility enhancement approaches such as, salt formation, co-solvency, use of surfactants; micronization, pH regulation etc have their own limited applicability as well as few limitations of each of above method also. Therefore interest in finding novel methods to increase solubility and dissolution rate is growing and many novel techniques are developed and successfully implemented by pharmacy industry.

Current Novel approaches of solubility enhancement

Here in this review will go through brief information about important approaches of current novel solubility enhancement techniques which are now a day utilized for enhancement of solubility of poorly soluble drug molecules.

Dried Nano-suspensions

Pharmaceutical nano-suspensions are defined as biphasic dispersion of finely divided nano drug particles in a suitable vehicle for all the routes of administration. Nano-suspension is nano sized colloidal dispersion prepared which is stabilized by the using surfactants. The particle size of

nano-suspension resides in range between 200-600 nm[6-7]. Lyophilization or spray freeze drying technique used for preparation of the dried nano-suspensions. *Eerdenbrugh etal* utilized this technique, to enhance solubility, dissolution and ultimately bioavailability of hydrophobic drugs. In this technique aggregates of drug crystals are formed by liquid bridges. By shaking the drug crystals in a liquid in presence of binding agent the agglomerates are formed. The binding liquid should be immiscible in the suspending medium but capable of joining the particles which are processed [8-11]. *Dixit et al., 2010-11,* enhanced solubility of Indomethacin and Mefenamic acid using dried nano-suspension technique[12-13].

Floating Granulation

To enhance the solubility of poorly soluble drugs *Patel etal*, developed a new technique called floating granules by increasing the mean gastric residence time of drug in gastrointestinal tract. By using this floating granulation technique by preparing floating granules they enhance the dissolution of ibuprofen. Floating of drug granules is requiring for increasing residence time of granules in stomach. For optimum absorption Ibuprofen should be resides in stomach so its maximum absorption will occur because it is mostly permeable through stomach. By preparing various floating granules formulation of ibuprofen with immediate release floating granule like gelucire 44/14 and sustained release floating granules containing gelucire 43/01 and small amount of gelucire 44/14 they enhance the dissolution of ibuprofen[14].

Hot Melt Extrusion (HME) Technique

Since short twentieth century hot melt extrusion process has been utilized in plastic industry[15]. Extrusion can be basically characterized as the way of forming a new material (the extrudate) by compelling it through an orifice or die under controlled conditions, like feed-rate, mixing temperature, and pressure. This technique is used in the formulation of poorly soluble drugs because of the improvement not only in dissolution properties but also absorption and therapeutic efficacy of drug[16-17]. Main feature of this technique is polymers itself act as solvent as well as binders so no requirement addition of separate solvent. Till date this technique is successfully used for enhancement in dissolution of itraconazole with hydroxypropyl methylcellulose, ibuprofen with Ethyl cellulose, , nimodipine with eudragit and nifedipine with poly (oxy) ethylene glycol, Poly(vinyl alcohol) hydroxypropyl methylcellulose[16-21].

Hydrotropy

The technique in which enhancement in the solubility of a poorly soluble solute in solvent by the addition of low concentrations of alkali metal salts of different organic acids is called as hydrotropy. This name was coined by *Carl Neuberg*. The compounds with both a hydrophobic

aromatic ring and anionic group are called as Hydrotropes. The ring system interacts with the solute to be dissolved and hydrophilicity is enhanced by anionic group[22]. By including the various molecules like anionic, cationic or neutral molecules having an aromatic ring structure the virtue of hydrotropic compounds was broadened by *Saleh co-workers*[23]. Further research on molecules used in hydrotropy revels that N, N-dimethylbenzamide and N, N-diethylnicotinamide can be used for solubility enhancement and also identified N-Picolylnicotinamide was one of the best hydrotropes for paclitaxel[24-25]. The research by *Maheshwari et al. shows that* enhancement in the solubility of Paracetamol can be done by using Urea and of aceclofenac using mixed combination of Urea and Sodium acetate by mixed hydrotropic phenomenon[26]. For enhancement in the mass transfer coefficient of salicylic acid the utilization of sodium acetate was as a hydrotropic agent by *Theneshkumar et al.*[27].

Hydrotropy was also successfully utilized for developing a chromatographical and spectrophotometrical method of estimation of Cefixime by *Tambe et al.* as well as for analytical estimation of ketoprofen tablet dosage form by using potassium acetate by *Pandey et al.* [28, 29]. (Table 1)

Table 1: Various Agents Used For Hydrotropic Solubilization of Drugs [23-30]

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

Sono-crystallization

The technique in which process of nucleation of crystal development modified with the help of power of ultrasound energy is known as sono-crystallization. The most crucial effect of ultrasound energy on crystallization process is the initiation of nucleation for crystal development. Physical properties of the products synthesized by sono-crystallization have been manipulated by changing and controlling the insonation regime, in this way the development of such molecule with higher solubility as compared to synthesized by non sono-crystallization is possible and it is useful for enhancement of solubility of poorly soluble drug molecules [31].

Steam Aided Granulation

The introduction of stream of steam into particles is to be granulated is called as steam aided granulation technique which was invented by *Karl Hammer* [32]. The research of *Rodriguez et al.*

shows that accelerated-release granules diclofenac – polyethylene glycol 4000 which showed improved dissolution as compared to pure drug[33].

Albertini et al., developed enhanced release piroxicam granules by steam aided granulation technique by utilizing various excipients like, β-lactose and Polyvinylpyrrolidone of two grades with enhanced dissolution properties. As compared to water steam has more penetrability and also leaves a thin layer of water on the particle surface[34-35].

Cryo Techniques

Cryo techniques intechnique in which amorphous nanostructured aggregates are developed with enhanced dissolution rates which include thin film freezing, spray freezing drying and spray freezing into liquid[36]. By combination of lyophollisation with atomization the spray freeze drying invented by *Erik Thuse, et al.* in the year 1964. This technique includes spraying of a solution of poorly soluble drug into liquefied gases like nitrogen; Argon etc. the spraying droplets formed after spraying are get condensed into porous spherical particles. *Williams et al., utilizes* spray freezing to increase the dissolution energy to further progress of the nucleation. This originates as predictable and repeatable crystallization process[37].

Liquisolid Technology

The technique in which conversion of liquid form such as suspension, solution of poorly soluble drugs into solid compacts or compressible forms is known as Liquisolid compact technology of liquisolid technology. Basic principle of this technique is utilization of carrier and coating material to convert liquid form in to a dried solid compacts or compressible forms which has free flow, non adhesive charachteristics[38-39]. The Researchers such as *Spiras et al. and Javadzadeh et al.* utilized starch, different grades of cellulose and sorbitol as carrier material; silica and modified silica grades as coating materials and non volatile sliquids such as propylene glycols, glycerin and fixed oils as solvents. The desirable feature of this technique includes enhanced bioavailability as well as dissolution characteristics; low working as compared to capsular dosage form, the formulation as sustained release dosage forms can be possible using this technique[40-42].

Spherical Agglomeration

The process in which combination of unit process of crystallization such as spheronization and agglomeration is used for dosage form development is called as Spherical agglomeration. The crystals formed by utilizing this process are known as spherical agglomerates. Due to the their spherical shape, the resultant crystals shows improved particles physical properties such as flowability and compressibility, which is more useful for direct tableting or coating without any

further processing. By utilizing three methods such as physical mixture, kneading method, and solvent evaporation method the granules of furosemide with Hydroxylpropyl β- cyclodextrin is prepared which shows complete dissolution with in 30 minutes[43-44].

CONCLUSION:

The rate determining step for oral absorption of the poorly water soluble drugs is its dissolution. Solubility is the crucial major requirement for the absorption of the drug into systemic circulation after oral administration. The different novel techniques described above single or in combination of two or more techniques can be utilized to enhance the solubility of the drugs. Correct and suitable selection of solubility enhancement technique is the crucial step to achieve the goals of a standard formulation like better oral bioavailability, minimum frequency of dosing and improved patient compliance in combination with a economical cost as well as low cost production. Selection of correct and suitable technique for improved solubility based upon not only on physical, chemical as well as physiological properties of drugs like solubility, melting point, physical nature, chemical nature, absorption site, pharmacokinetic properties and dosage form requirement like type of formulation, strength, modified release but also on regulatory requirements. By correct selecting the method for enhancement in solubility of poorly soluble drug can be achieved.

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