DOI: 10.2478/cipms-2019-0035 Curr. Issues Pharm. Med. Sci., Vol. 32, No. 4, Pages 203-209

sciendo

Current Issues in Pharmacy and Medical Sciences

Formerly ANNALES UNIVERSITATIS MARIAE CURIE-SKLODOWSKA, SECTIO DDD, PHARMACIA

journal homepage: http://www.curipms.umlub.pl/

An overview of techniques for multifold enhancement in solubility of poorly soluble drugs

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ARTICLE INFO

Received 05 February 2019
Accepted 24 April 2019

Keywords:
poorly soluble drugs,
solubility, dissolution,
bioavailability,
salt formation,
solid dispersion,
complexation,
co-crystallization.

ABSTRACT

Poor water solubility of newly discovered compounds has become the most common challenge in the drug development process. Indeed, poor solubility is considered as the root cause of failure of drug during drug development phases. Moreover, it has also been reported to be the main reason for bioavailability issues such as poor, inconsistent, incomplete and highly variable bioavailability of the marketed products. As per an estimate, approximately 90% of drug molecules suffer with poor water solubility at early stage and approximately 40% of the marketed drugs have bioavailability problems mainly due to poor water solubility. Solubility enhancement of the newly discovered compounds is primary research area for the pharmaceutical industries and research institutions. The conventional techniques to improve aqueous solubility of drugs employ salt formation, prodrug formation, co-crystallization, complexation, amorphous solid dispersion and use of co-solvent, surfactants or hydrotropic agents. Current advancement in the science and technology has enabled the use of relatively new techniques under the umbrella of nanotechnology. These include the development of nanocrystals, nanosuspensions, nanoemulsions, microemulsions, liposomes and nanoparticles to enhance the solubility. This review focuses on the conventional and current approaches of multifold enhancement in the solubility of poorly soluble marketed drugs, including newly discovered compounds.

INTRODUCTION

Combinatorial chemistry and high throughput screening techniques have been employed by pharmaceutical industries to hasten their drug discovery and development processes [1,2]. These techniques have enabled to synthesize and test a very huge number of compounds per day. As a result, a large number of new chemical entities or potential drug candidates are introduced or discovered for a particular diseased condition. However, that is not the end of the process, as further drug development encounters several challenges. Among these are solubility, permeability, stability, safety and efficacy etc. The aforementioned deaccelerate drug development and delay the drug approval process [3-5]. Among these challenges, poor water solubility of the newly discovered compounds has appeared as the most common challenge in the early drug development, while inefficacy was found as main reason of drug failure in later drug development phases such as phase II. It has been reported that high throughput screening (HTS)-based approaches are linked with lipophilicity, molecular weight and H-bonding properties leading to poor aqueous solubility of the newly discovered compounds [6]. As per an estimate, approximately 90% of drug molecules suffer with poor water solubility at early stage, while approximately 40% of the marketed drugs have bioavailability problems mainly due to poor water solubility [7].

The poor solubility challenge can be overcome by using various conventional and advanced techniques. For instance, conventional methods such as salt formation [8], prodrug [9], co-solvent [10], micellar solublization [11], hydrotrophy [12], complexation [13], co-crystallization [14] and amorphous solid dispersion [15] have been employed to enhance solubility of several poorly soluble drugs. Advanced methods for solubility enhancement are generally based on nanotechnology that include either nanonization or nanoencapsulation of poorly soluble drugs. In this regard, nanocrystal [16], nanosuspension [17], nanoemulsion [18], microemulsion [19] and nanoparticles [20] have been investigated for the improvement of solubility or bioavailability of challenging drug candidates.

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CONVENTIONAL TECHNIQUES TO IMPROVE SOLUBILITY OF DRUGS

There are several conventional techniques to improve solubility of the drugs as shown in Figure 1.

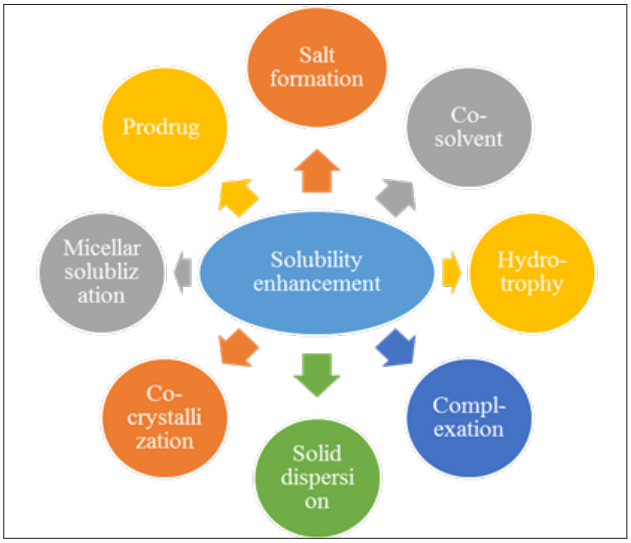

Figure 1. Conventional techniques of solubility enhancement

1. Enhancement in solubility of drugs through salt formation

Improvement of solubility of drug by preparing its salt is a classical technique and can be traced back to the 1970s [21,22]. As most of the newly discovered drugs are either acidic or basic in nature, these can be converted to their soluble salt forms to enhance water solubility (Table 1).

Table 1. List of some poorly soluble drugs, their salt forms and degree of solubility enhancement

Drug	Salt form	Solubility enhancement	Reference
Pyridoclax	Dihydrochloride	4 fold	[23]
Sildenafil	Glutarate salt	3.2 fold	[24]
Furosemide	Sodium salt	20 fold	[25]
Phenytoin	Sodium salt	60 fold	[26]
Bupivacaine	Chloride salt	200 fold	[27]
Indomethacin	Arginine & lysine	10000 & 2296 fold	[28]

2. Enhancement in solubility through prodrug approach

The prodrug approach is also one of the classical techniques for solubility enhancement. Prodrugs are inactive compounds consisting of parent drug with or without carrier that are potentiated due to release of active drug in the body through some chemical or enzymatic cleavage. Prodrugs can either be bipartite wherein the drug is directly attached with the carrier or tripartite – containing a spacer between drug and carrier. The inert carriers are commonly attached with the drug by functional groups – amides, carbamates, carbonates, esters, ethers, imines and phosphates, etc. [29] (Table 2).

Table 2. Poorly soluble drugs, prodrug derivatives and degree of solubility enhancement

Drug	Prodrug derivative	Solubility enhancement	Reference
Bupivacaine base	N-butanoyloxymethyl derivative	10,000 fold	[30]
Trifluoromethyl ketone	1,1,1-trifluoro-3-(octane-1-sulfonyl)-propan-2,2-diol & 1,1,1-trifluoro-3-octylsulfanyl-propan-2-one derivative	10 fold	[31]
Paclitaxel	Dihydroxyl derivative	50 fold	[32]
Phosphoramidates	Tyrosine derivative	30 fold	[33]
Thiabendazole	N-alkoxycarbonyl & N-(4-amino-methylbenzoyl)oxymethyl derivative	12 & 300 fold	[34]
Lamivudine	5′-O-carbonates	70 fold	[35]
3-Carboranyl Thymidine Analogs	L-valine-, L-glutamate-, and glycine ester derivatives	48-6600 fold	[36]
Metronidazole	N, N-diethylglycinate hydrochloride (3a) & 4-ethylpiperazinoacetate (3e) derivatives	140 & 100 fold	[37]

3. Enhancement in solubility through co-solvent approach

The co-solvent approach of enhancing water solubility of poorly soluble drugs involves mixing water-miscible nontoxic organic solvent with water. This improves the solvent action of water, leading to the solublization of poorly soluble drugs. The commonly used co-solvents include ethanol, glycerol, propylene glycol and polyethylene glycols [38] (Table 3).

Table 3. Poorly soluble drugs, co-solvent derivatives and degree of solubility enhancement

Drug	Co-solvents	Solubility enhancement	Reference
Methyl propyl trisulfide	Ethanol and cremophur	2900 fold	[39]
Ethyl-paraben	Nicotinamide	2 fold	[40]
6-mercaptopurine	Sodium benzoate & sodium hippurate	6 fold	[41]
Phosphoramidates	Tyrosine derivative	30 fold	[42]
Enrofloxacin	Ethanol, glycerol, PEG 400, propylene glycol	1.1-3.3 fold	[43]
Ferulic acid	Isopropanol	Approx. 53 fold	[44]

4. Enhancement in solubility through micellar solublization

The micellar solublization approach is based on the fact that surfactants, owing to their amphiphilic nature, associate spontaneously in anisotropic clusters known as ‘micelles’. These contain a hydrophobic center and hydrophilic surfaces. Poorly soluble or water insoluble drugs are enclosed in the hydrophobic centers of micelles, thus become solubilized. It is noteworthy that association or aggregation of surfactant molecules occur at a particular concentration called the ‘critical micelle concentration’ (CMC). The lower the CMC value of a particular surfactant, the more stable a micelle is formed [45] (Table 4).

Table 4. Poorly soluble drugs, surfactants and degree of solubility enhancement

Drug	Surfactants	Solubility Enhancement	References
Apigenin	Soluplus® and Pluronic F127	3442 fold	[46]
Ibuprofen	Poloxamer 407	18 fold	[47]
Fenofibrate	Sodium lauryl sulfate	2000 fold	[48]
Raloxifene	Igepal CO-890	2 fold	[49]
Celecoxib	Quaternary-ammonium-palmitoyl-glycol-chitosan	60 fold	[50]
Sirolimus	Tocopheryl polyethylene glycol succinate	400 fold	[51]
Artemisinin	Sodium dodecyl sulphate	50 fold	[52]
Griseofulvin	SDS, CTAB, Tween 80, and Cremophor EL.	104, 31, 4 & 3 fold	[53]
Penicillin V	Polyoxyethylene-23-lauryl ether	3 fold	[54]

5. Enhancment in solubility through hydrotropic agents

The hydrotropic solublization approach involves the addition of excess hydrotropic agents (hydrophilic inert solutes or polymers) to improve the solubility. Hydrotropic agents are amphiphilic and contain both a hydrophilic head group and a hydrophobic tail group. This is similar to the surfactants, however, herein, the hydrophobic tail is too small to cause spontaneous self-aggregation as observed in micellar solublization. Nevertheless, a unique association (stack-type aggregation) does occur at substantially higher concentrations of hydrotropic agents [55] (Table 5).

Table 5. Poorly soluble drugs, hydrotropic agents and degree of solubility enhancement

Drugs	Hydrotropic agents	Solubility Enhancement	References
Nevirapine	Urea, lactose, citric acid and mannitol	27, 11, 42 & 10 fold	[56]
Carbamazepine	Nicotinamide and urea	30 fold	[57]
Lurasidone	Nicotinamide, sodium citrate, urea and sodium benzoate	12-61 fold	[58]
Furosemide	Urea, sodium acetate, sodium benzoate, sodium citrate	16-296 fold	[59]
Riboflavin	Nicotinamide and urea	20 fold	[60]

6. Enhancement in solubility through complexation approach

The complexation approach of enhancing drug solubility is a classical and commonly used method. Moreover, this approach is one of the most successful – as evident by several challenging drug products on the market, the solubility of which was improved by complexation. Examples include Prostarmon-E™ sublingual tablets (prostaglandin complexed with cyclodextrin, 1976), Brexin® tablets (Piroxicam complexed with β-CD, 1977) and Sporanox® (itraconazole/2-hydroxypropyl-βCD oral solution) [61,62]. Inclusion complexes are special kinds of complexes wherein the guest molecule (the hydrophobic drug to be included) fits non-covalently in the inner hydrophobic cavity of the host molecule (the complexing agent). Thus, the poorly soluble hydrophobic drug substance becomes more soluble as it is in a water that contains complexing agents. Complexation of drugs with complexing agents depends on the polarity and size of the host and guest molecule. Cyclodextrins, the cyclic sugars, are the most commonly used complexing agent for the improvement of solubility, owing to the availability of different host molecule cavity sizes [63] (Table 6).

Table 6. Poorly soluble drugs, their complexing agents and degree of solubility enhancement

Drugs	Complexing agents	Solubility Enhancement	References
Nerolidol	Hydroxypropyl-beta-cyclodextrin	70 fold	[64]
Pseudolaric acid	Hydroxypropyl-beta-cyclodextrin	600 fold	[65]
SN-38 (irinotecan metabolite)	Cyclodextrin derivatives	30-1,400 fold	[66]
Astilbin	β-cyclodextrin	122 fold	[67]
Dihydroartemisinin	Hydroxypropyl-beta-cyclodextrin	89 fold	[68]
Glyburide	Hydroxybutenyl-beta-cyclodextrin	400 fold	[69]
Phenytoin	Hydroxypropyl betacyclodextrin and Methyl beta-cyclodextrin	420 & 578-fold	[70]
Icariin	β-cyclodextrin	36 fold	[71]
Naringin	β-cyclodextrin	15 fold	[72]
Silymarin	β-cyclodextrin	6.7 fold	[73]

7. Enhancment in solubility through co-crystal approach

Cocrystals are a crystalline mixture consisting of an active pharmaceutical agent bonded non-covalently with an inactive pharmaceutical agent called a 'conformer' [74]. The advantage of co-crystal enhancement is that any kind of drug, whether acid, base or neutral, can be co-crystallized, unlike salt formations which require that the drug must possess certain characteristics. Cocrystals are high energy forms and are known to increase solubility of the included drugs due to rapid dissociation in the medium, thus creating a supersaturated drug [75] (Table 7).

Table 7. Poorly soluble drugs, their coformers and the degree of solubility enhancement

Drug	Coformers	Solubility Enhancement	References
Hydrochlorothiazide	Nicotinic acid, nicotinamide, succinamide, p-aminobenzoic acid, resorcinol and pyrogallol	1.5-6 fold	[76]
Carbamazepine	Cinnamic acid	152 fold	[77]
Indomethacin	Saccharin	13-65 fold	[78]
Furosemide	Caffeine, Adenine & Cytosine	6, 7 & 11 fold	[79]
Andrographolide	Salicylic acid	12 fold	[80]

8. Enhancment in solubility through solid dispersions

Solid dispersions are amorphous mixtures of solid drug in solid matrix (inactive small molecule or polymer) at molecular levels. Solid dispersions result in supersaturated drug solutions which may precipitate before being absorbed, therefore, components to inhibit drug precipitation should be added into solid dispersions [81]. Fortunately, the most commonly used polymer matrix for solid dispersions, polyvinylpyrrolidone and hydroxypropyl methylcellulose, are known to prevent drug precipitation [81]. The solid dispersion approach is considered a successful and commercially viable method as evidenced by various marketed solid dispersion formulations (Table 8).

Table 8. Poorly soluble drugs, their dispersants and degree of solubility enhancement

Drug	Dispersants	Solubility Enhancement	References
Cefdinir	Hydroxypropyl-methylcellulose, carboxymethylcellulose-Na, polyvinyl pyrrolidone K30	9 fold	[82]
Clotrimazole	D-mannitol, d-fructose, d-dextrose and d-maltose	43-806 fold	[83]
Docetaxel	Soluplus	93 fold	[84]
Carvedilol	Tween 80/PVP K30	11,500	[85]
Tranilast	Eudragit EPO	3000 fold	[86]
Tacrolimus	Hydroxypropyl-beta-cyclodextrin	900 fold	[87]
Itraconazole	Eudragit E 100	141.4-146.9-fold	[88]
Carvedilol	Hydroxypropyl-β-cyclodextrin + tartric acid	340 fold	[89]
Carvedilol	Hydroxypropyl-β-cyclodextrin + Polyvinylpyrrolidone K-30	70 fold	[90]
Repaglinide	Eudragit E100	100 fold	[91]
Nilotinib	Soluplus	630 fold	[92]
Ritonavir	Lyophilized milk	30 fold	[93]
Miconazole Nitrate	Beta-cyclodextrin (β-CD) + PVP	72 folds and 316 folds	[94]
Candesartan cilexetil	Hydroxypropyl-β-cyclodextrin = PEG 6000	22 fold	[95]
Curcumin	PVP K30	880 fold	[96]

NANOTECHNOLOGY APPROACH TO IMPROVE SOLUBILITY OF DRUGS

Nanotechnology is a recently emerged multidisciplinary scientific technology dealing with objects or materials at nanoscale. It is not a new discipline of science such as physics or chemistry, rather it is a new technology expanding into almost every domain of science, including material sciences, chemical sciences, electronic and health sciences. Nano-medicine and nanotechnology in drug delivery has witnessed a substantial growth in health-care researches owing to its huge potential. In 2014, the global market share was ~41 bn USD and this is expected to reach ~120 bn USD by 2023 [97]. Nano carriers – liposomes, microemulsions, nano-emulsions, nanoparticles, nano-suspensions and nano-crystals – have been investigated to address issues such as poor solubility, poor permeability, instability, and the unsuitable pharmacokinetic profiles of certain existing drugs. The investigation of nano formulations to address specific disease or drug related issues could be traced back to 1970s, however, their application to improve drug solubility has only bee recently approved [98,99]. The nanofabrication techniques of solubility enhancement (Figure 2), whether based on lipoid carriers such as fabrication of liposomes, microemulsions, nano-emulsions, or based on polymeric carriers such as fabrication of nanoparticles, nano-suspensions and nano-crystals, generally result in enormous increase in surface area of the fabricated nano-medicines, thereby improving saturated solubility and rate of dissolution [100].

Liposomes are nano-sized bilayer vesicles of phospholipids that contain hydrophobic bilayer periphery and an aqueous hydrophilic cavity [101]. These are capable of enclosing both hydrophilic, as well as hydrophobic drugs. Microemulsions and nanoemulsions are colloidal emulsions

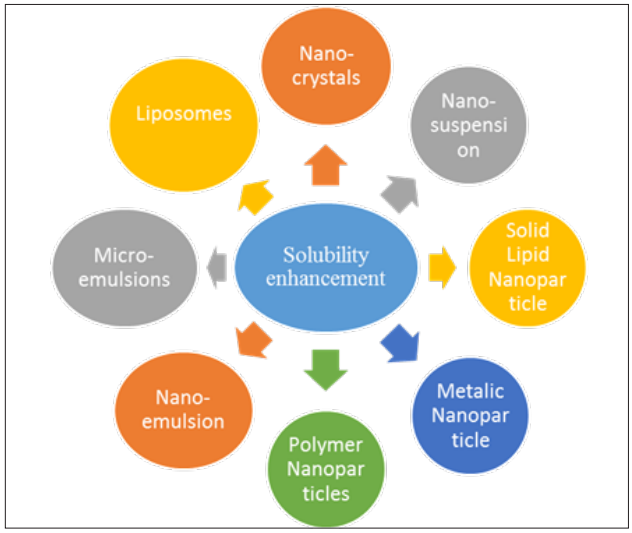

Figure 2. Nanofabrication techniques of solubility enhancement

containing a dispersed phase at nano-sized scale. Microemulsions are produced spontaneously by gentle mixing of oil, water and appropriate amounts of emulsifier and co-emulsifier [102]. Nanoemulsions, in contrast, are produced with the help of high-energy mixers or homogenizers. Polymeric nanoparticles or nanosuspensions are nanosized drug materials enclosed within a polymeric matrix or shell generally produced by way of utilizing the nanoprecipitation technique. Herein, slow addition of the organic solution of drug and polymer in an antisolvent induces nanoprecipitation and stabilization of the drug after encapsulation within polymeric nanoparticles [103] (Table 9).

Table 9. Poorly soluble drugs, the nanotechnology employed and the degree of solubility enhancement

Drug	Dispersants	Solubility Enhancement	References
Fusidic acid	Poloxamer-188	8 fold	[104]
Curcumin	β-lactoglobulin	~35-fold	[105]
Lacidipine	Sodium deoxycholate	70 fold	[106]
Apigenin	Phospholipid phytosome	36 fold	[107]
Silymarin	Water-soluble chitosan	7.7 fold	[108]
Lutein	Poly (lactic-co-glycolic acid) (PLGA)-polyethylene glycol (PEG)	735 fold	[109]
Pyridoclax	Tween 80	1000 fold	[110]
10-methoxy-9-nitrocamptothecin	Lipoid E80 and cremophor EL	200 fold	[111]
Resveratrol	Castor oil, Capmul, Cremophor EL/RH 40/ RH 60)	23 fold	[112]
Progesterone and indomethacin	Isopropyl myristate-based microemulsion	500-3300	[113]

CONCLUSIONS

There are several conventional and advanced methods of solubility enhancement. Each method has its own merits and demerits, which need to be considered at the time of selection of the method. Moreover, permeability and stability inside the body are also needed to be considered, as mere solubility enhancement in the laboratory would not be beneficial in real application of improvement of performance of the drug.

CONFLICT OF INTEREST

We declare that there is conflict of interest.

AUTHOR CONTRIBUTIONS

Mohammad Javed Ansari: Conceptualization, Literature search and Manuscript writing.

Saad M Al-Shahrani: Draft Editing and final reviewing.

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