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Solubility Enhancement Techniques and Use of Dendrimers in the Solubilization of Water Insoluble and Poorly Soluble Drugs-A Review

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Abstract

Solubility of a drug is an important parameter in the formulation development. Hence various techniques are used for the improvement of the solubility of poorly water-soluble and water insoluble drugs include Particle Size Reduction, Solid Dispersion, Nanosuspension, Supercritical Fluid Technology, Cryogenic Technology, Inclusion Complex Formation Techniques, and Floating Granules etc. The purpose of this review article is to describe the techniques of solubilizaton for the attainment of effective absorption and improved bioavailability. Solubility is the phenomenon of dissolution of solid in liquid phase to give a homogenous system. Solubility is one of the important parameter to achieve desired concentration of drug in systemic circulation for pharmacological response to be shown. Poorly water soluble drugs often require high doses in order to reach therapeutic plasma concentrations after oral administration. Low aqueous solubility is the major problem encountered with formulation development of new chemical entities. Any drug to be absorbed must be present in the form of an aqueous solution at the site of absorption. Water is the solvent of choice for liquid pharmaceutical formulations. Most of drugs weakly acidic and weakly basic with poor aqueous solubility. Dendrimers are the novel class of polymer and it is used to enhance the solubility for the delivery of many water insoluble drugs, eg; anticancer, anti-inflammatory etc.

Keywords: Solubility, solubility enhancement, bioavailability, dendrimers etc.

Contents

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1. Introduction

The term 'solubility' is defined as maximum amount of solute that can be dissolved in a given amount of solvent. It can also be defined quantitatively as well as qualitatively. Quantitatively it is defined as the concentration of the solute in a saturated solution at a certain temperature. In qualitative terms, solubility may be defined as the spontaneous interaction of two or more substances to form a homogenous molecular dispersion. A saturated solution is one in which the solute is in equilibrium with the solvent. The solubility of a drug is represented through various concentration expressions such as parts, percentage, molarity, molality, volume fraction, mole fraction [1-3]. There are various techniques available to improve the solubility of hydrophobic drugs.

The solubility of the poorly soluble drug is increased compared to water alone, so if compounds can permeate through the epithelium orally, the fraction of orally absorbed drug may be increased. pH adjustment is also frequently combined with co-solvents to further increase the solubility of the poorly soluble drug. If the precipitation upon dilution is fine or amorphous, bioavailability can be increased due to an increased concentration gradient and enhanced surface area for dissolution. In situations where the drug precipitates into poorly soluble particles that require dissolution and do not rapidly redissolve, bioavailability may not be sufficiently increased. This approach is used frequently in Survey as pre-clinically pH adjustment is a good technique to assess the efficacy of poorly soluble drugs due to its universality and relative simplicity. However, if precipitation of the poorly soluble drug occurs uncontrollably after contact with a pH at which the drug is much less soluble (oral as well as parenteral), the interpretation of the results may be misleading.Some traditional and novel approaches to improve the solubility are:

Particle Size Reduction

The solubility of drug is often intrinsically related to drug particle size as a particle becomes smaller, the surface area to volume ratio increases. The larger surface area allows a greater interaction with the solvent which cause increase in solubility [4]. Conventional methods of particle size reduction, such as comminution and spray drying, rely upon mechanical stress to disaggregate the active compound. The critical parameters of comminution are well-known to the industry, thus permitting an efficient, reproducible and economic means of particle size reduction. However, the mechanical forces inherent to comminution, such as milling and grinding, 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. Also, this traditional methods are often incapable of reducing the particle size of nearly insoluble drugs (<0.1mg/mL) [5-7].

Micronization is another conventional technique for the particle size reduction. Micronisation increases the dissolution rate of drugs through increased surface area; it does not increase equilibrium solubility[8]. Decreasing the particle size of these drugs which cause increase in surface area, improves their rate of dissolution. Micronization of drugs is done by milling techniques using jet mill, rotor stator colloid mills etc. Micronization is not suitable for drugs having a high dose number because it does not change the saturation solubility of the drug. These processes were applied to griseofulvin, progesterone, spironolactone and diosmin, fenofibrate. For each drug, micronization improved their digestive absorption, and consequently their bioavailability and clinical efficacy [9-10].

2. Solid Dispersion

The concept of solid dispersions was originally proposed by Sekiguchi and Obi, who investigated the generation and dissolution performance of eutectic melts of a sulfonamide drug and a water-soluble carrier in the early 1960s.8 Solid dispersions represent a useful pharmaceutical technique for increasing the dissolution, absorption and therapeutic efficacy of drugs in dosage forms. The term solid dispersion refers to a group of solid products consisting of at least two different components, generally a hydrophilic matrix and a hydrophobic drug. The most commonly used hydrophilic carriers for solid dispersions include polyvinylpyrrolidone, polyethylene glycols, Plasdone-S630. Many times surfactants may also used in the formation of solid dispersion. Surfactants like Tween-80, Docusate sodium, Myrj-52, Pluronic-F68 and Sodium Lauryl Sulphate used. The solubility of celecoxib[9], halofantrine [10], ritonavir [11] can be improved by solid dispersion using suitable hydrophilic carriers. There are various techniques to prepare the solid dispersion of hydrophobic drugs to improve their aqueous solubility.

Hot melt method (fusion method):

The main advantages of this direct melting method is its simplicity and economy**.** The melting or fusion method was first proposed by Sekiguchi and Obi to prepare fast release solid dispersion dosage forms [10]. In this method, the physical mixture of a drug and a water-soluble carrier was heated directly until it melted. The melted mixture was then cooled and solidified rapidly in an ice bath under rigorous stirring. The final solid mass was crushed, pulverized, and sieved, which can be compressed into tablets with the help of tabletting agents. The melting point of a binary system is dependent upon its composition, i.e., the selection of the carrier and the weight fraction of the drug in the system [11]. An important requisite for the formation of solid dispersion by the hot melt method is the

miscibility of the drug and the carrier in the molten form. Another important requisite is the thermostability of the drug and carrier.

Solvent Evaporation Method:

Tachibana and Nakumara were the first to dissolve both the drug and the carrier in a common solvent and then evaporate the solvent under vacuum to produce a solid solution. This enabled them to produce a solid solution of the highly lipophilic β-carotene in the highly water soluble carrier polyvinylpyrrolidone. Many investigators studied solid dispersion of meloxicam, naproxen and nimesulide using solvent evaporation technique. These findings suggest that the above-mentioned technique can be employed successfully for improvement and stability of solid dispersions of poorly water soluble drugs [12-16]. The main advantage of the solvent method is that thermal decomposition of drugs or carriers can be prevented because of the low temperature required for the evaporation of organic solvents. However, some disadvantages associated with this method are the higher cost of preparation, the difficulty in completely removing liquid solvent, the possible adverse effect of the supposedly negligible amount of the solvent on the chemical stability of the drug, the selection of a common volatile solvent, and the difficulty of reproducing crystal forms [17].

Hot melt extrusion:

Hot melt extrusion is essentially the same as the fusion method except that intense mixing of the components is induced by the extruder. Just like in the traditional fusion process, miscibility of drug and matrix can be a problem. High shear forces resulting in high local temperature in the extruder is a problem for heat sensitive materials. However, compared to the traditional fusion method, this technique offers the possibility of continuous production, which makes it suitable for large-scale production. Furthermore, the product is easier to handle because at the outlet of the extruder the shape can be adapted to the next processing step without grinding [18].

Nanosuspension

Nanosuspension technology has been developed as a promising candidate for efficient delivery of hydrophobic drugs[19]. This technology is applied to poorly soluble drugs that are insoluble in both water and oils. A pharmaceutical nanosuspension is biphasic systems consisting of nanosized drug particles stabilized by surfactants for either oral and topical use or parenteral and pulmonary administration. The particle size distribution of the solid particles in nanosuspensions is usually less than one micron with an average particle size ranging between 200 and 600 nm [20-22]. There are various methods for preparation of nanosuspension includes Media Milling (Nanocrystals), High Pressure Homogenization in water (Dissocubes), High Pressure Homogenization in nonaqueous media (Nanopure) and combination of Precipitation and High-Pressure Homogenization (Nanoedege) [23, 24].

Precipitation Techniques:

In precipitation technique the drug is dissolved in a solvent, which is then added to non-solvent to precipitate the crystals. The basic advantage of precipitation technique is the use of simple and low cost equipments. The basic challenge of this technique is that during the precipitation procedure the growing of the drug crystals needs to be controlled by addition of surfactant to avoid formation of microparticles. The limitation of this precipitation technique is that the drug needs to be soluble in at least one solvent and this solvent needs to be miscible with nonsolvent. Moreover precipitation technique is not applicable to drugs, which are simultaneously poorly soluble in aqueous and nonaqueous media[25]. Nanosuspension of Danazol Naproxen prepared by precipitation technique to improve their dissolution rate and oral bioavailability [26].

Media milling (Nanocrystals or Nanosystems):

The method is first developed and reported by Liversidge et.al. (1992) the nanosuspensions are prepared by using high-shear media mills. The milling chamber charged with milling media, water, drug and stabilizer is rotated at a very high shear rate under controlled temperatures for several days (at least 2-7 days). The milling medium is composed of glass, Zirconium oxide or highly cross-linked polystyrene resin. The high energy shear forces are generated as a result of the impaction of the milling media with the drug resulting into breaking of microparticulate drug to nanosized particles [27, 28]. Dissolution rate and bioavailability of poorly soluble drugs such as Cilostazol, Danazol Naproxen have been improved by reducing their particle size by nanocrystal techniques [28, 29].

High pressure homogenization:

High pressure homogenization has been used to prepare nanosuspension of many poorly water soluble drugs. In the high pressure homogenization method, the suspension of a drug and surfactant is forced under pressure through a nanosized aperture valve of a high pressure homogenizer. The principle of this method is based on cavitation in the aqueous phase. The particles cavitations forces are sufficiently high to convert the drug micro particles into nanoparticles. The concern with this method is the need for small sample particles before loading and the fact that many cycles of homogenization are required[30]. Disso Cubes technology is an example of this technology developed by R.H. Müller using a piston-gap-type high pressure homogenizer, which was recently released as a patent owned by Skye Pharm plc [31].

Combined precipitation and homogenization (Nanoedege):

The precipitated drug nanoparticles have tendency to continue crystal growth to the size of microcrystals. They need to be processed with high-energy forces (Homogenisation). They are in completely amorphous, partially

amorphous or completely crystalline which create problems in long term stability as well as in bioavailability, so the precipitated particle suspension is subsequently homogenized which preserve the particle size obtained after the precipitation step [32].

Supercritical Fluid Process

Another novel nanosizing and solubilisation technology whose application has increased in recent years is particle size reduction via supercritical fluid (SCF) processes. Supercritical fluids are fluids whose temperature and pressure are greater than its critical temperature (Tc) and critical pressure (Tp), allowing it to assume the properties of both a liquid and a gas. At near-critical temperatures, SCFs are high compressible, allowing moderate changes in pressure to greatly alter the density and mass transport characteristics of a fluid that largely determine its solvent power[33-36]. Once the drug particles are solubilised within SCF, they may be recrystallised at greatly reduced particle sizes. The flexibility and precision offered by SCF processes allows micronisation of drug particles within narrow ranges of particle size, often to sub-micron levels. Current SCF processes have demonstrated the ability to create nanoparticulate suspensions of particles 5-2,000nm in diameter. Several pharmaceutical companies, such as Nektar Therapeutics and Lavipharm, are specializing particle engineering via SCF technologies for particle size reduction and solubility enhancement[37-38].Several methods of SCF processing have been developed to address individual aspects of these shortcomings, such as precipitation with compressed antisolvents process (PCA), solution enhanced dispersion by SCF (SEDS), supercritical antisolvents processes (SAS), Rapid Expansion of Supercritical Solutions (RESS), Gas Anti Solvent Recrystallization (GAS) and aerosol supercritical extraction system (ASES) [39-40].

Cryogenic Techniques

Cryogenic techniques have been developed to enhance the dissolution rate of drugs by creating nanostructured amorphous drug particles with high degree of porosity at very low temperature conditions. Cryogenic inventions can be defined by the type of injection device (capillary, rotary, pneumatic, ultrasonic nozzle), location of nozzle (above or under the liquid level) and the composition of cryogenic liquid (hydrofluoroalkanes, N2, Ar, O2, organic solvents). After cryogenic processing, dry powder can be obtained by various drying processes like spray freeze drying44, atmospheric freeze drying, vacuum freeze drying and lyophilisation [41].

Spray freezing onto cryogenic fluids:

Briggs and maxwell invented the process of spray freezing onto cryogenic fluid. In this technique, the drug and the carrier (mannitol, maltose, lactose, inositol or dextran) were dissolved in water and atomized above the surface of a boiling agitated fluorocarbon refrigerant. Sonication probe can be placed in the stirred refrigerant to enhance the dispersion of aqueous solution [42].

Spray freezing into cryogenic fluids (SFL):

The SFL particle engineering technology has been used to produce amorphous nanostructured aggregates of drug powder with high surface area and good wettability48. It incorporates direct liquid – liquid impingement between the automized feed solution and cyogenic liquid to provide more intense atomization into microdroplets and consequently significantly faster freezing rates. The frozen particles are then lyophilized to obtain dry and free flowing micronized powders. Hua et al produced the rapid dissolving high potency Danazol powders by using Spray Freezing into liquid process [43].

Spray freezing into vapor over liquid (SFV/L):

Freezing of drugs solution in cryogenic fluid vapours and subsequent removal of frozen solvent produces fine drug particles with high wettability.50 During SFV/L the atomized droplets typically start to freeze in the vapor phase before they contact the cryogenic liquid. As the solvent freezes, the drug becomes supersaturated in the unfrozen regions of the atomized droplet, so fine drug particles may nucleate and grow [44-46].

Ultra-Rapid Freezing (URF):

Ultra rapid freezing is a novel cryogenic technology that creates nanostructured drug particles with greatly enhanced surface area and desired surface morphology by using solid cryogenic substances. Application of drugs solution to the solid surface of cryogenic substrate leading to instantaneous freezing and subsequent lyophilization for removal of solvent forms micronized drug powder with improved solubility. Ultra rapid freezing hinders the phase separation and the crystallization of the pharmaceutical ingredients leading to intimately mixed, amorphous drug carrier solid dispersions and solid solutions. This technique has been investigated for the solubility enhancement of repaglinide [47-50].

Inclusion Complex Formation Based Techniques

Among all the solubility enhancement techniques inclusion complex formation technique has been employed more precisely to improve the aqueous solubility, dissolution rate, and bioavailability of poorly water soluble drugs[51]. Inclusion complexes are formed by the insertion of the nonpolar molecule or the nonpolar region of one molecule (known as guest) into the cavity of another molecule or group of molecules (known as host). The most commonly used host molecules are cyclodextrins. The enzymatic degradation of starch by cyclodextrin-glycosyltransferase (CGT) produces cyclic oligomers, Cyclodextrins. Cyclodextrins are non-reducing, crystalline, water soluble, cyclic, oligosaccharides. Cyclodextrins consist of glucose monomers arranged in a donut shape ring. Three naturally occurring CDs are α-Cyclodextrin, β-Cyclodextrin, and γ- Cyclodextrin [52-55]. Solubility and oral bioavailability of Glipizide[56], Rofecoxib[57], Piroxicam [58] and Carvedilol [59] can be improved by using cyclodextrins

inclusion complex. There are various technologies adapted to prepare the inclusion complexes of poorly of poorly water soluble drugs with cyclodextrins.

Kneading method:

This method is based on impregnating the CDs with little amount of water or hydroalcoholic solutions to converted into a paste. The drug is then added to the above paste and kneaded for a specified time. The kneaded mixture is then dried and passed through sieve if required [60]. Parik et al. [61] have reported the dissolution enhancement of nimesulide using complexation method. In laboratory scale kneading can be achieved by using a mortar and pestle [62-64]. In large scale the kneading can be done by utilizing the extruders and other machines. This is the most common and simple method used to prepare the inclusion complexes and it presents very low cost of production.

Lyophilization/ Freeze drying technique:

In order to get a porous, amorphous powder with high degree of interaction between drug & CD, lyophilization/ freeze drying technique is considered as a suitable[65, 66]. In this technique, the solvent system from the solution is eliminated through a primary freezing and subsequent drying of the solution containing both drug & CD at reduced pressure. Thermolabile substances can be successfully made into complex form by this method. The limitations of this technique are long time process and yield poor flowing powdered product. Lyophilization/ freeze drying technique are considered as an alternative to solvent evaporation and involve molecular mixing of drug and carrier in a common solvent [67].

Microwave irradiation method:

This technique involves the microwave irradiation reaction between drug and complexing agent using a microwave oven. The drug and CD in definite molar ratio are dissolved in a mixture of water and organic solvent in a specified proportion into a round bottom flask. The mixture is reacted for short time of about one to two minutes at 60 °C in the microwave oven. After the reaction completes, adequate amount of solvent mixture is added to the above reaction mixture to remove the residual, uncomplexed free drug and CD. The precipitate so obtained is separated using whatman filter paper, and dried in vaccum oven at 40 °C for 48 hrs. Deshmukh et al. [68] have developed inclusion complexes of ziprasidone hydrochloride with beta-cyclodextrin and hydroxypropyl beta-cyclodextrin to design the fast dissolving formulation using various superdisintegrants. Microwave irradiation method is a novel method for industrial scale preparation due to its major advantage of shorter reaction time and higher yield of the product[69-71].

Supercritical Antisolvent technique:

This method has been introduced in the late 1980s. Since the first experiences of Hannoy et al in 1879, a number of techniques have been developed & patented in the field of supercritical fluid-assisted particle design. In the supercritical fluid antisolvent technique, carbon dioxide is used as anti-solvent for the solute but as a solvent with respect to the organic solvent. The use of supercritical carbon dioxide is advantageous as its low critical temperature and pressure makes it attractive for processing heat-labile pharmaceuticals. It is also non-toxic, nonflammable, inexpensive and is much easier to remove from the polymeric materials when the process is complete, even through small amount of carbon dioxide remains trapped inside the polymer, it poses no danger to the consumer. Supercritical particle generation processes are new and efficient route for improving bioavailability of pharmaceutically active compounds [39].

In addition, supercritical fluid processes were recently proposed as a new alternative method for the preparation of drug cyclodextrin complexes. Supercritical carbon dioxide is suggested as a new complexation medium due to its properties of improved mass transfer and increased solvating power [72-76]. This method constitutes one of the most innovators methods to prepare the inclusion complex of drug with CD in solid state. This is a non-toxic method as it is not utilizing any organic solvent, fast process, maintenance cost is low with promising results, but it requires a quite high initial cost. In this technique, first, drug and CD are dissolved in a good solvent then the solution is fed into a pressure vessel under supercritical conditions, through a nozzle (i.e. sprayed into supercritical fluid anti-solvent). When the solution is sprayed into supercritical fluid anti-solvent, the anti-solvent rapidly diffuses into that liquid solvent as the carrier liquid solvent counter diffuses into the anti-solvent. Because of the supercritical fluid expanded solvent has lower solvent power than the pure solvent, the mixture becomes supersaturated resulting in the precipitation of the solute and the solvent is carried away with the supercritical fluid flow[77, 78].

Floating Granules

Patel Rajanikant et al. [79] utilized a novel approach for dissolution enhancement of ibuprofen by preparing floating formulation. Ibuprofen, a weekly acidic, non-steroidal anti inflammatory drug having high permeability through stomach because it remain 99.9 % unionize in stomach (pKa of Ibuprofen - 4.43, pH of gastric fluid - 1.2). Ibuprofen mostly permeable through stomach but due to its solubility limitation it can't enter in to systemic circulation and gastric empting time is 30 min to 2 hr. After this time ibuprofen goes in to small intestine where it is solubilised but can't permeate through its membrane (Ibuprofen having pH depended solubility and permeability). It was logically decided to design such formulations which retain in stomach for more than 2 hrs because drug was not completely soluble within 2 hrs hence to dissolve completely in stomach region, this can be achieved by making floating dosage form. Floating ibuprofen granules were prepared by fusion method. 200 mg ibuprofen divided in to 50 mg and 150

mg, 350 mg gelucire 44/14 melted and 50 mg ibuprofen added, disperse with glass road for uniform distribution of drug in to molted carrier, remaining 150 mg ibuprofen added in to molted Gelucire 44/14, this whole dispersion added in to molted gelucire 43/01. In optimized formulation, Granules remain floated for 3 hrs., gave 100% drug release in 150 minute in stomach region where it remain in 99.9% unionize form and absorbed to systemic circulation.

Role of Dendrimers in the Solubility Enhancement of Drug

Capable of 40% of innovative chemical entities (ICEs) discovered by the pharmaceutical industries are hydrophobic compounds in present time. The solubility issues complicating the delivery of these new drugs also affect the delivery of many existing drugs. The ability to deliver poorly soluble drugs will grow in significance in the coming years as ICEs are relied upon for a larger share of the revenue within the pharmaceutical market by innovator companies. Relative to highly soluble compounds, low drug solubility often manifests itself in a host of in vivo consequences including decreased bioavailability, increased chance of food effect, incomplete release from the dosage form, and higher interpatient variability. Poorly soluble compounds also present many in vitro formulation obstacles, such as severely limited choices of delivery technologies and increasingly complex dissolution testing with limited or poor correlation to the in vivo absorption.

These in vivo/in vitro correlations are often sufficiently formidable to halt development of many newly synthesized compounds due to solubility issues. Poorly soluble drugs such as Nifedipine and Felodipine have motivated the development of drug delivery technologies to overcome the obstacles to their solubilization through either chemical or mechanical modification of the environment surrounding the drug molecule or physically altering the macromolecular characteristics of aggregated drug particles. These technologies include both traditional methods of solubility enhancement such as particle size reduction via comminution and spray drying, miceller solubilization, and cyclodextrin mediated inclusion complexes[80-82]. Cyclodextins and micelles share something in common: their hydrophobic interior is capable of encapsulating hydrophobic drugs and their hydrophilic exterior is responsible for solubilization. Bountiful literature reporting cyclodextrin-mediated solubilization of drugs is available[83-86]. High costs and nephrotoxicity on parenteral administration limit the use of cyclodextrins. Moreover, the aqueous solubility of the most commonly used cyclodextrin, *â*-CD (1.8 g/100 mL at 25 °C), is often insufficient to stabilize drugs at therapeutic doses[87]. The reports on micelle- and polymeric-micelle-mediated solubilization are also in abundance. The disruption of micellar structure on dilution with body fluids below critical micellar concentration (CMC) leads to the burst release of the entrapped drugs [88-104].

Table 1. List of the Solubilizates Whose Aqueous Solubility Is Enhanced by Using Various Dendrimers

S.No	Dendrimer used for solubilization	Solubilizate
1	amine- and ester-terminated polyamidoamine (PAMAM) dendrimers[105]	Nifedipine
2	-OH-terminated PAMAM dendrimer[106]	benzoic acid 3-amino 1,5 -dibromo phenol iodine salicylic acid 2, 6 dibromo 4-nitrophenol
3	[Gn]-PGLSA-OH dendrimers[107]	Reichardt's dye (2,8-diphenyl)4-(2,4,6-triphenyl pyridinio phenolate)10 hydroxy camptothecin (10-HCPT)
4	PAMAM NH2 and PAMAM –OH Dendrimers[108]	Indomethacin
5	PEG polyether dendrimers[109]	Indomethacin
6	PAMAM dendrimers[109]	Flurbiprofen
7	Polyglycerol dendrimer[110]	Paclitaxel
8	PEGylated PAMAM dendrimers[111]	Pyrene
9	polypropylene imine dendrimers[112]	Pyrene
10	polyether-PEG dendrimer[96]	Pyrene
11	polyether dendrimer[113]	Pyrene
12	poly(aryl alkyl ether) dendrimer[114]	Pyrene
13	PEGylated PAMAM dendrimer[115]	5-fluorouracil
14	polypropylene imine-oligoethyleneoxy dendrimer[116]	Bengal Rose 4,5,6,7-tetra chlorofluorescein
15	PEO- and t-BOC-terminated poly-R-2- lysine dendrimer[117]	Orange OT
16	ester- and NH2-terminated PAMAM dendrimer[118]	SiO2
17	PEG-PAMAM dendrimer[119]	Methotrexate
18	PAMAM dendrimer[120]	Methotrexate

19	PEG-PAMAM dendrimer[119]	Adriamycin
20	polyether dendrimer[113]	Anthracene 1,4-diamino anthraquinone 2,3,6,7-tetranitro fluorescein
21	PAMAM and Lauroyl PAMAM Dendrimer[121]	Propranolol
22	citric acid-PEG-citric acid dendrimer[121]	5-amino salicylic acid, pyridine Mefenamic acid Diclofenac
23	amphiphilic dendrimer[114]	Proflavine
24	PAMAM dendrimers[123]	Piroxicam
25	PEGylated diaminobutane PPI Dendrimers[124]	Pyrene *â*-methasone valerate *â*-methasone dipropinate
26	PAMAM dendrimers[125]	Ibuprofen
27	PAMAM dendrimers[126]	Niclosamide
28	PAMAM dendrimers[127,128]	Naproxen, Ibuprofen, Diflunisal, Ketoprofen
29	PAMAM dendrimers[129]	nicotinic acid
30	PEGylated lysine dendrimers[130]	Artemether

3. Conclusion

Solubility is the most critical factor in the formulation development that controls the formulation of the drug as well as therapeutic efficacy of the drug. Dissolution of drug is the rate determining step for oral absorption of the poorly water soluble drugs and solubility is also the basic requirement for the formulation and development of different dosage form of different drugs. The various techniques designated above alone or in combination can be used to enhance the solubility of the drug. Solubility can be enhanced by many techniques and number of folds increase in solubility. Because of solubility problem of many drugs the bioavailability of them gets affected and hence solubility enhancement becomes necessary. It is now possible that to increase the solubility of poorly soluble drugs. Defferent types of dendrimers are also useful in the solubility enhancement for the delivery of many class of drugs.

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