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Review Article

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Dissolution Enhancement of Drugs Part II: Effect of Carriers

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Abstract

Recent high throughput screening and combinatorial and parallel synthesis are increasing the number of drug molecules which are highly lipophilic. The oral route is the most preferred route of drug administration due to its convenience, good patient compliance and low medicine production costs. The challenges to formulation scientists have tremendously increased due to the pressure of formulating these lipophilic drugs into oral drug delivery systems. Reports in patent and scientific literature are also increasing day by day which shows the interest of industrial and academic research in dissolution enhancement of poorly water soluble drugs. Part I [Int J Health Res, Jun 2009; 2(2):107-124] of this review was a technological overview on various dissolution enhancement techniques for poorly water soluble drugs and role of few water soluble carriers, viz. polymers, superdisintegrants and surfactants, in dissolution enhancement. This part describes the use of cyclodextrin, carbohydrates, hydrotropes, polyglocolized glycerides, dendrimers, acids and miscellaneous carriers in enhancing dissolution of drugs.

Keywords: Dissolution enhancement; aqueous solubility, water soluble carriers; lipophilic, excipients.

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Introduction

Studies on oral drugs in World Health Organization (WHO) essential medicines list revealed that 67% were determined to be high-solubility drugs (1). More than 50% of the top 200 drug products lists from United States, Greatt Britain, Spain and Japan on each list were determined to be high solubility drugs (2). These data signifies that oral drug products with immediate release characteristics are essential and highly in demand in the market. High aqueous solubility of the drug and good dissolution in aqueous medium also assist in absorbing the drug in a fast manner resulting in good bioavailability of the drug from a drug product.

As per FDA guidance (3), for the eligibility of biowaivers, the test product should dissolve ≥85% in ≤30 min by the USP I (basket) dissolution test at 100 rpm or the USP II (paddle) dissolution test at 50 rpm in ≤900 mL of 0.1 N HCl, pH 4.5, and pH 6.8 buffers and should meet the f2 criteria of ≥50. When the dissolution is very rapid, 85% in ≤15 min, f2 criteria are not required. The biowaiver awarded to such products eliminates the need to conduct costly bioequivalence testing and in vitro dissolution testing whish are simpler, more easily implemented, routinely monitored, more reliable, rapid and more affordable. Thus dissolution test may ensure clinical performance of such marketed drug products.

Recent advances in biotechnology, coupled with combinatorial chemistry and parallel synthesis are continnously increasing the number of lipophilic molecules which are difficult to deliver due to bioavailability issues (4). Formulation scientists have tried delivery of such difficult molecules by physically modifying them to suitable forms which makes the drug dissolution faster. For such physical modifications several carriers like cyclodextrin, carbohydrates, hydrotropes, polyglocolized glycerides, dendrimers, acids have been described. Part I of this review [Int J Health Res, Jun 2009; 2(2):107-124] highlighted various dissolution enhancement techniques for poorly water soluble drugs as well as role of few water soluble carriers, viz. polymers, superdisintegrants and surfactants, in dissolution enhancement.

Cyclodextrins

Cyclodextrins although belongs to the category of carbohydrate but its wide applications and role in dissolution enhancement (Table 1) make it deserving candidate to be described separately. Cyclodextrins (CDs) are cyclic malto-oligosaccharides of 6, 7 or 8 glucose units, joined together by α-1,4 glucosidic linkages and are respectively called as α-, β- and γ-CDs. β-CDs are most commonly used carrier due to its suitable cavity diameter (7-8 A^o) for guest molecules (5). CDs act as a drug carrier to improve solubility and stability, enhancement of dissolution rate and bioavailability, reduction in volatility etc (6).

β-Cyclodextrins act as dissolution enhancers because it consist truncated cone type structure. The outer surface is hydrophilic due to the presence of hydroxyl groups and the interior of the cone is hydrophobic due to presence of glycosidic ether oxygen at O-4 and the hydrogen attached to C-3 and C-5 and thereby provides a lipophillic microenvironment into which drug can enter and can be partially or fully included without covalent bonding, while outer hydrophilic environment contributes to drug dissolution. The water molecules located inside the cavity cannot satisfy their hydrogen bonding potentials; therefore they are of higher enthalpy. The energy is lowered, when suitable guest molecules that are less polar than water replace these enthalpy rich water molecules (6,7). Partial methylation of some of the cyclodextrins reduces the intermolecular hydrogen bonding, leaving some hydroxyl groups free to interact with water, thus increasing the aqueous solubility of CDs. So a low degree of substitution is preferable to enhance dissolution rate (8).

Table 1: Cyclodextrins and techniques employed for enhancing dissolution of poorly water soluble drugs

S/N	Drug	Cyclodextrins	Technique	Mechanism of Dissolution Enhancement	Refe-rence
1.	Naproxen	Cyclodextrin	Inclusion complex	Formation of inclusion complexes	(28)
2.	Norfloxacin	β-Cyclodextrin and Hydroxypropyl β-Cyclodextrin	Inclusion complex by freeze drying	Transformation of crystalline drug to amorphous state by formation of an inclusion complex with cyclodextrins and improved wettability	(10)
3.	Gliclazide	β-Cyclodextrin	Inclusion complexes by kneading, coprecipitation, co-grinding, spray-drying	Formation of inclusion complex in solid state and reduction in crystallinity of the product	(11)
4.	Carbamazepine	β-Cyclodextrin	Inclusion complexes by solvent method	Formation of inclusion complexes	(12)
5.	Nifedipine	β-Cyclodextrin	Inclusion complex	Formation of inclusion complexes	(29)
6.	Gliclazide	β-Cyclodextrin	Inclusion complexes by neutralization and recrystallization	Formation of high energetic amorphous state and inclusion complexation	(13)
7.	Danazol	Hydroxypropyl β-Cyclodextrin	Inclusion complexes by spray freezing	Higher surface areas and stabilized inclusion complexes	(14)
8.	Nicardipine	β-Cyclodextrin, Hydroxypropyl β-Cyclodextrin	Inclusion compounds by kneading, evaporation, freeze drying, spray drying	Local solubilization action of the carrier which improved drugs wettability and/or solubility, in situ formation of readily soluble complexes, surfactant like properties of the carriers, high energetic amorphous state/reduction of the crystallinity following complexation	(15)
9.	Meloxicam	β-Cyclodextrin and Hydroxypropyl β-Cyclodextrin	Inclusion complex by freeze drying	Increase in both wettability and solubility of the drug	(16)
10.	Norfloxacin	β-Cyclodextrin	Inclusion complexes by kneading method	Formation of inclusion complexes	(17)
11.	Piroxicam	β-Cyclodextrin, Randomly metahydrated β-Cyclodextrin	Inclusion complex by freeze drying	Increased diffusion of drug by increasing the amount of diffusible species in the donor phase by complexation	(18)

Table 1: Cyclodextrins and techniques employed for enhancing dissolution of poorly water soluble drugs (continued)

S/N	Drug	Cyclodextrins	Technique	Mechanism of Dissolution Enhancement	Refe-rence
12.	Celecoxib	β-Cyclodextrin	Solid inclusion complexes by kneading method	Interaction of drug with β-Cyclodextrin	(19)
13.	Nimesulide	β-Cyclodextrin	Inclusion complexes by kneading method	Formation of inclusion complexes	(7)
14.	Satranidazole	β-Cyclodextrin	Inclusion complexes by kneading method	Reduction in crystallinity of the drug caused by kneading process and the inclusion into the hydrophobic cavity of the β-CD	(20)
15.	Carbamazepine	β-Cyclodextrin	Inclusion complexes by kneading method	Decrease in drug crystallinity leading to increased solubility of the solid complex	(21)
16.	Glyburide	β-Cyclodextrin, Hydroxypropyl β-Cyclodextrin,Chitosan	Inclusion complex solubility study	Formation of inclusion complexes	(22)
17.	Gliclazide	β-Cyclodextrin	Inclusion complexes by liquid/liquid extraction and neutralization	Increase in the drug wettability	(23)
18.	Ziprasidone hydrochloride	β-Cyclodextrin, Hydroxypropyl β-Cyclodextrin	Inclusion complexes by kneading, coprecipitation, microwave irradiation method	Formation of inclusion complexes	(24)
19.	Piroxicam	β-Cyclodextrin	Inclusion complexes by kneading, freeze drying, neutralization method	Formation of inclusion complexes	(25)
20.	Glipizide	β-Cyclodextrin, Hydroxypropyl β-Cyclodextrin	Inclusion complexes by kneading method	Formation of inclusion complexes	(26)
21.	Piroxicam	β-Cyclodextrin	Steam-aided granulation	Action of both the mechanical energy (shearing stress produced by the impeller) and/or the thermal energy (steam) which causes larger physical interaction between piroxicam and β-cyclodextrin Increased surface area exposed to dissolution medium	(27)

The drug-load is low and inclusion complexation with cyclodextrins only works with drugs which fit into the cavity of the cyclodextrin and which have a high complex-forming constant. The molecular structure, the polarity, the size and the possibility for interactions with the cyclodextrin molecule are important factors determining the success of cyclodextrin preparations. Cyclodextrins are hygroscopic and can pick up moisture when exposed to humidity. Thus water content of the cyclodextrins is an important factor while preparing samples to achieve a given concentration (9).

Solid complexes of norfloxacin-β-CD/ HP-β-CD in 1:1 and 1:2 molar ratios were prepared by freeze drying method. Solubility studies revealed more efficiency of HP-β-CD as compared to β-CD in solubilizing norfloxacin and dissolution studies revealed increase in dissolution rate of drug complexes compared to drug alone and physical mixtures (10). Solid complexes of gliclazide-β-CD in 1:2 molar ratio were prepared by neutralization, kneading, coprecipitation, co-grinding and spray-drying method. Coprecipitated, neutralized, co-ground and spray-dried systems showed higher dissolution rates than pure drug, physical mixture and kneaded product (11). Solid complexes of carbamazepine-HP-β-CD in 1:1 molar ratio were prepared by solvent method using absolute ethanol with enhanced dissolution of drug (12).

Solid complexes of gliclazide-CDs in 1:1, 1:2, 1.5:1 molar ratio were prepared by neutralization and recrystallization method. Phase solubility studies showed the effect of three CD polymers on solubility of gliclazide increased in the order of β-CD > α-CD > γ-CD due to optimum cavity size of β-CD to entrap the gliclazide molecule and consequently provides the greatest solubilization effect. Highest dissolution rate of gliclazide was observed by neutralization method and ratio of the complex 1.5:1. This behavior may be attributed to the high energetic amorphous state and inclusion complex formation (13).

Solid complexes of danazol-HP-β-CD were prepared by spray freezing into liquid (SFL) process. Dissolution results suggested that equilibration of the danazol-HP-β-CD solution prior to SFL processing was required to produce the most soluble conformation of the resulting inclusion complex following SFL. Results indicated that micronized SFL powders dissolved faster in aqueous dissolution media than inclusion complexes formed by conventional techniques due to higher surface areas and stabilized inclusion complexes obtained by ultra rapid freezing (14).

Solid complexes of nicardipine-β-CD/ HP-β-CD were prepared by kneading, evaporation, freeze drying and spray drying method. The increment in drug dissolution from nicardipine- HP-β-CD system was higher than nicardipine-β-CD system due to greater water solubility, higher amorphizing, wetting, solubilizing and complexing power in solid state of HP-β-CD towards nicardipine. Enhancement of dissolution with kneaded product was attributed to local solubilization action of the carrier which improved drugs wettability and/or solubility and in situ formation of readily soluble complexes in the dissolution medium. The significant enhancement of the dissolution with evaporation, freeze drying and spray drying method was attributed to surfactant like properties of the carriers which can reduce the interfacial tension between water insoluble drugs and dissolution medium, an increase of drug solubility upon complexation in the solid state and to the high energetic amorphous state/reduction of the crystallinity following complexation (15).

Solid complexes of meloxicam-β-CD/ HP-β-CD were prepared by freeze drying method and used to prepare tablets by direct compression method. Drug release studies revealed that tablet containing meloxicam-HP-β-CD freeze dried complex (1:2) had better release profile as compared to tablets containing meloxicam-β-CD freeze dried complex (1:2). The dissolution studies revealed increased rate and more in alkaline

media due to weak acid nature of the drug. The improvement in dissolution rate of the drug/CD systems may be attributed to the degree of crystallinity of the active material together with the increase in both wettability and solubility of the drug. Stability study of tablets revealed that storage temperature not exceeding 40° C and moisture proof packing are essential to ensure stability of formulation (16).

Physical mixtures and solid complexes of norfloxacin in 1:0.5, 1:1, 1:2 w/w and 1:1 molar ratio were prepared by kneading method. Solubility studies revealed that increase in aqueous solubility of drug is a linear function of β-CD concentration (0-16M) (17). Physical mixtures and solid complexes of piroxicam- β-CD by freeze drying method were prepared with enhanced dissolution of piroxicam. Gels were prepared by dispersing HPMC in hot water. The dispersions were mixed until cooling at room temperature and then piroxicam or piroxicam-CD complexes were added. Final concentration in gels was 1%. Permeation of piroxicam from prepared gel was studied and results revealed that permeation of the drug involved three consecutive processes: dissolution of the solid phase, diffusion across the swollen polymer matrix and drug permeation through the membrane. Complexation increased piroxicam diffusion by increasing the amount of diffusible species in the donor phase. Drug diffusion through the HPMC matrix was the rate limiting step in the overall diffusion process (18).

Physical mixtures and solid complexes of celecoxib-β-CD by kneading method alone and along with an additive (citric acid or sodium bicarbonate) were prepared. The improvement of dissolution was found to be in the order celecoxib-β-CD with additives > celecoxib-β-CD > physical mixtures > celecoxib. The drug-CD complex showed three fold increases in dissolution as compared to physical mixture due to better interaction of drug with β-CD complex prepared by kneading method. Celecoxib-β-CD with additives was better than celecoxib-β-CD because of the incorporation of solubility enhancing additives, which provide a slightly alkaline microenvironment to drug thereby enhancing dissolution further (19).

The complex of nimesulide and β-CD in 1:1, 1:1.5, 1:2 molar ratio were prepared by kneading method resulted in improved flow property, direct compressible property, fast disintegration and enhanced dissolution. The highest drug release of 74.89% was found in 1:2 nimesulide:β-CD complex. This method can be easily scaled up to the industrial level which could otherwise be a challenge in case of cyclodextrins (7).

Solid complexes of satranidazole-β-CD in 1:1 molar ratio were prepared by kneading and physical mixing method. Phase solubility studies revealed increase in aqueous solubility of drug linearly as a function of β-CD concentration. Kneaded mixtures showed high dissolution rate compared to physical mixtures due to intensive mixing. The complexation with β-CD on the solubility of drug was due to reduction in crystallinity of the drug caused by kneading process and the inclusion into the hydrophobic cavity of the β-CD (20).

Solid complexes of carbamazepine-β-CD were prepared in 1:2 molar ratios by kneading method and used to prepare dispersible tablets by wet granulation method. Phase solubility studies revealed increase in aqueous solubility of drug linearly as a function of β-CD concentration. The decrease in drug crystallinity was responsible for increased solubility of the solid complex when compared to that of the pure drug (21).

Influence of cyclodextrins and chitosan on glyburide solubility and permeability was studied and it was concluded that cyclodextrins were more effective than chitosan in enhancing the drug dissolution. The aqueous glyburide solubility was improved 40-fold in the presence of 25 mM HP-β-CD, 25 fold in the presence of 13 mM β-CD (saturation solubility) and only 3-fold in

the presence of chitosan at its saturation concentration (0.5%w/v).When chitosan and cyclodextrins were simultaneously present, a strong reduction of the cyclodextrins solubilizing efficiency towards the drug was observed and it was attributed to a possible competition effect of polymer and glyburide for the interaction with the macrocycle (22).

Solid complexes of gliclazide-β-CD in 1:1 molar ratio were prepared by liquid/liquid extraction and neutralization method. The dissolution rates for two solid complexes were greater than physical mixtures and gliclazide alone. The formed solid complexes increase the drug wettability and then enhanced its dissolution rates as well. Complexes prepared by liquid/liquid extraction method exhibited highest dissolution rates than other solid complexes indicating importance of method of preparation of complexes (23).

Inclusion complexes of ziprasidone-β-CD/HP-β-CD were prepared by kneading, coprecipitation and microwave irradiation method. In microwave irradiation method molar (1:1) quantities of drug and cyclodextrins were weighed and transferred to round bottom flask. Minimum amount of solvent mixture (methanol:water, 1:1 v/v) was then added to it. The mixture was reacted for 2 min. at 60^{o} C in the microwave oven. After reaction was complete adequate amount of solvent mixture was added to remove the residual free drug and β-CD or HP-β-CD. Precipitate obtained was filtered using whatman filter paper and dried in vacuum oven at 40^{o} C for 48 hrs. Inclusion complexes prepared with HP-β-CD by microwave irradiation method showed highest enhancement in the solubility of drug than that of prepared with β-CD and fastest dissolution profile (24).

Solid complexes of piroxicam-β-CD were prepared by neutralization, kneading and freeze-drying method. Dissolution studies revealed that all formulations showed an increased rate and were more in alkaline medium, which may be due to an ionization of drug as it is a weak acid. Of the entire complex prepared, neutralization method was superior with respect to enhancing dissolution, resistance to thermal and photo-degradation constant (25).

Quantity of cyclodextrins in complexation is limited due to its high cost. Therefore water soluble polymers can be included to improve dissolution with reduced cost. Binary and ternary mixtures of glipizide with β-CD or HP-β-CD and water soluble polymers, viz., hydroxypropyl methylcellulose, polyvinyl-pyrrolidone in a concentration of 5%, 10%, 15%, 20% and PEG 4000, PEG 6000 in a concentration of 2.5%, 5.0%, 10% were prepared by kneading method. Dissolution studies revealed high dissolution rate of drug complex with β-CD compared to that of the complex with HP-β-CD due to the higher inclusion ability of β-CD due to its cavity size. Ternary system showed higher dissolution than binary system. The dissolution rate of the drug from ternary systems containing PEG 4000 or PEG 6000 seems to be generally higher than from systems containing HPMC or PVP. An optimum increase in the dissolution rate of the drug was observed at a polymer concentration of 5% for PEG 4000 or PEG 6000 and at 20% concentration of HPMC or PVP. The dissolution rate of the drug from ternary system glipizide- HP-β-CD-5% PEG 4000 was high compared to the other systems. The increase dissolution rate of drug in presence of polymers was observed because molecules of glipizide-CDs complex are present in a dispersed state within the polymer matrix through interactions between exterior of the complex and the polymer (26).

Steam aided granules of piroxicam and β-cyclodextrins in 1:2.5 molar ratio were prepared using a one-step rotogranulator with improved dissolution due to the action of both the mechanical energy (shearing stress produced by the impeller) and/or the thermal energy (steam) which causes larger physical interaction between piroxicam and β-cyclodextrin. Moreover granules displays a higher porosity and a more irregular surface

which increase the surface area exposed to the dissolution process. This process require few stages, is less time consuming, yield uniform particle size of granules (27).

Carbohydrates

Carbohydrates like lactose, soluble starches, sorbitol, mannitol, british gum, amylodextrin, roast dextrin etc also have their role in dissolution enhancement (Table 2). Enhancement in dissolution is mainly attributed to increase in surface area of drug exposed to large carrier molecules, increase wettability and consequently solubility due to polar effect of carbohydrates containing polar groups.

The dissolution of diazepam (1-10%) in lactose interactive mixture prepared by placing micronised drug between two layers of carrier in a glass vial and shaking vigorously by hand was studied. The dissolution rate of the interactive mixes was observed concentration dependent and occurred rapidly, i. e. greater than 95% dissolved within 10 and 20 min. for the 1 and 10% mixture respectively and the rotational speed (50-200 rpm) of the paddle type dissolution apparatus appeared to have little effect on dissolution rate (30).

Fentanyl tablets (100 µg, 200 µg, and 400 µg) were prepared by ordered mixing using adhesion method in which coarse mannitol particles were covered with fentanyl citrate by dry mixing to form an interactive mixture which then mixed with other ingredients and compressed into tablets with enhanced dissolution rate of the fentanyl (31).

Binary and ternary interactive mixtures of indomethacin were prepared using spray-dried lactose or lactose monohydrate (106-250 µm) and fine lactose to find out the effect of fine lactose on dissolution of indomethacin. Increased dissolution of indomethacin on addition of fine lactose was observed because dissolved lactose left an agglomerate structure of indomethacin with a much greater porosity and ability to disperse (32).

Formulations of nifedipine using chitosan base and chitosan glutamate salt were achieved by solid dispersion using 1:2 drug to carrier ratio, kneaded mixture using 1:2 drug to carrier ratio, co-ground mixture using 1:1, 1:2, 1:3, 1:4. 1:6, 1:8 drug to carrier ratio and physical mixture using 1:2 drug to carrier ratio method. The improvement of drug dissolution was observed in the descending order of solid dispersion, kneaded mixture, co-ground mixture, physical mixture and this might be due to a more intimate dispersion of nifedipine within the chitosan. Coground mixture of nifedipine with chitosan and chitosan glutamate enhanced drug dissolution at an optimum at a ratio of 3:1 of carier:drug. The drug dissolution enhancement by coground mixture was attributed to the decreased drug crystallinity and size of the drug and polymer wetting effect. Chitosan glutamate led to faster drug dissolution than chitosan due to high wetting capacity, solubility and swelling capacity (33).

Griseofulvin solid dispersions were prepared using lactose, corn starch, linear dextrin, amylodextrin and processed starches (british gum, pregelatinized corn starch, roast dextrin) by roll mixing method using roller mill. The mixture became amorphous and solubility of drug increased. Solubility of drug was higher in mixture of high molecular weight carriers i.e. corn starch and processed starch. Griseofulvin roll mixture containing amylodextrin as main excipient slowly decomposed and the dissolution of drug components was slow. Surface tension of carrier material was markedly low in roast dextrin and british gum which have branched sugar chain structure which also contributes to increase dissolution rate (34).

Physical mixtures and solid dispersion of nifedipine with mannitol containing 10 and 50% w/w of drug were prepared by blending the components in a mortar and hot melt method respectively. Dissolution studies

Table 2: Carbohydrates and techniques employed for enhancing dissolution of poorly water soluble drugs

S/N	Drug	Carbohydrates	Technique	Mechanism of Dissolution enhancement	Refe-rence
1.	Griseofulvin	Lactose	Interactive mixing	Increase in the surface area of drug directly exposed to the carrier material	(37)
2.	Diazepam	Lactose	Interactive mixing	Increase in the surface area of drug directly exposed to the carrier material	(30)
3.	Fentanyl	Coarse mannitol	Interactive mixing	Increase in the surface area of drug directly exposed to the carrier material	(31)
4.	Indomethacin	Fine Lactose	Interactive mixing	Dissolved lactose left an agglomerate structure of indomethacin with a much greater porosity and ability to disperse	(32)
5.	Nifedipine	Chitosan, Chitosan glutamate	Solid dispersion by solvent method	Decreased drug crystallinity and size of the drug and wetting effect.	(33)
6.	Griseofulvin	Maltose, Lactose, Corn starch	Solid dispersion by roll mixing method	Increase in the surface area of griseofulvin directly exposed to the carrier materials	(34)
7.	Nifedipine	Mannitol	Solid dispersion by hot melt method	Improved wetting of drug crystal surface mainly due to attached mannitol particles which provoked the solubilizing effect	(35)
8.	Rofecoxib	Mannitol, Sorbitol	Solid dispersion	Polar environment provided by the carrier	(36)

revealed marked increase of nifedipine dissolution comparing to physical mixtures due to improved wetting of drug crystal surface mainly due to attached mannitol particles which provoked the solubilizing effect (35).

Solid dispersion of rofecoxib was prepared using mannitol and sorbitol in 50%, 75%,

90% concentration by hot melt method and dissolution studies revealed marginally improvement in dissolution of drug at high carrier concentration and decrease in dissolution rate at lower carrier concentration (10%) due to strong drug-carrier interaction than drug-water and carrier-carrier interactions (36).

Hydrotropes

The term hydrotropy designates the increase in aqueous solubility of various poorly water-soluble compounds due to the presence of large amount of additives. Concentrated solutions of sodium benzoate, sodium-o-hydroxy benzoate, sodium-p-hydroxy benzoate, sodium salicylate, urea, nicotinamide, sodium citrate and sodium acetate have been employed to enhance the aqueous solubilities (Table 3) of a large number of drugs (38). Enhancement in solubility of the drugs was due to salting in effect or due to change in solvent character i.e. hydrotrope solubilization phenomenon (39). The advantages of this phenomenon include simplicity of method, cost effective, environmentally friendly, easily scale up to industrial level.

Hydrotropic solid dispersion of paracetamol was prepared by using 50% w/v urea solution. Dissolution studies revealed five fold increases in aqueous solubility of drug in urea solution as compared to solubility in distilled water. IR analysis of pure drug, urea, and solid dispersion revealed that drug was not degraded in the presence of urea. Similarly paracetamol syrup using urea as hydrotropic agent were prepared with good chemical stability and improved bioavailability as compared to corresponding suspensions (40).

Aqueous injection of nimesulide (20 mg/ml) was prepared using sodium benzoate, sodium-o-hydroxy benzoate, and sodium-p-hydroxy benzoate in 2% concentration. Solubility enhancement power of hydrotropes was observed in the order sodium benzoate > sodium-o-hydroxy benzoate > sodium-p-hydroxy benzoate. Solubility study using

Table 3: Hydrotropes and techniques employed for enhancing dissolution of poorly water soluble drugs

S/N	Drug	Hydrotropes	Technique	Mechanism of Dissolution Enhancement	Refe-rence
1.	Paracetamol	Urea	Hydrotropic solid dispersion	Hydrotropic solubilization phenomenon	(40)
2.	Nimesulide	Sodium benzoate, Sodium-o-hydroxy benzoate, Sodium-p-hydroxy benzoate	Hydrotropic solution	Reduction in the polarity of water caused by the hydrotrope	(38)
3.	Frusemide	Sodium benzoate	Hydrotropic solution	Hydrotropic solubilization phenomenon	(41)
4.	Norfloxacin	Urea	Hydrotropic solution	Hydrotropic solubilization phenomenon	(39)
5.	Hydrochlorothiazide, Indomethacin	Sodium benzoate	Hydrotropic solution	Hydrotropic solubilization phenomenon	(42)
6.	Rofecoxib	Urea, Nicotinamide	Hydrotropic solid dispersion	Ability of carrier to destroy water structure, and/or to form complexes with certain drugs on the basis of π-electron donor-acceptor interaction, and/or to undergo hydrogen bonding	(36)

hydrotropes in 0.5 to 2.5 % concentration revealed that the increase in solubility is not the linear function of the hydrotrope concentration. On increasing the hydrotrope concentration, initially the drug solubility increases but slowed after a particular concentration (2%) i.e. critical solute concentration of the hydrotrope. Reduction in the polarity of water caused by the hydrotrope may contribute to the increase in the solubility of nimesulide. Thus the dielectric constant of the medium played a significant role in the solubilization (38).

The solubility of frusemide in 2.0 M sodium benzoate solution was observed to be more than 90 fold as compared to its solubility in distilled water (41). Improvement (10 fold) in solubility of norfloxacin using urea (8.0 M) as hydrotrope was observed (39). Similarly improvement in solubility of hydrochlorothiazide, indomethacin using sodium benzoate has been reported (42).

Hydrotropic solid dispersions of rofecoxib were prepared using urea and nicotinamide as hydrotropes in 50%, 75% and 90% proportion. Relatively higher drug release enhancement was observed with urea systems vis-a-vis nicotinamide systems. The hydrotropic solubilization by these carriers has been attributed mainly to their ability to destroy water structure, and/or to form complexes with certain drugs on the basis of π-electron donor-acceptor interaction, and/or to undergo hydrogen bonding (36).

Polyglycolized Glycerides

Gelucires (saturated polyglycolized glycerides consisting of mono-, di-, and triglycerides and of mono- and di-fatty esters of polyethylene glycol) are solid waxy water soluble materials, which are amphiphilic in nature and identified by two values: their melting points and their HLB (hydrophilic-lipophilic balance) values. Gelucires with low HLB can be used to decrease the dissolution rate of drugs and high HLB ones for fast release (Table 4). Examples of gelucire include Gelucire 44/14, Gelucire 50/13, Gelucire 62/05 etc.

The increase of drug solubility by using amphiphilic gelucires is due to the improvement of wettability characteristics, micellar solubilization of the drug and chemical interactions between drug and mono-, di-, and tri-glycerides, fatty alcohols, polyglycolized fatty acid esters etc. Solid dispersion of glibenclamide using Gelucire 44/14 as carrier was prepared by fusion method. Result of dissolution studies revealed improvement in dissolution. Gelucires 44/14 has a nominal melting point of 44ºC and a HLB value of 14. Gelucire 44/14 is characterized by a unique balance of short, medium, and long chain fatty acids, which provide exceptionally fine dispersion upon contact with gastrointestinal fluids at body temperature (43).

Semisolid dispersions of piroxicam using Gelucire 44/14 in 1/6, 1/10, 1/20, 1/30 drug to excipient ratio were prepared by hot melt method. Dissolution testing of semisolid dispersions and pure piroxicam revealed increase in dissolution by adding Gelucire due to solubilization effect. Addition of 60% and 80% w/w Labrasol to Gelucire without changing drug to excipient ratio leads to further enhancement of dissolution due to wetting and micellar solubilization effect of the Labrasol (44).

Solid dispersion by spray drying technique using polyglycolized glycomass produces sticky and tacky mass due to sticky and tachy nature of Gelucire. This problem can be solved by using silicon dioxide as an adsorbent. Silicon dioxide due to presence of surface silanol groups may be able to form hydrogen bond with drug molecule leading to increase in wettability and consequently enhanced dissolution rate. Solid dispersion of glibenclamide with Geluride was prepared using silicon dioxide as an adsorbent by spray drying technique with enhanced dissolution rate (45).

Table 4: Polyglycolized glycerides and techniques employed for enhancing dissolution of poorly water soluble drugs

S/N	Drug	Polyglycolized glycerides	Technique	Mechanism of Dissolution Enhancement	Refe-rence
1.	Glibenclamide	Gelucire 44/14	Solid dispersion by fusion method	Amphiphilic nature of Gelucire	(43)
2.	Piroxicam	Gelucire 44/14, Gelucire 50/13, Gelucire 62/05	Semisolid dispersion	Solubilization effect of carrier and its amphiphilic nature	(44)
3.	Glibenclamide	Gelucire 44/14, Gelucire 50/13 and Silicon dioxide as adsorbent	Spray dried solid dispersion	Amphiphilic nature of Gelucire, increase wettability of drug due to H-bond between drug and silanol groups of silicon dioxide	(45)

Table 5: Dendrimers and techniques employed for enhancing dissolution of poorly water soluble drugs

S/N	Drug	Dendrimers	Technique	Mechanism of Dissolution Enhancement	Refe-rence
1.	Ibuprofen	Starburst® polyamidoamine (PAMAM)	Dendrimer	An electrostatic interaction between the surface amine groups of the dendrimer molecule and the carboxyl group of Ibuprofen leading to enhancement in solubility	(46)
2.	Nifedipine	PAMAM dendrimer	Dendrimer	Interaction between a drug and the surface of a dendrimer	(48)

Dendrimers

Dendrimers are highly branched three-dimentional macromolecules having specific size, shape and chemical functionality and used for enhancing solubility of low aqueous soluble drugs (Table 5). Structurally these are composed of a central core branched cell, interior branch cells, and branched cells possessing surface groups (46). Action of dendrimers is due to entrapment of drugs within the dendritic architecture (involving electrostatic, hydrophobic and hydrogen bond interactions) and the interaction between a drug and the surface of a dendrimer (electrostatic and covalent interactions) which leads to increase in solubility and bioavailability of drugs (47).

Starburst® polyamidoamine (PAMAM) dendrimers are a specific family of dendritic polymers, which are based on an ethylene diamine core and an amidoamine repeat branching structure. Solubility of hydrophobic ibuprofen was enhanced by using PAMAM dendrimers. It is proposed that the solubility enhancement is due to an electrostatic interaction between the surface amine groups of the dendrimer molecule and the carboxyl group of Ibuprofen (46).

The effect of PAMAM dendrimer size and surface functional group on the aqueous solubility of nifedipine was studied and results showed that the solubility enhancement of nifedipine was higher in the presence of ester-terminated dendrimers than their amino-terminated analogues

possessing the same number of surface groups and the nifedipine solubility increased with the size of the dendrimers (48).

Acids

Acids like citric acid, succinic acid, phosphoric acids are very useful to form prodrugs to increase water solubility of poorly aqueous soluble drugs. These acids form ester by reacting hydroxyl moiety of drug to render the moiety more water soluble. Some of the example of prodrug with enhanced oral delivery includes Miproxifene phosphate, Estramustine phosphate, Clindamycin phosphate, Etoposide diphosphate, Stachyflin phosphate, Oxazepam sodium succinate, Prednisolone sodium succinate, Hydroxydione sodium succinate, (49) Chloramphenicol sodium succinate, Tocopherol sodium succinate (50).

Solid dispersion of drugs are prepared by hot melt method using water soluble organic acid carriers like citric acid, succinic acid etc to improve dissolution of drugs. Advantage of hot melt method includes its simplicity and its economy, as no solvents are involved. The dissolution enhancement in citric acid system is reported due to formation of glass dispersions associated with very high dissolution rates. Solid dispersions of rofecoxib were prepared employing citric acid by hot-melt method with improved dissolution of rofecoxib (36).

Miscellaneous Carriers

Apart from above mentioned categories of carriers role of sodium chloride, microcrystalline cellulose, dicalcium phosphate, silica gel, and skimmed milk also has been established in enhancing dissolution of poorly water soluble drugs (Table 6). Ordered mixtures of griseofulvin were prepared using sodium chloride as a carrier material. Dissolution rate was increased due to soluble nature of sodium chloride, thereby rapid delivery of drugs in the form of discrete primary particles (37).

Solvent deposited system of piroxicam using microcrystalline cellulose in 1:1, 1:9, 1:19 ratios of drug to carrier were prepared. The drug dissolution for the 1:9 and 1:19 solid dispersions was more than 10 times that of the drug powder due to reduced particle size of drug deposited on the carrier and enhanced wettability of the particles brought about by the carrier. No improvement in dissolution on increasing ratio of drug to carrier from 1:9 to 1:19 was observed due to enclosure of drug particles in the polymer matrix (51). Similarly increased dissolution of solvent deposition system of indomethacin on microcrystalline cellulose was observed (52).

Solvent deposited system of flurbiprofen were prepared using lactose, microcrystalline cellulose (MCC), soluble starch, dicalcium phosphate (DCP), silica gel in different ratios.The increase in dissolution rate of flurbiprofen with various excipients were MCC>DCP>silica gel>lactose>soluble starch at 1:1 ratio of drug and excipients. The order of increase in the dissolution rate was lactose>DCP>MCC>silica gel>soluble starch at 1:2 ratio of drug and excipient. At lower proportion of excipient, i.e., at 1:1 insoluble excipients (MCC, DCP, and silica gel) gave higher dissolution rates than the soluble excipients (lactose and soluble starch). The soluble excipients dissolve rapidly leaving the particles of insoluble drug with poor dissolution and insoluble excipients remain suspended and gave good contact between the deposited drug and the surrounding dissolution medium and hence higher dissolution rates (53).

Comicronization of 2-(Chloro-4-iodo-phenyl-amino)-N-cyclopropylmethoxyl-3,4-difluoro-benzamide with microcrystalline cellulose was performed using fluid energy aljet micronizer with a vibratory feeder at 100 psi micronization pressure and 40 psi feed pressure. Increase in dissolution of the drug was concluded be due to increased

Table 6: Miscellaneous carriers and techniques employed for enhancing dissolution of poorly water soluble drugs

S/N	Drug	Carrier	Technique	Mechanism of Dissolution Enhancement	Refe-rence
1.	Griseofulvin	Sodium Chloride	Interactive mixtures	Soluble nature of sodium chloride, thereby rapid delivery of drugs in the form of discrete primary particles	(37)
2.	Indomethacin	Microcrystalline cellulose	Solvent deposition	Reduced particle size of drug deposited on the carrier and enhanced wettability of the particles brought about by the carrier	(52)
3.	Piroxicam	Microcrystalline cellulose	Solvent deposition	Reduced particle size of drug deposited on the carrier and enhanced wettability of the particles brought about by the carrier	(51)
4.	Flurbiprofen	Microcrystalline cellulose, Dicalcium phosphate, Lactose, Soluble starch, Silica gel	Solvent deposition	Soluble excipients dissolve rapidly leaving the particles of insoluble drug with poor dissolution and insoluble excipients remain suspended and gave good contact between the deposited drug and the surrounding dissolution medium and hence enhance dissolution rates	(53)
5.	2-(Chloro-4-iodo-phenyl amino)-N-cyclopropylmethoxyl-3,4-difluoroben-zamide	Microcrystalline cellulose	Comicronization	Increased wettability of drug due to the wicking properties of microcrystalline cellulose, increased apparent surface area available for dissolution by creating an ordered mixture and an increase in true surface area of powder mixture due to the surface roughness and porosity of the drug-microcrystalline cellulose mixture	(54)
6.	Flurbiprofen	Urea, Xylitol	Solid dispersion by fusion method	Enhanced wettability of drug in the presence of hydrophilic carrier, particle size reduction, decrease in the aggregation and agglomeration of the hydrophobic drug particles and improvement in the dispersibility of the drug	(55)
7.	Meloxicam	Skimmed milk	Solid dispersion by rotary vacuum evaporation	Polar effect provide by the carrier, Reduced crystallinity of the drug	(56)
8.	Rofecoxib	Citric acid, Succinic acid	Solid dispersion by hot melt method	Formation of glass dispersions associated with very high dissolution rates	(36)

wettability of drug due to the wicking properties of microcrystalline cellulose, increased apparent surface area available for dissolution by creating an ordered mixture and an increase in true surface area of powder mixture due to the surface roughness and porosity of the drug-microcrystalline cellulose mixture (54).

Solid dispersions of flurbiprofen using urea and xylitol in 1:1, 1:5, 1:9 drug to carrier ratio were prepared by fusion method. The enhanced dissolution rate was attributed to enhanced wettability of drug in the presence of hydrophilic carrier. Also other factors like particle size reduction, decrease in the aggregation and agglomeration of the hydrophobic drug particles and improvement in the dispersibility of the drug might have contributed to the enhancement in the dissolution rate of the drug. As the concentration of carrier increases in solid dispersion, increase in dissolution rate was observed and urea was observed more effective than xylitol in enhancing dissolution of drugs (55). Solid dispersions of meloxicam were prepared with skimmed milk using rotary vacuum evaporation technique with enhanced aqueous solubility and dissolution rate due to presence of lactose in skimmed which provide polar effect and also due to reduced crystallinity of the drug (56).

Conclusion

Various formulation techniques and wide range of carriers, as discussed in Part I [Int J Health Res Jun 2009; 2(2):107-124] and in this article are supportive to the formulation scientist to alleviate the problems of slow dissolution rate of drugs. Dissolution rate enhancement of drug depends on multitude of factors which includes physicochemical properties of drug and carrier, drug carrier interaction, and drug carrier ratio. Most of these carriers used for improving solubility and dissolution rate are highly water soluble and thereby provides polar environment around drug particles. When drug is formulated with such highly water soluble carrier(s), the drug is immediately exposed to aqueous environment in an amorphous form which the dissolve in a fast manner. Dispersing poorly soluble drugs in such carriers also alleviate problems of wetting and low specific surface area. Dissolution enhancement results obtained in the reported studies may be extrapolated to other poorly soluble BCS class II and Class IV drugs giving due considerations to correlation with improvement in their in vivo oral absorption. This could alleviate the problems of delayed and inconsistent rate of drug absorption from gastro intestinal tract, minimize therapeutic doses and reduction in drug-related side effects.

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