REVIEW

Natural polymers: Best carriers for improving bioavailability of poorly water soluble drugs in solid dispersions

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ABSTRACT

Natural polymers and its modified forms can be used as best alternative for improving bioavailability of poorly water soluble drugs in solid dispersion. Most of the natural polymers are hydrophilic and having high swelling capacity. Recent trend towards the use of natural polymer demands the replacement of synthetic additives with natural ones. Many plant derived natural polymers are studied for use in solid dispersion systems, out of which natural gums, cyclodextrin and carbohydrate are most extensively studied and used. This review discusses about the majority of these natural polymers, its uses and some recent investigations about modification of natural polymer in solid dispersion systems.

KEYWORDS: Modified natural gum, carbohydrate, dissolution enhancement, solid dispersion.

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INTRODUCTION

The enhancement of oral bioavailability of poorly water soluble drugs remains one of the most challenging aspects of drug development. So that salt formation, solubilization, and particle size reduction have commonly been used to increase dissolution rate and thereby oral absorption and bioavailability of such drugs but there are practical limitations of these techniques. The salt formation is not applicable for neutral compounds and the synthesis of appropriate salt forms of drugs that are weakly acidic or weakly basic may often not be practical. Even when salts can be prepared, an increased dissolution rate in the gastrointestinal tract may not be achieved due to the reconversion of salts into aggregates of their respective acid or base forms. The solubilization of drugs in organic solvents or in aqueous media using surfactants and cosolvents leads to liquid formulations that are usually undesirable from the viewpoints of patient acceptability and commercialization. Although particle size reduction is commonly used to increase dissolution rate, there is a practical limit to how much size reduction can be achieved by such commonly used methods as controlled crystallization, grinding, etc. The use of very fine powders in a dosage form may also be problematic because of handling difficulties and poor wettability.

Solid dispersion techniques have been used to enhance the dissolution and oral bioavailability of many poorly water soluble drugs (1). To overcome the solubility problem discussed above, many authors formulated solid dispersions using number of various polymers and methods. In spite of tremendous research activity on solid dispersions since 1961, their commercial application is limited. Only a few products have been marketed so far. One aspect of solid dispersion technology on which most workers in the field would agree is that the number of marketed products arising from this approach has been disappointing. Research for alternative carriers has been increasing to suit for the industrial applications as well as to reduce the production cost and toxic effects. Recently, many natural polymers have been evaluated for their uses in formulation of solid disper-

sion.Cost effective pharmaceutical excipients are always desirable. Pharmaceutical excipients developed from natural sources are economic. Present day consumers look for natural ingredients in food, drugs and cosmetics as they believe that anything natural will be more safe and devoid of side effects (2). Natural excipients show lack of toxicity, easy availability and economic considerations in pharmaceutical industry as compared to their synthetic counterparts. Naturally, derived excipients have shown promising results in the modification of drug release from the formulations (3).

SELECTION CRITERIA OF A CARRIER FOR SOLID DISPERSION (4)

Following criteria should be considered during selection of carriers:

(a) High water solubility which improve wettability and enhance dissolution
(b) High glass transition point which improve stability
(c) Minimal water uptake (reduces Tg)
(d) Soluble in common solvent with drug (solvent evaporation)
(e) Relatively low melting point (melting process)
(f) Capable of forming a solid solution with the drug (similar solubility parameters)
(g) Low viscosity and high swelling capacity

NATURAL POLYMERS USED AS CARRIERS FOR DISSOLUTION ENHANCEMENT IN SOLID DISPERSION

Recently, many natural polymers have been evaluated for their use in new applications. Naturally occurring carriers, which are soluble and dissolve in water at a fast rate, are widely used in pharmaceutical formulations to enhance dissolution of drugs (13). The carriers which have been reported in literature are presented in Table 1 and are described in detail under different categories.

TABLE 1. Different Natural polymer used as carriers for solid dispersions

Category	Example of carriers	References
1. Natural gums and its modified forms	Locust bean gum, Karaya gum, Guar gum, Xanthan gum, Hupu gum, Aegle marmalos gum etc.	(6-12)
2. Cyclodextrins	α, β & γ Cyclodextrin, Hydroxypropyl β-Cyclodextrin, meta hydratedβ-Cyclodextrin.	(18-27)
3. Carbohydrates	Lactose, corn starch, Sorbitol, Mannitol, Chitosan, Maltose etc.	(28-34)
4. Miscellaneous	Gelatin, Egg albumin, Skimmed milk, Silica gel, Urea etc.	(35-39)

NATURAL GUMS AND ITS MODIFIED FORMS

Natural gums, polysaccharides & their derivatives represents group of polymers widely used in pharmaceutical dosage forms. Polysaccharides are the choice of materials among the hydrophilic polymers used, because they are non-toxic & acceptable by the regulatory authority. Natural gums like Guar gum, Xanthan gum, Locust bean gum etc when used in optimum concentration lead to increase in dissolution rate due to low viscosity and high swelling capacity which offers better alternative for these types of polymers (5). The dissolution rate of drugs from the formulations containing viscous carriers is generally low due to the formation of gel layer on the hydrated surfaces, which prevents the drug release during dissolution. This can be overcome during tablet formulation by adding disintegrants. Pulverization of the product is also another important draw back with the high viscosity carriers, which can be overcome by using decreasing order of polymer/drug ratio during formulation. However, it is reported that the swelling ability of the carrier improves dissolution rate of poorly water soluble drug. As the viscosity of the carrier reduces the dissolution rate, it is useful to modify the gum in such a way that its swelling ability remains same and viscosity reduced. This can be achieved by heating (6).

Solid dispersions (SDs) of Lovastatin (LS) were prepared by modified locust bean gum (MLBG) as a carrier. The locust bean gum (LBG) was modified by heating and there observed irreversible decrease in viscosity, whereas swelling property remains unaffected. The advantage of modification of LBG was illustrated by difference in dissolution profiles of their SD. The result of solubility study showed increase in solubility of LS with increase in concentration of MLBG. It was found that the dissolution rate of LS from its SD was dependent on the method of preparation of solid dispersions. Dissolution study revealed that the modified solvent evaporation is most convenient and effective method for solubility enhancement of poorly water soluble drug LS, among various methods of preparation of SD. Increased wettability, dispersibility, and solubilization effect of LBG and MLBG enhances the solubility of LS . In vivo study indicates better performance of SD than LS as there observed significant reduction in activity of HMG Co A reductase enzyme. Overall studies showed that MLBG could be used as a potential carrier in the dissolution rate enhancement of Lovastatin (6).

Solid dispersions of Nimodipine (NM) were prepared by Modified gum karaya (MGK); on the basis of same mechanisms i.e. Modifying the gum in such a way that it's swelling ability is remained same and viscosity is reduced. It is found that method of preparation of solid mixtures was significantly affected the dissolution rate of NM from solid mixtures. Though, the solid mixtures prepared by other methods like solid dispersion, swollen carrier mixture and kneading technique gave faster release, co-grinding mixture prepared in 1:9 w/w ratio (NM:MGK) was found to exhibit a significant improvement in dissolution rate. No drug carrier interaction in the solid mixtures has been evidenced, increased wettability, dispersibility and reduced crystallinity of NM can account for the increased dissolution rate in systems containing GK or MGK. In conclusion, above studies showed that, MGK could be used as a potential carrier in the dissolution rate enhancement of NM (7).

Solid dispersions of Licofelone were prepared by using Guar gum (GG) and Modified guar gum (MGG). Modified guar gum (MGG) was prepared using heat treatment (125-130^{o}C for 2 to 3 hours) method. The physical and co-grinding mixtures of licofelone with GG and MGG were prepared in 1:6 drugs to gum ratio. The results of present investigation indicated that co-grinding mixture of licofelone with modified guar gum could be useful in developing an oral dosage form with increased solubility and hence improved dissolution and oral

TABLE 2. Natural gums & method used for enhancing solubility of poorly water soluble drug

Sr.no	Drug	Polymer	Technique	Mechanisms	Ref.
1.	Lovastatin	Locust bean gum and Modified locust bean gum	solvent evaporation	Increased wettability, dispersibility and solubilization effect	(6)
2.	Nimodipine	Karaya gum, Modified gum karaya	co-grinding technique	increased wettability, dispersibility and reduced crystallinity	(7)
3.	Licofelone	Modified guar gum	co-grinding mixture	Swelling action result in increased surface area	(8)
4.	Cefixime	Guar gum	solvent evaporation	Solubilization effect	(9)
5.	Gliclazide	Xanthan gum, Guar gum and Hupu gum	co-grinding mixture	Swelling action result in increased surface area	(10)
6.	Glimepiride	Modified gum karaya	solvent evaporation	Conversion of crystalline form to amorphous form	(11)
7.	Aceclofenac	Modified Aegle marmalos gum	Physical mixture, co- grinding mixture	Increased wettability, surface area and solubilization effect	(12)

bioavailability of poorly water soluble drug. Due to the swelling nature of the carrier, the extensive surface of carrier is increased during dissolution, and the dissolution rate of deposited drug is markedly enhanced. Water retention capacity of carrier is the amount of water retained in it that indicates ability of carrier towards hydrophilic nature (8).

The solubility of Cefixime is increased by preparing its solid dispersions using natural polymer, Guar gum. Various techniques used for preparing solid dispersions are by physical mixture, kneading and solvent evaporation methods using different drug-polymer ratio. The result obtained from above studies indicated that, the solubility and dissolution of Cefixime solid dispersions was improved as compared to pure drug by all the methods employed. A maximum increase in dissolution rate was obtained with Cefixime: guar gum solid dispersion with a weight ratio of 1:3 prepared by solvent evaporation method. The observed increase in the solubility of Cefixime in solid dispersions is thought to be attributable to the solubilization effect of the guar gum. Thus it can be concluded that the solubility of the poorly soluble drug, Cefixime can be improved markedly by using solid dispersion technique and the carrier, guar gum has increased the dissolution of the drug without any interaction (9).

The enhancement of dissolution profile of Gliclazide (GLZ) was carried out using Xanthan gum, Guar gum and Hupu gum as carriers by solid dispersion technique. Among the solid dispersions prepared formulation prepared by co-grinding method using Guar gum as carrier in 1:3 ratio shown the better release of Gliclazide (96.79 %) with in 60 min. The FTIR spectrum of pure drug, xanthan gum, guar gum, hupu gum and solid dispersion prepared by co-grinding method were obtained which shows no chemical interaction between drug and polymers. The enhanced dissolution may be due to enhanced wettability and dispersibility of drug in dissolution medium (10).

Solid dispersions of Glimepiride were prepared by Modified gum karaya (MGK), by solvent evaporation method. Maximum solubility and invitro dissolution were observed with solid dispersion of Modified gum karaya (MGK). No significant enhancement of dissolution characteristics were observed in corresponding physical mixture. Low viscosity with comparable swelling characteristics as compared to Gum karaya (GK) of modified form of gum karaya may lead to improvement in dissolution behavior of solid dispersion batches. The dissolution enhancement occurs due to conversion of crystalline form to amorphous form (11).

Solid dispersions of Aceclofenac were prepared by using Aegle marmalos gum (AMG) and Modified Aegle marmalos gum (MAMG). Modified Aegle marmalos gum (MAMG) was prepared using heat treatment technique. Effect of polymer concentration and methods of preparation on solubility enhancement were studied using solubility and dissolution studies, respectively. The result of solubility study showed increase in solubility of Aceclofenac with increase in concentration of AMG and MAMG, and change of technique from physical mixture to co-grinding to solid dispersion. Increased wettability, surface area and solubilization effect of AMG and MAMG enhances solubility in water. From study it can be concluded that, MAMG could be used as a potential carrier in the dissolution rate enhancement of Aceclofenac (12).

CYCLODEXTRINS

Cyclodextrins although belongs to the category of carbohydrate but its wide applications and role in dissolution enhancement make it deserving candidate to be described separately (13). Cyclodextrins (CD) are cyclic oligomers typically composed of 6–8 glucose units. CDs represent a class of solubilizing agents that form non-covalent, dynamic complexes with lipophilic molecules by inclusion. The inclusion complex modifies temporarily the physical properties of the substance, governed by the equilibrium constant between the free drug, free CDs and the drug-CD complex; the drug will be released constantly and rapidly on dilution. CDs have been demonstrated to improve the stability of substances like proteins or peptides. The CDs that are approved for pharmaceutical products can be classified into three major types differing only in their molecular weight and respective central cavity diameter. Alpha-cyclodextrin (α-CD) has a molecular weight of 972 and a central cavity diameter of around 5A˚, these increases to MW 1135 and 6.2A˚ for β-CD and MW 1297 and 8A˚ for γ-CD, respectively (14).

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 low-

ered, when suitable guest molecules that are less polar than water replace these enthalpy rich water molecules (15, 16). Partial methylation of some of the cyclodextrin 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 (17).

Solid complexes of Norfloxacin β -Cyclodextrins/Hydroxypropyl β-Cyclodextrin in 1:1 and 1:2 molar ratios were prepared by freeze drying method. Solubility studies revealed more efficiency of Hydroxypropyl β-Cyclodextrin as compared to β -Cyclodextrins in solubilizing norfloxacin and dissolution studies revealed increase in dissolution rate of drug complexes compared to drug alone and physical mixtures (18).

Solid complexes of Gliclazide-β-Cyclodextrins in 1:2 molar ratios were prepared by neutralization, kneading, coprecipitation, cogrinding and spray-drying method. Coprecipitated, neutralized, co-ground and spray-dried systems showed higher dissolution rates than pure drug, physical mixture and kneaded product (19).

Solid complexes of Carbamazepine- Hydroxypropyl β-Cyclodextrin in 1:1 molar ratio were prepared by solvent method using absolute ethanol with enhanced dissolution of drug (20).

Solid complexes of Danazol- Hydroxypropyl β-Cyclodextrin were prepared by spray freezing into liquid (SFL) process. Dissolution results suggested that equilibration of the danazol- Hydroxypropyl β-Cyclodextrin 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 (21).

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-Cyclodextrin concentration (0-16M) (22).

The complex of Nimesulide and β-Cyclodextrin in 1:1, 1:1.5, 1:2 molar ratios 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-Cyclodextrin complex. This method can be easily scaled up to the industrial level which could otherwise be a challenge in case of cyclodextrins (23).

Solid complexes of Satranidazole- β-Cyclodextrin 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-Cyclodextrin concentration. Kneaded mixtures showed high dissolution rate compared to physical mixtures due to intensive mixing. The complexation with β-Cyclodextrin 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-Cyclodextrin (24).

Solid complexes of Carbamazepine-β-Cyclodextrin 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-Cyclodextrin concentration. The decrease in drug crystallinity was responsible for increased solubility of the solid complex when compared to that of the pure drug (25).

Solid complexes of Gliclazide-β-Cyclodextrin 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

TABLE 3. Cyclodextrins & methods used for enhancing solubility of poorly water soluble drug

Sr.no	Drug	Polymer	Technique	Mechanisms	Ref.
1.	Norfloxacin	β–Cyclodextrins, Hydroxypropyl β-Cyclodextrin	Inclusion complexes by Freeze drying	Formation of inclusion Complexes	(18)
2.	Gliclazide	β -Cyclodextrins	Inclusion complexes by kneading, coprecipitation, cogrinding, spray drying	Formation of inclusion complex in solid state and reduction in crystallinity of the product	(19)
3.	Carbamazepine	Hydroxypropyl β-Cyclodextrin	Inclusion complexes By solvent method	Formation of inclusion Complexes	(20)
4.	Danazol	Hydroxypropyl β-Cyclodextrin	Inclusion complexes by spray freezing	Higher surface areas and stabilized inclusion complexes	(21)
5.	Norfloxacin	β -Cyclodextrins	Inclusion complexes by kneading method	Formation of inclusion Complexes	(22)
6.	Nimesulide	β -Cyclodextrin	Inclusion complexes by kneading method	Formation of inclusion Complexes	(23)
7.	Satranidazole	β -Cyclodextrin	Inclusion complexes by kneading method	Reduction in crystallinity of the drug	(24)
8.	Carbamazepine	β -Cyclodextrin	Inclusion complexes by kneading method	decrease in crystallinity of the drug	(25)
9.	Gliclazide	β -Cyclodextrin	Inclusion complexes by liquid/liquid extraction and neutralization	Increase in the drug Wettability	(26)
10.	Piroxicam	β -Cyclodextrin	Inclusion complexes by kneading, freeze drying, neutralization method	Formation of inclusion Complexes	(27)

rates than other solid complexes indicating importance of method of preparation of complexes (26).

Solid complexes of Piroxicam- β-Cyclodextrin 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 photodegradation constant (27).

CARBOHYDRATES

Carbohydrates like lactose, soluble starches, sorbitol, mannitol, maltose, galactose, xylitol, dextran etc also have their role in dissolution enhancement. Enhancement in dissolution is mainly attributed to increase in surface area of drug exposed to large carrier molecules, increased wettability and consequently solubility due to polar effect of carbohydrates containing polar groups (13).

The dissolution of Diazepam (1-10%) in lactose interactive mixture prepared by placing micronized 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 (28).

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 (29).

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 (30).

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 drugs 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 carrier: 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 (31).

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 (32).

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 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 (33).

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 (34).

TABLE 4. Carbohydrates & methods used for enhancing solubility of poorly water soluble drug

Sr.no	Drug	Polymer	Technique	Mechanisms	Ref.
1.	Diazepam	Lactose	Interactive mixing	Increase in the surface area of drug directly exposed to the carrier material	(28)
2.	Fentanyl	Coarse mannitol	Interactive mixing	Increase in the surface area of drug directly exposed to the carrier material	(29)
3.	Indomethacin	Fine Lactose	Interactive mixing	Dissolved lactose left an agglomerate structure of indomethacin with a much greater porosity and ability to disperse	(30)
4.	Nifedipine	Chitosan, Chitosan glutamate	Solid dispersion by solvent method	Decreased drug crystallinity and size of the drug and wetting effect.	(31)
5.	Griseofulvin	Maltose, Lactose, Corn Starch	Solid dispersion by roll mixing method	Increase in the surface area of griseofulvin directly exposed to the carrier materials	(32)
6.	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	(33)
7.	Rofecoxib	Mannitol, Sorbitol	Solid dispersion	Polar environment provided by the carrier	(34)

TABLE 5. Miscellaneous & methods used for enhancing solubility of poorly water soluble drug

Sr.no	Drug	Polymer	Technique	Mechanisms	Ref.
1.	Valsartan	Skimmed milk powder	Physical mixture and dispersion method	decrease in the crystallinity of the drug which increases the surface area	(35)
2.	Meloxicam	Skimmed milk powder	rotary vacuum evaporation method	polar effect and reduced crystallinity	(36)
3.	Nifedipine	Gelatin, egg albumin and β-cyclodextrin	kneading technique		(37)
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	(38)
5.	Flurbiprofen	urea and 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	(39)

MISCELLANEOUS

Apart from these categories, some of miscellaneous carriers play important role in dissolution enhancement of poorly water soluble drugs, for example skimmed milk, silica gel, gelatin and egg albumin etc.

Solid dispersions of Valsartan were prepared by Skimmed milk powder (SMP), by dispersion method. Four different formulations were prepared with varying drug: carrier ratios viz.1:1, 1:3, 1:5 and 1:9 and the corresponding physical mixtures were also prepared. All the formulations showed marked improvement in the solubility behavior and improved drug release. Formulation containing drug: polymer ratio of 1:9 showed the best release with a cumulative release of 81.60% as compared to 34.91 % for the pure drug. The interaction studies showed no interaction between the drug and the carrier and there was a considerable decrease in the crystallinity of the drug which increases the surface area thereby increasing the dissolution (35).

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 (36).

The solid dispersions of Nifedipine were prepared using gelatin and egg albumin and comparison of such polymers was carried out by complexation with β-cyclodextrin. Solid mixtures of nifedipine and polymer in various ratios were prepared by the kneading technique and their dissolution was carried out according to the dispersed amount method. It was found that water-soluble gelatin and β-cyclodextrin resulted in a significant increase in the rate of dissolution of nifedipine as compared to drug alone. Further, water-soluble gelatin may be particularly useful for the enhancement of dissolution of nifedipine (37).

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 excipients, 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 (38).

Solid dispersions of Flurbiprofen using urea and xylitol in 1:1, 1:5, 1:9 drugs 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 (39).

CONCLUSION

The natural excipients and their application in solid dispersions have been reviewed in detail in this article. This article emphasizes the essential criteria of carrier for solid dispersion, modification of natural polymer and combinations of different natural polymer in solid dispersion. The use of natural polymer for pharmaceutical applications is attractive because they are economical, readily available, non-toxic, and capable of chemical modifications. They have a major role to play in pharmaceutical industry. Most of these carriers used for improving solubility and dissolution rate are highly water soluble and thereby provides polar environment around drug particles. The swelling ability of the carrier improves dissolution rate of poorly water soluble drug. Some of the carriers are especially capable of forming highly water soluble amorphous forms when the drugs are dispersed in them. Complexation of drug with suitable carrier also alters the solubility and dissolution characteristics due to extremely high aqueous solubility of the carrier. The solubility and dissolution rate improvements are also expected due to co-solvency effect and solubilisation effect of carriers in aqueous vehicles.

Doğal polimerler: Katı dispersiyon sistemlerinde suda çözünürlüğü düşük ilaçların biyoyararlanımını arttıran en iyi taşıyıcılar

ÖZET: Doğal polimerler ve modifiye formlarının, suda çözünürlüğü düşük ilaçların biyoyararlanımı arttırmak için kullanılan bileşenler arasında en iyi alternatif olduğu bilinmektedir. Doğal polimerlerin birçoğu hidrofiliktir ve yüksek oranda şişme kabiliyetine sahiptir. Son zamanlarda yapılan çalışmalarda ilaç formülasyonunda kullanılan sentetik özellikli yardımcı maddelerin doğal olanlar ile değiştirilmesi ön planda tutulmaktadır. Katı dispersiyon sistemlerinin oluşturulmasında bitkilerden hareketle kazanılan birçok doğal polimerin kullanılması yönünde çalışmalar yapılmıştır. Doğal polimerler dışında siklodekstrin ve karbonhidrat yapılı bileşikler de birçok çalışmaya konu olmuştur. Bu çalışma kapsamında bahsi geçen yapıdaki polimerlerin birçoğunun kullanım özelliklerine değinilmiş ve katı dispersiyon sistemlerinde doğal polimerlerin modifikasyonları ile ilgili güncel araştırmalar derlenmiştir.

ANAHTAR KELİMELER: Modifiye edilmiş doğal reçineler, karbonhidratlar, çözünürlüğün arttırılması, katı dispersiyon

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