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SOLUBILITY ENHANCEMENT OF LUTEIN ESTER USING SOLID DISPERSION TECHINQUE.

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ABSTRACT

The oral drug delivery is preferred to be the most common and simple route of administration due to its usefulness and ease of ingestion but sometimes it is tricky if the drug is poorly soluble or poor membrane permeability. To amend the dissolution of drugs which are poorly water soluble also eventually amending their bioavailability, the dispersion of one or more API in a carrier that too a solid state are employed. This anomaly is known as Solid Dispersion. This technique is mostly applicative for upgrading the solubility, dissolution rates also bioavailability of poorly soluble drugs. Lutein is a xanthophyll carotenoid that is found in various fruits, vegetables, and flower. Lutein is an arduous compound to assimilate into food, as it is poorly soluble and unstable in aqueous solutions. Natural polymers and their modified forms can be used as a best alternative for upgrading solubility of poor water soluble drugs in solid dispersion. Various natural polymers like carbohydrate and cyclodextrin are most broadly used as carrier for enhancing the solubility. Hence, this approach is anticipated to form basis for commercialization of poorly water soluble drugs by enhancing their solubility by incorporating the solid dispersion technique including natural polymers.

KEYWORDS:

Solubility, Solid dispersion, Lutein ester, antioxidant, natural polymer.

INTRODUCTION

The simplest and uncomplicated way of dealing drug is through oral route. Compared to alternative dosage forms, oral dosage forms have various benefits, including increased stability, precise dosing, reduced volume, and Production may be done with ease. Currently, one of the biggest issues facing formulation scientists in the pharmaceutical sector is the formulation of poorly soluble drugs for oral delivery. The pharmaceutical industry has discovered nearly 40% of prospective novel drugs that have low water solubility. Therefore, a large dose is needed to have the desired effect, but this could make the medicine hazardous. Improvement of the solubility through formulation strategies is therefore the greatest choice for raising the release rate (1, 2). Drug when delivered orally, must dissolve in intestinal and gastric fluids in order to permeate membranes of GIT to reach the systemic circulation. However it is considered that a poorly aqueous soluble drug exhibits dissolution rate limited absorption also poorly membrane permeable drug exhibits permeation rate limited absorption. Solubility is a significant physicochemical factor affecting absorption of drug and its therapeutic effectiveness. Formulation development would lead to be failure if

drug having poor aqueous solubility. The low dissolution rate and low solubility of drug substances in water in aqueous G.I.T fluid frequently leads to inadequate bioavailability. The venture to improve the solubility and dissolution of hydrophobic drugs remain one of the difficult tasks in drug development. Several methods have been introduced to triumph over this problem .Various methods to increase the solubility of drugs are .available such as liquid solid, in which drug in solution state or dissolved drug is adsorbed over insoluble carrier.

Descriptive term (solubility definition)	Parts of solvent required for one part of solute	Solubility range (mg/mL)	Solubility assigned (mg/mL)
Very soluble (vs)	<1	≥1,000	1,000
Freely soluble (fs)	From 1 to 10	100–1,000	100
Soluble (s)	From 10 to 30	33–100	33
Sparingly soluble (sps)	From 30 to 100	10–33	10
Slightly soluble (ss)	From 100 to 1,000	1–10	1
Very slightly soluble (vss)	From 1,000 to 10,000	0.1–1	0.1
Practically insoluble (pi)	≥10,000	<0.1	0.01

SOLID DISPERSION

Solid dispersion is defined as dispersion of one or more active ingredients (hydrophobic) in an inert carrier (hydrophilic) at solid state prepared by melting (fusion), solvent, melting solvent method. The product formed contains different components i.e. a hydrophilic matrix and a hydrophobic drug (3). In solid dispersions, a portion of drug dissolves immediately to saturate the gastrointestinal tract fluid, and excess drug precipitates as fine colloidal particles or oily globules of submicron size. The development of solid dispersions as a practically viable method to enhance bioavailability of poorly water-soluble drugs overcame the limitations of previous approaches such as salt formation, solubilization, cosolvency, and particle size reduction. Moreover, not the preparation method but the molecular arrangement governs the properties of solid dispersions.

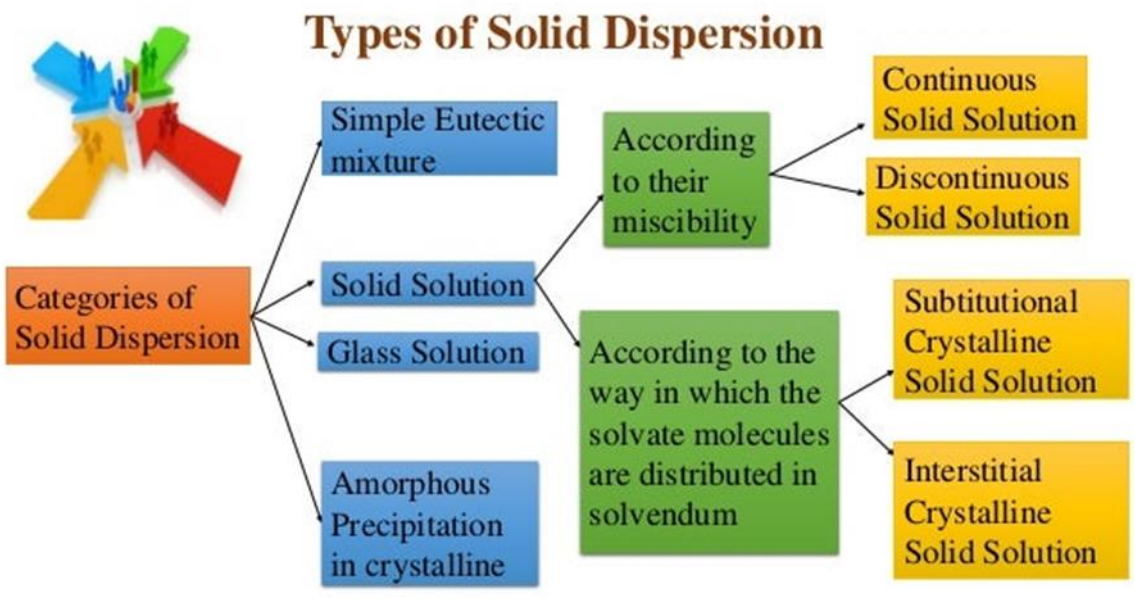

Fig: Categories of Solid Dispersion

CLASSIFICATION OF SOLID DISPERSION

Solid dispersions can be classified as follows, depending on the molecular configuration.

1] EUTECTIC MIXTURES

In order to create a physical mixture of very thin crystals of the two components, solid eutectic mixes are typically created by rapidly chilling the co-melt of the two components (4).

2] Solid solution

The two different categories of solid solutions, depending on the miscibility, are: 1] Continuous solid solution- The components in continuous solid solutions are miscible in all ratios, which means that the bonds between the components are stronger than those between the individual components.

2]Discontinuous solid solution-The solubility of each component in the other component is constrained in discontinuous solid solutions.Solid solutions can be classified into one of two categories, depending on how the solvates are distributed in the solvendum:

1] Substitutional crystalline solution- These are the types of solid solutions that are crystalline in nature. In the crystal lattice, the solute molecules take the place of the solvent molecules.

2] Interstitial crystalline solid solution- These are those solid solutions where the dissolved molecules fill the voids in the crystal lattice between the solvent molecules.

3]Amorphous solid solution-In amorphous solid solutions, the solute molecules are dispersed molecularly but irregularly within the amorphous solvent.

4]Glass solution and glass suspension-A homogenous system known as a glass solution, the solute dissolves in the glassy solvent. Transparency and brittleness are characteristics of the glassy state, which exists below the glass transition temperature. A pure chemical or a combination of pure chemicals, in the glassy condition is referred to as glass(3).

Classification of solid dispersion on the basis of recent advancement

1]First generation solid dispersion-Crystalline carriers are used to create these solid dispersions.

The first crystalline carriers to be employed in the creation of solid dispersions were urea and sugars. These are thermodynamically unstable and do not release drugs more quickly, which is a drawback.

2]Second generation solid dispertion-Instead of crystalline carriers, amorphous carriers are used to create these solid dispersions. The polymeric carrier contains the medication molecularly distributed. The polymeric carriers are divided into two groups:

1]Synthetic polymer – povidone, polyethylene glycols and polymethacrylates.

2] Natural polymers – hydroxypropylmethylcellulose, ethyl cellulose, starch derivatives like cyclodextrin.

3]Third generation solid dispersion-A surfactant carrier or a combination of amorphous polymers and surfactants serves as the carrier in these solid dispersions.For medications with weak solubility, these achieve the highest level of bioavailability. The third generation solid dispersion uses surfactants like inulin, poloxamer 407 and others(5).

METHODS OF SOLID DISPERSION TECHNIQUE

Various methods used for preparation of solid dispersion system. These methods are given below.

1. Melting method
2. Solvent method
3. Melting solvent method (melt evaporation)
4. Melt extrusion methods
5. Lyophilization techniques
6. Melt agglomeration Process
7. The use of surfactant
8. Electrospinning
9. Super Critical Fluid (SCF) technology

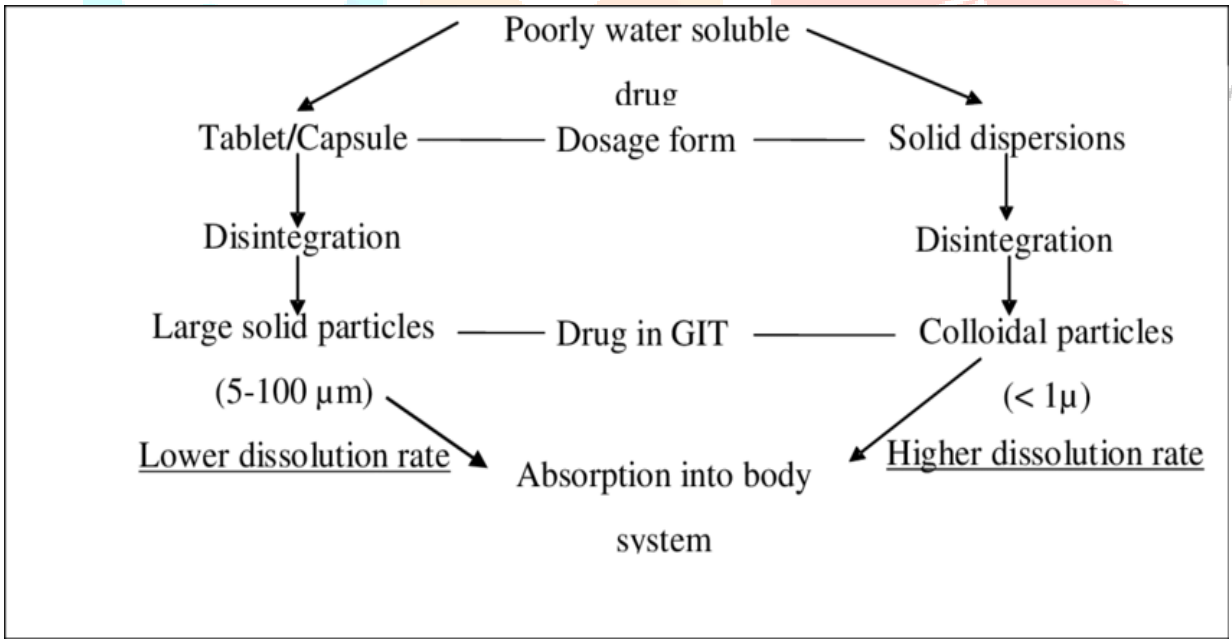

Table 1

BCS Class	Solubility	Permeability	Oral Dosage Form Approach	Chances of Non-oral Dosage Form being Required
1	High	High	Simple solid oral dosage form	 Lubrizol Life Science
2	Low	High	• Techniques to increase surface area like particle size reduction, solid solution, solid dispersion • Solutions using solvents and/ or surfactants	
3	High	Low	Incorporate permeability enhancers, maximize local lumenal concentration	
4	Low	Low	Combine 2 and 3	

Applications of solid dispersion

- It makes less soluble substances more soluble. increasing the solubility of medicines It speeds up the absorption and medication bioavailability.
- To prevent unstable medications from being destroyed by processes like oxidation and hydrolysis, among others.
- For reducing the adverse effects of some medications.
- Masking of the odour and taste of medications.
- To prevent harmful incompatibility.
- To obtain a homogeneous distribution of a small amount of drug in solid state.
- Dispensing of liquid (up to 10%) or gaseous compounds in a solid dosage[6].

Lutein

Lutein, known as a fat-soluble carotenoid pigment, consisting of 40 carbons with sequence of dominant, conjugated double bonds. It is believed that the presence of double bonds in their structure has led to their prominent red colour and ability supply free radicals (7). Egg yolk and corn are two foods that contain a lot of lutein. Other foods that contain a lot of lutein include kiwi, grapes, spinach, orange juice, and zucchini. Due of its potential nutritional value, lutein has drawn the attention of researchers all around the world. According to a previous study, lutein is mostly found in human retina, protecting it from short-wavelength visible light. According to reports, oxidised lutein and zeaxanthin function as antioxidants, defending the retina. Additionally, higher fasting plasma carotenoids concentration and an increase in skin yellowness after lutein ingestion indicate that lutein is also present in other areas of the human body, such as the skin, breast, brain, and cervix (8). It is believed that lutein's antioxidant capability plays a major role in the protective benefits it has on the human body. According to some research, lutein plasma concentrations between 0.6 and 1.05 mmol/l are considered safe for humans and still exert the anticipated positive benefits. Additionally, due to lutein's volatility and potential chemical alterations during food processing, its application in the animal and fish feed sectors is restricted. However, due to its outstanding advantages to the human body, lutein's use in medications and health supplements

continues to be significant. Lutein must be consumed in order to be obtained, therefore taking supplements can assist assure an appropriate supply. The biological benefits of lutein's various biological features are widely recognised as being beneficial to human health. Its market is divided into the pharmaceutical, food, animal, dietary supplement, and sh feed businesses. There is, however, no extensive evidence to back up its paucity of health advantages. As a result, we sought to present an updated and thorough study of lutein, including its chemistry and biological characteristics, in order to reveal its potential and hasten its development and application in the food and phytopharmaceutical industries.

NATURAL POLYMERS USED AS CARRIERS FOR DISSOLUTION ENHANCEMENT IN SOLID DISPERSION

Various natural polymers have recently undergone evaluation in order to be used in brand-new applications. Pharmaceutical formulations frequently use naturally occurring carriers that are soluble and dissolve quickly in water to speed up the dissolution of medicines (9). The carriers that have been mentioned in literature and provides detailed descriptions of each category. (Table no 1).

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.	(10-16)
2. Cyclodextrins	α , β & γ Cyclodextrin,Hydroxypropyl β-Cyclodextrin, meta hydratedβ-Cyclodextrin.	(17-26)
3. Carbohydrates	Lactose, corn starch, Sorbitol, Mannitol, Chitosan, Maltose etc.	(27-33)
4.Miscellaneous	Gelatin, Egg albumin, Skimmed milk, Silica gel, Urea etc.	(34-38)

Table 1. Different Natural polymer used as carriers for solid dispersions NATURAL GUMS

AND ITS MODIFIED FORMS

The group of polymers known as natural gums, polysaccharides, and their derivatives is one that is frequently employed in pharmaceutical dosage forms. Among the hydrophilic polymers employed, polysaccharides are the material of choice because they are non-toxic and accepted by the regulatory body. Due to their low viscosity and high swelling capacity, natural gums like guar gum, xanthan gum, locust bean gum, etc., when employed in the best concentration, accelerate the rate at which these types of polymers dissolve.(39). If a gel layer forms on the hydrated surfaces of formulations containing viscous carriers, which limits drug release during dissolution, the dissolution rate of drugs from these formulations is often poor.By include disintegrants in the tablet formulation process, this can be avoided. Another significant drawback of high viscosity carriers is product pulverisation, which can be avoided by utilising a decreasing order of polymer/drug ratio during formulation. However, it has been claimed that a weakly water soluble medicine dissolves more quickly thanks to the carrier's capacity to swell. It is useful to change the gum so that its swelling ability is maintained while its viscosity is decreased since the viscosity of the carrier lowers the dissolution rate.This can be achieved by heating.(40)

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 (40).

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 (125-130oC 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 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 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 (41)

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 (9).

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 (19).

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 (20).

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 (9).

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, coground 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 (30).

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 (31).

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.

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 (36).

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