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An Updated Review on The Utilization of Various Carriers and Methods to Prepare Solid Dispersions of BCS Classified Drugs

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Research Article

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ABSTRACT

In preparation of formulation, the solubility factor remains a key concern. Now a day, many drugs especially in BCS class II and IV are observed to have less solubility. Among all solubility enhancing techniques practiced in pharmaceutical field, solid dispersions have proved to be most suitable for improving the bioavailability of these chemical entities. During the preparation of solid dispersion, carriers play a vital role in enhancing the dissolution of hydrophobic drugs. This article however reviews various methods and carriers used for the preparation of solid dispersion, with main emphasis on which carriers and methods have been widely used by researchers over the decades, till now.

INTRODUCTION

Among the drug administration methods, oral route is the most suitable and preferable method for drug delivery, owing to its easy ingestion and convenience. Taking drug orally is more compliant then other routes of administration, but this route of administration presents serious problems regarding the mode of delivery for a significant number of reasons. Poor bioavailability is the major issue [1]. Multiple techniques including: co-solvent-solubilization method, particle size reduction, complex formation using cyclodextrin, salt formation and many others were used to combat these issues, but all had some limitations [2].

Solid dispersion, in comparison to all other approaches proved to be the best suitable technique. Sekiguchi and obi were the first, who came with the idea of preparing solid dispersion to overcome the issue of poor bioavailability and for sustained release of drug [3]. A dispersion containing a minimum of two components in inert matrix (one hydrophilic and other hydrophobic), in order to increase the dissolution rate and permeability of poorly water-soluble drugs, is known as solid dispersion [4]. The carriers used in the preparation of solid dispersion vary in grades and nature (crystalline or amorphous). However, various grades of PEGs, PVPs, urea and sugar, are the among the most used carriers in the preparation of solid dispersions [3,5].

The literature review indicates that the use of solid dispersion has been for decades. Moreover, the main aim of this review is to provide a background on solid dispersion, its various methods of preparation, the selection of carrier owing to the drug characteristics. However, the main emphasis is on the carriers and type of methods used to prepare solid dispersion over the past few decades, along with the comparison that which method and carriers were found most suitable for its preparation.

METHODS OF PREPARATION OF SOLID DISPERSION

Various methods of preparation are suggested for the preparation of solid dispersions and researchers have utilized them accordingly.

Fusion (melting) Method

In this process, a physical mixture containing drug and carrier is prepared and melted until a liquid state is achieved. This liquid mixture is later cooled to form dry mass. Sekiguchi and obi used this method for the preparation of sulfathiazole. However, this method is not preferable for thermolabile drugs owing to its immiscibility between the drug and carrier [3].

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Solvent Evaporation Method

This process involves the dissolution of drug and carrier in a same solvent at the same time. The resultant solution is then subjected to evaporation, using various techniques such as: vacuum or slow evaporation methods, heating, spray drying, or freeze drying. The substances which has its limitations in fusion method could use this technique [6].

Spray Drying

This is a sophisticated technique, where after the preparation of physical mixture of drug and carrier, the solution is evaporated in chamber. The solution is sprayed under specified conditions in the chamber and later separated after drying [7].

Melting Solvent Method

This process is the amalgamation of melting and solvent evaporation method, that's why known as melting solvent method. This technique involves the dissolution of drug in specified solvent and later in carrier. The final solution is then cooled until a dry mass is achieved. This method is most suitable for thermolabile drugs and carriers [8].

Lyophilization

Lyophilization also known as freeze drying, is a method in which the drug-carrier solution containing solvent is initially subjected to freezing followed by drying at less pressure. However, this is a time taking process yet giving less yield [9].

Kneading Method

In this technique, a paste is produced using suitable carrier and water as a solvent. The drug is then incorporated and kneaded for drying. Moisture sensitive drugs have its limitations in this method [10].

Co-grinding Method

The blender containing the drug and carrier is blended at a specified speed to form a powder, which is later transferred to a vibrating ball mill. The resultant mixture is pulverized and gathered for future use [11].

Co-precipitation Method

In this process, the carrier is primarily mixed with a suitable solvent to form a solution. The drug is later added to this solution and subjected to agitation under magnetic stirrer. The final precipitates formed are collected via vacuum filtration, and later dried [12].

Super Critical Fluid Technique

This is an advanced technique, where the physical mixture of drug and carrier is dissolved in a suitable solvent. The final solution is sprayed in a chamber using atomizer, where particles are formed [13]. The chamber, which is occupied with super critical fluids (mainly CO_2) captures the solvent as soon as the drug carrier solution enters the chamber, leading to the formation of solid dispersed particles. These particles are later collected from the walls of chamber [14].

However, solid dispersions are classified into seven major types, which are explained in the following chart [15] **(Table 1)**.

Table 1. Classifications of solid dispersions.

solid dispersions	Matrix	Drug**	no. of phases	Remarks
1. Eutectics	c	c	2	1st solid dispersion
2. Amorphous precipitations in crystalline matrix	c	A		Rarely encountered
3. solid solutions				
continuous solid solutions	c	M	1	Never prepared
Discontinuous solid solutions	c	M	2	partially miscible, drug is molecularly dispersed
Substitutional solid solutions	c	M	1 OR 2	molecular diameter of drug is £ 15% of polymer
Interstitial solid solutions	c	M	2	molecular diameter of drug is £ 59% of polymer
				Limited miscibility and discontinuous
4. Glass suspension	A	C	2	Particle size of dispersed phase depends upon cooling/ evaporation rate
5. Glass suspension	A	A	2	Particle size of dispersed phase depends upon cooling/ evaporation rate mostly encountered
6. Glass suspension	A	M	1	Requires miscibility/solid solubility, complex formation or upon fast cooling /evaporation during preparation

*A: Matrix in the amorphous state; c: Matrix in the crystalline state; **A: drug dispersed as amorphous clusters in the matrix; c: drug dispersed as crystalline particles in the matrix

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CARRIERS USED IN THE PREPARATION OF SOLID DISPERSION

Polyethylene glycol (PEG)

PEG (molecular weight: 200-300000), are polymers of ethylene oxide. The molecular weight (MW) plays a vital role in the preparation of solid dispersion, as the molecular weight and viscosity are directly proportional to each other (greater the MW, greater will be the viscosity) [16]. However, MW ranging from 1500-20000 is desired for the preparation of solid dispersion.

They are soluble in water, also improves the wettability of compound which gives it the advantage in enhancing the dissolution rate of drug [9].

Polyvinylpyrrolidone (PVP)

PVP, a polymer of vinylpyrrolidone, has a molecular weight falling between 2500-3000000. Moisture content and MW are responsible for the maintenance of PVP's temperature [17]. It is used in various methods of solid dispersions such as: solvent evaporation method owing to its increase solubility [18]. It is also used in hot melt extrusion method due to its high melting point.

Cellulose Derivatives

Hydroxypropylmethylcellulose (HPMC), molecular weight (10000-1500000), are unsymmetrical ethers of cellulose. Due to its excellent solubility in water, HPMCs are widely used in the formation of solid dispersion [4]. Researchers have seen enhanced solubility of nilvadipine (poorly water-soluble drug), when used with HPMC [19].

Hydroxypropylcellulose (HPC), a derivative of cellulose has a MW of 37000-1150000. The solubility of HPC in solvents is high and varies to a wide range of solvents (ethanol, chloroform, water) [20].

Carboxymethylethylcellulose (CMEC), is a class of cellulose with mixed ethers. In comparison to other cellulose derivatives, the dissolution rate of CMEC is altered in stomach due to acidic pH. Its dissolution in many solvents like ethanol, acetone and isopropanol is excellent and quick. However, its dissolution is rapid at pH above 6 [21].

Hydroxypropylmethylcellulose phthalate (HPMCP), esters of cellulose, have a MW between 20000-20000. Their pH of dissolution falls between 5-5.5. however, their solubility in different solvents depends on the type of HPMCP used [12].

Polyacrylates and Polymethacrylates

These are the type of polymers which owing to their transparency are known as plastics. Methacrylate and acrylic acid undergo process of polymerization to produce these polymers [5]. In market, they appear by the name of Eudragit (varying in grades). Some of the eudragit grades like eudragit L prevents the release of drug in gastric pH. However, other grades like eudragit E, due to its high solubility, increases the drug release. They are mainly used to coat the drugs, in order to control their release [22].

Urea

Urea, which is produced in the final step of metabolism of human protein, is considered to be sparingly soluble in water and many solvents. Due to their non-toxic effect in human body, they are also used as carrier for the preparation of solid dispersion by many researchers [3] **(Table 2)** [23-61].

Table 2. Preparation of solid dispersion using various methods and carriers on BCS class drugs.

S. no	Drug name and BCS class	Therapeutic class	Method	Carrier	Conclusion	Reference
1	Glyburide (Class II)	oral hypoglycemic	melt and solvent methods	PEG 4000, PEG 6000	Increased dissolution rate with glyburide PEG solid dispersion	[9]
2	Nifedipine (class II)	calcium-channel blockers	Co-precipitation method	PEG PC-PEG	Increased dissolution of Nifedipine PC-PEG solid dispersion than Nifedipine PEG solid dispersion.	[23]
3	Griseofulvin (class II)	Anti-fungal	eutectic mixture system (fusion melt method).	succinic acid	Increased dissolution rates of Griseofulvin	[24,25]
4	Fenofibrate (class II)	Fibrate class	Melting method	PEG 6000 and PVP	Dissolution rate of Fenofibrate was decreased.	[25]
5	Indomethacin (IMC) (class II)	NSAID	spray-drying method	Aerosil 200 Sylysia 350	The dissolution rate of IMC with Sylysia 350 was faster than that of Aerosil 200	[26]

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6	Gliclazide (class II)	antidiabetic agent	solvent evaporation method	(PEG) 6000	Increased in Gliclazide dissolution in the presence of PEG 6000 was followed by improved in vivo data.	[27]
7	Indomethacin (class II)	NSAID	co-precipitation and spray drying	(PVP) 17 or 90	PVP 17 has faster dissolution rate than PVP 90	[28]
8	Diflunisal (class II)	NSAID	Solvent evaporation method	PEG	Increase solubility of drug	[29]
9	Spironolactone (class II)	Potassium-sparing diuretics.	Solvent method	Sylysia 730 and Sylysia 350	Dissolution rate is faster with Sylysia 350	[30]
10	Nifedipine (class II)	calcium-channel blockers	Amorphous precipitation in crystalline matrix:	PEG	Amount of Crystalline drug with polymer decreased the dissolution rate	[31]
11	Meloxicam (class II)	non-steroidal anti-inflammatory drug	Rotary vacuum evaporation technique	skimmed milk	Increased dissolution	[32]
12	Piroxicam (class II)	non-steroidal anti-inflammatory drug	fusion method	Nicotinamide	PNC1 capsule solid dispersion has higher dissolution and absorption rate then PNC1A capsule	[33]
13	Vemurafenib (class IV)	anticancer	Precipitation method	hypromellose acetate succinate (HPMCAS)	enhancing solubility with an amorphous-solid dispersion is a preferable technique for the development of insoluble drugs	[34]
14	Bropirimine (class II)	anticancer	Co-precipitation method	β-cyclodextrin polyethylene glycol 6000	βCD inclusion complex had faster dissolution rate then PEG 6000 solid dispersions	[35]
15	Itraconazole (class II)	antifungal	evaporation and freeze drying	polymers (PVP K-12, K29/32, K90; PVP VA S-630; HPMC-P 55; and HPMC-AS HG)	Amorphous solid dispersion is preferable in increasing the bioavailability	[36]
16	Carvedilol (class II)	beta blocker	Spray drying method	Polyvinylpyrrolidone(PVP)	PVP had a role in the release property of carvedilol and increased the dissolution rate	[37]
17	Glibenclamide (class II)	antidiabetic drug	solvent evaporation/ co-precipitation techniques fusion method	Hydrophilic and hydrophobic polymers	Increase bioavailability and prolonged duration of action	[38]
18	Meloxicam (class II)	nonsteroidal anti-inflammatory drug	dropping method	polyethylene glycol (PEG) 4000	The crystalline phase can help increase the dissolution rate from round particles.	[39]
19	Miconazole nitrate (class II)	antifungal	fusion or co-precipitation	PEG-6000 PVP-10,000 urea	Solubilization and wetting is found to be more essential then particle size reduction in increasing the dissolution	[40]
20	Metformin hydrochloride (class III)	Oral Hypoglycemic.	solvent evaporation closed melt method	compritol 888 ATO	SD prepared by solvent evaporation method is more effective in preparing sustained release action	[41]
21	Simvastatin (class II)	Antihyperlipidemic	fusion-cooling and solvent evaporation	PEG 4000 Polyvinylpyrrolidone K30 (PVP K30)	Increased dissolution rate of drug with PEG and PVP	[42]
22	Cefuroxime (class II)	cephalosporin	Spray drying	Gelucire 50/13 Aerosil 200	Improved bioavailability	[43]
23	Piroxicam (class II)	NSAID	solvent method melting method melting-solvent method, co- grinding method, kneading method (KM)	Pluronic F-98	increased dissolution rate because of wettability and dispersibility, particle size reduction	[44]
24	Carbamazepine (CBZ) (class II)	Antiepileptic	solvent method	phospholipid (PL) dimyristoylphosphatidylglycerol	CBZ:PL solid dispersions cause increase bioavailability	[45]
25	Benznidazole (BNZ) (class II)	Anti-parasitic	solid dispersion method	(PEG 6000) (PVP K-30)	Increased solubility with PVP as compare to PEG	[46]

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26	Efavirenz (class II)	antiretroviral	solvent evaporation and physical mixture methods	polyethylene glycol	improvement in the dissolution from 16% to 70% with solid dispersion technology	[47]
27	Telmisartan (class II)	Cardiovascular Agent	Solvent evaporation method	Poloxamer 407, PEG 6000	Improved solubility od drug with polymers	[48]
28	Albendazole (class II)	Anthelmintic	solid dispersion method	Polyvinylpyrrolidone (PVP) hydroxypropyl β-cyclodextrin (HPβCD)	Ternary inclusion complex had more bioavailability then solid dispersion	[49]
29	Pioglitazone (class II)	antidiabetic agent	spray drying method	PVP K17, PVP K30, and HPMC E3	Increased solubility and dissolution of Pioglitazone SD	[50]
30	Meloxicam (class II)	NSAID	Kneading method	Poloxamer 188	Enhance solubility	[51]
31	Nimodipine (class II)	Calcium channel blocker	Hot melting and solvent method	Poloxamer 407 PEG 6000	Solubility with P407 was 3 times greater than PEG 6000	[52]
32	Ketoconazole (class II)	Anti-fungal	Co-precipitation method	PVP, polyacrylic acid, poly(2-hydroxyethylmethacrylate)	Drug in amorphous form increases the solubility of drug.	[53]
33	Pelubiprofen (class II)	Anti-inflammatory	Solvent evaporation technique	Eudragit RS	Sustained release formulation is effective	[54]
34	Metformin hydrochloride (class II)	Anti-diabetic	Solvent evaporation and co-grinding method	Methocel K100	1:4 and 1:5 ratios were found effective in the sustained release of drug.	[55]
35	Tacrolimus (class II)	Immunosuppressive agent	Solvent evaporation method	Lactose Ethylcellulose(EC) Hydroxypropylmethylcellulose (HPMC).	Formulation of tacrolimus with EC and HPMC were found effective.	[56]
36	Resveratrol (class II)	Stillbenoid	hot-melt extrusion method	PEG 6000, poloxamer 188 propylene glycol monocaprylate, castor oil	Dissolution rate was increased.	[57]
37	Efavirenz and ritonavir (class II)	Anti-retroviral drugs	Co-precipitation method	CMC, butyrate, acetate, propionate, adepate and sebacate	Enhanced dissolution was observed in comparison to drug alone.	[58]
38	Rifampin (class II)	Anti-tuberculosis	Spray drying technique	cellulose ω-carboxyalkanoates	Bioavailability was enhanced	[59]
39	Atovaquone (class II)	Antipneumocystic drug	Hot-melt extrusion	polysorbate 80 and 20, HPMC, PEG 400, Kollidon VA64 and 30	Bioavailability was enhanced	[60]
40	Ritonavir (class II)	Anti-viral drug	Co-precipitation method	alkyl cellulose ω-carboxyesters	Solubility was enhanced	[61]

CONCLUSION

The poor dissolution and bioavailability of orally administered drugs had been a concern. With many solubility enhancing techniques, solid dispersions have proved to be the most suitable method to overcome this issue. The review demonstrates that the researchers have mostly utilized drugs mentioned in BCS class II for enhancing the solubility of orally administered, poorly water-soluble drugs. However, very few works have been done on drugs with high solubility and low permeability (BCS class III). Moreover, multiple methods explained in this review are utilized for the preparation of solid dispersion but among all the preparation techniques and carriers, solvent evaporation and co-precipitation technique has found to be widely used technique. Among carriers, different grades of PVP and PEGs are being mostly employed. However, the recent advancement includes the use of different classes of alkyl cellulose ω-carboxyesters, for the preparation of amorphous solid dispersion.

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