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Review Article

GRISEOFULVINE: BCS CLASSIFICATION AND SOLUBILITY ENHANCEMENT TECHNIQUES

Marvania Akshay[1]*, Deshpande Ashwini[2]

1. School of Pharmacy and Technology Management, Shirpur Campus.
2. SVKM's NMIMS University, Babulde, Shirpur, Maharashtra, India- 425405.

***Corresponding Author: Email** akshay_marvania@yahoo.com, akshay.marvania@gmail.com

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ABSTRACT

The BCS is a scientific system for classifying drug substance based upon their aqueous solubility as related to dose and permeability. The BCS is guiding for prediction of *in vivo* performance of the drug substance in new drug discovery and lead optimization due to the dependence of drug absorption and pharmacokinetics properties. The solubility behaviour of drugs remains one of the most challenging in formulation development. Due to poor aqueous solubility of BCS Class II result in the poor oral bioavailability makes drug formulation development more difficult. Hence, various approaches have been developed with a focus on enhancement of the solubility, dissolution rate, and oral bioavailability of poorly water-soluble drugs. Present article overviews the concept of Biopharmaceutical classification systems (BCS), Biopharmaceutical Drug Disposition Classification System (BDDCS) & recent classification for solubility enhancement of poorly water soluble drugs. The article also reviews various efforts taken for solubility enhancement of Gresiofulvine using various techniques from 1996 to 2012.

Keywords: Solubility, Dissolution, Bioavailability, Griseofulvine.

INTRODUCTION

BCS CLASSIFICATION

The BCS is a scientific system for classifying drug substance based upon their aqueous solubility as related to dose and permeability. The concept of BCS has been used for the biowaiver as well as for the formulation design from biopharmaceutical point of view. For BCS Class II or IV drugs, formulation designs are based on both the physicochemical and biopharmaceutical properties of the drugs which to obtained sufficient and reproducible bioavailability after oral administration. When combined with the dissolution of the drug product, the BCS depend on rate and extent of the drug absorption from immediate release solid dosage forms viz: dissolution rate, solubility and permeability. [1, 2]

SOLUBILITY

The drug substance is considered to be highly soluble when the highest dose strength is soluble in 250 ml or less of the aqueous media over pH range of 1.0-7.5.The volume estimate of 250 ml is derived from BE study protocols that prescribe administration of a drug product to fasting human volunteers with a glass (about 8 ounces) of water.[2] The solubility class as per IP is described in table 1.[3]

Table 1: Expression for approximate solubility

Descriptive term	Parts of Solvent required for Part of Solute
Very soluble	Less than 1
Freely soluble	From 1 to 10
Soluble	From 10 to 30
Sparingly soluble	From 30 to 100
Slightly soluble	From 100 to 1000
Very slightly soluble	From 1000 to 10,000
Practically insoluble, or Insoluble	10,000 or more

PERMEABILITY

It is indirectly based on extent of the absorption (fraction of dose absorbed, not systemic BA) of a drug substance in humans and directly on measurement of the rate of mass transfer across human intestinal membrane. Drugs are considered as highly permeable when it is absorbed equal to or more than 90%.

Permeability determination

- ✓ Pharmacokinetic and absolute bioavailability studies.
- ✓ Intestinal permeability method likes the effects of drug application on apical-tobasolateral absorption and on basolateral-to-apical absorption.
- ✓ In vivo or in situ intestinal perfusion studies in animal.
- ✓ In vitro permeation experimental with excised human or animal tissue.

BCS classification is based on the 3 parameters

1. *Absorption number* defined as the ratio of the mean residence time to mean absorption time.
2. *Dissolution number* defined as the ratio of the mean residence time to mean dissolution time.
3. *Dose number* defined as the mass divided by the product of uptake volume (250 ml) and solubility of drug.[2]

FDA proposed changes in class boundaries for biowaiver study on solubility and permeability based on the underlying physiology of the gastrointestinal tract are: 1.Narrowed the required solubility pH ranges from 1.0-7.5 to 1.0-6.8. 2. Reduced the high permeability requirement from 90% to 85%. [5]

The active pharmaceutical ingredient in a solid dosage form must undergo dissolution before it is available for absorption from the gastrointestinal tract. Generally the bioavailability of BCS class II drug is rate limited by its dissolution, so that even a small increase in dissolution rate sometimes results in large increase in bioavailability. Therefore, the solubility behaviour BCS Class II remains one of the most challenging aspects in formulation development for oral use. Modified Noyes-Whitney equation provides some ideas to how the dissolution rate of even very poorly soluble compounds might be improved to minimize the limitations to oral availability:

$$\frac{dc}{dt} = \frac{DA(Cs - C)}{h}$$

Where,

dC/dt : the rate of dissolution

A : the surface area available for dissolution

D : the diffusion coefficient of the compound

C_s : the solubility of the compound in the dissolution medium

C : the concentration of drug in the medium at time t and h is the thickness of the diffusion boundary layer adjacent to the surface of the dissolving compound

According to Noyes-Whitney equation, the dissolution rate can be improved by increasing surface area available for dissolution, decreasing the particle size of the solid compound which can be accomplished by conventional methods like grinding, ball milling, fluid energy micronization, salt formation, etc., and/or by optimizing the wetting characteristics of the compound surface, decreasing the boundary layer thickness, ensuring sink conditions for dissolution and, last but definitely not least, increasing

apparent solubility of the drug under physiologically relevant conditions.[4]

BIOPHARMACEUTICAL DRUG DISPOSITION CLASSIFICATION SYSTEM

The primary purpose of BDDCS was to predict drug disposition of new molecular entities and the importance of transporters in drug absorption and elimination. The BDDCS classifies drug substances into four classes based on aqueous solubility and extent of metabolism.

Table 2: BDDCS classification of drugs

Class 1	**Class 2**
High solubility	Low solubility
Extensive metabolism	Extensive metabolism
Class 3	**Class 4**
High solubility	Low solubility
Poor metabolism	Poor metabolism

BDDCS relates to the rate of intestine and/or liver permeation. Therefore, a high degree of metabolism (≥90% of the dose) will dictate high extent of absorption (≥90%), but not vice versa. The high permeability classification in BCS reflects high extent of absorption (≥90%) as defined by the FDA Guidance. However, when the drug is extensively absorbed and classified as highly permeable under BCS, it may not have high metabolism. For BDDCS Class 2 compounds, intestinal uptake (or absorptive) transporters will be unimportant due to the rapid permeation of the molecules.[6, 7, 8]

Presented article represents the research work done on Gresiofulvine belonging to Class II. For class II drugs, the bioavailability is often low and variable due to insufficient dissolution in the gastrointestinal tract (GIT). Hence, increase in solubility of selected API is first critical aspect to improve the absorption and the bioavailability of drug. Techniques widely used for enhancing solubility and dissolution rate of poorly soluble drugs are mention in table 5.The physicochemical and pharmacodynemic properties of Gresiofulvine are describe in table 4.[9]

Table 4: Gresiofulvine profile

Pharmacological	
Absorption	Poorly absorbed from GI ranging from 25 to 70% of an oral dose. Absorption is significantly enhanced by administration with or after a fatty meal.
Metabolism	Primarily hepatic with major metabolites being 6-methyl-griseofulvin and its glucuronide conjugate.
Half life	9-21 hours
Categories	Antibiotics, Antifungal Antibacterial Agents
Properties	
Melting point	220 °C
water solubility	8.64 mg/L
Log P	2
Log S	-4.61
Caco2 permeability	-4.4
polar surface area	71.06
rotatable bond count	3
polarizabilities	34.25
hydrogen acceptor count	6
hydrogen donar count	0

Table 5: The various methods to improve the solubility of poorly water soluble drugs

Solid Dispersion Techniques [10,11,12,13]	**a. Use of crystalline carriers &Use of polymeric carriers**	
	Water soluble carriers	Polyethylene Glycol (PEG), Poly vinyl pyrrolidone (PVP), Polyvinyl Alcohol (PVA), Poloxamers (Lutrol F127 and F68) Polyglycolized fatty acid ester (Gelucire_ 44/14), Hydrotropes (urea, nicotinamide)
	Cellulose Derivatives	Hydroxypropyl methylcellulose (HPMC), Hydroxypropyl cellulose (HPC), Carboxy methyl ethyl cellulose (CMEC)
	Sugars	Dextrose, sorbitol, Sucrose, Maltose, Mannitol, Lactose
	Acids	Citric acid, bile
	b. Use of mixture of polymer and surfactants	
	c. Solid solution	
	d. Eutectic mixtures	
	e. Amorphous ppt. of drug in crystalline carrier	
	f. Complex formation between drug & carrier	
Reduction in particle size [14,15,16,]	**Approaches**	**Techniques**
	Micronisation	Comminution Spray drying Milling techniques using jet mill, rotor stator colloid mills etc
	Nanosuspension	Homogenization Wet milling Spray drying
	Sonocrystallisation	Crystallization by using ultrasound
	Nanocrystallisation	Milling techniques using tumbling ball mill and a stirred media mill, etc. High pressure homogenization Precipitation Cryo-vacuum method Other: Nanomorph, Nanoedge, NanoGate, BioSilicon

RESEARCH ENVISAGED FOR SOLUBILITY ENHANCEMENT TECHNIQUES FOR BCS CLASS II DRUG, GRESIOFULVINE:

Use of water soluble carriers

- **Nagila R. *et* al.** increased the solubility of Gresiofulvin by increasing the solubilisation capacity of micellar solutions of Pluronic F127 by co-formulating with a water-soluble polymer likes PEG and PVP. Solubility curve of Gresiofulvine in F127 solution and low molecular weight polymers (PEG 6000 & PVP K30) were identical. Similarity was observed in high molecular weight polymer (PEG 35000 & PVP K90).Sharp increasing solubility of GF was observed at 0.5 % concentration of polymer. Spectrophotometric and DLS (Dynamic light scattering) measurement showed no

	Types	Examples
Complexation [17,18]	Inorganics	Iodine
	Chelates	EGTA
	Metal-olefin	Ferrocene
	Inclusion	α-Cyclodextrin, β-Cyclodextrin, and γ- Cyclodextrin, Choleic acid
		2 hydroxyl propyl β-Cyclodextrin
		Sulfo butyl ether β-Cyclodextrin sodium salt
		Randomly methylated β-Cyclodextrin
		6-O-Maltosyl β-Cyclodextrin
Chemical Modification	use of soluble pro drug or salt form	
Others	Microemulsions	
	Self- emulsifying systems	
	Liposome	
	Super fluid based approach	
	Miceller solublisation	
	Alteration of pH of surrounding medium	
	Non-aqueous granulation	

interaction between F127 and PVP, so increase in solubility of GF may be due to transfer of hydrophobic chains of PVP and hydrophobically bonded water which decreases Gibs energy. Higher increase in solubility with PVP K 90 compaired to PVP K 30 may be attributed to increase in greater chain length in PVP K 90.[19]

- **Alden M. *et al.*** investigated the critical surfactant concentration for solubility of hydrophobic drug in different polyethylene glycols. They prepared solid dispersion of GF in different grades of PEG with or without addition of surfactant alkali dodecyl sulphates (MDS) by using melting method and observed that highest concentration is required for PEG 3000. In PEG 3000, the lowest critical concentration for formation of solid solutions was showed by use of Li^+ as the counterion of the surfactant which increased stability of system.[20]
- **Nozawa Y. *et al.*** enhanced solubility and dissolution of GF with saccharides as the dispersion carrier using a roll mixing method. They showed that stability of solid dispersion of GF with saccharides increases with increasing molecular weight. Initial dissolution of GF was increased by 117 fold when dispersed with corn starch or amylo starch whereas 170 fold increases was observed with British gum when roll mixed for 5 minutes as compared to GF alone. This increase in dissolution was due to reduction in interfacial tension of GF particles when solid dispersed with saccharides.[21]

Use of surfactants/stabilizers

- **Lukac M. *et al.*** enhanced the solubility of griseofulvin using micellar solutions of mixtures of Gemini (**N**) (N,N0-didecyl-N,N,N0 ,N0-tetramethylethane-1,2-diyldiammonium dibromide) and heterogemini (**P**) (decyl 2-[decyl (dimethyl) ammonio] ethyl phosphate) surfactants. The solvent surface tension values were measured by the Wilhelmy plate technique using a Kruss 100 MK2 tensiometer. The plots of surface tension vs. log concentration of surfactants gave the values of cmc. Solubilisation of griseofulvin indicates that it was solubilised by non-specific hydrophobic interaction between the drug and the micelle core which is independent on the compositions of mixtures of

dialkylphosphocholines and bisammonium salts in solution. The results indicate that anionic surfactants are better solubilisers of griseofulvin than cationic, zwitterionic or nonionic surfactants. Micellar solutions of surfactant mixtures have better solubilisation properties than the solution of N and P itself.[22]

- **Hisham Al-Obaidi *et al.*** prepared griseofulvin binary and ternary solid dispersions with hydroxypropyl methylcellulose acetate succinate (HPMCAS) and poly[N-(2-hydroxypropyl) methacrylate] (PHPMA) as stabilizer using the spray drying method. Binary solid dispersions (GF/HPMCAS, 50:50%) was prepared by addition of distilled water (85 ml) in solution of GF (2.5 g dissolved in 185ml of acetone).While ternary solid dispersion (GF/PHPMA/HPMCAS, 50:25:25%) was prepared same as binary but extra addition of PHPMA. From x-ray diffraction study, crystallinity was observed with alone HPMCAS while with PHPMA increased stability (formation of amorphous form) was observed due to greater interaction with GF. Increase in dissolution as well as stability were observed with both solid dispersion formulation compared with GF.[23]

Complexation with β-cyclodextrin

- **Dhanaraju M. *et al.*** enhanced the bioavailability of GF by its Complexation with β-Cyclodextrin using co precipitation method. The inclusion complex was prepared in various molar ratios of 1: l, 2:1, 3:1, and 1:2 of the drug and β-cyclodextrin, respectively using ethanol as solvent. UV, HPLC and dissolution study indicated that the 1:2 molar ratio complex form of the drug significantly increased the dissolution rate when compared to the alone GF. Toxicity studies were carried out in Swiss Albino mice and 1:2 molar ratio complex form of GF was found to be safe. In vivo studies carried out in both animals and human volunteers and faster dissolution rate of the complex and its relative bioavailability was found to be 73-84% (fourfold higher than that of pure Griseofulvin).[24]

Nanocrystallisation / microcrystallisation by Emulsion solvent diffusion method

- **Phanchaxari M. *et al.*** enhanced the solubility of griseofulvin by nanocrystallization by emulsion solvent diffusion method. A homogenous dispersion was prepared by adding the drug solution of ethanol and acetone to an aqueous phase in the presence of cyclodextrin and SLS by emulsion solvent diffusion method. The dispersion was centrifuged and washed thoroughly to remove traces of organic solvent and finally the dispersion in water was freeze dried. Dynamic light scattering method was used to determine the particle size of freeze dried samples. All formulations were found in the size range of 600-900 nm and marked incresed in dissolution velocity was observed compared to pure drug (3-4 m), thus greater bioavailability. Out of all, formulations made of acetone were of smaller size as well as better dissolution velocity as compared to formulations prepared using ethanol as solvent. As per ICH guidelines, short term stability studies were carried out and it was observed that nanocrystal formulation of griseofulvin remain stable at ambient temperature then at elevated temperature and humidity condition.[25]

- **Jadhav PA *et al.*** studied enhancement of solubility and dissolution rate of griseofulvin by preparing its microcrystal using emulsion solvent diffusion method with various surfactants (HPMC E5 HPMC E15, PVP K 30,PVP K 90 and β Cyclodextrin) as well as granules using melt granulation technique using polymer like PEG 4000 and surfactant poloxamer 188. Formation of GF microcrystal with β-Cyclodextrin, PVP K 30 and PVP K 90 showed about 84.3 % to 87.3% cumulative drug release, microcrystal by using HPMC E 15 and HPMC E 5 showed 96.3 % cumulative drug release compared with 75.3 % drug release of GF within 90 minutes. While formation of GF granules with PEG 4000 and poloxamer 188 showed 94 % and 98.1 % drug release in 90 minutes respectively. Decrease in particle size and increase in surface area of particles were observed with use of HPMC due to high mass transfer. Decrease in peak area of granules of GF/ poloxamer due to change in internal energy of drug in DSC study indicated incorporation of GF into poloxamer. Melt granulation technique showed best results of dissolution rate.[26]

- **V. B. Yadav *et al.*** studied effect of different stabilizers and polymers on spherical agglomerates of GF by emulsion solvent diffusion system in which distilled water

as an external phase and dichloromethane as internal phase acts as good solvent as well as bridging liquid for recrystallization and agglomeration process. Spherical agglomerates were prepared with or without polymers ((hydroxyl propyl cellulose, Eudragit-RLPO) and stabilizers (Beta cyclodextrin, poloxomer-F68 and Polyethylene glycol 6000).Decrease in crystallinity or partial amorphilization was observed in agglomerates of GF from DSC and X-ray diffraction study. Faster dissolution was observed with polymer and stabilizer containing agglomerates compaired with alone GF.[27]

Table 6: Summary of research work done on Gresiofulvine

Method used	Mechanism	Conclusion	References
Using water soluble carriers (PEG,PVP)	Increasing the solubilisation capacity of micellar solutions of Pluronic F127.	Increase in solubility with PVP K 90.	19
Solid dispersion using PEG	Formation of solid solution with use of surfactant.	Increase in solubility.	20
Use of saccharides by roll mixing method.	Reduction in interfacial tension of GF.	117 fold increased with corn starch or amylo starch. 170 fold increased with British gum.	21
Using micellar solutions of mixtures of Gemini & heterogemini surfactants.	Reduction in solvent surface tension.	Anionic surfactants are better solubilisers of griseofulvin than cationic, zwitterionic.	22
Preparing solid dispersion by spray drying method.	Formation of amorphous form.	Increase in dissolution as well as stability with use of stabilizer (PHPMA).	23
Complexation with β-Cyclodextrin using co precipitation method.	Formation of inclusion complexes.	Fourfold higher dissolution rate was observed with 1:2 molar ratios.	24
ESD method using cyclodextrin and SLS.	Formation of Nanocrystal.	Increased in dissolution velocity was observed.	25
ESD	Formation of Microocrystal.	With β-Cyclodextrin, PVP showed about 84.3 % to 87.3% while with HPMC showed 96.3 % cumulative drug release within 90 minutes.	26
Using melt granulation.	Formation of Microocrystal.	Granules with PEG 4000 and poloxamer 188 showed 94 % and 98.1 % drug release in 90 minutes respectively.	
ESD	Formation of spherical agglomerates.	Faster dissolution was observed with polymer and stabilizer containing	27

Using Liquisolid method	Preparing fast-disintegrating Freeze-drying o/w dry emulsions tablet.	Absorption of GF was found 85 % more than fulvin marketed tablet.	28
Using Liquisolid compact method.	--	Release rate increases with rising amount of dissolved drug in the liquid portion. With Neusilin® sevenfold higher liquid adsorption capacity than Avicel® and Aerosil®.	29
Shake flask method, fusion method and solvent evaporation method.	solubilisation of griseofulvin in aqueous micellar solutions of di-block copolymers	Formation of spherical micells reduces the solublisation of GF. When B- block exceeds about 15 B units, no influence on solubilisation.	30

From FTIR study it was observed that there were no chemical changes in prepared recrystallized agglomerates.

Using Liquisolid method

- **Iman Saad A. *et al.*** studied in vitro and in vivo evaluation of a fast-disintegrating Freeze-drying o/w dry emulsions tablet containing griseofulvin. Aqueous phase was prepared by adding 2 % w/v of gelatin in water. Emulsifiers (HPMC, Tween-80 & span-80) and glycine or sorbitol added to aqueous phase. GF was added to oil phase of miglyol or seasame oil. Oil phase was mixed with aqueous phase and homogenized for 30 minutes at 25000 RPM; prepared emulsion was poured in blister pack containing 125 mg GF and freeze dried to -22 °C. Emulsions containing HPMC showed the highest viscosity while with Tween 80 and Span 80 were less viscous. Miglyol as the oil-phase showed shorter disintegration time and fast dissolution compaired to seasame oil. In dissolution study, coalesced lipid droplets on the surface of the water with HPMC while with Tween 80/span 80 no aggregation of droplets and rapiddispersion in dissolution media were observed i.e. faster dissolution was observed with Tween-80/Span -80 (7 %) while with HPMC (1.5 to 4 %) compaired with fulvin marketed tablet (3.9 %) and GF powder (less than 1%). Absorption of GF was found 85 % more than fulvin marketed tablet due to presence of oily components in formulation as well as use of Tween-80/Span-80 increased wettability of GF in dissolution media. Thus there was no need of fatty meals to improve bioavailability of GF due to presence of oily component in formulation.[28]

  Leopold C. *et al.* enhanced the release of Gresiofulvine from hydrophilic aerogel formulations and liquisolid systems. Liquisolid formulations were prepared by adding the liquid portion (drug in PEG 300) to the blend of carrier (Avicel®) and coating material (Aerosil®) and finally mixed with Kollidon-CL. In vitro release rates of amount of dissolved drug in the liquid portion. But it requires high amounts of carrier and coating materials as dose of drug is high and drug solubility in liquid vehicle is low which results in increase in tablet weight. Hence, replacement of coating and carrier material with Neusilin® (highly adsorptive silicate) can be used to reduce tablet weight.[29]

- ***Others***

  David A. *et al.* examined solubilisation of griseofulvin in aqueous micellar solutions of di-block copolymers of

ethylene oxide and 1, 2-butylene oxide with lengthy B-blocks. Griseofulvin was loaded into solutions (1 wt% copolymer) by 3 methods i.e. shake flask method, fusion method and solvent evaporation method. The solubilisation capacity at 25 ◦C increased linearly as the B-block length was increased and form worm-like micelles. The influence of hydrophobic-block length on solubilisation capacity was examined for micelles of E*m* B*n* copolymers (E = oxyethylene, B = oxybutylene, subscripts denote number-average block lengths in repeat units) with B-block lengths in the range of 30–76 and with E-blocks of sufficient length to ensure the formation of spherical micelles (cmc≈0.1 wt %,), which reduces the extent of solubilisation. When B- block exceeds about 15 B units, no influence on solubilisation was observed.[21] Above mention research works for solubility enhancement of Gresiofulvine are summarized in table 6.

Conclusion:

BCS gives opportunities for decreasing regulatory burden with scientific justification via replacing certain bioequivalence studies by accurate in vitro dissolution tests. It is giving direction for prediction of in vivo performance of drug substances in new drug discovery & lead optimization due to dependence of drug absorption and pharmacokinetics properties. The present article described the basis of BCS, BDDCS and periodic research envisaged for enhancement of solubility for Griseofulvine from 1996 to 2012. Use of water soluble polymers (PEG, PVP, and saccharides), complexing agent (β-CD), liquisolid method, ESD method, use of surfactant can help in enhancing the solubility of Griseofulvine.

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