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A Review on Enhancement of Solubility of Poorly Soluble Drugs of BCS Class II by Nanosuspension

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ABSTRACT

The Biopharmaceutical classification system depends upon the solubility of drugs. The level of bioavailability rises as solubility rises. II of BCS has less solubility, which leads to reducing the level of bioavailability of the drug in the body. Nanotechnology is used in cases to improve the solubility of poorly soluble drugs. In particular, nanosuspension is used in these cases. High-pressure homogenization, media milling, melt emulsification, micro emulsification, and supercritical fluid method are among the methods used in the preparation of nanosuspension. These are the methods that are used to improve the solubility of poorly soluble drugs by producing nanosuspension to improve dissolution velocity and saturation solubility and to increase bio adhesiveness and also dissolution due to very small particle size. Nanosuspension can be delivered by oral, parenteral, pulmonary, and ocular routes. It can be used for targeted drug delivery systems to produce drugs with high solubility to use in the treatment of targeted tissue.

INTRODUCTION:

According to BCS (Biopharmaceutical classification system) Which it having four classes depends upon the solubility and permeability. In class II, solubility is low as well as bioavailability. (1) Solubility can be defined as the ability of the solute to dissolve in the solvent at a constant temperature. Some factors may affect the solubility process like the nature of solvent and solute, pressure, temperature, etc So, according to BCS class, II is having low solubility which leads to low bioavailability and High permeability. (2,3) To enhance the solubility levels many approaches can be applied to increase the solubility of the drugs, It includes. Micronation, co-solvent, salt formulations, fatty solutions, etc.(4)

To date, more than 40% of new chemical entities being generated through drug discovery programs are lipophilic or poorly water-soluble drugs. (5) Nanotechnology can also be used to solve the problems associated with low solubility drugs, where it can improve the solubility of drugs. (6)

Nanotechnology:

Nanotechnology can be defined as the science and engineering carried out on the nanoscale that's 10^{-9} Nano suspension is derived from a very small biphasic dosage form. (7) Whereas suspension has two phases, one is the dispersion phase and the other is the dispersion medium. Nano suspension is a colloidal formulation of very small particles (nano size) of the drug in water stabilized by surface-active agents. (8)

Techniques such as Bottom-Up and Top-Down technology are used to transfer drug microparticles/micronized drug power to drug nanoparticles. It consists of poorly water-soluble.

drugs without any matrix material suspended in dispersion. It can be used to enhance the solubility of poorly water-soluble compounds Low soluble drugs cannot be freely soluble in lipid or water media. (9-11)

Advantages: -(12,13)

-Enhanced the solubility of drugs

-High drug loading

-Increased bioavailability

-Enhanced stability

-Provide passive targeting

-Improve physical and chemical parameters of drugs

Disadvantages:

-physical stability, sedimentation, and compaction can cause problems.

-sufficient care must be taken during handling and transport.

-Uniform and accurate dose cannot be achieved unless the suspension.

BIOPHARMACEUTICAL CLASSIFICATION SYSTEM (BCS)

BCS is the biopharmaceutical classification system. It is introduced in the 1990s. it involves the classifications of drug substances concerning their aqueous solubility and membrane permeability.

According to the Biopharmaceutical classification system (BCS), The drug with poor solubility but having high permeability is classified as a drug of BCS class II.[14-16]

Due to the low rate of dissolution bioavailability gets low. The bioavailability of a BCS class II drugs is rate limited by their dissolution rate So that even a small increase in dissolution rate sometimes results in a large increase in bioavailability.

Therefore, an enhancement of the dissolution rate of the drug leads to improving the bioavailability of BCS class II drugs.[17-19]

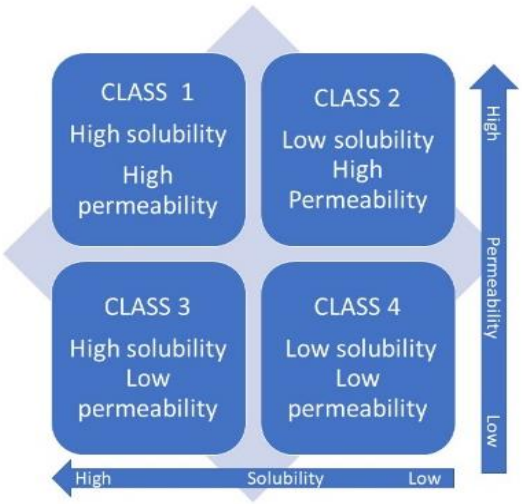

Figure No. 1: BCS Classification [20]

Nanosuspension preparation methods:[22-25]

Mainly the nanosuspension is about two main methods to prepared which are:

v Bottom-up technology.

v Top-down technology.

- Media milling.
- High-pressure homogenization.
- Nano pure
- Nano jet
- Nano edge

But to be considered also there are additional methods to prepare nanosuspension which are:

v Precipitation method.

v Dry co-grinding method.

v Supercritical fluid method

v Microemulsion template.

v Melt emulsification method.

v **Bottom-up technology:**

Bottom-up technology can be described as the conventional method which starts from the molecular level and goes up to the molecular association for the formulation of small solid particles which leads to the reduction of solvent quantity. (26)

Advantages:

1. The equipment is at a low cost.
2. The process I simple.
3. High saturation solubility.

This method is mainly used for the nanosuspension of drugs with poor aqueous solubility. (31)

This method involves three steps to be performed which are:

To form the pre-suspension, in a stabilizer solution the drug powders must be dispersed.

For the pre-milling, the pre-suspension is homogenized in high pressure up to 1500 bar the homogenizer at low pressure.

In the final step to form the desired size of the nanosuspension, it must be homogenized at high pressure for 10 to 25 cycles (it's preferred to be 20 only) and pressure of 1500 bar. (32-34)

Advantages:

1. Low risk of product contamination.
2. Allows aseptic production of nanosuspension for parenteral administration.

Disadvantages:

1. Prerequisite of micronized drug particles.

2. Prerequisite of suspension formation using high-speed mixers before subjecting it to homogenization.

- **Nano pure**:

This method is also called deep freeze homogenization because it must be homogenized at 0° c or less than the freezing point which also involves homogenization in water mixture or water-free media. (35)

Advantages:

1. For drugs that sensitive to temperature this method is suitable.
2. Evaporation is faster and under milder conditions.

Nano jet: This method is also is called the opposite stream and it's mostly used as the application of high pressure to passes the suspension stream to be separated into two parts or more, due to this high pressure these parts impact each other producing a high shear force which is giving rise to reducing the particle size. (36-38)

advantages:

1. Easy to control the particle size.
2. Expansion of simplicity

Disadvantages:

1. A low water-soluble compound is not formulated.
2. Obtained product contains large particles of nanosuspension.
3. Costly technique.
4. Stabilizers and surfactants are required in a large amount.

- **Nano edge:**

This is a combination between precipitation and homogenization (having a similar principle as the precipitation and homogenization) which provides particle size at the nano range, better stability, and in much less time. (39)

The anode is called like that because the drug is dissolved in an organic solvent then it must be mixed with miscible anti-solvent for precipitation.

The precipitated particle suspension is homogenized due to the low solubility and the high shear pressure. (40)

Advantages:

1. A drawback of the precipitation technique, such as crystal growth and long-term stability.
2. Can be resolved.

Supercritical fluid method:

This method is eco-friendly which has no hazardous to health or the environment.

This method is used to form nanoparticles in the size range of 5-2000 nm by using liquid solvent as solute is not soluble in supercritical fluid so the liquid solvent can play an indispensable role and micronize the solute particles. (41)

Microemulsions template:

This is the most useful for the preparation of nanosuspension which can be done by following the organic solvent with the drug dispersed in an aqueous phase containing suitable surfactants to form an emulsion, the organic phase is evaporated under reduced pressure to form the nanosuspension which is stabilized by surfactants. (42)

Advantages:

1. No need for special equipment.
2. Easy to control the particle size.
3. Easy scale up if the formulation is optimized properly.

Disadvantages:

1. Not applicable for the poorly soluble in aqueous and organic media.
2. The need for ultrafiltration is slightly costly.
3. Requires a high amount of surfactant.

Melt emulsification method:

In this method the drug must be dissolved in the aqueous solution of stabilizer, then to be heated up to the drug melting point, then homogenized to give emulsion.

During this process the emulsion temperature must be maintained above the drug melting point, then it can be cooled down to room temperature or by using an ice bath.[44]

Advantages:

During the process, the organic solvent has been avoided.

Figure No. 2: Applications of nanosuspension[45]

Table No. 1: Currently Marketed Pharmaceutical Nanosuspension Products

Dosage form/route of administration	Drug name	Therapeutic class	Company	REFRENCES
Freeze-dried powder for injection/parenteral	paclitaxel	Metastatic breast cancer	Abraxane/ abraxia biosciences	***45***
Capsule/oral	Coprecipitation	Antiemetic	Cesamet	***46***
Capsule/oral	Nanocryta	Antiemetic	Emend	***47***
Tablet /oral	Griseofulivin	Antifungal	Giris-peg	***48***
Liquid suspension/parenteral	Palperidone palmitate	Schizophrenia	Invega sustenna	***49***
Liquid suspension/oral	Megetrol-acetate	Anti-anorexic	Megace es	***50***
Tablet/oral	Sirolimus	Immunosuppressant	Rapammune	***51***
Tablet/oral	Fenofibrate	Hypercholesterolemia	Tricor	***52***
Tablet/oral	Fenoibrate	Hypercholesterolemia psych simulant	Triglide	***53***
Tablet/oral	Morphine sulphate	muscle relaxant	Avinza	***54***
tablet/oral	Methyl phenidatehcl	Muscale relaxant	Ritalin	***55***
Capsule/oral	Tizanidine	Cns stimulant	Zanaflex	***56***
Capsule/oral	Dexmethylphenidate hydrochloride	Bone substitute	Focalin	***57***
Topical	Silver	Eczema	Nucryst	***58***
Form pack, form strips/injection	Calcium phosphate	Bone	Vitoss	***59,60***

CONCLUSION:

Nanosuspension is the best technology that can solve the problem of solubility of poorly soluble drugs to enhance bioavailability. To produce large-scale production of nanosuspension, some methods are used, including media milling and high-pressure homogenization. These technologies have been successfully used to enhance the solubility of BCS class-II drugs. Nanosuspension can be administered through different routes of administration. The application of nanosuspension in oral and parental routes has been very well established. And the route of pulmonary and ocular delivery has been evaluated. But, their delivery through buccal, nasal, and topical delivery is yet to be done.

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