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Micronization Technique for Solubility Enhancement

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Abstract

Aqueous solubility of API's has a critical role in drug dissolution or availability of drug at the site of action or bioavailability when a dosage form is administered orally. The fact that about 90 % of newly discovered API's or new molecular entity (NME) have little or no water solubility, presents a serious challenge to the successful development & commercialization of new drugs in the pharmaceutical industry. Numerous techniques are available for solubility enhancement, but all individual techniques have their own limitations for commercialization.

Micronization technique can reduce the particle size of material, which reduces particles down to the micrometer or nanometer size and increases the dissolution rate of drugs through increasing particle surface area, accelerating dissolution rates and ultimately improves the bioavailability of poorly soluble APIs. Micronization of poorly water-soluble drugs can be performed by Air Jet Mill or Ball Mill.

Keywords: Solubility enhancement; Micronization; Air Jet Mill

Introduction

The oral importantly very or administration is still widely acceptable drug delivery route because of its assorted application along with versatility, simplicity of ingestion, cost effectiveness, flexibility of dosage form design and most important high patient compliance [1]. Aqueous solubility of API's plays a vital role in drug dissolution or absorption of the drug from the oral dosage form and hence its bioavailability. When a drug is administered orally in solid dosage form (such as tablets or capsules), it is designed to undergo a series of predetermined stages. The first step towards the absorption process is the disintegration of the dosage form (for immediate release) or diffusion or erosion (for Modified release) of drug from a Tablet. The second step is slowest or rate-limiting step includes dissolution of drug in the fluid at the absorption site (Figure 1). The fact that most of the newly discovered API's or new molecular entity (NME) have little or no aqueous solubility, causes a serious challenge to the successful development & commercialization of new drugs in the pharmaceutical industry. Although the pharmaceutical companies have been able to overcome difficulties with very slightly soluble " drugs, but those with aqueous solubility of less than 0.1 mg/ml present some unique challenges [2,3].

In the oral administration process, Absorption of drug is said to be dissolution rate-limited, when solubility of API's or dissolution is the rate controlling step. Hence, dissolution of drug is the rate-limiting step in the absorption process and any factors which can influence the dissolution rate can also influence the absorption rate. As per the theory of dissolution [4], dissolution rate of an APIs in a given medium are prominently depends on:

a) The solubility of the APIs in the medium, where dissolution is performed and

b) The particle size or active surface area of the API's, which are directly brought in contact with dissolution medium.

The availability of drug at the absorption site is the controlling factor for the successful development and commercialization of a pharmaceutical product in any pharmaceutical industry. If an active ingredient or a new molecular entity (NME) does not qualify the above said property, it will not be a viable candidate for

mew product development. Most of the newly discovered drugs candidates are porn to poor or limited or 'NO' aqueous solubility. Thus, pharmaceutical Industries are not able to furnish rigorous preclinical and clinical studies. Hence, a development of NME becomes limited, and their potential is not realized or confirmed [5,6]. Drug substances or NMEs are classified into four categories (Figure 2) upon their solubility and permeability according to the Biopharmaceutical Classification System (BCS) [3,7-12].

The solubility of drug / NME's is defined as the amount of drug that goes into solution when equilibrium is established between the drug solute in solution and any excess, un-dissolved drug to produce a saturated solution at a specified temperature. When the highest dose strength of API's is not completely soluble in aqueous media volume 250 ml over the pH range of 1.2 to 6.8, the NME's is considered as poorly aqueous soluble [10-13]. United State Pharmacopeias also define solubility table 1 as a part of solvent required per part of solute [14]:

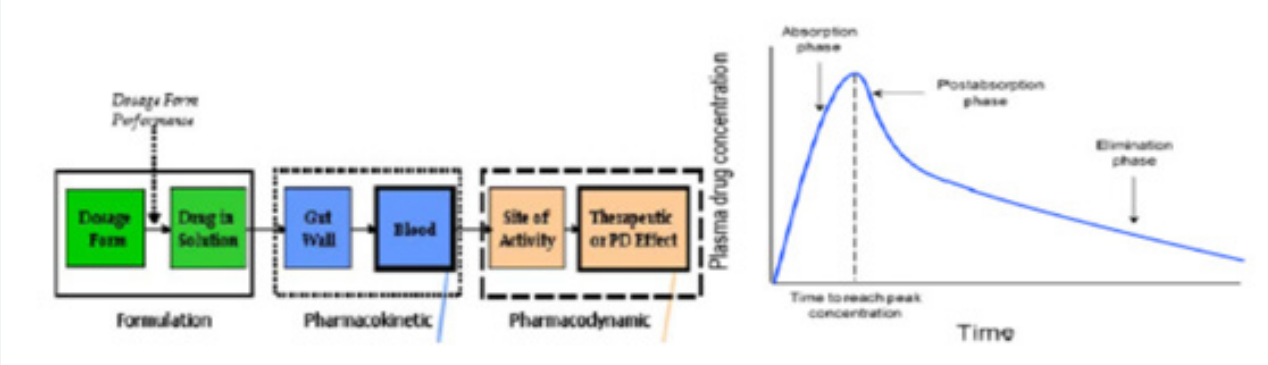

Figure 1: Schematic representation of oral dosage form and its absorption.

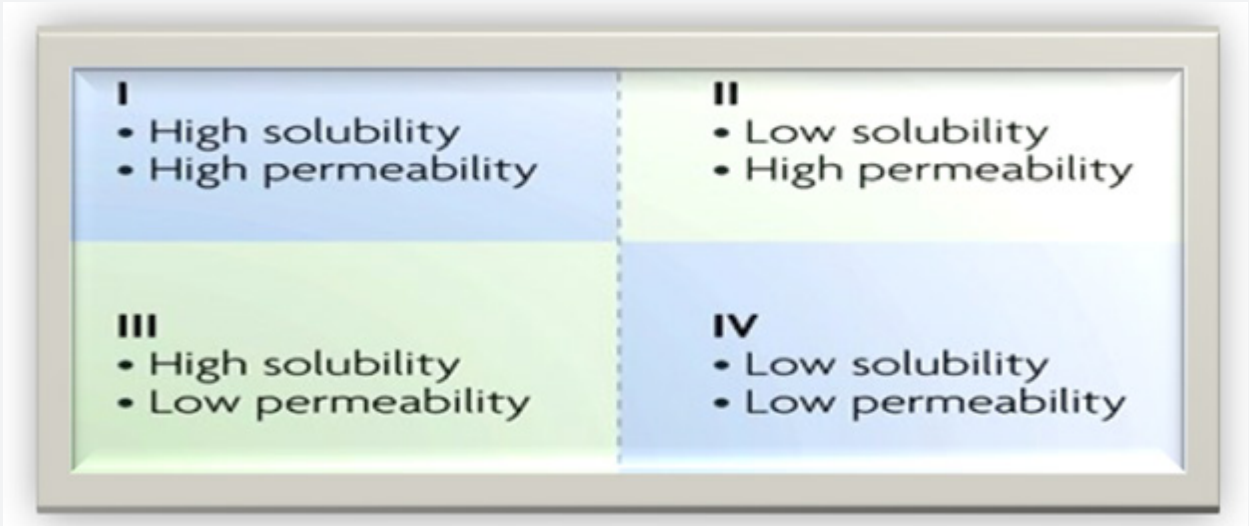

Figure 2: Biopharmaceutical classification system (BCS).

BCS class II & class IV drug candidates have poor aqueous solubility and need a solubility enhancement approach for successful development& commercialization of oral dosage form with enhanced bioavailability [9-12]. Modified release Tablet dosage form containing poorly water-soluble drugs shows higher batch to batch or tablet to tablet variation in In-vitro drug dissolution process [15]. Hence, improvement in the solubility of the drug is an essential requirement for the development of a

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product. Numerous technologies have been unfolded in the recent past. A lot of approaches are being currently used the solubility enhancement of poorly aqueous soluble drugs [12,13,15,16]. Some widely used available approaches table 2 are as per following:

Table 1: USPNF solubility criteria.

USPNF Solubility Criteria		Solubility Range (mg/ml)
Descriptive Term	**Part of Solvent required Per Part of Solute**	
Very soluble	Less than 1	> 1000
Freely soluble	From 1 to 10	100 - 1000
Soluble	From 10 to 30	33 – 100
Sparingly soluble	From 30 to 100	10-33
Slightly soluble	From 100 to 1000	1 – 10
Very slightly soluble	From 1000 to 10,000	0.1 – 1
Practically insoluble	10,000 and over	< 0.1

Table 2: Solubility enhancement approaches.

Approaches	Techniques
Physical	· Particle Size Reduction
	Conventional Method
	Micronization
	Nanoparticle or Nanosuspension
	· Crystal Habit Modification
	Polymorphs
	Pseudo poly morphs
	· Complexation
	Physical Mixture
	Kneading Method
	Co-precipitation Method
	· Inclusion Complexation
	Kneading Method
	Lyophilization
	Microwave irradiation Method
	· Surfactant based Solubilization
	Microemulsion
	· Solid Dispersion
	Physical Kneading
	Melting /Fusion
	Solvent Evaporation
	Spray Freeze Drying
	Hot melt Extrusion
Chemical	· Pro drug approach
	· pH Adjustment
	· Buffer balance

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	· Derivatization,
	· Salt formation.
	· Polymeric micelles formation
	· Self-emulsifying systems
Miscellaneous	·Supercritical fluid process,
	· Adsorption

Among the various approaches, Physical approach like Micronization and Solid dispersion are being broadly employed for solubility enhancement. These approaches are highlighted briefly in subsequent sections.

Solubility Enhancement by Micronization Technique

Micronization is conventional technique for the particle size reduction, which reduces particles down to the micrometer or nanometer size. Micronization increases the dissolution rate of drugs through increasing particle surface area, accelerating dissolution rates and ultimately improves the bioavailability of poorly soluble APIs. Micronization not only reduces the particle size but also improves amorphous property and structural disordering of the drug crystals. Micronization of drugs can be achieved by milling techniques using Fluid Energy Mills; Air Jet Mill or by a Mechanical Means; Rotor Stator Colloid Mills [17-25].

Fluid Energy Mill: Air Jet Mill

Air Jet milling is a highly effective and efficient technology for particle size reduction of APIs for parenteral, inhalation or respiratory and other drug delivery products where the size of the particle is relevant to achieve effective drug delivery. Jet Mills are used for grinding of a friable or crystalline and powdered solid material, to reduced particle size from 100 µm to 1µm range and classify them in a very narrow particle size range at same time. Fluid Jet mill was developed in the 1960s. There are various kinds of jet mills, spiral or loop jet mills, impact and counter flow jet mills. These entire mills are operated on the same principle where grinding and impact breakdown of particles can occur by the application of fluid energy [26-29].

Principle of Operation of Air Jet Mill's

Air Jet Mills are easy to operate and provide higher operational yield. The powdered material is slowly tangentially fed into a flat circular, enclosed collision milling chamber through a venture. In this milling chamber, a jet/ stream of moisture free compressed air or inert gas (nitrogen) is introduced in vortex motion at a specific pressure along with feed material (Figure 3). This jet of air streams causes rapid particle-to-particle collisions. This leads to regular impaction and abrasion on the particles in fast motion and thereby reduction in the particle size takes place due to high velocity of air/gas instead of pins, Jaws, or Hammers. The fine particles are carried up stacked into the particle classifier. Particle classification is made by inertia, the larger particles due to their inertia continue through the down stack and re-enter the milling chamber for further grinding. The Micronization or pulverization yield and extent of size reduction are depending upon the operational conditions like nature or characteristics of feed material, grinding pressure, injector pressure, flow rate of compressed air, duration of exposure of material and mill geometric parameters like feed size, chamber size, number of holes& angle of grinding nozzles pressure [17-32].

Advantages of Air Jet Milling [21-37]

a) Grinding temperature is low due to no moving parts. Hence, can be used for grinding of low melting point and heat sensitive materials. It is also observed that, when an air or inert gas is injected from the nozzle, it adiabatically expands and the air or gas will cool itself, thereby offsetting the heat generated by the collision and friction of the material.

b) Higher output or collection rate with short production duration of time due to high-speed collision and in a closed grinding chamber.

c) Very high purity and uniform particle size distribution of micronized powder material production.

d) Dry-milling process to obtain uniform and fine powder.

e) A variety of combined manufacturing operations can be proceeding, and the drying process can also be proceeding at the same time as grinding.

f) Most of the API's are synthesized or precipitated at the nanometer particle size range in an agglomeration stage. Air Jet Mill can also be used to de-agglomerate these API's and provides accurate nanometer sized range particle size materials.

g) Simple, cost effective, solvent free and environmentally friendly operation.

h) Applicable to producing amorphous characteristics of material.

Limitations of Air Jet Milling [21-36]:

i. High energy input,

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ii. Limitation in feed size due to product injection method, and

iii. Large equipment size with necessary accessories.

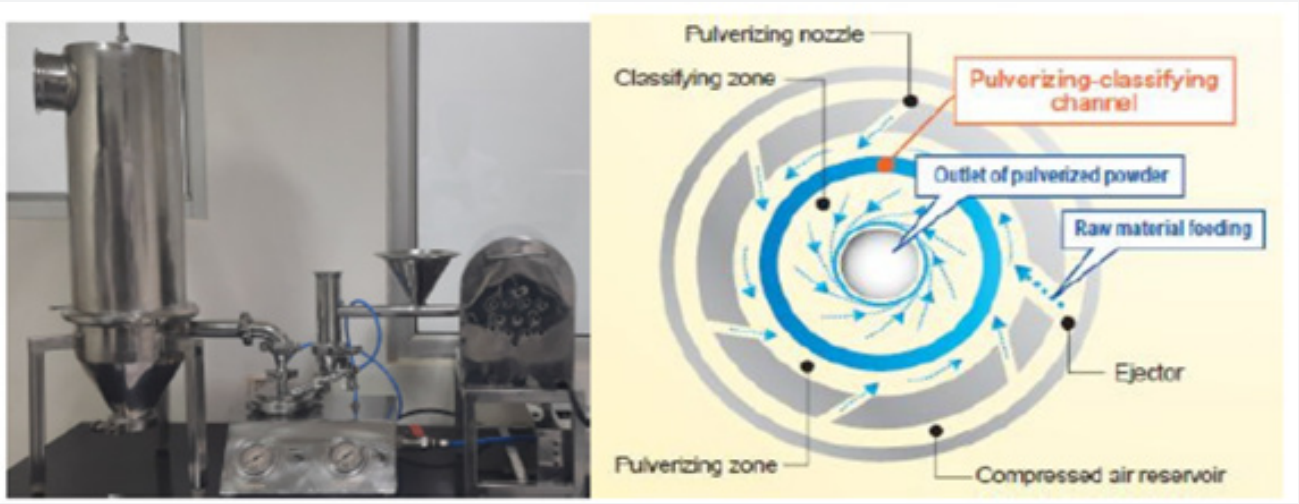

Figure 3: Air Jet Mill and cross-sectional view of milling chamber.

Application of Air Jet Mill in Pharmaceutical Industry

It has been observed that the Air Jet Mill can play an important role in the pharmaceutical powder grinding process in the pharmaceutical industry. The status of the jet mill will continue to rise with the continuous development of the pharmaceutical product in industry. Traditional powder grinders have certain limitations in many aspects such as non-uniform particle size distribution, low material extraction rate, material collection rate, and limited purity of ingredients. Air jet milling technology will not only provide a new way to develop a micronized uniform size pharmaceutical powdered material but also improves solubility of material by increasing their surface area.

In the future development, if the Jet Mill grinding technology is incorporated with product manufacturing facilities. It will not only improve product performance, but also improve product quality [17-35].

Conclusion & Limitation of Micronization Process

Micronization process increases the dissolution rate of drugs through increasing particle surface area and ultimately improves the bioavailability of poorly soluble, but it produces charged micronized material and it may lead to segregation, clumping, and other possible physical instabilities during long term storage or in the formulation, if it is not well controlled. Due to the above reasons, it remains a challenge for the scientific community for handling of micronized material during formulation development [24,36-38].

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