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Methods of Nanonization of Drugs for Enhancing their Dissolution

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ABSTRACT

This review seeks to provide an overview of various methods by which active ingredients of drugs can be nanonized (converted into sizes ranging in the order of 1-100 nm) in order to improve their dissolution characteristics. It explores why drug dissolution is important for their bioavailability and how particle size, in turn, can affect this process in accordance with the Noyes- Whitney equation. Various techniques involving both bottom-up and top-down approaches for the nanonization of drugs are possible, however some methods prove better than others especially those of the bottom-up type due to lesser energy requirement and time of operation. Though many novel methods for the nanonization of drugs are being introduced for the purpose of improving dissolution of poorly-water soluble drugs, it cannot be substantiated for its use because such methods do not increase the saturation solubility of such drugs.

Key words: Nanonization, drug dissolution, solubility, bioavailability, pharmaceutical nanotechnology

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INTRODUCTION

Nanoscience and nanotechnology encompasses a wide range of applications in almost every field of science and technology. The property of this technology that makes it so versatile is the fact that when particle size reduces to the nanometer range from the micrometer or macro range, the properties of the same molecules change in ways that can be exploited for advantageous purposes. Since the 1970's, the significance of nanotechnology in bringing forward drug carriers for increasing the site-specificity and bioavailability of drugs has been prevalent, reducing possible side effects of the orally administered drug as well as being systems that almost completely contain only active pharmaceutical ingredients (APIs) [20-22].

In contrast with the introduction of nanotechnology into pharmaceuticals and drug development, studies of drug dissolution span as far back as the 1800's and the importance of dissolution on a drug's therapeutic effect was discovered in 1897 [1,2]. The use of nanonization versus other strategies for improving drug dissolution characteristics by innovators rests with the fact that this strategy is a universally viable option. Changing and controlling particle size and particle size distribution is well within the hands of formulators and drug developers and this can be exploited to suit a wide variety of drug molecules [22, 28].

According to the drug molecule involved and the final form of the nanonized product, various bottom-up and top-down methods can be used for this purpose. Comparison and analysis of the best methods to use for particular API's is tied with the success of bioequivalence studies or IVIVC studies [5].

OVERVIEW OF DISSOLUTION AND DISSOLUTION STUDIES

For almost a hundred years, oral administration of drugs has been the primary route versus other routes for administration. Physical chemists have been exploring the dissolution process since the end of the 1800's but the importance of this process in the bioavailability of drugs was realized only about half a century ago. The foundation for dissolution research was provided by Noyes and Whitney in 1897 [2] where they described that: the rate of dissolution is proportional to the difference between the instantaneous concentration, C at time t, and the saturation solubility C_S.

Mathematically, this is represented as: $\frac{dC}{dt} = k(C_S - C)$ where k is a constant (1)

The mechanism of dissolution proposed involved the existence of a thin diffusion layer around the solid's surface that enables molecular diffusion into the bulk aqueous phase. Brunner and Tollockzo furthered the existing study on drug dissolution and proved that dissolution rate also depends on factor like the exposed surface of the drug, temperature, structure of the surface etc. [3] The model is mathematically represented as:

$$\frac{dC}{dt} = k_1 S(C_S - C) \quad (2)$$

Where S is the surface area and from Eq. 1, k is replaced with $k_1 S$. Further development came in the form of the Nernst-Brunner equation [4] which was based on the concept of the diffusion layer and combined with Fick's second law of diffusion:

$$\frac{dC}{dt} = \frac{D.SK_{w/o}(C_S - C)}{V_h} \quad (3)$$

Here, k_1 from Eq. 2 is replaces with $\frac{D}{V_h}$. Where D is the diffusion coefficient, h is the thickness of the diffusion layer and $k_{w/o}$ is the water/oil partition coefficient of the drug and V is the volume of the dissolution medium. This equation is also known as the modified Noyes-Whitney equation and is used for modern dissolution studies.

OVERVIEW OF THE BCS SYSTEM

According to the Biopharmaceutics classification system introduced in 1995, there are four classifications of drugs based on their kinetics and thermodynamic properties. The classification system is a regulatory tool that can be used to perform in-vitro dissolution tests and correlate their results to the in-vivo performance of the drug. These studies are called in-vitro in-vivo correlation studies (IVIVC) studies and are performed on generic drugs [5].

In order to identify and determine the BCS class of a drug, there exist three class boundary parameters: solubility, permeability and dissolution where dissolution is [7]: "..the amount of drug substance that goes into solution per unit time under standardized conditions of liquid/solid interface, temperature and solvent composition".

For BCS class II drugs, aqueous solubility is poor but their transport across the GI mucosa is easily viable. Thus, dissolution is the rate limiting step for the absorption process across the GI mucosa unless the drug is administered at high doses [8, 6, 9]. Solubility of a drug substance in the GI tract depends on various factors [10] such as the surface area of a solid wetted by luminal fluids, aqueous solubility, crystalline structure lipophilicity, relative pKa to the GI tract etc. Examples of BCS class II drugs include Fenofibrate, Glibenclamide, and Ezetimibe etc.

Table - 1 The Biopharmaceutical Classification System of Drugs [5-6]

BCS class	Permeability	Solubility
I	High	High
II	High	Low
III	Low	High
IV	Low	Low

IMPORTANCE OF DISSOLUTION AND DISSOLUTION RATE OF DRUGS

About 60% of new chemical entities (NCEs) produced during drug discovery show poor solubility in aqueous mediums [12]. These poorly soluble drugs have low bioavailability, uncontrolled absorption in the GI tract and low saturation solubility [11].

Dissolution and dissolution studies are important for the following reasons [5] [7]:

i) It is one of the most crucial quality control tests for drug dosage forms
ii) It is an important method used to predict bioavailability
iii) It can replace clinical bioequivalence studies
iv) It has a significant effect on the pharmacological activity of a drug

However, it is not a suitable method to replace tests for safety and efficacy of a tablet on humans [7]. Dissolution and dissolution rates determine drug absorption across the GI barrier as well as the physiological availability of the drug in the bloodstream [7]. The dissolution rate can control the speed at which certain drugs are built up in the bloodstream and thus affect their bioavailability and therapeutic action.

Factors affecting dissolution

"A drug product is considered rapidly dissolving when 85% or more of the labeled amount of drug substance dissolves within 30 min using USP Apparatus 1 or 2 in a volume of 900 mL or less of buffer solutions" [13-14]

Here, USP dissolution Apparatus 1 refers to the Basket (at 37^{o}C) and USP Dissolution Apparatus 2 refers to the Paddle (at 37^{o}C) according to the standardized specifications by the US Pharmacopeia [19]. Various physicochemical of a drug and physiological conditions in the GI tract influence the dissolution properties of a drug substance. These include the following, summarized in the table -2:

Table - 2 Factors Affecting the Rate of the Dissolution Process [15-18]

Factor	Physicochemical properties	Physiological properties
Surface area of drug	Particle size, wettability	Surfactants in gastric juice and bile
Diffusivity of drugs	Molecular size	Viscosity of luminal contents
Boundary layer thickness	Concentration of the drug	Motility patterns and flow rate
Solubility	Hydrophilicity, crystal structure, solubilization,	Buffer capacity, pH, bile and food composition
Amount of drug already dissolved	Hydrophilic, lipophilic nature of the drug	Permeability
Volume of solvent available	Type of body fluid	Secretion, co-administered fluids

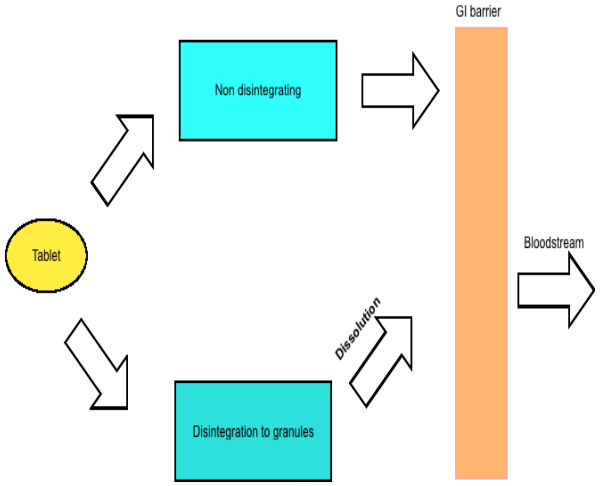

Fig. 1 Schematic diagram of the dissolution process [7]

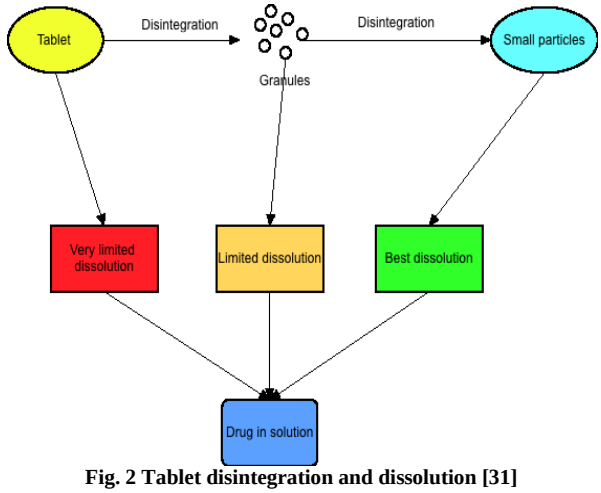

Fig. 2 Tablet disintegration and dissolution [31]

NANONIZATION FOR DISSOLUTION ENHANCEMENT

Since the 1970s, nanostructures were developed in order to act as drug carriers [20, 21]. Nanonized drugs pose the advantage of being increasingly site-specific and reducing possible side effects of the orally administered drug as well as being systems that almost completely contain only active pharmaceutical ingredients (APIs) [22].

Since this review focuses on enhancing dissolution characteristics of drugs through nanonization, the main idea is based on the effect of the surface area of the drug and the diffusivity of the drug as a result of reduced particle size through scaling the active ingredient down to the nanometre level.

Other methods to improve dissolution of drugs include: salt formulations, pH adjustment, cosolvency, complexation [11], dispersion of drugs in carriers [23-27] etc. The reason why the nanonization approach was studied versus others, is because nanonization is a universally applicable method for improving drug dissolution properties. Nanonization is considered so, because many or all of the factors governing drug solubility are not controllable by the manufacture while particle size is a parameter that can be greatly controlled [22]. The micronization of drugs has been studied prior to nanonization studies but though it has improved the dissolution velocity of drugs, it has not yet yielded significant results in increasing the saturation solubility [28] which is the main factor that decides the viability of a formulation technique [11]. Also, conventional techniques such as particle size reduction, spray drying and micronization, ball milling etc. rely on mechanical forces that can degrade solid drug particles while trying to achieve disaggregation [29].

A crucial property that substances inherit when scaled down to the nanometre level is their large ratio of surface area to volume. This property can be better understood using a thought experiment [30]: "consider a cube of edge W=1 meter, and cut it into two pieces, thereby exposing additional 'faces' of the material. That is, new visible or usable areas are added while the total volume remains the same. Repeat this exercise until all particles reach a size of approximately one nanometer. The result is a group of small particles with enormous surface area which occupy the same volume we started with"

As a consequence of a large surface area exposed in a small volume, nanoparticles are easily soluble in liquids which is a pertinent feature in improving the dissolution properties of drug substances in aqueous solutions. The correlation between increased solubility and surface area can be explained by the modified Noyes Whitney

equation introduced in previous sections of this review. Another postulate that has been introduced states that in agitated systems, a reduction in the particle size reduces the thickness of the hydrodynamic layer around the dissolving particles and thus reduces the distance for the dissolution process itself [32]. Drugs such as Estradiol, Doxorubicin, Cyclosporine and Paclitaxel are already being prepared by nanonization for commercial use [33].

Nanosized carriers are also a viable option for the delivery of poorly water soluble drugs, however nanonization of drugs only involves nanonizing the active ingredient in the drug itself for enhancing solubility [34].

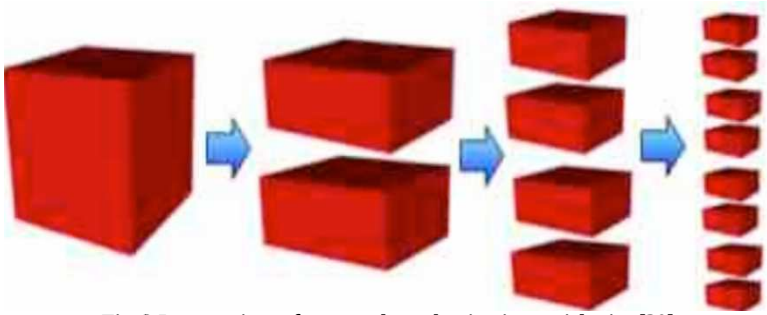

Fig. 3 Increase in surface area by reduction in particle size [30]

METHODS FOR DRUG NANONIZATION: BOTTOM UP METHODS

The following table summarizes the various forms in which nanonized drugs can be synthesized. The details of each method shall follow in subsequent subsections.

Table - 3 Methods for Preparation of Nanonized Drugs [11] [22] [33] [35] [36]

Nanonized form of drug	Bottom-up synthesis methods	Top-down synthesis methods
Nanosuspension	1. Nanoprecipitation 2. Supercriticalfluid technology 3. Emulsions and microemulsions	1. Media milling 2. Dry co-grinding 3. High pressure homogenization
Nanodispersion	Nanoprecipitation	1. Bead milling 2. High pressure homogenization
Nanocrystals	1. Supercritical fluid technology 2. Ultrasonic precipitation	1. Bead milling 2. High pressure homogenization

Nanoprecipitation [11] [37-44] [50]
This bottom-up method involves a poorly water-soluble drug, a suitable solvent, a miscible anti-solvent and an agitator. The process is based on the principle of transferring a polymer from a good solvent to a poor solvent state. This leads to self-assembly-mediated growth of nanoparticles by formation of precipitated polymeric chains. The poorly water soluble drug is dissolved in the solvent and added to the miscible anti-solvent with continuous stirring and agitation. The solvent and anti-solvent should be completely miscible so that phase separation is caused when the poorly soluble compound is added and its solubility limit is exceeded. This process can be used for the formation of drug nanosuspensions, nano dispersions as well as nanocrystals. The phase separation process usually takes time in the order of a few ms to a few µs. The final morphology of the nanoparticles is affected by the following factors:

i.
i) types of solvents
ii) the volume ratio of anti-solvent to solvent
iii) stirring rate and
iv) drug content

Nanoprecipitation can also be performed in conjunction with the use of ultrasonic waves to enhance disaggregation for example for the drug furosemide, where particles are sonicated in an ultrasonic bath.

Supercritical Fluid Technology [22] [45-49] [53] [54]
Super-critical fluids can be defined as fluids that are in a state where their temperature and pressure are greater than their critical temperature and pressure causing them to possess properties vacillates between those of a liquid and a gas.

In this process, free-flowing small particles with a large surface area are produced with small amounts of organic solvents as by-products. This technique also allows controlled particle size of the final products via co-solvents, polymers etc. In supercritical crystallization, the supercritical fluid expands to form a liquid solvent, and the dissolved drug precipitates due to decompression of the supercritical fluid. The use of this process to form nanonized drug particles is a considerable example for the universality of the process since a large variety of

crystalline materials can be reagents in this method through the combination of other special methods (eg. freeze drying, spray drying, specialized nozzles etc.).

CO_2 is the most common gas used due to its low critical temperature and pressure (Tc = 31.1oC and Pc = 73.8 bar respectively). Specifically, a process called Rapid Expansion of Supercritical Solution (RESS) can be used to make particles in the range of µm to nm by using Supercritical CO2 (SC-CO2). The poorly soluble solute is dissolved in SC-CO2 after which an extremely fast phase transfer from supercritical to gas phase occurs as the gas expands to the atmospheric conditions. Particles of narrow size distribution and small size can be obtained due to high supersaturation in SC-CO2 and due to the speed of the phase separation. Dexamethasone phosphate drug nanoparticles (for microencapsulation) and griseofulvin nanoparticles were prepared by using this method.

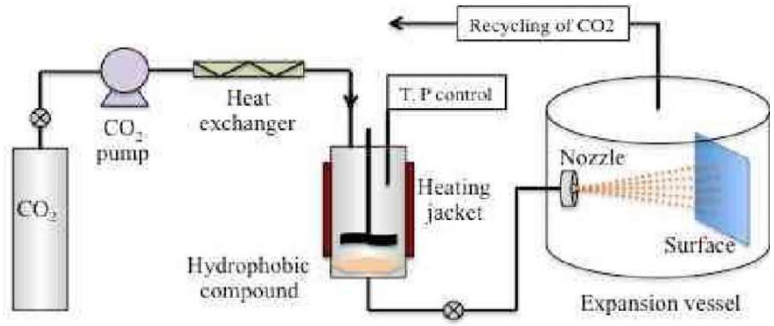

Fig. 4 Synthesis of nanoparticles by use of supercritical CO_2 [49]

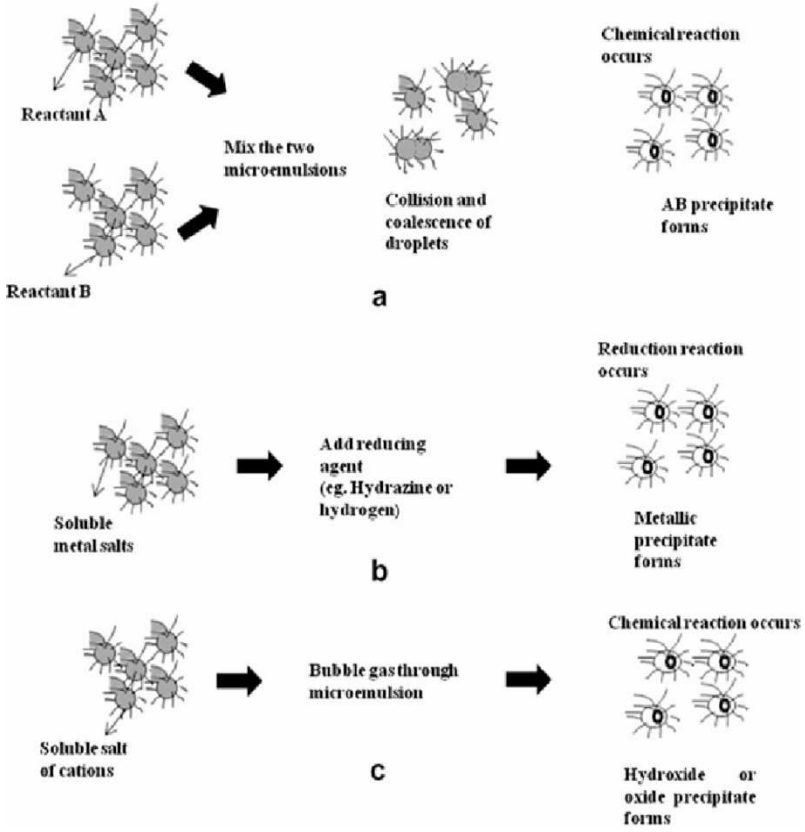

Fig. 5 Mechanism for synthesis of nanosuspensions using microemulsion based templates

Emulsions and Micro Emulsions [11] [28] [51, 52]

In this method, emulsions and micro emulsions serve as templates for the synthesis of nanosuspensions. Microemulsions can be defined as thermodynamically stable, homogenous and transparent dispersions of water in oil stabilized by a surfactant, sometimes in combination with a surfactant. An example of a drug nano suspension prepared by this method is Griseofulvin where butyl lactate acts as the oil phase in water, lecithin and the sodium salt of taurodeoxycholate as surfactant. There are two possible methods by which nano emulsions can be prepared using these templates which are compared in the table -4. The Fig. 5 displays a schematic process by which nanosuspensions can be synthesized using microemulsion based templates.

Table -4 Methods for Synthesis of Nanonized Drugs using Microemulsion based Templates [28]

Method	I	II
Material dispersed in aqueous phase to form an emulsion	Organic mixture of solvents/mixture of solvents loaded with drug + surfactants	Partially water-miscible solvents
Step for obtaining nanoparticles in suspension	Evaporation of organic phase under reduced pressure	Dilution of the emulsion

METHODS FOR DRUG NANONIZATION: TOP DOWN METHODS

Compared to other techniques and bottom-up processes these techniques require larger input energy and longer operation time.

This technique, also called as pearl milling, was developed by Liversidge et. al. The principle of this method is similar to the ball milling method used for the production of nanoparticles but the differences lie in the grinding media used, the sample size of the material to be ground, the chamber size, final particle size distribution etc. Nanosuspensions containing Cilostazol Danazol Naproxen can be prepared by this method. The above table summarizes the different parameters involved in this method.

One of the most common instruments used for this purpose is the Dynomill which is an agitator bead mill. Specially designed agitator discs, mounted symmetrically on a shaft, transfer the energy required for dispersion and wet grinding to the spherical grinding beads. An external pump feeds the product into the mill. The advantages of this instrument include:

- Completely enclosed system
- Highest efficiency
- Easy operation and easy-to-service
- Optimal geometry of grinding container and agitator discs
- The appropriate mill size for every application
- Different materials available for wear parts in contact with the product
- Fields of application

One disadvantage of this method is the risk of contamination of the particles obtained by eroded particles from the bead mills.

Media Milling/Bead Milling [56-59, 61]

Table -5 Parameters Involved in the Bead/Media/Pearl Milling techniQue for Drug Nanonization [11]

Component	Details
Grinding media used	Zirconium oxide beads, highly cross-linked polystyrene resin beads and glass beads
Working principle	High energy and shear forces generated as a result of the attrition of the milling media with the drug
Working mechanism	Nanosuspensions are produced milling of the drug with milling media in simple glass vials for certain hours or days, and nanosuspensions are produced
Factors affecting final nanosuspension	The sizes of beads, number of beads, milling time, milling speed, characteristics of drug, and temperature

Fig. 6 Agitator shaft of Dynomill (left) and agitator discs in the Dynomill (right)

Dry Co-Grinding [62-70]

While media milling is a wet-grinding technique, nanonization can be achieved via dry milling techniques as well. Nanosuspensions in this case are prepared by dry grinding of poorly soluble drugs with soluble polymers and copolymers. Polymers and co-polymers like polyvinylpyrrolidone (PVP), sodium dodecylsulfate (SDS), polyethylene glycol (PEG), hydroxypropyl methylcellulose (HPMC), and cyclodextrin derivatives are used in dry co-grinding techniques for preparation of nanosuspensions.

The dry co-grinding process enables improvements in surface polarity and aids transformation from a crystalline to an amorphous form. This is important because amorphous forms of drug candidate show better solubility than crystalline forms in aqueous phase. Drugs prepared using this method includes: Clarithromycin, Glibenclamide and Griseofulvin, Glisentide, Naproxen, Phenytoin, Nifedipine, Indomethacin, Pranlukast, Fenofibrate etc.

High Pressure Homogenization [71, 72]
High pressure homogenization techniques include microfluidization and piston-gap homogenization. The former is based on the principle of using a jet stream, where two fluid streams collide in a Y-shaped chamber under high pressure to achieve particle size reduction. The latter technique uses force to allow a particulate suspension to flow through a small gap (about 5 µm) with the use of high pressure. Particle size reduction to the nanometer range is achieved due to cavitation, shear forces and turbulent flow. The advantages of this method include homogenous particle size distribution, reproducibility, lower production time, and continuous production

The following figure presents a schematic diagram of the parameters involved in the high pressure homogenization process:

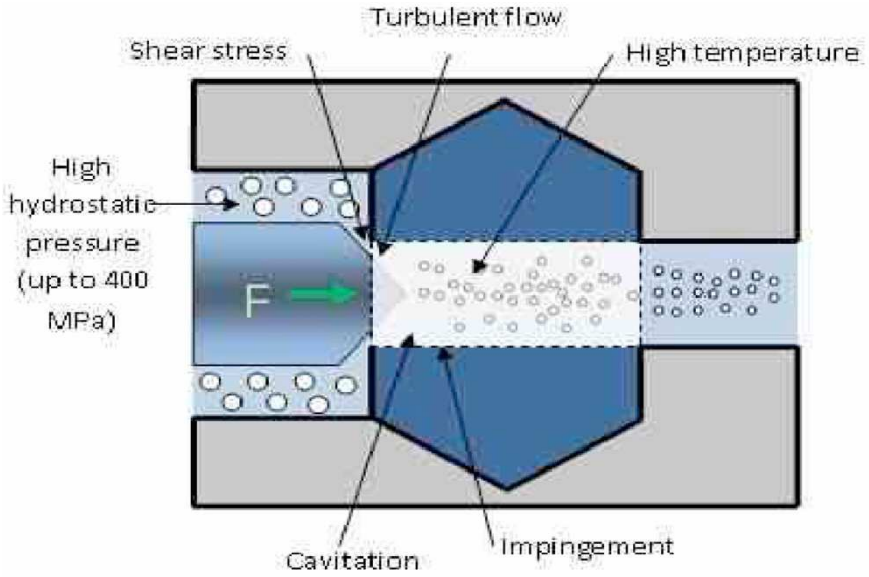

Fig. 7 Various physical phenomena simultaneously affecting a fluid during high pressure homogenization

CONCLUSION

Nanonization of drugs is a promising technique in enhancing the dissolution strategies of drugs for example: Clarithromycin, Glibenclamide and Griseofulvin, Glisentide, Naproxen, Phenytoin, Nifedipine, Indomethacin, Pranlukast, Fenofibrate etc. The use of nanonization over micronization technologies and other methods for the improvement of drug dissolution can be attributed to the fact that nanonization strategies are:

- Universally applicable to a wide variety of drug molecules
- Improves dissolution rate due to increase in surface area availability
- Improves saturation solubility
- Increases site-specificity of a drug
- Avoids the danger of toxic dosage levels of drugs for the improvement of its bioavailability

The challenges to this include the lack of firm evidence in the form of clinical trials for the improvement in dissolution of drugs where only in-vitro dissolution characteristics were studied for a particular drug. Also, the optimization of the process especially in top-down technologies where greater time and energy is expended for the purpose of nanonization presents scope for improvement.

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