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REVIEW

An overview on *in situ* micronization technique – An emerging novel concept in advanced drug delivery

K.R. Vandana *, Y. Prasanna Raju, V. Harini Chowdary, M. Sushma, N. Vijay Kumar

Department of Pharmaceutics, Sree Vidyanikethan College of Pharmacy, A.Rangampet, Tirupati 517102, India

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Abstract The use of drug powders containing micronized drug particles has been increasing in several pharmaceutical dosage forms to overcome the dissolution and bioavailability problems. Most of the newly developed drugs are poorly water soluble which limits dissolution rate and bioavailability. The dissolution rate can be enhanced by micronization of the drug particles. The properties of the micronized drug substance such as particle size, size distribution, shape, surface properties, and agglomeration behaviour and powder flow are affected by the type of micronization technique used. Mechanical communition, spray drying and supercritical fluid (SCF) technology are the most commonly employed techniques for production of micronized drug particles but the characteristics of the resulting drug product cannot be controlled using these techniques. Hence, a newer technique called *in situ* micronization is developed in order to overcome the limitations associated with the other techniques. This review summarizes the existing knowledge on *in situ* micronization techniques. The properties of the resulting drug substance obtained by *in situ* micronization were also compared.

Contents

* Corresponding author. Molile: +91 9652805576.
E-mail address: vandu57@gmail.com (K.R. Vandana).

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1. Introduction

In the recent years, it is estimated that 90% of the New Chemical Entities (NCEs) are poorly water soluble compounds which come under Biopharmaceutical classification system (BCS) class II or class IV (Filippos and Yunhui, 2008). According to BCS, dissolution is the rate limiting factor for the drug absorption rate of both class II and class IV compounds which result in poor bioavailability. Owing to their low poor water solubility and bioavailability, several potential drugs are abandoned in pharmacological screenings (Robinson, 1993; Rasenack and Muller, 2002a). It is a well-known major hurdle for the formulators to handle such poorly water soluble compounds. The chemical and physical properties of the poorly soluble compounds can be optimized to improve oral bioavailability of water insoluble compounds. Various formulation strategies have been reported to improve solubility and dissolution rate of poorly water soluble drugs such as inclusion of complexation with cyclodextrins, solid dispersion, salt formation, particle size reduction, use of surfactants, cosolvency, hydrotrophy, etc. Amongst above mentioned methods, the most reliable technique to improve the dissolution rate is micronization (Rasenack and Muller, 2004; Jalay, 2011).

Micronization is a term used to describe size reduction technique where the resulting particle size distribution is less than 10 μ. Since the morphology of particles, particle size and size distribution produced in different industries are usually not appropriate for the subsequent use of such materials; particle design has been gaining importance in manufacturing advanced coating materials, microsensors, polymers, pharmaceuticals, and many other chemicals. The present article thoroughly reviews about *in situ* micronization as a novel micronization technique.

2. *In-situ* micronization

In-situ micronization is a novel particle engineering technique where micron sized crystals are obtained during its production itself without the need for any further particle size reduction (Rasenack and Muller, 2002a; Rasenack et al., 2002a). In contrast to other techniques where external processing conditions like mechanical force, temperature and pressure are required, the drug is obtained in micron size during the crystal formation. Hence this technique is described as *in situ* micronization. Each and every aspect of *in situ* micronization technique is discussed in the following sections.

2.1. Equipment and processing conditions

In-situ micronization is one of the easiest methods to produce microcrystals which is a one-step process that requires common equipment (Rasenack et al., 2002a, 2003) whereas other micronization techniques like milling, spray drying, and supercritical fluid (SCF) require specialized containment facilities that pose typical issues which include expensive processing conditions, intensive labour, loss of material, dust explosion risks etc.

Spray drying is a comprehensive technique where it requires high shear rates and specialized atomizer for micronization of drug substances where the size of the atomizer determines the particle size of the resulting drug substance (Chiou and Langrish, 2008; Sunday and Simon, 2006). It requires more processing time ranging from several hours to days. Whereas in SCF technology supercritical carbondioxide (SCO_2) is used which requires specialized conditions like temperature at 304.2 K and pressure at 7.38 MPa to maintain CO_2 at supercritical conditions (Masoud and Sima, 2007; Pasquali et al., 2006; Rasenack and Muller, 2004; Deelip et al., 2010). It requires supersonic speeds for rapid expansion of SCO_2. SCF requires less processing time for micronization but the major drawback of using SCFs is the limited number of drugs that can be processed in super critical CO_2. These techniques lead to increased cost of both the drug development process as well as the final drug product. *In-situ* micronization technique is beneficial in these aspects as it does not require any external processing conditions except mild agitation using magnetic stirrer (Rasenack and Muller, 2002a) and the processing time is less compared to the other techniques.

2.2. Particle size and size distribution

According to the Noyes–Whitney postulations, the administration of a drug in micron size is a prominent method to improve bioavailability of poorly water soluble drug substances (Kawashima, 2001; Chaumeil, 1998) which can increase solubility and

dissolution rate. Drug particle size and size distribution are very important characteristics which have significant effects on flowability, dissolution properties and release kinetics (Mullarney and Leyva, 2009; Miranda et al., 2007; Koennings et al., 2007). Milling, spray drying and SCF technologies are mostly employed micronization techniques which can enhance the solubility and dissolution rates. Although these techniques can produce particles of micron size, there will be a non-homogenous particle size distribution due to the agglomeration of the particles (Yohei et al., 2011) which decreases the surface available for dissolution (Irngartinger et al., 2004; Sunday and Simon, 2006). Whereas, *in situ* micronization technique (Kim et al., 2003; Varshosaz et al., 2008) was proved as novel technique which has produced micron size crystals with homogenous particle size distribution as it was observed in case of gliclazide micocrystals. Further, particle size can be controlled in this technique because agitation is employed in this technique. Rasenack and Muller optimized the crystal properties of ibuprofen using *in situ* micronization technique which diminished the agglomerative tendency of ibuprofen crystals (Rasenack and Muller, 2002b).

2.3. Surface modification and stability enhancement

Formation of amorphous regions as in case of milling, spray drying and SCF technology is undesirable because they lead to poor stability. Micronization alone, however, can lead to many processing problems related to poor flow and dispersion properties. Mechanical activation of the drug substance occurs due to milling which may lead to unstable product which is evidenced from the reduced physical stability of salbutamol sulphate (Brodka et al., 2003) and simvastatin (Fang et al., 2009).

It is therefore important to micronize a drug substance along with simultaneous surface modification. *In-situ* micronization is such a technique where microcrystallization and surface modification can be done using hydrophilic polymers which act as stabilizing agents in order to enhance wetting properties and stability of the microcrystals. Further, the stabilizing agents prevent the crystal growth behaviour of the microcrystals (Schott, 1985; Rasenack and Muller, 2002a).

The type of stabilizing agent had a significant effect on morphology of particles and hence on their flow (Roya et al., 2009). Stabilizing agents possess high affinity towards the newly formed hydrophobic surface which sterically stabilizes the microcrystals against the crystal growth by forming a protective layer around the microcrystals (Schott, 1985). Stabilizing agent covers the hydrophobic surface which results in microcrystals with low adhesivity, low agglomeration, and low electrostatic behaviour that would improve powder flow although fine particle fraction is increased (Rasenack et al., 2003). On other hand, the selection and use of effective stabilizer are important tasks to obtain high drug load in powders (Rasenack and Muller, 2004).

Intensive investigation has been carried out in the recent past to evaluate the ability of stabilizing agents viz. dextran, gelatin, hydroxyethyl starch (HES), hydroxyethyl cellulose (HEC), hydroxyl propyl cellulose (HPC), methyl cellulose (MC), methyl hydroxy ethyl cellulose (MHEC), hydroxyl propyl methyl cellulose (HPMC), sodium carboxy methyl cellulose (NaCMC), sodium alginate, pectin, polyvinyl alcohol (PVA) polyvinyl pyrrolidone (PVP) and polyethylene glycols (PEG). The drawings of those findings, say that the stabilizing agent with more polar substituted cellulose ethers such as dextran, PEG and HES are not able to show sufficient stabilization on ibuprofen crystals (Rasenack and Muller, 2002b; Bunyan et al., 1991). This could be due to the poor affinity of the polar substituents towards the newly formed hydrophobic crystal surface. In contrast, MC, MHEC, HPMC and PVA possess alkyl substituents which have more affinity towards the hydrophobic crystal surface and stabilized the drug substance (Chang and Gray, 1978; Daniels and Barta, 1994; Rasenack and Muller, 2002a). Due to the surface adsorption of these alkyl substituted cellulose ethers, the interfacial tension was found low. Further, it was concluded that HPMC showed better stability compared to MC, MHEC because of higher degree of alkyl substitution. It was also assimilated that, after 60 and 120 min precipitation of drug substance has not shown any significant increase in particle size (Rasenack et al., 2003). Thus, stability of the resultant product was based on surface modification by the type of stabilizing agent. The amount of stabilizing agent has no effect on the particle size. The use of higher amounts of HPMC did not result in smaller itraconazole particles (Rasenack and Muller, 2002a). Based on this, it is concluded that the choice of stabilizer is specific to each drug candidate.

Anti-inflammatory drugs like beclomethasone-17,21-dipropionate (BDP), betamethasone-17-valerate (BV), triamcinolone acetonide, budesonide and prednisolone were micronized by controlled crystallization followed by drying using HPMC as stabilizing agents. The respirable fraction was increased compared to jet milled products. The side effects like drug deposition in the throat can be avoided using this technique (Rasenack et al., 2002a; Varshosaz et al., 2008).

2.4. Crystalline habit

The main reason to select crystalline state of drugs is their thermodynamic instability in amorphous state. Disruption of crystal lattice occurs due to high energy input in case of milling and spray drying which gives thermodynamically activated amorphous surface which further convert back to crystalline material upon storage (Rasenack et al., 2004; Ward and Schultz, 1995; Ogura and Sobue, 1970).

Crystal modification affects agglomeration tendency, flow properties and dissolution behaviour (Gordon and Chowhan, 1990; Rasenack and Muller, 2002b). Employing *in situ* micronization has converted the rod shaped gliclazide (Varshosaz et al., 2008) and glibenclamide crystals (Amal et al., 2012) to cube shaped crystals with enhanced dissolution properties without any polymorphic changes. Spherical shaped crystals with enhanced flow properties were observed in case of betamethasone-17-valerate (Rasenack et al., 2002a). Enhanced crystal properties were observed for disodium cromoglycate (DSCG) when compared to jet milled product (Steckel et al., 2003).

2.5. Flow properties

Powders having a particle size $< 10\ \mu$ are highly cohesive and oppose flow under gravity. The powder flow properties are unable to control in traditional micronization techniques such as milling and spray drying. Even simple micronization, was not promising in increase of effective surface area and resulted in no effect on dissolution rate (Kendall and Stainton, 2001; Xi

et al., 2011). The high cohesiveness of the micronized powders has greater tendency to agglomerate which subsequently gives rise to increased electrostatic charges and poor flowability which affect processing and handling (Perrut et al., 2005a,b; Liversidge and Cundy, 1995; De Villiers, 1995, 1996).

Micronization by milling and spray drying leads to amorphous substances (White and Cakebread, 1966; Chiou and Langrish, 2008) which lead to poor flow and deposition of powders on the walls of spray dryer (Adhikari et al., 2003; Bhandari et al., 1997; Chan and Chew, 2003). The number and location of amorphous regions are difficult to control. Reduced cohesiveness in micronized materials can be achieved by crystallization. *In-situ* micronization gives more crystalline substances that can reduce the cohesiveness and can improve the flow properties (Rasenack and Muller, 2002b). The flowability and dispersibility of the *in situ* micronized powder were improved effectively and used in pulmonary drug delivery. Flow properties of fluticasone-17-propionate, an anti-inflammatory drug used in chronic obstructive pulmonary disease (COPD) was enhanced using *in situ* micronization technique compared to jet-milled product (Steckel et al., 2003).

2.6. Dissolution enhancement

Drugs with low solubility lead to poor dissolution rate which further leads to issues such as non-linear pharmacokinetics, intra and inter-individual absorption variability (Yohei et al., 2011). Micronization of poorly water soluble drugs leads to increased absolute surface area but the effective surface area required for wetting is less which leads to flotation as could be observed from dry milling (Rasenack et al., 2004). Due to this reason, dissolution rate of the milled products was not increased as it is expected from the Noyes-Whitney equation (Sharma et al., 2009; Leena and Jouni, 2010). Spray-drying technique is easy to handle, if water-soluble drugs are to be micronized. However, in the case of poorly soluble drugs, organic liquids are required that necessitate high machine expenditure (Reinhard, 2008). SCF technology is suitable for dissolution enhancement of drugs that are soluble in SCO_2 like lysozyme particles (Young et al., 1999), nifedipine and lidocaine (Perrut et al., 2005a,b). Drugs that are not soluble in SCO_2 are difficult to process through SCF technology. *In-situ* micronization can be used in such cases to enhance flow properties and dissolution rate. When a hydrophobic substance is micronized, a hydrophobic surface is formed. As hydrophilic polymers are used as stabilizing agents in case of *in situ* micronization technique, they can enhance the wetting properties and dissolution rate. Surface adsorption of hydrophilic polymers like HPMC and MHEC show enhanced wetting properties which can there by enhance dissolution rate. Dissolution rate was enhanced for gliclazide, betamethazone, prednisolone, budesonide, itraconazole and ketoconazole by *in situ* micronization technique using HPMC (Varshosaz et al., 2008; Rasenack et al., 2002a,b).

2.7. Drug degradation behaviour

There is less chance for physical or chemical degradation in case of *in situ* micronization technique as external processing conditions like high shear rates, temperature or pressure are not required. Whereas in other techniques like the drug degradation chances are more because of high shear forces and rapid decompression (expansion) in case of milling, spray drying and SCF technology (Snow et al., 1984; Sunday and Simon, 2006; Abhijit and Patravale, 2004). These techniques produce more amorphous particles which are rapidly cleared from systemic circulation due to enzymatic degradation which is due to their high reactivity (Lee et al., 2005).

2.8. Methods of preparation

Solvent change method and pH shift method are to be used in *in situ* micronization technique (Rasenack and Muller, 2002c). These methods are proved to be promising to enhance flow properties, dissolution rate and stability of poorly water soluble substances and to enhance flow properties of water-soluble drugs (Steckel et al., 2003).

2.8.1. Solvent change method

This technique involves precipitation in the presence of protective hydrophilic polymers followed by drying. Solvent change method is effectively applicable to both water soluble and insoluble drugs. The non-solvent is used as precipitating medium. For poorly water soluble drugs, drug is to be dissolved in suitable organic solvent. The majority of stabilizing agents are usually hydrophilic polymers, are to be dissolved in aqueous solvent which acts as non-solvent to the drug. Both the solutions are to be mixed batch-wise in 1:4 (Rasenack et al., 2004) or 1:8 ratios (Steckel et al., 2003). The resulting microcrystals are to be dried using oven or by spray dryer (Rasenack et al., 2003). Spray dryer is used only to dry the pre-formed particles but not for size reduction (Rasenack et al., 2003; Steckel et al., 2003). The stabilizers present in aqueous phase adsorb on the nucleated drug particles hindering the crystal growth.

Gliclazide microcrystals, betamethasone, budesonide and prednisolone were prepared by solvent change method using HPMC as stabilizing agent which showed an enhanced dissolution rate (Rasenack et al., 2003; Varshosaz et al., 2008). DSCG microcrystals were prepared by batch-wise mixing of the drug solution in isopropyl alcohol and aqueous HPMC solution at 1:8 ratio to enhance the flow properties and aerodynamic behaviour of DSCG (Steckel et al., 2003). The same procedure was used to prepare ibuprofen microcrystals by batch-wise mixing of drug solution in isopropyl alcohol and HPMC aqueous solution in 1:4 ratio (Rasenack et al., 2004).

2.8.2. pH shift method

pH shift method is well suitable for drugs with pH dependent solubility. In this method pH of the system needs to be altered slowly from basic to acidic or vice versa. 0.1 N NaOH and 0.1 N HCl are commonly used to alter pH. A high speed homogenizer with a speed of 26,000 rpm is employed to prevent aggregation while altering pH from basic to acidic or vice versa within a time gap of 5 min for effective microcrystallization (Roya et al., 2009).

Gliclazide microcrystals were prepared by pH shift method using PEG, CMC, PVP and pluronics and freeze dried. It was observed that freeze drying has no effect on particle size distribution (Roya et al., 2009; Mauludin et al., 2009) and an enhanced dissolution rate was observed compared to untreated

gliclazide. Similarly, indomethacin microcrystals were prepared by pH shift method using zinc acetate to alter the pH which also acts as stabilizer. Plate shaped microcrystals were obtained with an enhanced dissolution rate (Sung et al., 2003; Gibson, 2001).

2.9. Merits

- Critical effects resulting from milling processes can be avoided as all crystals are naturally grown.
- The microcrystals produced by this technique are *in situ* surface modified due to adsorption of hydrophilic polymers which enhances wettability.
- The *in situ* micronized crystals form homogeneous suspensions with less sedimentation due to the small particle size and hydrophilized surface which can be easily dispersible (Steckel et al., 2003).
- The aerodynamic behaviour can be improved to improve the powder flow with increased fine particle fraction.
- It is also applicable for the pulmonary use. Compared to the jet-milled drugs, the respirable fraction of these microcrystals is increased which can prevent the side effects like drug deposition in throat (Steckel et al., 2003; Rasenack et al., 2003; Rasenack et al., 2002a,b).
- *In-situ* micronization gives microcrystals with high drug load compared to other techniques like spray drying where yield is 20–50% (Labrude et al., 1989; Sunday and Simon, 2006).
- Evaporative precipitation into aqueous solution (EPAS) is also a precipitation technique but it requires high pressure for the evaporation of organic solvent from the solution whereas *in situ* micronization does not require any external forces (Chen et al., 2002; Sarkari et al., 2002).

2.10. Limitations

- In case of rapid solvent change process; the affinity of the hydrophilic polymer towards the newly formed crystal surface, partition coefficient of drug between the solvent and non-solvent limit the formation of microcrystals (Rasenack et al., 2002a,b).
- *In-situ* micronization of hydrophilic drugs may lead to formation of larger particles (Rasenack et al., 2002b).
- Controlling of crystal size is not an easy task in this method.

2.11. Applications

The microcrystals prepared by this technique can be used in liquid preparations without any crystal growth with less sedimentation rate which can be redispersed easily.

These microcrystals can be incorporated into suitable semisolid dosage forms for therapeutic and cosmetic purposes (Rasenack and Muller, 2002c).

In-situ micronization technique is well suitable for pulmonary drug delivery systems which require a particle size around 5 μ. Microparticles obtained by *in situ* micronization can be formulated into dry powder inhalers (DPI) or aerosols because of improved aerodynamic behaviour (Steckel et al., 2003). DSCG microcrystals were prepared by *in situ* micronization technique with enhanced respirable fraction compared to jet-milled DSCG to formulate into DPIs (Rasenack et al., 2004).

They can be used as solids in solid dosage forms such as capsules, tablets or pills. They are also suitable to formulate as parenterals.

3. Conclusion

Although many other techniques are available for micronization like spray drying and supercritical fluid technology, they are more complicated and require high processing conditions that make the resultant product highly expensive. Furthermore the stability of particles obtained by these techniques is less due to the formation of amorphous surfaces which limits their application in pharmaceutical industry. *In-situ* micronization is a new class of micronization technique which can overcome the limitations associated with the other techniques. It can be able to produce microcrystals of homogenous particle size distribution with improved flow properties, dissolution behaviour and stability. It reduces the cost of the final product because of simple process involved in the production of microcrystals. Further studies on the choice of stabilizing agents and the scale up techniques are required for the effective use of this technique in pharmaceutical industry.

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