Formation of Drug Nanoparticles from Microemulsions

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ABSTRACT

Reduction in particle size of poorly water-soluble drugs leads to enhanced dissolution and improved bioavailability. A new method for preparation of hydrophobic drug nanoparticles, in a form of water dispersible powder will be described. The method is based on rapid conversion of nanodroplets into nanoparticles, by evaporation of all volatile solvents from microemulsions containing a dissolved drug in the dispersed oil phase. The new method does not require any special instrumentation such as high pressure homogenizers since the nanodroplets are formed by spontaneous assembly. Typically, powders composed of either amorphous or crystalline particles at the size range of 10-100 nm are obtained. Dispersing these powders in water yields transparent systems. The simplicity and the low cost of the new processes make it very attractive for application for the pharmaceutical industry. Formation of nanometric powders by this process will be demonstrated for several hydrophobic drugs.

Keywords: nanoparticles, microemulsions, celecoxib, simvastatin, solubility enhancement

1 INTRODUCTION

Low aqueous solubility of active pharmaceutical ingredients presents a major problem while developing a final dosage form for drugs belonging to classes 2 and 4 of the Biopharmaceutical Classification System.

It is well known that bioavailability of poorly water soluble drugs is improved by reducing the drug particle size to the nanometric range [1]. Greater dissolution rate and higher saturation solubility are achieved as the result of nanometric dimensions of the particles [2-4]. In the case of oral route delivery, additional bioavalability increase may be obtained due to greater bioadhesiveness of nanoparticles compared to particulate drugs [5].

Solvent evaporation from oil-in-water emulsions is a common method for preparation of drug particle. By this method, a drug is dissolved in a volatile water-immiscible solvent and this solution is emulsified in water using high energy-consuming equipment, such as high pressure homogenizers. Eventually, the organic solvent is removed and drug particles are formed from the emulsion droplets.

Small droplet size can also be achieved by using microemulsions, which are spontaneously formed without any energy-consuming equipment and are thermodynamically stable. The simplicity and the low cost of the preparation process make the microemulsion very attractive for preparation of nanoparticles.

The new process for formation of nanoparticles from microemulsions is based on the following steps (Fig. 1):

A. The water insoluble drug substance is dissolved in a water-immiscible solvent that has a high evaporation rate. Pharmaceutically approved surfactants, co-surfactants and water are added to this organic solution;

B. The microemulsion is spontaneously formed upon mixing all components;

C. Solvent evaporation is performed either by spray drying or by freeze drying (lyophillization) to remove all the solvents at once;

D. A dry powder composed of nanoparticles is obtained;

E. Upon contact of this powder, in a tablet, capsule etc., with water, immediate wetting and dispersion formation occurs.

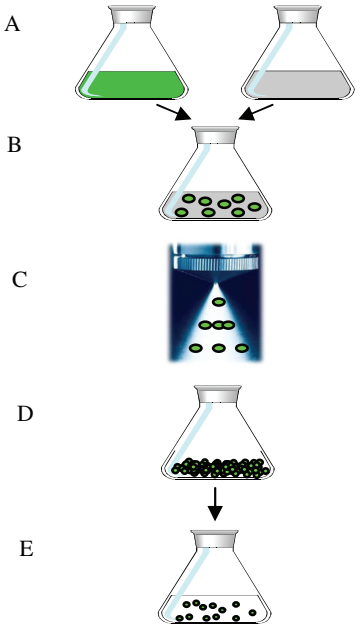

Figure 1. Schematic presentation of preparation process of nanoparticle from microemulsions

The new method for preparation of nanoparticle have several advantages over previously reported methods, such as low cost and simplicity, very small particle size (usually below 100nm, since the size of the microemulsion droplets is below 30 nm), prolonged storage and easy handling of the final product which is in the form of a solid powder.

The resultant nanopowder may be easily incorporated into various drug dosage forms to enhance bioavailability [6].

2 METHODS

2.1 Microemulsion Preparation

Microemulsion preparation is carried out by mixing all the components and enabling the mixture to equilibrate at constant temperature until isotropic, optically clear system forms. Phase diagrams' construction is conducted by changing microemulsion composition according to diagram and detecting the microemulsion formation region.

2.2 Microemulsion Structure Characterization

Microemulsion structure characterization is performed by electrical conductivity, viscosity and optionally SANS and SD-NMR measurements. Droplets' size is estimated by dynamic light scattering (DLS), cryoTEM observation, SANS and SAXS.

2.3 Nanoparticle Formation and Characterization

Solvent evaporation process is carried out by spray drying or lyophilizing (freeze drying).

Dry power characterization is performed by XRD, DSC, light microscopy and contact angle measurements.

Dispersion of the dry powder in aqueous medium is carried out in distilled water or in various buffers, to mimic physiological conditions. Characterization of aqueous dispersions of nanoparticles includes measuring particle size (by DLS , SANS, SAXS for nanoparticles and by laser obscuration time measurement or light microscopy for micron size particles), detecting the fraction of active substance in nanoparticles or dissolved (by filtering the dispersion with nanometeric size pore filter and subsequent determination of the active substance concentration in the filtrate by HPLC or UV-spectrophotometer), measuring ζ potential (by Zetamaster, NanoZS), and performing dissolution tests (using dissolution bath and suitable pharmacopeial monograph, if applicable).

3 RESULTS

3.1 Formation of Simvastatin Nanoparticles

Nanoparticles of the poorly water-soluble cholesterol-lowering drug, simvastatin (Fig.2), were prepared by solvent evaporation from microemulsion stabilized by lecithin and tween 80® [7].

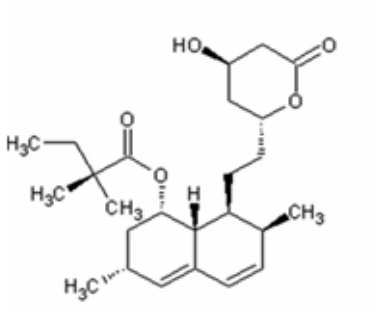

Figure 2. Simvastatin structure

Phase diagram of this microemulsion system and the specific composition chosen for experiments with the drug are presented in Fig. 3. Although it is possible to load up to 10 wt% of simvastatin in this microemulsion composition, the most easily dispersible product is achieved when the concentration of simvastatin is about 5 wt% (about 11wt% drug in the final powder).

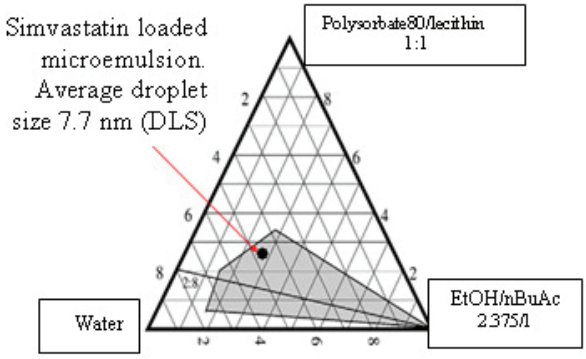

Figure 3. Phase diagram of microemulsions

Solvent evaporation was performed by freeze drying and water dispersible flakes of simvastatin were formed. The product is easily dispersible in distilled water, yielding nanoparticles with an average particle size of 50-70nm, as determined by DLS and cryoTEM (Fig. 4). It was found that simvastatin is initially amorphous in the freshly prepared powder, but a slow crystallization process takes place upon storage at room temperature. Nanometric crystals of simvastatin are eventually formed.

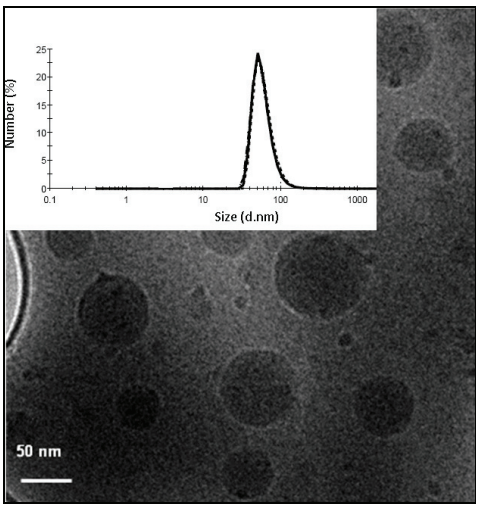

Figure 4: Size distribution of simvastatin nanoparticles measured by DLS and cryoTEM

Dissolution tests were conducted with tablets containing nanoparticles of simvastatin and with tablets containing bulk simvastatin (10mg simvastatin each, table 1). In case of nanoparticle containing tablet, within 30 minutes, 96 % w/w of the simvastatin in the tablet was dissolved or present as particles smaller than 0.1 µm. In comparison, the dissolution test of the conventional tablets revealed that under these testing conditions only 2 % w/w of simvastatin was dissolved. These results demonstrate the significant advantage of simvastatin nanoparticles over the conventional particulate drug, and the feasibility of the proposed method.

Time / % released drug	10min	20min	30min
Tablets containing nanoparticles	52%	91%	96%
Commercial simvastatin tablets	0%	1%	2%

Table 1. Comparision of dissolution profiles of tablets containing nanoparticles and commercial simvastatin 10mg tablets

3.2 Formation of Celecoxib Nanoparticles

Celecoxib is a poorly water-soluble anti-inflammatory drug and a chemotherapy adjuvant (Fig. 5). Celecoxib was solubilized in microemulsion system formed by lecithin (soybean phosphatidylcholine) and natural, pharmaceutically approved saponin (Fig. 6) [8].

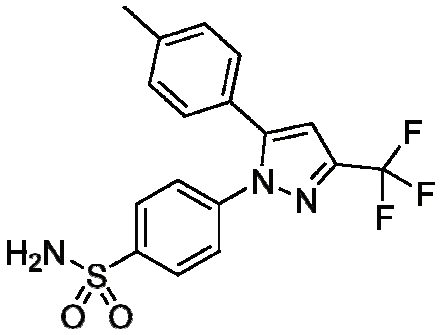

Figure 5. Celecoxib structure

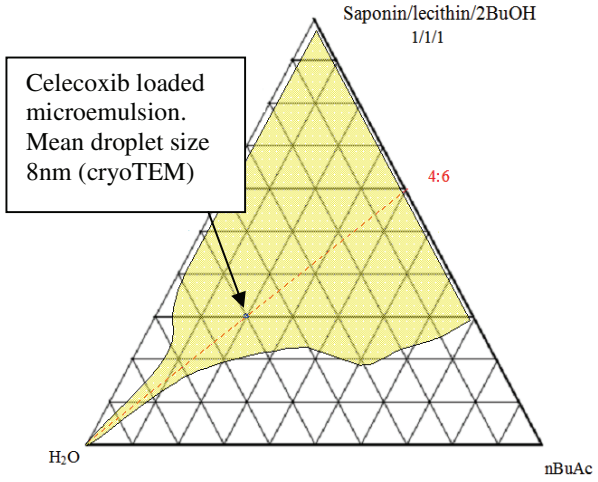

Figure 6. Phase diagram of microemulsion system which served as a template for nanoparticle formation

The drug-loaded microemulsion was spray dried and yielded a dry, free-flowing powder. Celecoxib concentration in this powder was 11.1%.
XRD measurements performed on this powder indicated that celecoxib is present as an amorphous form (Fig. 7). The drug remained in its amorphous form for several months.

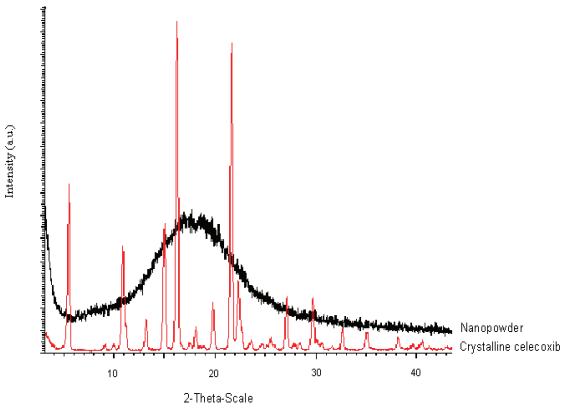

Figure 7. XRD patterns of nanopowder and crystalline celecoxib

It was found that this powder was easily dispersible (1 wt%) in water, forming an optically transparent dispersion. The average particle size in this dispersion as measured by DLS was 16.7±0.7 nm.
The dispersion was also observed by cryo-TEM. Image analysis result of the cryo-TEM image indicates that the mean diameter of the particles is 15.8±4.2 nm, in agreement with the DLS measurements.

Comparative dissolution tests were conducted with the nano-powder and celecoxib bulk powder in presence of the same surfactants used in microemulsion formation. (Table 2). It was found that the dissolution rate of the nano-powder is about 10 times higher than that of the particulate celecoxib in presence of surfactants.

Time / % released drug	1 min	2 min	5 min	10 min	15 min	30 min
Nanopowder of celecoxib	58%	70%	89%	92%	93%	94%
Celecoxib bulk powder with surfactants	1%	4%	7%	8%	9%	9%

Table 2. Comparision of dissolution profiles of nanopowder obtained by the described process and the bulk powder of celecoxib dispersed within micellar solution of surfactants

4 SUMMARY

A new process for obtaining nano-powder of poorly water-soluble drugs was demonstrated. The process is based on spontaneous emulsification and rapid evaporation of drug-loaded volatile microemulsions. For both drugs presented here, the product obtained by the described method has shown tremendous increase in dissolution profile compared to conventional particulate drug.

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