Formulation of water insoluble drugs

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Poor water solubility and the resulting low oral bioavailability of drugs is one of the major challenges encountered by drug discovery and development scientists. Drug candidates with a solubility of less than 1 μg/ml are considered poorly soluble which show unacceptable bioavailability from conventional dosage forms. Formulation plays a major role in determining the rate and extent of absorption of such drugs. There are a number of formulation strategies that could be used to improve the bioavailability of such drugs, primarily either by increasing the dissolution rate or by presenting the drug in solution. Various approaches to enhance the solubility and dissolution rate of drugs have been already reported e.g. inclusion complexation, colloidal systems, solid lipid nanoparticles and nano-structured lipid carriers etc.

1. Drug-cyclodextrin complexation using supercritical carbon dioxide ($scCO_2$).

Several processing methods have been developed to prepare drug-CD inclusion complexes in the solid-state, *e.g.* grinding kneading, roll mixing, ultrasound compaction, co-precipitation from various solvents, freeze-drying and spray drying. Most of these processing methods require either comparatively high energy input, employ organic solvents, or both which could be avoided by the application of $scCO_2$.

CO_2 becomes supercritical above its critical temperature (31.25 °C) and critical pressure (73.8 bar). $scCO_2$ is a non-toxic, inexpensive, chemically stable, environmentally acceptable solvent that can be readily removed from the drugs or drug–CD complexes after processing. The solvation properties of scCO2 can be beneficially tailored to dissolve a diverse range of solutes by simply regulating the temperature and pressure. It can be an attractive alternative to many of the methods currently used to produce these complexes in the solid-state as it avoids the use of organic solvents.

We have studied drug-CD complexation of a number of lipophilic APIs including econazole, indomethacin and olanzapine in $scCO_2$ without the use of any organic solvent. The drug-CD complexes prepared by $scCO_2$ were comparable to or better than the conventional methods.

2. Drug loading on mesoporous materials using $SCCO_2$.

Mesoporous nanoparticles (MNs) have attracted the attention of several scientists over the last decade due to their potential applications in drug delivery. Among the main features of mesoporous materials is the high surface area, pore volume and the highly ordered pore network which is very homogeneous in size. As a result of these features MNs are excellent candidates as drug delivery systems. The three main reported methods for the drug inclusion in MNs are the solvent method, the impregnation method and the melt method.

We studied the application of $scCO_2$ media either as a drug loading vehicle or to promote drug loading in the MNs. The study of the inclusion of carbamazepine on mesoporous silica nanoparticles suggested that the $scCO_2$ can facilitate high drug loading and improve the dissolution of poorly water soluble actives. Moreover, it is a single step process where drug loading and the efficient evaporation of the solvent could be achieved to produce dry powder at the end of the process. Similar results were also obtained for the loading of theophylline and salbutamol on zeolite.

3. Solid lipid nanoparticles and Nano-structured lipid carriers.

Solid lipid nanoparticles (SLN) were developed as an alternative carrier system to emulsions, liposomes and polymeric nanoparticles. SLN are produced using solid lipids including high-melting point glycerides or waxes, replacing liquid lipid used in emulsions. SLNs can provide prolonged delivery of actives by reservoir action. However, SLN may have some limitations in drug loading capacity depending on the solubility of the drug in the solid lipid and/or drug loss during storage due to lipid crystallization to the stable β-modification and relatively high water content. NLC, the second generation of SLN are produced using spatially incompatible lipids together. Incorporation of liquid lipid into the solid structure ensures to overcome possible limitations related to SLN. SLN and NLC are sophisticated colloidal drug carrier systems suitable for various applications. The most common method to prepare SLNs and NLCs is the high pressure homogenization which has an excellent reproducibility in the large scale production. Other methods such as sonoprocessing can also produce SLNs and NLCs of varying sizes and surface morphology.

We recently prepared and compared SLNs and NLCs for anticancer agents. The SLNs had limited drug loading capacity as expected which was increased significantly by the preparation of NLCs. The drug loading capacity and the stability of NLCs was also better than SLNs alone. The animal studies data suggested that both SLNs and NLCs were effective in the reduction of tumour and were very well tolerated.