

### 3. Review of Work Done

#### 3.1 Review of Work Done for Nanosuspension

**Liversidge et al**<sup>1</sup> prepared nanoparticulate naproxen dispersion in a roller mill. The nanoparticle dispersion was sized by photon correlation spectroscopy and found to have a weight average particle size of 270 nm with no particles above 400 nm. The formulation was physically and chemically stable when stored at 4°C for up to 4 weeks. The unmilled naproxen had significantly higher irritation scores (t-test,  $p = 0.01$ ) than the milled naproxen formulation when administered orally. The AUC for the oral nanoparticle formulation was significantly higher than for the unmilled suspension ( $p = 0.03$ ). The  $C_{max}$  for the nanosuspension was significantly higher than for the unmilled suspension ( $p = 0.02$ ).

**Weidmann et al**<sup>2</sup> prepared Beclomethasone Dipropionate nanosuspension using ball mill for nebulisation. A nebulized Beclomethasone Dipropionate nanosuspension has a greater fraction of respirable drug in comparison to nebulized micronized suspension of Beclomethasone Dipropionate. They conclude that this is an efficient method for respiratory drug delivery of Beclomethasone Dipropionate.

**Sigfridsson et al**<sup>3</sup> administered AZ68 as a solution and compared with those from an amorphous and a crystalline nanosuspension using rats as in vivo specie. All formulations were administered intravenously (i.v.) and orally. The results indicate that AZ68 is absorbed at a lower rate for crystalline nanosuspensions compared to amorphous nanosuspensions and solutions. However, the absorbed extent of the compound is similar. The dissolution process is excluded for a solution, resulting in the fastest absorption rate. No significant difference was found between pharmacokinetic parameters when comparison was made between the formulations after i.v. administration. There were no adverse events observed after i.v. administration of the nanosuspensions.

**Pignatello et al**<sup>4</sup> improved the availability of sodium ibuprofen (IBU) at the intraocular level, IBU-loaded polymeric nanoparticle suspensions were made from

inert polymer resins (Eudragit RS100 ). Nanosuspensions had mean sizes around 100 nm and a positive charge ( z -potential of 140 / 160 mV), this makes them suitable for ophthalmic applications. In vitro dissolution tests indicated a controlled release profile of IBU from nanoparticles. IBU-loaded nanosuspensions did not show toxicity on ocular tissues.

**Madhusudan Rao et al**<sup>5</sup> prepared Nanosuspensions of Albendazole for Oral Administration for enhancement of bioavailability and therapeutic efficacy. These studies showed the feasibility of formulating a stable formulation of albendazole with minimum particle size through high pressure homogenization technique. The preparation of nanosuspensions of albendazole was attempted through the screening of several techniques. The comparison between different techniques has clearly proven the advantages of using high pressure homogenization technique to achieve stable and optimum nanosuspension formulations.

**Trotta et al**<sup>6</sup> prepared Mitotane nanosuspensions by a solvent quenching technique. Preparation was by emulsifying an organic solution of the drug in an aqueous solution of a stabilising agent followed by rapid displacement of the solvent from the internal into the external phase, provoking solid particle formation. Drug particles of about 80 nm were obtained using butyl lactate, supporting the hypothesis that drug particle formation by the emulsification diffusion process involves generating regions of local supersaturation. They conclude that because of the increase in available surface area, the dissolution rate of dialultrafiltrated suspensions increased greatly compared to commercial product.

**Williams et al**<sup>7</sup> developed evaporative precipitation into aqueous solution (EPAS) to coat poorly water soluble drug, carbamazepine, with hydrophilic stabilizers to enhance dissolution rates. The rapid evaporation of the organic solvent produces high supersaturation and rapid precipitation of the drug in the form of a colloidal suspension that is stabilized by a variety of low molecular weight and polymeric surfactants. They

conclude that For PVP K15 stabilized powders, these dissolution rates are much faster than those produced earlier by solvent evaporation without an aqueous phase.

**Jian-Feng Chen et al**<sup>8</sup> prepared amorphous nanoparticles of cefuroxime axetil (CFA), a poorly water-soluble drug, by the controlled nanoprecipitation method without any surfactants at room temperature. Results showed that the amorphous CFA nanoparticles exhibited significantly enhanced dissolution property when compared to the commercial spray-dried product. The results also demonstrated that the controlled nanoprecipitation method is a direct and feasible technology which could be utilized for preparation of the poorly water-soluble pharmaceutical nanoparticles.

**Douroumis et al**<sup>9</sup> used fast precipitation by continuous turbulent mixing of two liquid flows, an aqueous phase and an organic phase, respectively for four model active pharmaceutical ingredients (APIs) (Progesterone (PRG), b-Methasone valerate 17 (BMZ) Carbamazepine (CBZ), Oxcarbazepine (OXC)) with a variety of polymers, lipids or surfactants underwent intensive mixing and the final suspensions showed a narrow size distribution. Result shows the developed static mixer technique has been proved sufficient to produce formulations for different administration routes in the nano- or micro-scale.

**Zohra Zili et al**<sup>10</sup> prepared polycaprolactone nanospheres and nanocapsules of griseofulvin by nanoprecipitation and characterized them. Nanoparticles of griseofulvin were obtained with high encapsulation efficiency. The particle size was about 250–326 nm for nanospheres and 390–400 nm for nanocapsules. The dissolution rate of griseofulvin nanoparticles was higher than that of micronized griseofulvin therefore recourse to nanoencapsulation of griseofulvin should enhance its bioavailability and possibly its efficiency for the treatment of dermatomycosis.

**Trotta et al**<sup>11</sup> prepared Nanoparticles of griseofulvin from water dilutable microemulsions by the solvent diffusion technique. They conclude that the microemulsion-diffusion technique using pharmaceutically acceptable solvents, such as

butyl lactate, led to successful fabrication of drug nanosuspensions. In their optimised formulations, griseofulvin nanoparticles below 100 nm with low polydispersity were obtained. Dissolution rates of griseofulvin particles obtained by the solvent diffusion procedure were higher than that commercial product.

**Jianfeng Chen et al**<sup>12</sup> used combined reactive precipitation and liquid anti-solvent precipitation technique under high gravity environment, to prepare nanosized cephadrine with narrow particle size distribution. The width of as-prepared cephadrine was about 200–400 nm and the mean particle size was about 300 nm. The specific surface area increased from 2.95 to 10.87 m<sup>2</sup>/g after micronization. The nanosized cephadrine for injection also showed a shorter dissolving time than that of commercial crude cephadrine.

**Johnston et al**<sup>13</sup> prepared cyclosporine A nanosuspension using evaporative precipitation into aqueous solution (EPAS). They found that the rapid evaporation of the heated organic solution in EPAS results in fast nucleation leading to amorphous nanoparticle suspensions. Nanoparticle suspensions with low drug crystallinity were formed for cyclosporine A with L-phosphatidylcholine vesicles, low molecular weight ethoxylated nonionic surfactants, and high molecular weight homopolymers.

**N Gu, et al**<sup>14</sup> prepared All-Trans Retinoic Acid (ATRA) nanosuspensions using a modified precipitation method. Photon correlation spectroscopy results showed that the mean particle size of ATRA nanoparticles in nanosuspensions reduced from 337 nm to 155 nm as the injection velocity increased and the polydispersity index was 0.45–0.50. It could be concluded that this modified precipitation method could produce stable and controllable ATRA nanosuspension to a certain extent, thus benefit for higher saturation solubility.

**Dong et al**<sup>15</sup> prepared Nanosuspensions of beta cypermethrin with narrow size distribution using O/W microemulsions technique. These carrier-free nanoparticles with high drug loading offer an alternative way with improved drug solubility and

delivery. Moreover, this approach can be used to formulate water insoluble drugs in submicron particles, with prolonged release and environmental friendly solvent.

**Kayser**<sup>16</sup> prepared mucoadhesive nanosuspension to deliver antibiotics to the Cryptosporidium -infected gastrointestinal tract is presented. They have the ability to reside in the gastrointestinal tract for an extended period. The hydrogel contained bupravaquone nanosuspensions and an adhesive polymer (chitosan) powder dispersed in water. By the development of mucoadhesive nanosuspensions, a potential drug delivery system for poorly soluble drugs has been investigated to overcome bioavailability problems caused by the pathophysiological diarrhoeic situation in patients suffering from cryptosporidiosis. Adapting drug delivery systems to the situation of Cryptosporidium parvum infections in man allows increased retention times with a prolonged action at reduced elimination in the gastrointestinal tract. The use of mucoadhesive bupravaquone nanosuspensions would allow one to reduce the dose of bupravaquone, which is important from the view- point of reducing adverse effects and application frequency for the patient. Chitosan is an acceptable polymer that permits a stable hydrogel without incompatibilities with the nanosuspension.

**Krause and Muller**<sup>17</sup> prepared RMKK99Nanosuspensions with 20 and 30% solid content were produced, the effect of surfactant concentration assessed and their quality (size data) compared with the lower standard concentrations of 1 – 10% solid. He summarise, nanosuspensions up to 30% solid content can be produced, and even higher concentrations are possible when using a modified homogeniser design.

**Muller and Peters**<sup>18</sup> studied nanosuspension of RMKP 22, RMKP 23, Prednisolone, Carbamazepine. They study the effect of the production parameters pressure and cycle number on the mean particle size and on the polydispersity of the nanosuspension was investigated with special attention to contamination by microparticles the limiting factor for i.v. injection. Results shows the properties

of the nanosuspensions are increased saturation solubility  $C_s$  and dissolution rate  $dc/dt$ . These phenomena are explained using the Prandtl and the Ostwald – Freundlich equations. These properties promote the dissolution of the nanosuspensions in the blood after i.v. injection. The size distribution obtained and the use of an APV Gaulin homogenizer (FDA approved for parenterals) lead to a pharmaceutical product considered acceptable by the regulatory authorities.

**Kayser**<sup>19</sup> developed aphidicolin, a tetradecanhydro-3,9-dihydroxy-4,11b -dimethyl-8,11a-methano-11aH-cyclo-hepta[a]naph- thalin-4,9-dimethanol nanosuspension to improve drug targeting effects aphidicolin and retested for its enhanced activity. . In conclusion, our study provides that aphidicolin itself exhibit high antileishmanial properties with moderate toxicity for mammalian host cells. Nanosuspensions showed a circa 140-fold increase in antileishmania activity in comparison to DMSO dissolved drug, indicating that endocytotic uptake of nanoparticles are of main importance for its improved activity.

**Muller et al**<sup>20</sup> improved the in vivo performance of tarazepide by reducing the particles size of the drug thus leading to an increased surface area and an increased dissolution velocity. They create a formulation with this drug as nanosuspension which is suitable for intravenous administration. The nanosuspension was well tolerated when administered intra- venously in rats and mice (data unpublished). It was also demonstrated that a long-term stable nanosuspension, when using a sufficient high con- centration of surfactant, can be obtained.

**Muller et al**<sup>21</sup> were studied reproducibility of small scale production parameters (particle size, size distribution, content of microparticles) was exemplary studied for the drug RMKP22. They studied time and cost effective production in an initial phase of R&D can be conducted on lab scale by using the Micron Lab 40. They conclude the milling process by high pressure homogenisation for the production of drug nanoparticles is highly reproducible with regard to the

mean size and width of the distribution of the bulk population (PCS data) but also regarding the low content of micrometer particles (LD data).

**Muller et al**<sup>22</sup> developed mucoadhesive nanosuspension to overcome the problem of the high elimination rate caused by diarrhoea, typical for *C. parvum* infections, bupravaquone was formulated as a mucoadhesive nanosuspension, i.e. combining the properties of mucoadhesive drug delivery systems, in this case hydro gels, with nanosuspensions. In this study different polymers:hydro gels were employed to create a prolonged retention time for the drug in the infected gastrointestinal tract (GIT). The second step to improve the bioavailability of bupravaquone was the formulation as nanosuspension. Therefore various concentrations of bupravaquone with different surfactants were tested. The delivery system proved to be physically stable for 3 months and was successfully investigated in vivo.

**Khalil et al**<sup>23</sup> studied, the high pressure homogenization method used to prepare nanosuspensions of three practically insoluble glucocorticoid drugs; hydrocortisone, prednisolone and dexamethasone. The effect of particle size in the micron and nano-size ranges as well as the effect of viscosity of the nanosuspension on the ocular bioavailability was studied by measuring the intraocular pressure of normotensive Albino rabbits using ShiØetz tonometer. The results show that compared to solution and micro-crystalline suspensions it is a common feature of the three drugs that the nanosuspensions always enhance the rate and extent of ophthalmic drug absorption as well as the intensity of drug action. In the majority of cases nanosuspensions extend the duration of drug effect to a significant extent. The data presented confirms that nanosuspensions differ from micro-crystalline suspensions and solution as ophthalmic drug delivery systems and that the differences are statistically, highly to very highly significant.

**Muller and Jacobs**<sup>24</sup> produced buparvaquone nanosuspension by high pressure homogenisation. The buparvaquone nanosuspension had a bulk population of

about 600 nm (analysed by photon correlation spectroscopy (PCS)). The additional analysis performed with laser diffraction showed that only a very small content of microparticles occurred, which is, for the special features of nanosuspensions, negligible because they were still below 3  $\mu$ m. Another feature of nanosuspensions is the adhesion properties to surfaces, e.g. mucosa. The nanosuspension/hydrogel systems were physically long-term stable over a period of 6 months as indicated by the unchanged particle sizes.

**Kayser et al**<sup>25</sup> studied a nanosuspension of Amphotericin B as a new oral drug delivery system for the treatment of experimental visceral leishmaniasis. Amphotericin B (AmB) nanosuspensions were produced by high pressure homogenisation obtaining particles with a PCS diameter of 528 nm. Environmental stability was determined in artificial gastrointestinal fluids at different pH and electrolyte concentrations. In vivo efficacy was determined in a mouse model of visceral leishmaniasis. Following oral administration (5 mg kg<sup>-1</sup>), micronized Amphotericin B did not show any curative effect. However, administrations of Amphotericin B nanosuspension, reduced liver parasite load by 28.6% compared to untreated controls.

**Langguth et al**<sup>26</sup> studied bioavailability of the poorly soluble fenofibrate following oral administration was investigated in rats. Four formulations were tested: a nanosuspension type DissoCube®, one solid lipid nanoparticle (SLN) preparation and two suspensions of micronized fenofibrate as reference formulations, one suspension in sirupus simplex and a second in a solution of hydroxyethyl-cellulose in physiological saline. They conclude that the nanosuspensions may be a suitable delivery system to improve the bioavailability of drugs with low water solubility.

**Jacobs and Muller**<sup>27</sup> produced of a budesonide nano- suspension by high-pressure homogenization for pulmonary delivery from 40 mL up to 300 mL. The aim was to obtain a nanosuspension that can be nebulized and is also long-term stable. They

obtain a long-term stable budesonide nanosuspension with mean particle size of about 500–600nm and conclude that High-pressure homogenization is a production method to obtain nanosuspensions with budesonide for pulmonary application.

**Craig et al**<sup>28</sup> prepared nanosuspensions comprising a model drug (RMKP 22) with varying concentrations of Phospholipon 90 were prepared using high pressure homogenization and analyzed using low frequency dielectric spectroscopy as a novel means of characterizing the distribution of Phospholipon 90 within the suspensions. Through investigations of dispersions and nanosuspensions with varying Phospholipon 90 concentrations a model was developed which attributed the observed dielectric behaviour to the Phospholipon 90 surface cover on the nanoparticles and the related presence of liposomes.

**Muller et al**<sup>29</sup> showed the feasibility of omeprazole stabilization using the DissoCubes<sup>W</sup> technology and to find optimal production parameters for a stable, highly concentrated omeprazole nanosuspension. They produced nanosuspension by high pressure homogenization. Even 1 month after production no discoloration or drug loss was recognizable when the nanosuspension was produced at 0 8C. As a result it can be stated that the production of nanosuspensions by high pressure homogenization is suitable for preventing degradation of labile drugs.

**Muller et al**<sup>30</sup> study the heavy metal (Fe) contamination of nanosuspensions produced by high pressure homogenisation was determined. Therefore nanosuspensions were analysed by atom absorption spectroscopy concerning their load of iron which is chosen as reference metal. The results show that the erosion of metal is below 1 ppm and will not cause any toxicological problems.

**Zhang et al**<sup>31</sup> investigated the effects of particle size on the pharmacokinetics and tissue distribution of oridonin nanosuspensions after intravenous administration. Two oridonin nanosuspensions with markedly different size were prepared by high pressure homogenization method. The particle size of nanosuspension A is  $103.3 \pm$

1.5 nm, while B is  $897.2 \pm 14.2$  nm. Dissolution studies showed that complete dissolution could be obtained within 10 min for nanosuspension A, however, nanosuspension B showed a slower dissolution, only 85.2% dissolved by 2 h. The pharmacokinetics and tissue distribution of oridonin nanosuspensions A and B were studied after intravenous administration using New Zealand rabbits and Kunming mice as experimental animals, respectively. An Oridonin control solution was studied parallelly. The results showed that oridonin nanosuspension A exhibited pharmacokinetic and biodistribution properties similar to solution due to its rapid dissolution in blood circulation. Oridonin nanosuspension B, however, showed a high uptake in RES organs, meanwhile exhibited a markedly different pharmacokinetic property compared to nanosuspension A. These differences could be attributed to the different particle size of the two nanosuspensions considering their zeta potential had no significant difference. They concluded that particle size showed obvious effects on pharmacokinetics and tissue distribution of nanosuspensions.

**Zhang et al**<sup>32</sup> prepared of an oridonin (ORI) nanosuspension by high-pressure homogenization (HPH) to obtain a stable nanosuspension with an increased drug saturation solubility and dissolution velocity. It has been shown that formulation of ORI as a nanocrystal suspension has exhibited great success in dissolution rate and saturation solubility enhancement due to its size and enormous surface area. The HPH method was shown to be a simple and efficient technique for particle size reduction with the help of optimized stabilizers. Furthermore, the crystalline state of ORI was not altered through the process of particle size reduction, which is beneficial for the long-term stability of ORI nanosuspensions.

**Langguth et al**<sup>33</sup> studied seven oral and one i.v. formulations were tested in an in vivo pharmacokinetic study in rats with the aim of characterizing the bioavailability of spironolactone on the basis of its metabolites canrenone and 7-a-thiomethylspiro lactone. The study was carried out using nonmicronized spironolactone suspension as well as a nanosuspension type DissoCubes<sup>R</sup>. On the

basis of AUC as well as C<sub>max</sub> ratios, three groups of formulations were distinguished. The biggest improvement was seen with a solid lipid nanoparticle formulation yielding a 5.7-fold increase in AUC for canrenone and a similar improvement based on the C<sub>max</sub> metric, followed by a group of three formulations containing nanosized, micronized, and coarse drug material and surfactant. The DissoCubes1 nanosuspension yielded highly significant improvements in bioavailability averaging 3.3-fold in AUC and 3.0-fold in terms of C<sub>max</sub> for canrenone.

**Zhang et al**<sup>34</sup> produced azithromycin nanosuspensions by high pressure homogenization with the purpose of increasing its saturation solubility and dissolution velocity. They conclude that it was possible to obtain an azithromycin nanosuspensions with fine solubility and dissolution properties, and the nanosuspensions possessed a high drug-loading (1%), which could reduce the administration dosage and gastrointestinal response. By the transformation of the nanosuspensions into lyophilized powders, the physical stability of this system could be further enhanced.

### 3.2 Review of Work Done for Nifedipine

**Remunan-Lopez et al**<sup>35</sup> studied, a significant effect of chitosan increasing nifedipine dissolution. This effect was dependent on the polymer:drug mixing weight ratio, the chitosan type and the method used to disperse the drug within the polymer. The greater the chitosan content the higher the drug dissolution was, up to a maximum corresponding to a polymer:drug ratio of 3:1. Significant differences within the various tested chitosans were observed. The drug dissolution enhancement was attributed to the decreased drug crystallinity and size and polymer wetting effect. Co-grinding of chitosan along with nifedipine in a 3:1 ratio, which leads to solid mixtures exhibiting a significantly improved dissolution profile without requiring the addition of organic solvents or high temperatures for its preparation, appears to be the more simple and convenient method.

**Bayomi et al**<sup>36</sup> prepared solid inclusion complexes of nifedipine with  $\beta$ -cyclodextrin ( $\beta$ -CD), hydroxypropyl- $\beta$ -cyclodextrin (HP- $\beta$ -CD) and dimethyl- $\beta$ -cyclodextrin (DM- $\beta$ -CD) using the coprecipitation method. Inclusion complexation of nifedipine showed to retard drug photodegradation as indicated by degradation rate constant lowering with values depended on light source and type of complexing agent. It was also interesting to notice that inclusion complexation of nifedipine offered much higher protection against the effect of fluorescent lamp than that of sunlight and also associated with a dramatic enhancement of drug dissolution with magnitudes depended on the type of CD.

**Thau-Ming Cham et al**<sup>37</sup> prepared solid dispersions containing 5%, 10%, 20%, 30% and 50% of nifedipine were prepared with polyethylene glycol (PEG) 6000 as carrier, respectively, by the fusion method. Drug release from four different size fractions of nifedipine-polyethylene glycol 6000 solid dispersions were examined. They found that the dissolution rates and values of available surface area ( $S(t)$ ) were particle size dependent for the solid dispersions with higher contents of nifedipine (20%, 30% and 50%) and smaller particles possessed higher dissolution rates or higher initial values than larger particles.

**Yamamoto et al**<sup>38</sup> prepared solid dispersions of nifedipine (NP) with polyethylene glycols (PEG4000 and PEG6000), hydroxypropyl- $\beta$ -cyclodextrin (HP $\beta$ CD), and poloxamer 407 (PXM 407) in four mixing ratios were prepared by melting, solvent, and kneading methods in order to improve the dissolution of NP. The presence of intermolecular hydrogen bonding between NP and PEGs and between HP $\beta$ CD and PXM 407 was shown by infrared (IR) spectroscopy. The highest dissolution rate and the T80% as short as 15 min were obtained from PXM 407 solid dispersion prepared by the melting method at the mixing ratio of 1:10.

**Lalitha and Lakshmi**<sup>39</sup> enhance the dissolution of nifedipine, a poorly water soluble drug by surface solid dispersion technique using different carriers and to study the effect of each carrier on the in vitro dissolution profile. The optimized dispersion was formulated in to sublingual tablets by using kyron T-314, crospovidone, croscarmellose sodium and sodium starch glycolate as disintegrants and was evaluated for friability, hardness, weight variation, disintegration and in vitro dissolution. The sublingual tablets prepared with kyron T-314 as disintegrant gave good disintegration.

**Remon et al**<sup>40</sup> studied dissolution rate enhancement properties of sucrose esters using nifedipine as poorly soluble drug. The use of sucrose palmitate of high HLB value dramatically improved the dissolution rate, especially when a drug/ester ratio of 1: 14 was used. Increasing the drug/ester ratio produced a more amorphous product, progressively increasing the dissolution rate. Although the results are promising, the use of sucrose esters is probably very much restricted due to their hydrolytic instability during storage and the progressively increasing crystallinity of the coprecipitate.

**Chun-Ren C et al**<sup>41</sup> investigated the dissolution enhancement of nifedipine by the solvent deposition technique using superdisintegrants including Ac-Di-Sol, Kollidon CL, and Explotab as excipients. The effect of solvent on dissolution of nifedipine in the solvent deposition system was also investigated. They found that the solvent and disintegrants used can influence the dissolution rate also. The solvent deposition system

using both Kollidon CL as excipient and dichloromethane as solvent has the highest dissolution rate.

**Zia H. et al**<sup>42</sup> found mechanisms responsible for solubility enhancement of nifedipine in solid dispersions of vitamin E TPGS and/or solutol HS-15. Solid dispersions of nifedipine with selected polymers such as vitamin E TPGS, solutol HS-15, PEG1000, and lipocol C-10 of varying drug/polymer ratios were prepared by a fusion method. The solubility enhancement was found to be in the order of vitamin E TPGS>solutol HS-15>lipocol C-10 > PEG1000. Lipocol C-10, with a similar hydrophilic-lipophilic value as vitamin E TPGS, showed a comparable retained solubility enhancement during saturation solubility studies but had lower dissolution profile. They concluded that enhanced solubility using vitamin E TPGS and solutol HS-15 resulted from a partial conversion of crystalline drug to the amorphous form, increase in wettability of the drug by water soluble polymers, better separation of drug particles, micellar solubilization of drug by high concentrations of surfactant polymers, and interaction between polymer and drug at the molecular level.

**Emara et al**<sup>43</sup> improve the therapeutic efficacy of Nifedipine via incorporation into different types of carriers, and to investigate their in vitro dissolution and bioavailability in rabbits. Nifedipine solid dispersions were prepared by fusion, solvent, and freeze-drying methods with polyethylene glycol (PEG) 6000 and PEG monomethylether 5000 (PEG MME 5000). Complexation of NF with  $\beta$ -cyclodextrin ( $\beta$ -CyD) and solubilization by sodium lauryl sulfate (SLS) have also been studied. They found the highest Nifedipine dissolution rate was obtained from solid dispersions containing 95% PEG 6000 prepared by the solvent method. While, unexpectedly, the highest absorption in rabbits was obtained from 95% PEG 6000 prepared by the fusion method.

**Srcic et al**<sup>44</sup> prepared Solid dispersions of nifedipine (NIF) with mannitol in preparations containing 10 and 50% (w/w) of drug by the hot melt method. They concluded that the dissolution rate of NIF from solid dispersions was markedly enhanced, the effect being stronger at higher drug loading (50%, w/w, NIF). The dissolution rate enhancement was

attributed to improved wetting of NIF crystals due to mannitol particles, attached on the surface, as inspected by means of SEM.

**Gohel et al**<sup>45</sup> studied solid dispersions containing PVP and PEG, inclusion complex with beta cyclodextrin (Bcyd), and kneaded mixtures with hydrophilic adjuvants such as watersoluble gelatin (WSG) and microcrystalline cellulose (MCC) were prepared in order to enhance the dissolution rate of nifedipine (NF) in simulated gastric fluid. The dissolution rate of NF from solid dispersions increased in the order of PVP K-30 > PEG 6000 > PEG 4000 > pure drug. About a threefold increase in solubility of NF was observed from NF-Bcyd inclusion complex. They concluded that the drug was released at a quicker rate from hard gelatin capsules containing physical mixture of inclusion complex of NF-Bcyd and WSG and also from tablets.

**Venkitachalam and Save**<sup>46</sup> prepared Nifedipine-Polyethylene glycol solid dispersions using melting or fusion method in order to improve nifedipine solubility in the aqueous body fluids. The dissolution rate of the drug was markedly increased in these solid dispersion systems. They also conclude that after storage at room temperature for six months, solid dispersions showed no change in the dissolution rate and the X-ray diffraction pattern showed slight enhancement in crystallinity.

**Acarturk et al**<sup>47</sup> investigated the effect of natural polymers, such as water-soluble gelatin and egg albumin, on the solubility and dissolution characteristics of nifedipine. The interaction of nifedipine with these polymers both in aqueous solution and in the solid state was examined by performing solubility analysis, powder X-ray diffractometry and differential scanning calorimetry measurements. It was found that water-soluble gelatin and  $\beta$ -cyclodextrin resulted in a significant increase in the rate of dissolution of nifedipine as compared to drug alone.

**Villiers Melgardt and Yang**<sup>48</sup> studied the solubilizing effect of 4-sulphonic calix[n]arenes on the poorly water soluble drug nifedipine. They prepared complex of nifedipine and sulphonic calix[n]arenes are water-soluble phenolic cyclooligomers. They showed

that the size of the 4-sulphonic calix[n]arenes, the pH of solubility medium, and the concentration of the calix[n]arenes all significantly changed the solubility of nifedipine. 4-Sulphonic calix[8]arene improved the solubility of nifedipine the most, about 3 times the control at 0.008 M and pH 5, followed by 4-sulphonic calix[4]arene, about 1.5 times the control at 0.008 M and pH 5, while in the presence of 4-sulphonic calix[6]arene, the solubility of nifedipine was decreased.

**Law et al**<sup>49</sup> studied *in vitro* dissolution and *in vivo* absorption of solid dispersions of nifedipine-polyethylene glycol (nifedipine-PEG) and nifedipine-phosphatidylcholine-polyethylene glycol (nifedipine-PC-PEG). The dissolution of nifedipine from the solid dispersions was markedly enhanced as compared with the pure drug. The incorporation of PC into the nifedipine-PEG solid dispersion resulted in a 2.6- and 2.2-fold increase in nifedipine initial dissolution rate and dissolution after 60 minutes, respectively. This was attributed to the formation of lipid vesicles which entrapped a certain concentration of nifedipine during dissolution. The area under the curve after oral administration of the nifedipine-PC-PEG solid dispersion was 3.4-fold greater than that of the nifedipine-PEG solid dispersion.

**Becirevic-Lacan et al**<sup>50</sup> prepared Nifedipine complexes with  $\beta$ -cyclodextrin, hydroxypropyl- $\beta$ -cyclodextrin, and DIMEB in solution and was studied by the phase solubility method. Solid complexes of nifedipine were prepared by partial and complete solubilization of nifedipine using the freeze- and spray-drying techniques. The relative potency of  $\beta$ -cyclodextrins to enhance the dissolution rate of nifedipine was in order:  $\beta$ -cyclodextrin < hydroxypropyl- $\beta$ -cyclodextrin < DIMEB, which clearly fits the magnitude of stability constant data of the complexes.

**Bodmeier et al**<sup>51</sup> prepared Co-ground powders of the poorly water-soluble drug nifedipine and a hydrophilic carrier, [partially hydrolyzed gelatin (PHG), polyvinylpyrrolidone (PVP), sodium dodecyl sulfate (SDS), hydroxypropyl methylcellulose (HPMC), polyethylene glycol (PEG), urea or Pluronic F108] in order to improve the dissolution rate of nifedipine. Grinding nifedipine together with these

carriers improved the dissolution rate. PHG-ground mixtures resulted in the fastest dissolution rate followed by PVP, SDS, HPMC, Pluronic, urea, and PEG. They conclude that effect was not only due to particle size reduction, which increased in the order PHG<PEG=SDS<Pluronic<drug<urea<HPMC<PVP, but also resulted from the ability of some carriers (PVP and HPMC) to prevent reaggregation of the finely divided drug particles. PVP, HPMC, and PHG formed a powder with amorphous drug. They also found that the carriers improved the wettability of the ground products in the order HPMC<drug<urea<PVP<SDS<PHG<PEG<Pluronic.

**Grant David et al**<sup>52</sup> characterized the nature and solid-state properties of a solid dispersion system of nifedipine (33.3% w/w) in a polymer matrix consisting of Pluronic F68 (33.3% w/w) and Gelucire 50/13 (33.3% w/w). The results indicate that the nifedipine solid dispersion is physically stable over 8 weeks. Nifedipine is released faster from the solid dispersion than from the pure crystalline drug of the same particle size.

**Amighi et al**<sup>53</sup> prepared nifedipine nanoparticles using high pressure homogenization in order to enhance the dissolution characteristics. Nanoparticles were characterized in terms of size, morphology and redispersion characteristics following water-removal. Saturation solubility and dissolution characteristics were investigated and compared to the un-milled commercial NIF to verify the theoretical hypothesis on the benefit of increased surface area. Crystalline state evaluation before and following particle size reduction was also conducted through differential scanning calorimetry (DSC) and powder X-ray diffraction (PXRD) to denote eventual transformation to amorphous state during the homogenization process. Through this study, they found that initial crystalline state is maintained following particle size reduction and that the dissolution characteristics of nifedipine nanoparticles were significantly increased in regards to the commercial product.

### 3.3 Review of Work Done for Nimodipine

**Yang et al**<sup>54</sup> developed a new solid self-microemulsifying drug delivery system (SMEDDS) for oral poorly water-soluble drugs such as nimodipine; and second, to evaluate its oral bioavailability in healthy rabbits. The liquid SMEDDS consisted of ethyl oleate, Labrasol, Cremophor RH 40 and nimodipine. The solid SMEDDS was prepared by spray-drying the liquid SMEDDS in a laboratory spray dryer, using dextran as solid carrier. Both DSC measurements and X-ray diffraction analysis suggested that nimodipine in the solid SMEDDS was in the amorphous or molecular dispersion state. In vitro dissolution test showed that the solid SMEDDS had a faster in vitro release rate than the conventional tablet. . AUC and C<sub>max</sub> after oral administration of the solid SMEDDS were 2.6- and 6.6-fold higher, respectively, compared with those of the conventional tablet. In vivo absorption study showed that presenting nimodipine in the form of solid SMEDDS kept the absorption enhancement as high as with liquid SMEDDS.. Thus, this solid selfmicroemulsifying system may provide a useful solid dosage form for oral poorly water-soluble drugs.

**Wang et al**<sup>55</sup> investigated the correlation between the growth behaviour and in-vitro dissolution rate of water-insoluble drugs prepared with high-shear wet granulation. Granules containing nimodipine, microcrystalline cellulose, low-substituted hydroxypropylcellulose and aqueous solution of hydroxypropylcellulose were prepared and the effects of independent process variables, including impeller speed and liquid-to-solid ratio were taken into consideration. The in-vitro dissolution rate of drug was high for the early stages of granulation and sharply decreased when coalescence and consolidation of granules started, approaching a flat and low level when granules were sufficiently consolidated. It was concluded that the dissolution properties of nimodipine basically correlated with the growth behaviour of granules in a high-shear mixer. The simulation method based on GSD can be used as a convenient and rapid way to predict the dissolution properties for formulation development and granulation optimization.

**Docoslis et al**<sup>56</sup> studied a series of solid dispersions of the drug nimodipine to increase the dissolution rate of a drug with low aqueous solubility, thereby improving its

bioavailability, using polyethylene glycol as carrier were prepared following the hot-melt method. They qualitatively and quantitatively characterize the solid state of a drug, as well as its dispersion physical form and spatial distribution in a polymer matrix (inert drug carrier). They found, in samples examined 6 months after preparation it was found that the drug crystals were mainly heterochiral. Examination of the same samples after 18 months of storage showed the presence of only homochiral crystals (mod II), indicating that this storage period was long enough for the transformation in the crystalline structure of the drug to occur.

**Ramana Murthy et al**<sup>57</sup> evaluated Modified gum karaya (MGK), as carrier for dissolution enhancement of poorly soluble drug, nimodipine (NM) The advantages of MGK over the parent gum karaya (GK) were illustrated by differences in the in vitro dissolution profiles of respective solid mixtures prepared by co-grinding technique. Their studies showed that, MGK could be used as a potential carrier in the dissolution rate enhancement of NM. Though there is no much difference in the crystallinity of NM in GK and MGK solid mixtures (as evident by DSC and XRD patterns), the dissolution rate of NM from solid mixture of GK, was low when compared with solid mixture of MGK. This may be due to the high viscosity generated by GK in the microenvironment of drug-carrier particle during dissolution reducing the diffusion rate of NM, there by decreasing the dissolution efficiency. Due to high viscosity and toughness of GK, it also posed processing problems during trituration.

**Murthy et al**<sup>58</sup> studied the influence of modified gum karaya (MGK) on the oral bioavailability of a poorly water-soluble drug, nimodipine (NM), in comparison with that of gum karaya (GK). The in vitro release rate of NM from both cogrinding mixtures was significantly higher than that of physical mixtures or pure NM. The in vivo study revealed that the bioavailability of NM from pure drug was significantly lower when compared to the cogrinding mixtures. The oral bioavailability was found to be NM powder < cogrinding mixtures of NM and GK < cogrinding mixtures of NM and MGK < NM solution. It can be inferred from the above results that MGK, an economical carrier, could be used for the dissolution enhancement of NM.

**Tang Xing et al**<sup>59</sup> studied mixture of Eudragit® EPO and polyvinylpyrrolidone/vinyl acetate copolymer (PVP/VA) (Kollidon VA64) as carriers, and a nimodipine solid dispersion (NM-SD) prepared by hot-melt extrusion (HME) to achieve high dissolution. In vitro dissolution of the water-insoluble drug NM was greatly enhanced by HME in the present study. DSC and PXRD have proved that NM is present in the carriers in an amorphous form. NM-SD tablets (NM-T-SD) was made by wet granulation and direct compression. The results showed that the dissolution of NM-T-SD was slightly reduced after 2 months storage (40°C, RH 75%), which implied that aging occurred to some degree. However, no NM crystals could be observed by PXRD after 2 months storage for NM-T-SD prepared by direct compression.

**Xing et al**<sup>60</sup> improved the dissolution and, therefore, bioavailability of the poorly water soluble and highly permeable drug nimodipine (NMD). They prepared of a solid dispersion (SD) consisting of NMD, Eudragit-E100 and Plasdone-S630 by hot-melt extrusion (HME) and compared with pure drug and physical mixture, the dissolution of NMD was enhanced dramatically (about 80% within 30 min). Adding the nimodipine solid dispersion (NMD-SD) powder to a mixture of Plasdone-S630 and PEG400, and then transferring it to hard HPMC capsules, resulted in nimodipine semi-solid capsules (NMD-SSC). The dissolution from NMD-SSC was increased further (about 95% in 20 min). In addition, the relative bioavailability of the NMD-SSC (test) and Nimotop® (reference) was determined in beagle dogs after a single dose (120mg NMD) in a randomized crossover, own-control study. The results suggested that there was no significant difference in the areas under the plasma concentration–time curve and the mean peak concentration between NMD-SSC and Nimotop® ( $P > 0.05$ ). However, the apparent rate of absorption of NMD from NMD-SSC ( $t_{max} = 1.3$  h) was markedly faster than that from Nimotop® ( $t_{max} = 3.1$  h) ( $P < 0.05$ ), which indicates that as a fast release preparation, NMD-SSC is well absorbed.

**Zheng et al**<sup>61</sup> investigated the in vitro dissolution properties and oral bioavailability of three solid dispersions of nimodipine. The solid dispersions were compared with pure nimodipine, their physical mixtures, and the marketed drug product

Nimotop®. Nimodipine solid dispersions were prepared by a hot-melt extrusion process with hydroxypropyl methylcellulose (HPMC, Methocel E5), polyvinylpyrrolidone/vinyl acetate copolymer (PVP/VA, Plasdone S630®), and ethyl acrylate, methyl methacrylate polymer (Eudragit® EPO). The dissolution profiles of the three dispersion systems showed that the release was improved compared with the unmanipulated drug. The mean bioavailability of nimodipine was comparable after administration of the Eudragit® EPO solid dispersion and Nimotop®, but the HPMC and PVP/VA dispersions exhibited much lower bioavailability. However, the AUC<sub>0–12 hr</sub> values of all three solid dispersions were significantly higher than physical mixtures with the same carriers and nimodipine powder.

**Shah et al**<sup>62</sup> improved solubility of nimodipine by complexation with cyclodextrin to modify the solubility and dissolution pattern and would enhance the physical characteristics like compressibility; which would be beneficial for tablet compression. Inclusion complexes were prepared by different techniques viz. physical mixing, kneading and co-precipitation; out of which co-precipitation technique was found most suitable. Dissolution behaviour of complexes was compared with pure drug, which revealed significant improvement in dissolution behaviour of the drug. The solubility of nimodipine improved linearly upon increasing the amount of methyl beta cyclodextrin.

**Weigen Lu et al**<sup>63</sup> prepared better tolerated injectable nimodipine nanosuspension compared with commercially available ethanol solution. In this study, nimodipine nanosuspension was prepared by high-pressure homogenization (HPH). The number of large particles in the nimodipine nanosuspension was much fewer than that of the fat emulsions for parenteral nutrition. And the saturation solubility was increased as the reduction of particle size into nanometer range, which led to the fast dissolution of drug nanocrystals. Irritability study in rabbits showed that this formulation provided less local irritation and phlebitis risks than the commercial ethanol product, which represented a promising new drug formulation for intravenous therapy of subarachnoid hemorrhage (SAH)-related vasospasm.

**Kachrimanis et al**<sup>64</sup> investigated the use of nimodipine–polyethylene glycol solid dispersions for the development of effervescent controlled release floating tablet formulations. The combination of experimental design and modern machine learning algorithms such as ANNs and GP showed increased prediction efficiency during the optimization procedure. It was found that nimodipine exists as mod I microcrystals in the solid dispersions and is stable for at least a three-month period. The tablets showed good floating properties and controlled release profiles, with drug release proceeding via the concomitant operation of swelling and erosion of the polymer matrix.

**Urbanetz and Lippold**<sup>65</sup> studied Solid dispersions of nimodipine and polyethylene glycol 2000. They found that the absence of crystalline drug material in solid dispersions containing nimodipine and polyethylene glycol 2000 is the prerequisite for a high dissolution rate and a remarkable supersaturation in the dissolution medium. Finally they conclude that the dissolution characteristics of nimodipine in water may be improved by the formation of solid dispersions with polyethylene glycol 2000 as carrier by the melting method.

**Urbanetz**<sup>66</sup> studied the solid dispersions of nimodipine and polyethylene glycol 2000 to prevent recrystallization for the development of thermodynamically stable solid solutions by using solvents aiming to enhance the solubility of nimodipine in the carrier material. Macrogol cetostearyl ether, macrogol glycerol monostearate, polysorbate 60, cetostearyl alcohol, glycerol monostearate and sodium lauryl sulphate as well as hydroxypropylcellulose, butylmethacrylat - (2-dimethylaminoethyl) methacrylatmethyl methacrylat - copolymer, polyacrylic acid, polyvinyl alcohol and povidone K17 were included in the study. It could be shown that povidone K17 effectively prevents recrystallization in solid solutions containing 20% (m/m) of nimodipine during storage at +25 °C over silica gel thereby ensuring a substantial increase in the dissolution rate and degree of supersaturation in water.

**Majahar et al**<sup>67</sup> studied the effect of  $\beta$ -cyclodextrin ( $\beta$ CD) on the aqueous solubility and dissolution rate of nimodipine. Phase solubility profiles indicated that the solubility of

nimodipine was significantly increased in the presence of  $\beta$ -cyclodextrin and was classified as  $A_L$ -type, indicating the formation of 1:1 stoichiometric inclusion complexes with a stability constant of  $572 \text{ M}^{-1}$ . In vitro studies showed that the solubility and dissolution rate of nimodipine significantly improved by complexation with  $\beta$ -cyclodextrin with respect to the drug alone and lends an ample credence for better therapeutic efficacy.

**Maysinger et al**<sup>68</sup> prepared nanocarrier based on  $A_2B$  type miktoarm polymers (A = polyethylene glycol (PEG); B= polycaprolactone (PCL)) for nimodipine (NIM). The  $A_2B$  star polymers were constructed on a core with orthogonal functionalities that facilitated the performance of “click” chemistry followed by ring-opening polymerization. These star polymers assemble into spherical micelles into which NIM can be easily loaded by the co-solvent evaporation method. The micelles obtained from the star polymer PEG7752ePCL5800 showed NIM encapsulation efficiency of up to 78 wt% at a feed weight ratio of 5.0%. The loading efficiency of the micelles was dependent on the length of the PCL arm in the  $A_2B$  miktoarm polymers. Aqueous solubility of NIM was increased by approx 200 fold via micellar encapsulation. The in vitro release of NIM from the micelles was found to occur at a much slower rate than from its solution. They also conclude that NIM-loaded miktoarm micelles could be useful in the treatment of neuroinflammation.

### 3.4 Review of Work Done for Nitrendipine

**Zhonggui He et al**<sup>69</sup> developed and evaluate the new solid self-emulsifying (SE) pellets of nitrendipine (NTD). The pellets were prepared via extrusion/spheronization technique, using liquid SEDDS (NTD, Miglyol® 812, Cremophor® RH 40, Tween 80, and Transcutol® P), adsorbents (silicon dioxide and crospovidone), microcrystalline cellulose and lactose. The resulting SE pellets with 30% liquid SEDDS exhibited uniform size (80-1000micron) and round shape, droplet size distribution following selfemulsification was nearly same to the liquid SEDDS (72±16nm and 64±12 nm). The in vitro release was similar for the two SE formulations (over 80% within 30 min), both significantly higher than the conventional tablets (only 35% within 30 min). The oral bioavailability was evaluated for the SE pellets, liquid SEDDS and conventional tablets in fasted beagle dogs. AUC of NTD from the SE pellets showed 1.6-fold greater than the conventional tablets and no significant difference compared with the liquid SEDDS. In conclusion, of the studies they illustrated that extrusion/spheronization technique could be a useful large-scale producing method to prepare the solid SE pellets from liquid SEDDS, which can improve oral absorption of NTD, nearly equivalent to the liquid SEDDS, but better in the formulation stability, drugs leakage and precipitation, etc.

**Cui et al**<sup>70</sup> prepared and characterized nitrendipine nanosuspensions to enhance the dissolution rate and oral bioavailability of this drug. Nanosuspensions were prepared by the precipitation–ultrasonication method. They found the particle size and zeta potential of nanocrystals were 209nm (±9 nm) and -13.9mV (±1.9 mV), respectively. The X-ray powder diffraction (XRPD) and differential scanning calorimetry (DSC) analysis indicated that there was no substantial crystalline change in the nanocrystals compared with raw crystals. The in vitro dissolution rate of nitrendipine was significantly increased by reducing the particle size. The in vivo test demonstrated that the  $C_{max}$  and  $AUC_{0\rightarrow 12}$  values of nanosuspension in rats were approximately 6.1-fold and 5.0-fold greater than that of commercial tablets, respectively.

**Sunada et al**<sup>71</sup> prepared solid dispersions (SD) of nitrendipine (NTD) using the meltmixing method with hydrophilic silica particles (Aerosil and Sylysia) with different

particle size and specific surface areas as carriers for enhancement of dissolution property. The dissolution property of NTD in the SDs was remarkably improved regardless of the grade of silica. At the end of the dissolution test (60 min) the concentrations of NTD for the SDs with Aerosil 200 and Sylysia 350 were 8.88 and 10.09m g/ml, corresponding to 28 and 31 times that of the original NTD crystals, respectively. The specific surface area and the adsorbed water amount of the SDs were also significantly improved. The rapid dissolution rate from the SDs was attributed to the amorphization of drug, improved specific surface area and wettability than the original drug crystals.

**Sunada et al**<sup>72</sup> studied solid dispersions (SDs) of nitrendipine (NTD), prepared with the Hypulcon pulse combustion dryer system, and the physicochemical properties of particles were compared with those of particles prepared with a spray dryer. The SD particles prepared with Hypulcon using Aerosil and Tween 80 as carriers showed improved properties over those prepared with a conventional spray dryer, such as smaller particle size, tighter particle size distribution, and no agglomeration. They showed that aerosil had greater ability to improve the dissolution of NTD than Sylysia and other polymers. The highest drug supersaturation concentration was maintained continuously during the dissolution test of the NTD–Aerosil SD prepared with 5% (v/v) Tween 80 solution using Hypulcon.

**Yong et al**<sup>73</sup> studied a significant increase in solubility and dissolution rate of nitrendipine, by inclusion complexation with hydroxypropyl- $\beta$ -cyclodextrin (HP- $\beta$ -CD). The solubility of nitrendipine increased linearly as a function of HP- $\beta$ -CD concentration, resulting in AL-type phase solubility diagram which revealed a formation of inclusion complex in a molar ratio of 1:1, with the apparent association constant of  $108.3 \text{ M}^{-1}$ . The AUC of inclusion complex was significantly larger than that of nitrendipine powder.  $T_{\max}$  of inclusion complex was significantly shorter and  $C_{\max}$  was significantly higher than those of nitrendipine powder.  $C_{\max}$  of physical mixture was higher than that of nitrendipine powder.  $T_{\max}$  of physical mixture, however, remained the same. The results

indicated that the bioavailability of nitrendipine could be improved markedly by inclusion complexation, possibly due to an increased dissolution rate.

**Zhonggui He et al**<sup>74</sup> develop stable parenteral submicron emulsion, to enhance the solubility of nitrendipine (NTD). The nitrendipine submicron emulsion (NTDSE) was prepared using egg lecithin, soybean oil, medium-chain triglyceride and oleic acid. The optimum formulation consists of NTD 0.1% (w/v), MCT 5% (w/v), LCT 5% (w/v), egg lecithin 1.2% (w/v), F68 0.3% (w/v), oleic acid 0.03% (w/v) and glycerol 2.5% (w/v). Results showed that stable NTDSE was developed with a mean size of  $154 \pm 21$  nm and a Zeta potential of  $-26.35$  mV. The submicron emulsion can maintain stable for at least 6 months at  $25^{\circ}\text{C}$  and 9 months at  $6^{\circ}\text{C}$ . The study demonstrated that NTDSE was successfully prepared with stable physicochemical properties.

**Cui et al**<sup>75</sup> investigated the effect of crystal size on the dissolution and oral absorption of nitrendipine. Five types of nitrendipine crystal suspensions with different particle sizes (200 nm, 620 nm, 2.7  $\mu\text{m}$ , 4.1  $\mu\text{m}$ , 20.2  $\mu\text{m}$ ) were prepared either by the precipitationultrasonication or the anti-solvent precipitation method. The result showed that the dissolution rate of nitrendipine was significantly increased by a reduction in particle size. From the simulated  $T_{50\%}$  values (50% dissolution time), the dissolution rates of crystals with particle sizes of 200 nm, 620 nm, 2.7  $\mu\text{m}$ , 4.1  $\mu\text{m}$  and 20.2  $\mu\text{m}$  were calculated to be  $5.1 \times 10^4$ ,  $1.0 \times 10^4$ , 237, 64 and 11-fold greater than that of the raw crystals and resulted in absolute bioavailability of 61.4%, 51.5%, 29.4%, 26.7%, 24.7%, respectively. The reduction in the drug particle size correlated well with incremental improvements in oral absorption. A good linear relationship was observed between the  $\text{Log}(T_{50\%})$  and the absolute bioavailability of nitrendipine.

**Fude Cui et al**<sup>76</sup> compared several methods of improving its dissolution rate of nitrendipine. Nitrendipine dispersions were prepared by micronization, solvent deposition, the solvent evaporation method, and the solvent evaporation-deposition method. The results obtained show that the nitrendipine dissolution rate could be markedly improved by micronization, deposition and solid dispersion preparation,

especially using the solvent evaporation-deposition method. The dissolution rate of nitrendipine was greatly improved in dispersions, particularly in the solid dispersions prepared by the solvent evaporation-deposition method, in which nitrendipine was present in amorphous form and the percentage of nitrendipine dissolved in the first 10 min was more than 80%.

**Zhixuan Wang et al**<sup>77</sup> studied the application of tertiary butyl alcohol (TBA) in the preparation of hydrophobic drug, ketoprofen and nitrendipine –hydroxypropyl b-cyclodextrin (HPbCD) complex. The data of differential scanning calorimetry (DSC) and X-ray diffractometry (XRD), showed that the drugs were amorphous in freeze-dried samples. Dissolution experiments showed that the hydrophobic drug dissolved rapidly from the HPbCD complex in both simulated gastric juice and simulated intestinal fluid. These results confirmed that this technique produced a hydrophobic drug–HPbCD complex. TBA was found to be a suitable freeze-drying medium for the preparation of hydrophobic drug–HPbCD complex.

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