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Effect of arginine hydrochloride and hydroxypropyl cellulose as stabilizers on the physical stability of high drug loading nanosuspensions of a poorly soluble compound

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Abstract

The objective of the present study is to formulate Naproxen nanosuspensions at high drug concentrations of up to 300 mg/ml using ball milling and is to investigate the additive effect between hydroxypropyl cellulose (HPC) and arginine hydrochloride as stabilizers. The nanosuspensions were obtained at different arginine hydrochloride/polymer weight ratios. Stability of Naproxen suspensions at 100 and 300 mg/ml was determined over a period of 14 days by measuring the particle size. The control, which contained only drug and buffers without the stabilizers agglomerated immediately after preparation. The study of the effect of arginine hydrochloride as a primary stabilizer indicated that arginine hydrochloride levels of up to 0.8% (w/v) were not able to help reduce particle size below one micron, and were also not able to provide stabilization to the suspensions on storage. Therefore, HPC was also added to the system to increase suspensions stability, presumably by a steric repulsion mechanism. When the Naproxen concentration was increased to 300 mg/ml, 1% (w/v) HPC was not able to provide good stabilization and it was found that arginine hydrochloride increased the stabilization efficiency of 1% (w/v) HPC by preventing flocculation. When HPC level was increased to 4% (w/v), HPC was high enough to sufficiently stabilize the nanosuspensions for 2 weeks and thereby could maintain the mean size diameter of the suspensions without the presence of arginine hydrochloride. Furthermore, stable nanosuspensions were successfully lyophilized without the use of additional cryoprotectants.

Keywords: Naproxen; Poorly soluble drug; Hydroxypropyl cellulose; Nanosuspensions; Arginine hydrochloride; Stabilizer

1. Introduction

Finely dispersed particles in an aqueous phase have a high tendency to agglomerate together leading to the formation of larger aggregates (Müller and Peters, 1998). Aggregation of the particles lowers the stability of nanoparticle systems and the crisis is even more severe when a suspension contains a high concentration of particles (Kai et al., 1996; Lieberman et al., 1998; Muller et al., 2000) and/or the particle size is in the nano-range. Currently, many researchers are facing the problems of stability of nanosuspension systems. The use of stabilizing agents is therefore necessary to overcome the stability problem of nanosuspensions.

In this study a novel approach was used to stabilize the nanoparticles in an aqueous suspension. The method is based on coating the particles with non-covalently (electrostatically and sterically) bound polymer and a cationic molecule, arginine hydrochloride. Based on the previous work in our lab, we observed the feasibility of using hydroxypropyl cellulose (HPC) and arginine hydrochloride as stabilizers for Naproxen nanosuspensions. HPC and cationic arginine hydrochloride were selected based on the study in which 100 mg/ml Naproxen suspensions containing 1% (w/v) level of HPC was able to prevent the particle size change in suspension during 25 days of storage and this is likely due to a better steric hindrance as compared to 1% (w/v) level of Tween 80, Pluronic F 68, and Pluronic F 108. Furthermore when HPC was used in combination with arginine hydrochloride, the mean particle size dropped to a range of 300–400 nm in which suspension containing both HPC and arginine hydrochloride were able to provide smaller particle size compared to those containing only HPC or combinations

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of HPC with other arginine hydrochloride peptides (di-, tri-, and tetra-arginine hydrochloride).

Currently, physically stable nanosuspensions containing poorly soluble drug concentrations between 10 and 100 mg/ml have been successfully formulated (Krause and Müller, 2001). Nanosuspensions of buparvaquone, a poorly soluble compound, were produced with the drug contents of 10, 25, and 100 mg/ml by high pressure homogenization. The nanosuspensions were then incorporated in mucoadhesive gels and it was found that nanosuspensions containing hydrogels were physically stable over a period of six months (Müller and Jacob, 2002). Ball milling is one of the currently used technologies for production of nanosuspensions. Nanocrystal® is a nano-milling method in which drug particle size in an aqueous suspension is reduced by a pearl mill containing glass or zirconium oxide pearls as milling media in order to obtain a nanosuspension (Muller et al., 2000).

In this study, Naproxen was used as a model drug and is (*S*)-2-(6-methoxynaphth-2-yl) propionic acid. It is an anti-inflammatory agent that can inhibit cyclooxygenase and reduce prostaglandin concentrations. It is a very poorly water-soluble drug and is very challenging to formulate a high dose of a poorly soluble compound like Naproxen.

The goal of this work was to investigate the production of nanosuspensions at high drug loading of up to 300 mg/ml using ball milling and the additive effect between HPC and arginine hydrochloride as stabilizers. This study deals with the optimization of nanosuspensions containing arginine hydrochloride, HPC, and combinations of arginine hydrochloride/HPC.

The benefit of high drug loading is that these suspensions studied are models of oral and/or parenteral suspensions. For oral formulations, the material could be processed further to have solid dosage forms for suspension, rapid disintegration or lyophilized for suspension. For example, nanosuspensions can be coated onto beads of suitable size, which can be incorporated into capsule or tablet forms, or nanosuspensions can be lyophilized and the powder can be incorporated into a granulation mixture during tablet granulation process.

To overcome the particle growth during long-term storage of nanosuspensions containing high drug concentrations, lyophilization was carried out in order to assess the feasibility of transferring nanosuspensions in a dry product (Krause and Müller, 2001).

2. Materials and methods

2.1. Materials

Naproxen USP 24 was purchased from Kalchem International (Lindsay, OK). Hydroxypropyl cellulose (Klucel® type EXF) was obtained from Aqualon (Wilmington, DE). L-Arginine hydrochloride was purchased from Sigma-Aldrich (St. Louis, MO). All the other chemicals were purchased from Sigma-Aldrich (St. Louis, MO) and were of analytical grade.

2.2. Preparation of colloidal suspensions

Naproxen, hydroxypropyl cellulose, arginine hydrochloride, grinding beads, and sodium citrate buffer solution were weighed for each of the suspension. Two different Naproxen concentrations of 100 and 300 mg/ml were used. The grinding media used was 0.8 mm Yttria-Doped zirconium beads (product no. 1001124KG, Performance ceramics company, Peninsula, OH). The mixture was added to the ceramic jar (Advanced ceramic technology, Orange, CA, outside diameter of 1.5 cm, inside diameter of 1.1 cm, and inside depth of 2.2 cm. This gives a total volume of about 2 ml to the jar). Particle size reduction was optimized with respect to milling time, total volume in the jar, and size and amount of grinding media which consisted of zirconia grinding beads. Based on the optimized conditions, the typical parameters were (i) volume of jar = 2 ml, (ii) volume of media (with drug) = 1 ml of 10 mM citrate/HCL buffer, (iii) weight of grinding beads = 3 g, (iv) milling speed = 400 rpm (centrifugal ball mill, S100 Retsch, Christison Scientific, Germany), (v) milling processing time = 1 h. Milling was carried out under ambient conditions. The suspension was buffered to a pH of 3 using 10 mM of sodium citrate/hydrochloric acid buffer to keep the surface of the Naproxen particles poorly ionized to minimize crystal growth in the formulated suspensions due to Oswald ripening, and to help maintain the stability. In each of these suspensions, different concentrations of arginine hydrochloride (0, 0.1, 0.2, 0.4, 0.8 and 1.2% w/v) and HPC (0, 1, and 4% w/v) were added. After milling, the suspensions were evaluated visually for agglomeration. Only those suspensions that were not obviously agglomerated based on visual evaluation were pipetted out from the grinding beads and were subject to particle size analysis.

2.3. Particle size analysis

Particle sizing was performed using the N4MD coulter submicron particle analyzer. The settings were as follows; scattering angle = 90 °C, temperature = 25 °C, medium refractive index = 1.33, and measurement time = 30 s. Samples of 20 μl of 100 mg/ml and 7 μl of 300 mg/ml Naproxen suspensions were pipetted and diluted with 10 ml of deionized water. The diluted nanosuspensions were sonicated briefly (typically for 15–30 s) prior to size analysis to disperse any aggregates. The mean particle size and standard deviation were calculated based on the particle size values of three measurements.

2.4. Stability studies of the suspensions

The physical stability of the suspensions was evaluated after 0, 1, and 2 weeks of storage. The suspensions were kept in a closed clear glass vial and stored at 5 °C. The suspensions were stored at low temperature to avoid any bacterial growth since they were not preserved. At the pre-determined time, aliquots were taken and subjected to particle size analysis, as described above. The 2 week evaluation of suspension stability was performed to evaluate whether the suspensions were sufficiently stable for further processing into the lyophilized form.

In order to assess the feasibility of lyophilization and subsequent stability, aliquots of selected suspensions were lyophilized. The samples were frozen at −70 °C, and then lyophilized using a lyophilizer (Unitor 200, Virtis research equipment, Gardiner, New York) at a controlled temperature of −40 °C and the pump operating at a pressure of 60 mTorr over a period of 48–72 h. The lyophilized samples were stored at room temperature for 1 month before particle size measurement.

2.5. *In vitro* dissolution study

A Spectapor membrane (cut-off: 6–8000 Da) was used as a dialysis system to study the dissolution of Naproxen from nanosuspensions. A 100 mg/ml nanosuspension, equivalent to 5 mg Naproxen, was filled in the dialysis bag having 5 in. length and 23 mm diameter. Nanosuspensions that were stable for 2 weeks as indicated by no significant change in particle size were subjected to *in vitro* dissolution. For dissolution, the nanosuspensions were freshly prepared and tested within 24 h of preparation. The unmilled suspension and a clear solution of Naproxen in methanol:HCl were used as controls. The dialysis bag was placed in a 120 ml clear glass container, containing 75 ml of 0.1 M HCL solution. This container was placed in the incubator at 37 °C on a rotary shaker and shaken at 100 rpm to give the system a gentle stirring. At 15, 30, 60, 120, 240, 480, and 1260 min, 10 ml of the dialyzate was withdrawn for the drug content analysis and was replaced by equal volume of dissolution medium. The dialyzate was then subject to the UV analysis against the blank (0.1 M HCL solution). Percent cumulative release of Naproxen was calculated based on the standard UV calibration curve at 270 nm (Eerikäinen et al., 2004). Lack of interference from HPC and arginine hydrochloride was verified by running samples containing these analytes in control samples.

3. Results and discussion

Naproxen is a very hydrophobic compound and disperses poorly in water (Sangalli et al., 2001). Thus, it is challenging to enhance the dispersion of Naproxen particles in an aqueous solution. Naproxen, which has a pK_a of 4.2, can fully ionize under basic conditions, and can have significantly higher solubility as compared with conditions of acidic pH, especially when the pH of the medium is well below the pK_a of the drug (Somasundaram et al., 1997). In this study, the method employed involved steric and/or electrostatic coating of the particles with a cationic molecule, arginine hydrochloride. An effective stabilizer should be able to wet the drug particles and provide sufficient steric and/or electrostatic barrier to the drug particles in order to prevent aggregation with time.

This study examined the additive effect between arginine hydrochloride and HPC as they provide different energy barriers and these barriers may be electrical (in case of arginine hydrochloride) or non-electrical in nature. In general, macromolecular compounds, like HPC, and positively charged arginine hydrochloride are expected to adsorb onto the particle surface mainly by steric and electrical interactions, respectively.

The suspension containing 100 mg/ml Naproxen only, without any stabilizer, showed rapid agglomeration immediately after preparation. The agglomeration of Naproxen particles is not just due to the attractive forces between the particles in the absence of significant energy barrier. Much more importantly, it is a result of the so-called "hydrophobic effect". The presence of hydrophobic particles or molecules in water causes distortion and re-arrangement of hydrogen bondings in the aqueous medium; therefore, greatly increasing the free energy of the system. As a result, these hydrophobic particles tend to agglomerate to reduce the system free energy. The addition of arginine hydrochloride to this suspension at the concentrations of 0.1, 0.2, 0.4, and 0.8% (w/v), resulted in agglomerated material that could not be dispersed with sonication due to high air entrapment. This was observed immediately after the grinding process was finished. This agglomeration indicated that these arginine hydrochloride concentrations were not able to act as a good stabilizer for the suspensions. The suspension containing 1.2% (w/v) arginine hydrochloride showed good dispersion for at least 2 weeks. This suspension was observed visually and found to be a free-flowing material after freshly prepared, 1 week, and 2 week time periods. However, its particle size measured immediately after grinding was larger than 1000 nm. All these low concentrations studied, arginine hydrochloride was not able to reduce the particle size to a nano-range. Arginine hydrochloride, at these levels, is not sufficient to stabilize Naproxen suspensions. It can be suggestive of the fact that arginine hydrochloride by itself cannot produce sufficient electrostatic repulsion to prevent particle agglomeration.

The effect of arginine hydrochloride as a secondary stabilizer in 100 mg/ml Naproxen suspensions was investigated when 1% (w/v) HPC and 4% (w/v) HPC were used as primary stabilizers. Suspensions containing 1% (w/v) HPC along with the different concentrations (0, 0.1, 0.2, 0.4, 0.8, and 1.2% w/v) of arginine hydrochloride as a secondary stabilizer, gave a particle size in the range of 320–500 nm after 2 weeks of storage (Fig. 1). It is likely that there was no effect of arginine hydrochloride concen-

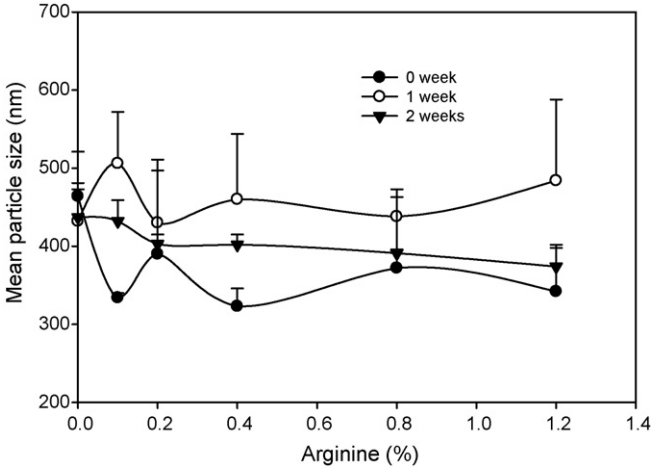

Fig. 1. Effect of arginine hydrochloride concentrations on the particle size of 100 mg/ml Naproxen nanosuspensions at 1% (w/v) HPC. (Error bars are standard deviations of three replicates.)

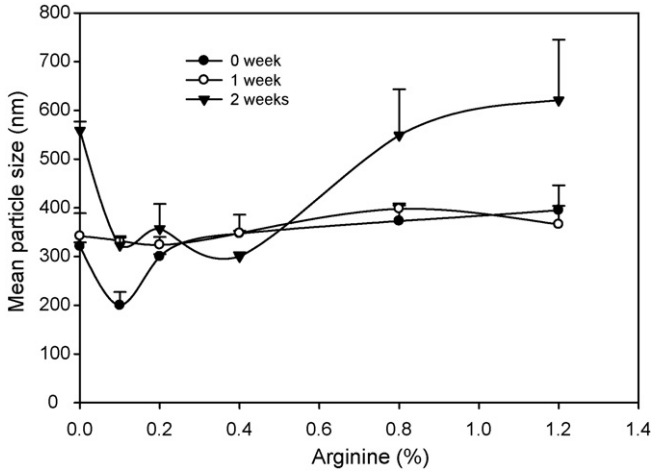

Fig. 2. Effect of arginine hydrochloride concentrations on the particle size of 100 mg/ml Naproxen nanosuspensions at 4% (w/v) HPC. (Error bars are standard deviations of three replicates.)

trations on particle size. All of the formulations were relatively stable over a period of 2 weeks and 1% (w/v) HPC concentration was enough to stabilize and produce suspensions in a nano-range.

When the concentration of HPC was increased from 1 to 4% (w/v), particle size in the range of 200–600 nm was observed after 2 weeks of storage. Addition of arginine hydrochloride is likely to have no further effect on the particle size of Naproxen suspensions. This means that 1 and 4% (w/v) HPC can produce and stabilize 100 mg/ml of Naproxen suspensions without the presence of arginine hydrochloride (see Fig. 2).

Naproxen concentration was increased three-fold for the next study. The control suspension of 300 mg/ml Naproxen, which contained only drug, agglomerated immediately after preparation. This agglomeration was likely due to particle collisions in the absence of energy barrier. When arginine hydrochloride was added in different concentrations (0.1, 0.2, 0.4, 0.8, and 1.2% w/v), all the suspensions agglomerated immediately after preparation at 5 °C. None of the arginine hydrochloride concentrations was able to prevent agglomeration, or reduce the drug particle size into a nano-range. Thus, incorporation of HPC in the formulations was necessary for suspensions containing a high dose of Naproxen.

Results of the addition of 1% (w/v) HPC along with arginine hydrochloride in the suspension formulations is shown in Table 1. At time zero, suspensions containing 1% (w/v) HPC with 0, 0.1, 0.2, 0.4, 0.8, 1.2% (w/v) arginine hydrochloride gave the particle size in the range of 410–780 nm. Agglomeration was observed in the suspensions with low arginine hydrochloride concentration after 1 week of storage. Suspensions with high arginine hydrochloride concentration of 0.8 and 1.2% (w/v) were stable even after 2-weeks of storage. It implies that the addition of arginine hydrochloride to the dispersion was likely to increase the stability of nanosuspensions. The 0.8 and 1.2% (w/v) of arginine hydrochloride levels are likely to provide significant electrostatic repulsion between the particles. This, in addition to steric effect from the polymer helps prevent aggregation of the 300 mg/ml drug concentration suspension for 2 weeks.

Table 1
Effect of particle size with different concentrations of arginine hydrochloride at 300 mg/ml Naproxen in suspensions containing 1% (w/v) HPC

Arginine hydrochloride (% w/v)	Time (weeks)	Mean suspension particle size (nm)	S.D.
0	0	460	19
	1	>1000	na
	2	>1000	na
0.1	0	417	129
	1	>1000	na
	2	>1000	na
0.2	0	791	76
	1	>1000	na
	2	>1000	na
0.4	0	777	146
	1	>1000	na
	2	>1000	na
0.8	0	528	79
	1	494	24
	2	455	15
1.2	0	536	90
	1	328	62
	2	354	76

When the concentration of HPC was increased from 1 to 4% (w/v) (Fig. 3), there was no increase in particle size and a good stability was observed over a period of 2 weeks at 5 °C. The particle size in the range of 300–600 nm particle size was detected at all arginine hydrochloride concentrations studied under these conditions. The result indicated that only 4% (w/v) HPC concentration, without addition of arginine hydrochloride, is enough to stabilize 300 mg/ml Naproxen nanosuspensions for 2 weeks.

The arginine hydrochloride concentrations used in this study (0.1, 0.2, 0.4, 0.8, and 1.2% w/v) were not high enough to prevent agglomeration and reduce the drug particle size in the suspensions when there was no polymer in the system. In addition to

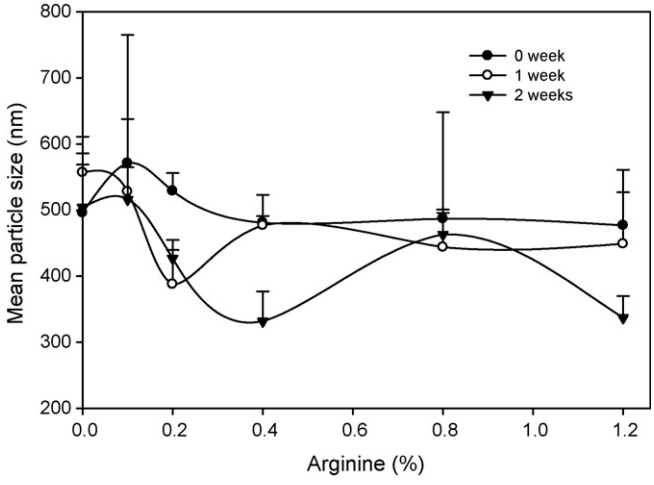

Fig. 3. Effect of arginine hydrochloride concentrations on the particle size of 300 mg/ml Naproxen nanosuspensions at 4% (w/v) HPC. (Error bars are standard deviations of three replicates.)

the hydrophobic effect, there is a balance between repulsive and attractive potential energies of Naproxen particles. The concentration of arginine hydrochloride used has to overcome the Van Der Waals interparticle forces or attractive interactions between the particles in order to disperse the particles. This means that repulsive interactions must be greater than the attractive interactions. It implies that electrostatic repulsion alone was likely not enough to stabilize Naproxen nanosuspensions at the high drug concentrations (300 mg/ml).

It was found that the use of nonionic HPC was essential to stabilize nanosuspensions. The mechanism of the adsorption of HPC is likely by the formation of steric barriers. Steric barriers are produced when the adsorbed polymer extends its chain to the water phase, which helps maintaining the distance between closely approaching solid particles.

However, when the drug concentration was increased to three times, lower HPC concentration (1% w/v) was not enough to prevent the agglomeration, the addition of arginine hydrochloride to the dispersion generally increases the stability of the nanosuspensions. The adsorption of arginine hydrochloride onto the particles is likely to raise the amount of positive charge on the surface. In this case, it could enhance the repulsion and dispersion of the dispersed particles in the aqueous system. It can be seen that 0.8 and 1.2% (w/v) arginine hydrochloride when combined with HPC are likely to give enough electrostatic repulsion and steric barrier to prevent aggregation of the very high drug concentration suspension.

Lyophilization is another approach to overcome stability problems of nanosuspension of poorly soluble drugs. The drug can be converted into a dry form; thus increasing a storage-shelf life (Jacobs et al., 2001). In this study, nanosuspensions found to be stable based on particle size measurements were lyophilized immediately after production, and then stored at room temperature for 1 month. After one month, the lyophilized powder was reconstituted in deionized water, and sonicated prior to measurement of the particle size. After 1 month, all the lyophilized particles completely re-dispersed and gave the particle size close to their original size between 300 and 600 nm (Figs. 4–6). As shown in Fig. 4, the nanoparticles containing 1% w/v HPC had a mean particle size of 470 nm before lyophilization, and a mean size of 480 nm after re-suspension of the lyophilized particles in deionized water. Based on these results, in both concentrations of Naproxen (100 mg/ml and 300 mg/ml), the suspensions, with or without arginine hydrochloride, were successfully lyophilized in the absence of additional cryoprotectors.

There are three main steps for lyophilization: freezing, sublimation, and elimination of unfrozen and adsorbed water (Zingel et al., 1996). During the lyophilization process, nanoparticles are likely to agglomerate and are not able to return to their original size upon reconstitution. Thus, the use of a cryoprotector is crucial to protect nanoparticles from undergoing changes during lyophilization. Some examples of cryoprotectors include materials such as sugars, sugar alcohols, low molecular weight polyvinylpyrrolidone, and its derivatives. In our studies, HPC at 1 and 4% (w/v) levels in the suspensions studied were able to prevent adverse circumstances for Naproxen nanoparticles during lyophilization process.

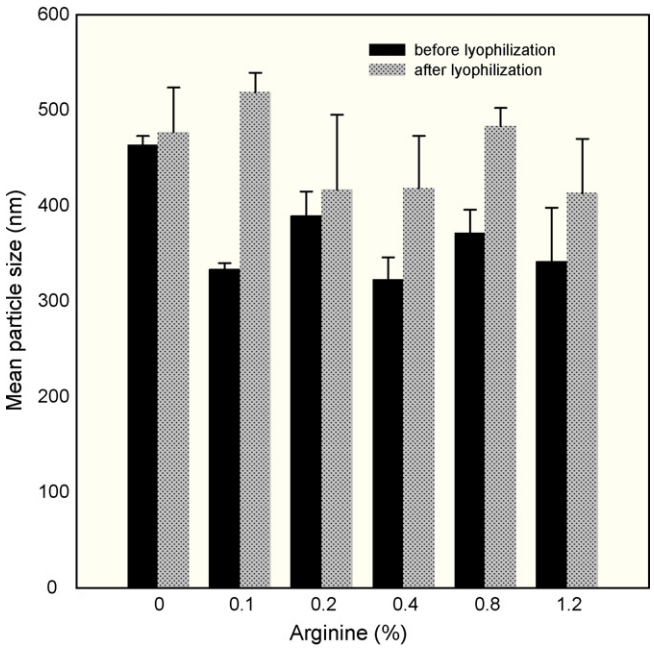

Fig. 4. Particle size of 100 mg/ml Naproxen nanosuspensions at 1% (w/v) HPC. Particle size was measured before lyophilization (control) and after lyophilization and subsequent rehydration. (Error bars are standard deviations of three replicates.)

The *in vitro* dissolution of a drug is an indirect method to predict its bioavailability from a formulation (Kipp, 2004; Tiyaboonchai and Limpeanchob, 2007; Wu et al., 2004). The development of a clinical nano-formulation of poorly soluble MK-0869, a potent substance P antagonist, showed that the nanoparticle formulation increased bioavailability and elimi-

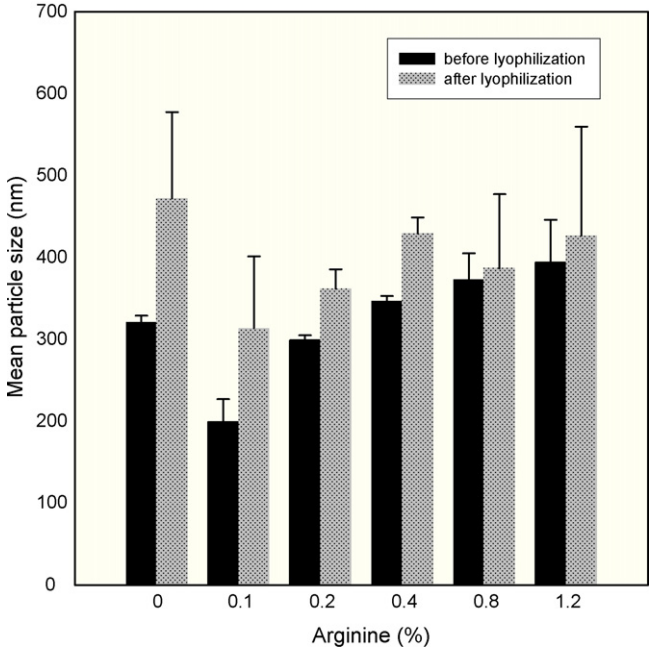

Fig. 5. Particle size of 100 mg/ml Naproxen nanosuspensions at 4% (w/v) HPC. Particle size was measured before lyophilization (control) and after lyophilization and subsequent rehydration. (Error bars are standard deviations of three replicates.)

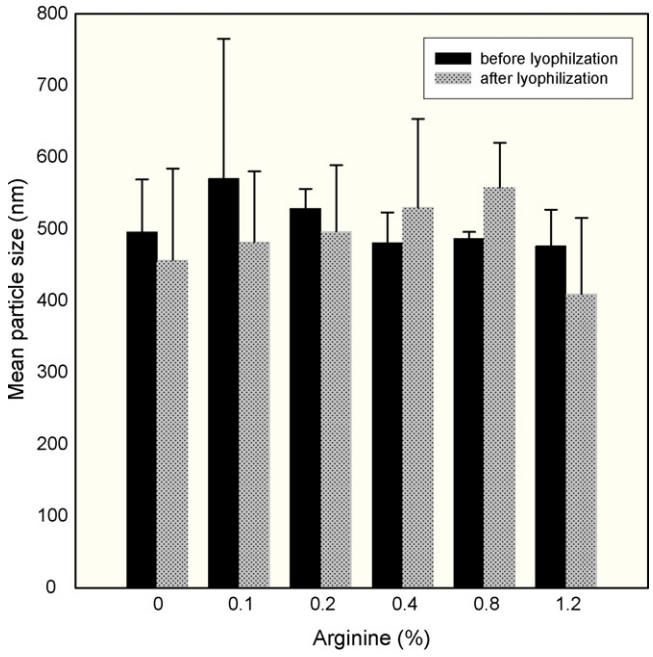

Fig. 6. Particle size of 300 mg/ml Naproxen nanosuspensions at 4% (w/v) HPC. Particle size was measured before lyophilization (control) and after lyophilization and subsequent rehydration. (Error bars are standard deviations of three replicates.)

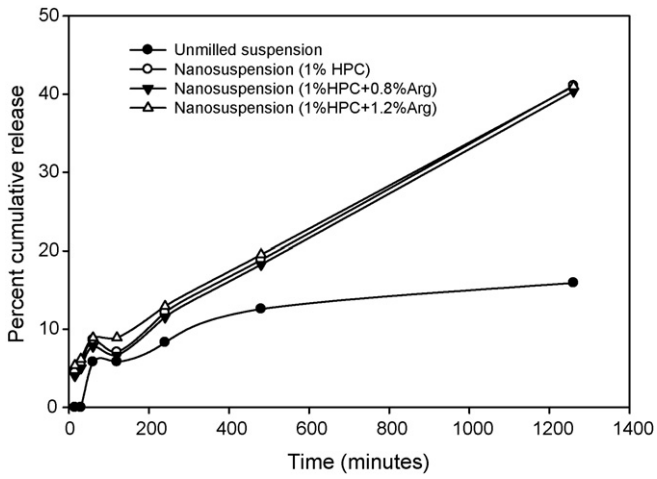

Fig. 7. Dissolution profiles of 100 mg/ml Naproxen nanosuspensions immediately post-milling. Hydrochloric acid (0.1 M) was used as the dissolution medium. Each data point is an average of three determinations. Typical standard deviations ranged between 0.01 and 0.70 and have been left out for clarity.

nated food effect on absorption compared with the conventional micronized formulation (Wu et al., 2004). The MK-0869 NanoCrystal® colloidal dispersion was prepared using a ball milling method (Liversidge and Cundy, 1995) with 4% hydroxypropyl cellulose, 0.08% SDS, and 20% sucrose as stabilizers at a drug concentration of 50 mg/ml in water (Wu et al., 2004). In our studies, we wanted to look at similar effect of particle size change.

The effect of naproxen particle size, HPC and arginine hydrochloride on the drug dissolution was examined for freshly prepared Naproxen nanosuspensions containing 100 mg/ml of drug. The unmilled control suspensions, containing no stabilizer, showed the slowest drug dissolution profile as compared to the others as shown in Fig. 7. From all other nanosuspensions, other than control, approximately 45% (w/v) of the Naproxen was in the solution at the end of the dissolution study from the nanosuspensions containing 1% (w/v) HPC, 1% (w/v) HPC with 0.8% (w/v) arginine hydrochloride, and 1% (w/v) HPC with 1.2% (w/v) arginine hydrochloride. The dissolution of the drug from the control suspension was less than 15% (w/v). Another observation from the dissolution data is that at initial time points of up to 60 min, there is no significant difference in apparent dissolution rates of milled and unmilled suspensions. One possible explanation for this is that there is contribution from Naproxen that is already in solution at time zero, and is released into the dissolution medium over the first 60 min. Following this initial time period, the slopes of the curves for milled suspensions are significantly higher from that of unmilled suspension. No difference was observed between nano-suspensions containing only HPC or the ones containing HPC and arginine. This could indicate that the observed differences in dissolution rates of nano-suspensions from unmilled suspension are not due to the presence of arginine, but due to the smaller particle size.

In order to verify the effect of drug solution to the observed burst effect, we carried out a dissolution experiment with the solution of Naproxen in the bag. The data is shown as inset in Fig. 7. As is evident from the inset of Fig. 7, the equilibration time for Naproxen under the dissolution studies is about 60 min, which agrees with the burst effect time in dissolution data. Based on the mathematical treatment of such data by Washington (1990), for a slow release process, the dissolution proceeds rapidly compared with the release rate from the dialysis bag. In such a case a saturated solution is maintained in the dialysis bag and the resulting curve after the initial burst effect is linear with time indicating a zero order process. Indeed, this is what is observed for the milled samples. However, for the unmilled drug, the curve is not linear after the burst effect but has a decreasing slope with time. This indicates that the dissolution in the bag is not fast enough to maintain a saturated drug concentration, resulting in progressively decreasing rate of release from the bag.

Initially, dissolution studies were carried out at pH 4–5 (data not shown). No significant difference in the release profile were observed at these high pH values, presumably due to ionization of Naproxen resulting in higher solubility. Therefore, the pH value of 1 was chosen to have lower solubility of the drug, thereby allowing the differences in dissolution rate to be observed. The milled samples contain HPC and it could be argued that the polymer could enhance the total solubility of the drug due to surfactant action. We believe that this effect is likely not significant because the initial burst effect during the first 60 min is the same for the unmilled and milled drug, indicating the presence of the same amount of dissolved drug in the system. Subsequent to the burst effect, the curves deviate due to different rates of dissolution.

L-Arginine has been shown to enhance Naproxen dissolution in the investigation on the effect of hydroxypropyl-b-

cyclodextrin and a series of amino acids on the Naproxen aqueous solubility. It has been shown that L-arginine was the most effective basic additive that can increase the intrinsic solubility of Naproxen and can increase the cyclodextrin solubilizing power toward the drug, presumably as a result of the effect of salt formation and inclusion complexation (Mura et al., 2003). The role of L-arginine in enhancing the dissolution properties of Naproxen was further investigated by Mura et al. (2005). The result of these solid state studies showed strong interactions between Naproxen, L-arginine, and cyclodextrin in the systems obtained by cogrinding or coevaporation. The dissolution results indicated that Naproxen–arginine binary system has better dissolution than Naproxen–cyclodextrin systems. This means that salt formation is more successful than complexation method in increasing drug dissolution. Additional studies showed that arginine is likely to interact with cyclodextrin via hydrogen bonding and the drug via electrostatic interactions and salt formation (Berge et al., 1977; Laveneziana et al., 1996). In all of these studies, arginine was used as a base. In our studies, we used the hydrochloride salt of arginine at relatively low pH values of the system. This could explain the lack of help from arginine to the rate of dissolution.

4. Conclusions

Arginine hydrochloride cannot stabilize Naproxen nanosuspensions when used as a primary stabilizer. However, when used as secondary stabilizer in addition to HPC, arginine hydrochloride significantly enhanced the effect of HPC on Naproxen nanosuspension stability. The use of HPC at concentrations of 1% (w/v) or higher is necessary to stabilize Naproxen nanosuspensions containing 100 mg/ml drug. However, when the concentration of Naproxen was increased from 100 to 300 mg/ml in the nanosuspensions, 1% (w/v) HPC alone cannot prevent particle aggregation or growth. Addition of 0.8 and 1.2% (w/v) arginine hydrochloride to this system significantly improved the stability over a period of 2 weeks. Advantages of aqueous based nanotechnology systems include the ease of manufacturing without using any organic solvents. Furthermore, stable nanosuspensions can be successfully lyophilized without the use of additional cryoprotectants. While the stability data over a period of 2 weeks for suspensions and 1 month for lyophilized materials is promising, long-term stability studies will be needed to determine whether the lyophilized Naproxen nanosuspensions have an acceptable shelf life.

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