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A comparative study of top-down and bottom-up approaches for the preparation of micro/nanosuspensions

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ABSTRACT

Nano-sizing offers a promising method for the formulation of poorly aqueous soluble compounds. Nanosuspensions can be prepared by top-down or bottom-up approaches. The different conditions encountered in these two approaches can greatly affect nanosuspension characteristics. In this study, milling via microfluidization and precipitation via sonication were compared to study their effects on the formation and stability of ibuprofen nanosuspensions. Various stabilizers (SLS, PVP K-30, Pluronic F-68 and F-127, Tween 80 and different hydroxypropyl methylcelluloses (HPMCs)) were evaluated. Both processes resulted in a similar trend in the initial particle size and comparable short-term physical stability of suspensions. Of all the stabilizers investigated, the HPMCs were the most effective both in terms of particle size reduction and short-term physical stability. Differences in stabilizer efficacy were observed between the two processing methods. The initial particle size of the suspensions prepared using microfluidization correlated with the solubility of ibuprofen in the respective stabilizer solutions. Whereas, the initial particle size of suspensions prepared using precipitation under sonication correlated with the HLB values of the stabilizers. The solubility of ibuprofen in the stabilizer solution also played a significant role in the increase in particle size on storage, indicating Ostwald ripening.

1. Introduction

Recent advances in synthetic, analytical and purification chemistry along with the development of specialized tools such as high throughput screening, combinatorial chemistry and proteomics have lead to a sharp influx of discovery compounds entering in to development. Many of these compounds are highly lipophilic, since the *in vitro* screening techniques place considerable emphasis on interaction of the compounds with defined molecular targets (Lomabardino and Lowe, 2004). Hydrophilicity and lipophilicity are two contradicting and often competing prerequisites necessary for the success of an experimental molecule as a commercial drug. Although high lipophilicity helps in transporting molecules across biological membranes and plays an important role in its biological activity and metabolism, it also renders the compound water insoluble (Lewis et al., 2004). Poor aqueous solubility is one of the major hurdles in the development of new compounds into oral dosage forms, since dissolution is the first step in the absorption of the drugs (Lipinslki, 2002).

Poorly soluble molecules have been successfully formulated by employing a variety of techniques such as: (i) solubilization in surfactant solutions; (ii) use of cosolvents; (iii) pH adjusted solutions; (iv) emulsions; (v) liposomes; (vi) complexation with cyclodextrins; and (vii) solid dispersions (Kesisoglou et al., 2007; Patravale et al., 2004). However, most of these techniques require a large amount of additives limiting their use from the safety perspective. Moreover, these techniques offer little or no help in the formulation of molecules that are poorly soluble in both aqueous and non-aqueous solvents (Rabinow, 2004). Nanosuspensions by the virtue of their large surface area to volume ratio provide an alternative method to formulate poorly soluble compounds. Nanosuspensions are sub-micron colloidal dispersions of discrete particles that have been stabilized using surfactants, polymers or a mixture of both.

Nanosuspension preparation can be broadly classified into two categories: (i) top-down processes and (ii) bottom-up processes. Top-down processes consist of particle size reduction of large drug particles into smaller particles using various wet milling techniques such as: media milling, microfluidization and high pressure homogenization. No harsh solvents are used in these techniques. However, all media milling processes involve high energy input and are highly inefficient (Parrot, 1990). Considerable amount of heat is generated in these operations making processing of thermolabile materials difficult. In the bottom-up approach the drug is dissolved in an

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organic solvent and is then precipitated on addition of an anti-solvent in the presence of a stabilizer. Various adaptations of this approach include: (i) solvent–anti-solvent method; (ii) supercritical fluid processes; (iii) spray drying; and (iv) emulsion–solvent evaporation (Date and Patravale, 2004; Rabinow, 2004).

The method of manufacture can significantly impact the formation and stability of nanosuspensions and hence their overall performance (Parsons et al., 1992; Phillips and Bryon, 1994; Williams et al., 1999). In the top-down process considerable heat is generated which may cause degradation of heat sensitive active pharmaceutical ingredients (APIs). Milling has been shown to cause mechanical activation at drug particle surfaces (Hütterauch et al., 1985). Crystal defects due to disordering of the crystal surface and generation of localized amorphous regions have been implicated in increased surface energetics (Heng et al., 2006). Reordering of crystal defects and re-crystallization of amorphous regions has resulted in both physical and chemical instability of processed materials on storage. Joshi et al. (2002) observed an increase in the specific surface area of budesonide on storage after micronization. Temperature dependent stress relaxation by intra-particle crack formation, crack propagation with time and particle fracture was proposed as a likely mechanism for increased surface area. On the other hand agglomeration of micronized revatropate hydrobromide on storage was attributed to the re-crystallization of disordered regions generated during micronization (Ticehurst et al., 2000).

Alternatively, the bottom-up process can adversely influence nanosuspension formulations as well by the generation of various unstable polymorphs, hydrates and solvates during processing. These approaches involve the use of solvents which are usually difficult to completely remove (Patravale et al., 2004). Any residual solvent can cause physical and chemical instability of the formulation. Moreover, bottom-up approaches usually result in needle shaped particles due to rapid growth in one direction which influences the physical stability of the nanosuspensions (Rabinow, 2004).

The aim of this study was to compare top-down and bottom-up approaches and evaluate the effect of the processing method and stabilizer suitability on nanosuspension preparation and stability. Ibuprofen was chosen as a model drug. The various stabilizers investigated were: sodium lauryl sulfate (SLS), polyvinyl pyrrolidone (PVP K-30), Pluronic F-68 and F-127, Tween 80 and different grades of hydroxypropyl methyl celluloses (HPMCs). The potential for Ostwald ripening of the suspensions was evaluated by conducting short-term stability studies following storage at 4 and 25 °C. Microfluidization and precipitation under sonication were used for nanosuspension preparation. In the microfluidization process, a sample dispersion of large particles (macro-suspension) is made to pass through specially designed interaction chambers at high pressure. In the interaction chambers the liquid feed is divided into two parts which are then made to impinge against each other and against the walls of the chambers. Particle size reduction occurs due to attrition between the particles and against the chamber walls at high velocities. Cavitation fields generated inside the chambers also contribute to particle size reduction. Microfluidization causes minimal contamination of the product and can be easily scaled up (Illig et al., 1996). Precipitation under sonication is a bottom-up approach in which ultrasonication is applied during the precipitation of water insoluble drugs. In this technique an organic solution of the drug is added to an aqueous solution of stabilizer, under sonication, to precipitate the drug. The presence of the appropriate stabilizer in the solution prevents rapid particle growth, which results in particles of very small size. Rapid precipitation often generates needle shaped particles which are more friable than those obtained by crystallization. Cavitation fields developed due to ultrasonication assist in generating nanoparticles in several ways such as: (i) creating turbulent flow conditions inside the system ensuring efficient mixing; (ii) atomization of organic solutions of the drug, during addition into the aqueous stabilizer solution, into very fine droplets resulting in precipitation of fine particles; and (iii) particle size reduction of the newly formed particles.

2. Materials and methods

2.1. Materials

Ibuprofen USP, 2-[4-(2-methylpropyl) phenyl] propanoic acid, was purchased from PCCA (Houston, TX). Methocel (hydroxypropyl methylcellulose) E5, E3, E15, K3 and A15 premium LV grades, were generously gifted by Dow Chemical Company (Midland, MI). Glycerin USP was purchased from PCCA (Houston, TX). Pluronic F-68 (poloxamer 188), Pluronic F-127 (poloxamer 407) and kollidon 30 (PVP K-30) were purchased from BASF (Parsippany, NJ). Sodium lauryl sulfate (SLS) was purchased from Sigma–Aldrich (St. Louis, MO). Tween 80 was purchased from Fisher Chemical Company (Fair Lawn NJ).

2.2. Preparation of nanosuspensions

2.2.1. Bottom-up process

Precipitation under sonication was used to prepare ibuprofen suspensions. Briefly 1 g of ibuprofen was dissolved in 2 ml of acetone to prepare an organic solution of ibuprofen. 250 μl of this solution was injected into 25 ml of 0.5% (w/v) of stabilizer solution maintained at 5 °C under stirred conditions. Continuous sonication was applied via the probe sonicator (Model 550 Sonic Dismembrator, Fisher Scientific) for the initial 5 min followed by intermittent sonication of 10 s after every 10 s interval to a total sonication time of 1 h. The suspensions were kept under vacuum at room temperature for 1 h to remove the acetone.

2.2.2. Top-down process

Microfluidization was used as a top-down process for the preparation of ibuprofen nanosuspensions. 0.5 g of ibuprofen was dispersed in 100 ml of 0.5% (w/v) stabilizer solution using mechanical stirring to form a macro-suspension of the drug. The macro-suspension was homogenized at 10,000 rpm for 10 min using a PowerGen 700 D (Fisher Scientific) lab homogenizer to break any lumps of drug that may be present in the macro-suspension. Particle size reduction was carried out by milling this pre-conditioned macro-suspension through a microfluidizer model 110T (Microfluidics, Newton, MA) at 5000, 10,000 and 15,000 psi for 6 min each with a total processing time of 18 min. Low pressures were used initially to prevent the blockage of the interaction chambers. The temperature of the suspension was maintained at 5 °C during the processing using a circulating water bath (Grant Ltd. 6, Grant Instruments, Cambridge, UK).

2.3. Characterization of nanosuspensions

2.3.1. Particle size distribution

The particle size distribution of the nanosuspension was determined by dynamic light scattering using a Sub-micron Particle Sizer Autodilute Model 370 (Nicomp Particle Sizing Systems, Santa Barbara, CA). Samples were diluted with 30% glycerin (saturated with ibuprofen) before measuring the particle size. The viscosities of the diluted samples were measured using a Brookfield viscometer (Model DV III, Stoughton, MA) and these values were used in the particle size calculations. All measurements were made in triplicate and the mean values and standard deviations were reported.

2.3.2. Zeta potential

The zeta potential of the nanosuspensions was determined using a Zeta Plus (Brookhaven Instruments Corporation, Holtsville, NY). Samples were diluted in a similar fashion to that described above for the particle size distribution. All measurements were made in triplicate and the mean values and standard deviations were reported.

2.3.3. Solubility determination

10 ml of the suspension was centrifuged at 12,000 rpm using a minispin centrifuge (Eppendorf, Westbury, NY) for 10 min to separate the solids. The supernatant was then filtered using a 0.1 μm filter to obtain a clear solution and the amount of ibuprofen dissolved was analyzed by HPLC as per USP NF 2006 method. Three samples were analyzed for each stabilizer solution and the mean values and standard deviations were reported.

3. Results and discussion

3.1. Selection of drug

Ibuprofen is an anti-inflammatory drug with a molecular weight of 206.28 g/mol and an aqueous solubility of 0.049 mg/ml. A number of crystal morphologies of racemic ibuprofen have been obtained using different preparation methods and solvents but all of these are isomorphic in nature. Therefore, no true stable polymorphs of ibuprofen are known to exist (Dudognon et al., 2008). For this reason, racemic ibuprofen was selected as the model drug since any difference in the physicochemical characteristics of batches made using the different processing methods will be a result of the process itself and will not be due to polymorphic changes that may have occurred in the drug.

3.2. Precipitation under sonication process

Intensity weighted particle size distribution is the primary size distribution given by dynamic light scattering instruments and is based on the intensity of light scattered by the suspended particles. Assuming the particles are perfect spheres, volume weighted distributions are typically calculated by performing an appropriate mathematical manipulation. The bottom-up method of preparation of precipitation under sonication resulted in the formation of needle shaped particles. Consequently, the assumption with respect to spherical particle shape is invalid and therefore intensity weighted size distributions rather that volume weighted size distributions are reported in this study. Fig. 1 shows the mean intensity weighted particle size distribution obtained with various stabilizer solutions using the precipitation under sonication process. It can be seen that with the exception of those particles prepared with a few of the HPMCs, the mean particle size obtained with all other stabilizers is above 1 μm and technically outside the nanoparticle size range.

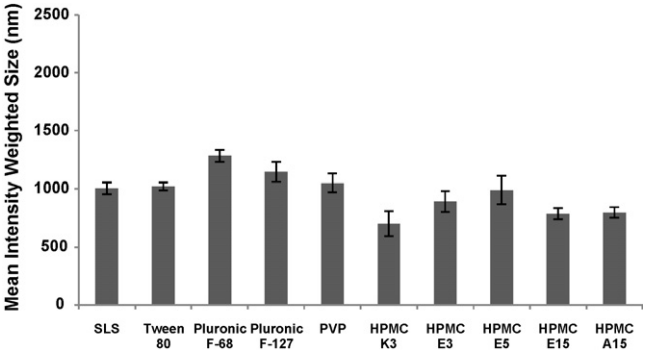

Fig. 1. Mean particle size of ibuprofen suspensions obtained with various stabilizers using the precipitation method.

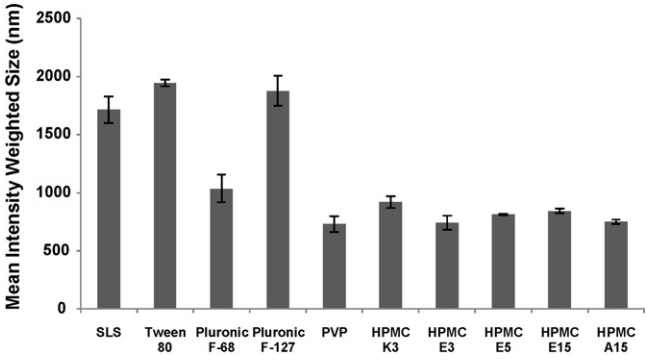

Fig. 2. Mean particle size of ibuprofen suspensions obtained with various stabilizers using microfluidization.

The smallest mean particle size of 702 nm (±106 nm) was obtained when ibuprofen was precipitated in the presence with HPMC K3, while the largest mean particle size of 1282 nm (±51 nm) was obtained in the presence of Pluronic F-68. Careful analysis of the complete particle size distributions obtained with the various stabilizers revealed that only HPMCs were able to stabilize a significant portion (25%) of ibuprofen particles below 500 nm. All stabilizers had X50 (50% of the distribution less than) values below 1 μm and X99 (99% of the distribution less than) values below 5 μm.

3.3. Microfluidization

Fig. 2 shows the particle size distribution of ibuprofen micro/nanosuspensions prepared using microfluidization. Irregular particles were observed in all the batches obtained by microfluidization. As occurred with the precipitation process, the HPMCs were successful in achieving a particle size of less than 1 μm. Microfluidization generally resulted in ibuprofen suspensions with lower mean particle size values compared to the precipitation process. This may be attributed to the greater interaction between the stabilizer and the ibuprofen particles and the high impact that occurs among the particles and between the particles and the walls of the interaction chamber of the microfluidizer, where they are made to pass through a very small orifice. However, significantly higher particle sizes were obtained in the case of suspensions made with SLS, Tween 80 and Pluronic F-127. This discrepancy is explained below, in the section describing the effect of stabilizers. With the exceptions of SLS, Tween 80 and Pluronic F-127 based suspensions all others had X99 values less than 5 μm. All the formulations containing HPMC had X25 values less than 500 nm which is similar to those obtained with the precipitation method.

3.4. Zeta potential

Fig. 3 compares the zeta potential of various ibuprofen micro/nanosuspensions manufactured by both the precipitation under sonication and microfluidization methods. Comparable zeta potential values were observed for formulations made with either processing method. The anionic nature of sodium lauryl sulfate resulted in a high negative zeta potential (−60.70 to −65.00 mV) on the ibuprofen particles. All other stabilizers were non-ionic in nature and the formulations processed with them exhibited zeta potential values ranging from −25 mV to 2 mV. Ibuprofen is a carboxylic acid derivative. Ionization of the carboxyl group in an aqueous environment should impart a negative charge to the ibuprofen particles. However, adsorption of non-ionic stabilizers results in an increase in the thickness of the diffuse double layer and

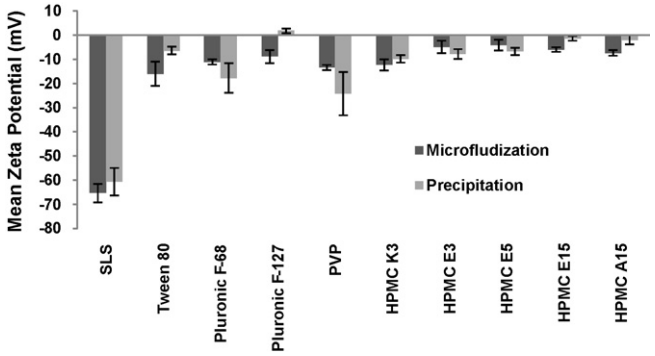

Fig. 3. Mean zeta potential of ibuprofen suspensions with various stabilizers.

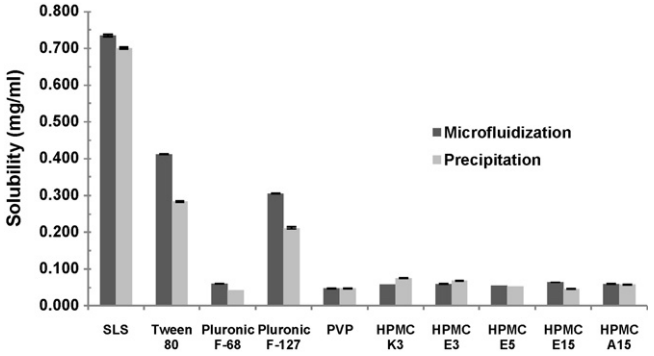

Fig. 5. Solubility (at 25 °C) of ibuprofen in suspension prepared by different methods.

hence a lower zeta potential. Depending on the nature of the interaction of the stabilizer with the ibuprofen surface the properties of the adsorbed layer (such as thickness, completeness, strength, and robustness) will vary and so will the zeta potential. The zeta potential data suggests that the HPMCs result in a more complete surface coverage as they are better able to mask the negative charge on the ibuprofen particles.

3.5. Effect of stabilizer

Substituted cellulosic stabilizers (HPMCs) were the most successful of all the stabilizing agents investigated for the formation of ibuprofen suspensions. HPMCs can adsorb onto ibuprofen particles due to interaction of the hydrophobic (methoxyl) and hydrophilic (hydroxypropyl) groups (present in the polymeric chains) with the ibuprofen surface. To investigate the role of the physicochemical properties of the HPMC stabilizers on the formation of nanosuspensions, the chemistry of the different HPMCs investigated was considered together with the nanosuspension particle size obtained (Table 1). HPMC E3, E5 and E15 have similar chemistry, except their molecular weights vary (due to different chain lengths), as evident from their increasing viscosities at 25 °C. There was no correlation between the stabilizer molecular weight or solution viscosity and the suspension particle size obtained with either preparation method. There was no difference in terms of either the initial particle size or particle size following storage (Figs. 1, 2, 7 and 8) between HPMC E15 and A15. HPMC E15 and A15 have similar molecular weight and similar methoxyl content, but differ in terms of the presence or absence of the hydrophilic hydroxypropyl group. Consequently, it can be concluded that the hydrophilic hydroxypropyl group does not affect the ability of the HPMC to form/stabilize the micro/nanosuspensions. Although, HPMC K3 can be considered the least hydrophobic of all the HPMCs investigated (based on the lowest methoxyl substitution), its hydrophobicity appears to be sufficient to form comparable suspensions to the other HPMCs suspensions.

Table 1
Physicochemical properties of various HPMCs (Methocel, 2006).

HPMC (methocel) grade	% Methoxyl content	% Hydroxypropyl content	Viscosity (cps)[a]
K3	19–24	7–12	2.4–3.6
E3	28–30	7–12	2.4–3.6
E5	28–30	7–12	4–6
E15	28–30	7–12	12–18
A15	27.5–31.5	Nil	12–18

[a] Viscosity of 2% (w/v) aqueous solutions.

To determine the effect of stabilizer characteristics on the formation of micro/nanosuspensions of ibuprofen various stabilizer properties such as their effect on interfacial tension, contact angle, solubility of ibuprofen, surface energy and hydrophilic lipophilic balance value (HLB) were considered. Choi et al. (2005) and Lee et al. (2008) calculated surface energies of the drug and stabilizers based on contact angle measurements. They attempted to correlate the surface energies of drugs with those of various stabilizers in order to assist in nanosuspensions stabilizer selection. However, no correlation was observed between the surface energies and the ability to form nanosuspension. Therefore, out of these properties only HLB values of various stabilizers and their effects on ibuprofen solubility were considered further for comparison with the particle size data obtained (Figs. 4–6). Table 2 lists the HLB values of the various non-ionic stabilizers used in the study. SLS cannot

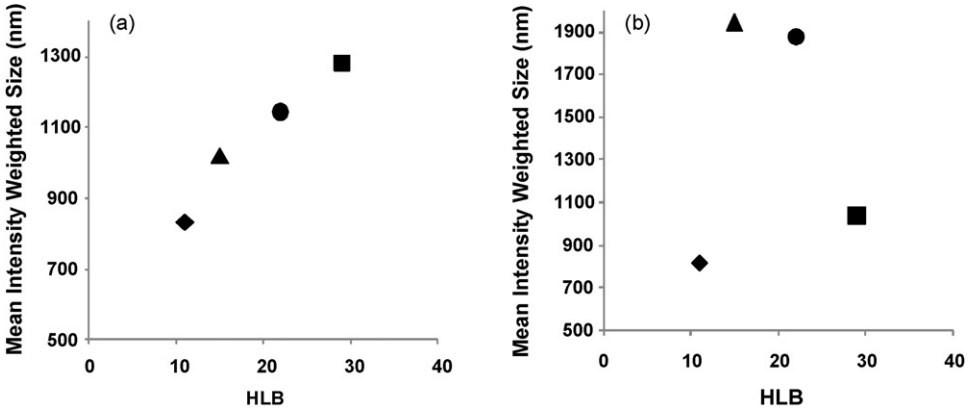

Fig. 4. Particle size of ibuprofen suspensions as a function of HLB value of the stabilizer: (a) precipitation, and (b) microfluidization. (♦) HPMCs, (▲) Tween 80, (●) Pluronic F-127 and (■) Pluronic F-68.

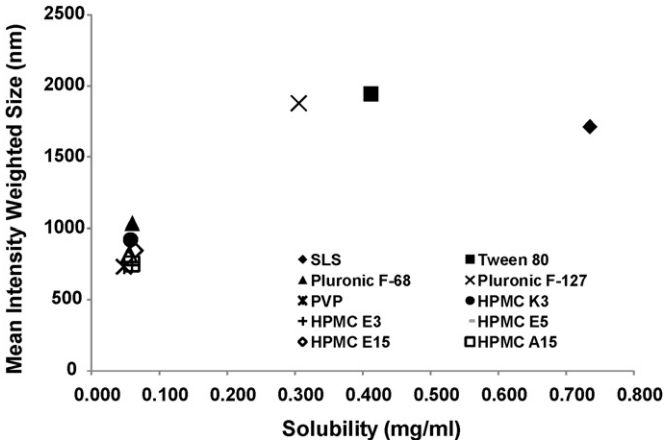

Fig. 6. Particle size of ibuprofen suspensions prepared by microfluidizaition as a function of solubility in stabilizers.

be compared since the HLB system does not determine the functionality of ionic surfactants (Walstra, 1983). HLB is a measure of the hydrophilicity and lipophilicity of a stabilizer molecule. The lower the HLB value is, the more lipophilic the stabilizer is and *vice versa*. Lipophilic (hydrophobic) molecules should exhibit a higher probability of interacting with the hydrophobic ibuprofen particles and thus achieving a smaller particle size. A positive correlation was obtained between particle size and the HLB of the non-ionic stabilizer in the case of suspensions prepared using the bottom-up approach (Fig. 4a). However, no such correlation was achieved for the suspensions prepared with the microfluidization method (Fig. 4b).

Table 2
HLB values of different non-ionic stabilizers.

Stabilizer	HLB value
HPMCs	10–12[a]
Tween 80	15[b]
Pluronic F-127	22[c]
Pluronic F-68	29[b]
PVP K 30	–

[a] Methocel (2009).
[b] Wade and Weller (1994).
[c] Quadir (2005).

The difference in the behavior of stabilizers under different processing conditions may be explained by aspects of the precipitation technique being similar in nature to the formation of emulsions (for which the HLB system was primarily developed) since the particles are formed from solution by phase incompatibility. However, HLB values are unlikely to play a dominant role in nanosuspensions prepared by microfluidization. The particle size obtained with microfluidization appeared to correlate with the ibuprofen solubility (at 25 °C) in solutions of the various stabilizers (Figs. 5 and 6). The stabilizers (PVP K-30, Pluronic F-68 and HPMCs) which minimally affect the intrinsic aqueous solubility of the ibuprofen (0.049 mg/ml) (Wishart et al., 2006) resulted in lower mean particle size compared to stabilizers that significantly increased ibuprofen solubility (SLS, Tween 80 and Pluronic F-127).

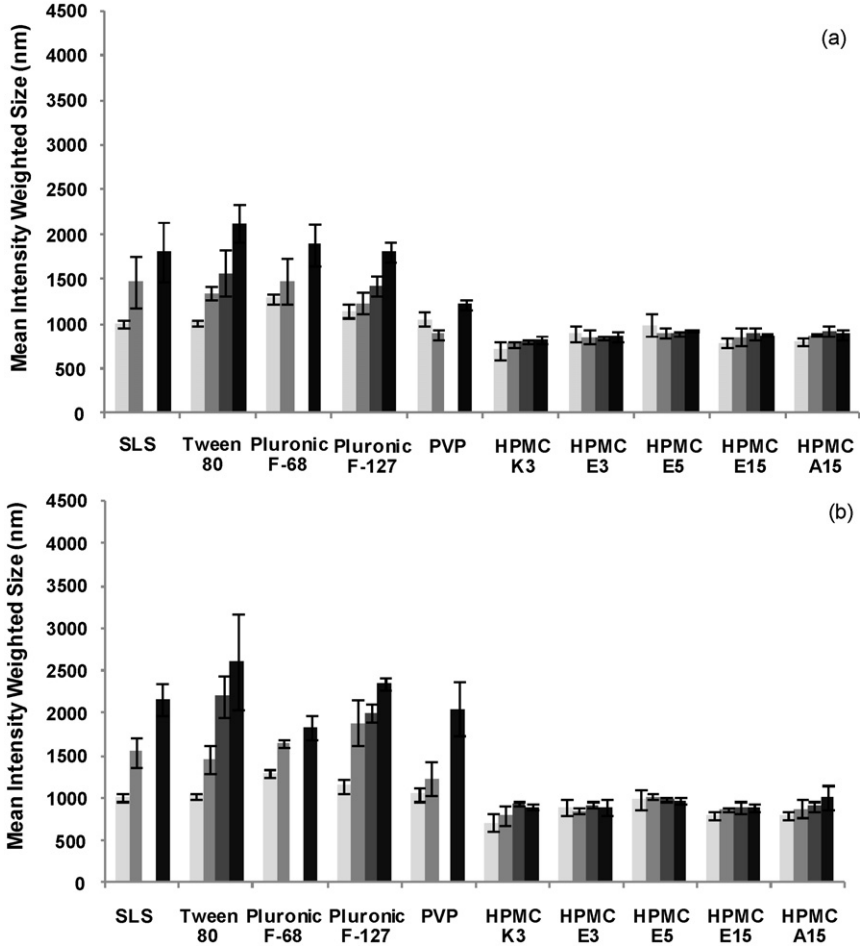

Fig. 7. Effect of storage on ibuprofen suspensions prepared using the precipitation method: (a) 4 °C, and (b) 25 °C. ( ) Initial, ( ) day 1, ( ) day 3 and ( ) day 7.

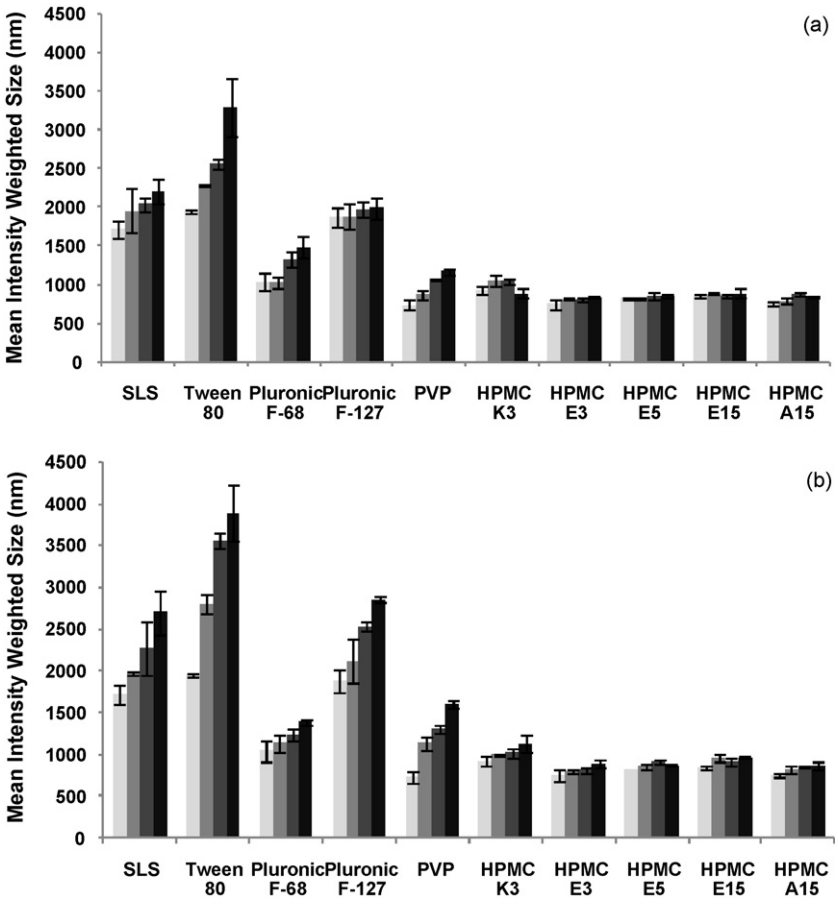

Fig. 8. Effect of storage on ibuprofen suspensions prepared using microfluidization: (a) 4 °C, and (b) 25 °C. ( ) Initial, ( ) day 1, ( ) day 3 and ( ) day 7.

Higher ibuprofen solubility during processing in the presence of SLS, Tween 80 and Pluronic F-127 can lead to Ostwald ripening and this may be responsible for the higher particle size obtained in these suspensions.

3.6. Stability of suspensions on storage

The change in the particle size of the micro/nanosuspensions was investigated as a function of time and temperature to determine which stabilizers had the best stabilizing efficiency. The micro/nanosuspensions were divided into two parts and stored in 30 ml glass vials at different temperatures. One part was stored at 4 °C and the other at 25 °C and the particle size was monitored for a period of 7 days with sampling at days 1, 3 and 7. HPMC-based formulations prepared by either method were able to maintain their size for 7 days at both conditions (4 and 25 °C). Increase in mean particle size was observed in all other formulations with a greater increase at 25 °C compared to 4 °C (Figs. 7 and 8). Given the polydisperse nature of the distributions it is difficult to pin-point the exact mechanism for the observed particle size increase. Agglomeration, crystal growth due to Ostwald ripening or both may be the contributing factors. The higher increase in particle size observed in formulations made with SLS, Tween 80 and Pluronic F-127 as stabilizers suggests that Ostwald ripening may be a key driving force. All these stabilizers increase ibuprofen solubility (Fig. 5) and according to the LSW (Lifshitz–Slyozov–Wagner) theory, the rate of Ostwald ripening is directly proportional to the concentration of the dispersed phase in the system. However, this does not explain the increase in particle size observed in PVP K-30 and Pluronic F-68 based formulations. The effect of these stabilizers on the solubility of ibuprofen is low and is of the same order of magnitude as the HPMCs (Fig. 5), suggesting that there may be other contributing factors. The specific interactions between the stabilizers and the surface of the ibuprofen particles are likely to differ based on their physicochemical properties and this can result in differences in the surface coverage and the robustness of the adsorbed layer. Such variations can help to explain the observed micro/nanosuspension stability. The zeta potential data suggests that PVP K-30 and Pluronic F-68 result in poorer surface coverage since they are unable to completely mask the surface charge on the ibuprofen particles. Whereas, the HPMCs resulted in zeta potential values close to zero indicative of a complete coverage of the ibuprofen particles, explaining their enhanced stability on storage.

4. Conclusions

Both the top-down and bottom-up processes gave similar initial formulations with comparable short-term stability. Stabilizer HLB values can assist in stabilizer selection for bottom-up processes, since this process is primarily a variant of emulsification technique. On the other hand in the top-down processes drug solubility in the stabilizer solutions plays a dominant role. There was a relationship between drug solubility in the stabilizer solution and stability of the particle size observed on storage for formulations made with both processing methods. This implies that Ostwald ripening plays a significant role in nanosuspension stability. Accordingly, only stabilizers which have a minimal/negligible effect on drug solubility should be used in the preparation of nanosuspensions. Micro/nanosuspensions are usually converted into dried powders for further processing into solid dosage forms.

Steric stabilization with HPMCs were sufficient to stabilize ibuprofen micro/nanosuspensions for a period of 7 days and thus can provide sufficient lead time to process the formulation further. The data strongly suggests that HPMC molecules interacted well with the ibuprofen surface and resulted in the best surface coverage. This may be primarily responsible for their superior performance with respect to stability studies. However, further investigations into specific interactions between HPMC and ibuprofen are needed to confirm this hypothesis.

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