W5118

Toward Amorphous Indomethacin Ocular Suspensions and the Importance of Preparation Methods on the Physical Stability

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PURPOSE

The bioavailability of ocular suspensions is partly dependent on the dissolution properties of the active pharmaceutical ingredient (API) of interest. The dissolution of poorly water soluble drugs can be increased by the use of higher energy solid state forms such as the amorphous form or metastable polymorphic forms.

Indomethacin is a well-studied Biopharmaceutical Classification System (BCS) class II API which is used in ocular suspensions for treatment of ocular inflammation, often following surgery. The apparent solubility and dissolution of indomethacin is increased by the use of the amorphous form.[1,2] This could be applied to ocular suspension formulations to improve the dissolution properties if the suspended API can remain in the amorphous form. Polymers such as HPMC have shown potential to inhibit crystallization and other solid state changes of various drugs including indomethacin in aqueous media.[3] Furthermore, the stability of amorphous indomethacin is dependent on the preparation method, with quench cooled amorphous drug being more physically stable than those prepared by milling or spray drying.[4] An important consideration for ocular formulations is that the particle size of the suspended particles are below 10 µm diameter to prevent irritation.

The aim of this study was to prepare and characterize amorphous indomethacin ocular suspensions and investigate the effect of preparation method on solid state behavior. The effect of HPMC and milling conditions on the particle size and solid state stability of the amorphous indomethacin in suspension with a buffered HPMC vehicle was investigated using a design of experiments (DOE) approach.

METHODS

Amorphous indomethacin was produced by quench cooling. Particle size reduction was carried out by using ball milling with a Pulverisette 6 mill (Fritsch, Germany) with 20 mm peals, 80 mL stainless steel bowl and 400 rpm milling speed. The length of milling time, wet/dry conditions and presence/absence of HPMC during milling was studied using DOE (full factorial). The suspension vehicle consisted of phosphate buffered solution (pH 6) and all final formulations contained 0.3 % HPMC and 0.5 % indomethacin. In some samples the HPMC was dissolved in solution, in others it was co-milled with the amorphous indomethacin. A summary of the DOE samples is given in Table 1.

Differential scanning calorimetry (DSC) (Mettler DSC 823e (Mettler-Toledo AG, Switzerland)), attenuated total reflectance-infrared (ATR-IR) (Vertex 70, Bruker Optics, Germany) and Raman spectroscopy (Raman RXN system with PhAT probe, Kaiser optics, USA) were used for solid state analysis of the indomethacin before and after addition to the suspension. The particles were also imaged with scanning electron microscopy (SEM) (Quanta 250 Field emission gun SEM (FEI, USA).

Table 1. DOE based set of experiments to look at the effect of milling time and milling conditions for stability of amorphous indomethacin in suspension

Experiment Name	Drug amount (g)	Milling speed (rpm)	HPMC - dry (g)	HPMC - in solution (g)	Milling cycles	Milling type (wet milling includes 10 mL of buffer)
Am01	2	400	0	0.01	0	wet milling
Am02	2	400	0.01	0	0	wet milling
Am03	2	400	0	0.01	1	wet milling
Am04	2	400	0.01	0	1	wet milling
Am05	2	400	0	0.01	5	wet milling
Am06	2	400	0.01	0	5	wet milling
Am07	2	400	0	0.01	0	dry milling
Am08	2	400	0.01	0	0	dry milling
Am09	2	400	0	0.01	1	dry milling
Am10	2	400	0.01	0	1	dry milling
Am11	2	400	0	0.01	5	dry milling
Am12	2	400	0.01	0	5	dry milling
Am13	2	400	0.005	0.005	1	dry milling
Am14	2	400	0.005	0.005	1	dry milling
Am15	2	400	0.005	0.005	1	dry milling
Am-no HPMC	2	400	0	0	0	n/a

RESULTS

Amorphous indomethacin was present after quench cooling and dry milling according to DSC and vibrational spectroscopic analyses. The recrystallization temperature observed in DSC was lowered by~16 ºC after dry milling (Fig. 1) . This may be due to an increased number of nucleation sites introduced via milling with the samples remaining amorphous. No changes were observed with vibrational spectroscopy.

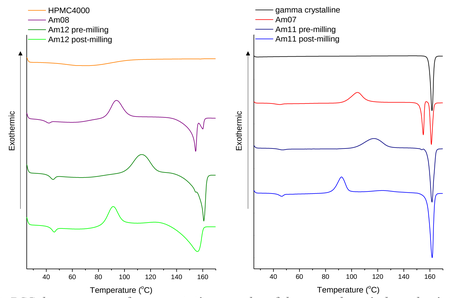

Figure 1. DSC thermograms of representative samples of the amorphous indomethacin before and after dry milling before addition to the suspension vehicle.

PCA was carried out on the IR and Raman spectra. Similar results were obtained with both techniques (only IR results shown). PCA of the IR spectra separated samples in the PC scores space based on the solid state form of indomethacin (Fig. 2). Samples which were wet milled changed progressively during milling . The presence of HPMC during wet milling altered the solid state form produced. Milling without HPMC showed initial formation of the ε-form, (1 cycle – sample Am03) followed by further transformation to the α-form (5 cycles – sample Am05), which is the same pattern as that observed over time with the unmilled sample without HPMC. The presence of HPMC during milling stablized the ε-form, with no α-form spectral freatures observed.

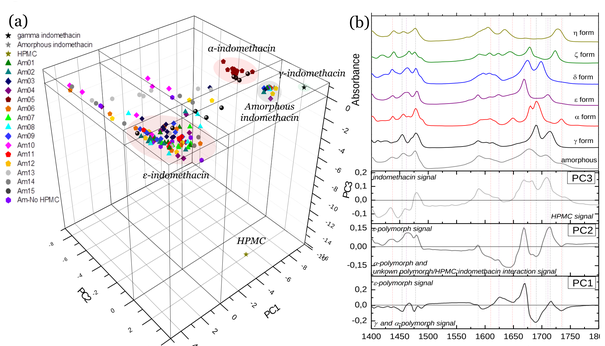

Figure 2. PCA analysis of the ATR-IR spectra collected from the samples at various time points. (a) Scores plot of the first three principal components (PCs) and (b) the associated loadings for these PCs with IR spectra of the indomethacin polymorphs for comparison.

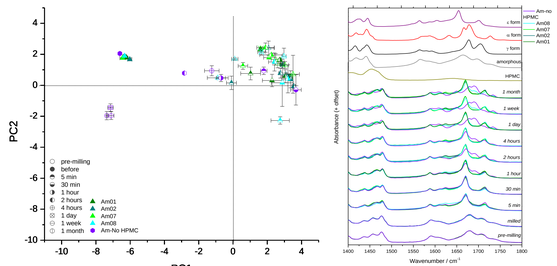

Figure 3. Simplified PCA analysis results of the ATR-IR spectra collected from the samples which were not milled at various time points. (a) Scores plot of spectra (mean ± sd, n=3) and (b) the associated representative spectra of these samples with reference indomethacin polymorph spectra for comparison.

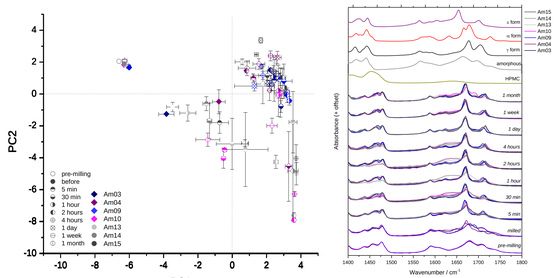

Figure 4. Simplified PCA analysis results of the ATR-IR spectra collected from the samples which were milled for one cycles at various time points. (a) Scores plot of spectra (mean ± sd, n=3) and (b) the associated representative spectra of these samples with reference indomethacin polymorph spectra.

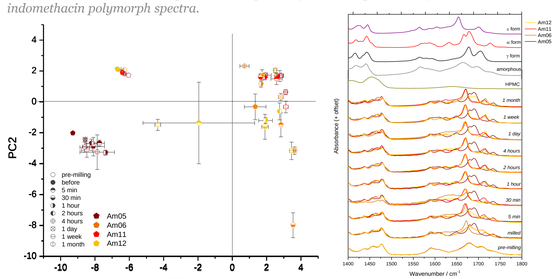

Figure 5. Simplified PCA analysis results of the ATR-IR spectra collected from the samples which were milled for 5 cycles at various time points. (a) Scores plot of the first two principal components (PCs) and (b) the associated representative spectra of these samples with reference indomethacin polymorph spectra for comparison.

Upon addition to the buffered suspension, the samples which were not milled converted within 30 min to the ε-form and remained there for the study duration (Fig. 3). The Am-no HPMC sample initially converted to the ε-form and then started to transform to the α-form within one hour (Fig. 3). Thus, the HPMC stabilizes the samples in the ε-form, preventing further transformations.

Samples which had been milled for 1 cycle with HPMC in the vehicle (Am03 and Am09) converted to the ε-form after 5 min in suspension and remained in this form (Fig 4). Samples with HPMC co-milled with the amorphous indomethacin for 1 cycle also contained the ε-form, however many also contained a broad absorption around 1640 cm^{-1} (Fig. 4). This is the same region as the HMPC signal, but these samples did not have strong HPMC features in the 1400-1500 cm^{-1} region. This may indicate an HPMC-indomethacin interaction. Sample Am10 started transforming to the α-form by one month.

The samples which had been milled for 5 cycles varied depending on the other milling parameters. Am05 remained in the α-form (formed produced by milling) while Am11 converted to the ε-form within 5 min of forming the suspension, and remained in this form (Fig. 5). Samples where the HPMC was co-milled (Am06 an Am12) with the amorphous indomethacin also contained the ε-form, however they also contained a broad absorption around 1640 cm^{-1}, suggesting an HPMC-Indomethacin interaction. Am12 had transformed to the α-form by one month whereas Am06 remained in the ε-form, showing that the wet milled sample was more stable.

SEM imaging suggested that the ε-form formed large agglomerates, much larger than 10 µm in diameter, making these suspensions unsuitable for ocular drug delivery (Fig. 6). The sample Am05, with the α- form, consisted of small needle-like morphology with a larger specific surface area, typically ~5 µm long, making these an ideal candidate for testing a different solid state form in ocular drug delivery.

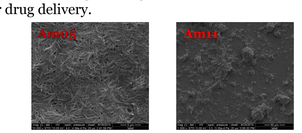

Figure 6. SEM images of a representative alpha (left) and epsilon (right) indomethacin solid from suspension. These samples were both milled for 5 cycles, however the sample on the left was wet milled and the sample on the right dry milled.

CONCLUSION

With the variables studied, amorphous indomethacin crystallization occurs in a pH 6 buffered HPMC suspension. The crystallization behavior did not differ significantly in the dry milled samples, however milling duration and presence of HPMC affected the outcome in solid state form in wet media milling. Whilst two polymorphic forms formed stable suspensions (α and ε) only the α-form was able to be produced in an appropriate particle size for ocular delivery. This is a potential candidate to study the effect of solid state form on the dissolution and bioavailability in ocular suspensions.

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