Effect of mixing on the solubilization of poorly water soluble drug in DC formulation using Soluplus® as solubilizer in high shear granulator

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Abstract
This investigation analyzed the solubilization capacity of Soluplus® in dry granulation. Soluplus® is novel, graft copolymer of poly(oxyethylene)-poly(oxypropylene)-poly(oxyethylene) glycol. Carbamazepine was blended with Soluplus® in ratios of 1:5 and 1:10 drug to Soluplus® weight. The ratios of drug to Soluplus® were selected as the drug to Soluplus® weight ratio that would allow the most effective and robust mixing of the dry mixture with the active pharmaceutical ingredient (API). This is due to an economical process but is also the most challenging method of manufacturing to achieve a robust formulation. The difficulty to achieve good content uniformity and even particle interactions of the particles that have similar particle sizes is a trade-off of the API’s active pharmaceutical ingredients (APIs) making the method undesirable to use for larger scale production. The particle size distribution of the APIs (active pharmaceutical ingredients) are generally small in size, however the drug particles need to be long enough to enhance the band homogeneity, but short enough to avoid particle desegregation. Another important factor is the choice of adequate mixing time. This is necessary to maintain uniform drug particle distribution in the mixing equipment in order to achieve the adequate and uniform drug release from all sample points.

Introduction
It is widely accepted that the simplest and fastest method of solid dosage manufacture is dry granulation method where the active ingredient is weighed out and the excipients are often blended to achieve homogeneity of the mixed particles with the active pharmaceutical ingredient (API). This is done to ensure economical process but is also the most challenging method of manufacturing to achieve a robust formulation. The difficulty to achieve good content uniformity and even particle interactions of the particles that have similar particle sizes is a trade-off of the active pharmaceutical ingredients (APIs) making the method undesirable to use for larger scale production. The particle size distribution of the APIs (active pharmaceutical ingredients) are generally small in size, however the drug particles need to be long enough to enhance the band homogeneity, but short enough to avoid particle desegregation. Another important factor is the choice of adequate mixing time. This is necessary to maintain uniform drug particle distribution in the mixing equipment in order to achieve the adequate and uniform drug release from all sample points.

Materials
- Carbamazepine, Soluplus®, Kollidon®, Crossolan® (S-MCC) and Lutrol® were obtained from BASF.
- Calcium Carbonate was obtained from Dicalcium Co.
- Pre-D®-Stabilized Monocryostabilized Cellose®-MCC was obtained from JRS Pharmaceuticals.

Methods
Carbamazepine was blended with Soluplus® at 9% (1:10) and 17% (1:5), and granulated in a 25 inch top drive high shear granulator (GMX - Freund Vector Machine) without the chopper blades, with a bench of calcium carbonate or Lutrol® as filler, Kollidon® as super disintegrant, and Pro-Clon® (S-MCC) as disintegrant. The contact time was seen to be 30 minutes. The ratio of drug to Soluplus® weight ratio (see Table 1) was kept constant for comparative analysis.

Results

Discussion
The granule mixture of different mixing time intervals showed a decrease in band uniformity as the mixing time was decreased. The band uniformity was 88.5% at 15 minutes, decreased 87.5% at 8 minutes, 75% at 6 minutes, and 60% at 1 minute of mixing time. There was shown uniform drug release at all sample points for formulation I (see Figure 3) as well as formulation II (see Figure 4). This was due to part of the particle size of carbamazepine being larger than that of Soluplus®. The deaggregation of the non-uniform particles increased as the mixing time was increased causing the decrease in the low drug release for both Formulations I and II. There was shown a better performance of the particle size distribution for a larger overall particle size for 15 min than 10 min for the ratios of 1:5 (see Figure 5) and 1:10 (see Figure 6). The solubilization effect at the 1:5 ratio mixture of drug to Soluplus® was shown to be lower than that of the 1:10 ratio mixture. This was probably due to continuous cycle mixing effect as the comparison of the drug distribution in the bowl after 3, 6 and 10 minutes of mixing time showed that the homogeneity of the carbamazepine (Formulation I at 15 min) was achieved only at the 3 and 10 minutes mixing time when compared to the 5 and 10 minutes mixing time. This showed that robust blend uniformity was achieved at the 3 minutes of high shear mixing (Formulation I) and at the 10 minute mixing-time of high shear mixing (Formulation II) and the particle size distribution increased at the 10 minutes mixing time of high shear mixing for both Formulations I and II. The drug Soluplus® at 110 min of circulation in Formulations I achieved a better content uniformity than the 10 minutes mixing times. This was evidenced by the convergence of the pit of the sample points. Figures 4 and 5 showed that 90-95% of carbamazepine was released within 5 hours, however, in Figure 10 on 2T and 3T of carbamazepine was released, and this was possibly due to particle aggregation as a result of centrifugal force during granulation of cisplatin high shear high speed.

Conclusions
- The use of High Shear Mixer can increase the carbamazepine release to 100% in 5 hrs.
- Long mixing time in DC formulation using Soluplus® as the solubilizer in a High Shear High speed Mixer, causes particle segregation.
- As a result of non-uniformity of drug distribution, the drug solubilization and dissolution decreased with increase in mixing time.
- Homogeneity of powder mixture with API can be achieved in 6 minutes of mixing time using a High Shear Mixer.
- Choice of compatible binder increases the robustness of the formulation.
- Uneven distribution results in irregular and low drug release in all sample points.
- Solubilization of poorly soluble drugs may be achievable in DC formulations using a high shear granulator at short mixing time to manufacture a compressible granulation.

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