Effect of Mixing Time on the Solubilization Of Poorly – Water Soluble Drug in DC Formulation, Using Soluplus® as Solubilizer in High Shear Granulator

Timothy J. Smith[1] , Charles Onyiuke[2]

[1] Freund-Vector Corporation, Marion, IA 52302

[2] BASF Corporation, Pharma Ingredients and Services, 500 White Plains Road, NY 10591

tim.smith@freund-vector.com, charles.onyiuke@basf.com

BASF
The Chemical Company

Abstract

This investigation analyzed the solubilization capacity of Soluplus® in dry granulation. Soluplus® is a novel, graft copolymer of polyvinyl caprolactam – polyvinyl acetate – polyethylene glycol. Carbamazepine was used as a model drug, and the homogeneity of the mixture of various excipients' particles in the high shear mixing bowl was determined. The robustness of dry granulation method in DC formulation was measured by the content uniformity of the mixture at a given length of mixing time and quantified by the percent of drug released at different sample points and levels (top and bottom).

Introduction

It is widely accepted that the simplest and fastest method of solid dosage manufacture is dry granulation method where the active ingredient(s) and the excipients were often blended to achieve homogeneity of the mixed particles with the active pharmaceutical ingredient (API). This is an ideal and economical process but it is also the most challenging method of manufacturing to achieve a robust formulation. The difficulty to achieve good content uniformity and inter-particle interactions of excipients that have similar particle sizes as those of the APIs (active pharmaceutical ingredients) make this method unachievable to many formulators for consistent results. One of the critical parameters in this process is the mixing time of the dry particles which need to be long enough to enhance the blend homogeneity, but short enough to avoid particle desegregation. Another important factor is the choice of adequate mixing equipment. 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®, Crospovidone (Kollidon® CL) and Ludipress® were obtained from BASF
- Calcium Carbonate was obtained from Jost Chemical Co.
- Pro-Solv®, (Silicified Microcrystalline Cellulose (S-MCC)), was obtained from JRS Pharma LP.

Methods

Carbamazepine was blended with Soluplus® at 9 wt% (1:10) and 17 wt% (1:5), and granulated in a 25 liter top drive high shear Vector granulator (GMX – Freund Vector Machine without the chopper blades) with a blend of calcium carbonate or Ludipress as filler, Kollidon® CL as super disintegrant, and Pro-Solv® (SMCC, silicified microcrystalline cellulose) as filler and glidant. The control formulations were then blended without use of Soluplus® at (1:5) and (1:10) drug to Soluplus® weight% ratios (see Formulation tables 1 and 2 below) for comparative analysis.

Formulation 1			
Components	**Control Blend (%)**	**Soluplus® (1:5) (%)**	**Soluplus® (1:10) (%)**
Carbamazepine	5.0	5.0	5.0
Calcium Carbonate	69.5	59.0	39.0
Kollidon® CL	12.5	10.5	5.5
Pro-Solv® (S-MCC)	13.0	0.5	0.5
Soluplus®	0.0	25.0	50.0
Total	**100.0**	**100.0**	**100.0**

Table 1. DC Formulation I

Formulation 2			
Components	**Control Blend (%)**	**Soluplus® (1:5) (%)**	**Soluplus® (1:10) (%)**
Carbamazepine	5.0	5.0	5.0
Ludipress®	70.0	60.5	42.0
Kollidon® CL	9.0	9.0	2.5
Pro-Solv® (S-MCC)	16.0	0.5	0.5
Soluplus®	0.0	25.0	50.0
Total	**100.0**	**100.0**	**100.0**

Table 2. DC Formulation II

Mixing of the dry formulations was performed in a 25 liter top drive high shear mixer (Freund- Vector Granumeist™ GMX – 25; (see photo Figure 1)) at a nominal 40% fill volume (5.75 Kg for Formulation 1 and 6.01 Kg for Formulation 2). Mixer impeller tip speed was held constant at 5.3 meters per second. Chopper blades were removed from the bowl for the tests. Samples of dry granulates were taken using a 5 ml sample thief at 1, 3, 6, and 10 minutes intervals of mixing for Formulation 1; and at 6 and 10 minutes of mixing for Formulation 2. These samples were taken from two levels (top and bottom) of the mixing bowl from left, middle and right locations of the bowl (see photo Figure 2).

Sampling Location Key				
Sampling Level (Locations)	**Sampling Time (Min) (Across Diameter Of Bowl)**			
Top (T)	1T	3T	6T	10T
Bottom (B)	1B	3B	6B	10B

Table 3. Sampling Location Table

Figure 1. Freund-Vector Granumeist™ GMX-25

Figure 2. Sampling Points in the Mixing Bowl

Particle size analyses of the individual components and the resulting blends from formulation II were done using a Sympatec QicPic® Image Analyzer (model equipped with VIBRI/L and RODOS/L feeders).

The granulation from formulation I had very poor flow rate with angle of repose of 24°, and therefore was not compressible. The granulation from formulation II had good flow properties and was lubricated with 0.5% magnesium stearate and blended for 4 minutes. The blend was compressed into 400 mg caplets using Korsch XL 100 tablet machine.

The dissolution profile of carbamazepine was measured using a DISTEC Dissolution System 2100C and analyzed using Waters 2690D Separation Module HPLC Apparatus.

The percent drug released at each sample point per mixing time showed the uniformity or non-uniformity of drug distribution in the bowl after mixing. This helped to determine the most effective and robust mixing time using high shear mixing/granulator equipment.

Results

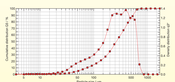

Figure 3. Particle Size Distribution
(Formulation 2 CONTROL BATCH @ 10 Minutes)

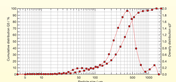

Figure 4. Particle Size Determination
(Formulation 2 SOLUPLUS® 1:10 RATIO at 6 Minutes)

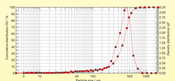

Figure 5. Particle Size Distribution
(Formulation 2 SOLUPLUS® 1:10 RATIO @ 10 Minutes)

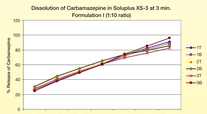

Figure 6. Dissolution of CBZ at 3 min. Mixing Time
(Formulation I)

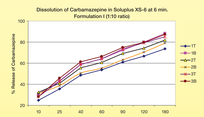

Figure 7. Dissolution of CBZ at 6 min. Mixing Time
(Formulation I)

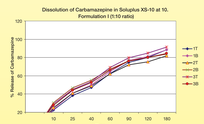

Figure 8. Dissolution of CBZ at 10 min. Mixing Time
(Formulation I)

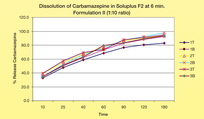

Figure 9. Dissolution of CBZ at 6 min. Mixing Time
(Formulation II)

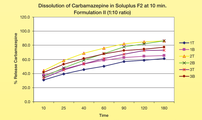

Figure 10. Dissolution of CBZ at 10 min. Mixing Time
(Formulation II)

Discussion

The granulate mixture of different mixing time intervals showed a decrease in blend uniformity as the mixing time was increased. At 3 min. of mixing time, 82% to 99% of drug was released in 3 hours and showed uniform drug release at all sample points for Formulation 1 (see Figure 6). This was due in part to the particle size of Soluplus® being larger than that of carbamazepine. The desegregation of the non-uniform particles increased as the mixing time was increased causing the divergence in the low drug release (see Figure 8). This resulted in lowering of the drug release profile.

The particle size analysis of the Formulation 2 granulation showed a uniform distribution of the ingredients both in the 1:5 and 1:10 ratios at the 10 minutes of mixing time (see Figures 4 and 5). However, there was an increase in density distribution towards a larger overall particle size for the 1:10 ratios than for the 1:5 ratios (see Figure 5 and Figure 4).

The solubilizing effect at the 1:5 ratio mixture of drug to solubilizer was shown to be less pronounced than in the 1:10 ratio[8]. There was good content uniformity in the high shear granulation I of the 1:10 ratios (Drug:Soluplus) at the 10 minutes mixing time that led to 92% of drug released at 3T sample point in 3 hours (see Figure 10) as opposed to the 6 minutes plot which showed a wide desegregation of the particles with divergent low drug release (see Figure 7). This was probably due to continuous cycle mixing effect. The comparison of the drug distribution in the bowl after 3, 6 and 10 minutes of mixing time showed that the homogeneity of the powder mixture (Formulation 1 at 1:5 ratio) was achieved mostly at the 3 and 10 minutes mixing time when compared to the 1 and 6 minutes mixing time[8]. This showed that robust blend uniformity was achieved at the 3 or 6 minutes of high shear mixing[8]. Formulation 2 was processed at 6 and 10 minutes of mixing based on the results of content uniformity analysis seen in Formulation 1. The Drug:Soluplus ratio of 1:10 mixture at 6 minutes in Formulation 2 achieved a better content uniformity than the mixture at 10 minutes of mixing. This was evidenced by the convergence of the plot of the sample points. Figure 9 also showed that 82-98% of carbamazepine was released within 3 hours, while in Figure 10 only 62-82% of carbamazepine was released, and this was apparently due to particle segregation as a result of centripetal force generated during continuous high shear gyration.

Conclusions

- The use of High Shear Mixer can increase the carbamazepine release to 100% in 3 hrs.
- Long mixing time in DC formulation using Soluplus® as the solubilizer in a High Shear 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 at 6 minutes of mixing time using a High Shear Mixer.
- Choice of compatible binder increases the robustness of the formulation
- Uneven drug distribution results in irregular and low drug release in all sample points.
- Solubilization of poorly soluble drug(s) may be achievable in a DC formulation using a High Shear Mixer Granulator at short mixing time to manufacture a compressible granulation.

References

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