Comparison of Solubilization Effect of Different Solubilizers on Poorly Soluble Drug in DC Formulation Using High Shear Granulator

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Abstract

The objective of this study was a comparative investigation of release profiles of a poorly soluble model drug, carbamazepine, by the dry granulation method using Poloxamers as the solubilizing agents. The solubilizing capacity of Poloxamers 237 and 338 (Kolliphor™ P 237 and P 338, respectively) were compared to Poloxamer 188 and 407 (Kolliphor™ P 188 and P 407 respectively) in dry granulation using High Shear Granulator. The study involved carbamazepine as a model poorly - water soluble drug, and the mixture of various excipients' particles using a high shear mixer granulator. The robustness of this dry granulation method in DC formulation is measured by the release profile of the drug solubilized by each of the Poloxamers.

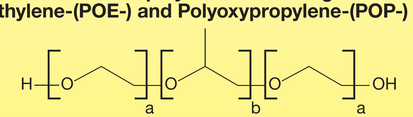
Introduction

The simplest and fastest method of solid dosage formulation and manufacture has always been dry granulation where the active ingredient(s) and the excipients are blended to achieve content uniformity of the mixed particles with the active pharmaceutical ingredient (API). This is an ideal economical process but it is often the most challenging method in achieving a robust formulation. The difficulty to achieve good content uniformity and inter-particle interactions of excipients that have similar particle sizes as that of the API (active pharmaceutical ingredient) make this method challenging for many formulators in the pharmaceutical industries. 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. Another process parameter is the choice of adequate mixing equipment. This is necessary to maintain uniform drug particle distribution in the mixing equipment in order to achieve consistency of drug release and stability.

Materials

- Carbamazepine, Poloxamers 188, 237, 338 and 407 (Kolliphor™ P 188, 237, 338 and 407), 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.

Poloxamers are block-copolymers consisting of Polyoxyethylene-(POE-) and Polyoxypropylene-(POP-) units.



[POE] Unit	[POP] Unit	[POE] Unit
Poloxamer 188	a = ca. 79 b = ca. 28	Kolliphor™ P 188
Poloxamer 407	a = ca. 98 b = ca. 57	Kolliphor™ P 407
Pharmacopeia name		**trade name**

Methods

Carbamazepine was used as a marker drug and blended with Ludipress® as filler, Kollidon® CL as super disintegrant, and Pro-Solv® (silicified microcrystalline cellulose, SMCC)) as filler and glidant to make the control formulation. The control formulation was then modified to add Poloxamers 188, 237, 338 and 407 at (1:10) drug to Poloxamer weight% ratio (see formulation Table I below).

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 of 6.01 Kg. Mixer impeller tip speed was held constant at 5.3 meter per second. Chopper blades were removed from the bowl for the tests.

Figure 1. Freund-Vector Granumeist™ GMX-25

Samples of dry granulates were taken using a 5 ml sample thief at 6 and 10 minutes of mixing.

The granulation at 6 and 10 minutes of mixing time were compressed into 400 mg Carbamazepine tablets. Particle size analyses of the individual components, as well as the resulting blends from the formulation, were carried out on a Sympatec QicPic® image analyzer (model equipped with VIBRI/L and RODOS/L feeders). See Figures 2 and 4

The granulation from the formulations containing different Poloxamer grades had good flow properties and each was lubricated with 0.5 percent of Magnesium Stearate. The blend was compressed into 400 mg caplets using Korsch XL 100 tablet machine.

Materials	Drug : Poloxamer Ratio (w/w%)				
	(1:0) Control	(1:10)	(1:10)	(1:10)	(1:10)
Carbamazepine	5.0	5.0/5.0	5.0	5.0	5.0
Lutrol® F68 Prill/Micro	0.0	50.0/50.0	0.0	0.0	0.0
Lutrol® F127 Micro	0.0	0.0/0.0	50.0	0.0	0.0
Lutrol® F87 Prill	0.0	0.0/0.0	0.0	50.0	0.0
Lutrol® F108 Prill	0.0	0.0/0.0	0.0	0.0	50.0
Kollidon® CL	12.5	5.0/5.0	5.0	5.0	5.0
Ludipress®	69.5	39.0/39.0	39.0	39.0	39.0
Pro-Solv® (S-MCC)	13.0	0.5/0.5	0.5	0.5	0.5
Total	**100.0**	**100.0/100.0**	**100.0**	**100.0**	**100.0**

Table I: DC Formulations Using Different Poloxamers

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 formulation showed the uniformity or non-uniformity of drug distribution in the bowl after mixing and therefore the solubilization effect of each Poloxamer. This helped to determine the most effective solubilizer among the Poloxamers in this study using a high shear mixing equipment.

Results

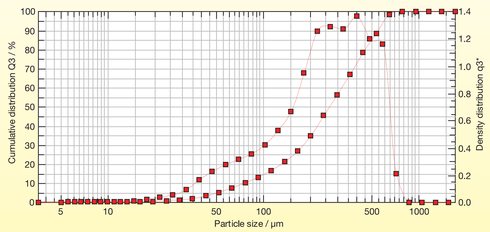


Figure 2. Particle Size Distribution (CONTROL Formulation @ 10 Minutes Mixing Time)

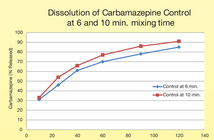


Figure 3. Dissolution of Control Formulation

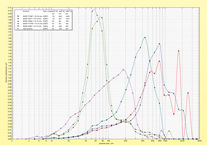


Figure 4. Particle Size Distribution
(Poloxamer Grades Formulations at 10 Min. Mixing Time)

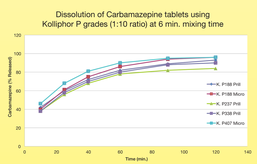


Figure 5. Dissolution of CBZ at 6 min. Mixing Time

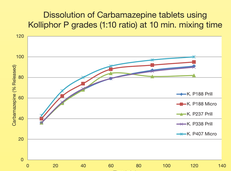


Figure 6. Dissolution of CBZ at 10 min. Mixing Time

Discussion

The particle size analysis of the control formulation granulation showed a uniform distribution of the ingredients in 1:10 ratio at the 10 minutes of mixing time (see Figure 2). They were densification of the particles in Figure 2 as evident in the particle size distribution.

The percent of Carbamazepine released in the control batch in 2 hours, after 6 min. mixing time, was 85% when compared to 90% for the 10 min. mixing time in the 1:10 ratio (see Figure 3). This showed clearly that 10 min. mixing time increased the blend uniformity better than the 6 min. The Particle Size Distribution among the Poloxamer grades showed that both Poloxamers 188 Micro and 407 Micro have the highest density and smallest particle size (see Figure 4) when compared to the particle size distribution of the Prill Poloxamers (Kolliphor™ P 188, 237 and 338 Prill) . The solubilizing effects of the five Poloxamer grades compared here indicated that the amounts of drug released at 10 min. mixing time was higher than at 6 min. mixing time. Kolliphor™ P 188 Micro and 407 Micro showed that robust blend uniformity was achieved and 96% and 100% of drug was released respectively in 2 hours (see Figure 5). This is in contrast to the control batch of 6 and 10 min. of mixing time where only 85% and 90% respectively of Carbamazepine were released in 2 hrs. The release profile of all Poloxamer grades formulations showed above 90% of Carbamazepine (CBZ) release both in 6 and 10 minutes of mixing except for Kolliphor™ P 237 Prill with the lowest solubilization effect of 84% and 82% respectively (see Figures 5 and 6). This indicates that the mixing end point in DC formulation using High Shear Granulator is 10 minutes. The poor solubilizing effect of Kolliphor™ P 237 Prill may be due in part to low molecular weight and particle-particle interaction that causes little or no molecular entanglement. Kolliphor™ P 407 Micro showed the highest solubilization capacity as 100% of Carbamazepine was released in 2 hours as compared to 96% both in 10 and 6 minutes of mixing time respectively (see Figures 6 and 5). Apparently, this is due to the long chain length and high molecular weight of this poloxamer with very high hydrophobic polyoxypropylene units which enhances drug dissolution and solubilization. The small particle size of Poloxamers 188 and 407 Micro (Kolliphor™ P 188 and 407 Micro) increased the homogeneity of the powder blend and consequently the solubilization capacity.

Conclusions

- The use of High Shear Mixer can increase the carbamazepine release to 100% in 2 hrs.
- Homogeneity of powder mixture with API can be achieved at 6 and 10 minutes of mixing time using a High Shear Mixer Granulator.
- Most of the Kolliphor™ P grades solubilized Carbamazepine better than the control.
- Kolliphor™ P 237 showed relatively poor solubilization of CBZ both at 6 and 10 minutes mixing time.
- Solubilization of poorly soluble drug(s) may be achievable in a DC formulation using a High Shear Granulator (at 6 or 10 minutes mixing time) to manufacture a compressible granulation.

References

1. The influence of three poly(oxyethylene)poly(oxypropylene) surface – active block co-polymers on the solubility behavior of Indomethacine Pharma Acta Helv. 60 No. 12 (1985) 339-344
2. Kinetic studies on the stability of Indomethacin in alkaline aqueous solution containing poly(oxyethylene)poly(oxypropylene) surface-active block copolymers. Pharma Acta Helv. 60 No. 12 (1985) 345-350
3. Pluronic surfactants affecting Diazepan solubility, compatibility and adsorption; from i.v. admixture solutions. J. Parent. Sci & Tech Vol. 41 No. 3, May-June (1987) 83-87
4. A Comparative study of Prill and Micronized Poloxamers - Using Different Conventional Granulation Techniques, AAPS Poster presentation 2005
5. Effect of Micronized Poloxamers on Poorly – Water Soluble Drugs, AAPS 2003
6. Solubilization of selected poorly soluble Drugs in directly compressible formulations using micronized Poloxamers, AAPS Poster presentation 2007
7. Comparison of the Solubilization Effect of Micronized Poloxamers, on a poorly water-soluble model drug in capsule formulation by dry Granulation, AAPS Poster presentation 2010

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