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Short communication

Influence of formulation and process variables on physical characteristics and dissolution behavior of controlled release matrix tablets

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Introduction

Control release matrix systems are among the most commonly used systems for oral controlled drug delivery as they can reproduce a desirable drug profile and are cost effective. The primary mechanism of drug release from hydrophilic matrices occurs when the polymer swells on contact with the aqueous media to form a gel layer on the surface of the system. Among literature, many studies have shown that the state of binder as well as its concentration when used as a solution have great influence of the resulting granules and subsequently on drug release (D'alonzo, O'connor and Schwartz, 1990). Binder addition in wet granulation process can be achieved either by adding a liquid binder, characterized by a certain viscosity or a solid binder that dissolves in the low viscosity liquid, in most cases purified water (Chitu et al., 2011). Sieve size in step dry sieving is another critical parameter that influences the particle size of the granules and consecutively dissolution, especialy when the active substance is poorly soluble. (Chu et al., 2012).

The aim of this study was to determine the effect of binder and sieve size used for dry sieving on release rate of BCS Class II active substance formulated as controlled release matrix system.

Materials and methods

Materials

Hydroxypropyl methylcellulose (HPMC) E5 LV and Sodium Alginate (SA) were both used as binders. As for sieves used for dry sieving of the granulate, 1016 (1 mm) and 1575 (1.5 mm) grated sieve for Quadro Comil were chosen.

Methods

High-shear granulation was chosen as a manufacturing process, performed in Diosna P 1/6. Total of 5 formulations were produced using binder solution of HPMC E5LV with concentrations of 6.10% and 10.00%, SA as binder solution with concentration of 1.41% and addition of one of the binders as extragranular phase. When one of the binders was used as a solution, the other was added as an external phase, except in one case where both binders were prepared as solutions. Binder solution of HPMC was prepared by dissolving in hot water and adding cold water to the viscous solution, whereas SA solution was prepared by dissolving in cold water. The binder solutions were added in the granulation phase by peristaltic pump with rate of 45 mL/min.

Dried granulate was screened on Quadro comil, sieve size 1016 and 1575, depending of the selected formulation. Formulation 2 was passed through sieve 1016, and the remaining formulations (3, 4, 5.1 and 6) were passed through sieve 1575. Machine for homogenization Erweka type AR 403 was used for addition of the lubricant. Each

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formulation was compressed on a Korsch XL 100 Pro rotary tablet press.

The formulations were evaluated in terms of bulk and tapped density (Tapped volumeter, Ph.Eur.method 2.9.34), flow rate and angle of repose (Granulate flow tester, Ph. Eur. method 2.9.36) compressibility index, Hausner's ratio (calculated values). Particle size distribution was determined using vibrational sieve analysis (Ph. Eur. Method 2.9.38)

Release rate was studied up to 10 h using Apparatus 2 for dissolution according to Ph Eur. 2.9.3. Each vessel contained 1000 ml of 0.1M HCl previously degassed; paddle apparatus with 100rpm speed was used, at temperature of 37 °C.

Results and discussion

Influence of concentration and state of binder on flow properties and particle size distribution

From the obtained results it was shown that higher concentration of binder solution of HPMC promotes better flow rate and blend with higher bulk density (10.5 – 10.9 s/100g, 0.500 – 0.514 g/mL, for flow rate and bulk density respectively) in comparison to SA when used as binder solution (11.6 s/100g and 0.491 g/mL for flow rate and bulk density respectively) all passed through sieve no. 1575. Formulation 3, which was made with 10% solution of HPMC and sieved through sieve 1016, showed significantly higher values for flow rate (70 s/100g) in comparison with others, probably due to wider size distribution and larger fraction of smaller particles (Shekunov et al., 2006). In terms of angle of repose and Hausner's ratio, comparable results were obtained.

ANOVA Single factor analysis showed that there is statistically no significant difference in terms of particle size distribution regarding the solid or dissolved state of the binders and their concentration ($F_{stat} < F_{crit}$, $p > 0.05$). All formulations passed through sieve no. 1575 showed bimodal size distribution, while formulation 2 sieved through 1016 showed more uniform size distribution.

Influence of concentration, state of binder and sieve size on release rate of active substance

Because of poor flow characteristics and problems with compression of formulation 2, it was excluded from the dissolution studies. Obtained results for the remaining four formulations showed statistically no significant difference at all time points (average dissolution of 16.70-17.92%; 26.79-29.12%; 58.54-61.14% and 77.10-80.97% for 1h, 2h, 6h and 10h respectively) (ANOVA, single factor analysis, $F_{stat} < F_{crit}$, $p > 0.05$).

Conclusion

According to the obtained results, it can be concluded that binder concentration and the state of which it is added does not influence the characteristics of the granules, as well as the dissolution profiles of the tablets, which is critical for this type of formulations. This indicates a robust controlled release matrix system containing BCS Class II active substance containing HPMC and SA as binders.

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