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Optimization of wet granulation of a dothiepin HCl formulation

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Wet granulation and application of a binding agent in tablet formulations are common in Pharmaceutical industry . These are in order to improve flow and compressibility of granules leading to weight uniformity and robust tablets. It has been reported that the type and concentration of binders are the major factors in the quality of the granules (Seager et al 1981). Here in this work we report on the application of organic and aqueous polyvinylpyrrolidone (PVP) binder solutions in the presence and absence of tricalcium phosphate (TCP) in a Dothiepin HCl 75mg formulation.

Small batches (10Kg) of 75mg Dothiepin HCl formulations were prepared using TCP or lactose (46.7%w/w) and starch (20%w/w) as diluents and 4%w/w PVP as the binding agent. PVP binder solutions were prepared by dissolving PVP in isopropyl alcohol (IPA) or in water. Each formulation was thoroughly mixed and then wet massed using a Diosna high shear granulator. The wet granules were dried using a fluid bed drier (3-4%w/w final moisture content). The dried granules were passed through a 16# screen and then lubricated with 1%w/w magnesium stearate for 5 minutes. Convex tablets (9.5mm dameter, 300mg weight) were prepared using a Manesty D3A rotary tablet press. These 75mg Dothiepin tablets are, in practice, used as cores for sugar coating.

The traditional formulation with TCP and starch as the diluents, granulated with the organic binder solution (mean granule size 265μm), produced soft tablets with maximum tablet hardness of 3-3.5 kP, even at a low speed of tableting. In addition, sticking and capping of the tablets were recurrent. It was found that this formulation was not a suitable formulation for sugar coating. When the same formulation was granulated with an aqueous PVP binder solution the granulation end-point became difficult to control and a marginal over run produced heavy end-point (mean granule size 540μm). Although this formulation produced harder tablets at low to medium end-point (7 kP) with no capping and sticking, with a heavy end-point granulation, the tablets were soft (~3kP). In addition, tablet weight variation did not comply with the standard limits.

Wet granulation of the formulation with lactose (instead of TCP) and starch granulated with aqueous PVP binder solution produced the most reproducible and high quality granules (mean granule size 220μm). This formulation produced hard tablets (~8kP) and no capping or sticking with a weight variation within the standard limits, at high speed tablet production.

The tablet disintegration of all the formulations remained between 6-12 minutes and the dissolution studies of the tablets showed that 100% drug dissolved in 30 minutes.

Replacing the organic to an aqueous solvent to prepare PVP binder solution, in the presence of TCP, lead to heavy granulation end-point and large mean granule size. It is thought that PVP and TCP interacted during wet massing and produced hard granules rapidly, with a reduction in their compressibility. The nature of this interaction is currently under investigation. When TCP was replaced by lactose in the formulation and granulated with aqueous PVP, the granulation process and final tablet characteristics were improved, suitable for sugar coating.

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