Effect of Formulation and Process Variables on the Critical Quality Attributes of Warfarin Sodium Tablets

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Purpose
The objective of this study was to understand the effect of formulation and process variables on critical quality attributes (CQAs) of warfarin sodium (WS) tablets.

Methods
Formulation variables included two grades of lactose ie lactose monohydrate (LM) or lactose anhydrous (LA). Three granulating fluids were studied which included Ethanol, isopropyl alcohol (IPA) or IPA water mixture (50:50). Two methods of tablet manufacture ie direct compression and wet granulation method were investigated. Eight formulations of WS were developed to investigate the effect of the above variables.

Formulation ingredients were passed through sieve # 40 followed by blending in a V-mixer at 10 rpm for 10 minutes prior to lubrication with magnesium stearate. When wet granulation process was used, the wet granulations were dried at 50°C until loss on drying of less than 1% w/w was attained. WS tablets were compressed to a hardness of 8-10 KP on a rotary tablet press.

Formulations were characterized for IPA and water content, hardness, disintegration time (DT), assay and dissolution. Tablets were also evaluated by scanning electron microscopy (SEM), near infrared chemical imaging (NIR-CI), X-ray powder diffraction (XRPD) and solid state nuclear magnetic resonance (ssNMR)). Stability of the formulations was investigated under accelerated storage conditions (40°C/75% RH) for three days.

Results
The DT and dissolution of WS tablets manufactured by direct compression method were faster than tablets manufactured by wet granulation method. The drug changed from crystalline to amorphous form in tablets manufactured by wet granulation method (using water or IPA+water as granulation fluid) and behaved more like a binder. This observation was supported by SEM, NIR-CI, XRPD and ssNMR data. This resulted into slower dissolution of these tablets. Similarly, tablets containing LM exhibited faster disintegration and dissolution than tablets containing LA.

Storage under accelerated conditions resulted in increase in hardness and DT, and a decrease in the rate and extent of dissolution. This was also attributed to phase transformation of the drug and consolidation with particles' bonding.

Conclusion
CQAs of WS Product are significantly affected by manufacturing and formulation variables.