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Identifying and Optimizing the Critical Excipients in Moisture Activated Dry Granulation Process for Two Anti TB Drugs of Different Aqueous Solubilities

Authors : K. Srujana, Vinay U. Rao, M. Sudhakar

Abstract : Isoniazide (INH) a freely water soluble and pyrazinamide (Z) a practically water insoluble first line anti tubercular (TB) drugs were identified as candidates for optimizing the Moisture Activated Dry Granulation (MADG) process. The work focuses on identifying the effect of binder type and concentration as well as the effect of magnesium stearate level on critical quality attributes of Disintegration time (DT) and in vitro dissolution test when the tablets are processed by the MADG process. Also, the level of the drug concentration, binder concentration and fluid addition during the agglomeration stage of the MADG process was evaluated and optimized. For INH, it was identified that for tablets with HPMC as binder at both 2% w/w and 5% w/w level and Magnesium stearate upto 1%w/w as lubrication the DT is within 1 minute and the dissolution rate is the fastest (> 80% in 15 minutes) as compared to when PVP or pregelatinized starch is used as binder. Regarding the process, fast disintegrating and rapidly dissolving tablets are obtained when the level of drug, binder and fluid uptake in agglomeration stage is 25% w/w 0% w/w binder and 0.033%. w/w. At the other 2 levels of these three ingredients, the DT is significantly impacted and dissolution is also slower. For pyrazinamide,it was identified that for the tablets with 2% w/w level of each of PVP as binder and Cross Caramellose Sodium disintegrant the DT is within 2 minutes and the dissolution rate is the fastest(>80 in 15 minutes)as compared to when HPMC or pregelatinized starch is used as binder. This may be attributed to the fact that PVP may be acting as a solubilizer for the practically insoluble Pyrazinamide. Regarding the process,fast dispersing and rapidly disintegrating tablets are obtained when the level of drug, binder and fluid uptake in agglomeration stage is 10% w/w,25% w/w binder and 1% w/w.At the other 2 levels of these three ingredients, the DT is significantly impacted and dissolution is comparatively slower and less complete.

Keywords : agglomeration stage, isoniazide, MADG, moisture distribution stage, pyrazinamide
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