A Comparison and Process Optimization of Poorly Compressible Drug Tablets Produced by Direct Compression and Top Spray Granulation Technique

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Purpose
Paracetamol and Ibuprofen are well known for their poor compressibility and bad flowability characteristics. Paracetamol and ibuprofen direct compression always been a challenging task because paracetamol crystals are very hard, brittle and fracture very easily when compressed producing capping and laminate compacts, the paracetamol crystals have no plasticity/elasticity. The large Paracetamol crystals have the disadvantage of being slowly dissolved in the body and required additional tableting aids to increase the rate of dissolution. Similarly ibuprofen exhibits bad dissolution behavior due to its hydrophobic structure another problem in its manufacturing is its high tendency of sticking to punches. As a result ibuprofen and paracetamol tablets manufactured by conventional wet granulation method which is a time-consuming expensive process in comparison to direct compression, Hence due to above-mentioned characteristics of both drugs and disadvantages with wet granulation method the present experimental study was carried out. The purpose of this study was to compare directly compressible formulation of ibuprofen and paracetamol produced by using direct compression and top spray granulation technique and to explore the other process, top spray granulation with optimized process parameters, through which directly compressible granules of good flowability and compressibility can be obtained.

Methods
Excipients were selected based on the drug-excipient compatibility study and data collected during the literature survey. Preliminary trials (F1-F7) were performed by direct compression method using dibasic calcium phosphate, lactose anhydrous grade (DCL 21), microcrystalline cellulose grade (Avicel PH 101) as directly compressible diluents, crospovidone, magnesium stearate and colloidal silicon dioxide were also used. Compression was carried out in 16-station rotary compression machine using 21×10.5 mm oval shaped punches, plain on upper punches and plain on lower punches with a suitable die. Physical parameters such as thickness, hardness, friability, disintegration time were optimized, further, two more trials (F8 and F9) were performed for formula optimization with different concentration of diluents and disintegrating agents. In order to obtain directly compressible granules, top spray granulation process was used. A fluidized bed processor was used for granulation. 10% binder solution of povidone K-30 in purified water was used as granulating solution. Three trials (T1,T2 and T3) were performed with different ranges of process parameters to optimize the top spray granulation process such as the effect of inlet air temperature, spray rate (for loss on drying optimization), blending time and hardness were selected for process optimization. They prepared granules were evaluated for precompression parameters such as bulk density, tapped density, Hausner ratio and compressibility index, among them batch (T3) found optimized batch on the basis of precompression and post compression evaluation parameters. Both the optimized formulations (F7 and T3) prepared by direct compression and top spray granulation technique were compared for their physical parameters and dissolution profile with reference product.

Results
Nine preliminary trials (F1-F9) were performed by using direct compression method to optimize directly formulation among them batch F7, F8, and F9 shows good results and within acceptable limits. Formulation (F7) selects as optimize product on the basis of hardness 12.1 kp, friability 0.5%, disintegration time 22 sec. and dissolution rate (Ibuprofen 88.7% and paracetamol 90.7% respectively). Directly compressible granules were prepared by using top spray granulation technique. Batch (T3) was found optimized batch with different ranges of process parameters such as inlet air temperature, spray rate, loss on drying and blending time in which inlet air temperature 54-56°C, spray rate 24-27 gm/min, pump rpm 74-76, loss on drying 2.4% and blending time 15 min was found optimum for the establishment of process parameters. Pre-compression parameters such as bulk density 0.63 cc/gm, tapped density 0.74 cc/gm, compressibility index 14.8 and Hausner ratio 1.17 was recorded for granules of batch T3, when subjected to compression the batch T3 passes all the physical evaluation test with hardness 9-12 kp, friability 0.20%, disintegration time 6.01 sec. and dissolution rate was found (Ibuprofen 90.7% and paracetamol 93.0% respectively) near to reference product (Ibuprofen 95.6% and paracetamol 98.6% respectively). When both optimized formulation (F7 and T3) were compared for their dissolution profile with reference product formulation (T3) prepared by top spray granulation was selected as optimized formulation on the basis of good compressibility and dissolution profile.

Conclusion
It can be concluded from this investigation that top spray granulation resolves the issues concerned with conventional wet granulation technique, enables the direct compression of ibuprofen and paracetamol possible along with that offers the advantage of increase in productivity, decrease in cost of product and low process validation.