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Short communication

Evaluation of influence of different manufacturing technologies on impurity profile of immediate release formulation comprising highly degradable ACE inhibitor as model active substance

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Introduction

Impurity profiling and control is one of the most regulated areas in the pharmaceutical industry. According to ICH Q3A (R) "Impurities in the New Drug Substance" and ICH Q3B (R) "Impurities in the New Drug Product", a drug substance impurity is "*any component of the new drug substance that is not the chemical entity defined as the new drug substance*," and a drug product impurity is "*any component of the new drug product that is not the drug substance or an excipient in the drug product*." In a pharmaceutical product, an impurity is a quality issue, since it could potentially compromise the efficacy and safety of the drug product (Qiu and Norwood, 2007).

The sources and routes of formation of impurities may originate from starting materials, by-products and residual solvents from the drug substance synthesis, formulation, manufacturing technology and type of packaging. Impurity formation and drug stability can be influenced by various factors, such as environmental conditions, temperature, light, and relative humidity on the drug product (Kovaleski et al., 2007).

Angiotensin-converting enzyme (ACE) inhibitors are effective blood pressure lowering agents, prodrugs, ester-type, which are characterized with high degradation potential under different environmental conditions like humidity, temperature and light and their degradation impurities have been also identified (Regulska et al., 2013).

Choice of manufacturing technology can have a huge impact on drug product stability and impurity profile, especially when the drug substance is highly degradable. The aim of this study was to evaluate the influence of different manufacturing technologies: direct compression, dry granulation (roller compaction) and wet granulation (high shear method) on stability and impurity profile on immediate release (IR) tablets containing highly degradable ACE inhibitor as model active substance and point potential degradation parameters related with manufacturing process.

Materials and methods

The active pharmaceutical ingredient (*API*, ACE inhibitor, BCS class III) was provided by Glenmark Pharmaceuticals Limited, India; Lactose anhydrous (*LA*, Super Tab 21, DFE Pharma, DE); Lactose monohydrate (*LM*, M100 and M200, Meggle, DE); Maltodextrin (*MD*, Lycatab DSH, Barentz, NL), Sodium starch glycolate (*SSG*, Primojel, DFE Pharma, DE); Colloidal silicon dioxide (*CSD*, Aerosil 200, Evonik, DE) and Magnesium stearate (*Mg stearate*, FaciSpa Carasco, IT).

Formulation composition was kept constant (*API* 5.55%, *LA/LM* 80.48%, *MD* 9.98%, *SSG* 2.99%, *CSD* 0.50% and *Mg stearate* 0.50%) to minimize its influence on final product quality.

Direct compression method (F1) was carried out in a high shear mixer (*HS*, Diosna, DE). Prior to the mixing, all excipients were sieved through 0.813 mm sieve. *API, LA, MD, SSG* and *CSD* were mixed in the *HS* (10 min, impeller: 300 rpm, chopper: 1000 rpm). After that, *Mg stearate* was added (1 min, 250 rpm, chopper: off).

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Wet granulation method (F2-with water, F3-with ethanol anhydrous as granulation fluid) was carried out in a *HS* where *API* was pre-blended with *LM M200, MD* and ½ of SSG (3 min, 300 rpm/1000 rpm). Afterwards, granulation fluid (water/ethanol, accordingly) was added (300 rpm/1000 rpm and 1 min 30 sec- F2; 1 min- F3) and granulated F2- 40 sec, F3- 1 min 30 sec, 400 rpm/1500 rpm. The wet mass was sieved (Quadro Commil, CA, sieve 6350 µm), dried until *LOD* max. 3% (Mycrolab Fluid Bed drier, DE). Dried granules were sieved (0.813mm sieve) and transferred into drum blender (PM5, Erweka GmbH, DE; 10 min, 350 rpm) mixed with *LM M100*, CSD and other ½ of SSG and finally lubricated with Mg stearate (5 min, 300 rpm).

Dry granulation method (F4), was carried out on laboratory scale roller compactor (The Fitzpatrick Company, IDEX MPT Inc, USA), where *API* was pre-blended with *½ LA, CSD, MD, ½ SSG* and *½ Mg stearate* in drum blender (20 min, 350 rpm). Afterwards, pre-blend was granulated with compaction speed/pressure 5rpm/25.00 bar; horizontal/vertical feeding 20 rpm/180 rpm and milling size/speed 0.813 mm/650 rpm. Granulate was mixed with extra granular excipients in drum blender (*½ LA, ½ SSG;* 10 min, 350 rpm) and lubricated with *Mg stearate* (5 min, 350 rpm).

Final blends were subsequently compacted into round 6.0 mm tablets with compression force of 6.5-7.5 kN (Korsch XL 100, DE).

Prepared final blends were fully characterized according to Ph.Eur 10.5 methods (SVM 102 tester, ERWEKA GmbH). Prepared IR tablets were evaluated for mass and mass variation (SECURA224-1CEU, Sartorius, AG) hardness, thickness and diameter (TBH 425 TD, Erweka GmBh, DE). Prepared tablets were stressed 30 days in stability testing chambers in open petri dishes, at temperature of 30 °C with a relative humidity (RH) of 65%. In order to evaluate the effect of manufacturing process on impurity profile tablets were analyzed initially and after completion of the study. A HPLC method (*Column*: Infinity Poroshell 100x2.1mm 1.7 µm; *Detection*: UV 230 nm; *Injection Volume*: 10 µL of the standard and sample solutions; *Flow rate*: 0.2 mL/min; *Temperature*: 55 °C) was used for determination of the related and degradation products.

Results and discussion

Tablets can be produced by several different methods, but direct compression is a method of the first choice, owing to its simplicity, cost effectiveness and also avoidance of water and heat for moisture or heat sensitive drug substances. Results obtained for total impurities at initial analyses meet the acceptance criteria (NMT 1.0%) for all formulations. Slight, but significant changes, increment was observed during the stability study. Obtained results for total impurities for *F1* were below the established specification limits at initial analysis (0.28%) but there was an increase (0.68%) when stored at 30 ˚C/65 % RH for 30-day stability period.

F4- has shown slightly higher initial % of impurities (0.30%) and therefore increment during stability study (0.78%) compared to *F1*. Taking in consideration the fact that both methods are dry methods, this phenomenon was evaluated as potential influence of higher compression forces (needed for forming appropriate ribbons) and longer time needed for manufacturing where granulate is exposed on not controlled ambient conditions.

On the other hand, significant increase of total impurity profile was noted on wet granulation methods- *F2* (0.78%) and *F3* (0.85%) at initial analyses, which compared to dry methods *F1* (0.28%) and *F4* (0.30%) were few times bigger. Increase of total impurity results were noted on both laboratory trials regardless the type of granulation fluid (water or anhydrous ethanol) which was in accordance with literature evaluation on degradation potential of API under exposure to higher % of humidity and temperature (Regulska et al., 2013).

Conclusion

According to the obtained results for impurity profile from this study, it can be concluded that manufacturing technology has a huge impact on impurity profile, especially when the API is characterized with high degradation potential. Based on overall results from this study, direct compression and dry granulation with further appropriate optimization should be manufacturing technologies from choice for this kind of APIs, due to lower potential of impurities formation.

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