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Short communication

Selection of appropriate manufacturing technology for development of Oxycodone prolonged release film-coated tablets using QbD approach

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Introduction

The concept of Quality by Design (*QbD*) has become a new concept for the development of quality pharmaceutical products and it was mentioned in the ICH Q8 guideline, which states that "*quality cannot be tested into products, i.e., quality should be built in by design*". According to ICH Q8, *QbD* is defined as a systematic approach to development that begins with predefined objectives and emphasizes product and process understanding and process control, based on sound science and quality risk management (Singh and Sharma, 2015).

The design and development process of the generic drug product with modified-release properties using a *QbD* approach is a systematic, efficient, risk-controlled and knowledge-based method to improve the pharmaceutical process development and eventually improve the product quality (Thapa et al., 2019).

Development processes of solid dosage forms in general is divided in two main phases. *Phase I* – Design, development and optimization of formulation of final product and *Phase II* – Design, development and optimization of manufacturing process. Selection of appropriate manufacturing process is of crucial manner in order to modulate final product quality. Therefore, during *one factor - at a time* experiments at early development phase, it is highly important to evaluate different manufacturing technologies due to the fact that optimization of process variables is very tedious, expensive and time-consuming phase (Huang et al., 2003). The study aims to make detail evaluation of the influence of different manufacturing technologies: direct compression, wet granulation (high shear method) and dry granulation (roller compaction) on critical quality attributes (*CQAs)* of final product. The knowledge gained was intended to be used in order to make appropriate selection of manufacturing process for development of generic drug product of Oxycodone 40 mg prolonged release film-coated tablets (*OH-PRT*).

Materials and methods

Oxycodone hydrochloride (*OH*) was provided by S.A.L.A.R.S. S.p.A., Italy; Hydroxypropyl methylcellulose (HPMC K 100 Premium) was provided by DOW Chem. Comp., Colorcon, Germany; Cellulose microcrystalline (MCC-Avicel PH 101) was provided from FMC Biopolymer, Cork Ireland; Magnesium stearate was provided from Faci SpA, Carasco GE, Italy and Opadry 20A220058 Yellow fron Colorcon, DE. OH reference standard and OH impurity D were provided by European Directorate for the Quality of Medicines and Health Care Council of Europe (EDQM–Strasbourg, France). All other chemicals used were of pharmaceutical grade and were used without further modifications.

The formulation composition of *OH-PRT* was kept constant (*OH 30.76%; HPMC K100 30,00%; MCC 38,23%* and *Mg-stearate 1,00%)* in order to minimize their influence on final product quality.

Direct compression method (sample L01-1) was carried out in drum blender (PM5, Erweka GmbH, Germany. Prior to the mixing, all excipients were sieved through 0.813 mm sieve. *OH, HPMC* and *MCC* were

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transferred into a mixing drum (15 min, 250 rpm). After that, Mg-stearate was added (5 min, 250 rpm).

Wet granulation method (L01-2) was carried out in high shear granulator (Diosna, DE), where *OH* was pre-blended with *MCC* and *HPMC (*3 min, 300 rpm). Afterwards, granulation liquid was added (315 rpm/1000 rpm and 2 min) and granulated 1min 30 sec, 400 rpm/1000 rpm. The wet mass was passed through 0.620 mm sieve and the granules were subsequently oven dried on 50 °C (MOV-212S; Panasonic, JP). The dried granules where sieved through 0.813 mm sieve and blended with Mg-stearate as stated above.

Dry granulation method (L01-3), was carried out on laboratory scale dry granulator (The Fitzpatrick Company, IDEX MPT Inc.), where *OH* was pre-blended with *MCC* and *HPMC* in drum blender (10 min, 350 rpm). Afterwards, pre-blend was granulated with compaction speed/pressure 5rpm/25.00 bar; horizontal/vertical feeding 35 rpm/180 rpm and milling size/speed 0.813 mm/550 rpm.

Final blends obtained from all three manufacturing techniques were compacted into round 7.0 mm tablets with compression force 5.0 – 5.5 kN and compression speed 25 -30 rpm (Kosrh XL 100, DE). All prepared tablet cores were film-coated appropriately (O'HARA Labcoat M).

Prepared final blends were fully characterized according to Ph. Eur 8.9 methods (SVM 102 tester, ERWEKA GmbH). Prepared *OH-PRT* were evaluated for mass and mass variation (SECURA224-1CEU, Sartorius, AG) hardness, thickness and diameter (TBH 425 TD, Erweka GmBh, DE). Assay of *OH-PRT* and uniformity of dosage units were determined with HPLC method (Column: Kromasil C18 150x4.6mm.Detection: 230 nm; Inj. vol: 20 µL; Flow rate: 8 mL/min; Temperature: 55 °C). *In vitro OH* release was performed in 900 ml phosphate buffer pH 6.8 at 37±0.5°C for 12h. Obtained DSS profiles were compared with reference drug product (OxyContin 40 mg PR film-coated tablets, Purdue pharma, DE), in phosphate buffer pH 6.8, as most discriminatory media. Impurity profile was analyzed by HPLC (Column: Kromasil C18 150x4.6 mm, 5 µm; Detection: 230 nm; Inj. Vol: 20 µL; Flow rate: 0.2 mL/min; Temperature: 40 °C).

Results and discussion

Dry mixing is a manufacturing technology of choice for the pharmaceutical industry (especially for generic industry, which should be competitive on the market in every aspect) because it has significant advantages compared with other granulation techniques in terms of time, handling and cost. The results from final blend characterization obtained from all tri batches showed differences in flow properties, namely *L01-1* and *L02-1* had passable flow, while *L01-3* had poor flow properties (Carr-index was 21, 24 and 28 for *L01-1*, *L02-1* and *L01-3*, respectively). An inadequate flow of sample *L01-3* could be attributed to the excessive compression force required to form suitable ribbons which lead to the formation of a harder granule that required multiphase milling, which resulted in a relatively wide size distribution of final granulate with high % of fine fraction. This assumption was also confirmed with the results for assay, where, even the results for all three trials where within the acceptance criteria (98.64-100.36%), the biggest value of *RSD* was observed for *L01-3* (8.93). Results from physical characterization of prepared film-coated tablets where within acceptance criteria according to *QTPP* of the reference product (round biconvex film-coated tablets with mass of 135.00 mg±7.5%, hardness 11-13 kP, diameter 7.00mm±7.5% and thickness 3.1-3.6 mm), except for *L01-3* where uniformity of weight was bigger than ± 7.5%. Obtained results from *in vitro* release studies pointed that even there were significant differences between the quality of *OH-PRT* samples (based on other evaluated parameter), there were no significant difference with respect to the release rate of *OH* compared to reference product (similarity factor f_2 50.08-62.11). The data obtained from impurity profile evaluation were within the specification limits suggestion good stability of *OH* and final product irrespectively to formulation and/or manufacturing process used.

Conclusion

From this study it could be concluded that the type of manufacturing process significantly affects the final product quality-*OH-PRT* especially parameters flowability of final blends, appearance and mass variation of film-coated tablets. Based on overall results, the wet granulation (high-shear) method was chosen for Oh-PRT production and critical process parameters should be defined in future.

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