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Short communication

Formulation and in-vitro evaluation of prolonged-release matrix tablets

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Introduction

The aim of this formulation development was to design a prolonged-release matrix tablet for 12-hour delivery of an opioid analgesic. The main challenge during formulation development was selection of the type and the concentration of the matrix-formers for obtaining the desired in-vitro dissolution rate. Similar in-vitro dissolution profiles between the generic and the reference product are pre-requisite for the performance of the bioequivalence study. Therefore, the formulation development was guided by an assessment of the in-vitro similarity of the dissolution profiles between products using similarity factor f_2 according to the Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr, 2010).

Two matrix-forming excipients: polyvinyl acetate/povidone and hypromellose (viscosity app. 100 000 cps) were selected and tested in different ratios in the formulation for creating the specified dissolution rate.

Polyvinyl acetate/povidone enables prolonged-release by a diffusion-controlled mechanism. This matrix-former contains a water-insoluble part (polyvinyl acetate) and a water-soluble part (povidone). Povidone dissolves in contact with water and creates pores within the matrix which enable further water penetration in the core and subsequent dissolution of the active ingredient (Buhler, 2008).

Hypromellose, as a matrix-forming agent, controls the dissolution rate by mechanisms of both diffusion and erosion. Upon contact with water, the polymer chains on the tablet surface hydrate and form a viscous gel layer, which controls the penetration of additional water into the tablet and also controls the diffusion rate of the dissolved drug molecules from the tablet. When the gel becomes fully hydrated, the polymer chains start to relax, disentangle, loose their structure, and are finally eroded (dissolved) from the tablet surface. So, the release is controlled by diffusion through, and erosion of, the gel layer (Chinmaya et al., 2015).

Besides obtaining desired in-vitro dissolution rate, the formulation should also be characterized with suitable flowable and compressible properties, so that tablets with uniform mass and appropriate hardness are produced.

Materials and methods

Materials

Opioid analgesic active substance, Povidone (Kollidon K30), Lactose monohydrate 200M (GRANULAC 200), Polyvinyl acetate/Povidone (Kollidon SR), Hypromellose (Methocel K100M Premium CR), Magnesium stearate, Opadry green, water purified and reference product.

Methods

Six formulations were prepared with varying quantities (%w/w) of two matrix-formers and pore former to find the optimal formulation with the most similar critical quality attributes (CQAs) as the reference product. The quantity of Kollidon SR varied in the range of 35-45%w/w, the quantity of hypromellose varied from 10%-23%w/w, and lactose 5.65%-8.65%w/w. All formulations were prepared with wet granulation technology (high-shear granulation with fluid bed drying), followed by extragranular mixing with the matrix-formers and the lubricant in a suitable homogenization machine.

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The flowability and the compressibility of the final blends were evaluated through the parameters compressibility index, Hausner ratio, and angle of repose. The final blend was compressed into tablets, which were afterwards film-coated with Opadry green to protect the photosensitive API from light.

Uniformity of mass and hardness of tablets were measured as in-process controls. While uniformity of mass is related to the CQA uniformity of dosage units, the hardness is related to the dissolution rate, so these in-process parameters should be adequately controlled. The comparative dissolution profile studies were performed in all regulatory media using apparatus 2 (paddle, 50 rpm, 900 ml buffer) according to the recommendation in the Guideline on the investigation of bioequivalence (Simulated Gastric Fluid, buffer pH 4.5 and buffer pH 6.8). Additionally, the formulation of choice was tested in SGF with 40%v/v alcohol for assessment of alcohol-induced dose-dumping (CDER/FDA, 2019 Bioavailability Studies Submitted in NDAs or INDs).

Results and discussion

The results from the process control parameters performed on the final blends showed satisfactory values (compressibility index 17-20%, Hausner ratio 1.20-1.25, angle of repose 32.1–36.2°), which indicates that the formulations possessed properties suitable for tableting. This was confirmed during the tableting process by obtaining tablet cores with a uniform mass within ± 5% and appropriate hardness values (5.0-11.0 kP).

The factors of similarity (f_2) obtained from the comparative in-vitro dissolution profiles studies, for SGF medium were in the range 64.18-79.59, for buffer pH 4.5 from 66.43 to78.77, and buffer pH 6.8 from 53.83 to 73.44.

According to the Guideline on the investigation of bioequivalence, Appendix I, an f_2 value between 50 and 100 suggests that the two dissolution profiles are similar. The obtained f_2 values for all formulations showed similarity with the reference product, but one of them (formulation 6) had the highest f_2 values in all media (79.59 in SGF, 78.77 in pH 4.5, and 73.44 in pH 6.8), indicating most similar in-vitro release rate. This formulation contained a combination of two matrices: Polyvinyl acetate/Povidone and hypromellose in concentrations such as 35%w/w and 23%w/w respectively, and 5.65% w/w Lactose monohydrate as pore former. The dissolution profile in SGF with 40%v/v alcohol demonstrated that no dose dumping occurs, so there is no safety risk in case of concomitant administration with alcohol.

Conclusion

The formulation development of a prolonged-release matrix tablet for 12-hour delivery of the API has been successfully performed. The selected formulation enabled obtaining a product with very similar CQAs as the reference product.

The performed comparative dissolution profile studies showed adequate similarity factors with the reference product in all media, leading to the conclusion that the designed formulation and process is a suitable candidate for the performance of a bioequivalence study.

References

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