Macedonian pharmaceutical bulletin, 68 (Suppl 1) 279 - 280 (2022)
Online ISSN 1857 - 8969
DOI:10.33320/maced.pharm.bull.2022.68.03.134
Short communication

Improving the dissolution rate of Nebivolol hydrochloride by using nonionic surfactant and polymer combination

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Introduction

One of the main guiding tools in development of various oral drug delivery technologies is the Biopharmaceutics Classification System (BCS). The BCS is a scientific framework for classifying the drugs into four classes I, II, III and IV based on their aqueous solubility and intestinal permeability. Drugs which belong to class II of the BCS are characterized with high membrane permeability and poor aqueous solubility which results with slow dissolution rate (Chavda et al., 2010; Yadav et al., 2013).

More than 40% of the drugs that are approved and nearly 70% of developmental pipeline candidates are poorly soluble, because of which they result with poor oral bioavailability. During the development of the ideal solid dosage forms, poor aqueous solubility is a challenging issue which can lead to failure in formulation development process. Absorption of drug and its therapeutic effectiveness is affected by solubility. The solubility is a significant physicochemical factor and the main reason behind low dissolution rate and inadequate bioavailability of the drug. For drugs from BCS class II absorption is dissolution-rate limited. Therefore, enhancement of the solubility and dissolution is an essential and rate-limiting step to obtain therapeutic effect (Feng et al., 2012; Nikghalb et al., 2012). Through the years various technological methods for enhancing the dissolution rate were used such as micronization, adsorption onto high surface area carriers, lyophilization, co-grinding, formulation of inclusion complexes, solubilization by surfactants, solid dispersions, solid solutions, hydrotrophy, inclusion of a drug solution or liquid drug into soft gelatin capsules and co-solvency (Mahapatra et al., 2020).

Nebivolol is a beta-adrenergic receptor blocking agent, and has T_{max} of 1.5-4 hours. Since it belongs to BCS class II, it has very low aqueous solubility, which results into poor dissolution rates. The main objective of this work was to investigate the possibility of achieving similar dissolution profile of Nebivolol with the reference product in three different pH mediums (pH 0.01, pH 4.5 and buffer pH 6.8) by improving its dissolution rate.

Nowadays a large number of polymer carriers are available for use in formulations as wettability and controlled release agents. Based on the literature data, we prepared three formulations by using "solubilization by surfactants" technique (surfactants concentration above the critical micelle concentration increases the drug solubility due to solubilization and thereby increases the dissolution rate) in combination with biodegradable, biocompatible hydrophobic polymer to ensure controlled drug release. In this study we will focus and try to explain the effect of surfactants and polymers on dissolution rate (Tekade and Yadav, 2020).

Materials and methods

Materials

Nebivolol Hydrochloride (Hetero Drugs Limited) was used as an active pharmaceutical ingredient (API), polymer Hydroxypropylmethyl Cellulose ((HPMC), JRS Pharma) in range of 2% - 5%, and surfactant Polylosorbate 80 (KLK Kolb) in range 0.1% - 3%. Other excipients used in formulations were: Lactose Monohydrate 200 mesh (Granulac®200), Maize Starch, Croscarmellose sodium (Vivasol®); Cellulose Microcrystalline PH 102 (Vivapur®102), Sillica Colloidal anhydrous (Cab-o-sil®) and Magnesium stearate. Nebilet® (Berlin – Chemie AG) was used as a reference product (R).

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Method

Nebivolol tablets were produced by wet granulation. Tablet formulations were prepared with different ratios of dispersed Nebivolol in binding solution (polysorbate 80 and HPMC) versus Nebivolol in dry mixture (50:50; 30:70 and 70:30).

Dissolution and drug content

According to Ph.Eur 10th edition drug content was measured by an HPLC method (2.2.29). The dissolution rate of the API was measured using apparatus II (paddle type) at 50 rpm.

Results and discussion

The quality control of all three formulations was with an aim to characterize the drug content and comparative dissolution profile with R. In each formulation the results for drug content were 96% - 100%. Unlike the results for drug content, the comparative dissolution profile of the formulations exhibited different dissolution rate in pH 0.01; acetate buffer (pH 4.5) and phosphate buffer (pH 6.8).

Main indicator for comparative dissolution profile is similarity factor (f2) which is defined with the dissolution values (%) of the developing and reference products over all time points. Formulation in which the ratio of Nebivolol was 50:50 - showed the predicted dissolution profile and similarity factor with R in all three mediums pH 0.01 (f_2=57.54); pH 4.5 (f_2=77.21) and pH 6.8 (f_2=53). Second formulation where ratio of Nebivolol was 70:30 showed good results for dissolution and similarity factor only in two mediums pH 0.01 (f_2=53.02) and pH 4.5 (f_2=66.38). Similarity factor for this formulation in pH 6.8 medium was f_2=44.04. The similarity factor of the third formulation where the ratio of Nebivolol was 30:70, was under f_2=35 in all three pH mediums. This ratio of API in binding solution versus API in dry mixture is not a ratio of choice for achieving the desired dissolution profile.

In our formulations critical step was ratio of the API dispersed in binding solution versus API in dry mixture. According to this in formulations where a higher content of the API was dispersed in binding solution (HPMC and polysorbate 80) better values for similarity factor with R were achieved. When higher content of API is dispersed in solution with polymer and surfactant - during drug dissolution a larger number of drug molecules are in close proximity with HPMC (facilitated by the effect of surfactant) and desired dissolution profile is achieved. In formulation where smaller number of drug molecules were dispersed (ratio 30:70), HPMC and polysorbate 80 did not have the same effect (acting together) on the dissolution profile of the drug. In this formulation the drug release profile is retained due to effect of HPMC. Values for dissolution rate are higher than those for dissolution rate of R in each time point. The reason behind this could be that, when molecules are not dispersed in the solution they are directly exposed on effect of the surfactant.

Conclusion

According to the obtained results, similar dissolution profiles with those of R in all pH mediums were achieved with formulation with ratio of 50:50 in which half of the drug molecules were dispersed in the binding solution and the other half was in dry mixture. Also through this study we can come to some conclusion that using surfactants in combination with polymers is a potential method for increasing solubility of drugs from BCS class II by achieving their fine dispersion at absorption level.

Despite the good initial results, it is necessary a scale - up and validation of the process to be performed. Also, stability study should be completed in order to prove the effectiveness of the method.

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