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PREPARATION AND IN VITRO EVALUATION OF REPAGLINIDE TABLETS

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Abstract: The purpose of this article was to prepare and optimize the ingredients of Repaglinide tablets. The impacts of ingredients (diluent, disintegrants and lubricants) content on tablets were evaluated. The optimum prescription contained Repaglinide, meglumine, poloxamer, MCC, maize starch, PVPP, magnesium stearate and appropriate PVP K30. The tablets were evaluated by Carr's index, hardness, friability and dissolution study. The dissolution of self-made tablets were compared with that of the commercial brand Novo Norm in 4 dissolution media: 0.1mol/L HCL, citrate buffer at pH values of 5.0, phosphate buffer at pH values of 6.8 and distilled water. The dissolution samples were assayed using a HPLC method. The dissolution results were analyzed by similarity factors (f_2). The results show optimum tablets had similar dissolution profiles with the commercial brand.

Keywords: Repaglinide, tablet, diluents, dissolution study, formulation



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INTRODUCTION

Repaglinide is the first of new oral antidiabetic agents developed by German Boehringer Ingelheim company as non-sulfonylurea insulin secretion agent. It come to the United States market in 1998. The drug is used for the treatment of patients with type 2 diabetes whose disease cannot be controlled by food control, exercise and weight loss alone¹⁻⁵. The drug can targeting the early-phase insulin secretion lower the postprandial glucose excursions, which is important in reducing long-term cardiovascular complications of diabetes⁶⁻⁹. The tablet imported into China in 2000 and the trade name is NovoNorm.

The goals of this study were to developed and optimize Repaglinide tablets. The physical characteristics such as their drug content, hardness, thickness, friability, and in vitro dissolution characteristics were evaluated. The dissolution data obtained from the optimized tablets in the four dissolution media after 60 min were compared with those of the commercial product and the similarity of the dissolution profiles was evaluated by f_2 values methods.

MATERIALS AND METHODS:

Materials: Repaglinide was obtained from China National Pharmaceutical Foreign Trade Corporation. Meglumine was got from Libang Pharmaceutical Co. Ltd (Xi'an, China), Poloxamer was obtained from Yaoda Pharmaceutical Co. Ltd (Shenyang, China), Maize starch, dextrin was supplied by Dongyuan Pharmaceutical Co. Ltd (Liaoning, China), microcrystalline cellulose (MCC), povidone (PVP), crospovidone (PVPP), was purchased from Shanhe Pharmaceutical Excipients Co. Ltd (Anhui, China), and Magnesium stearate were obtained from Aoda Pharmaceutical Co. Ltd (Liaoning, China).

Preparation of the tablets: 95% ethanol contained 10% of the PVP K30, repaglinide and meglumine were added to it to obtain the adhesive. Microcrystalline cellulose, starch, dextrin, poloxamer, PVP K30 were weighed and blended, Then the adhesive solution was added and blended for 5 mins to obtain granules. The granules were dried in an oven maintained at $60^{\circ}\text{C} \pm 5^{\circ}\text{C}$ for 1h. The final granules were then passed through a 20 mesh nylon sieve. Magnesium stearate was blended with the mixture and then tableting. The weight was 100mg/tablet.

Carr's index: The bulk and tap densities were determined as follows. Each of sample (20 g) was poured into a 100 mL graduated cylinder. The cylinder was then lightly tapped to collect all the powder sticking on the wall of the cylinder. The volume was read directly from the cylinder and used to calculate the bulk density. For tap density, the cylinder was tapped on a wooden bench to attain a constant volume reading from the cylinder. Carr's index was calculated using the equation $([ptap - pbul] / ptap) * 100\%$.

Hardness: Hardness of ten randomly selected tablets was determined. The mean hardness and coefficient of hardness variation were calculated.

Friability: The friability (F) test was performed according to the Chinese pharmacopoeia. After 4 minutes of rotation at 25 rpm, dust of tablets was accurately weighed and percentage weight loss was calculated. A maximum weight loss of not more than 1.0% was considered acceptable.

HPLC Determination of Repaglinide: Twenty tablets of were precisely weighed and grinded. Transfer an accurately weighed portion of the powder, equivalent to about 2.5mg of drug, to a suitable volumetric flask, add 100.0 mL of 0.1mol/L hydrochloric acid, shake for 30 minutes, and the solution was filtered through 0.45- μ m filter. Then the resultant solutions were determined by HPLC method.

The HPLC analysis system consisted of a LC-20AT liquid chromatogram and SPD-20A UV/VIS detector (Shimadzu, Japan) and the chromatographic column was a C-18 (5 μ m, 250 \times 4.6 mm). Ammonium acetate buffer solution was prepared by transferring 3.85 g of ammonium acetate to a 1000mL volumetric flask and diluted with water, the pH was adjusted to 4.0 with glacial acetic acid and diluted to volume with water and mixed. Mixture of the above ammonium acetate buffer solution: methanol (20:80,v/v) was used as the mobile phase. UV-detection was at a wavelength of 243 nm.

Dissolution study: In vitro drug dissolution studies were according to the Chinese Pharmacopoeia 2010 edition the second part appendix XC third method, The dissolution medium was 100mL of 0.1mol/L HCl, the tablets were added to the medium at the speed of 50 rpm. A sample was withdrawn after 45min and filtered through a 0.45- μ m membrane filter. Then measuring 20 μ l filtrate and injected into the liquid chromatography, recording the chromatograms. Not less than 75% of the labeled amount of drug should be dissolved in 45 minutes.

RESULTS AND DISCUSSION:

The evaluation of optimized formulation: In this paper, repaglinide tablets by direct compression technique, using microcrystalline cellulose and maize starch as diluent, PVP K30 as adhesive, PVPP as disintegrant and magnesium stearate as lubricant. The optimum prescription was 1g repaglinide, 0.5g meglumine, 1.0g poloxamer, 65g MCC, 13g maize starch, 7.7g PVPP, 0.5g magnesium stearate and appropriate PVP K30. Friability (0.24%-0.38%) showed the good mechanical resistance of the tablets. And all the tablets had smooth surface with hardness range of 40-70N.

The dissolution behavior is important and should be investigated. Table 1 listed the different formulations of different diluents. The dissolution profile of repaglinide from different tablet formulations are shown in Figure 1. From Figure 1 we could see that F5 has similar dissolution

profile compared with commercial. So F5 was considered to be optimum and therefore we selected F5 for future research.

TABLE 1: FORMULATIONS OF DIFFERENT DILUENTS

FORMULATION (g)	F1	F2	F3	F4	F5
Repaglinide	1.0	1.0	1.0	1.0	1.0
Meglumine	0.5	0.5	0.5	0.5	0.5
Poloxamer	0.3	0.8	1.0	1.0	1.0
MCC	70	70	70	70	65
Maize starch	13	13	13	13	13
PVPP	6	6	8	8	7.7
Magnesium stearate	0.5	0.5	0.5	0.5	0.5

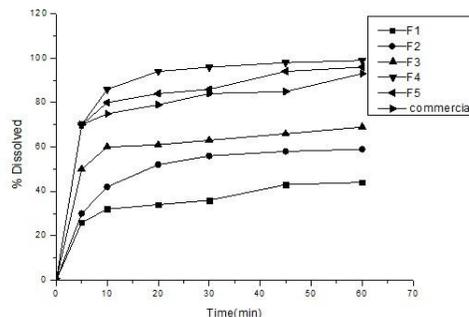


FIGURE 1: EFFECT OF POLYMER CONCENTRATION ON DISSOLUTION PROFILE OF REPAGLINIDE FROM DIFFERENT TABLET FORMULATIONS COMPARED WITH COMMERCIAL

The dissolution of optimized formulation and commercial formulation: Generic drug products must have the same quality and safety standards as those of the innovator product. In vitro dissolution serves as a guide in assessing in vivo drug product performance for pharmaceutical products and development of new formulations¹⁰⁻¹³. The dissolution data obtained from the two different tablets in the four dissolution media after 60 min and their calculated f_2 values are shown in Figure 2. For two dissolution profiles to be considered similar, f_2 should be between 50 and 100. Similarity factors (f_2) were employed using the following equations:

$$f_2 = 50 \cdot \log \left\{ \left[1 + \frac{1}{n} \sum_{t=1}^n (R_t - T_t)^2 \right]^{-0.5} \times 100 \right\}$$

Where n is the number of time points, R_t is the dissolution value of reference product at time t , and T_t is the dissolution value for the test product at time t .

The f_2 values obtained from our optimized formulations in the four media further support the similarity of the dissolution profiles to those of the reference product. There is low variation in the dissolution of the drug in the chosen dissolution media.

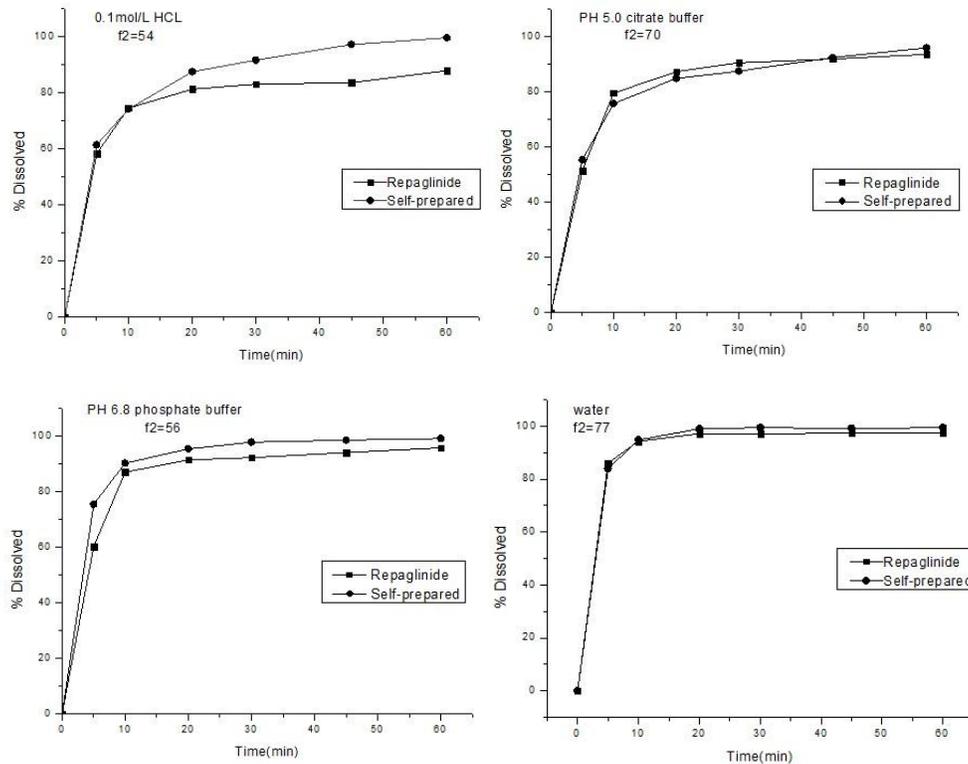


FIGURE 2: THE DISSOLUTION OF REPAGLINIDE COMMERCIAL PRODUCTS AND SELF-PREPARED IN THE FOUR DISSOLUTION MEDIA

CONCLUSION: In this study repaglinide tablets were developed and optimized. The physical characteristics such as their drug content, hardness, thickness, friability, and in vitro dissolution characteristics were evaluated. The dissolution profiles of optimized tablets in four dissolution media: 0.1 mol/L HCL, citrate buffer at pH values of 5.0, phosphate buffer at pH values of 6.8 and distilled water. These were compared with those of commercial products and analysed by similarity factors (f_2) method. There is low variation in the dissolution of the drug in the chosen dissolution media.

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