APPLYING DESIGN OF EXPERIMENTS METHODOLOGY TO DEVELOP EXTENDED-RELEASE METFORMIN GRANULES WITH LINSEED MUCILAGE

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Introduction

It is estimated that 25% of all plant species have some type of medicinal use[1]. From nature, humans managed to isolate active principles for the formulation of medicines, as well as molecules that allowed technological advances. In this regard, linseed is a seed of a multipurpose plant species of pharmaceutical interest, as its mucilage can be used as a hydrophilic polymer matrix in the formulation of extended-release drugs[2]. The advantage of using it in the development of an antidiabetic, such as a dosage form of metformin, includes: (i) the replacement of synthetic polymers in extended-release dosage forms, hydroxypropyl methylcellulose (HPMC), and; (ii) a possible synergism of effect, due to the hypoglycemic effect of the mucilage[3]. Therefore, the aim of this work was to obtain an extend-release metformin-granule using linseed mucilage, and to evaluate the effect of drug and mucilage concentration using the design of experiments (DoE) approach.

Method

The seeds were purchased in the market of Niterói, in the state of Rio de Janeiro, Brazil. The mucilage was extracted from the whole seeds, using water in the ratio of 1:13 m/v (seed:water)[2], at room temperature in a dynamic maceration for 24 hours. Then, the aqueous extract was lyophilized and used to prepare 11 granules, according to a 3^2 factorial design with two replicates of the central point. Levels of 8, 13 and 18% of mucilage and 40, 60 and 80% of metformin were tested and an extra dosage form was prepared using 13% HPMC K4M and 60% metformin, for comparison purposes. The DoE was prepared using Statistica® v.13 (TIBCO Software), and the results were compared through Analysis of Variance (ANOVA) in the same software.

The granules were obtained by wet granulation. Assays such as friability, drug content and dissolution were carried out according to the Brazilian pharmacopoeia[4], with some adaptations. Dissolution efficiency (DE)[5] was obtained from the dissolution profiles and it was used as a comparative parameter.

Results / Discussion

Metformin content of all granules were between 95 and 105%. Therefore, all samples were accepted for further analysis, since all of them met the intended drug dosage for the expected therapeutic use, according to the Brazilian Pharmacopoeia[4]. The lowest content was found in dosage form 4 (13% Mucilage (Mu.), 40% Metformin (Me.)) (95,42%), while the highest was found in dosage form 7 (18% Mu., 40% Me.) (104,40%). The average drug content of all dosage forms was 100,59%.

The Brazilian Pharmacopoeia recommends the friability test only for uncoated tablets, but since this evaluation is relevant in development studies, it is possible to find recommended methods in another compendium, such as in the European Pharmacopoeia[6]. The smallest percentage was obtained from dosage form 9 (18% Mu., 80% Me.) (3.0% mass loss) and the greatest, from dosage form 2 (8% Mu., 60% Me.)

(7.5%). In summary, when a dosage form has a higher percentage of mucilage and metformin, the friability is lower (Mu. p = 0,007028; Me. p = 0,041624).

In addition, five dosage forms (experiments 1 (8% Mu., 40% Me.), 4 (13% Mu., 40% Me.), 7 (18% Mu., 40% Me.), 8 (18% Mu., 60% Me.) and 11 (13% Mu., 60% Me.)) showed a longer release compared to the reference HPMC dosage form, regarding the dissolution profiles (Figure 1). None of these dosage forms used metformin at the highest tested level (80%). It was also found that DE values were higher when the percentage of metformin was high and the percentage of linseed mucilage was low. This indicates that the mucilage's polymers acted as a retarding agent suitable for extended-release dosage forms. However, only metformin was considered a significant variable (p = 0,049369).

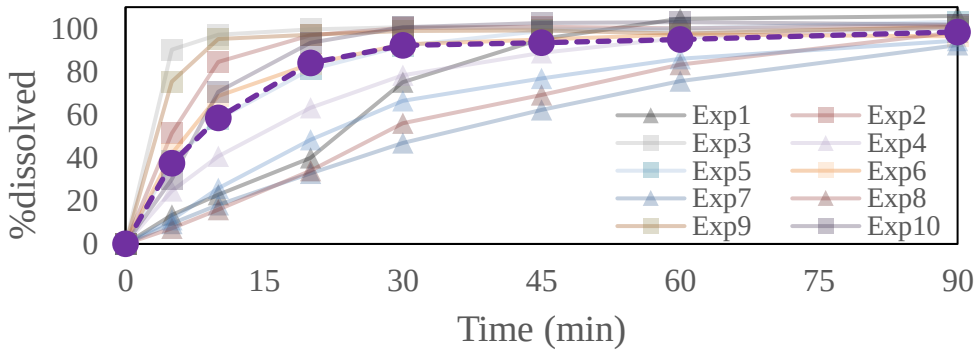

Figure 1: Dissolution of the manufactured dosage forms.

Conclusion

Higher percentages of mucilage yielded a less friable granule, which suggests that the fibrous content of the mucilage may help shield the granules from friction. Moreover, promising results show that the linseed mucilage is able to act as a retarding agent in high dose drugs, and the effect on drug release could be dependent on the drug concentration. In summary, more desirable results were obtained with higher percentages of mucilage and lower percentages of metformin.

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