ORIGINAL RESEARCH ARTICLES

DEVELOPMENT AND EVALUATION OF METFORMIN TABLETS: EFFECT OF SUPERDISINTEGRANTS

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(Received 12 July 2022) (Accepted 23 January 2024)

ABSTRACT

Metformin is an oral antihyperglycemic medication used to treat type 2 diabetes. BCS-III classification of medications includes metformin hydrochloride, which has a high solubility and a low permeability. This study's objective was to develop wet granulated metformin hydrochloride tablets using various synthetic superdisintegrants. On disintegration and dissolution, the effects of different superdisintegrants have been studied. After evaluation, it were observed that post-compression properties such as weight variability, thickness, hardness, and friability were within the IP ranges. The formulation F4 with Croscarmellose sodium (CCS) in low concentration was chosen as the best formulation. By increasing the quantity of Croscarmellose sodium (CCS), the *in vitro* dissolution profile increased, and *in vitro* disintegration time also increased in the formulated tablets using wet granulation method. The statistical significance was determined using one-way ANOVA, and there is no significant difference between formulations.

Keywords: Superdistingerants, metformin hydrochloride, Croscarmellose sodium (CCS), sodium starch glycolate (SSG), disintegration time, dissolution

INTRODUCTION

Conventional dosage forms are quite common due to their simplicity of use, small design, the convenience of manufacturing, and ability to provide an exact amount of dose[1]. The benefit of oral administration includes accessibility of consumption, discomfort reduction, adaptability (to accept a variety of medication candidates), and the most significant patient compliance. The disintegration rate and subsequent dissolution are primarily influenced by the addition of superdisintegrants through swelling, wicking and effervescent actions[2]. Disintegrants are substances that are added to tablets and some encapsulated formulations to encourage their splitting up of tablet slugs into finer particles in an aqueous environment. This increases the available surface area and speeds up the release of therapeutic components[3]. The study's objective was to assess the effect of superdisintegrants using the oral type-2 diabetes medication, metformin hydrochloride, as the model drug. The preparation of the drug substance is focused on ensuring faster disintegration and dissolution to assure that the drug is immediately available for absorption in the shortest period[4]. The disintegration performance was modified using a low amount of superdisintegrants, such as 2 % and 5 % by weight. The different concentration of superdisintegrants and combination of superdisintegrants was studied using metformin hydrochloride as a model drug. It has been observed how superdisintegrants influence tablet disintegration. The study was set to design and analyse tablets incorporating various superdisintegrants individually as well as in combination.

MATERIALS AND METHODS

Materials

Metformin hydrochloride, dicalcium phosphate and magnesium stearate were procured from HiMedia, Mumbai. Croscarmellose sodium (CCS) from Yarrow Chemicals, Mumbai, Microcrystalline cellulose (MCC) from Loba Chemicals, Mumbai and Sodium starch glycolate (SSG) from Loba Chemicals, Mumbai.

Standard calibration curve of metformin hydrochloride

Metformin hydrochloride 100 mg was dissolved in 100 mL of 0.1 N HCl buffer to get 1000 µg mL^{-1} are the

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https://doi.org/10.53879/id.61.03.13800

Table I: Formulation variables of metformin hydrochloride tablets

Sr. No.	Ingredient (mg)	F1	F2	F3	F4	F5	F6
1.	Metformin	500	500	500	500	500	500
2.	MCC	150	-	150	150	150	130
3.	CCS	32	32	12	32	20	42
4.	Povidone – K30	30	30	30	30	30	40
5.	SSG	-	-	20	-	12	-
6.	Dicalcium phosphate	-	150	-	-	-	-
7.	Magnesium stearate	8	8	8	8	8	8
8.	Purified water	q.s	q.s	q.s	q.s	q.s	q.s

prepared solution was labelled as stock-1. From stock-1, 10 mL was taken and transferred into a 100 mL standard flask, and made up to 100 mL with 0.1N HCl to get 100 µg mL^{-1}. This was labelled as stock-2.

From stock-2 dilution, 10 mL was taken and transferred into a 1000 mL standard flask and made up to 100 mL with 0.1 N HCl to get 10 µg mL^{-1}. This was labelled as stock-3.

From stock-3, various stock solutions, such as 2, 4, 6, 8 and 10 µg mL^{-1} were prepared. From stock-2, other stock solutions, such as 12, 14, 16 and 18 µg mL^{-1}, were prepared. The above stock solutions were analysed for absorbance at 233 nm.

Formulation of tablets

The wet granulation method was employed to formulate tablets using different superdisintegrants. Metformin hydrochloride and other excipients were weighed accurately and mixed thoroughly to prepare the tablets (Table I). To obtain the wet mass, povidone was mixed with water and the required quantity was added to the powdered mixture. Using mortar and pestle, the mixture was triturated until a coherent mass was attained. The uniformly sized granules were obtained by passing the moist mixture through sieve number 18. The formed granules were dried at 45 ° ± 7 ℃. The dried granules were sieved, and lubricant was added, then the granules were compressed into tablets.

Physical evaluation of prepared tablets

Weight variation

The weight of obtained tablets should remain constant, because weight variations could lead to dosage discrepancies. To assess if the produced tablets were all the same weight, weight variation parameter was used. About 10 tablets were taken and weighed in the electronic weighing balance to perform weight variation. The values for tablets were separately recorded. Percentage weight deviation for the individual tablets was calculated and compared with the standard weight.

$$\text{Percentage deviation} = \frac{\text{Individual weight - average weight}}{\text{average weight}}$$

Friability test

To evaluate tablet strength, the friability test was determined. The tablet should be suitably well-formulated to avoid tears or cracks during handling and packaging. Tablets were taken and precisely weighed using an electronic weighing balance to conduct the friability test. The Roche friabilator was loaded with the weighed tablets and set to 100 rpm. After that, the tablets were reweighed. To assess variations not more than 1 %, the percentage loss was determined.

$$\% \text{ Friability} = \frac{\text{Initial weight – Final weight}}{\text{Initial weight}} \times 100$$

Hardness

The compressed tablets were tested using digital erweka tester, the monsanto tester, and the pfizer tester. Randomly, 10 tablets were taken to test the hardness. It is carried out to evaluate the tensile strength of each compressed tablet.

Thickness

The tablet's, thickness was determined using a Vernier caliper. It's relationship to hardness is inverse, so as hardness increases, thickness decreases. The compressed tablets should be kept within a 5 % range of the usual values.

Table II: Post-compression studies F1 to F6 (n=3)

Formulation	Weight variation* (mg)	Thickness* (mm)	Hardness* (kg cm^{-2})	Friability* (%)	Disintegration time* (min)
F1	710 ± 6.2	0.67 ± 0.1	19.57 ± 0.42	0.03	29
F2	715 ± 2.2	0.67 ± 0.1	19.2 ± 0.47	0.034	10
F3	719 ± 0.414	0.60 ± 0.12	10 ± 0.40	0.021	18
F4	720 ± 0.212	0.60 ± 0.04	8.44 ± 0.50	0	9
F5	715.8 ± 2.2	0.65 ± 0.3	13 ± 0.37	0.039	27
F6	716 ± 3.5	0.66 ± 0.2	20 ± 0.41	0.051	30

**Note: Average of three values (n=3) ± Standard deviation*

Disintegration studies

The tablets were taken and weighed to analyse the disintegration time. Six tablets from different formulations (1 from each) were placed in the disintegration apparatus with suitable medium namely, water. The appropriate temperature suitable for dissolution was kept at 37 ± 0.5 ℃. The readings for the disintegration of tablets were noted. The values for each compressed tablet were noted separately with respect to time.

In vitro dissolution studies

Buffer pH 1.2 was prepared using 0.1 N HCl. 900 mL of 0.1 N HCl was added to the dissolution bowl. The suitable temperature for dissolution was kept at 37 ± 0.5 ℃. Tablets from each formulation were added to the dissolution medium. *In vitro* studies were performed using an apparatus, which is USP TYPE II paddle method with speed of 75 rpm. To examine the release from tablets, samples were taken at appropriate time intervals. During the time interval, 5 mL of samples were collected, to replace the sample collected a suitable solution was included to keep the sink condition. To assess the amount of drug release it was measured using a UV spectrophotometer at specified nm.

RESULTS AND DISCUSSION

Post-compression evaluation studies

Various post-compression properties were analysed for the tablet formulation (Table II). According to IP standards, weight variation results were within the limits (± 5 %). The other factor that was examined was thickness, which was between 0.60 - 0.67 mm. Friability results for the compressed tablets were within range (< 1 %). Even though the tablet was prepared using the wet granulation method employing superdisintegrants, there was a slight increase in hardness. The increase may be due to compression force exerted by punches and due to microcrystalline cellulose. Despite the increase in hardness, tablets were disintegrated in 9-30mins (Table II).

Formulation parameters

Several water-soluble components were chosen to develop this type of formulation. MCC was added to the formulation because of its high binding properties and diluent action which may also contributes for increase in the hardness. Indirectly, excellent flow properties in the tablet formulation can be attributed. Magnesium stearate was included to enhance the granules flow property during tablet compression. Croscarmellose sodium (CCS) and sodium starch glycolate (SSG) are incorporated as superdisintegrants (Table II).

CCS is a synthetic polymer which is derived from cellulose. To obtain the exact amount of CCS required to be added for formulation, various concentrations were included and assessed. The CCS concentration was taken based on the literature survey and studied in the range of 2 - 6 %. Our study, mainly focused to assess the best CCS concentration to promote the faster disintegration and dissolution. As per the study, the increase in the CCS concentration increased the disintegration time. It has the

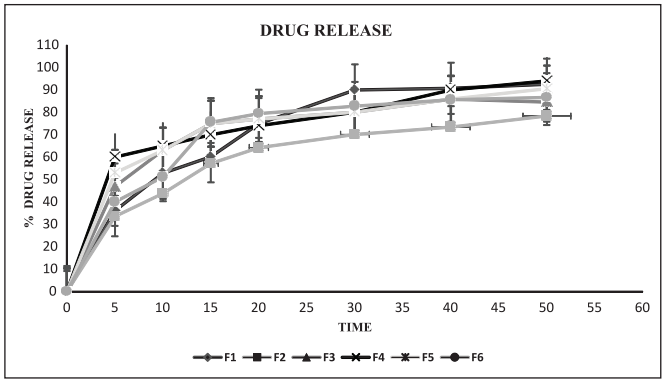

Fig. 1: % Drug release vs time in minutes

good water-wicking nature and has good disintegration properties compared to other superdisintegrants. But it swells over a longer period.

SSG is a synthetic polymer which is derived from starch. It has different swelling properties from CCS, (more than CCS). This may also be the reason for increased disintegration time when used in combination with CCS in formulations F3 and F5. To enhance disintegrant ability in tablet formulations, an optimal amount of SSG or CCS or a combination of both is necessary[5]. Additionally, it speeds up the dissolution (Fig. 1).

In vitro disintegration for formulated tablets

Different formulations were analysed for disintegration. The formulation containing CCS alone (F4) has shown good disintegration compared to other formulations followed by formulation F2 without MCC along with dicalcium phosphate showing good disintegration.

Increasing the amount of CCS increased disintegration time F6 compared to the formulation which contains combination of CCS and SSG. Formulations with a combination of superdisintegrants (F3 and F5) tend to increase the disintegration time. The reason behind the increase in disintegration time may be because of the slow swelling nature of CCS and SSG.

In vitro dissolution for compressed tablets

The release pattern for the compressed tablets is shown in Fig. 1. From the obtained results of drug release, formulation F4 has good drug release properties, and it was around 94 % in 50 minutes compared to formulations which contain a high amount of CCS and combination of superdisintegrants (F3 and F5). By using one-way ANOVA, the significance was interpreted ($p > 0.05$) between F4 formulation and F3 and F5 formulations.

CONCLUSION

In this work, the wet granulation method was employed to formulate oral fast-disintegrating tablets using synthetic superdisintegrants. Formulation with 5 % superdisintegrants was better than 7 % and a combination of superdisintegrants. The study's findings led to the following conclusion: F4 formulation containing CCS had a faster drug release and shorter disintegration time than formulations with combination superdisintegrants.

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