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DESIGNING OF ORODISPERSIBLE TABLET OF METFORMIN HYDROCHLORIDE FOR THE TREATMENT OF TYPE II DIABETES MELLITUS

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ABSTRACT

The main aim of the study was to develop orodispersible tablets of Metformin hydrochloride (an an oral antidiabetic biguinide agent) for improving patient compliance, especially those of paediatric & geriatric categories with difficulties in swallowing. In the wet granulation method orodispersible (ORD) tablets were prepared using disintegrants. The prepared batches of tablets were evaluated for weight variation, hardness, friability, wetting time, *invitro* dispersion time, drug content and *invitro* dissolution studies. The tablet formulation containing 50 mg of Metformin hydrochloride, 28 mg of lactose, 14 mg of micro crystalline cellulose, 17mg of starch, 8 mg of isapghula husk, 5mg of mannitol, 2mg of talc, 1 mg of mg stearate is considered as the overall best formulation (with an *In vitro* drug release of 98.2 %) Short term stability studies (at 40±2ºC/75±5% RH) on the best formulation indicated that there no significant changes in drug content. From the FTIR study indicated that there are no drug excipient interactions. Undoubtedly the availability of various technologies and the manifold advantages of orodispersible tablets will surely enhance the patient compliance providing rapid onset of action.

KEY WORDS: Metformin Hydrochloride, Orodispersible tablets, FTIR spectroscopy.

INTRODUCTION

Recent advances in novel drug delivery systems [1] aim for designing dosage forms, convenient to be manufactured and administered free side effects, offering immediate release and enhance bioavailability so as to achieve better patient compliance. Though oral drug delivery systems [2] preferably tablets are most widely accepted dosage forms for being compact offering uniform dose and painless delivery. But disphagia is a common problem for all age groups especially the elderly and paediatrics, because physiological changes associated with those groups [3,4]. The disphagia is seen nearly 35% of general population and associated with a number of conditions like parkinosonism, mental disabilities, motion sickness, unconsciousness, unavailability of water etc.. To overcome such problems certain innovative drug delivery system like mouth dissolving tablets have been developed. These are novel dosage forms which dissolve in saliva within few seconds when put on tongue. The orally disintegrating tablets are also called as orodispersible tablets, quick disintegrating tablets, fast disintegrating tablets, porous tablets, rapimelts [5,6]. The mouth dissolving tablets are absorbed from the mouth, pharynx and oesophagus as saliva passes down into the stomach. In these cases the bioavailability of drugs are significantly greater than those observed from conventional solid dosage forms such as tablets and capsules [7]. In the present study orodispersible tablets of Metformin Hydrochloride were designed using wet granulation method using various excipients with prime objective arriving of a cost effective product.

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MATERIALS AND METHODS

Metformin Hydrochloride was received as a gift sample from Suzikem Labs Pvt Ltd., cherlapally, A.P, Peppermint flavor and aspartame were obtained as gifts from Aurobindo labs Pvt Ltd, A.P. Sodium bicarbonate, Tartaric acid, Purified Talc, Starch, D-manitol and potassium dihydrogen-o-phosphate were procured from SD fine chem. Ltd Mumbai. Sodium hydroxide, sodium lauryl sulphate and methanol were procured from Qualigens fine chemicals Mumbai.

Drug excipient studies

The IR allows identification of functional groups in various chemicals as well as incompatibilities between the drug and excipients. From the IR study it can be concluded that the major peaks of drug remains intact and no interaction was found between the drug and excipients.

Preparation of Orodispersible Tablets

Accurately weighed quantities of ingredients mentioned in Table-I were passed through sieve no. 12. And isapghula husk passed through sieve no.20. All the ingredients lubricant magnesium stearate and talc(glidant) were manually blended homogenous by way of geometric dilution. The mixture was moistened with aqueous solution and granulated with sieve no.20 and placed in hot air oven at 60º C for sufficient 3-4 hrs. Then dried granules passed through sieve no.12 and blended with mg stearate and talc. The homogenous mixture were placed into tablet punching machine getting tablet weight 120 mg each using deep concave punch having diameter of 8 mm. (10 station rotary tablet machine Clint India)

EVALUATION OF GRANULES

Angle of repose

The angle of repose of granules was determined by the funnel method. The accurately weighed granules were taken in a funnel. The height of the funnel is adjusted in such a way that the tip of the funnel just touched the apex of the heap of the granules. The granules were allowed to flow through the funnel freely onto the surface. The diameter of the powder cone was measured and angle of repose was calculated using the following equation.

$$\tan \Theta = h/r$$

Therefore, $\Theta = \tan^{-1}(h/r)$

Where Θ = angle of repose.

h = height of the cone in cm.

r = radius of the cone base in cm.

Bulk density

Both loose bulk density (LBD) and tapped bulk density (TBD) were determined. A quantity of 2 g of powder from each formula previously lightly shaken to break any agglomerates formed was introduced into a 10 ml measuring cylinder. After the initial volume was observed, the cylinder was allowed to fall under its own weight onto a hard surface from the height of 2.5 cm at 2 second intervals. The tapping was continued until no further change in volume was noted. LBD and TBD were calculated using the following formulas

Bulk density = weight of the powder/bulk volume of the powder

Compressibility index

The compressibility index of the granules was determined By Carr's compressibility index.

Carr's index % = Dt - Db / Dt ×100

Where, Dt is the tapped density of the granules.

Db is the bulk density of the granules

EVALUATION OF TABLETS

Thickness

The thickness of six tablets was measured using vernier calipers. The extent to which the thickness of each tablet deviated from ± 5 % of the standard value was determined.

Hardness

Monsanto hardness tester determined hardness of the tablets. Six tablets from each batch were selected and evaluated, and the average value with standard deviation was recorded

Friability

Friability of tablets was performed in a Roche friabilator. Ten tablets were weighed together and then placed in the chamber. The friabilator was operated for 100 revolutions and the tablets were subjected to the combined effects of abrasion and shock because the Plastic chamber carrying the tablets drops them at a distance of six inches with every revolution. The tablets are then dusted and reweighed.

Weight variation test

Uniformity of weight test as described in the IP was followed. Twenty tablets were selected at random and average weight was determined. Then individual tablets were weighed and the individual weight was compared with the average weight. The percentage deviation was calculated and checked for weight variation.

Uniformity of drug content

Drug content for ORD tablet was done by the assay method. First the prepared tablet (50mg API) was crushed and added to 100ml of phosphate buffer pH 6.8. After 30 minutes the solution was filtered and from 100ml solution 2ml was withdrawn diluted upto 50 ml with phosphate buffer pH 6.8 which was the stock solution. From the stock solution 4ml was withdrawn and diluted upto 50ml getting desired concentration 8µg/ml. From the desired concentration, the drug content of formulations were

calculated using calibrated standard curve equation y=0.075x+0.088.

***In vitro* dissolution studies**

The release rate of Metformin hydrochloride Orodispersible tablets was determined using United States pharmacopeia (USP) Dissolution Testing Apparatus 2 (paddle method) .The dissolution test was performed using 900 ml of Phosphate buffer pH 6.8, at $37^0 \pm 0.5^0$ C and 50 rpm. A sample (5 ml) of the solution was withdrawn from the dissolution apparatus and the samples were replaced with fresh dissolution medium. The samples were filtered through filter paper. Absorbance of these solutions was measured at 233 nm using a UV/Visible Spectrophotometer (ELICO164). The drug release was plotted against time to determine the release profile

***In vitro* dispersion time**

This test is performed to ensure disintegration of tablets in the salivary fluid, if it is to be used as an orodispersible tablet. *In vitro* dispersion time was measured by dropping a tablet in a measuring cylinder containing 6ml of simulated salivary fluid of pH 6.8. Three tablets from each formulation were randomly selected and *In vitro* dispersion time was measured.

Wetting time

The Wetting time of the tablets can be measured using a simple procedure. Five circular tissue papers of 10 cm diameter are placed in petri dish with a 10 cm diameter. Wetting time was measured by placing a tablet on a piece of tissue paper folded twice, and was placed in a small Petri dish containing 6 ml of simulated saliva pH 6.8, and the time for complete wetting was measured. Five tablets from each batch were used and results were compared with commercial product.

***In vitro* disintegration test**

The test was carried out on 6 tablet using tablet disintegration tester. Distilled water at $37^0c \pm 2^0c$ was used as a disintegration media and the time in seconds taken for complete disintegration of the tablet with no palable mass remaining in the apparatus was measured.

Statistical analysis

Except dissolution all evaluation parameters were expressed as mean ± standard deviation.

Stability studies

Short term stability studies on the above promising formulation (at 40±2ºC/75±5% RH for 3 months) have shown no significance changes in physical appearance and drug content.

RESULTS AND DISCUSSION

All the compressible excipients (Table-I) with drug by wet granulation method was prepared using isapghula husk along with magnesium stearate and talc. This granules were evaluated for pre-compression parameters (Table-II) such as bulk density, tapped density, angle of repose and Carr's index. The post compression parameters such as hardness, weight variation, drug content uniformity, friability and thickness have given below (Table III).The other parameters such as wetting time, disintegration time and *In vitro* dispersion time have given below(Table IV).

The bulk density of pre-compression blends was found to be in the range of 0.54 to 0.68gm/cc, tapped density in the range of 0.66 to 0.74 gm/cc, the Carr's index values were in the range of 12 to 20% and angle of repose in the range of 31 to 34.The hardness of the tablet formulations was found to be in the range of 3.85to3.94 kg/cm^2. The friability values were found to be in the range of 0.49 to 0.57%. The weight of all the tablets was found to be uniform with low values of standard deviation and within the prescribed IP limits. The average weight of one tablet was found to be in range 120 to 121mg.The percent drug content of all the tablets was found to be in the range of 99.2 to 99.9% of the expected ORD content, which was within the acceptable limits. The disintegration time was in range 30 to44sec, wetting time was found be in range 32to 48sec and also *In vitro* dispersion time was in range 26 to 34 sec. The results are shown in Table IV.

***In vitro* dispersion time**

This test was performed to ensure disintegration of tablets in the salivary fluid, if it is to be used as an orodispersible tablet. Among all formulations ORD4 formulation was found to be best. The dispersion time was found to be 26 sec (Fig I).

***In vitro* drug release study**

In vitro drug release studies were performed in pH 6.8 phosphate buffer, on the above promising formulation (ORD4) gives maximum amount of drug release comparing to other formulations. The Percentage of drug release of ORD4 is best giving 98.2%. The dissolution profiles of the above formulations are depicted in figure II.

Short-term stability studies

Short-term stability studies on the above promising formulation (at 40 ± 2^o / 75±5% RH for 3 months) have shown no significant changes in physical appearance, drug content and *In vitro* dispersion time. Statistical analysis ('t'-test) of drug content data gives 't' value of 1.97 for ORD4 formulation which is much less compared to the table value of 4.3 ($p<0.05$). There are no appreciable changes in *In vitro* dispersion time up on storage at 40 ± 2^o / 75±5% RH for 3 months period. The IR spectrum of the pure drug with excipients exhibits no interactions in all ORD formulations.

Table 1. Composition of orodispersible tablet

Ingredients(mg)	ORD1	ORD2	ORD3	ORD4
API(Metformin HCL)	50	50	50	50
Lactose	25	28	30	28
MCC(Microcrystalline cellulose)	15	14	15	14
Starch	18	17	18	17
Crospovidone	04	08	-	-
Isapghula Husk	-	-	04	08
Mannitol	5	5	5	5
Talc	2	2	2	2
Magnesium Stearate	1	1	1	1
Total Weight	120	120	120	120

Table 2. Pre-compression parameters of ORD formulations

Formulation code	Bulk density (gm/cc) ±S.D	Tapped density (gm/cc) ±S.D	Angle of repo se (degree) ±S.D	Carr's index (%)±S.D
ORD1	0.56±0.02	0.66±0.08	33.0±0.03	15±0.13
ORD2	0.68±0.11	0.74±0.09	31.0±0.12	18±0.11
ORD3	0.54±0.13	0.68±0.11	34.0±0.11	20±0.13
ORD4	0.58±0.14	0.66±0.02	32.0±0.13	12±0.11

Table 3. Post-compression parameters of ORD formulations

Formulation code	Hardness(kg /cm^2) ±S.D	Friability (%)±S.D	%Drug content ±S.D	Average wt. of 1tablet(mg)±S.D	Thickness(mm) ±S.D
ORD1	3.9±0.02	0.49±0.11	99.2±0.01	121±0.1	5±0.10
ORD2	3.89±0.01	0.52±0.01	99.4±0.02	120±0.1	4.9±0.11
ORD3	3.85±0.02	0.57±0.02	99.3±0.03	120±0.1	5±0.14
ORD4	3.94±0.05	0.51±0.10	99.9±0.04	120±0.1	5±0.13

Table 4. Post-compression parameters of ORD formulations

Formulation code	Disintegration time(sec)	*In vitro* dispersion time(sec)	Wetting time(sec)
ORD1	44	34	48
ORD2	38	32	40
ORD3	34	30	36
ORD4	30	26	32

Fig 1. *In vitro* dispersion time of orodispersible tablets

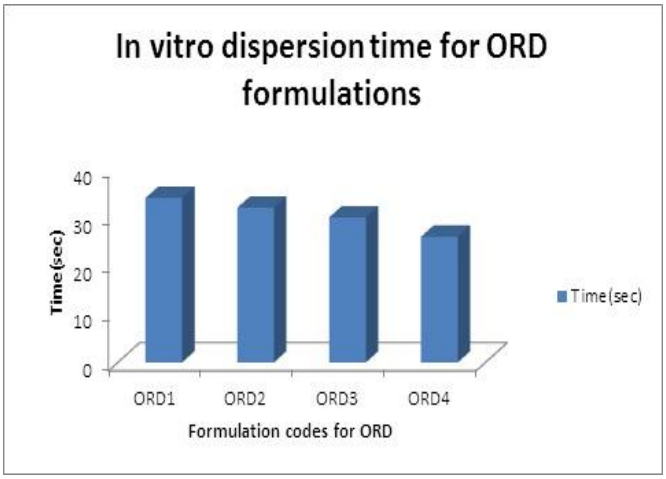
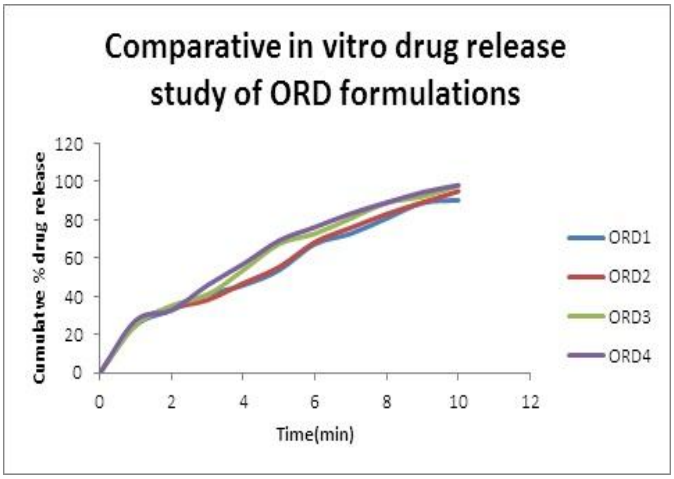


Fig 2. Comparative *In vitro* drug release study of ORD formulations



CONCLUSION

The study clearly demonstrates that orodispersible tablets of Metformin hydrochloride could be successfully prepared by wet granulation method in a cost effective manner employing isaphgula husk.It was evident from the results that rate of drug release can be optimized using disintegrants for orodispersible formulations. From the developed formulations the release of Metformin hydrochloride was best in ORD4 formulation i.e in-vitro studyand *In vitro* dispersion time study. From the FTIR study, it was confirmed that the drug & excipients in the formulations were compatible with each other.Undoubtedly the availability of various technologies and the manifold advantages of orodispersible tablets will surely enhance the patient compliance providing rapid onset of action.

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