INDO AMERICAN JOURNAL OF PHARMACEUTICAL RESEARCH

FORMULATION AND EVALUATION OF METFORMIN HYDROCHLORIDE ORAL DISPERSABLE TABLETS

Muggu SankaraBhavani, K.Sudha Rani, K.HarshaVardhan, M.BhavyaSalini
Hindu college of Pharmacy, Amaravathi Road, Guntur, A.P.

ARTICLE INFO

Article history
Received 11/08/2018
Available online
02/09/2018

Keywords
Oral Dissolution Tablets,
Metformin HCL,
Sodium Starch Glycolate,
And Croscarmellose Sodium,
Direct Compression Method.

ABSTRACT

Metformin HCL is a biguanide antihyperglycemic agent used for treating non-insulin-dependent diabetes mellitus (NIDDM). It improves glycemic control by decreasing hepatic glucose production, decreasing glucose absorption and increasing insulin mediated glucose uptake. In the present study an attempt has been made to prepare oral dissolving tablets of Metformin HCL which dissolves fast and easy in the oral cavity with enhanced dissolution rate. The tablets were prepared with two superdisintegrants e.g., Croscarmellose sodium, Sodium Starch Glycolate. The blend was examined for Angle of repose, Bulk density, Tapped density, Compressibility index and Hausners ratio. The tablets were evaluated for hardness, friability, disintegration time, dissolution rate, drug content were found to be within 30 sec. It was concluded that the mouth dissolving tablets with proper hardness, rapidly disintegrating with enhanced dissolution can be made using selected superdisintegrants.

Corresponding author
Muggu SankaraBhavani
Hindu college of Pharmacy,
Amaravathi Road, Guntur, A.P.
9701414099.

*Please cite this article in press as **Muggu SankaraBhavani** et al. Formulation and Evaluation of Metformin Hydrochloride Oral Dispersable Tablets. Indo American Journal of Pharmaceutical Research.2018:8(09).*

INTRODUCTION

Oral administration is the most popular route about 50-60% of total dosage forms are administered due to ease of ingestion, pain avoidance, versatility (to accommodate various types of drug candidates), and most importantly patient compliance. Solid oral delivery systems do not require sterile conditions and are therefore less expensive to manufacture[1]. Oral fast dissolving drug delivery system (OFDDS) is one such novel approach to increase consumer acceptance by virtue of rapid disintegration, self- administration without water or chewing.[2] Orally disintegrating tablets (ODT) are solid unit dosage forms like conventional tablets, but are composed of super disintegrants, which help them to disintegrate the tablet rapidly in saliva without the need to take it water. Orally disintegrating tablets (ODT) are not only indicated for people who have swallowing difficulties, but also are ideal for active people. United States Food and drug administration (FDA) defined ODT as "a solid dosage form containing medicinal substance or active ingredient which disintegrates rapidly usually within a matter of seconds when placed upon the tongue." Orally disintegrating tablets are also called as mouth-dissolving tablets, fast disintegrating tablets, fast dissolving tablets, orodispersible tablets, rapimelts, porous tablets, quick dissolving tablet.[3]Recently European pharmacopoeia also adopted the term, orodispersible tablet" as a tablet that is to be placed in the mouth where it disperses rapidly before swallowing[2].

Ideal properties of ODTs[4, 5]

- Require no water for oral administration, yet dissolve/disperse/ disintegrate in mouth in a matter of seconds.
- Have a pleasing mouth feel.
- Have an acceptable taste masking property.
- Be harder and less friable
- Leave minimal or no residue in mouth after administration. Exhibit low sensitivity to environmental conditions (temperature and humidity).
- Allow the manufacture of tablet using conventional processing and packaging equipment's.

Selection of drug candidates for ODTs[6]

Several factors must be considered when selecting drug candidates for delivery as FDT dosage forms. The ultimate characteristics of a drug for dissolution in the mouth and pre gastric absorption from ODTs include

- Free from bitter taste.
- Small to moderate molecular weight.
- Good solubility in water and saliva. Partially non– ionized at oral cavity's pH.
- Drugs having ability to diffuse and partition into the epithelium of the upper GIT (log P > 1, or preferable > 2).
- Patients who concurrently take anti cholinergic medications may not be the best candidates for these drugs.
- Patients with Sjogren's syndrome or dryness of the mouth due to decreased saliva production may not be good candidates for FDT formulations.
- Drugs with a short half-life and frequent dosing may not be suitable for ODTs.

Drugs which are very bitter or otherwise unacceptable taste because taste masking cannot be achieved

Techniques in preparation of orally disintegrating drug delivery system[5, 7]

1. Freeze drying or Lyophilization
2. Spray drying
3. Molding
4. Phase transition process
5. Melt granulation
6. Sublimation
7. Mass extrusion
8. Cotton candy process
9. Direct compression
10. Nano ionization
11. Effervescent method

The various technologies are developed for the preparation of orally disintegrating drug delivery system that are[8, 9]:

1. Zydis
2. Lyoc
3. Orasolv
4. Durasolv
5. Wowtab
6. Flashtab
7. Frosta
8. Advatab
9. Flashdose
10. Oraquick
11. Nanocrystal
12. Pharmaburst
13. Fast melt and multi flash

MATERIALS AND METHODS

Materials:

Metformin HCL was purchased from yarrow chem products, Mumbai Pvt. Ltd., Croscarmellose Sodium, Sodium Starch Glycolate, and other excipients are purchased from SD fine chemicals limited, Munmbai.

Methods:

Estimation of Metformin HCl

An UV Spectrophotometric method based on the measurement of absorbance at 236nm in distilled water and phosphate buffer pH 6.8 were used in the estimation of Metformin HCl. The method obeyed Lambert and Beer's law in the concentration range of 2-20 µg/ml. Thus the method was found to be suitable for the estimation of MeforminHCl content in various products and in vitro dissolution studies.

Preparation of Mixed blend of drug and excipients

All the ingredients were passed through mesh No.60. Required quantity of each ingredient was taken from each specified formulation (depicted in the Table 1) and all the ingredients were co-ground in a mortar and pestle. The powder blend was evaluated for flow properties as follows and the result is given in the Table 2.

Table 1: Formulae of Orodispersible tablets of Metformin.

		Quantity per tablet (mg) in batch no : FDT in (mg)					
S.NO	Ingredients	F1	F2	F3	F4	F5	F6
1	Metformin Hydrochloride	250	250	250	250	250	250
2	Sodium Starch Glycolate	10	20	30	---	---	---
3	Cross carrmellose sodium	---	---	---	10	20	30
4	Magnesium stearate	04	04	04	04	04	04
5	Mannitol	30	30	30	30	30	30
7	Micro crystalline cellulose	206	196	186	206	196	186
8	TOTAL WEIGHT (in mg)	500	500	500	500	500	500

Table 2: Evaluation of directly compressed blend.

Formulation code	Angle of repose (^{0})	Bulk density (gm/cc)	Tapped density (gm/cc)	Carr's index (%)	Hausner's ratio
F1	26.92± 0.13	0.650 ±0.045	0.768 ±0.036	17.23 ±0.18	1.140 ±0.32
F2	25.01±0.11	0.741 ±0.072	0.232 ±0.028	16.99 ± 0.11	1.161 ±0.28
F3	26.95±0.17	0.617 ±0.036	0.781 ±0.034	17.54 ±0.86	1.116 ±0.34
F4	26.73±0.11	0.540 ±0.081	0.697 ±0.076	22.54 ±0.19	1.217 ±0.32
F5	25.09±0.15	0.560 ±0.002	0.691 ±0.072	21.56±0.18	1.263 ±0.27
F	28.20±0.13	0.342 ±0.05	0.690 ±0.033	21.36±0.033	1.136 ±29

Table 3: Evaluation of Precompressed blend:

Formulation code	Weight variation (mg)	Hardness (kg/cm^2)	Friability (%)	Disintegration time (sec)
F1	5 02.2±1.92	3.9	0.45	21
F2	4 98.9±2.10	4.2	0.55	17
F3	4 96.3±2.19	3.5	0.43	33
F4	4 97.9±1.43	3.2	0.46	27
F5	4 02.8±1.67	3.0	0.50	25
F6	4 99.1±1.99	4.1	0.62	18

Angle of Repose:

It was calculated by using Funnel method. Powder blend was poured on vertically placed funnel until cone of maximum height was formed [13].

$$\mathbf{Tan\Theta = h/r} \text{ ---------- (1)}$$

Θ = Angle Of repose, h = Height of cone, r = Radius of the cone base[10].

Bulk Density:

Bulk density was calculated by pouring the powder blend in the graduated cylinder. Then bulk volume (V) was noted and after that mass (M) was noted by weighing on electric balance. Bulk density was noted by using following formula [10].

Bulk density = Weight of powder/ bulk volume

$$\mathbf{Bulk\ Density\ (\rho b) = m/vb} \text{ ---------- (2)}$$

m = mass of the powder, Vb = Bulk volume of the powder

Tapped Density:

The measuring cylinder containing measured amount of the powder was tapped for specified number of tapping and time. The volume (vt) occupied by the powder after tapping and mass (M) was noted [11].

$$\mathbf{Tapped\ Density\ (\rho t) = M/vt} \text{ ---------- (3)}$$

M = mass of the powder, vt = Tapped volume of the powder

Carr's Compressibility Index (I):

To determine the flow ability of the powder blend for compression was determined by using [12].

$$\mathbf{I = Vb\text{-}Vt/Vb\ x100} \text{ ---------- (4)}$$

Vb = freely settled volume of a given mass of powder, Vt = tapped volume of the same mass of the powder

Hausner Ratio:

Indirect index of powder flow can be determined from Hausner ratio calculation[12].

$$\mathbf{Haunser\ Ratio = Pt/Pd} \text{ ---------- (5)}$$

Pt = tapped density, Pd = bulk density

Post compression evaluation of Orodispersible tablets

Tablet Hardness:

Tablets were placed horizontally between two arms of the digital hardness tester (Pharma Test Germany). After breakdown of each tablet the hardness value was noted in Kg/cm^2 [12].

Tablet Thickness and Diameter:

Six tablets were randomly selected and the thickness of each was measured by Digital Vernier Calipers. Mean and standard deviation were computed and reported[13].

Friability:

The friability of the tablets was determined using Roche friabilator. Ten tablets were initially weighed and transferred into the friabilator. The friabilator was operated at 25 rpm for 4 min. After 4 min the tablets were dedusted and weighed again. The % friability was then calculated using the formula[13]:

Friability (f) = (1- Wo/W) X 100 ------- (6)

Weight Variation:

Twenty tablets were selected randomly from each formulation and weighed on electrical weighing balance (Shimadzu, Japan). After that average weight was calculated by dividing total weight with number of the tablets. Than weight variation range was established by ± 7.5 mg weight variation [12].

Tablet Disintegration:

One tablet was placed in each tube of disintegration apparatus. Buffer solution of pH 6.8 was placed in the basket and temperature was maintained at 37°C ± 2°C. pH of the solution was checked by pH meter. The time taken by tablets for complete disintegration was noted [11, 14].

Drug content uniformity:

Fast dissolving tablets of Metformin Hydrochloride from a batch was taken at random and was crushed to fine powder. The powder material equivalent to 10 mg of Metformin Hydrochloride was transferrd in to a 250ml volumetric flask and 100ml 0.1N Hcl was added to it. It was shaken occasionally for about 30 minutes and the volume was made up 250ml by adding same media. The mixture was then filtered and aliquot of filtrate was diluted and then the absorbance was measured at 236nm. completely was recorded[13].

Dissolution testing:

In vitro dissolution study of Metformin tablets was performed using phosphate buffer (pH 6.8) maintained at a temperature of 37 ± 0.5o C in USP II dissolution test apparatus and at rotation speed of 50 rpm. At a predetermined time interval, samples were withdrawn and filtered through Whatmann filter paper. Absorbance of suitably diluted samples was determined by UV spectrophotometer at 236 nm and the percentage of drug release was calculated. The dissolution experiments were conducted in triplicate [15].

RESULTS AND DISCUSSION

In present study we focused Metformin HCl Orodispersible tablets containing different concentration of superdisintegrants like Crosscarmellose sodium and Sodium starch Glycolate by Direct Compression method. We prepared the tablet containing 250 mg of Metformin HCl with different concentrations of Crosscarmellose sodium and Sodium starch Glycolate. A total of 6 formulations (F1 – F6) F2 formulation (containing 4% Sodium Starch Glycolate) has disintegrated rapidly (within 17±0.11sec) and release the drug at at a faster rate (i.e.99.9± 0.007 in 15 min) (Table 4) Hence it was selected as an optimized formulation. All ingredients were blended and compressed by direct compression method. Precompression evaluation were carried out and the results found to be within the prescribed limits (Table No. 2) having good flow properties. The compressed tablets were evaluated for weight variation, thickness, friability, hardness, drug content, disintegration time and dissolution studies as per official Pharmacopoeia. The disintegration time for each batch tablet was found to be less than one minute and F2 the tablets containing Sodium Starch Glycolate showed lowest disintegration time of 17 sec as compare to other formulations All the QC parameters of formulations were complied with the official specifications with drastic decrease in disintegration time and the result is given in the Table 3.. All the tablets released almost 70% of the drug within 10 min (Fig. 1&2) Showing its fast dissolving action. Dissolution profiles were shown in Fig. 1&2 and dissolution parameters for all batches were summarized in Table 4 Represents the cumulative % drug release and a graphical representation is shown in Figure 4. Among all the formulated tablets F2 which is based on Metformin HCl with 4% Sodium Starch Glycolate was found to be the highest dissolution (99.9.56%) in 10 mins. From the dissolution result it is clear that the 4% Sodium Starch Glycolate showed better dissolution rate as a compare to Crosscarmellose sodium .Hence Sodium Starch Glycolate was a good alternative as a disintegrant for the preparation of directly compressible mouth dissolving tablets of Metformin Hydrochloride.

Table 4: Dissolution profile of Metformin Hydrochloride FDT'S.

Time (min)	% Drug release from Metformin Hydrochloride tablets mean ± SD					
	F1	F2	F3	F4	F5	F6
0	0	0	0	0	0	0
5	35.7±0.005	79.6±0.005	63.1±0.005	59.1±0.002	65.1±0.006	64.4±0.007
10	45.4±0.005	89.9±0.003	75.2±0.002	67.2±0.003	78.4±0.002	79.4±0.003
15	57.5±0.001	99.9±0.007	84.1±0.003	78.5±0.006	89.6±0.002	86.9±0.004
20	72.9±0.002		89.4±0.004	82.5±0.003	99.3±0.002	90.9±0.005
25	89.9±0.002		95.1±0.002	89.9±0.001		98.9±0.006
30	95.9±0.002		97.5±0.003	92.5±0.004		
35			98.9±0.004	95.5±0.003		
40				98.2±0.009		

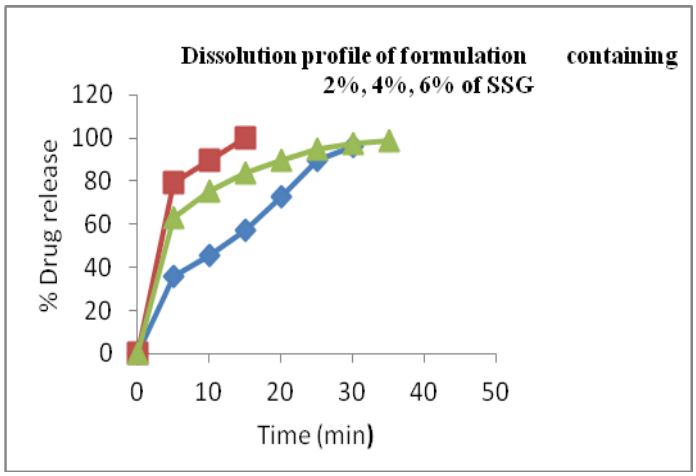

Fig: 1 Comparison of dissolution profile of formulation with 2%, 4%, 6% concentration of Sodium Starch Glycolate.

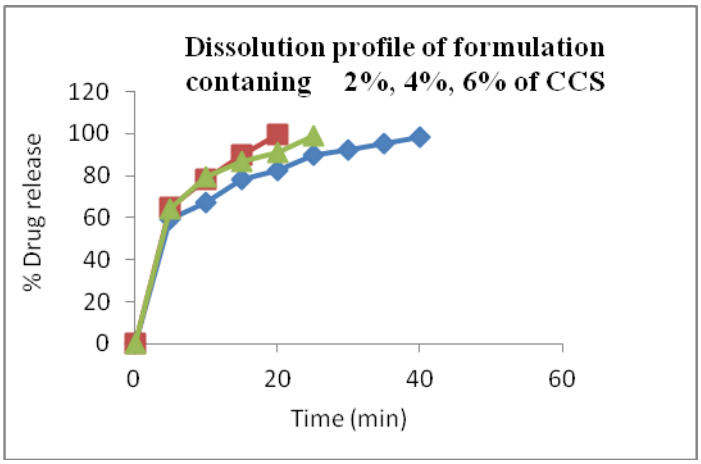

Fig: 2 Comparison of dissolution profile of formulation with 2%, 4%, 6% concentration of Crosscarmellose Sodium.

CONCLUSION

The present study of orodispersible Metformin HCl tablets by direct compression method using Sodium Starch Glycolate and Crosscarmellose sodium. It was found that the tablet containing 4% Sodium Starch Glycolate (F2) was a better formulation in terms of rapid disintegration and maximum percentage drug release when compared with all other formulations.

Sodium Starch Glycolate > Crosscarmellose sodium

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