

Formulation and Evaluation Of Metformin HCl Mouth Dissolving Tablet Using Sublimating Agent

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ABSTRACT

The present study was focused on the development of orodispersible tablets of Metformin HCl for improving patient compliance, especially pediatric and geriatric categories by sublimation technique and comparing the super disintegrating property of benzoic acid and camphor. The other ingredients used in the formulations are croscopolidone, xylitol, magnesium stearate, talc and directly compressible mannitol to enhance the mouth feel. The total seven batches were prepared (F1–F6) and F7 (without superdisintegrant). Tablets were evaluated for weight variation, friability, hardness, drug content uniformity, in-vitro disintegration and dissolution studies. Among all the formulated tablets F3 which is based on Metformin HCl with 40 mg benzoic acid was found to be the highest dissolution (92.56%) in 10 mins. From the dissolution result it is clear that the benzoic acid at different concentration showed better dissolution rate as a disintegrant as compare to camphor. Hence, benzoic acid was a good alternative as a disintegrant for the preparation of directly compressible mouth dissolving tablets of Metformin Hydrochloride.

Keywords: Benzoic acid, camphor, Metformin HCl, Sublimation, Superdisintegrant, Orodispersible

INTRODUCTION

Since the last two decades, there has been an increase focused on more patient compliant dosage forms. The pharmaceutical companies are now more focused on the development of new drug delivery systems for existing drug with an improved efficacy and bioavailability together with reduced dosing frequency to minimize side effects [1].

Dysphagia (Difficulty in swallowing) is a common problem in elderly and pediatrics patients, because of physiological changes associated with those groups [2,3,4]. Other categories that experience same problems include the mentally ill, uncooperative and patients suffering from nausea, motion sickness, sudden episodes of allergic attack. To overcome these problems led to the development of a novel type of solid oral dosage form called mouth dissolving tablet, which disintegrates/dissolves rapidly in saliva without the need of drinking water.

The orally disintegrating tablets are also called as orodispersible tablets, quick disintegrating tablets, fast disintegrating tablets, porous tablets and rapimelts. However the United States Pharmacopoeia (USP) approved these dosage forms as orodispersible tablets. Recently, European Pharmacopoeia has used the term "orodispersible tablet" for tablets that disperse readily and within three minutes before swallowing [5]. Upon ingestion, the saliva serves to disperse/dissolve the dosage form; the saliva containing the dissolved/dispersed medicament is then swallowed in the normal way. Some drugs are absorbed from the mouth, pharynx and esophagus as the saliva passes down into the stomach. In these cases, the bioavailabilities of drugs are significantly greater than those observed from conventional solid forms such as tablets and capsules [6]. In the present study, orodispersible tablets of Metformin HCl (an antidiabetic [7]), were designed using sublimating technique with directly compressible excipient with the aim of preparing a cost effective product. The formulated tablets were evaluated for hardness, friability, weight variation, drug content uniformity, in vitro dissolution rate (in pH 6.8 phosphate buffer).

Sublimation technique includes the subliming material like camphor and benzoic acid. The tablets were dried for 6h under vacuum (30 Kpa) at 50°C to render the tablets porous by sublimation of the camphor. These high porosity (approximately 30%) tablets rapidly dissolved within 15 seconds in saliva [8]. Other methods like dry granulation, wet granulation and direct compression with highly soluble excipients, super disintegrants and/or effervescent systems can also be used.

Sublimation [9, 10,11] Due to the low porosity of tablet, the dissolution of the compressed tablet containing even highly water-soluble ingredients is slow. So to overcome this problem some inert solid ingredients that volatilize readily (e.g. urea, ammonium carbonate, ammonium bicarbonate, hexamethylenetetramine, camphor

etc.) were added to the other tablet excipients and the mixture is compressed into tablets. The volatile materials were vaporized by sublimation, which generates pores on tablet surface. Some other solvents (e.g. cyclohexane, benzene) can also be used as pore forming agents [6].

Direct Compression- Direct compression is the simplest and [12] cost effective method of tablet manufacturing. This method can be used to prepare oral dispersible tablet, by using superdisintegrants and sugar based excipients.

a) **Superdisintegrants:** The addition of superdisintegrants in many orally disintegrating tablet technologies based on direct compression affects the rate of disintegration and dissolution. The other ingredients in the formulation such as water-soluble excipients and effervescent agents further increase the process of disintegration. By addition of super disintegrants, the tablet having quick dissolving property which is needed for fast dissolving tablets. Some examples of super disintegrants are crospovidone, croscarmellose, spray dried lactose, microcrystalline cellulose etc.

b) **Sugar Based Excipients:** The other approach for designing oral dispersible tablet is the use of sugar based excipients manufacture by direct compression. The sugar based excipients are dextrose, fructose, isomalt, lactilol, maltitol, maltose, mannitol, sorbitol, starch hydrolysate, polydextrose and xylitol, which enhance aqueous solubility and masking the unwanted taste by producing sweet taste to the tablet and a pleasing mouth feel.

The rationale behind the present study is to formulate metformin hydrochloride tablet by sublimation technique and to compare the superdisintegrant property of camphor and benzoic acid.

MATERIALS AND METHODS

Metformin hydrochloride is a gift sample from Sai Pharma, Pune. Benzoic acid, Camphor, Mannitol, Crospovidine, Xylitol, Magnesium stearate, and Purified talc purchased from Research Lab, Mumbai.

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.

Evaluation of precompressed blend:

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].

$$\tan\theta = h/r \text{ ----- (1)}$$

θ = Angle Of repose, h = Height of cone, r = Radius of the cone base

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 [14].

$$\text{Bulk Density } (\rho_b) = m/v_b \text{ ----- (2)}$$

m = mass of the powder, V_b = 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 (V_t) occupied by the powder after tapping and mass (M) was noted [16].

$$\text{Tapped Density } (\rho_t) = M/v_t \text{ ----- (3)}$$

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

Carr's Compressibility Index: To determine the flow ability of the powder blend for compression was determined by using [14].

$$I = V_b - V_t / V_b \times 100 \text{ ----- (4)}$$

V_b = freely settled volume of a given mass of powder, V_t = tapped volume of the same mass of the powder

Hausner Ratio: Indirect index of powder flow can be determined from hausner ratio calculation [14]. Hausner

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

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/cm² [14].

Tablet Thickness and Diameter To determine thickness of the tablets, tablets were placed vertically between two arms of the digital apparatus (Pharma Test Germany) and values were noted on screen of instrument [14].

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. Then weight variation range was established by ± 7.5 mg weight variation [14].

Friability Friability of the tablets was calculated by using Roche Friabilator (Pharma Test Germany). Twenty tablets were weighed on electronic weighing balance (Shimadzu, Japan) and their weight was noted. Tablets were placed in the Friabilator. The Friabilator was operated at a speed of 25 rpm for 4 minutes. After 4 minutes tablets were removed, dedusted and again weighed in order to determine final weight of the tablets [14].

$$\text{Friability (f)} = (1 - \text{Wo/W}) \times 100 \text{ ----- (6)}$$

Wo = Weight of tablets before the test, W = Weight of tablets after the test.

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 $37^\circ\text{C} \pm 2^\circ\text{C}$. pH of the solution was checked by pH meter. The time taken by tablets for complete disintegration was noted [15, 16].

Wetting time A glass Petri dish was partially filled with water and a tablet was placed on the surface of a band of filter paper supported on a glass slide. The uptake of water occurred from the lower surface of the tablet. The time required for water to reach the center of the upper surface of the tablet was noted as wetting time [16].

Content uniformity Test The drug contents of each formulation was determined and found to be between 95%-105% which was within the prescribed limits. Equal quantities of powder and standards were taken and assayed at respective wavelengths after suitable dilutions and filtration [17].

Dissolution testing

In vitro dissolution study of metformin tablets was performed using phosphate buffer (pH 6.8) maintained at a temperature of $37 \pm 0.5^\circ\text{C}$ 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 [18].

RESULTS AND DISCUSSION

In present study we focused Metformin HCl orodispersible tablets containing different concentration of superdisintegrants like camphor and benzoic acid by sublimation technique. We prepared the tablet containing 250 mg of Metformin HCl with different concentrations of camphor and benzoic acid. A total of 6 formulations (F1 – F6) and a control formulation F1 (Without Superdisintegrant) were designed. 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, wetting time, 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 F3 (Fig. 1) the tablets containing benzoic acid (F1, F2, F3) showed lowest disintegration time of 16 sec (F3) as compare to the formulation containing camphor (F4, F5, F6) having lowest disintegration time of 19 sec (F6). The control formulation F7 (without disintegrant) having disintegration time of 90 sec. 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. The wetting time for all the formulations was within the range (12-26sec). The lowest (12sec) was obtained with formulation F3. All the tablets released almost 70% of the drug within 10 min (Fig. 2) Showing its fast dissolving action.

Dissolution profiles were shown in Fig. 2 and dissolution parameters for all batches were summarized in Table 4. Among all the formulated tablets F3 which is based on Metformin HCl with 40 mg benzoic acid was found to be the highest dissolution (92.56%) in 10 mins. From the dissolution result it is clear that the benzoic acid at different concentration showed better dissolution rate as a disintegrant as compare to camphor. Hence benzoic acid was a good alternative as a disintegrant for the preparation of directly compressible mouth dissolving tablets of Metformin Hydrochloride.

CONCLUSION

The present study of orodispersible Metformin HCl tablets by sublimation technique using camphor and benzoic acid. It was found that the tablet containing 40mg benzoic acid (F3) was a better formulation in terms of rapid disintegration and maximum percentage drug release when compared with all other formulations and control formulation without superdisintegrant. From the dissolution result it is clear that the benzoic acid at different concentration showed better dissolution rate as a disintegrant as compare to camphor Hence benzoic acid was a good alternative as a disintegrant for the preparation of directly compressible mouth dissolving tablets of Metformin Hydrochloride.

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Table 1: Formulae of orodispersible tablets of Metformin HCl

Ingredient	F1	F2	F3	F4	F5	F6	F7
Metformin	250	250	250	250	250	250	250
Benzoic Acid	30	35	40	-----	-----	-----	-----
Camphor	----	-----	-----	30	35	40	----
Mannitol	32.5	27.5	22.5	32.5	27.5	22.5	62.5
Cross povidone	7.5	7.5	7.5	7.5	7.5	7.5	7.5
Xylitol	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Magnesium stearate	1.25	1.25	1.25	1.25	1.25	1.25	1.25
Talc	1.25	1.25	1.25	1.25	1.25	1.25	1.25
Total	325mg	325mg	325mg	325mg	325mg	325mg	325mg

Table 2: Evaluation of directly compressed blend

Ingredient	F1	F2	F3	F4	F5	F6	F7
Angle of repose(°)	29.56°	28.69°	26.65°	28.55°	28.93°	29.68°	25.75°
Bulk density(gm/cm ³)	0.50	0.47	0.45	0.45	0.51	0.53	0.44
Tapped density (gm/cm ³)	0.60	0.55	0.55	0.52	0.61	0.63	0.56
% Compressibility	16.66%	14.54%	13.18%	13.64%	15.52%	16.16%	16.16%
Hausner's ratio	1.22	1.25	1.19	1.22	1.19	1.18	1.15
Flowability	good	good	good	good	good	good	good

Table 3: Evaluation of formulations

Ingredient	F1	F2	F3	F4	F5	F6	F7
Average weight(mg)±S.D	0.323±0.25	0.327±0.21	0.323±0.19	0.324±0.16	0.321±0.45	0.326±0.16	0.325±0.13
Hardness(kg/cm ²)	3.42	3.56	3.67	3.46	3.54	3.77	3.55
Friability (%)	0.200	0.189	0.178	0.198	0.187	0.176	0.167
Thickness(mm) ±S.D							
Wetting time (sec)	20	15	12	23	19	16	30
Invitro Disintegration time(sec)	25	20	16	26	22	19	90
Drug content (%)	95.15	94.23	96.34	94.78	94.14	95.34	95.15

Table 4: Dissolution parameters of orodispersible Metformin Hcl tablets

Time(min.)	0	5	10	15	20	25
Formulation No.						
F1	0	65.55	76.85	83.3	88.67	92.24
F2	0	74.78	83.78	89.34	94.87	97.67
F3	0	82.06	92.56	95.67	97.58	98.54
F4	0	62.18	72.25	79.67	82.76	87.89
F5	0	72.56	81.78	87.9	92.89	95.76
F6	0	75.24	85.56	91.67	94.87	96.48
F7	0	58.78	69.89	76.78	83.78	87.06

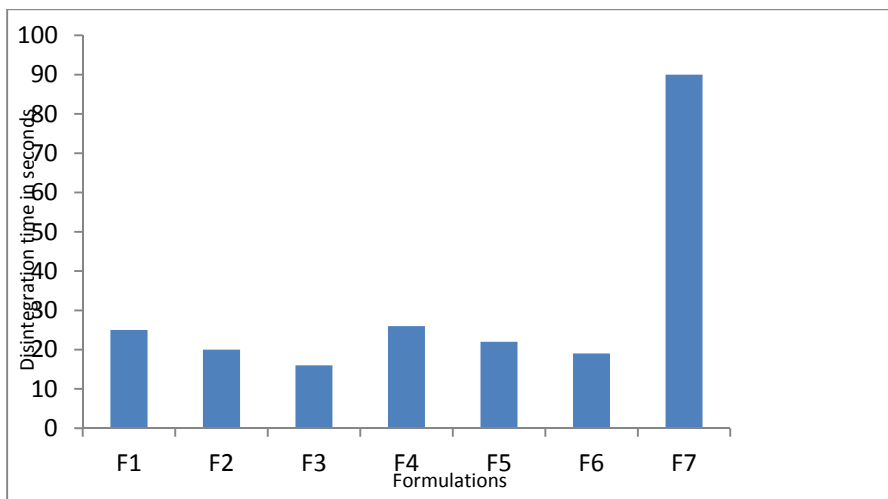


Figure 1: Invitro Disintegration Time

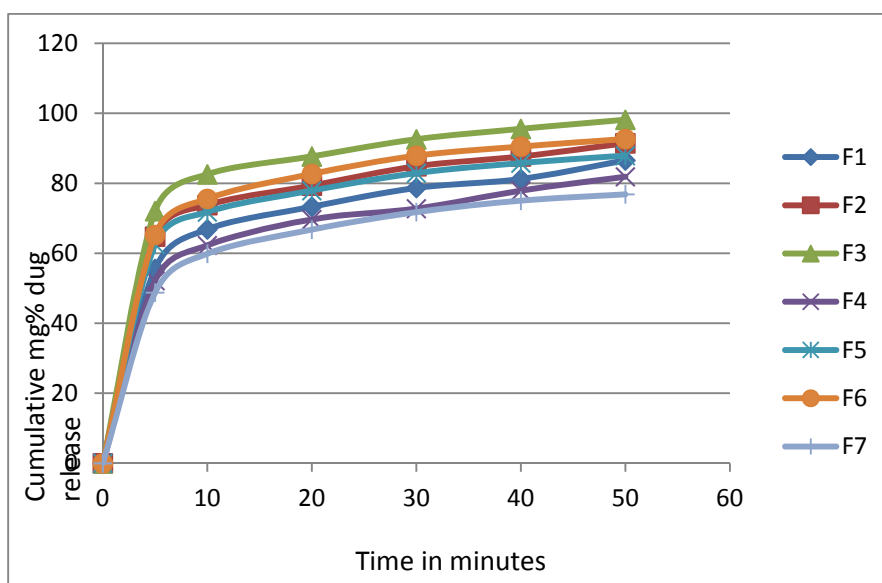


Figure 2: Percentage drug release