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Research Article

FORMULATION AND EVALUATION OF ORODISPERSIBLE METFORMIN TABLETS: A COMPARATIVE STUDY ON ISPHAGULA HUSK AND CROSSPOVIDONE AS SUPERDISINTEGRANTS

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ABSTRACT

Metformin Hcl (Met.Hcl) is an orally administered hypoglycemic agent, used in the management of non-insulin-dependent (type-2)diabetes. As precision of dosing and patient's compliance become important prerequisite for a long term antidiabetic treatment, there is a need to develop formulation for this drug which overcomes problems such as difficulty in swallowing, inconvenience in administration while travelling and patient's acceptability. Hence in the present study an attempt has been made to prepare fast disintegrating tablets of Met.Hcl in the oral cavity with enhanced dissolution rate. The tablets were prepared with Isphagula husk, natural superdisintegrant and Crosspovidone, synthetic superdisintegrant. The pure drug and formulation blend was examined for angle of repose, bulk density, tapped density, Compressibility index and Haussner's ratio. The tablets were evaluated for hardness, tensile strength, drug content, friability and were found satisfactory. The disintegration time in the oral cavity was also tested and was found to be around 10sec. Based on dissolution rate the disintegrants can be rated as Isphagula husk > Crosspovidone. Hence Ishagula husk was recommended as suitable disintegrant for the preparation of direct compression melt-in-mouth tablets of Met.Hcl. All the dissolution parameters were calculated and compared with market tablet. A 3.78 fold increase in the dissolution rate was observed with F4 formulation when compared to market tablet(Glucophage). It was concluded that the rapidly disintegrating tablets with proper hardness, rapid disintegration in the oral cavity with enhanced dissolution rate can be made using super disintegrants (natural and synthetic).

Keywords: Direct compression, Mouth dissolving, Fast disintegration, Met.Hcl.

INTRODUCTION

Convenience of administration and patient compliance are gaining significant importance in design of dosage forms. Tablet is most popular among all dosage forms existing today because of convenience of self administration, compactness and easy manufacturing. However many patients, especially elderly find it difficulty in swallowing tablets, capsules, fluids and thus do not comply with prescription which results in high incidence of non-compliance and ineffective therapy[1]. Patient convenience and compliance oriented research has resulted in bringing out many safer and newer drug delivery systems. Rapidly disintegrating/ dissolving tablet is one of such example, for the reason of rapid disintegration or dissolution in mouth with little amount of water or even with saliva[2-4]. Significance of this drug delivery system includes administration without water, accuracy of dosage forms, ease of portability, alternative to liquid dosage forms, ideal for pediatric and geriatric patients and rapid onset of action[5-7]

Metformin Hcl is chemically (*N, N*dimethylimidodicarbonimidic diamide hydrochloride) an orally administered hypoglycemic agent used in the treatment of non-insulin-dependent diabetes[8](Type 2). As the dose of the conventional tablet is high, it gives the problem of difficulty in swallowing. Other problems like hand tremors, dysphagia incase of geriatric patients and in case of non co-operative patients the problem of swallowing is common phenomenon which leads to poor patient compliance. To overcome these drawbacks Mouth dissolving tablets or orally disintegrating tablets or Fast dissolving tablets has emerged as an alternative oral dosage form.

In the present study an attempt had been made to prepare rapidly disintegrating tablets of Met.Hcl in the oral cavity with enhanced dissolution rate and hence improved patient compliance. The basic approach used in the development of mouth dissolving tablets is the use of synthetic and natural super disintegrants like Crosspovidone, Isphagula husk which provide instantaneous disintegration of tablet after putting on tongue, thereby releasing the drug in saliva. Isphagula husk is covering of seeds grown on the plant, Plantago Psyllium is found to possess tablet disintegrant properties. Crosspovidone is a water insoluble synthetic crosslinked homopolymer of N-vinyl-2-pyrrolidinone possessing tablet dintegration properties. These systems may offer superior profile with potential mucosal absorption thus increase the drug bioavailability. These systems are also called melt-in-mouth tablets, Repimelts, porous tablets, Orodispersible, quick dissolving or rapidly disintegrating tablets.

EXPERIMENTAL

MATERIALS AND METHODS

Met.Hcl IP (obtained as gift sample from Life line formulations, VJA), Isphagula husk obtained from local market, Lactose, Microcrystalline cellulose, Starch, Crosspovidone, Mannitol, Magnesium stearate, Talc used were of Pharmacoepial grade.

Estimation of Met.Hcl

An UV Spectrophotometric method based on the measurement of absorbance at 233nm in distilled water was used in the estimation of Met.Hcl. The method obeyed Beer's law in the concentration range of 2-10µg/ml. Low RSD values ensured reproducibility of the method. Thus the method was found to be suitable for the estimation of Met.Hcl content in various products and in vitro dissolution studies. The result was shown in Fig.1

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.

Angle of Repose: Angle of repose was determined using funnel method[9]. The blend was poured through a funnel that can be raised vertically until a maximum cone height (h) was obtained. Radius of the heap (r) was measured and the angle of repose (ɵ) was calculated using the formula:

$$\theta = \tan^{-}[h/r]$$

Bulk density: Apparent bulk density (ρ_b) was determined by pouring the blend into a graduated cylinder. The bulk volume (V_b)

and weight of the powder (M) was determined. The bulk density was calculated using the formula:

$$\rho_b = M/V$$

Tapped density: The measuring cylinder containing a known mass of blend was tapped for a fixed time. The minimum volume (V_t) occupied in the cylinder and the weight (M) of the blend was measured. The tapped density (ρ_t) was calculated using the formula:

$$\rho_t = M/V_t$$

Compressibility index: Compressibility index I is calculated as follows:

$$I = V_0 - V_t / V_0 \times 100$$

Where V_0 is the bulk volume

V_t is the tapped volume.

The value below 15%indicates a powder with usually give rise to good flow characteristics where as above 25% indicate poor flowability.

Haussner's ratio: Haussner's ratio[10] is an indirect index of ease of powder flow. It is calculated by the following formula: Haussner's ratio $=\rho_t/\rho_b$

ρ_t= tapped density ρ_b= bulk density

Lower Haussner's ratio (<1.25) indicates better flow properties than higher ones(>1.25)[11]

Infrared spectroscopy study

The study was carried out to determine the molecular structure serving as an identification test to ascertain the purity of the molecule. IR spectroscopy was obtained by a FTIR spectrophotometer (H400-84100,Shimadzu, Japan) using KBr pellets and scanning range used was 4400 to 400 cm^{-1} at a scan period of 1min.Spectra of Pure drug and blend of F4 are shown in fig. 2 & fig.3 respectively.

There is no change in the shape of the peak or shift of the peak hence drug and excipients are compatible.

Compression of tablets

The ingredients depicted in Table 1(except Talc & Magnesium stearate) were mixed homogenously and co ground in a mortar and pestle. Finally talc and Magnesium stearate were added and mixed for 5min.The mixed blend of drug and excipients was compressed using a single punch CADMACH punching machine to produce round tablets weighing 500mg with a diameter of 9mm. A minimum of 50 tablets were prepared for each batch.

Evaluation of tablets

All the prepared tablets were evaluated for the following parameters as per I.P guidelines and the results are given in the Table 3.

Weight variation: Twenty tablets were randomly selected from each batch, individually weighed, the average weight and standard deviation of 20 tablets was calculated.

Hardness: Hardness or tablet crushing strength (F_c); the force required to break a tablet in a diametric compression was measured using a PFIZER tablet hardness tester.

Tensile strength: Tensile strength of tablets was calculated using the following formula:

$T = 2F_c / d\ t$. where F_c- crushing strength, d- diameter, t-thickness of tablet.

Friability: Friability of tablets was determined using Roche friabilator (USP).

Preweighed sample of tablets was placed in the friabilator and were subjected to 100 revolutions at 25 rpm. Tablets were dedusted using a soft muslin cloth and reweighed. Percent friability = [initial wt-final wt/ initial wt] × 100.

Drug content uniformity: The drug content was determined by taking the powder equivalent to 10mg, then it was dissolved in distilled water and absorbance was taken against the blank at 233nm.

***In vitro* disintegration time:** The disintegration test was performed using an IP 85 disintegration apparatus with distilled water at 37± 0.5°C. Effect of superdisintegrants was studied and shown in fig.4

In vivo disintegration time: The time required for tablets to disintegrate in the mouth cavity was determined by holding the tablets in the mouth. The subjects were instructed to gently move the tablet against the upper part of the mouth with the tongue. It is emphasized to the subject that this is a gentle motion with no biting of the tablet. Immediately after the last noticeable granule was disintegrated, the time was again recorded. Test was conducted in duplicate and average time is reported. The test was performed in five healthy human volunteers in the age group of 23 to 28 years.

***In vitro* dispersion time**: Tablet was added to 10 ml of phosphate buffer solution (pH 6.8) at 37± 0.5°C time required for complete dispersion of a tablet was measured.

Measurement of liquid uptake (Wetting time):

A glass petridish 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. Effect of superdisintegrants on wetting time was studied and shown in fig.5

Water absorption ratio: A piece of tissue paper was folded twice was placed in a small petridish containing 6ml of water. A tablet was put on the paper and the time required for complete wetting was measured. The wetted tablet was then weighed. Water absorption ratio, R was determined using the following equation:$R = 100 \times W_a - W_b / W_b$ where W_b is weight of tablet before water absorption and $W_a$is weight of tablet after water absorption.

Dissolution rate studies: Dissolution rate of Met.Hcl from all formulations was performed using LABINDIA DISSO 2000 an eight stage dissolution rate testing apparatus with basket. The dissolution fluid was 900ml of 6.8 pH phosphate buffer a speed of 50rpm & a temperature of 37±0.5°C were used in each test. Samples of dissolution medium (5ml) were withdrawn through a filler of 0.45µm at different time intervals, suitably diluted and assayed for Met.Hcl by measuring absorbance at 233nm. The dissolution experiments were conducted in triplicate and the results are shown in the Fig.6&7. The dissolution parameters and correlation coefficient values were calculated and given in tables 4&5.

RESULTS AND DISCUSSION

Four set (F1-F4) of tablet formulations were prepared and evaluated accordingly. The composition of tablets is presented in table 1. Different concentrations of Super disintegrants (4% and 8%) were investigated. Drug load (50%) was maintained steady for all the formulations. The final blend of drug and excipients was evaluated for flow properties and was found that the flow property of prepared powdered blend was good and the result is given in the table 2. All the obtained formulations exhibited satisfactory tablet characteristics as discussed in Table 3

The disintegration time in relation to superdisintegrant concentration is shown in Fig.4 reflecting that the higher the concentration rapid will be the disintegration. The disintegration time for each batch tablet was found to be less than one minute and the tablets containing Isphagula husk (F3 & F4) showed lowest disintegration time(26 sec & 22 sec respectively). 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 (19-26sec).The lowest (19sec) was obtained with formulation F4. All the tablets released almost

70% of the drug within 10 min (Fig. 7) proving its fast dissolving action. Dissolution profiles were shown in Fig. 6 and dissolution parameters for all batches were summarized in Table 4. Analysis of dissolution data as per zero order and first order kinetic models based on correlation coefficient (r^2) values (Table 4) indicated that the dissolution of Met.Hcl from all the tablets followed first order kinetics. Among all the formulated tablets F4 which is based on Met.Hcl with 8%Isphagula husk gave the highest dissolution (98.7%) in 10 mins. A 3.78 fold increase in the dissolution rate of the drug was observed when compared to market formulations. Based on dissolution rate the disintegrants can be ranked as Isphagula husk> crosspovidone. Isphagula husk showed better dissolution and dissolution efficiency (DE_5%) than the superdisintegrant (Crosspovidone) studied at two levels (4% and 8%). Hence Isphagula husk was recommended as suitable disintegrant for the preparation of directly compressible mouth dissolving tablets of Met.Hcl as these are a very good alternative drug delivery to geriatric and paediatric patients.

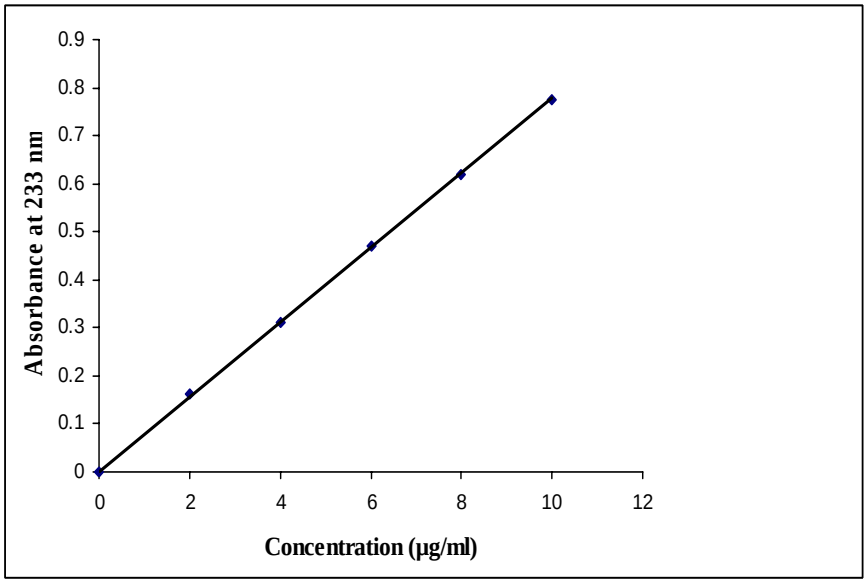

Fig. 1: Calibration curve of Met. Hcl

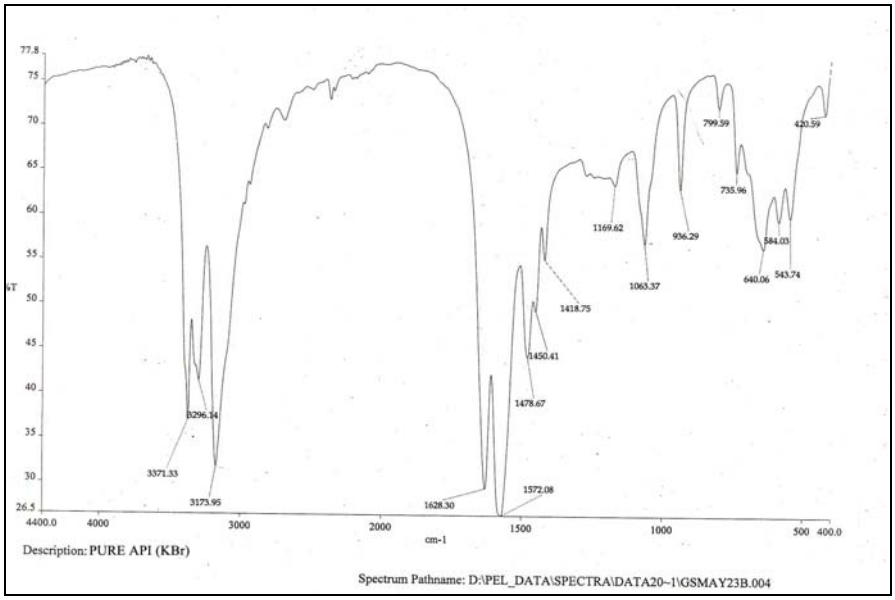

Fig. 2: Infra red spectrum of pure API

Material	Peak	Functional group
Pure API	3173.95	N-H stretching
	3371.33	
	3296.14	N-H_2 streching

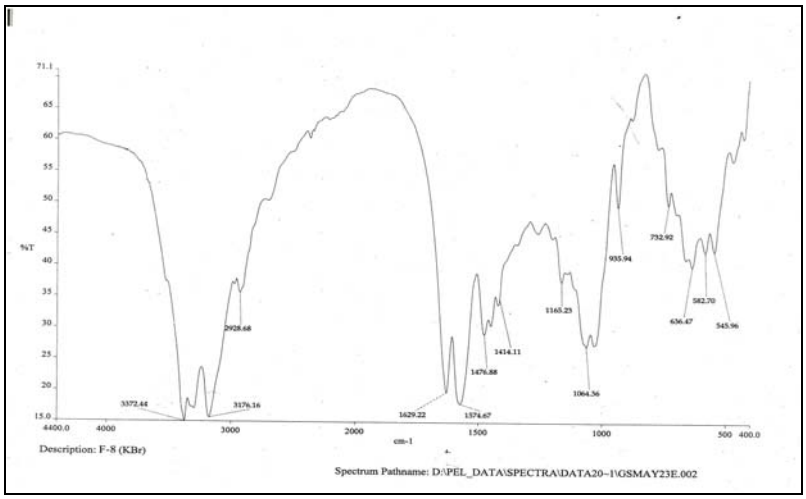

Fig. 3: IR Spectra of blend of F4 orodispersible tablets of Met.Hcl

Material	Peak	Functional group
Blend of F 4 Orodispersible tablets	3173.95 3371.33 3296.14	N-H stretching N-H_2 streching

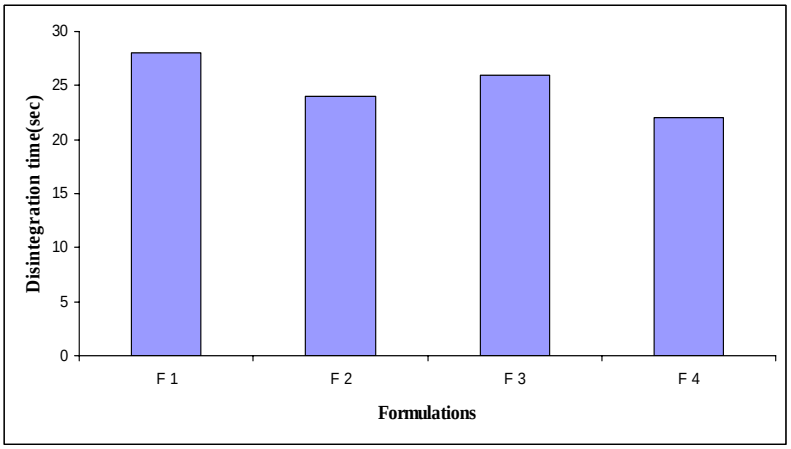

Fig. 4: Effect of superdisintegrants on disintegration time of orodispersible Met.Hcl tablets

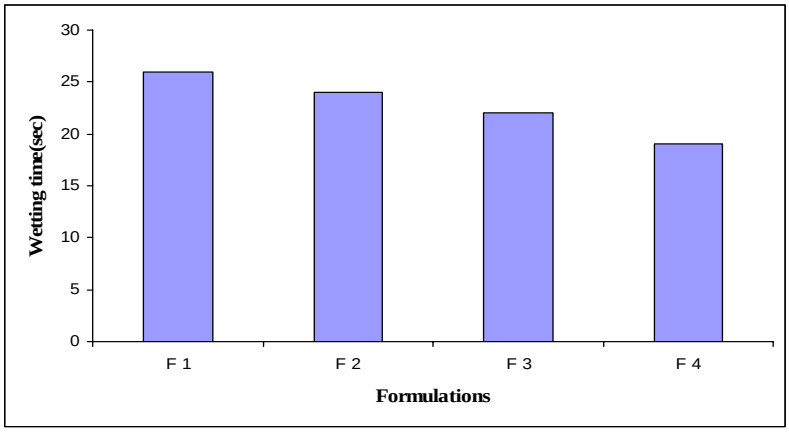

Fig. 5: Effect of superdisintegrants on wetting time of orodispersible Met.Hcl tablets

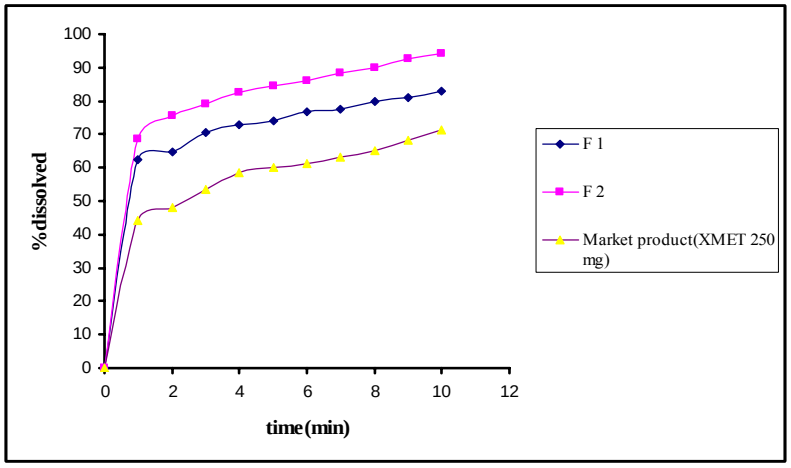

Fig. 6(a): Effect of crosspovidone level on release of Metformin

F 1: 4% Crosspovidone, F 2: 8% crosspovidone

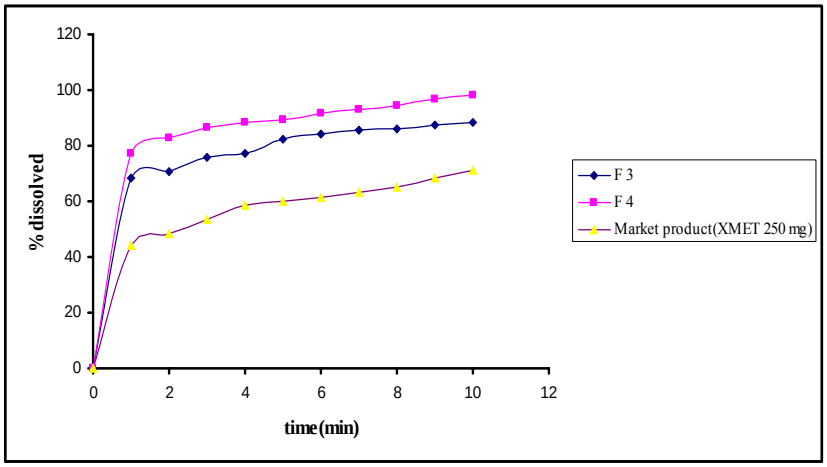

Fig. 6(b): Effect of isphagula husk level on release of Metformin

F 3: 4% Isphagula husk F 4: 8% Isphagula husk

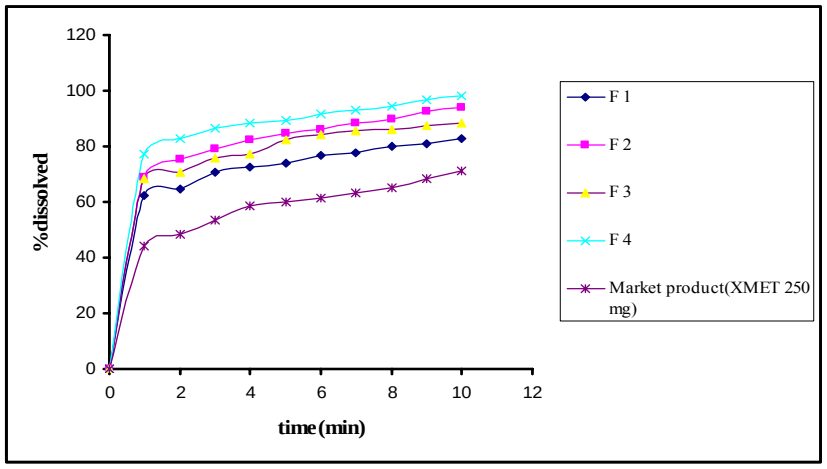

Fig. 6(c): Dissolution profiles of orodispersible Met.Hcl tablets

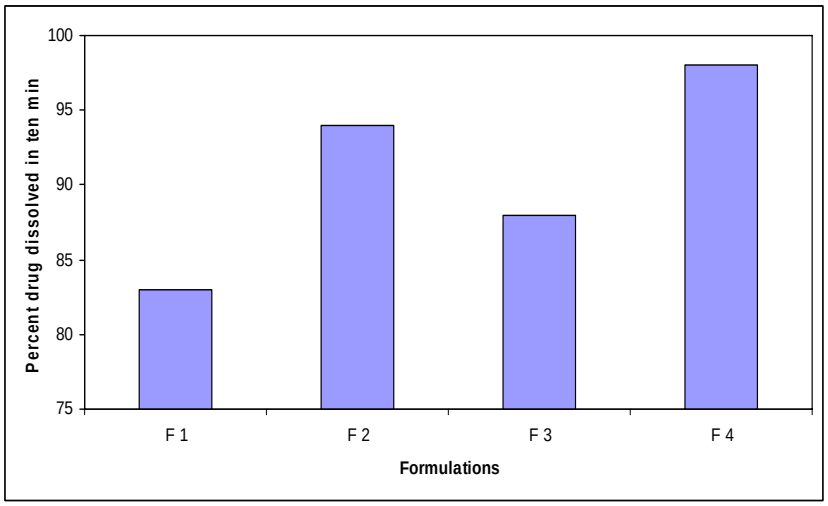

Fig 7: Percent drug dissolved in 10 minutes from orodispersible Met.Hcl tablets

Table 1: Formulae of fast dissolving tablets of Met. Hcl

INGREDIENT	F 1(%)	F 2(%)	F 3(%)	F 4(%)
Metformin Hcl	50	50	50	50
Lactose	15	18	20	18
MCC	10	9	10	9
Starch	15	14	15	14
Crosspovidone	4	8	—	—
Isphagula husk	—	—	4	8
Mannitol	5	5	5	5
Talc	0.5	0.5	0.5	0.5
Magnesium stearate	0.5	0.5	0.5	0.5

Table 2: Evaluation of directly compressed blend

Parameter	F 1	F 2	F 3	F 4
Angle of repose(◦)	33	31	34	32
Bulk density(gm/cm^3)	0.56	0.6	0.54	0.58
Tapped density (gm/cm^3)	0.66	0.74	0.68	0.66
% Compressibility	15	18	20	12
Haussner's ratio	1.17	1.23	1.25	1.13
Flowability	Good	Fair	Fair	Good

Table 3: Evaluation of formulations

PARAMETER	F 1	F 2	F 3	F 4
Average weight(mg)±S.D	507±0.34	508±0.24	508±0.24	505±0.36
Hardness(kg/cm^2) ±S.D	4±0.32	4±0.31	3±0.22	4±0.25
Tensile strength	0.298	0.304	0.255	0.312
Friability (%)	0.18	0.16	0.17	0.20
InvitroDisintegration time(sec)	28	24	26	22
Drug content (%)	96	98	86	90
Invitro dispersion time(sec)	14	12	12	13
Invivo disintegration time(sec)	11	10	11	10
Wetting time(sec)	26	24	22	19
Water absorption ratio(R)	0.52	0.44	0.58	0.41

Table 4: Correlation coefficient(r) values of orodispersible tablets of Met.Hcl formulated employing different super disintegrants as per zero order and first order kinetics

PARAMETER	F 1	F 2	F 3	F 4	MARKETED
Zero order(r^2)	0.8599	0.8699	0.8611	0.8153	0.8768
First order(r^2)	0.9524	0.9957	0.9247	0.9939	0.9726

Table 5: Dissolution parameters of orodispersible Met.Hcl tablets

PARAMETER	$t_{(10)}$(sec)	$t_{(50)}$(sec)	$t_{(90)}$(min)	DE_5(%)	K_{min}^{-1}
F 1	12	36	>10	62.6	0.193
F 2	12	30	8	71.4	0.325
F 3	12	36	>10	67.2	0.245
F 4	12	30	6	83.5	0.367
Marketed	16	121	>10	48.3	0.097

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