Evaluation of Disintegrating Properties of *Mangifera indica* gum

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ABSTRACT

In the present study, an attempt had been made to prepare mouth dissolving tablets of metformin HCl using *Mangifera indica* gum powder as disintegrant. Specifications for herbal raw materials and finished products were set according to Committee for Proprietary Medicinal Products. Gum extracted from the *Mangifera indica* tree was subjected to toxicity studies for its safety and preformulation studies for its suitability as a disintegrating agent. The gum extracted is devoid of toxicity. mouth dissolving tablets of metformin were prepared and compared with different concentrations viz; 2, 4, 6, 8 and 10 %(w/w) of *Mangifera indica* gum powder and crosspovidone®, and evaluated for physical parameters such as thickness, hardness, friability, weight variation, drug content, disintegration time and drug dissolution. The physical parameters of the fabricated tablet were within acceptable limits. The formulated tablets had good appearance and better drug release properties. The study revealed that *Mangifera indica* gum powder was effective as disintegrants in low concentrations (6%w/w). The study further revealed a poor relation between the swelling index and disintegrating efficiency. Studies indicated that the extracted mucilage is a good pharmaceutical adjuvant, specifically a disintegrating agent.

Keywords: Metformin HCl, Disintegrant, mouth dissolving tablets, *Mangifera indica* gum, Pharmaceutical excipients.

IINTRODUCTION

Robbins has stated, "in spite of the problems which have beset the gums market in recent years, the fact remains that in many cases the gums provide a valuable source of income for many poor smallholders or itinerant labourers, either in very poor countries or in the poorest regions rather than more developed countries as such they are important commodities[1].

For centuries man has made effective use of materials of natural origin in the medical and pharmaceutical field. Today, the whole world is increasingly interested in natural drugs and excipients. Natural materials have advantages over synthetic materials because they are non toxic, less expensive and freely available. Furthermore, they can be modified to obtain tailor made materials for drug delivery systems allowing them to compete with the synthetic products that are commercially available. Many kinds of natural gums are used in the food industry and are regarded as safe for human consumption. It should be noted that many 'old' materials are still popular today after almost a century of efforts to replace them. It is usual to strike a balance between economics and performance in the face of commercial realities[2-5].

Natural gums obtained from plants have diverse applications in drug delivery as disintegrant, emulsifying, suspending agents and as binders. They have also been found useful in formulating immediate and sustained release preparations[3-10].

For centuries, the Mango tree (Scientific name: *Mangifera indica*, Family: Anacardiaceae) has been an integral part of life in India. Each and every part of the tree (bark, leaves, root and kernel seed fruit) serves a certain purpose, for instance, as diuretic, astringent, aphthous stomatitis, diabetes, asthma, diarrhea, urethritis, dysentery, scabies and other parasitic skin diseases[11]. Literature survey reveals that comprehensive physicochemical characterization and pharmaceutical application of the *Mangifera indica* gum (MIG) as a disintegrating agent in tablet formulation has not been reported yet.

Many patients, especially elderly find it difficult in swallowing tablets, capsules, fluids and thus do not comply with prescription, which results in high incidence of non-compliance oriented research has resulted in bringing out

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many safer and newer drug delivery systems. Rapidly disintegrating/dissolving tablet is one of such example, for the reason of rapid disintegration or even with saliva. Significance of this drug delivery system includes administration without water, accuracy of dosage, ease of portability, alternative to liquid dosage forms, ideal for paediatric and geriatric patients and rapid onset of action[12-18].

Diabetes mellitus is a chronic metabolic disorder characterized by high blood glucose concentration-hyperglycemia-caused by insulin deficiency, often combined with insulin resistance[19]. Metformin HCl, an important drug of biguanide class, is currently available drug for treating hyperglycemia in (Non-Insulin Dependent Diabetes Mellitus (NIDDM); but has been associated with severe and sometimes fatal hypoglycemia and gastric disturbances like nausea, vomiting, heartburn, anorexia and increased appetite after oral therapy. Since these drugs are usually intended to be taken for a long period, patient compliance is also very important[20-21]. Metformin, which is slowly and partially absorbed by the gut, is taken in the form of oral tablets of 500 and 850mg, usually at a dose of 2g (maximum of 3g) per day. The absolute bioavailability of a 500mg immediate-release tablet is about 50 to 60%; the half-life is 2 -6h and the maximum plasma concentration is reached after 2.5h, Almost 80-100 % of the drug is excreted unchanged. In the Bioavailability Classification System (BCS), metformin is classified as a class III drug, because of its high water solubility.

The objective of the present study was to isolate MIG from its source and to study physicochemical and phytochemical parameters to ascertain its suitability as a disintegrant for developing fast disintegrating tablets (FDT's) of the selected model drug metformin HCl. The disintegration and swelling properties of FDT were compared with widely used super disintegrant like Crosspovidone®. Metformin HCl, an antidiabetic drug, was selected as the model drug as it was widely used in the treatment of Type–II diabetes.

MATERIALS AND METHODS

Materials:

Metformin HCl, talc, magnesium stearate, aspartame, aerosil were obtained from Zydus Research centre, Ahmedabad, India as gift samples. Mango gum resin was collected from the incised trunk of *Mangifera indica* in Ankola region (Uttar Kannada District) region. All the other solvents, reagents and chemicals used were of either Pharamcopoeial or analytical grade. Different instruments *viz*; Vernier calipers, Monsanto hardness tester, Roche friabilator and disintegration apparatus were supplied by Campbell Electronics, Mumbai. USP XXIII dissolution apparatus-2 was from Tab- Machines, Mumbai, 1601 PC Shimadzu UV Spectrophotometer from Tokyo, Japan and Shimadzu DSC-60, Shimadzu Limited Japan.

Methods:

Extraction of *Mangifera indica* Gum:[22-23]

The mango gum resin gum was collected from *Mangifera indica* trees (injured trunk site). It was dried, ground, and passed through sieve no 80. Dried gum (15 g) was stirred in distilled water (300 ml) for 6-8 h at room temperature. The supernatant was obtained by centrifugation. The residue was washed with water and the washings were added to separate supernatant. The procedure was repeated four more times. Finally the supernatant was made up to 500 ml and treated with twice the volume of acetone by continuous stirring. The precipitated material was washed with distilled water and dried at 50-60°C under vacuum. The dried gum was pulverized using a pulverizer and stored in tightly closed container.

Evaluation of Toxicity:

Toxicity studies were carried out according to the method of Knudsen and Curtis[24]. The animals used in the toxicity studies were sanctioned by the Institute Animal Ethical Committee (Approval No: KLECP/IAEC/45/2010-11). The male albino rats of Wistar strain weighing 160-200 g were divided into different groups comprising of six animals each. The control group received normal 0.5%CMC solution (20ml/kg i.p). The other groups received 500, 1000, 2000, 3000, 4000 and 5000 mg/kg of MIG suspension in normal saline orally. The animals were observed continuously for the behavioral changes for the first 4 hours and then observed for mortality if any for 72h. Since no mortality, no toxic manifestations were observed and behavioural pattern was unaffected. In chronic toxicity studies, 22 animals were used, divided in to two groups, 6 as control and 16 as test animals. In the test group a dose of 500 mg/kg was administered daily for a period of 30 days Body weights were recorded for both the groups at an interval of 10day and at the end of 30 days, hematological and biochemical parameters were studied in both the groups and after 30 days of chronic toxicity study the animals were scarified and subjected to histopathological studies.

Physicochemical characterization of mucilage:[25-28]

The physicochemical properties such as solubility, swelling index, ash values, loss on drying, precompression parameters and microbial load of the MIG were determined according to official Procedures. The following evaluation

parameters were carried out as per the procedures described below.

Solubility:

The separated gum was evaluated for solubility in water, acetone, chloroform, methanol, ether and ethanol in accordance with the British Pharmacopoeia specifications.

Determination of swelling index:

Swelling characteristics of the separated MIG powder was studied in different media such as 0.1 N hydrochloric acid, pH 7.4 phosphate buffer and distilled water. The swelling index is the volume in ml occupied by 1 g of drug; including any adhering gum after it has been swollen in an aqueous liquid for 4 h. The swelling index of MIG powder was determined according to the British Pharmacopoeia method. 1g of MIG powder was taken in a 25 ml ground glass stoppered cylinder graduated over a height of 120 to 130 mm in 0.5 divisions. To this 25 ml of respective medium was added and this was shaken vigorously every 10 m for 1 h and then allowed to stand for 24 h. The volume occupied by the MIG powder was measured.

The swelling index was computed using the equation

$$S = V2/V1.$$

Where; S = Swelling index

V1 = Volume occupied by the gum prior to hydration

V2 = Volume occupied by the gum after to hydration

The test was carried out in triplicate and the average value of swelling index was recorded

Loss on drying:

As the inherent moisture in MIG powder/excipients may influence the stability of the tablet dosage form containing moisture sensitive drugs, moisture content of the separated mucilage was detected by loss on drying method. The sample (1 g) was heated at 105°C until constant weight in a hot air oven and percentage loss of moisture on drying was calculated using the formula,

$$\text{LOD (\%)} = (\text{weight of water in sample/weight of dry sample}) \times 100.$$

Total ash:

The total ash was determined by placing 3 g of the ground air-dried material in a crucible, spreading the material in an even layer and igniting it by gradually increasing the temperature to 550°C until it is white, indicating the absence of carbon. The crucible was cooled in a desiccator, weighed and the content of total ash in mg per g of air-dried material was calculated.

Acid Insoluble ash:

Acid-insoluble ash is the residue obtained after boiling the total ash with dilute hydrochloric acid and igniting the remaining insoluble matter. To the crucible containing the total ash, 25 ml of hydrochloride acid was added, covered with a watch glass and boiled gently for 5 min. The watch glass was rinsed with 5 ml of hot water this liquid was added to the crucible. The insoluble matter on an ash less filter paper was collected and washed with hot water until the filtrate is neutral. The filter paper containing the insoluble matter was transferred to the original crucible, dried on a hot plate and ignited to constant weight. The residue was allowed to cool in a desiccator for 30 min, weighed without delay and the content of acid insoluble ash in mg per g of air-dried material was calculated.

Microbial load:

Microbial count for separated MIG powder was performed as outlined in Indian Pharmacopoeia-1996 for total aerobic microbial count using plate count method. The plate count for bacteria and fungi were measured.

pH determination:

This was done by shaking a 1%w/v dispersion of the sample in water for 5 min and the pH determined using a pH meter (Elico, Hyderabad). The data presented here is for triplicate determinations.

Angle of repose:

The static angle of repose, a, was measured according to the fixed funnel and free standing cone method. A funnel was clamped with its tip 2 cm above a graph paper placed on a flat horizontal surface. The powders were carefully poured through the funnel until the apex of the cone thus formed just reached the tip of the funnel. The mean diameters of the base of the powder cones were determined and the tangent of the angle of repose calculated using the equation:

$$\text{Tan } a = 2h/D$$

The data presented here is for triplicate determinations.

Bulk and Tapped densities:

2 g quantity each of the powder sample was placed in a 10ml measuring cylinder and the volume, V_0, occupied by each of the samples without tapping was noted. After 100 taps on the table, the occupied volume V_{100} was read. The bulk and tap densities were calculated as the ratio of weight to volume (V_0 and V_{100} respectively). The data presented here is for triplicate determinations.

Hausner's index:

This was calculated as the ratio of tapped density to bulk density of the samples.

Compressibility index:

This was calculated using the equation:

Compressibility = (Tapped density- bulk density)/Tapped density x 100.

Differential Scanning Calorimetry (DSC) Analysis:

Thermal properties of MIG powder were characterized using a Shimadzu DSC-60, Shimadzu Limited Tokyo, Japan. Nitrogen, at the rate of 20 ml/min, was used as purge gas; 2 mg of powdered material were sealed in aluminium pan and heated from 30°C up to 400°C at the rate of 10°C/min, followed by a cooling cycle back to 30°C at the same rate.

Fourier Transform Infra Red (FT-IR) Analysis:

The FT-IR spectrum of the sample was recorded in an IR spectrometer (FT–IR: 8101 M, Shimadzu, Japan), using potassium bromide (KBr) discs prepared from powdered samples mixed with dry KBr in the ratio 1:200. Triplicate measurements were made, and the spectrum with the clearest identifiable peaks was chosen.

Phytochemical Examination:[29]

Preliminary tests were performed to confirm the nature of gum obtained. The chemical tests that were conducted are: Ruthenium red test, Molisch test, test for reducing sugars and Ninhydrin test.

Characterization of Drug and Excipients

Drug-excipient compatibility studies:

This study has been done to check whether there is any compatibility related problems are associated with drug and the excipients used for the formulation of mouth dissolving tablets. The drug and excipients must be compatible with one another to produce a product that is stable, efficacious, attractive, and easy to administer and safe. If the excipients are new and not been used in formulations containing the active substance, the compatibility studies are of paramount importance. Thermal analysis, TLC, HPLC, FTIR, can be used to investigate and predict any physicochemical interactions between components in a formulation and can therefore be applied to the selection of suitable chemically compatible excipients.

Fourier Transform Infrared (FTIR) Spectroscopy:

FTIR spectra were recorded on samples prepared in potassium bromide (KBr) discs using a IR spectrometer (FT–IR: 8101 M, Shimadzu, Japan), Samples were prepared in KBr disks by means of a hydrostatic press at 6-8 tons pressure. The scanning range was 500 to 4000 cm^{-1}.

Differential Scanning Calorimetry (DSC):

DSC analysis was performed using Shimadzu DSC-60, Shimadzu Limited Japan. A 1:1 ratio of drug and excipient was weighed into aluminum crucible. And sample was analyzed by heating at a scanning rate of 20^0C over a temperature range 20^0-300^0C under nitrogen environment.

Standard Calibration Curve of Metformin Hcl:

Solutions ranging from 2 to 4 µg/ml were prepared in phosphate buffer (pH 6.8). Absorbance was measured for each solution at λ_{max} of 233 nm, using1601 PC Shimadzu UV Spectrophotometer. Correlation coefficient was found to be 0.9998 in phosphate buffer.

Formulation of Mouth Dissolving Tablets:

Mouth dissolve tablets of Metformin HCl were prepared by the conventional direct compression technique using MIG powder and compared with different concentrations viz; 2, 4, 6, 8 and 10 % (w/w) of *Mangifera indica* gum powder and crosspovidone®. All ingredients were passed through mesh no.60. Required quantity of each was taken for particular formulation and the blend was mixed by tumbling in a polythene bag. The composition of each formulation is given in Table 1.

Evaluation of powder Blend

Pre compression parameters:[30]

The prepared powder blend was evaluated for various parameters like bulkiness, bulk density, tapped density, angle of repose, compressibility index and Hausner ratio. After evaluation of powder blend the tablets were compressed with Cadmach single punch compression machine using 12mm flat faced punches.

Evaluation of tablets

Post compression parameters:[31]

After tablet compression, all the tablets were evaluated for different parameters as thickness, hardness, friability, uniformity of weight, disintegration time, water absorption ratio, wetting time, drug content. *In vitro* dissolution studies were carried out in USP dissolution test apparatus (Type 2), using simulated intestinal fluid (pH 6.8) (900ml, 37± 0.5^0C) at 50 rpm.

pH of the solution:

The pH of the solution was measured using pH meter, after dissolving the tablet in around 200 ml of water.

Accelerated stability studies:

Stability studies were carried out on optimized formulation as per ICH specifications. The tablets were stored at 25 ± 2°C / 60 ± 5% RH and 40 ± 2°C / 75 ± 5% RH for duration

Table 1: Formulation of Mouth Dissolving Tablets of Metformin HCl

Ingredients (mg/each tablet)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
Metformin HCl	500	500	500	500	500	500	500	500	500	500
MIG*	12	24	36	48	60	--	--	--	–	--
Crosspovidone®	--	–	--	--	--	12	24	36	48	60
Aspartame	6	6	6	6	6	6	6	6	6	6
Magnesium Stearate	12	12	12	12	12	12	12	12	12	12
Talc	3	3	3	3	3	3	3	3	3	3
Aerosil	3	3	3	3	3	3	3	3	3	3
Flavor (Mango)	6	6	6	6	6	6	6	6	6	6
Avicel q.s.to	58	46	34	22	10	58	46	34	22	10
Total weight of tablet	600	600	600	600	600	600	600	600	600	600

MIG* *Mangifera indica* gum

of three month. After an interval of one month samples were withdrawn and tested for various physical tests and *in vitro* drug release.

RESULTS AND DISCUSSION

Plant products serve as an alternative to synthetic products because of local accessibility, environment friendly nature and lower prices compared to imported synthetic products. Herbs are non-polluting renewable resources for sustainable supplies of cheaper pharmaceutical products. Today, we have a number of plant-based pharmaceutical excipients. A number of researchers have explored the utility of plant-based materials as pharmaceutical excipients. Majority of investigations on natural polymers in drug delivery systems are centered on polysaccharides and proteins, due to their ability to produce a wide range of materials and properties based on their molecular structures.

Gums derived from the plant of *Mangifera indica* was investigated as disintegrating agent for use in moth dissolving tablet formulations containing metformin HCl.

Physicochemical characterization of *Mangifera indica* gum

The average yield of dried gum obtained from *Mangifera indica* tree was 35% w/w. The gum obtained was an off white to cream yellow color powder, and the viscosity of its 1% aqueous dispersion was 600 cP. The powder was slightly soluble in water and practically insoluble in ether, acetone, chloroform, methanol and ethanol.

The swelling characteristic of MIG was studied in different media; 0.1N hydrochloric acid, phosphate buffer (PH 7.4) and water. The swelling was highest in water (20) followed by 0.1N HCl pH (15) and least in phosphate buffer (10). Generally, the results show that MIG has high swelling index suggesting that the gum may perform well as binder/disintegrant/matrixing agent. The gum is a pH responsive polymer, it is therefore a "smart polymer," and may find application in controlled release dosage formulations. The moisture content of MIG was low (1.5%), suggesting its suitability in formulations containing moisture sensitive drugs. The total ash, water soluble ash and acid insoluble ash value of MIG was found to be 2.23, 1.3 and 0.4%w/w respectively. Ash values reflect the level of adulteration or handling of the drug. The bulk and tapped densities give an insight on the packing and arrangement of the particles and the compaction profile of a material. The compressibility index, Hausner ratio and angle of repose of MIG were 16.33%, 0.15 and 22.35° respectively, implying that the MIG has a good flow with moderate compressibility. The loss on drying, ash value and microbial count were well within official limits. The gum obtained from *Mangifera indica* tree was subjected to physicochemical characteristics the results of which are summarized in table 2.

Phytochemical screening of *Mangifera indica* gum

Phytochemical tests carried out on MIG confirmed the absence of alkaloids, glycosides and tannins. On treatment of mucilage with ruthenium red, it showed red colour confirming the obtained product as mucilage. A violet ring was formed at the junction of two liquids on reaction with Molisch's reagent indicating the presence of carbohydrates. Mucilage could not reduce Fehling's solution, so the sugars present were non reducing sugars. It reduced Fehling's solution after hydrolysis for 1h with concentrated sulfuric acid under reflux. Mucilage on treating with ninhydrin reagent does not give purple

colouration indicating the absence of amino acids. The results of phytochemical screening of MIG are summarized in table 3.

Toxicity study of MIG

To determine the safety level of extracted MIG, acute and chronic toxicity studies were carried out. In acute toxicity study no mortality was observed even at 5000mg/kg of MIG on oral administration and all animals were found to be normal during and at the end of the observation period of three days. Food and water consumption also did not differ significantly and there was no change in general behavior or other physiological activities of the animals in both control and treated groups. To assess the suitability of MIG for the oral delivery we have recorded the body weight profile for the animals during the chronic toxicity studies at regular intervals of 10 days. It was found that the body weight of both control and treatment group and the rate of increase in body weight were comparable. Hence, it could be inferred that chronic administration of the gum might not influence either the food intake or growth. Biochemical and hematological parameters were determined at the end of 30 days of continuous administration of MIG suspension and the biochemical and hematological parameters were found to be comparable to that of normal mice. The results are shown in table 4 and 5 respectively. Histological examination of the main organs like liver, kidney, heart and brain were carried out at the end of 30days of chronic toxicity study. From this study it was revealed that there was no sign of pathological changes in both control and in treatment group.

Characterization of MIG

Differential Scanning Calorimetry

Differential scanning calorimetry (DSC) was used to measure the occurrence of exothermal or endothermal changes with increase in temperature. DSC, because of its sensitivity and accuracy, has been extensively used to study the phase transitions of polymers. The thermogram for MIG is shown in Figure1.It shows that the gum has both amorphous and crystalline portions. Glass transition (Tg) temperature occurred at 94°C while a melting peak was observed at about 320°C.

Fourier Transform Infra Red (FT-IR)

The IR spectrum of MIG is shown in Figure 2. The finger print region of the spectrum consists of two characteristic peaks between 700 and 1316 per cm, attributed to the C-O bond stretching. The band at 1604/cm was assigned to the O-H bending of water. There are absorptions (weak) in the 1730 per cm area that indicate carbonyls. The absence of significant aromatic stretches in the 1660-1690/cm region and the weakness of the stretches, imply that there is a modest amount of peptidic cross linking by amide bond formation. The sharp band at 2939 per cm is characteristic of methyl C-H stretching associated with aromatic rings. The broad band at 3286 cm^{-1} is due to the hydrogen-bonding that contributes to the complex irrational stretches associated with free inter and intra-molecular bound hydroxyl groups which make up the gross structure of carbohydrates.

Table 2: Physicochemical characterization of *Mangifera indica* gum

Parameters	Observation
Solubility	Slightly soluble in water, practically insoluble in alcohol, chloroform and acetone. Forms thick gel in water.
pH (1% w/v solution)	6.5
Loss on drying	1.5%
Ash value	2.23%
Water soluble ash	1.3%
Acid insoluble ash	0.4%
Sulphated ash	1.03%
Test for foreign matter	Less than 0.1%
Test for arsenic	Less than 1ppm
Swelling ratio	
In water	20.0
In 0.1 N HCl	15.0
In phosphate Buffer 7.4	10.0
True density	1.7g/dl
Bulk density	0.48 g/cc
Tapped density	0.56 g/cc
Compressibity index	16.33%
Hausner ratio	0.15
Angle of repose	22.35
State	Amorphous powder
Odor	No characteristic odor
Taste	Tasteless
Color	Off white- cream yellow color
Total bacterial count	
E.coli	Absent
Salmonella typhi	Absent
S.aureus	Absent
Yield (%)	35
Viscosity (1%)	600 centipoise

Drug Excipient Compatibility Study

Fourier Transform Infrared (FTIR) Spectroscopy

The IR spectral analysis of metformin HCl and the physical

Table 3: Phytochemical screening of *Mangifera indica* gum

	Tests	Observation
1.	Test for Carbohydrates(Molisch ' s test)	+
2.	Test for Tannins(Ferric chloride test)	-
3.	Test for proteins (Ninhydrin test)	-
4.	Test for alkaloids (Wagner ' s test)	-
5.	Test for glycosides (Keller – Killaini test)	-
6.	Test for mucilage (Ruthenium red test)	+
7.	Test for flavonoids (Shinoda test)	-
8.	Test for reducing sugar (Felhing ' s test)	-
9.	Mounted in 95% alcohol	Transparent angular masses under microscope
10.	Mounting in the iodine	No blue colored particles (starch absent)
11.	Test with cupric –tartaric solution	Red precipitate is produced
12.	Warming with 5M sodium hydroxide	A brown color is produced
13.	Test for chlorides(silver nitrate test)	-
14.	Test for sulphates (barium chloride test)	-

Table 4: Results of Biochemical parameters in rats treated with MIG

Treatment	ALP (U/L)	ACP (U/L)	AST (U/L)	ALT (U/L)	Urea (U/L)	Creatinine (U/L)
Control (0.5%CMC)***	65±4.15*	29±4.25	72±2.34	56±1.25	51±2.10	0.4±0.22
Treatment (MIG)**** 500 mg/kg)	68±4.38**	27±2.02	69±4.10	58±2.87	48±1.65	0.3±0.21

*Data represents as the mean SD of 6 animals; **Data represents as the mean SD of 16 animals; ***CMC; Carboxy methyl cellulose; **** MIG; *Mangifera indica* gum

Table 5: Results of Hematological changes observed in rats during and after treatment of MIG for 30 days

Treatment	RBC (10^6/mm^3)	WBC (10^3/mm^3)	Hb(g/dl)	N	L	E
Control (0.5% CMC)	4.3 ± 0.05*	7100 ± 0.10	13.58 ± 0.21	8 ± 0.52	85± 0.17	0±0.00
Test(MIG) 500 mg/kg)	4.1± 0.07**	6850± 0.13	14.12± 0.35	12± 0.41	90± 0.21	1± 0.22

*Data represents as the mean SD of 6 animals; **Data represents as the mean SD of 16 animals

mixture of metformin HCl and other excipients are presented in Figure 3 and 4 respectively. Pure metformin HCl spectra showed principal peaks at different wave numbers corresponding to its functional groups, confirming the purity of the drug as per established standards. All the above characteristic peaks appear in the spectra of physical mixture of metformin HCl and other excipients, indicating no modification or interaction between the drug and excipients.

Differential Scanning Calorimetry (DSC)

The DSC analysis (Figure 5) of pure metformin HCl showed a characteristic, sharp endotherm peak at 226°C corresponding to its melting point and indicates the crystalline nature of the drug. The DSC analysis of physical mixture of drug and excipients (figure 6) revealed negligible change in the melting point of metformin HCl in the presence excipients, indicating no modification or interaction between the drug and excipients.

Precompression parameters of powder blend

Since, the flow properties of the powder mixture are important for the uniformity of mass of the tablets, the flow of the powder mixture was analyzed before compression to tablets. Bulk density was found to be between 0.53 to 0.57 g/cc and tapped density between 0.67 to 0.74 g/cc, bulkiness between 1.72 to 1.89, carr's index between 16.9 to 23.7%, Hausner ratio between 1.22 to 1.32 and angle of repose was found to be between 24.6 to 33.6, indicating fair to good flow properties. Results of precompression parameters are shown in Table 6.

Fig.1: Differential scanning calorimetry curve of *Mangifera indica* gum Powder

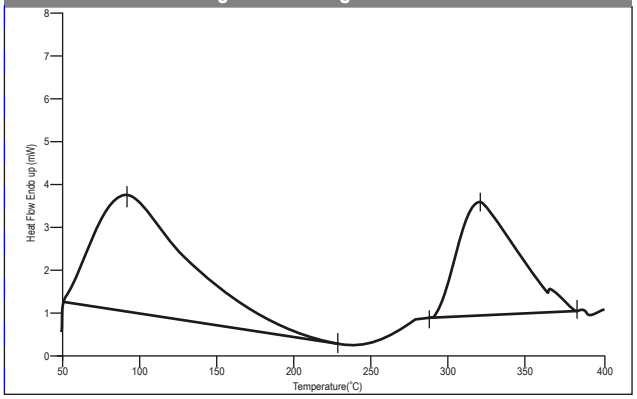


Fig.2: FTIR spectrum of *Mangifera indica* gum powder

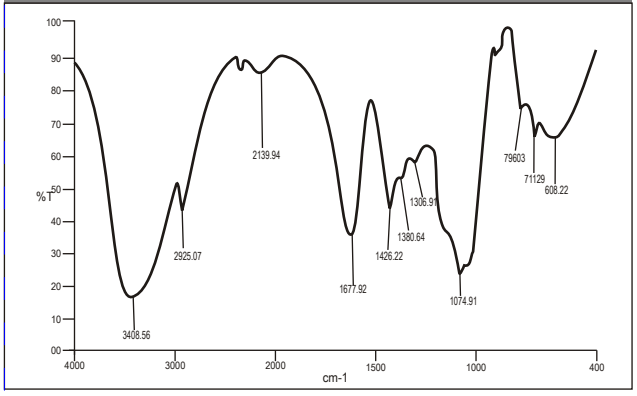


Fig.3: FTIR Spectra of Metformin HCl

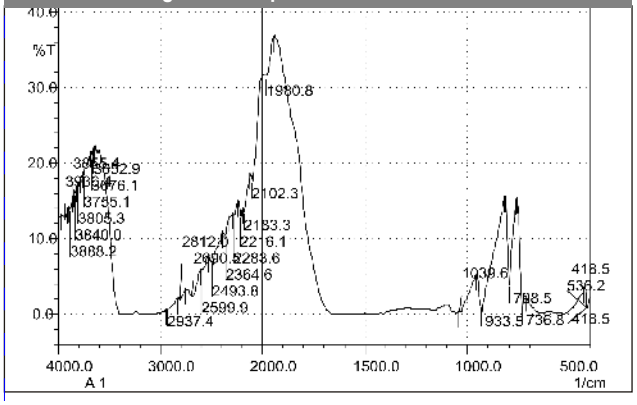


Fig.4: Spectra of physical mixture of Metformin HCl and excipients

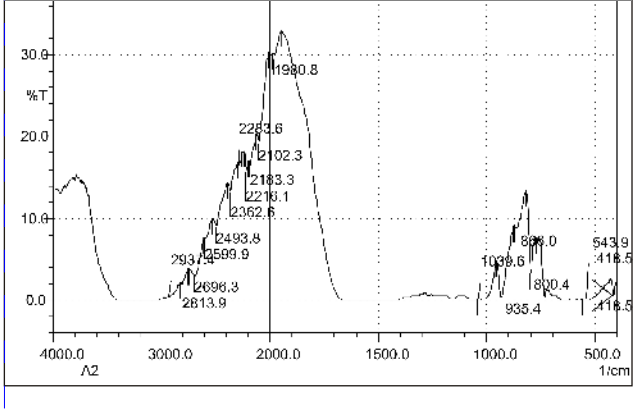


Fig.5: DSC Thermogram of Metformin HCl

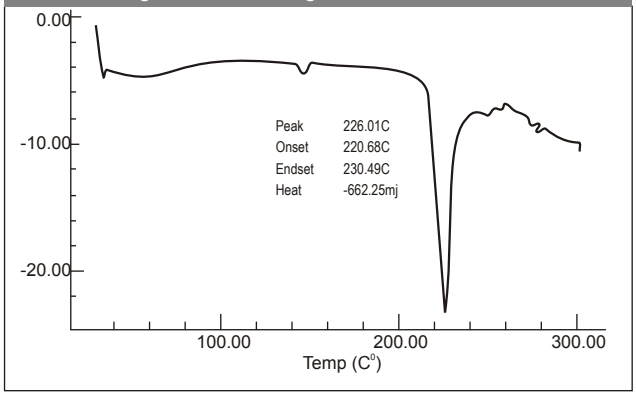


Fig. 6: DSC Thermogram of physical mixture of drug and excipients

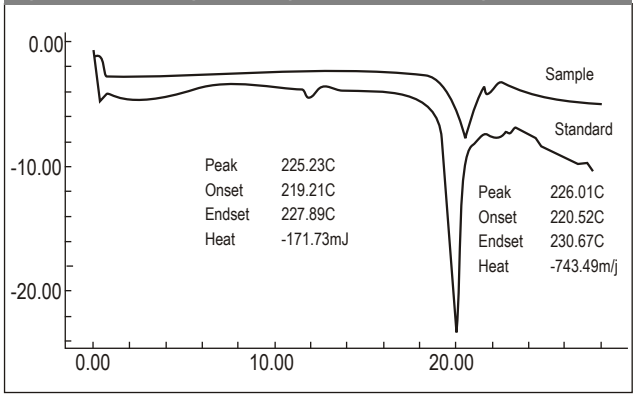


Fig.7: Comparison between disintegration time in oral cavity, wetting time and disintegration time (*in vitro*) for Metformin HCl Formulations

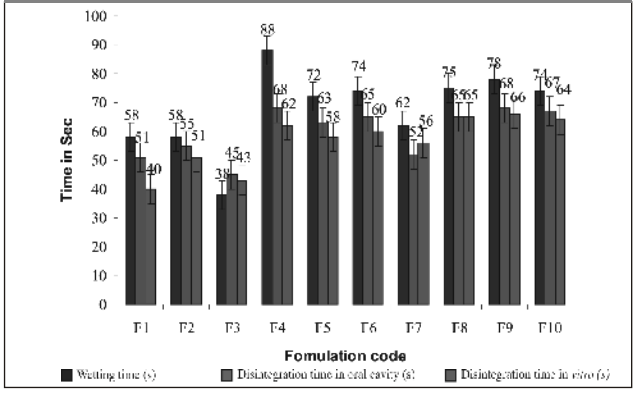
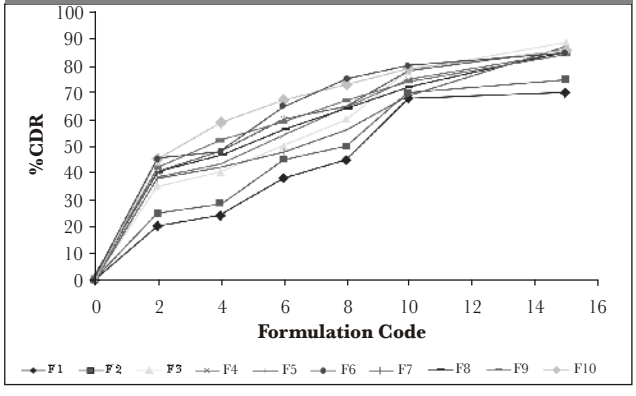


Fig.8: Comparison of *In Vitro* Release of Various Metformin Formulations



Post compression parameters of fast dissolving tablets

Tablets were prepared using direct compression. Tablets were obtained of uniform weight due to uniform die fill, with acceptable weight variation as per Pharmacopoeial specification. Hardness of the all the formulations were measured in kg/cm^2. The hardness of all formulations was found to be 3-4 kg/cm^2. Drug content of all the formulations were found to be in the range of 98-101%, which is within acceptable limits. Friability values of all the formulations were within the limit i.e. is less than 1.0% indicated that tablets had a good mechanical resistance. pH of the solution of all the tablets was found to be between 6.3 to 7.5, which suggest that the tablets can be conveniently administered orally and will not cause any discomfort. Results of post compression parameters are shown in Table7.

The separated MIG powder was evaluated for its performance as disintegrant in tablets at various concentrations (2, 4, 6, 8, 10 %w/w) and the optimum concentration found was 6 %. Its performance was compared with crosspovidone at optimum concentration (4%) and it was found better than crosspovidone in tablet formulations with less disintegration time (51 s) compared to that of crosspovidone (56 s).

Wetting time was used as a parameter to correlate with disintegration time in oral cavity. This is an important criterion for understanding the capacity of disintegrants to swell in presence of little amount of water. Since the dissolution process of a tablet depends upon the wetting followed by disintegration of the tablet, the measurement for the evaluation of dispersible tablets. The wetting time of formulated tablets was found in the range of 38- 88 s. *In vitro* and *In vivo* dispersion time was 43-65 s for all the formulations. The disintegration times of all the formulations were within official requirements that are less than 180s. Comparison between disintegration time in oral cavity, wetting time and disintegration time (*In vitro*) for MIG powder formulations are shown in Figure7. Disintegration time in oral cavity was found between 45-68 s for MIG powder. This showed good correlation between disintegration time in oral cavity and wetting time for all formulations.

All designed formulations using MIG powder and Crosspovidone showed rapid dissolution and percent

Table 6: Results of blend properties of metformin HCl.

Formulation code	Angle of repose(^{0})*	Bulk density (gm/cm^3)*	Tapped density (gm/cm 3)*	Carr's index (%)*	Hausner ratio (H R)*	Bulkiness (cc/g)*
F1	33.6±0.02	0.56±0.02	0.74±0.02	23.7±0.01	1.30±0.04	1.79±0.05
F2	26.3±0.01	0.54±0.04	0.73±0.03	22.8±0.01	1.32±0.01	1.75±0.01
F3	31±0.04	0.53±0.01	0.67±0.01	20.8±0.02	1.26±0.05	1.89±0.02
F4	24.6±0.02	0.55±0.01	0.70±0.02	19.9±0.04	1.27±0.02	1.82±0.03
F5	25.0±0.02	0.57±0.01	0.74±0.02	23.1±0.01	1.29±0.02	1.75±0.04
F6	25.1±0.02	0.57±0.02	0.71±0.03	19.0±0.01	1.24±0.02	1.75±0.02
F7	27.9±0.06	0.54±0.03	0.73±0.03	21.5±0.02	1.35±0.04	1.72±0.20.01
F8	28.3±0.04	0.55±0.03	0.67±0.02	16.9±0.03	1.22±0.03	1.79±0.03

*All values are expressed as mean ± SD, n=3.

Table 7: Results of Post Compression Properties of Metformin dispersible Tablets

Formulation code	Thickness (mm)*	Diameter (mm)*	Hardness (kg/cm^2)*	Friability (%)***	Drug content (%)**	Weight variation (mg)**	pH of the solution
F1	4.2±0.01	11.00±0.03	2.9±0.16	0.32±0.01	101.91±0.01	204±0.02	7.2
F2	3.8±0.05	11.00±0.02	3.2±0.14	0.33±0.03	100.12±0.04	198±0.04	6.5
F3	4.1±0.02	11.00±0.02	2.8±0.12	0.54±0.06	98.12±0.04	202±0.06	6.4
F4	3.9±0.03	12.00±0.01	2.9±0.10	0.55±0.04	99.12±0.01	199±0.01	6.2
F5	4.1±0.02	11.00±0.04	3.1±0.14	0.24±0.05	100.43±0.06	199±0.01	7.3
F6	4.2±0.01	12.00±0.03	3.0±0.16	0.21±0.05	101.34±0.05	201±0.05	6.6
F7	4.0±0.01	12.00±0.01	3.2±0.16	0.23±0.04	99.45±0.05	198±0.07	7.5
F8	4.0±0.01	11.00±0.01	2.8±0.12	0.65±0.02	98.34±0.02	200±0.03	6.3

*All values are expressed as mean ± SE, n=5; **All values are expressed as mean ± SE, n=20; ***All values are expressed as mean ± SE, n=10.

cumulative drug release (% CDR) at the end of 15 min was between 83-98%. The results are shown in Figure 8.

The optimized formulation F3 was kept at real time (25 ± 2C° C / 60 ± 5% RH) and accelerated (40±2C °/75±5% RH) storage conditions for a period of 3 months. After stability test period, tablets were analyzed for drug content, hardness, friability, *in vitro* release and disintegration tests. Stability studies result showed that there was no significant change in hardness, friability, drug content, and dissolution profile of formulation F3. The formulation was stable under accelerated conditions of temperature and humidity.

CONCLUSION

From the present study, it can be concluded that natural super disintegrants like MIG powder showed better disintegrating property than the most widely used synthetic super disintegrants like crosspovidone® in the formulations of FDTs and may be used as disintegrant at the level of 6%w/w in tablet formulations. As primary ingredients are cheap, biocompatible, biodegradable and easy to manufacture. They can be used as superdisintegrants in place of currently marketed synthetic superdisintegrating agents.

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