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# Studies of Disintegrant Properties of Seed Mucilage of *Ocimum gratissimum*

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Ravikumar, *et al.*: Disintegrant Properties of Seed Mucilage of *Ocimum gratissimum*

Dispersible tablets of Metformin Hydrochloride were prepared using *Ocimum gratissimum* mucilage powder and *Ocimum gratissimum* seed powder as disintegrants. Specifications for herbal raw materials and finished products were set according to the Committee for Proprietary Medicinal Products. Several formulations were prepared and evaluated for physical parameters such as thickness, hardness, friability, weight variation, drug content, and disintegration time and drug dissolution. The formulations were prepared with different proportions of *Ocimum gratissimum* mucilage powder and *Ocimum gratissimum* seed powder. The formulated tablets had good appearance and better drug release properties as compared to the marketed conventional tablets. The study revealed that *Ocimum gratissimum* mucilage powder and *Ocimum gratissimum* seed powder were effective as disintegrants in low concentrations (5%). The study further revealed a poor relation between the swelling index and disintegrating efficiency. Mucilage extracted from *Ocimum gratissimum* seeds was subjected to toxicity studies for its safety and preformulation studies for its suitability as a disintegrating agent. The mucilage extracted is devoid of toxicity. Studies indicated that the extracted mucilage is a good pharmaceutical adjuvant, specifically a disintegrating agent.

**Key words:** Metformin hydrochloride, *Ocimum gratissimum*, mucilage, seed powder, disintegrating agent

Mouth dissolving tablets rapidly disperse, when kept on the tongue, and instantaneously release the drug. It may be absorbed from the mouth, pharynx and oesophagus as the saliva passes into the stomach and may produce rapid onset of action<sup>1-6</sup>. The advantages of mouth dissolving dosage forms are increasingly being recognized in both, industry and academia. Their growing importance was underlined recently when the European Pharmacopoeia<sup>7</sup> adopted the term “orodispersible tablet” as a tablet that is to be placed in the mouth where it disperse rapidly before swallowing. The main criterion for mouth dissolving tablets is its rapid disintegration or dissolution in the oral cavity with saliva in 15 to 60 s, without any water<sup>8</sup> and it should have a pleasant mouth feel<sup>9</sup>.

Metformin HCl, chemically, N,N-dimethylimidodidicarbonylhydrazine hydrochloride, has

been widely used for the management of non-insulin dependent diabetes mellitus (NIDDM). Unlike other biguanide drugs, metformin HCl does not induce lactic acidosis. It is freely soluble in water and has a limited window of absorption i.e. less than 60% which further decreases with an increase in dose. Almost 80-100% of the drug is excreted unchanged<sup>10-11</sup>. Oral absorption is confined to upper part of the intestine.

Mucilage and gums have been known since ancient times for their medicinal uses. In the modern era also they are widely used in the pharmaceutical industries as thickeners, water retention agents, emulsion stabilizers, suspending agents, binders and film formers<sup>12,13</sup>. Apart from its use in finished medicines, newer uses have been found in the preparation of cosmetics, textiles, and paint paper. Hence the demand for these substances is increasing and new sources are getting tapped<sup>14,15</sup>. Though, India, due to geographical and environmental positioning has traditionally been a good source for such products among the Asian countries, a large quantity of this is still being

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imported from the European countries to meet up the ever-increasing demand<sup>16</sup>.

*Ocimum gratissimum* Linn., Var. *cinerifolium*, Fam: Labiatae, is a semi woody tender perennial 3 to 8 feet in height, which is grown widely in India, because of its social and religious importance. The plant oil is an established mosquito repellent, antibacterial and local anesthetic<sup>17</sup>. The present work is an attempt to extract and investigate the pharmaceutical properties of the gum and to assess its suitability as a disintegrant agent in the pharmaceutical formulations.

## MATERIALS AND METHODS

Metformin HCl, talc, magnesium stearate and aspartame were all obtained from Zydus Research Centre, Ahmedabad, India as gift samples. *Ocimum gratissimum* seeds were procured from the local market. All the other solvents and chemicals used were of either pharmacopoeial or analytical grade. 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 and 1601 PC UV Spectrophotometer is from Shimadzu, Tokyo, Japan.

### Extraction of mucilage:

The mucilage of *Ocimum gratissimum* was extracted and precipitated separately by previously reported methods<sup>18,19</sup>. The precipitated gum was filtered, treated with acetone to remove the traces of water and dried in an oven at 40°.

### Determination of swelling index:

The swelling index is the volume in ml occupied by 1 g of drug; including any adhering mucilage after it has been swollen in an aqueous liquid for 4 h. The swelling index of *Ocimum gratissimum* mucilage powder, seed powder were determined according to the BP method<sup>20</sup>. One gram of each disintegrant 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 water 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 disintegrating agent including adhering mucilage was measured. The swelling index was calculated from the mean of three determinations.

### Evaluation of toxicity:

Toxicity studies were carried out according to the method of Knudsen and Curtis<sup>21</sup>. Preformulation studies were carried out according to official monographs and drug–excipient compatibility studies were done by using FTIR.

### Standard calibration curve of metformin HCl:

Solutions ranging from 2 to 4 µg/ml were prepared in phosphate buffer (pH 6.8 fluid). Absorbance was measured for each solution at  $\lambda_{\max}$  of 233 nm, using 1601 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 *Ocimum gratissimum* mucilage powder and seed powder at concentrations of 5, 10, 15, 20%. The composition of each formulation is given in Table 1.

### Preparation and evaluation of mixed blend of drug and excipients:

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. Prior to compression into tablets, the blend was evaluated for the following properties.

Angle of repose was determined by using funnel method<sup>22</sup>. Powder was poured from a funnel that can be raised vertically until a maximum cone height, 'h' was obtained. Diameter of heap, 'D' was measured. The angle of repose 'Θ' was calculated by formula  $\tan \Theta = h/r$ ,  $\Theta = \tan^{-1}(h/r)$ , where, Θ is the angle of repose, 'h' is the height in cm and 'r' is the radius.

Apparent bulk density was determined by pouring pre-sieved drug excipient blend into a graduated

**TABLE 1: FORMULATION OF DISPERSIBLE TABLETS OF METFORMIN HCL BY USING OGM\*/OGS\***

Ingredients	A	B	C	D
Metformin HCl	500	500	500	500
OGM*/OGS*	26.6	53.24	79.9	106.5
Aspartame	12	12	12	12
Magnesium stearate	9	9	9	9
Talc	9	9	9	9
Flavour (orange)	2.4	2.4	2.4	2.4

OGM\* *Ocimum gratissimum* mucilage and OGS\* *Ocimum gratissimum* seed powder

cylinder and measuring the volume and weight “as it is”. It is expressed in g/ml and is given by  $D_b = M/V_0$ , where, M is the mass of powder and  $V_0$  is the Bulk volume of the powder. Tapped density was determined by placing a graduated cylinder, containing a known mass of drug-excipient blend, on mechanical tapping apparatus. The tapped volume was measured by tapping the powder to constant volume. It is expressed in g/ml and is given by  $D_t = M/V_t$  where M is the mass of powder and  $V_t$  is the tapped volume of the powder.

The flow properties<sup>23</sup> were determined by Carr’s Index and Hausner ratio. Carr’s index is expressed in percentage by  $I = (D_t - D_b)/D_t$ , where,  $D_t$  is the tapped density of the powder and  $D_b$  is the bulk density of the powder. Hausner ratio is expressed in percentage by  $H = D_t/D_b$ , where,  $D_t$  is the tapped density of the powder and  $D_b$  is the bulk density of the powder. Mixed blend of drug and excipients were compressed on a single punch Cadmach machine with 500 mg die cavity under hardness of 3-4 kg/cm<sup>2</sup>.

#### Evaluation of tablets:

Twenty tablets were selected at random and average weights were determined. Then individual tablets weighed and the individual weight was compared with the average. Hardness<sup>24</sup> of the tablet was determined by using a Monsanto hardness tester, which is expressed in kg/cm<sup>2</sup>. Friability of the tablet was determined using Roche Friabilator, which is expressed in percentage (%). Twenty tablets were initially weighed ( $W_{initial}$ ) and transferred into the friabilator. The friabilator was operated at 25 rpm per min for 4 mins (100 revolutions). The tablets were weighed again ( $W_{final}$ ) and the % friability was then calculated by using the following formula,  $F = (W_{initial} - W_{final})/W_{initial} \times 100$ .

Content uniformity for 20 tablets was determined according to the monograph specification for metformin HCl<sup>25</sup>, by UV Spectrophotometer. Thickness of the tablets was measured by Vernier Calipers, and is expressed in mm. *In vitro* disintegration time was determined using disintegration test apparatus. For this, a tablet was placed in each of the six tubes of the apparatus and one disc was added to each tube. The time in seconds taken for complete disintegration of the tablet with no palpable mass remaining in the apparatus was measured. Disintegration time in the oral cavity of human volunteers was measured

by placing the tablet on the tongue until no lumps remain, and is expressed in seconds. Wetting time was determined by keeping a piece of tissue paper folded twice, which was placed in a small Petri plate (internal diameter= 6.5 cm) containing 6 ml of water. A tablet was placed on the paper, and the time for complete wetting of the tablet was measured in seconds. The method was slightly modified by maintaining water at 37°. *In vitro* dissolution study<sup>26,27</sup> was carried out in USP dissolution test apparatus Type II.

## RESULTS AND DISCUSSION

The average yield of dried mucilage obtained from *Ocimum gratissimum* seeds was 15%. To determine the safety level of extracted mucilage, acute toxicity studies were carried out. In this study it showed no manifestations of toxic syndromes. During acute toxicity studies were performed to assess the suitability of extracted mucilage for oral delivery. For that we have assessed hematological parameters for 15 days were observed. This study has inferred that there was no change in hematological parameters, which was comparable with the control.

Swelling indices of *Ocimum gratissimum* mucilage powder and seed powder were found to be 20 and 25, respectively. Tablets prepared by using the *Ocimum gratissimum* seed powder imparted its color to the tablet. The hardness of the *Ocimum gratissimum* mucilage powder was high compared to seed powder, which shows that the mucilage has strong intermolecular binding efficiency to hold the powder firmly during compression. This study revealed that the mucilage not only act as a disintegrant but also a strong binder for the tablets.

The IR spectra revealed that there was no compatibility related problems between the drug and excipients used in the formulation as shown in figs. 1a to 1c. Pre compression parameters for the formulations of *Ocimum gratissimum* mucilage powder and seed powders are shown in Table 2.

Bulk density was found to be between 0.52 to 0.58 g/cc and tapped density between 0.67 to 0.75 g/cc, bulkiness between 1.73 to 1.9, Carr’s index between 16 to 27%, Hausner ratio between 0.97 to 1.4 and angle of repose was found to be between 28 to 32°, indicating fair to good flow properties. The formulations containing *Ocimum gratissimum*

**TABLE 2: PRECOMPRESSION PARAMETERS OF METFORMIN HCL BY USING OGM\*/OGS\***

Parameters	A	B	C	D
<b>OGM*</b>				
Bulk density (g/cc)	0.56	0.57	0.54	0.57
Tapped density (g/cc)	0.67	0.73	0.71	0.73
Bulkiness (cc/g)	1.78	1.75	1.90	1.85
Carr's indeed (%)	16.4	21.9	22.8	23
Hausner ratio	0.97	1.22	1.28	1.40
Angle of repose ( $\theta$ )	28	30.6	32	31.28
<b>OGS*</b>				
Bulk density (g/cc)	0.57	0.58	0.52	0.56
Tapped density (g/cc)	0.74	0.75	0.72	0.74
Bulkiness (cc/g)	1.77	1.73	1.92	1.77
Carr's indeed (%)	22.9	22.6	27.7	24.1
Hausner ratio	1.29	1.293	1.38	1.34
Angle of repose ( $\theta$ )	28.1	27.6	32	30.4

OGM\* *Ocimum gratissimum* mucilage and OGS\* *Ocimum gratissimum* seed powder

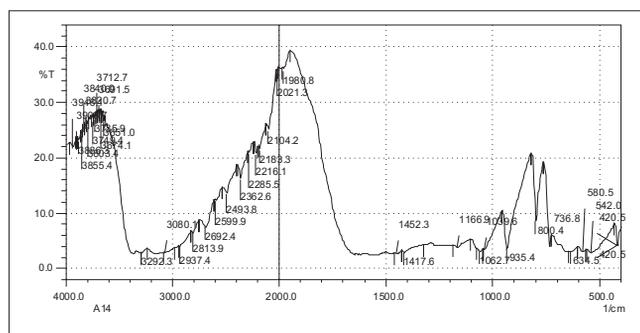
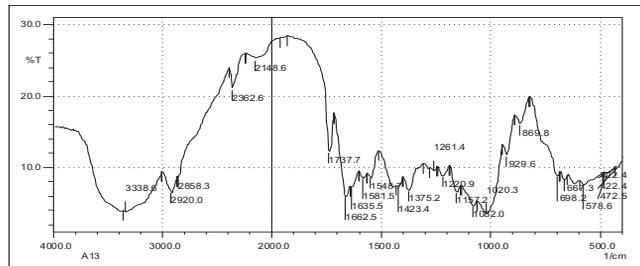
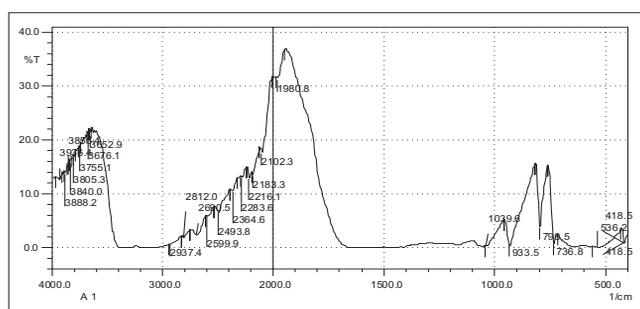


Fig. 1: IR spectra of metformin HCl alone and metformin HCl with all excipients or mucilage

IR spectra of a. metformin HCl alone, b. of metformin HCl and all excipients consolidated (1:1) and c. of metformin HCl and mucilage (1:1)

mucilage powder and seed powder at concentrations of 15 and 20% (Formulation C and D) showed the angle of repose values  $> 30^\circ$  indicating only a fair flow properties of the powder mixture. Hardness of the all the formulations were measured in  $\text{kg}/\text{cm}^2$ .

The hardness of all formulations were found to be  $3-4 \text{ kg}/\text{cm}^2$ .

Post compression parameters of the formulations of *Ocimum gratissimum* mucilage powder and seed powders are shown in Table 3. Hardness of all the formulations was kept constant within the above-mentioned range to compare the disintegration time between the formulations prepared using different disintegrant combinations. Friability values of all the formulations were within the limit i.e. is less than 1.0% except for formulation C and D of both which clearly inferred that the mucilage and seed powder from *Ocimum gratissimum* has strong binding capacity at 5 and 10% beyond this concentration the binding efficiency decreased. Thickness of all tablets was between 5.60-5.62 mm. As the powder blend had good flow properties, tablets obtained were of uniform weight. Drug content of all the formulations were found to be in the range of 96-99%, which is within acceptable limits.

*In vitro* and *in vivo* dispersion time was 40-68 s for all the formulations. The disintegration times of all the formulations were within official requirements that is

**TABLE 3: POST COMPRESSION PARAMETERS OF METFORMIN HCL BY USING OGM\*/OGS\***

Parameters	A	B	C	D
<b>OGM*</b>				
Hardness	2.9	2.8	4.3	3.8
Friability (%)	0.96	0.88	1.03	1.1
Thickness (mm)	5.61	5.60	5.61	5.62
Weight variation	4.5	4.0	4.5	4.0
Content Uniformity (%)	98.9	98.0	97.0	98.6
<b>OGS*</b>				
Hardness	2.8	3.0	3.2	3.0
Friability (%)	0.82	0.92	1.21	1.32
Thickness (mm)	5.60	5.61	5.60	5.61
Weight variation	4.5	4.0	4.5	4.0
Content Uniformity (%)	98.2	96.0	97.3	98.5

OGM\* *Ocimum gratissimum* mucilage and OGS\* *Ocimum gratissimum* seed powder

**TABLE 4: COMPARISON BETWEEN DISINTEGRATION TIME AND WETTING TIME FOR METFORMIN HCL FORMULATIONS BY USING OGM\*/OGS\***

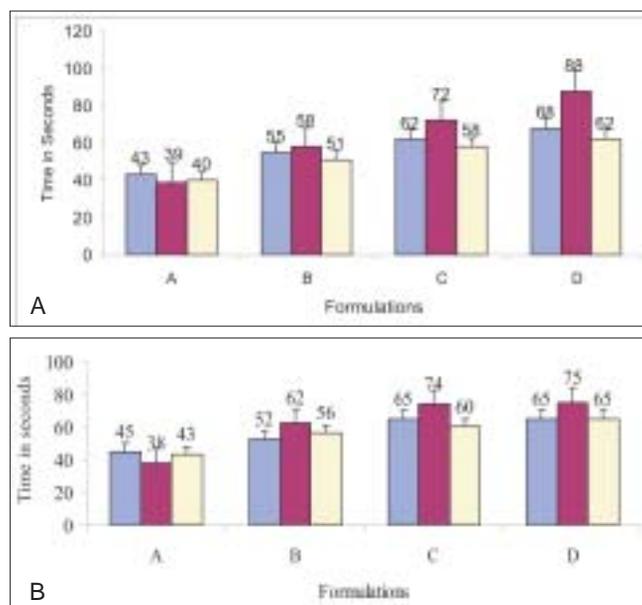
Parameters	A	B	C	D
<b>OGM*</b>				
Disintegration time in oral cavity (sec)	43	55	62	68
Wetting time (sec)	39	58	72	88
Disintegration time <i>in vitro</i> (sec)	40	51	58	62
<b>OGS*</b>				
Disintegration time in oral cavity (sec)	45	52	65	65
Wetting time (sec)	38	62	74	75
Disintegration time <i>in vitro</i> (sec)	43	56	60	65

OGM\* *Ocimum gratissimum* mucilage and OGS\* *Ocimum gratissimum* seed powder

**TABLE 5: COMPARISON OF *IN VITRO* RELEASE OF VARIOUS FORMULATIONS**

Formulation of OGM	% CDR	Formulation of OGS	% CDR
A	77.4	A	75.0
B	84.15	B	81.0
C	93.15	C	91.0
D	97.65	D	93.0
Marketed product	12.825	Marketed product	12.825

OGM *Ocimum gratissimum* mucilage and OGS *Ocimum gratissimum* seed powder



**Fig. 2: Comparison of disintegration time and wetting time using OGM\*/OGS\***

■ Disintegration time *in vitro* (s), ■ wetting time (s), ■ disintegration time in oral cavity (s). OGM\* *Ocimum gratissimum* mucilage and OGS\* *Ocimum gratissimum* and OGS\* *Ocimum gratissimum* Seed Powder

less than 180 s. Comparison between disintegration time in oral cavity, wetting time, and disintegration time (*in vitro*) for *Ocimum gratissimum* mucilage and seed powder formulations are shown in Table 4, (fig. 2), respectively. 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. Disintegration time in oral cavity was found between 43-68 s and 45-65 s for *Ocimum gratissimum* mucilage powder, and seed powder respectively. Wetting time was found between 40-88 s and 38-75 s for *Ocimum gratissimum* mucilage powder and seed powder respectively. This showed good correlation between disintegration time in oral cavity and wetting time for all formulations. All designed formulations using *Ocimum gratissimum* mucilage powder and seed powder showed rapid

dissolution and percent cumulative drug release (%CDR) at the end of 5 min was 75-97% for all formulations, shown in Table 5, while conventional marketed tablet of Metformin HCl (Glyciphage®) required around 35 minutes for same amount of drug to be released.

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