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Original Article

Formulation and Evaluation Fast Dissolving Tablet of *Hibiscus rosa-sinensis* Leaf Mucilage as Superdisintegrant

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ABSTRACT

Natural polymers remain attractive primarily because they are natural products of plants, readily available, inexpensive and capable of multitude of chemical modification. Leaves of *Hibiscus rosa-sinensis* Linn (family: Malvaceae) contains high proportion of mucilage which can be used as additives in pharmaceutical formulations. The objective of the studide to extract mucilage from the leaves Hibiscus rosa-sinensis and examine the disintegrant property of the dried mucilage to assess its functionality as a pharmaceutical excipient. The Present work was carried out to study the disintergant property of *Hibiscus rosa-sinensis* mucilage using Imipramine as a model drug. The present work was carried out to develop fast dissolving tablet of Imipramine using natural disintegrant isolated from Hibiscus rosa-sinensis leaves and its efficiency was compared with synthetic superdisintegrant like crosspovidone. *Hibiscus rosa-sinensis* mucilage was isolated and characterised for its identification by chemical test and micrometric properties. Fast dissolving tablets of Imipramine were formulated by direct compression method using *Hibiscus rosa-sinensis* mouth feel and compressibility and aspartame as sweetener. The formulated tablets were evaluated for their pre and post compression parameters like tablet hardness, thickness, % friability, wetting time which was found to be in permissible limits. The in vitro disintegration time of tablet formulations containing 6% of mucilage was found to be 24 sec and that of tablet containing 4% of crosspovidone was 42secs. Based upon in vitro disintegration time in vitro drug release studies put and in between were carried out in phosphate buffer p H 6.8 which showed 100% drug release in 12 minutes of F3 formulation containing 6% of mucilage. Stability studies performed on F3 formulation indicated that the prepared tablets remain stable for the period of 90 days and showed no change in *in-vitro* drug release pattern.

Key words: Imipramine, *Hibiscus rosa-sinensis*, superdisintegrant, mucilage, Fast dissolving tablet

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1. INTRODUCTION

Oral route of administration still continues to be the most preferred route due to its diverse advantages including ease of administration, precise dosage, self - medication, versatility, pain avoidance leading to high level of patient compliance [1]. Tablets and capsules are the most popular dosage forms, but main drawback of such dosage form is dysphasia or difficulty in swallowing. This leads to the development of novel dosage forms such as fast disintegrating/ dissolving tablets (FDT). FDT are a solid single-unit dosage forms that are placed in mouth, allowed to disperse/dissolve in the saliva without the need of water and provides a quick onset of action [2]. Some drugs are absorbed from mouth, pharynx and esophagus as the saliva passes down into the stomach. In such cases bioavailability of drug is significantly greater than those observed from conventional tablet dosage form. The Centre for Drug Evaluation and Research (CDER), US (FDA) defined FDT as "a solid dosage form containing medicinal substance or active ingredient which disintegrates rapidly usually within a matter of seconds when placed upon the tongue." The disintegration time for FDTs generally ranges from several seconds to about a minute [3-5]. The bioavailability of some drugs may be increased due to absorption of drugs in oral cavity and also due to pre gastric absorption of saliva containing dispersed drugs that pass down into the stomach. Recently immediate release tablets have started gaining popularity and acceptance as a drug delivery system, mainly because they are easy to administer, has quick onset of action is economical and lead to better patient compliance [6, 7]. They are also a tool for expanding markets, extending product life cycles and generating opportunities. In the formulation of FDT, superdisintegrants are added to facilitate the breakup or disintegration of tablet content into smaller particles that can dissolve more rapidly than in the absence of disintegrants. Common superdisintegrants used are croscarmellose sodium (Vivasol, Ac-Di-Sol), crospovidone (Polyplasdone), carmellose (NS-300), carmellose calcium (ECG-505), sodium starch glycolate (SSG) etc. Similarly, various natural polymers like gum karaya, starch, agar, plantago ovata mucilage have been used in the formulation of FDT. Mucilage of natural origin is preferred over semisynthetic and synthetic substances because they are comparatively cheaper, abundantly available, non irritating and non toxic in nature. Hence, in the present study, mucilage of *Hibiscus rosa-sinensis* linn was used to develop FDT of the selected model drug Imipramine. Imipramine is a tricyclic antidepressant with general pharmacological properties similar to those of structurally related tricyclic antidepressant drugs such as Amitriptyline and Doxepin A tertiary amine, Imipramine inhibits the reuptake of serotonin more so than most secondary amine tricyclics, meaning that it blocks the reuptake of neurotransmitters serotonin and nor adrenaline almost equally. It binds the Sodium-dependent serotonin transporter and sodium-dependent nor adrenaline transporter, preventing or reducing the reuptake of nor epinephrine and serotonin by nerve cells. Peak plasma levels are reached in 2 to 8 hours, and plasma half-life ranges from 11 to 25 hours. It is excreted in the urine, mainly in the form of its metabolites, either free or in conjugated form; small amount are excreted in the faeces via the bile. Imipramine is one of the less sedating tricyclics and has moderate antimuscarinic activity. Imipramine is used for the treatment of nocturnal enuresis in children. Tricyclic anti- depressants are not recommended under 6 years of age.

2. MATERIAL AND METHODS

Material

Imipramine was received as a gift sample from Biocon Pharmaceutical, Bangalore , India. Crospovidone, mannitol, and Avicel were purchased from Lobe Chem Ltd., Mumbai, India. Aspartame was purchased from Himedia Lab Pvt. Ltd., Mumbai, India. *Hibiscus rosa-sinensis*was collected from Vikas herbal garden. All other chemicals used were of analytical grade and were used without further purification.

Methods

Isolation and Characterization of Mucilage form *Hibiscus rosa-sinensis*

The leaves of *Hibiscus rosa-sinensis* linn were collected, from Chitkara University, Punjab. The fresh Hibiscus rosa-sinensis linn leaves were collected and washed with water to remove dirts and debries [8]. Leaves were powdered and soaked in water for 5-6 hrs, boiled for 30 minutes and left stand for 1hours to allow complete release of mucilage into water. The mucilage was extracted using multi-layer muslin cloth bag to remove the marc from the solution. Acetone (in the volumes of three times to the volume of filtrate) was added to precipitate the mucilage. The mucilage was separated, dried in an oven at <50º C, collected, ground, passed through #80 sieve and stored in desiccators at room temperature for further use. Dried powdered mucilage was characterized for various physicochemical properties like percentage yield, particle size, swelling index, angle of repose etc.

Pre-formulation studies

In the preparation of tablet formulations, drug and polymer may interact as they are in close contact with each other, which could lead to the instability of drug. Preformulation studies regarding the drug-polymer interaction are therefore carried out for selecting appropriate polymers. FT-IR spectroscopy was employed to ascertain the compatibility between Imipramine Hydrochloride and selected polymers. The pure drug, drug-polymers combinations and formulations were subjected to FT-IR studies. Potassium bromide, pure drug, and the polymers were heated to 1050C for one hour to remove the moisture content if present in a hot air oven. Then in presence of IR lamp, potassium bromide was mixed with drug and /or polymer in 1:1 ratio.

Grinding in smooth mortar can effect mixing. The mixtures were then placed in the sample holder of the instrument and the spectra were taken. The spectra were run from 3500 cm-1 to500 cm-1 wave number. FT-IR spectrum of Imipramine Hydrochloride was compared with FT-IR spectrum of Imipramine Hydrochloride with polymer. The pure drug and the drug with excipients were scanned separately. Disappearance of Imipramine Hydrochloride peaks or shifting of peak in any of the spectra was studied [9, 10].

Preparation of standard calibration curve of Imipramine

Standard calibration curve of Imipramine hydrochloride was prepared by dissolving accurately weighed 10 mg of imipramine hydrochloride in phosphate buffer (pH 6.8) solution in a 100 ml volumetric flask and the volume was made up to 100 ml by using phosphate buffer (pH 6.8) solution to obtain a stock solution of 100 µg/ml. From stock solution, appropriate aliquots were pipetted into different 10ml volumetric flasks and volumes were made up to 10 ml with phosphate buffer (pH 6.8) solution so as to get drug concentrations of 2, 4, 6, 8 and 10 µg/ml. The absorbance of these drug solutions were measured at 250.8 nm. This procedure was performed in triplicate to validate the calibration curve.

Formulation of Fast Dissolving Tablets of Imipramine using *Hibiscus rosa-sinensis* mucilage

Fast dissolving tablets of Imipramine were prepared by direct compression method, in this powder blends of active ingredient and suitable excipient, which flow uniformly in the die cavity and forms a firm compact was prepared as per the composition given in the table 1 [11, 12]. Powdered drug was mixed with *Hibiscus rosa-sinensis* mucilage as superdisintegrants in 2%, 4%, 6% and 8%, microcrystalline cellulose as diluent, talc as glidant, and magnesium stearate as lubricant and mannitol was used as filler. All blends passed through mesh #60. Before compression, hardness was adjusted. Each tablet weighed 200 mg.

Table 1: Composition of fast dissolving tablets of Imipramine

Ingredients (mg)	Formulation batches							
	F1	F2	F3	F4	F5	F6	F7	F8
Imipramine	10	10	10	10	10	10	10	10
Crosspovidone	-	-	-	-	2%	4%	6%	8%
Mucilage	2%	4%	6%	8%	-	-	-	-
AvicelPH102	50	48	46	44	50	48	46	44
Mannitol	30	30	30	30	30	30	30	30
Aspartame	5	5	5	5	5	5	5	5
Magnesium stearate	1	1	1	1	1	1	1	1
Talc	2	2	2	2	2	2	2	2

Evaluation of precompression parameters

Formulation blends were evaluated for all precompression parameters like angle of repose, bulk density, tapped density, bulkiness, Hausner's ratio and compressibility index. The evaluation was done using all the methods as per specified in pharmacopoeias [13-15].

Evaluation of Imipramine hydrochloride tablets.

Weight variation

All prepared tablets were evaluated for weight variation as per USP XXIV monograph. Twenty tablets of each batch were used to evaluate weight variation among tablets and mean and standard deviation was calculated.

Friability

Tablets of all batches were used to evaluate friability as per USP XXIV monograph. Friability testing was done by Roche Friabilator. Twenty tablets were weighed and placed in a Roche friabilator and rotated at 25 rpm for 4 min. The tablets were taken out, de-dusted and reweighed. The percentage friability of the tablets was calculated by the formula,

% Friability = Initial weight – Final weight x Initial weight

Hardness

Hardness of all batches was determined using Monsanto hardness tester. The test was carried out in triplicate for all batches as per USP XXIV monograph for uncoated tablets.

Thickness

The thickness of the matrix tablets was determined using vernier caliper (Mitutoyo Dial Thickness Gauge, Mitutoyo, Japan) and the results were expressed as mean values of 10 determinations, with standard deviations.

Drug content

The tablets were powdered, and 5mg equivalent weight of Imipramine in tablet powder was accurately weighted and transferred into a 100 ml volumetric flask. Initially, 10 ml of phosphate buffer (pH6.8) was added and shaken for 10 min. Thereafter, the volume was made up to 100 ml with buffer. Subsequently, the solution in volumetric flask was filtered, and 1 ml of the filtrate was diluted and analyzed at 250 nm using UV-visible spectrophotometer Shimadzu UV-2450, Japan).

***In vitro* drug release study**

In vitro drug release was studied using Lab India Dissolution Apparatus (LABINDIA DS 80 00, India), in 900 ml phosphate buffer pH 6.8, maintained at 37±1°C for 30 minutes, at 75 rpm. 5ml of sample was withdrawn after specified time interval, and was replaced by an equal volume of fresh dissolution medium. Collected samples were analyzed spectrophotometrically at measured wavelength of 250 nm, and cumulative percent drug release was calculated. The test was performed in triplicate to assure significance of results. Drug release profile was studied using percentage drug release versus time (hr) plot.

Stability studies

In order to determine the change in in-vitro release profile on storage, stability study of batch F3 was carried out at 40 C in a humidity chamber having 75% RH. Samples were withdrawn at regular intervals during the study of 60 days. Formulation is evaluated for change in in-vitro drug release pattern, hardness and disintegration time.

3. RESULTS AND DISCUSSIONS

Characterization of Mucilage form *Hibiscus rosa-sinensis*

Mucilage isolated from *Hibiscus rosa-sinensis* was characterized for its physical and chemical properties the results of which are given in table 2 and 3.

Table 2: Physical characterizations

S.No	Physical Parameters	Observations
1	Appearance	Greenish powder
2	Odor	Characteristics
3	Percentage yield	26%
4	Weight loss on drying(mg)	28.56±0.159
5	Solubility	Slowly soluble in water to produce viscous solution
6	Density of liquid	1.058±0.018
7	pH	7.1±0.11

Table 3: Chemical characterization

S.No	Chemical characterization	Observations
1	Mounted in 90% ethanol	transparent
2	Mounted in Ruthenium red	Particles stained red
3	Mounted in iodine solution	Particles stained blue
4	Molisch test (for carbohydrates)	Positive
5	Ferric chloride test (for tannins)	Negative
6	Silver nitrate (for chlorides)	Negative
7	Barium chloride (for sulphates)	Negative

Preformulation study

To study the compatibility of the drug with various polymers, IR spectra of drug and mucilage were carried out. The FTIR spectra of drug, mucilage and physical mixture of drug and mucilage (1:1) were shown in figure 1. No major differences in the FTIR patterns of pure drug and mucilage were observed. Therefore, the FTIR studies ruled out the possibilities of any drug excipient interaction during the preparation of tablets

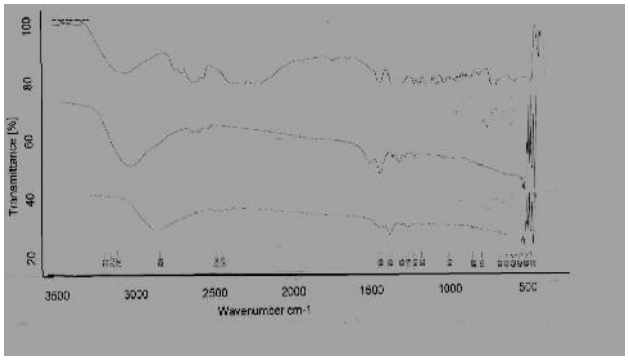

Fig 1: FTIR Spectra of a) Imipramine b) *Hibiscus rosa-sinensis* c) Imipramine + *Hibiscus rosa-sinensis*

Preparation of standard calibration curve of Imipramine

The standard calibration curve of Imipramine Hydrochloride was obtained by plotting Absorbance versus concentration as shown in figure 2. The standard calibration curve shows the correlation coefficient of 0.990. The curve was found to be linear in the concentration range of 2 to 10µg/ml (Beer's range) at 250.8 nm.

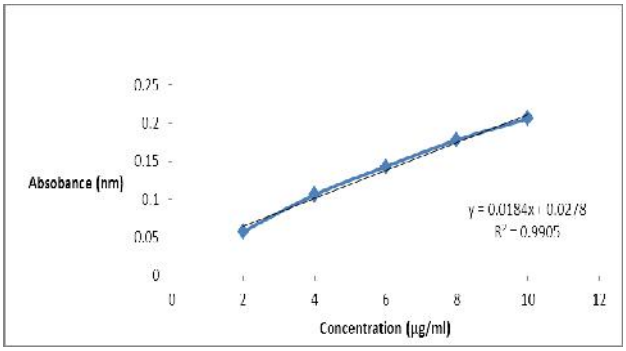

Fig 2: Standard calibration curve of Imipramine hydrochloride

Evaluation of precompression parameters

Results of evalution of precompression parameters of the formulation blends are given in table 4 which indicated good flow behaviour and compressibility of prepared formulation blends

Table 4: Precompression Parameters of blend for Imipramine-*Hibiscus rosa-sinensis* tablets

Parameters	Formulation Batches							
	F1	F2	F3	F4	F5	F6	F7	F8
Angle of repose	26.56	29.24	27.92	28.5	23.45	20.21	24.32	26.12
Bulk density (g/ml)	0.317	0.357	0.436	0.385	0.350	0.362	0.291	0.321
Tappeddensity(g/ml)	0.54	0.491	0.65	0.421	0.491	0.481	0.398	0.412
Carr's index (%)	41.2	27.3	32.9	33.2	28.71	24.74	26.88	22.1
Hausnor's ratio	1.19	1.24	1.20	1.21	1.24	1.26	1.19	1.25

Evaluation of post compression parameters of Imipramine hydrochloride tablets

The formulated tablets were evaluated for weight variation, hardness, thickness, *in vitro* disintegration time, dissolution rate, wetting time and uniformity of drug content. The formulated tablets were of uniform weight with acceptable limit as per the IP specifications.

Thickness of the formulated tablets was found in the range from 3.0±0.01 mm to 3.9±0.31mm. Uniformity in the values suggested that formulations were compressed without sticking to the dies and punches with uniform compression pressure. The hardness was found to be in the range of 3.0±0.01 to 3.9±0.01 kg/cm2 and was in correlation with disintegration time. Friability below 1% indicated good mechanical resistance of the tablets Disintegration time was found to be in the range of 82-24 seconds. Formulation F3 containing 6% of mucilage giving minimum disintegration time of 24 seconds which facilitate fast dispersion and dissolution within the oral cavity. *In vitro* drug release of all the formulations as shown in figure 3,4 and 5 were carried out in phosphate buffer pH 6.8 it was found that more than 85% of the drug was released within 10 minutes; with F3 formulation containing 6% of mucilage showed maximum release of 99.6% within 12 minutes. With increasing concentration of mucilage *in-vitro* disintegration time decrease resulting in fast *in-vitro* drug release. Formulation containing 8% of mucilage showed increased disintegration

time with slow *in vitro* drug release in comparison with F3 formulation which may be due to binding property of mucilage in increased concentration. Further, it was found that F7 containing 6% cross povidone showed disintegration time of 42 seconds which was greater than that of F3 containing same level of disintegrating agent i.e 6% of mucilage. Wetting time was found to be in the range of 13-21 seconds. Formulation F3 containing 6% of mucilage showed fastest wetting time of 13 seconds which results in faster disintegration. Results of evaluation of post compression parameters are given in table 5.

Table: 5 Evaluation of post compression parameters of Imipramine hydrochloride tablets

Parameters	Formulation batches							
	F1	F2	F3	F4	F5	F6	F7	F8
Disintegration time (sec)	68	35	24	82	80	60	42	34
Hardness (kg/cm2)	3.5±0.01	3.2±0.05	3.0±0.01	3.9±0.02	3.7±0.3	3.6±.2	3.5±0.03	3.9±0.01
Thickness (mm)	3.5±0.2	3.8±0.05	3.0±0.1	3.9±0.3	3.4±0.	3.5±0.05	3.6±0.2	3.3±0.4
Wetting time(sec)	16	14	13	21	20	19	18	15
Weight variation(mg)	96	97	95	96	101	97	98	101
Drug content	98.12±0.10	99.6±0.1	98.0±0.02	98.41±0.01	96.5±0.11	99.2±0.11	97.3±0.12	96.7±0.1
% friability	0.2	0.4	0.32	0.41	0.5	0.4	0.6	0.7
Disintegration time (sec)	68	35	24	82	80	60	42	34

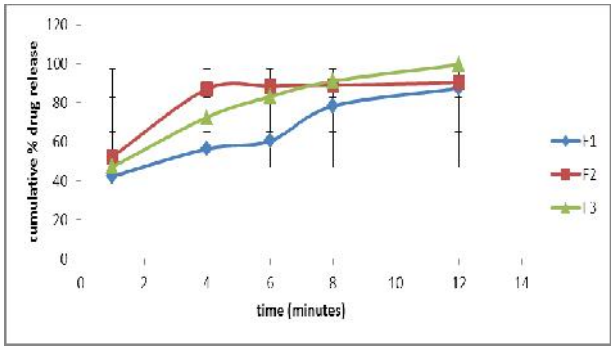

Fig 3: *In-vitro* Drug Release Studies of Formulation F1, F2and F3

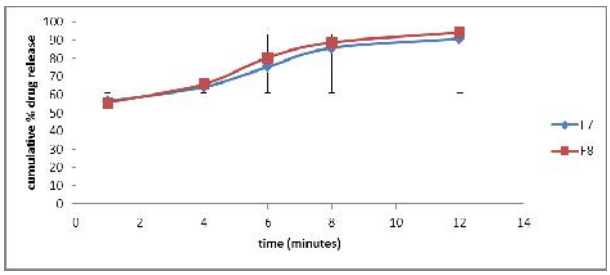

Fig 4: *In-vitro* Drug Release Studies of Formulation F7and F8

Stability studies

Stability studies performed on F3 formulation as per ICH guidelines for 60 days at 40°C±2°C / 75% RH±5%. Showed no remarkable change in the physical properties and release profile of the prepared tablets. Results of the stability studies are given in table 6

Table 6: stability studies of F3 formulation at 40°C±2°C/75% RH±5%

	Days			
Parameter	0	15	30	60
In vitro drug release	100	99.4	99	99.6
Hardness (kg/cm2)	3.0±0.01	3.0±0.01	3.0±0.01	3.0±0.01
Disintegration time (sec)	24	23.6	24	24

4. CONCLUSION

From the present study, it can be concluded that natural super disintegrants like *Hibiscus rosa sinensis* Linn mucilage powder showed better disintegrating property than the most widely used synthetic super disintegrants like Crosspovidone in the formulations of Fast dissolving tablets and may be used as disintegrant at the level of 6% w/w in tablet formulations. *Hibiscus rosa-sinensis* Linn mucilage powder can be used as superdisintegrants in place of currently marketed synthetic super disintegrating agent**.**

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