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FORMULATION AND EVALUATION OF ABELMOSCHUS ESCULENTUS MUCILAGE BASED METFORMIN HYDROCHLORIDE FLOATING MATRIX TABLETS

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Abstract

The present investigation was aimed at estimating the effectiveness of the edible gum of Abelmoschus esculentus as a polymer in the development of a gastric floating dosage form of Metformin HCl. Abelmoschus esculentus, popularly known as okra, was shown to aid in the formulation of floating tablets. In the present study, it was used as a pharmaceutical excipient along with HPMC E15 in the formulation of Metformin HCl floating tablets. The prepared tablets were tested for physicochemical properties, drug content uniformity, in vitro drug release patterns and FT-IR spectral analysis. From the study, it was evident that the formulations which included Abelmoschus esculentus gum (F1, F3, and F4) have lesser floating capacity but show a sustained release of drug where as the formulation (F2) which contained only HPMC has higher floating capacity but poor sustained release of drug. All in all, the formulation F3 (only Okra gum) manifested a prolonged release of the active ingredient.

Keywords: Floating matrix tablets, Metformin HCl, Abelmoschus esculentus.

Introduction

Diabetes mellitus is a group of metabolic diseases characterized by high blood sugar (glucose) levels that result from defects in insulin secretion, or action, or both. In 2000, according to the World Health Organization, at least 171 million people worldwide suffer from diabetes, or 2.8% of the population. Its incidence is increasing rapidly, and it is estimated that by 2030, this number will almost double.[1] Hence, in order to treat this highly prevalent condition, many pharmaceutical preparations have emerged in the recent past which are termed as Antidiabetic drugs. Anti-

diabetic medications treat diabetes mellitus by lowering glucose levels in the blood. With the exceptions of insulin, exenatide, and pramlintide, all are administered orally and are thus also called oral hypoglycemic agents or oral antihyperglycemic agents. There are different classes of anti-diabetic drugs like sulfonyl ureas, meglitinides, biguanides, thiazolidinediones, alpha-glucosidase inhibitors, peptide analogues to mention a few. The selection of drug depends on the nature of the diabetes, age and situation of the person, as well as other factors.[2] Of those drugs, Metformin Hydrochloride which comes under the class of Biguanides, is the most widely used antidiabetic agent which has got widespread use globally.

Gastric emptying of dosage forms is an extremely variable process and ability to prolong and control the emptying time is a valuable asset for dosage forms, which reside in the stomach for a longer period of time than conventional dosage forms. Several difficulties are faced in designing controlled release systems for better absorption and enhanced bioavailability. One of such difficulties is the inability to confine the dosage form in the desired area of the gastrointestinal tract. Drug absorption from the gastrointestinal tract is a complex procedure and is subject to many variables. It is widely acknowledged that the extent of gastrointestinal tract drug absorption is related to contact time with the small intestinal mucosa.[3] Thus, small intestinal transit time is an important parameter for drugs that are incompletely absorbed.

The controlled gastric retention of solid dosage forms may be achieved by the mechanisms of mucoadhesion,[4] floatation,[5] sedimentation,[6] expansion,[7] modified shape systems,[8] or by the simultaneous administration of pharmacological agents[9] that delay gastric emptying.

In the present investigation, with the incorporation of the mucilage extracted from the pods of Abelmoshus esculentus, its efficiency in the formulation of Metformin HCl floating tablets has been demonstrated.

Materials and Methods

Metformin HCl was a gift sample from Glenmark Pharmaceuticals; while HPMC E 15, Sodium bicarbonate, Citric acid, Magnesium stearate, Talc were purchased from S.d.Fine Chem., Hyderabad. Fresh Okra pods (Abelmoschus esculentus) were obtained from local market.

Extraction of 'Abelmoschus esculentus' fruit mucilage[10]: About 2kg of fresh immature fruit of Abelmoschus esculentus were obtained from a local market. After removal of the seeds, the fresh immature fruits were sliced, homogenized and extracted with cold water containing 1% (w/v) sodium metabisulphate. The crude mucilage was centrifuged at 3000 rpm for 5 min and the gum was precipitated from the supernatant with acetone. The precipitated gum was washed several times with acetone; the obtained cream coloured product was dried under vacuum in a desiccator. A light brown coloured powder was obtained after complete removal of moisture. The dried gum was pulverized using end runner mill and screened through a 0.25 mm stainless steel sieve. This was stored in a well closed amber colored specimen bottle till ready for use. The yield of crude Abelmoschus esculentus mucilage was 10 g /kg immature fruits.

Formulation and Evaluation of Metformin HCl floating matrix tablets[11]:

By Wet Granulation Method

Metformin HC1, sodium bicarbonate and citric acid were passed through # 40 sieve and mixed with hydroxypropyl methylcellulose E 15 by geometric mixing. The blend was granulated using distilled water as a granulation agent. The prepared mass was passed through # 20 and lubricated with magnesium stearate and talc. The lubricated blend was compressed on rotary tablet press.

Table-1: Composition of different formulations.

INGREDIENT	F 1 (mg)	F 2 (mg)	F 3 (mg)	F 4 (mg)
Metformin HCl	500	500	500	500
Abelmoschus esculentus	250	-	200	175
HPMC E 15	-	250	50	75
Distilled water	q.s.	q.s.	q.s.	q.s.
Sodium Bicarbonate	200	200	200	200
Citric Acid	10	10	10	10
Magnesium Stearate	5	5	5	5
Talc	5	5	5	5
Average Weight	970	970	970	970

Evaluation of extracted Okra mucilage:

Phytochemical Examination: Preliminary tests were performed to confirm the nature of mucilage obtained. The chemical tests that were conducted are: Ruthenium red test, Molisch test, test for reducing sugars and Ninhydrin test.[10]

Physicochemical parameters

The mucilage was evaluated for solubility, swelling index, loss on drying, density, and angle of repose as per the procedures described in IP and BP.

Density The bulk volume was determined by recording the volume occupied by a 50 g sample introduced in a 100 ml measuring cylinder.

Angle of repose A funnel of 0.8 and 8 cm in orifice and surface diameters respectively, was used, adopting the method of fixed funnel and free standing cone. A 50 g sample was allowed to flow through the funnel to form a cone. A cathetometer was used to determine the height of the heap (h). The base of the cone was traced out using a pencil and its radius (r) determined. The angle of repose was determined from the following relationship:

Tan e = h/R.[12]

Swelling index One tablet was weighed and placed in a beaker containing 200 ml of distilled water. After each hour the tablet was removed from beaker and weighed again upto 5 hours. The % weight gain by the tablet was calculated by the formula,

Swelling Index (S.I.) = {(Wt-Wo)/Wo} ×100 Where, S.I. = swelling index.,Wt = weight of tablet at time t. Wo = weight of tablet before immersion.[13]

Evaluation of Metformin HCl floating tablets:

Tablet Hardness Testing

Tablet requires a certain amount of strength or hardness and resistance to friability to withstand mechanical shakes of handling in manufacture, packaging and shipping. Hardness generally measures the tablet crushing strength. The hardness of the so formulated tablets was tested by using Monsanto hardness tester by holding one tablet between the

two faces provided by pushing forward the movable face inside by turning the plunger clockwise. The 'Zero' in the scale was coincided with the pointer. The front part is enclosed where tablet is held in a sample polybag. Pressure was applied on the tablet by gently rotating the plunger. When the tablet breaks, the hardness (in kg/sq.cm.) directly from the scale was noted. This was repeated for accurate results and the same procedure was followed for every type of formulation.[14]

Weight Variation Test (U.S.P.)

20 tablets were weighed individually and the average weight was calculated. The individual tablet weight was compared to the average. The tablet pass the U.S.P. test if no more that 2 tablets are outside the percentage limit and if no tablet differs by more than 2 times the percentage limit.[12]

Thickness

Tablet thickness is important for tablet packaging. The tablet thickness was determined with the help of micrometer.

Friability Test

The weight of 20 tablets selected from each batch at random was determined collectively as initial weight. The tablets were placed in a friabilator set to rotate at 25 rpm for 4 min. At the end of the run, the tablets were de-dusted and weighed and Friability was calculated.[12]

Drug content uniformity

For drug content uniformity, 20 tablets were weight and crushed. An accurately weighed 0.05 g drug equivalent powder was transferred to 100 ml of 0.1 N HCl. This suspension was stirred on a magnetic stirrer for 5 h. The suspension was then filtered and the drug content was determined at 233 nm by making suitable dilutions.[15]

Plate.1.Plate showing some of the formulations before subjecting to weight variation test

In vitro Disintegration Test (U.S.P.)

The U.S.P. device to test disintegration uses 6 glass tubes that are 3" long; open at the top and 10 mesh screen at the bottom end. To test for disintegration time, one tablet was placed in each tube and the basket rack was positioned in a 1-L beaker of 0.1 N Hydrochloric acid at 37 ± 20 C such that the tablet remain 2.5 cm below the surface of liquid on their upward movement and not closer than 2.5 cm from the bottom of the beaker in their downward movement. The basket containing the tablets was moved up and down through a distance of 5-6 cm at a frequency of 28 to 32 cycles per minute. Floating of the tablets can be prevented by placing perforated plastic discs on each tablet. According to the test, the tablet must disintegrate and all particles must pass through the 10 mesh screen in the time specified. If any residue remains, it must have a soft mass.

In Vitro Buoyancy Studies:

The in vitro buoyancy was determined by floating lag time, per the method described by Rosa et al. The tables were placed in a 100-mL beaker containing 0.1N HCL. The time required for the tablet to rise to the surface and float was determined as floating lag time.[16]

In Vitro Dissolution Profile Studies:

The rate of metformin hydrochloride release from metformin hydrochloride sustained release tablets was conducted using Dissolution Testing Apparatus II (Paddle method). The dissolution test was carried out using 900 ml of 0.1 N HCI, at 37 ± 0.5 Celsius and 75 rpm. A sample (10 ml) of the solution was withdrawn from the dissolution apparatus at every hour up to eight hours and withdrawn volume was replaced with fresh dissolution media. The samples were filtered through a 0.45 μ membrane filter, the sample was diluted to suitable concentration with 0.1N HCl. Absorbance of these solutions was measured at 233nm using UV spectrophotometer.[11]

Plate.2. Dissolution test apparatus (II)

Plotting Standard curve of Metformin HCl

Preparation of buffer (0.1 N HCl)

8.5 ml of concentrated Hydrochloric acid was diluted to 1000 ml of distilled water to obtain a concentration of 0.1N HCl. It was then tested for pH using pH meter.[17]

Preparation of Stock Solution

10 mg of Metformin HCl was dissolved in small quantity of 0.1N HCl and made up to 100 ml using 0.1N HCl which is the Stock solution. From this solution, 0.2ml was taken and dissolved in 10 ml of distilled water to obtain a concentration of 2 mcg/ml. Similarly, other concentrations were made.

Drug Release Patterns

The extent at which the drug releases from the tablet was calculated from the standard graph of Metformin HCl. Similarly, the drug release patterns of all the formulations were determined. The extent of drug release was estimated by plotting a graph of time versus percent cumulative drug release.

Plate.3.UV-Spectrophotometer

FT-IR Spectral Analysis

Infrared spectroscopy is one of the most powerful analytical techniques, which offers the possible chemical interaction between drug and excipients used. In the present work, IR spectra of floating tablets of Metformin HCl were determined using FT-IR spectrophotometer at STARTECH LABS, Hyderabad due to lack of facilities.

RESULTS AND DISCUSSION

Investigational results of the extracted mucilage

Phytochemical screening tests: The mucilage that was extracted from the Abelmoschus esculentus fruits showed the presence of high percentage of complex polysaccharides along with the presence of glucose in small amounts.

Physicochemical parameters

Table-2: Physicochemical parameters.

S. No.	Physicochemical parameter	Result
1.	Swelling ratio	27
2.	Solubility	slightly soluble in water, insoluble in ethanol, acetone, ether and chloroform.
3.	Bulk Density (g/cc) Tapped Density (g/cc)	0.61 0.74
4.	Angle of Repose	33^0
5.	Loss on drying	0.8%

Investigational results of the formulated Metformin HCl floating tablets

Table-3: Physical properties.

Formulation	Weight variation mg ± S.D (n=20)	Hardness $Kg.cm^2$ ± S.D. (n=3)	Thickness mm ± S.D. (n=5)	Friability (%)	Drug content % ± S.D. (n=20)
F1	967±0.12	5.375±0.13	5.2±0.11	0.59±0.13	99.23±0.12
F2	967.5±0.14	6.5±0.15	4.9±0.13	0.62±0.15	99.42±0.14
F3	966±0.16	5.0±0.17	5.3±0.15	0.61±0.17	99.84±0.16
F4	968±0.18	4.25±0.19	5.2±0.17	0.58±0.19	99.61±0.18

In vitro Tablet Disintegration Test

The disintegration time for each of the four formulations is as follows:

Table-4: Disintegration time.

S. No.	Formulation	Disintegration Time (in min)
1.	F1	118.00
2.	F2	7.36
3.	F3	56.00
4.	F4	25.00

Invitro Buoyancy Studies

The floating times of the four formulations is given below:

Table-5: Floating time.

S. No.	Formulation	Floating Time
1.	F1	6 min 25 sec
2.	F2	14 sec
3.	F3	5 min 49 sec
4.	F4	5 min 20 sec

Plate.4. Stage 1 in the floating study

Plate.5. Stage 2 in the floating study

Plate.6. Stage 3 in the floating study

Standard graph of Metformin HCl at λ_{max} = 233 nm.

Table.6.Standard graph values of Metformin

S. No.	Concentration (mcg/ml)	Absorbance (nm)
1.	0	0.000 ± 0.0000
2.	2	0.201 ± 0.0012
3.	4	0.404 ± 0.0016
4.	6	0.556 ± 0.0017
5.	8	0.717 ± 0.0016
6.	10	0.988 ± 0.0015

***Each reading is a mean of three determinations

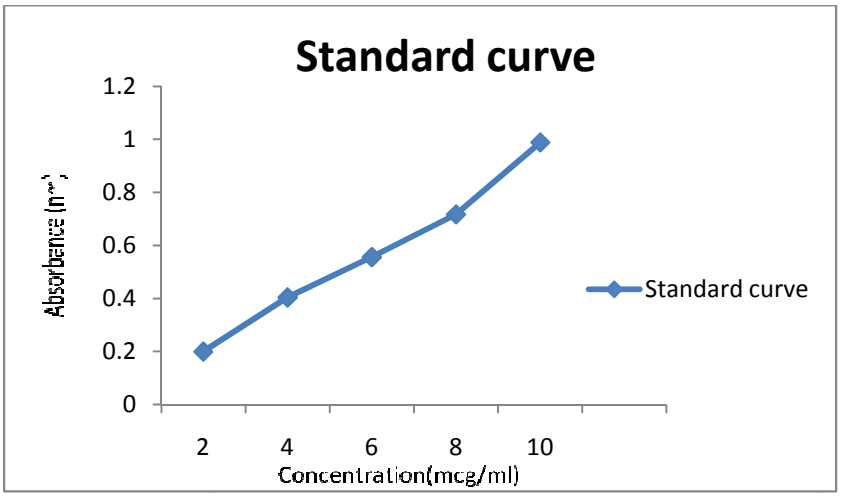


Fig.1. Standard calibration curve of Metformin HCl at λ_{max} = 233 nm.

Table-7: Drug release patterns.

S.No.	TIME (min)	% cumulative drug released			
		F1	F2	F3	F4
1.	**00**	0.000	0.000	0.000	0.000
2.	**30**	0.900	7.938	3.978	5.850
3.	**60**	2.358	17.674	9.846	12.906
4.	**90**	4.608	27.990	16.002	20.880
5.	**120**	8.550	38.934	22.644	29.376

6.	**150**	12.978	50.076	29.682	38.034
7.	**180**	18.000	61.686	37.062	47.394
8.	**210**	23.382	73.674	44.964	56.916
9.	**240**	29.232	86.150	53.082	66.816
10.	**270**	35.334	99.128	61.578	77.148
11.	**300**	41.976		70.776	88.272
12.	**330**	48.996		80.190	99.864
13.	**360**	56.286		90.522	
14.	**390**	64.242		99.899	
15.	**420**	72.792			
16.	**450**	82.116			
17.	**480**	91.584			

Comparison of drug release patterns of F1, F2, F3 and F4

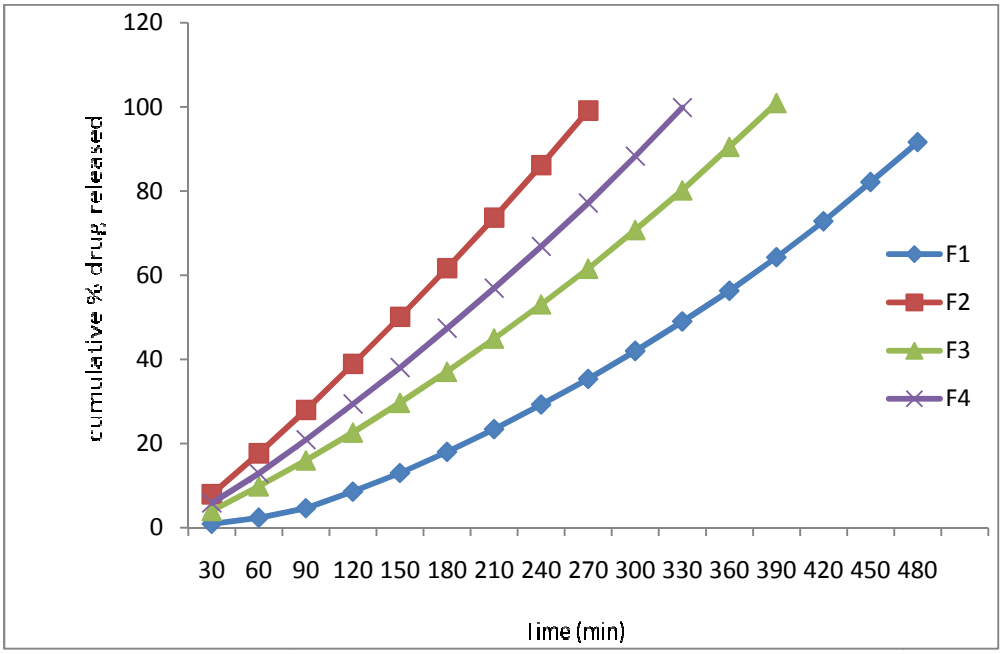


Fig.6.Comparison of drug release patterns

FT – IR Spectral Analysis

Fig.7.FT – IR Spectra of F1

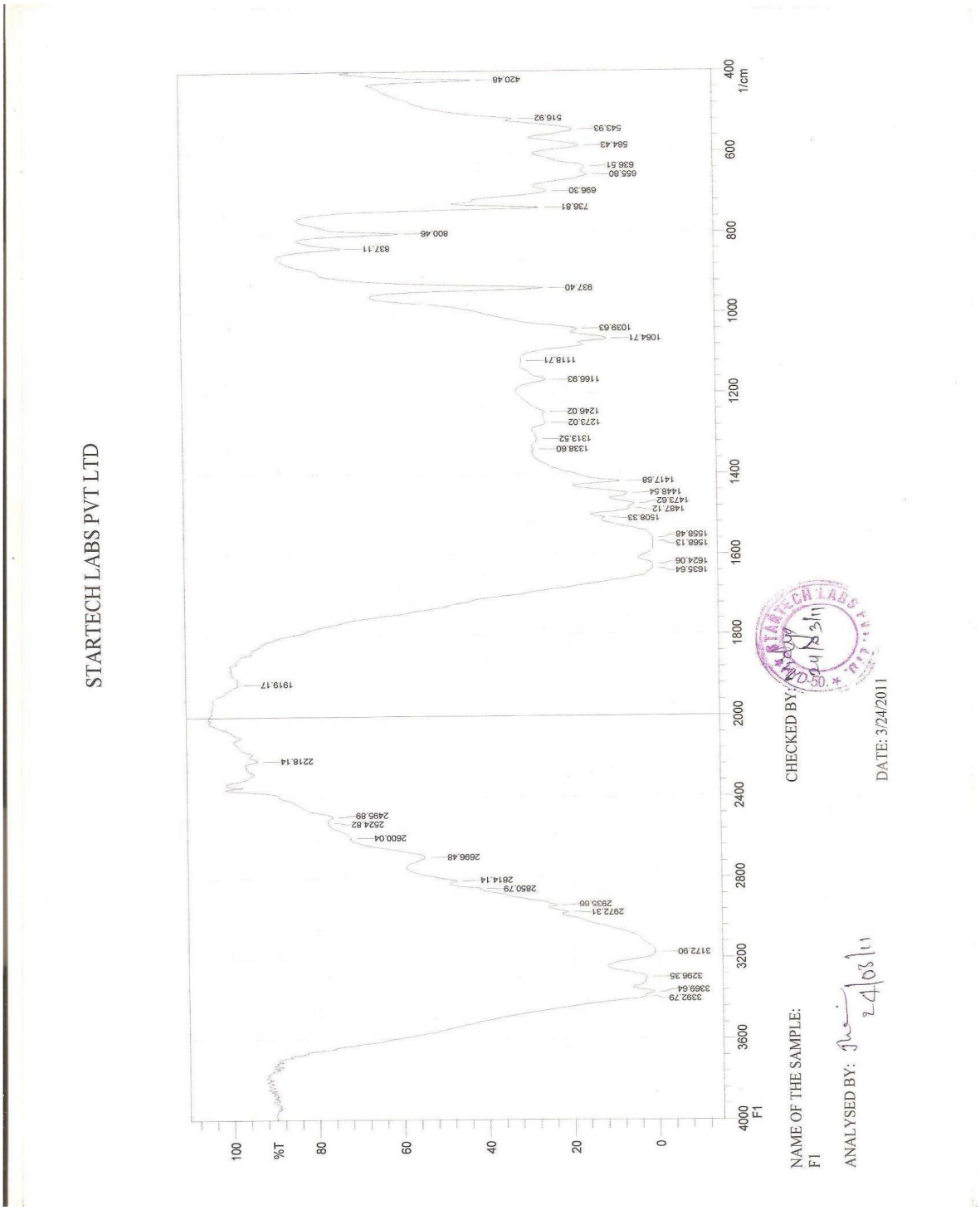


Fig.8.FT – IR Spectra of F2

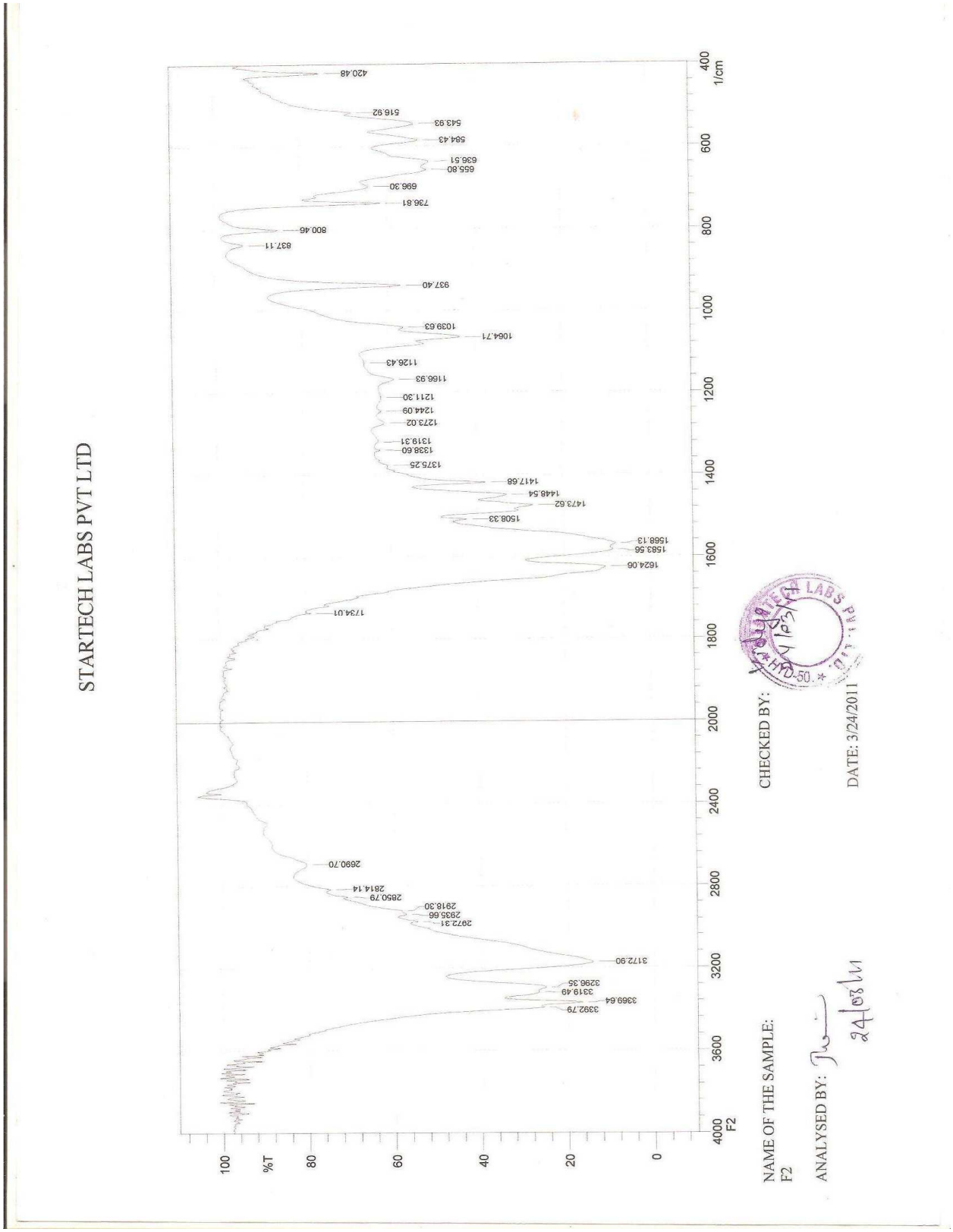


Fig.9.FT – IR Spectra of F3

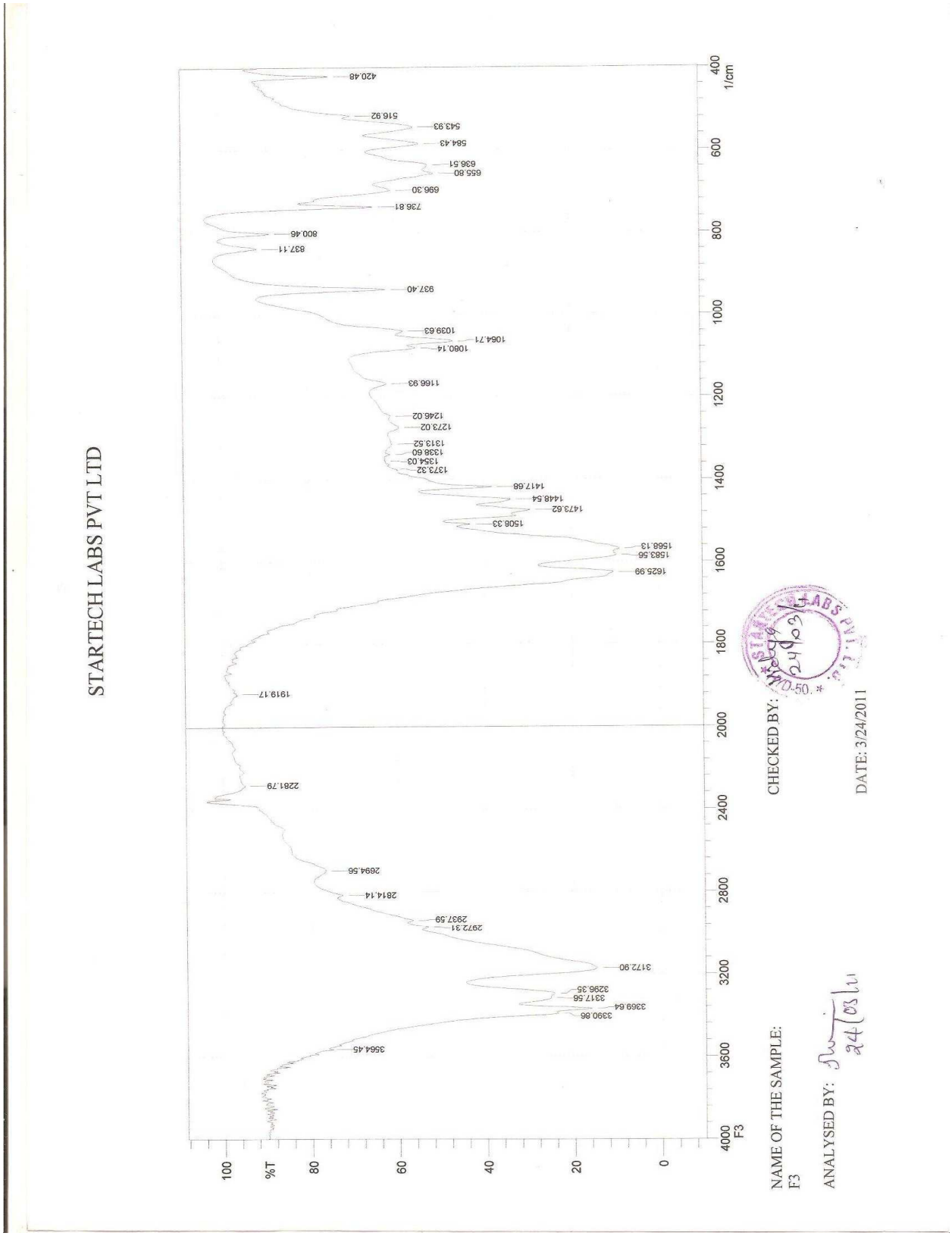
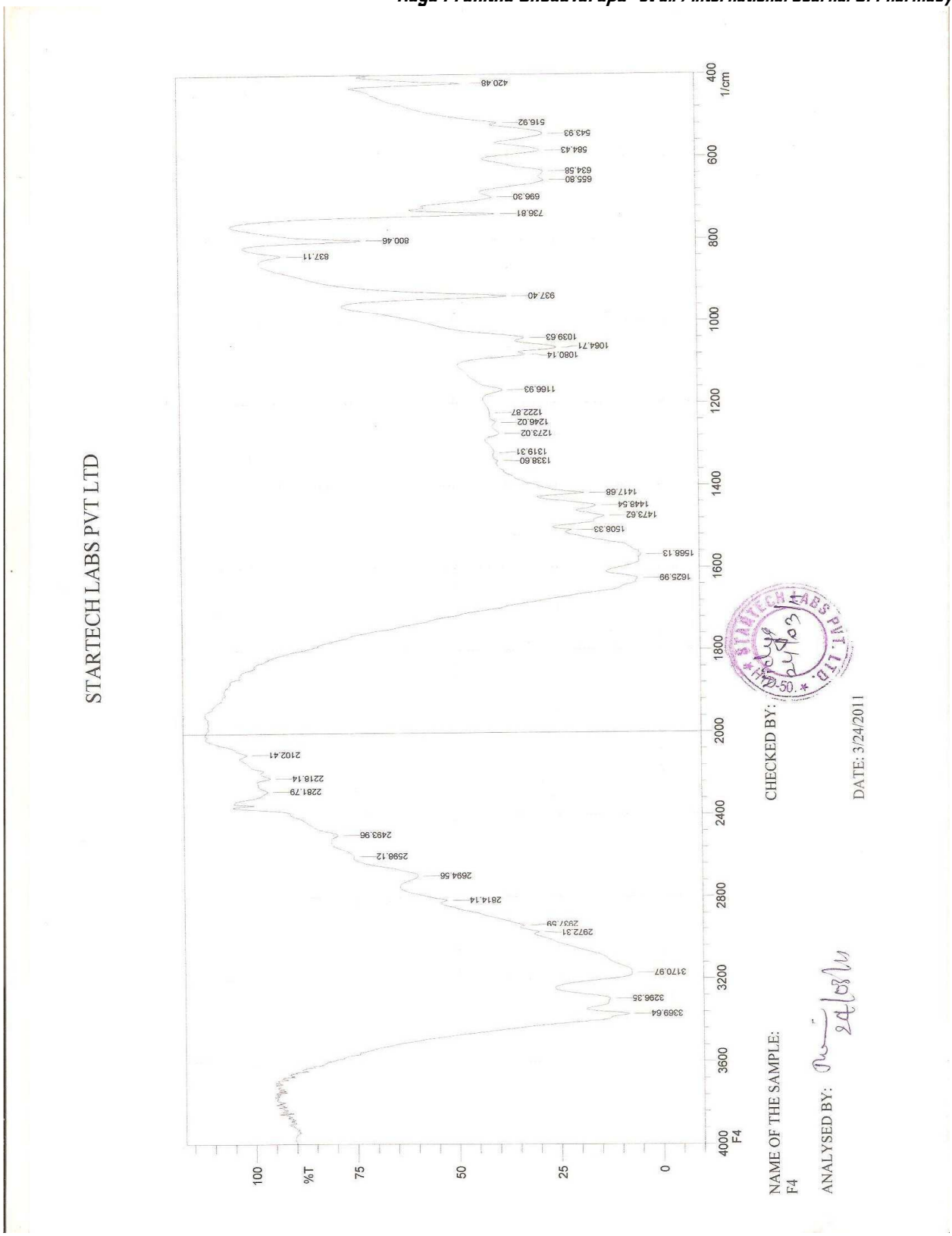


Fig.10.FT – IR Spectra of F4



Characterization of the extracted mucilage

The extracted and purified Ae gum is cream coloured and odourless. From the chemical tests, it is clear that the gum is composed mainly of monosaccharide units of galactose, rhamnose and galacturonic acid. The swelling index, density (bulk and tapped density), loss on drying, solubility and angle of repose were found to be complying with the standards.

Metformin HCl floating tablets

Weight Variation Test

All the tablets were found to comply with the standards prescribed in the U.S.P., and showed no much variation in the weight of the individual tablets.

Tablet Hardness

All the four types of formulations (F1, F2, F3, F4) were found to have the required hardness. The formulation, F2 that contained only HPMC E 15 showed greatest hardness while the formulation, F4 which has a mixture of Abelmoschus esculentus and HPMC in the ratio, 2.34:1, showed least hardness. The formulations, F1 and F3, showed almost equal hardness (~5).

Tablet thickness

The thickness of all the four types of tablets was optimum and their results can be found in the Table.3.

Friability

Friability values of all the formulations were within the limit i.e. is less than 1.0% indicated that tablets had a good mechanical strength.

Drug content uniformity

Drug content of all the formulations were found to be in the range of 98.5 – 101.0%, which is within acceptable limits. The results are shown in Table.3.

In vitro Tablet Disintegration Test: The formulation, F1 which included only fruit mucilage took more time to disintegrate while F2 which contained HPMC E 15 took least time to get disintegrated. When the formulations, F3 and F4 are considered, which have combination of both okra mucilage and HPMC, F3 which has the highest

percentage of fruit mucilage has taken more time to disintegrate when compared to F4, which has lower percentage of it. (Table.4.)

In vitro Buoyancy studies

The floating time of formulation, F1 is greatest among all the four formulations. On the other hand, the formulation, F2 took very less time to float in the simulated gastric fluids. Likewise, the formulations F3 and F4 which contained HPMC and Abelmoschus esculentus fruit mucilage, but in different ratios, showed almost equal floating times (~ 5 min). (Table.5).

In vitro Dissolution profile Studies and drug release patterns

The in vitro drug release was carried out in 0.1N HCl. For all the formulations(F1, F2, F3, F4), as the time increased, the dissolution of the drug into the simulated gastric fluids also increased which indicates increase in the concentration of drug as the time passes.

At the end of 480 min., the percentage amount of drug released from F1 was 91.584 and this indicates that the formulation (F1) which has only Ae gum released the drug very slowly. On the other hand, the drug from the formulation, F2 which has only HPMC E 15 was released very rapidly i.e., 99.128% within 270 min., which implies lesser sustained release in comparison with F1. Similarly, the percentage amount of drug released from the formulations, F3 and F4 were 99.899% (after 390 min.) and 99.864% (after 330 min.). From these results, it is clear that the formulation, F1 manifested sustained release of the drug, Metformin HCl among all the other formulations. (Tables: 7 – 10 and Figures: 2 – 6).

FT – IR Spectral Analysis

The peaks at 3171/cm., 1062/cm. and 1580/cm., show the presence of $–NH_2$, C-N stretching and NH groups respectively. From the FT-IR analysis, it was demonstrated that there was no chemical interaction between the drug and other excipients used in the formulation.

Conclusion

- The results from the physicochemical parameters of the mucilage manifested all the characteristics of a good pharmaceutical excipient that can be used for the formulation of floating tablets. In addition, the swelling ratio of the mucilage is optimum which aids in the floatation of the tablet in the gastric fluids.
- From the present investigation, it is quite evident that incorporation of Abelmoschus esculentus fruit mucilage as one of the pharmaceutical excipients facilitates controlled release of the drug for prolonged time by maintaining the tablet in a floating condition in the gastric fluids due to the matrix forming capability of the mucilage.
- Abelmoschus gum has swellable property; hence it can be used as a polymer in the development of a GRDDS either singly or in combination with polymers like HPMC. But, the formulation with only Ae gum is very much acceptable for formulating floating matrix tablets since it showed a sustained release effect for more period of time.
- It can be emphasized that Abelmoschus esculentus gum has shown much more floating capacity accompanied by sustained release than HPMC E 15 polymer.
- With optimal floating time, the Metformin HCl floating tablets with Ae help in increasing the residence time of Metformin HCl in stomach. This further helps to decrease the frequency of dosing; thus minimizing the side effects caused due to Metformin where it is known to cause damage to the kidneys.
- In addition, since Abelmoschus esculentus gum is easily available and the extraction includes very fewer steps, it is comparatively economical for bulk production of the drug.

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