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Floating Matrix Tablet of Metformin Hydrochloride Using Natural Polymers

Lad G.C.*, Gujrathi D.S. , Mhetre R.M., Shrisundar N.S.
Gandhi Natha Rangji College of D. Pharmacy, Solapur

ABSTRACT

The purpose of the study was to prolong the gastric residence time of metformin hydrochloride by designing its floating tablets and to study the influence of natural polymers like okra gum and fenugreek gum on its release rate. Sodium bicarbonate was added as a gas generating agent that releases carbon dioxide in the gastric acidic environment which helped in maintain the buoyancy. Metformin hydrochloride is a biguanide glucose-lowering agent that has been widely used in the management of NIDDM, whose hyperglycemia cannot be satisfactorily managed on diet alone. Metformin hydrochloride is incompletely absorbed from GI tract, with an absorption window confined to the upper part of GI tract. It also has a half life of about 2 hours and its absolute bioavailability is reported to be about 50-60% of the administered oral dose. An obstacle to the more successful use of metformin hydrochloride therapy is the high incidence of GI symptoms seen in about 30% patients, especially during initial weeks of treatment. Patient compliance decreases with frequent dosing regimen and side effects associated with the same. In order to optimize therapy research efforts have been focused on the development of oral sustained release (SR) preparations using natural polymers as well as controlled release gastroretentive dosage forms. The present study outlines a systematic approach for the development of hydrodynamically balanced tablet of metformin hydrochloride using natural polymers with a view to enhance its oral bioavailability and efficacy. Development of floating matrix tablets of metformin hydrochloride using natural polymers (okra and fenugreek).Comparative studies of both available marketed formulations and HPMC polymer.

Keywords: Metformin hydrochloride, Okra, Fenugreek, floating matrix tablet

*Corresponding Author Email: bimalatripathy09@gmail.com
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INTRODUCTION

Oral delivery of drugs is by far the most preferred route of drug delivery due to ease of administration, patient compliance and flexibility in formulation. Conventional oral dosage forms provide a specific drug concentration in systemic circulation without offering any control over drug delivery. These systems achieve as well as maintain drug concentration within therapeutically effective range needed for treatment only when taken several times a day. This results in significant fluctuation in drug levels.

Now-a-days most of the pharmaceutical scientists are involved in developing an ideal drug delivery system (DDS). An ideal oral drug delivery system should steadily deliver a measurable and reproducible amount of drug to the target site over a prolonged period[Lachman et al 2004].

Gastroretentive drug delivery systems

Dosage forms that can be retained in stomach are called gastroretentive drug delivery systems (GRDDS). GRDDS can improve controlled delivery of drugs that have an absorption window by continuously releasing the drug for a prolonged period of time before it reaches its absorption site, thus ensuring its optimal bioavailability [Chawla G et al 2003].

Drugs having narrow absorption window are mostly associated with improved absorption at jejunum and ileum due to their enhanced absorption properties e.g. large surface area, or because of enhanced solubility in stomach as opposed to the more distal parts of the GIT[Klausner EA et al 2003].

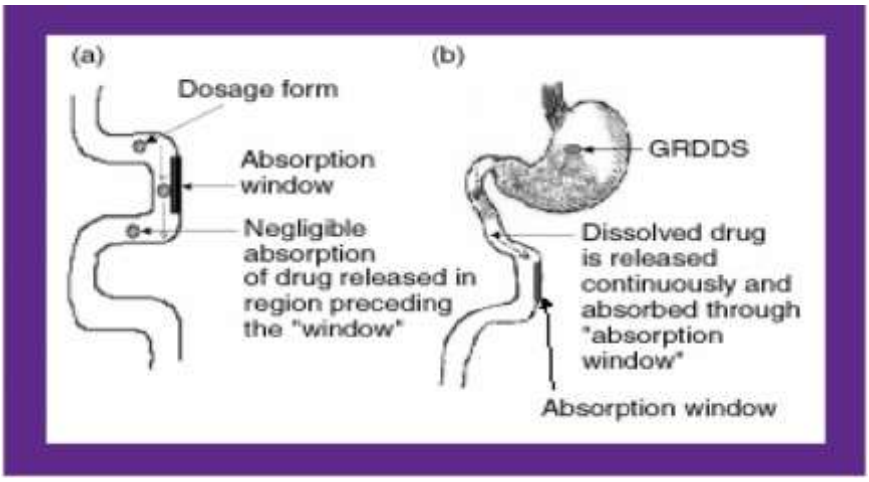

Figure 1: Drug absorption in case of (a) conventional dosage forms and (b) gastroretentive drug delivery systems.

Certain types of drugs that benefit from using gastric retentive devices includes:-

- Drugs acting locally in stomach e.g. Antacids
- Drugs that are primarily absorbed in stomach e.g. Albuterol

- Drugs that are poorly soluble at an alkaline pH
- Drugs with a narrow window of absorption i.e. drugs that are absorbed mainly from the proximal small intestine e.g. Riboflavin, Levodopa
- Drugs absorbed rapidly from GI tract e.g. Amoxycillin
- Drugs that degrade in colon e.g. Metoprolol. [Rocca JG et al 2003]

Longer residence time in stomach could be advantageous for local action in the upper part of small intestine, for example treatment of peptic ulcer disease.

Advantages of gastroretentive systems

Gastroretentive dosage forms (GRDFs) alter beneficially the absorption profile of active agent, thus enhancing its bioavailability. For example, a significant increase in the bioavailability of furosemide from a floating dosage form (42.9%) has been reported compared with commercially available tablets [Lasix® (33.4%)] and enteric products (29.5%).

GRDFs greatly improves pharmacotherapy of the stomach through local drug release leading to high drug concentrations at gastric mucosa (eradicating Helicobacter pylori from the submucosal tissue of the stomach), making it possible to treat stomach and duodenal ulcers, gastritis, and oesophagitis, reduce the risk of gastric carcinoma and administer non-systemic, controlled release antacid formulations (Calcium Carbonate).

GRDFs can be used as carriers for drugs with so-called absorption windows. These substances for example antiviral, antifungal and antibiotic agents (Sulphonamides,

Quinolones, Penicillins, Cephalosporins, Aminoglycosides and Tetracycline, etc.) are taken up only from very specific sites of the GI mucosa [Garg S et al 2003].

Ideal drug candidates for compounding in to GRDFs

- Drugs stable in gastric milieu.
- Drugs having narrow absorption window.
- Drugs to be used for gastro-duodenal local therapy.

Drugs incorporated into GRDFs:

The following are the list of drugs that have been incorporated into GRDF's as microspheres, granules, capsules, tablets or pills.

Table 1: list of drugs incorporated into GRDF's

Acyclovir	Atenolol
Cinnarizine	Cisapride
Glipizide	Levodopa

Disadvantages of gastroretentive systems:

There are certain situations where gastric retention is not desirable. Aspirin and non-steroidal anti-inflammatory drugs are known to cause gastric lesions and slow release of such drugs in the stomach is unwanted. Thus drugs that may irritate the stomach lining or are unstable in its acidic environment should not be formulated in gastroretentive systems. Furthermore, other drugs such as Isosorbide dinitrate, that are absorbed equally well throughout the GI tract will not benefit from incorporation into a gastric retention system.

Limitations of GRDDS:

1. Requirement of high levels of fluids in stomach for the delivery system to float and work efficiently.
2. Requires the presence of food to delay gastric emptying.
3. Drugs having solubility or stability problems in the highly acidic gastric environment or which are irritants to gastric mucosa cannot be formulated as GRDDS.
4. In case of bioadhesive systems, the acidic environment, thick mucous as well as high turnover rate of mucous prevents bond formation at the mucous-polymer interface

Polymers used.

OKRA ***(Albemoschus esculentus. A. esculentus*** **(syn.** ***Hisbiscus esculentus)***)

Okra gum is a natural polymer extracted from the pods of *Albemoschus esculentus*.

A. esculentus (syn. *Hisbiscus esculentus)* is a plant native to tropical Africa, Asia, and Northern Australia. Abelmoschus is a genus of about 15 species of flowering plants in the mallow family *malvaceae*.

It was formerly included within the hibiscus but now classified as a distinct genus.[1] The stem, leaves, and pods of this plant have mucilage. The performance of okra gum as a sustained release excipient was comparable to those of sodium carboxymethylcellulosea

(NaCMC) and hydroxyl propyl methyl cellulose (HPMC) when some researchers employed it as a mini matrix in a sustained release tablet formulations of furosemide and diclofenac sodium and paracetamol.

The binding, disintegrating, and bioadhesive properties of okra have been studied. A study has been made of the effects of drying methods on the physicochemical characteristics and compressibility of okra powder and the release properties of its metronidazole tablet formulation. To date there is no published study on the film coating potential of okra gum. The purpose of this paper is to report the preliminary investigation on the film coating potential of okra gum by using it to film coat paracetamol tablets as the model drug[Indah Mohd Amin et al 2011].

Fenugreek(*Trigonella Foenum-graceum*)

Trigonella Foenum-graceum, commonly known as Fenugreek, obtained from the fruits of *Trigonella Foenum-graceum* is an herbaceous plant of the leguminous family and is native to Western Asia, from where it has spread widely over Europe, the Mediterranean, and the rest of Asia. It is one of the oldest cultivated plants and has found wide applications as a food, a food additive, and as a traditional medicine in every region where it has been cultivated. The leaves and both the ripe and unripe seeds of Trigonella Foenum-graceum are used as vegetables.

The seeds also function as a food preservative and are added to pickles, chutneys, and other similar food products. The ripe seeds have numerous applications in cosmetic and traditional medicine system of India.

Fenugreek has been used in treating colic flatulence, dysentery, diarrhoea, dyspepsia with loss of appetite, chronic cough, dropsy, enlargement of liver and spleen, rickets, gout, and diabetes. It is also used as gastro protective, antiurolithiatic, diuretic, antidandruff agent, anti-inflammatory agent and as antioxidant.

The seed is stated to be a tonic. It also is used in post-natal care and to increase lactation in nursing mothers. Fenugreek seeds contain a high percentage of mucilage (a natural gummy substance present in the coatings of many seeds). The objective of present study was to isolate and investigate the suitability of the fenugreek seed mucilage as a sustained release matrix material to develop controlled release tablets of the selected model drug[Avachat M et al 2003].

The natural polymers used because of

- It is stable over wider pH and temperature ranges.
- It is non hygroscopic in nature.
- exhibit mucoadhesive properties.
- The viscosity of polymer will help in achieving controlled release.
- Natural origin/biodegradable /biocompatible.

Table 2 Marketed products of GRDFs

Sr. no.	Brand name	Drug (dose)	Company, country	Remarks
1.	Madopar®	Levodopa (100 mg), Benserazide (25 mg)	Roche Products, USA	Floating CR Capsule
2.	Valrelease®	Diazepam (15 mg)	Hoffmann-LaRoche, USA	Floating capsule

3.	Liquid Gaviscon®	Al hydroxide (95 mg), Mg carbonate (358 mg)	Glaxo Smith Kline, India	Effervescent floating liquid Alginate preparation
4.	Topalkan®	Al-Mg antacid	Pierre Fabre Drug, France	Floating liquid Alginate preparation
5.	Conviron	Ferrous sulphate	Ranbaxy, India	Colloidal gel forming FDDS
6.	Cifran OD®	Ciprofloxacin (1 gm)	Ranbaxy, India	Gas-generating floating tablet
7.	Cytotec®	Misoprostol (100 mcg/200 mcg)	Pharmacia, USA	Bilayer floating Capsule
8.	Oflin OD®	Ofloxacin (400mg)	Ranbaxy, India	Gas generating floating tablet

Rational of work

Rational for the present study is the use of natural polymers (okra and fenugreek) to prepare floating matrix tablets of metformin hydrochloride by effervescent technique to provide sustained release in the gastric medium.

Metformin hydrochloride an oral anti-hyperglycemic agent shows incomplete absorption from the gastrointestinal tract and the absolute bioavailability is 50 – 60 % with relatively short plasma half-life of 1.5 - 4.5 h. An obstacle to more successful use of metformin therapy is the high incidence of concomitant gastrointestinal symptoms, such as abdominal discomfort, nausea, and diarrhea, that especially occur during the initial weeks of treatment , side effects and the need for administration two or three times per day when larger doses are required that decreases patient compliance. A sustained-release (SR) formulation that would maintain plasma levels of the drug for 10 to 16 hours might be sufficient for once-daily dosing of metformin hydrochloride. Sustained release products are needed for metformin hydrochloride to prolong its duration of action and to improve patient compliance.

The natural polymers are used in this present study with a view to enhance its oral bioavailability and efficacy and are stable over wider pH and temperature ranges, non hygroscopic in nature, exhibit mucoadhesive properties. The viscosity of polymer will help in achieving controlled

release. Natural origin/biodegradable /biocompatible and cost effective that makes polymer suitable for controlled release.

MATERIALS AND METHOD

The following materials that were either AR/LR grade or the best possible Pharma grade available were used as supplied by the manufacturer. Table no.3

Sr.no	Material	Grade	Manufacturer
1	Metformin hydrochloride		Emcure Pharmaceuticals ltd, Pune, India
2	Okra		Local market
3	Fenugreek		Local market
4	Lactose	LR	Thermosil Fine chemical, Pune, India.
5	Talc	LR	Thermosil fine chemical industries ,Pune, India.
6	HCL	AR	Thermosil fine chemical industries ,Pune, India.
7	Magnesium sterate		Oxford lab,Mumbai, India
8	Alcohol	AR	CSS Chemicals, China.
9	$NaHCO_3$	AR	Fine chemicals Pvt. Ltd, Mumbai, India.
10	Iso propyl alcohol	LR	Poona chemical laboratory, Pune, India
11	Citric acid	LR	Fine chemicals Pvt. Ltd, Mumbai, India

Methods

Isolation of okra (*Abelmoschus esculantus*)

The fresh *Abelmoschus esculentus* fruits were collected and washed with water. Incisions were made on the fruits, left over night. The fruits were crushed and soaked in water for 5–6 h, boiled for 30 minutes and left to stand for 1 h to allow complete release of the mucilage into the water. The mucilage was extracted using a multi layer muslin cloth bag to remove the marc from the solution. Acetone (three times the volume of filtrate) was added to precipitate the mucilage. The mucilage was separated, dried in an oven at 40°C, collected, ground, passed through a # 80 sieve and stored in desiccator at 30°C & 45% relative humidity till use [Chodavarapu et al 2011].

Okra yield: The yield of crude Abelmoschus esculentus mucilage was 10g/kg of immature fruits

Isolation of fenugreek (*Trigonella foenum graceum*)

The seeds were powdered using pestle and mortar and 100 g of the powder was extracted with hexane to remove lipophilic compounds using a soxhelet apparatus. To remove pigments and to deactivate enzyme, the defatted powder was boiled in ethanol for 20 min. This treated powder was then soaked in 10 liters water and the pH was adjusted to 3.5 using 0.5 M Hydrochloric acid. The mixture was stirred by a mechanical stirrer for 12 h and then filtered through filtration paper. The filtrate was centrifuged (5000 g) and the supernatant was concentrated in vacuum to 50% of its initial volume. The resulting solution was mixed with the same volume of 96% ethanol and stored

in a refrigerator for 4 h. The precipitated mucilage was separated by centrifugation (5000 g). The collected mucilage was re-suspended in distilled water, agitated for 20 min and re-precipitated one more time to eliminate chloride ions and other impurities. Finally the residue was washed with diethyl ether and acetone and dried overnight at 45°C, resulting in an off-white powder [Malviya et al 2011].

Fenugreek yield:

The yield of Trigonella foenum graceum mucilage was 12g/20gm fenugreek seeds

Characterisation of isolated polymers (okra and fenugreek)

Loss on drying

A 10.0 g of gum was heated in a hot air oven at 105ºC. Loss on drying (LOD) was the difference between the initial weight and the final weight of the sample expressed as a percentage

$$\text{Loss on drying} = \frac{\text{Final weight} - \text{Initial weight}}{\text{Initial weight}} * 100$$

Solubility test

A 1.0 g of powdered gum of okra and fenugreek was weighed and suspended in the solvent and was agitated for 24 h over a magnetic plate. A 1.0 ml from the supernatant was filtered and dried at 50°C. The gain in weight of previously tarred porcelain was taken as the amount of solute in the filtrate and this was used to calculate the solubility of the substance in 100 ml of the solvent. The pH of 1% suspension was determined using digital pH meter 3310 at 25ºC.

Viscosity

The viscosity of 0.6% w/v suspension was determined with Brookfield LVDV - III + digital rheometer (Brookfield Engineering Lab. Inc). The mucilage was placed in a 600 ml beaker supplied by Brookfield Engineering Laboratory and the temperature was maintained at 25ºC with the aid of thermostatic water bath, and RV3 spindle was employed at varying revolutions

Preformulation Studies

It is one of the important prerequisite in development of any drug delivery system. Preformulation studies were performed on the drug which included melting point determination, solubility studies and compatibility studies.

Determination of melting Point

Melting point of metformin hydrochloride was determined by capillary method.

Solubility

Solubility of metformin hydrochloride was determined in water, 0.1N HCl, and chloroform.

Compatibility studies

The compatibility of the drug and polymer under experimental conditions is an important Prerequisite before formulation. It is necessary to confirm that the drug does not react with the polymer or excipients and affect the shelf life of the product. This can be confirmed by carrying out infrared spectroscopy studies.

The obtained drug, polymer and formulation were subjected to IR studies. In the present study potassium bromide disc (pellet) method was employed and the obtained IR spectra were analysed comparatively, with reference spectrum of metformin hydrochloride

Formulation of Floating matrix Tablets of metformin hydrochloride:

The composition of the various formulations prepared using Design expert by 3^2 factorial design listed in the table given below.

Table 4: Composition of Floating tablets of metformin Hydrochloride with varying quantities

Formulation code (Quantity in mg)										
Ingredients	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**	**F10**
Metformin HCl	500	500	500	500	500	500	500	500	500	500
Okra	300	241.2	100	200	300	58.58	200	241.2	100	-
Fenugreek	100	200	300	200	200	200	58.58	200	100	-
HPMC	-	-	-	-	-	-	-	-	-	350
$NaHCO_3$	30	30	30	30	30	30	30	30	30	30
Citric Acid	5	5	5	5	5	5	5	5	5	5
Total weight	900	900	900	900	900	900	900	900	900	900

All batches contained 1% w/w talc and 1% w/w magnesium stearate
HPMC K4M: Hydroxy propyl methyl cellulose
$NaHCO_3$: Sodium bicarbonate

RESULTS AND DISCUSSION

Hydrodynamically balanced tablets of metformin hydrochloride were prepared and evaluated for their use as gastroretentive drug delivery systems to increase its bioavailability.

Evaluation parameter of Preformulation study of polymers

Table 5 Physical properties of polymers

Name of polymers	Bulk density	Tapped density	Compressibility index	Hausner's ratio	Angle of repose	Swelling index
Okra	0.7161±0.5	0.8203±0.02	13.41±4.51	1.15±0.6	33.46±5	5.77±0.10
fenugrek	0.6823±0.6	0.8134±o.04	13.67.±3.43	1.12±0.3	31.32±0.4	4.99±0.08

All values are mean ±SD, (n=3)

From table 3 it can be concluded that the polymers shows good flowing property.

PREFORMULATION STUDIES OF DRUG:

Melting point determination:-

Melting point of metformin was found to be in the range of 223 – 225°C, which complied with IP standards, indicating purity of the drug sample.

Solubility:-

Metformin was found to be freely soluble in water, 0.1N HCl, phosphate buffer pH 6.8 and practically insoluble in chloroform

Determination of absorbance maxima

A typical UV absorption spectrum of metformin hydrochloride were given in figure. The UV absorbance wavelength maxima (λ_{max}) of metformin hydrochloride in 0.1 N HCl.

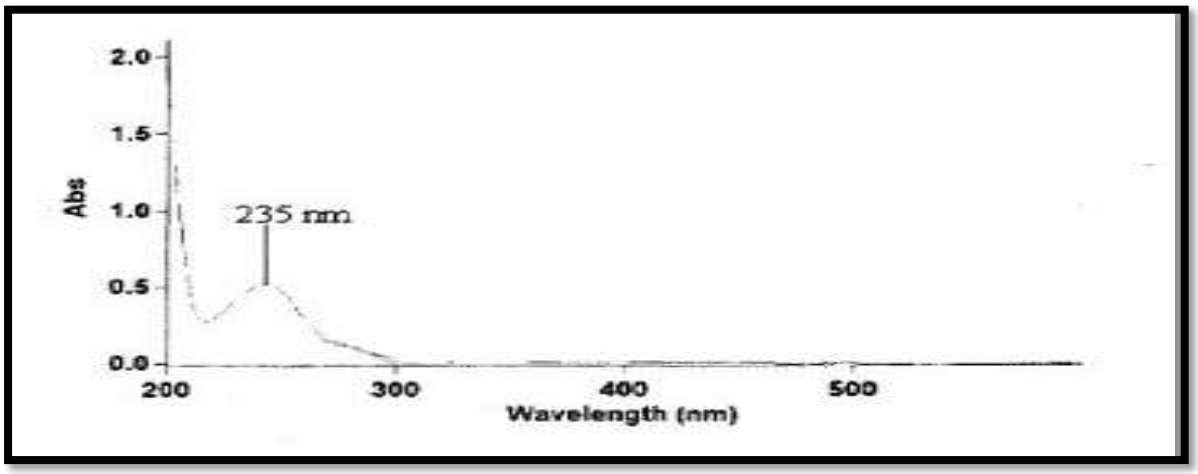

Figure 2: UV absorption spectrum of metformin hydrochloride

IR Spectroscopy:

The infrared spectrum reveals (Figure) that the frequencies and functional group assignments of the major absorption bands, as listed in Table, are consistent with the structure of metformin hydrochloride

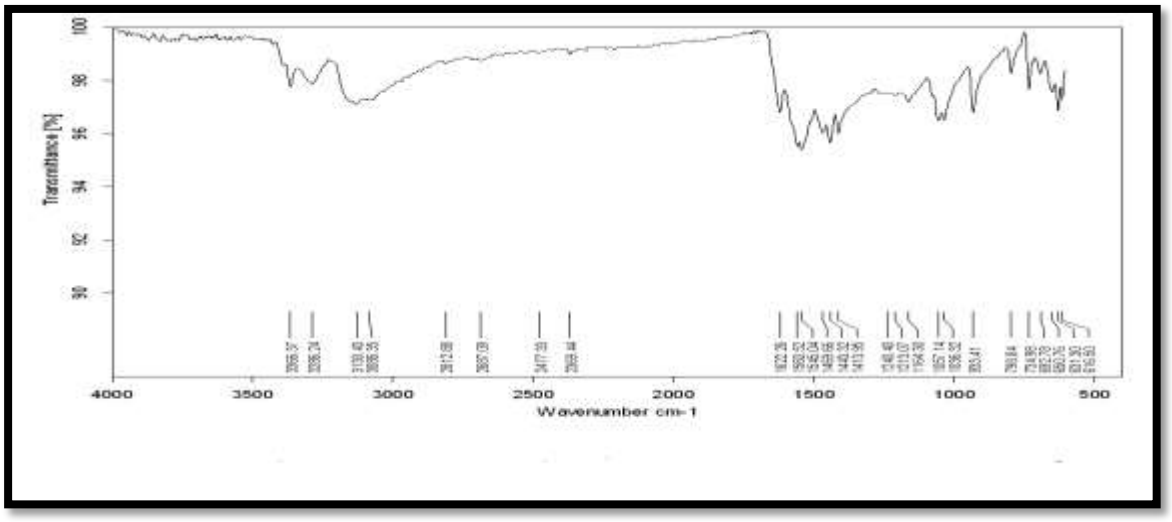

Figure 3: Infrared spectrum of metformin hydrochloride

FTIR studies revealed that metformin hydrochloride showed two typical bands at 3366 and 3286 cm–1 due to N-H primary stretching vibration and a band at 3130 cm–1 due to N-H secondary stretching, and characteristics bands at 1622 and 1560 cm–1 assigned to C=N stretching. No significant shifts of reduction in intensity of the FTIR bands of metformin hydrochloride were observed as shown in figure8

Differential scanning calorimetry (DSC)

The thermal curves of pure components and those of some representative ternary systems are shown in figure

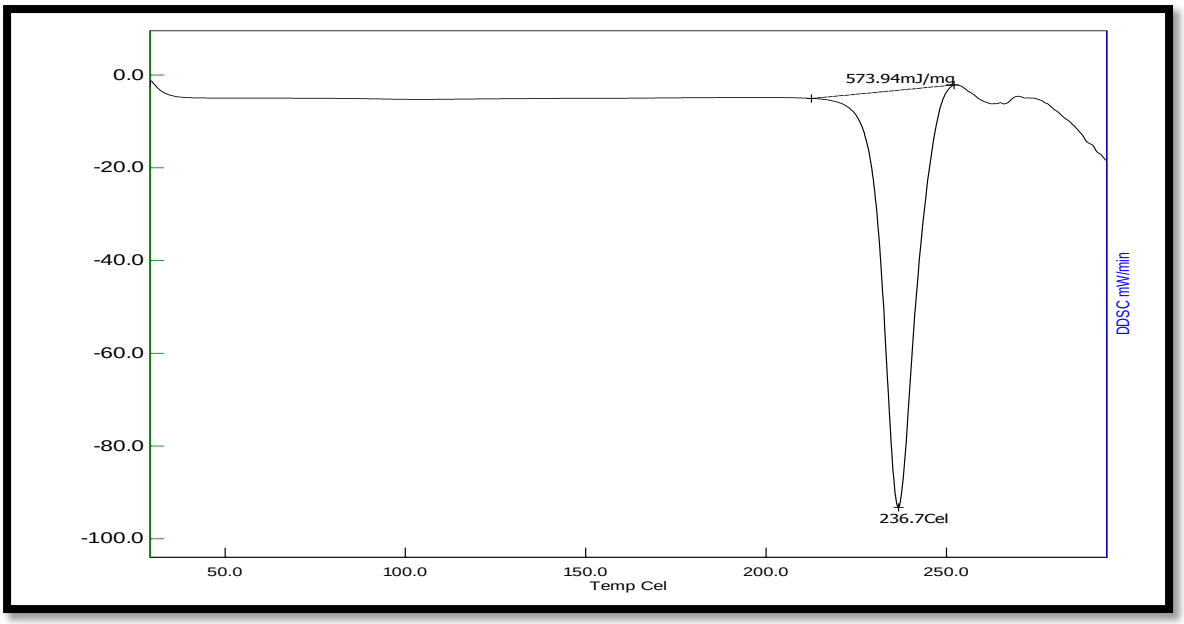

Figure 4: DSC Thermogram of pure metformin hydrochloride

Compatibility studies:

FTIR Study

A comparison between FT-IR spectra of the pure drug and the combination of drug with the polymers, it was observed that all the characteristic peaks of metformin hydrochloride were present in the combination spectra as well; thus indicating the compatibility of the drug with the polymers used. The individual FT-IR spectra of the pure form of metformin hydrochloride, combination of drug and polymers were shown in the Figure. All the characteristic peaks of metformin hydrochloride were present in Spectra thus indicating compatibility between drug and excipients.

DSC study

DSC has been proposed to be a rapid method for evaluating physicochemical interactions between components of the formulation through the comparison of thermal curves of pure substances with the curve obtained from a 1:1 physical mixture and, therefore, select adequate excipients with suitable compatibility. The DSC curve of pure metformin exhibited an initially flat profile, followed by a single sharp endothermic peak representing the melting of the substance in the range 223–237 ºC (T onset = 231.2, T peak = 233.33 and ΔH fusion = -313.51 J/g). There was no shift in the endotherms in the drug–excipient mixtures indicating compatibility of the drug with all the excipients. The comparative DSC thermograms of the drug, okra and fenugreek and drug–excipient mixtures are depicted in Fig.

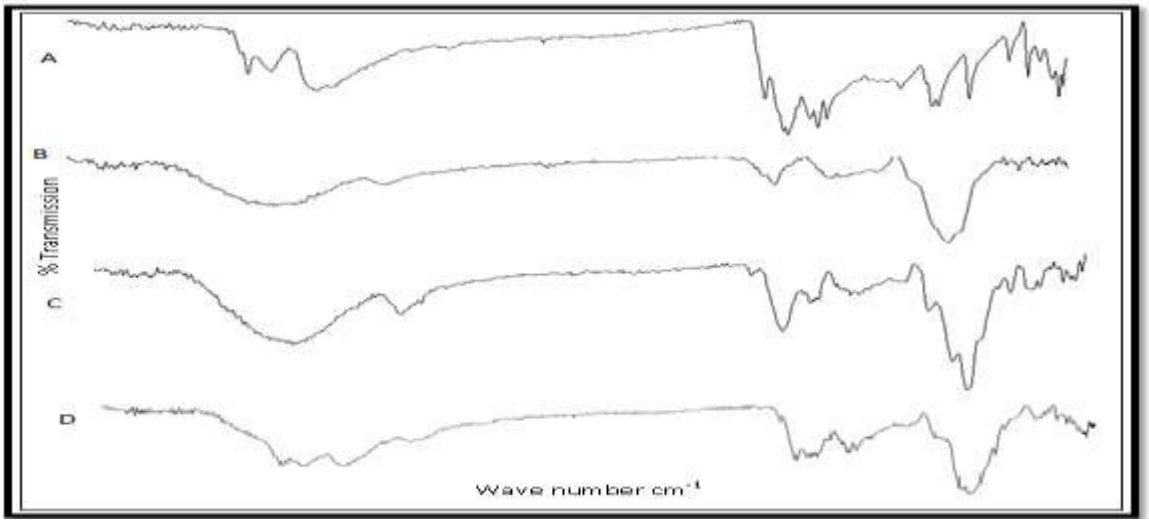

Figure 5:Infrared spectrum of A drug, B okra, C fenugreek, D Physical mixture

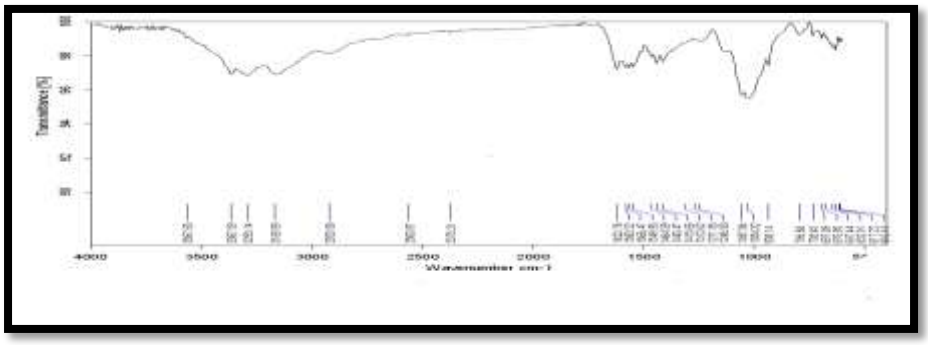

Figure 6: Infrared spectrum of physical mixture of drug with okra and fenugreek

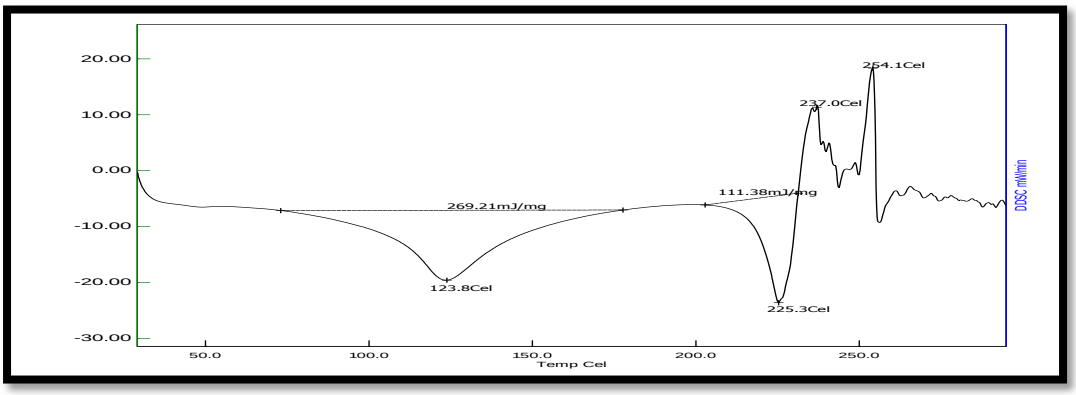

Figure 7: DSC Thermogram of metformin hydrochloride

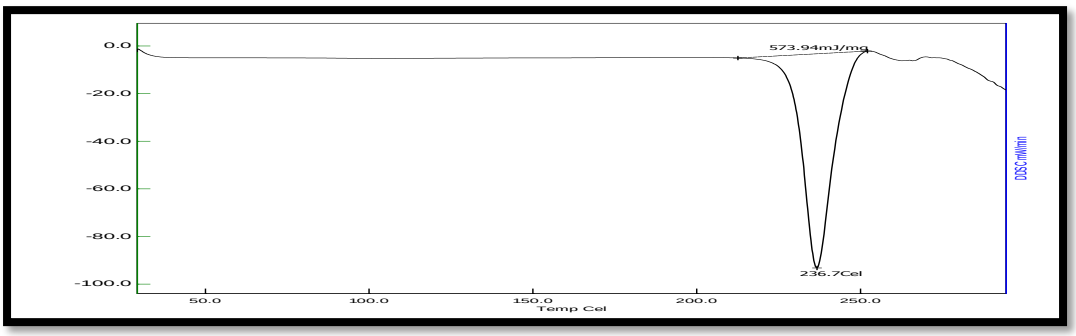

Figure 8: DSC Thermogram of mixture of drug and polymers

The thermal curves of both binary and ternary mixtures, obtained by simple blending corresponded to the superimposition of those of the single components, indicating Figure. Each point represents mean ± SD, n=3 the absence of solid-state interactions and allowing assessment of drug–polymers compatibility in all the examined formulations. As a further confirmation of the absence of any incompatibility problem, no variations in the thermal behavior of samples of binary and ternary combinations were observed after their tableting and subsequent powdering. Thus no definite solid-solid interaction could be concluded Examination of all the DSC thermograms

Standard calibration curve of metformin hydrochloride:

The λ max of Metformin HCl in simulated gastric fluid was found to be 230 nm. The absorbance values are tabulated in Table 2. Metformin obeyed Beer's law in the concentration range of 2-12 μ g/ml with regression coefficient of 0.9994. The standard calibration curve of Metformin HCl is shown in Figure.

Calibration curve of Metformin in 0.1 N HCl

The calibration curve for metformin in 0.1 N HCl was linear in the concentration range of 2-12 (µg/ml)

Table 6: Absorbance of standard solutions of metformin HCl in 0.1N HCl at 235 nm

Sr.no.	Concentration (µg/ml)	Absorbance at 235nm
1	0	0
2	2	0.163
3	4	0.321
4	6	0.481
5	8	0.634
6	10	0.792
7	12	0.956

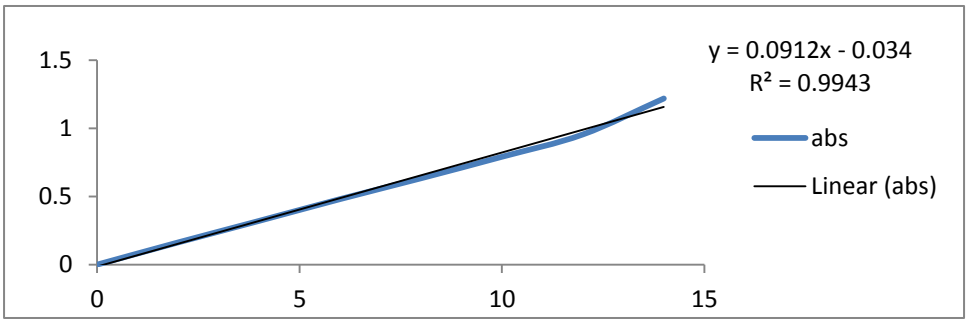

Figure 9: Calibration curve of Metformin in 0.1 N HCl

Correlation coefficient (r^2)=0.994

Equation for regressed line: y=0.0912x -0.034

Where X=value for concentration

Y= value for Absorbance

0.091= slope for regressed line

Drug content

Table 7: Drug content of metformin hydrochloride floating tablets

Formulation code	Uniformity of drug content(%)
F1	98.21
F2	99.23
F3	99.45
F4	98.69

F5	**100.76**
F6	101.28
F7	98.33
F8	99.34
F9	97.30
F10	98.43

From above result, it concluded that the batch F5 showed higher drug content and percentage drug release as compared to other batches. Therefore batch F5 considered for further study.

Evaluation parameter of prepared granules

Table 8: Evaluation parameter of prepared granules.

Batch	Angle of repose	Bulk Density (g/cm^3)	Tapped Density (g/cm^3)	Compressibility Index (%)	Hausner's Ratio
F1	28.32±0.41	0.57±0.012	0.63±0.055	09.52±0.88	1.10±0.025
F2	27.32±0.21	0.55±0.014	0.65±0.028	15.38±0.42	1.18±0.015
F3	31.29±0.18	0.56±0.015	0.66±0.032	15.15±0.62	1.17±0.028
F4	28.34±0.34	0.58±0.014	0.67±0.031	13.43±0.57	1.15±0.023
F5	**33.45±0.21**	**0.54±0.012**	**0.68±0.037**	**20.51±0.39**	**1.25±0.045**
F6	30.12±0.87	0.45±0.018	0.62±0.034	27.83±0.85	1.37±0.048
F7	29.32±0.32	0.48±0.019	0.60±0.021	20.32±0.32	1.25±0.051
F8	32.23±0.15	0.51±0.021	0.61±0..022	16.39±0.58	1.19±0.063
F9	30.32±0.23	0.55±0.045	0.62±0.034	11.25±0.92	1.12±0.045
F10	29.87±0.19	0.52±0.082	0.59±0.021	11.84±0.43	1.13±0.065

From table 8 it can be concluded that batch F5 shows good flow property as compared to other batches. Therefore, batch F5 was optimized for further study.

Formulation of metformin floating matrix tablet

Table 9: Evaluation of post compression parameter of floating matrix tablet

F1	3.9±0.22	4.8±0.27	890±0.25	0.12	23.25± 1.50
F2	5.32±0.22	5±0.5	891.4±0.27	0.45	34.00± 2.50
F3	6.2±0.35	4.8±0.27	885±0.23	0.7	73.25±4.75
F4	6.4±0.27	5.4±0.44	890±0.21	0.21	100.75±6.25
F5	**6.4±0.22**	**5.5±0.44**	**898±0.30**	**0.65**	**16.00±1.50**
F6	3.4±0.22	5.2±0.27	891±0.16	0.37	45.32±1.25
F7	5.2±0.27	5.4±0.22	893±0.31	0.80	116.50±4.75
F8	5.32±0.22	5±0.5	891.4±0.27	0.47	72.50±2.00
F9	4.92±0.43	4.9±0.3	894±0.29	0.54	31.25±2.50
F10	5.32±0.83	4.8±0.8	893±0.35	0.58	52.50±4.25

All values are mean ±SD, (n=3)

From the results of the uniformity of weight, hardness, thickness and friability, Buoyancy lag time of the formulated tablets are given in table. All the test product complied with the official

requirement. The friability indicates that the tablet are compact and hard. From table it can be concluded that the batch F5 showed higher drug content and percentage drug release as compared to other batches. Therefore batch F5 used for further study. Carbon dioxide is formed within the tablet containing effervescent agent when it is brought in contact with acidic medium. The low density as well as gelling capacity of Natural polymers, helps the tablet to float by entrapping the gas in the gel network. On immersion in 0.1 N HCl at 37°C, the tablets floated and remained buoyant without disintegration.

From the results of total floating time it can be concluded that all batches showed good duration of floating i.e. floating time more than 10 hours. This may be due to the amount of polymer and gas generating agent being constant.

In vitro buoyancy study

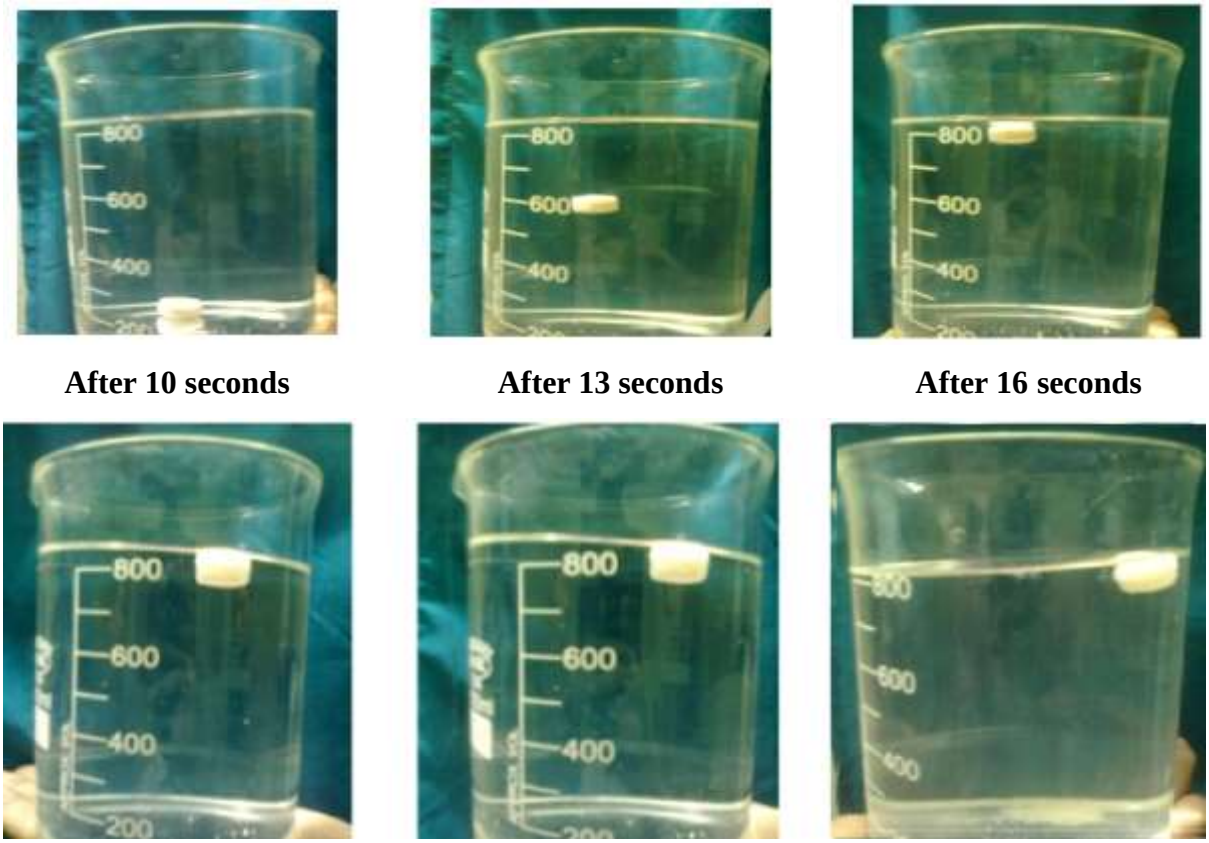

Figure 10: Photographs taken during in vitro buoyancy study of formula F5 in 900 mL 0.1N HCl at different time intervals.

All the tablets prepared by effervescent approach. Sodium bicarbonate was added as a gas-generating agent. Sodium bicarbonate induced CO2 generation in the presence of dissolution medium (0.1 M HCl). Generated gas was trapped and protected within the gel formed by hydration

of polymer, decreasing the density of the tablet. As density of the tablet falls below one the tablet became buoyant. Floating lag times were in the range of 16 to 116 sec.. On the other hand, combination of okra and fenugreek gum showed decrease in floating lag time and increased floating duration time. This might be due to viscous nature of guar gum, which maintains the integrity of the tablets for longer duration by reducing the effect of erosion thus resulting in increase in floating time. The selected formulation F5 showed floating lag time 16 sec, Fig. 15, with floating duration time >8h.

Swelling Index of all the formulated batches.

Swelling ratio describes the amount of water that is contained within the hydrogel at an equilibrium and is a function of the network structure, hydrophilicity and ionization of the functional groups. Swelling study was performed on all the batches for 5 hours. The results of swelling index is given in Table, while the plot of swelling index for the optimized batch against time (hr) is depicted in Figure .

Table 10: Swelling index of all the formulated batches.

Time (hrs)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
1	40 ± 0.77	39.2 ± 1.0	30 ± 0.84	27.56 ± 0.88	**32.56 ± 1.12**	29.56 ± 0.89	26.34 ± 0.57	28.45 ± 0.93	29.34 ± 0.88	28.45 ± 0.93
2	51.98 ± 0.77	43.56 ± 1.15	36.32 ± 1.04	41.23 ± 0.87	**48.23 ± 0.94**	42.2 ± 1.18	38.32 ± 0.96	34.43. ± 0.54	39.32 ± 0.86	41.23 ± 1.29
3	64.76 ± 1.75	56.23 ± 1.05	45.23 ± 1.04	57.23 ± 0.93	**61.23 ± 0.59**	53.5 ± 0.96	57.65 ± 0.74	46.23 ± 0.55	51.34 ± 0.93	52.52 ± 0.83
4	79.87 ± 0.50	68.21 ± 0.92	60.11 ± 0.91	74.2 ± 0.97	**81.2 ± 0.93**	61 ± 1.28	74.98 ± 0.65	62.11 ± 0.89	65.45 ± 1.28	70.32 ± 0.55
5	87.43 ± 0.99	80.34 ± 1.00	72.34 ± 1.01	83.34 ± 1.10	**91.34 ± 1.00**	76.45 ± 1.00	88.45 ± 0.89	78.34 ± 0.99	79.43 ± 0.99	82.34 ± 0.32

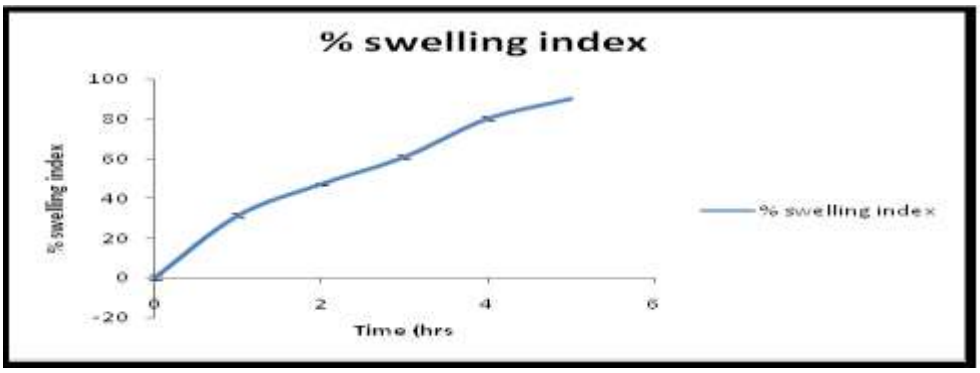

Figure 16: swelling index for the optimized batch

From the results it can be concluded that swelling increases with time because polymer gradually absorbs water due to hydrophilicity. The outermost layer of polymer hydrates, swells and a gel barrier is formed at the outer surface. As the gelatinous layer progressively dissolves and/or is dispersed, the hydration swelling release process is repeated towards new exposed surfaces, thus maintaining the integrity of the dosage form. In the present study, From Table it is evident that swelling index was highest for tablets of batch F5. This showed that Natural polymers had an influence on swelling process.

In vitro drug release study of floating matrix tablets

In vitro drug release profile of tablets from each batch and marketed product, using USP dissolution apparatus 2 are shown in Table 16,17. The plot of % cumulative drug released Vs. time (hr) was plotted for all formulations and depicted as shown in Figure 17,18.

Table 11: Cumulative % drug release of all batches F1 to F5

% cumulative drug release					
Time (h)	**F1**	**F2**	**F3**	**F4**	**F5**
1	8.72±1.09	8.734±1.26	6.747±0.99	6.72±1.14	5.715±0.78
2	13.33±1.24	17.43±2.17	10.33±2.57	16.33±3.37	11.32±1.10
3	33.14±2.23	23.45±3.02	15.49±3.98	28.14±3.42	19.62±0.84
4	44.71±2.07	28.62±3.90	24.83±2.72	44.71±3.56	33.32±1.41
5	52.09±3.07	37.55±3.09	28.83±3.28	52.09±2.14	46.71±1.10
6	60.05±0.89	44.34±2.45	39.34±3.74	60.05±1.79	59.09±1.38
7	64.22±1.33	52.68±2.63	49.88±2.48	64.22±1.22	72.05±0.55
8	63.87±1.29	61.56±3.02	68.37±1.93	72.35±0.32	81.58±1.08

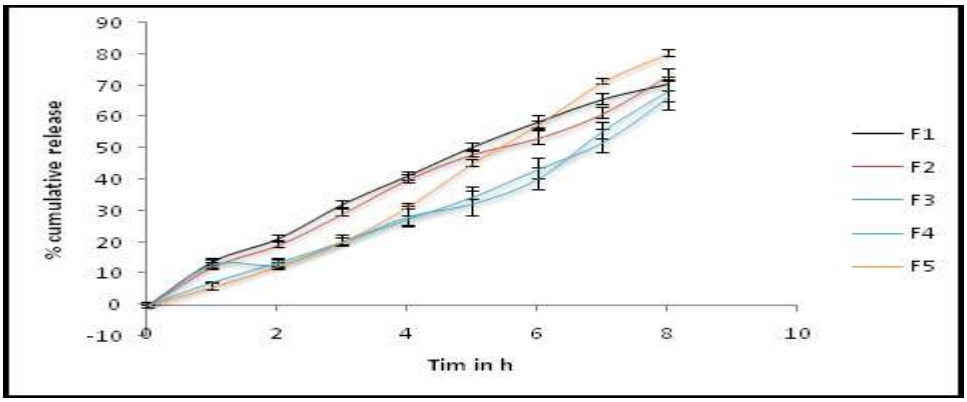

Figure.11: Comparative in vitro dissolution profile of F1 to F5 is shown graphically

Table 12: Cumulative % drug release of all batches F6 to F10

% cumulative drug release					
Time (h)	**F6**	**F7**	**F8**	**F9**	**F10**
1	8.705±1.13	8.715±1.25	8.715±0.006	11.734±1.14	8.715±1.69
2	19.84±2.18	21.62±0.577	21.62±2.37	19.43±1.20	21.62±1.32
3	33.22±3.11	33.22±2.17	33.32±0.85	27.45±2.91	33.32±4.44
4	44.71±0.54	44.71±0.61	44.71±2.91	34.62±3.90	44.71±3.94
5	52.02±0.83	52.09±0.84	52.09±2.97	41.55±2.60	52.09±2.12
6	60.05±1.32	60.05±0.85	60.05±4.41	49.34±2.88	60.05±1.88
7	64.22±1.10	71.58±0.66	71.58±4.21	57.68±4.25	71.58±0.30
8	67.81±1.56	74.34±0.577	79.30±2.07	62.56±1.46	79.30±0.55

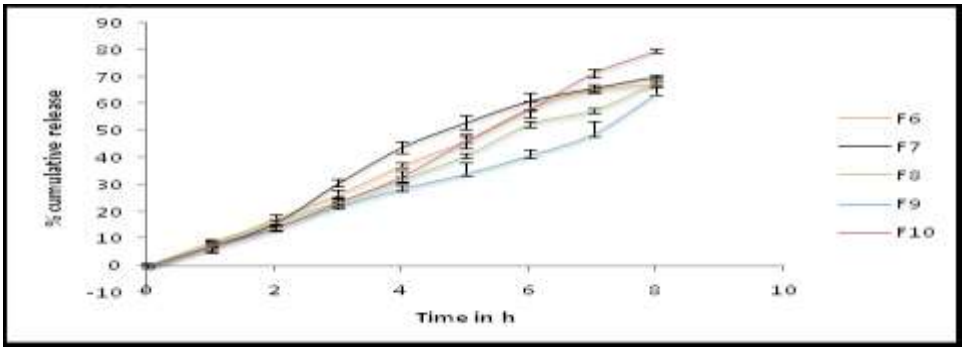

Figure.12 :Comparative *in vitro* dissolution profile of F6 to F10 is shown graphically

In case of mixed hydrophobic/hydrophilic matrix system the drug release involves Penetration of solvent into the matrix, 2) hydration and swelling of polymer and dissolution of active ingredients, 3)transfer of dissolved drug and soluble matrix components into the bulk. The release rate in f5 containing natural polymers showed better effect as compared to other batches.

In the current study, variable drug release profiles were successfully studied. The influence of Natural polymers (okra and fenugreek) ratio on the release of metformin HCl from the floating tablets in 0.1 N HCl (pH 1.2) at 37 ± 0.5^0C was shown in Fig19. It is clear that all formulae succeeded in controlling the rate of drug release for 10 h. However, the drug release rate was

dependent on the concentration of the natural polymers. Under experimental conditions, the drug diffusivity in natural polymer matrix, formula F5, was much lower. Indeed, formula F5 showed a significant drug release rate . The higher viscosity of natural polymers would promote the formation of highly viscous gels upon contact with aqueous fluids. This would promote retardation of the drug release rate. The drug release from polymer matrices is sequentially governed as follows: (i) At the beginning, steep water concentration gradients are formed at the polymer/water interface resulting in water imbibition into the matrix. (ii) Due to the imbibition of water, polymers swells resulting in dramatic changes of polymer and drug concentrations and increasing dimensions of the system. (iii) Upon contact with water, the drug dissolves and diffuses out of the device due to concentration gradients. (iv) With increasing water content, the diffusion coefficient of the drug increases substantially. It is worth to note that, a burst effect was observed with all formulations. This could be due to the fact that the gel layer, which controls the drug release rate, needs some time to become effective. The rapid drug dissolution from the surface of the tablets could be another possible explanation. Interestingly, this effect was less predominant with those formulae containing higher okra and fenugreek ratios; F5. The resulting gel-like networks surrounding these matrices, upon contact with aqueous media, would produce strong surface barriers that would effectively reduce the burst drug release. Taking into consideration the goal of the work of achieving a compromise between excellent floating behaviour (very short floating lag time and prolonged floating duration) and sustained drug release characteristics, formula F5 was chosen for further studies

Comparison of optimized formulated batch with marketed formulation and HPMC

Conventional oral SR formulation releases most of the drug content in colon, after crossing the absorption window. Since metformin hydrochloride has poor colonic absorption therefore there is very less utilization of the drug released. Hydrodynamically balanced dosage forms on the other hand are retained in stomach until all the drug is released for the desired period of time. Thus there will be complete utilization of the drug, increase in bioavailability, reduced frequency of dosing, reduced side effects and subsequently enhanced patient compliance.

Table 13: Comparison of optimized formulated batch with marketed formulation and HPMC polymer.

Time (h)	Optimized batch	HPMC	Marketed product (Gluformin XL 500)
1	15.6	12.4	9.2
2	23.6	21.2	19.4
3	40.3	33.5	34.45

4	48.7	44.2	45.5
5	59.09	53.65	54.76
6	63.5	60.6	61.5
7	72.05	69.98	72.87
8	80.1	79.7	78.2

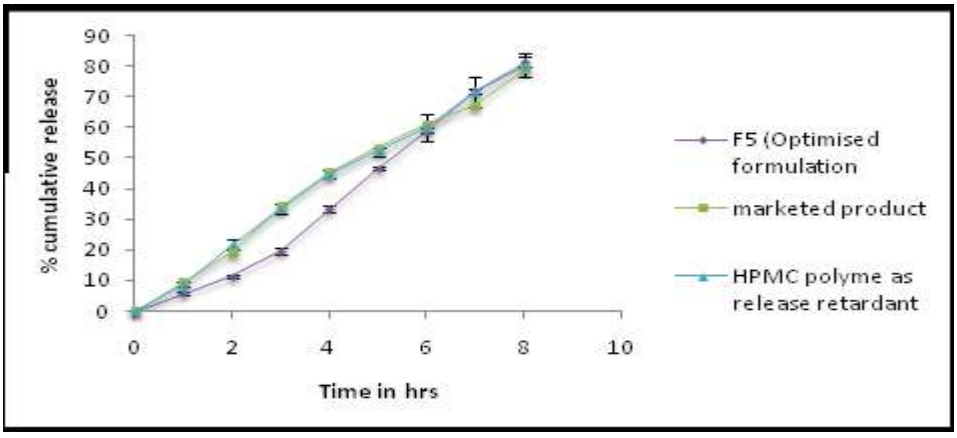

Figure 12: Comparative Dissolution profile of optimized batch with marketed product and HPMC polymer as release retardant

The promising formulation (F5) as found by evaluation studies was compared with marketed products of metformin, and sustained release tablet. The cumulative % drug release values are recorded in Table 7 and 10. At the end of 10 hours marketed metformin SR tablet showed 78.21% drug release, while formulation F5 showed 80.2%. Comparative *in vitro* dissolution profile of marketed sustained release product and HPMC polymer and the formulated batch (F5) is shown graphically in Figure 19. From the results it can thus be concluded that the drug released by formulation F5 (80.2%) is more bioavailable in comparison to 78..4.% release of marketed metformin product XL 500

Model Fitting of Release Profile of batches F1 to F10 using Different Models

Table 14

Formulation code	Zero order (R^2)	First order (R^2)	Higuchi (R^2)	Korsmeyer peppas (R^2)	Diffusional Exponent (n)	Order of release
F5	0.990	0.969	0.938	0.899	0.802	Non Fickian

Figure 13: Zero order release model

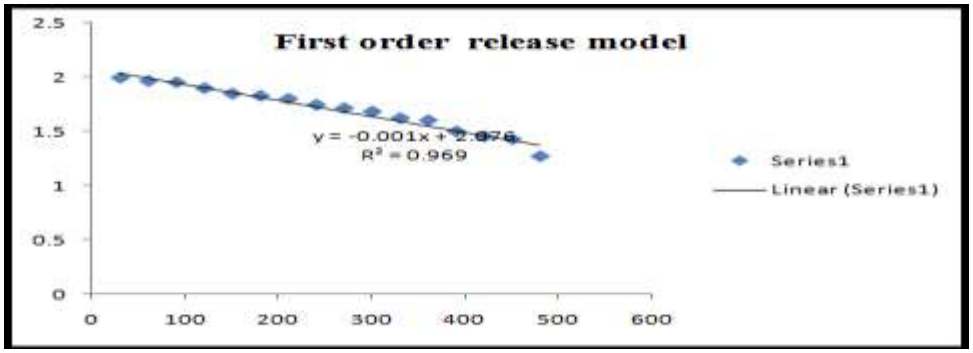

Figure 14: First order release model

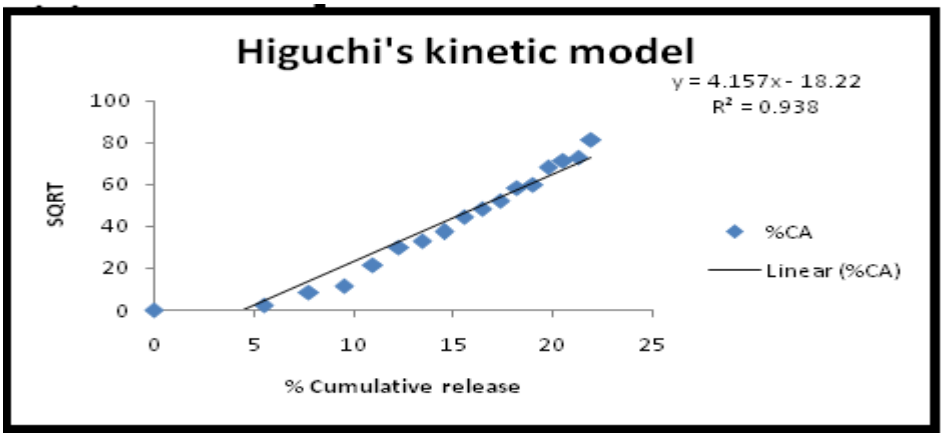

Figure 15: Higuchi's kinetic model

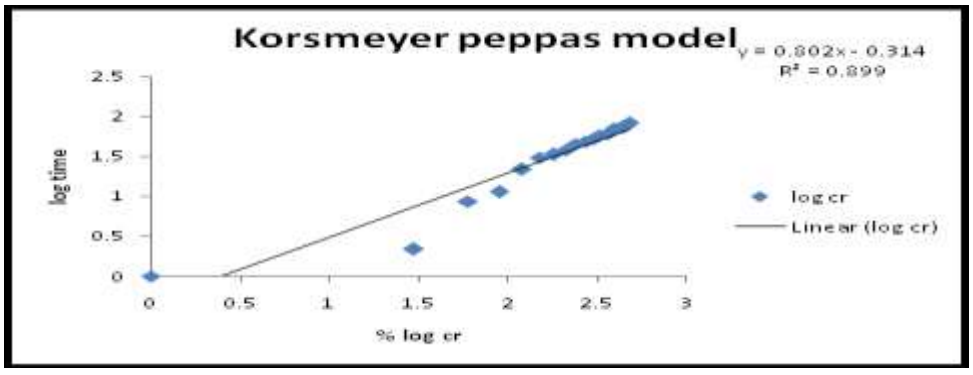

Figure 16: Korsmeyer peppas model

The results of dissolution data were fitted to various drug release kinetic equations. Correlation coefficient (r) value was highest for zero order release equation in all batches, thus indicating zero order release kinetics. The kinetic values obtained for different formulations are tabulated in Table 19. The dissolution data obtained from this was subjected to kinetic treatment. Correlation coefficient (r) value was highest for zero order release equation in all batches thus indicating **zero order** release kinetics.

Stability Studies

Accelerated stability study of an optimized batch of floating matrix tablet (F5) was carried out as per ICH guidelines. Tablets were kept for stability studies at 40 ± 2° C and 75 ± 5 % RH in an environmental test chamber (Thermolab, India) for a period of 3 months. These samples were kept in glass vials without rubber plugs. After 90 days, the samples were analysed for the in vitro drug release.

Table 15 .In vitro release profile of stability batch

Sr.no.	Time in min	% cumulative release
0	0	0
1	30	2.1758±1.30
2	60	5.7153±1.25
3	90	9.5153±1.27
4	120	13.828±2.17
5	150	18.612±0.47
6	180	21.623±0.61
7	210	26.185±1.10
8	240	36.234±0.84
9	270	41.234±1.26
10	300	46.654±0.85
11	330	53.845±0.64
12	360	61.637±0.66
13	390	66.768±0.58
14	420	74.485±0.57
15	450	77.485±0.54
16	480	80.345±1.23

All values are mean ±SD, (n=3)

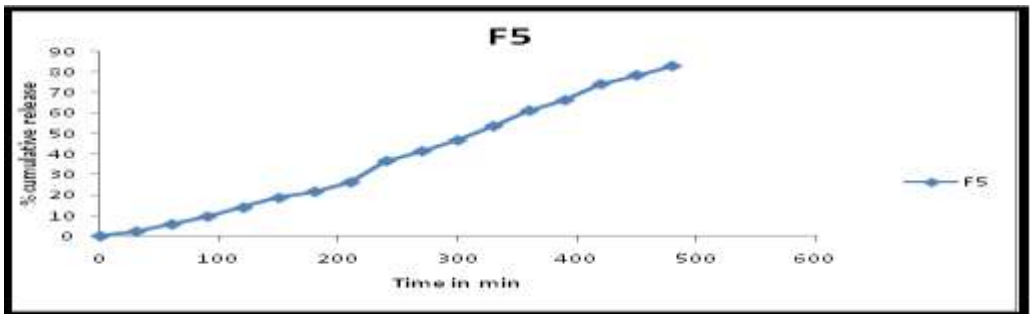

Figure 17: In vitro drug release profile of stability batch

Results reveal no significant changes in appearance, floating test and drug content. There was no much variation either in hardness, friability and drug release in formulations kept at the three storage conditions. Thus from the tables formulations were stable at all three storage conditions up to a period of 30 days. There was no significant change in F5 samples stored in refrigerator. Thus from the above results it can be concluded that metformin floating tablets are stable when stored at 2-8°C. The results indicate that there wasn't significant changes in the in vitro drug release of metformin hydrochloride from the prepared tablet in formulation.

CONCLUSION

Promising controlled- release floating matrix tablets of metformin hydrochloride using natural polymers were successfully formulated by effervescent technique. 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 esculantus* and *Trigonella foenum graceum* 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. Okra and fenugreeek has swellable property; hence it can be used as a polymer in the development of a Gastroretentive drug delivery system. With optimal floating time, the metformin hydrochloride floating tablets with okra and fenugreek help in increasing the residence time of metformin hydrochloride in stomach. This further helps to decrease the frequency of dosing, thus minimizing the side effects caused due to metformin hydrochloride where it is known to cause damage to the kidneys. In addition, since both the gum is easily available and the extraction includes very fewer steps, it is comparatively economical for bulk production of the drug. Comparative study with of sustained release tablet of metformin hydrochloride by using combination of natural polymers (okra and fenugreek) showed that the optimized formulation F5 had same control over release rate in comparison to the available marketed formulation and HPMC

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