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Okra Gum from *Abelmoshus esculentus* fruit pods: Isolation, Characterisation and Utilisation for the Formulation of Seaweed alginate based Antidiabetic Drug Loaded Gelibeads

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Abstract
The present work is aimed to isolate and characterise of Okra Gum from *Abelmoshus esculentus* unripe fruit pods. Okra gum was incorporated with seaweed alginate and antidiabetic drug loaded gelibeads were prepared by ionotropic gelation method. Biosynthetic polymers were also used to formulate gelibeads using calcium chloride as the crosslinking agent. The Metformin HCl- Okra gum compatibility studies were performed using FTIR. The prepared gelibeads showed good micromeritics properties. Six formulations were prepared by varying the drug polymer ratio. Drug release from Gelibead formulations with a Drug Okra gum in the 1:1 ratio showed good *in vitro* dissolution profile. Gastro-retentive mucoadhesive properties of the gelibeads were proved by in vitro wash off test. Okra gum was a proven antidiabetic molecule when incorporated with Metformin HCl gives a good synergistic activity in the treatment of Diabetes mellitus. The prepared gelibeads will serve as a novel controlled release formulations as a once daily dosage form in the treatment of Diabetes mellitus.

Keywords: okra gum; gelibeads; sodium alginate; diabetes mellitus; ionotropic gelation

Introduction

Gastroretentive mucoadhesive gelibeads was widely accepted as a means to targeted, site specific, and controlled drug delivery systems. The formulation of mucoadhesive gelibeads often require a compatible polymer as a drug carrier [1]. The utilisation of natural polymers is preferred over synthetic and biosynthetic polymers because they are proved to non-toxix, inert and safe. Okra mucilage gum is derived from the unripe fruit pods of the plant *Abelmoschus esculentus*. In this context Okra gum, a polymer has attracted major attention in the field of novel drug delivery system. It is biocompatible, biodegradable and bioadhesive at physiological pH and possesses hydroxyl (OH) group which can give rise to hydrogen bonding. Chemically it is a polysaccharides consisting of galactose, rhamnose, and galacturonic acid (Fig. 1). It is hygroscopic in nature and need to be stored in air-tight containers. It is soluble in warm water, slightly soluble in cold water and insoluble in benzene, ether, chloroform, n-butanol, ethanol, acetone, glycerine, and paraffin. A 0.25% w/v solutions of mucilage was found to be 0.0405 joule/m. Brownish colour, Odourless, Tasteless, The powder characteristics reveals that it is rough and irregular in shape. Total ash, acid insoluble ash and water soluble ash were found 7.53%, 0.93% and 4% respectively. Okra mucilage gum found to be show Antidiabetic, Antioxidant, Antiulcer, Hypolipidemic, and Antimicrobial activity [2, 3]. Metformin is a biguanide derivative used in the treatment of type II diabetes mellitus (Non-Insulin Dependent Diabetes mellitus) and chemically known as 1,1-Dimethyl biguainide Hydrochloride (Fig 2). It exerts pharmacological action by the decreasing peripheral insulin resistance and hepatic glucose output. The absolute oral bioavailability is 40–60% and the mean plasma elimination half-life was 6 h. Hence a multiple administration in a day is unavoidable [4]. A Controlled release site specific dosage form is the need of the hour to prolong the duration of action and increase the patient compliance [5].

Mucoadhesive Gelibeads

Gelibeads are microparticles composed of a polymeric matrix with the uniform dispersion of active drug. Sustained release properties, higher drug loading at the target tissue, and promising bioavailability are the advantages of gelibeads. Convention synthetic polymers used for the formulation of metformin tablets increase the production

cost. Moreover Okra gum is a proven for its antidiabetic potential. When it is combined with Metformin HCl it gives synergistic effect in the management of diabetes mellitus [6, 7].

Materials and Method

The unripe fruits of *A. esculentus* (usually known as bhindi and Ladies finger) were purchased from local market (Salem, India). Metformin Hydrochloride gift sample being collected were stored in airtight container in desiccator. Sodium alginate , Calcium Chloride, Formaldehyde, Ethanol (95%v/v), acetone used, Hydroxy Propylmethyl Cellulose (HPMC), Xanthan Gum, Chitosan used for extraction, characterization of Okra gum and formulation of drug loaded gelibeads were of analytical reagent grade.

Instruments Used

Temperature regulated Magnetic stirrer, Dissolution apparatus, Systronics UV-Vis Double beam Spectrophotometer - 2202, Perkin Elmer FTIR Spectrophotometer (Spectrum 100) were used for the extraction of Okra gum and formulation of Metformin HCl gelibeads.

Extraction of Okra Mucilage

About 1kg of fresh immature fruit of Okra (*Abelmoschus esculentus*) was purchased from a local market of Dharmapuri, Tamilnadu, India. The seeds were removed from the pods, and the fresh immature fruits were sliced, and chopped in to fine pieces and soaked in deionised water. It was boiled at 60^{O}C for 6 hours and cooled at room temperature. The crude mucilage was collected without cell debris. Equal volume of acetone was added to equal volume (1:1) Okra mucilage and the precipitated mucilage was collected. The precipitated gum was washed several times with acetone; the obtained cream colored mucilage was dried in oven and stored in a desiccators. A light brown colored powder was obtained after complete removal of moisture. The dried gum was pulverized using Grinder and screened through 80# 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 8-10% from fruits [8]

Formulation of Okra gum Metformin HCl loaded Gelibeads

Preformulation studies

Prior to the development of the mucoadhesive gelibeads formulation a preformulation study was carried out to evaluate the physic-chemical and compatibility characteristics of the drug and polymer. The pure drug is subjected to the following studies [9]:

- Determination of Meting point
- Determination of Solubility
- Determination of pH
- FTIR Drug Polymer Compatibility Studies

Determination of Melting point

The pure Metformin Hydrochloride was subjected to melting point determination using digital melting point apparatus. The determined melting point was compared w with the melting point of reference standard (Reference IP 2007).

Metformin Hydrochloride API showed a melting point in the range of 216-220°C. It is compared the melting point of reference standard. The determined Melting point coincides with the reference standard and the Metformin API was confirmed for its identity

Determination of Solubility

The solubility of Metformin Hydrochloride was determined in solvents of different polarities. The solubility of Metformin Hydrochloride is usually determined by the equilibrium solubility method, which employs a saturated solution of Metformin Hydrochloride, obtained by adding an excess amount of Metformin Hydrochloride in the solvent to promote drug precipitation. There was stirred in a magnetic stirrer for 2 hr until equilibrium was reached. The mixture was filtered and amount of Metformin Hydrochloride was determined by using UV spectrophotometer at 232nm.

Determination of pH

A specified amount of Metformin Hydrochloride API was dissolved in water.

The pH of the sample was determined by using a calibrated digital pH meter. The pH of the sample was determined. Metformin Hydrochloride (API) showed a pH of 6.8. It was compared with the pH of the reference standard and confirmed for its identity.

FTIR Drug Polymer Compatibility Studies

The *FT-IR* analysis of the Metformin Hydrochloride was carried out for qualitative compound identification. The *FT-IR* spectra for pure drug and with other excipients was obtained by pressed pellet technique and was determined by Perkin Elmer (Spectrum 100) *FT-IR* spectrophotometer in the wave number region of 4000-400 $cm^{-1.}$ The major peaks of the Metformin Hydrochloride was not affected when the comparing the drug polymer physical mixture with that of the pure Metformin Hydrochloride (Fig 4-6).

Evaluation of Okra Gum

Okra gum extracted from fresh pods of *A. esculentus* was subjected to chemical test to study the and confirm the presence of basic carbohydrate principle, purity, solubility behavior, pH and organoleptic properties

Determination of carbohydrates presence in Okra gum

Specified amount of water extract of mixed with Molish's reagent and mixed thoroughly. It was followed by addition of H_2SO_4. Appearance of violet colour ring at junction of two liquids confirmed the presence of carbohydrates [10]

Determination of purity of Okra gum

Purity of the extract was determined by performing chemical tests for alkaloids, amino acids, proteins, gum, fats, and tannins [11].

Organoleptic evaluation of isolated Okra gum

Isolated mucilage was characterized for organoleptic properties such as colour, odour, taste, fracture and texture [12].

Solubility behavior

Dry polymer powder was shaken with different solvents and further solubility was determined [13].

pH of Okra gum

A 1% w/v solution of Okra gum mucilage powder in water was prepared and the pH was determined by a using digital pH meter [14].

Formulation of Metformin HCl Gelibeads

Formulation and Metformin Hydrochloride loaded Seaweed alginate – Okra gum composite mucoadhesive gelibeads. Mucoadhesive gelibeads of Metformin Hydrochloride was prepared as per the formulation design depicted in the Table. 1

Inotropic gelation method

Aqueous phase was formed by slowly adding 2% sodium alginate in 20ml of distilled water and stirred with magnetic bead at constant temperature of 50-60°C. To the above mixture Okra gum powder at different concentration was added as per the formulation design given in the Fig No.7 with continuous stirring. Accurately weighed 500mg of Metformin Hydrochloride (drug) was added in each formulation with continuous stirring at 35-40°C. Stirring is continued to dissolve and make a uniform viscous solution. The mixture was sonicated for 15 m minutes to remove entrapped oxygen. Prepare a 5% w/v solution of calcium chloride in deionizer water and sonicated for ten minutes for complete dissolution. Aqueous phase was slowly added through 22# needle in the 3 and 5% calcium chloride solution within 15min with continuous stirring through magnetic bead at room temperature. The prepared beads were given a curing time of 30min in the cross linking solution for the completion of formulation process. The procedure was repeated for all the mucoadhesive microsphere formulations. After the stipulated curing time the gelibeads were filtered and washed two times with 50 ml distilled water and collected. Collected gelibeads were dried in a Hot air oven at 37-40°C till completely dried [15].

Evaluation of Metformin Gelibeads

The formulated mucoadhesive and floating gelibeads of Metformin Hydrochloride was characterized by performing the following evaluation methods to select the ideal formulation for further studies [16].

The following evaluation methods were implemented to characterise the gelibeads:

1. Angle of repose
2. True density
3. Bulk density
4. Tapped density
5. Percentage yield
6. Entrapment efficiency
7. *In-vitro* wash off test for mucoadhesivity
8. *In-vitro* dissolution test

Flow properties

Flow of gelibeads in an irregular manner from a hopper during tableting and capsule filling process affects the content uniformity and causes weight variation. Flow property depends on particle size, shape, porosity and density of the gelibeads. The flow properties of gelibeads were studied by determining various parameters like the angle of repose and bulk density. Bulk density is determined using digital bulk density apparatus (Electrolab, India).

Angle of repose

Angle of repose is the maximum angle possible between the surface of the pile of the powder and the horizontal plane. Angle of repose is used to measure the flow characteristics of gelibeads (Table.4). Fixed-base cone method was utilized to determine the angle of repose using the formula

$$t\theta = \frac{r}{h}$$

Where

$t\theta$ =Angle of repose

r =Radius

h = Height

Bulk Density

Bulk density is defined as the weight per unit volume of material. Bulk density is primarily used for powders or pellets. The test can provide a gross measure of particle size and dispersion which can affect material flow consistency and reflect packaging quantity. Each experiment was conducted in triplicate. (Table.5)

Percentage yield

All the dried mucoadhesive and floating gelibeads were accurately weighed separately (Tab.No-6). The percentage yield was calculated by multiplying the ration of total weight of gelibeads obtained by total weight of drug and polymer added and it was calculated using formula

$$\%\ Yield = \frac{Wt.\ of\ microspheres\ obtained}{Total\ weight\ of\ drug\ and\ polymer} \times 100$$

Drug entrapment efficiency

Drug entrapment efficiency of Metformin Hydrochloride was performed by accurately weighing 100 mg of micro particles and suspended in 100ml of simulated gastric fluid of pH 1.2±0.1 and it was kept for 12hrs. After 12 Hrs it was subjected to stirring for 15mins and filtered. After suitable dilution, Metformin content in the filtrate was analyzed by the developed UV spectrophotometry. The absorbance shown by the seven Metformin Hydrochloride loaded mucoadhesive gelibeads (MFNMA1 – MFNMA7) were determined (Tab.No-7). The measured absorbances were interpolated on the standard curve to get the concentration.The concentration of all the entrapment efficiency was calculated as percentage of drug entrapped in the gelibeads [16]. Encapsulation efficiency was calculated using the following formula

$$Entrapment\ efficiency = \frac{Estimated\ drug\ content}{Theoretical\ drug\ content} \times 100$$

***In vitro* Wash-Off Test**

The mucoadhesive behavior of all the Metformin Hydrochloride loaded gelibeads (MFNMA1 to MFNMA6) formulations were evaluated by an *In vitro* wash-off test method (Table No-8).

Freshly excised piece of goat intestinal mucosa with the dimension of 2 x 2 cm was mounted on a glass slide (3 x 1 inch) with acrylic glue. 50 mucoadhesive gelibeads were spread evenly on the wet rinsed tissue specimen. The tissue set up was made to hung on to the arm of a USP tablets disintegrating test equipment. During the operation of the apparatus the tissue specimen was subjected to experience

slow and regular up-and-down movement in the simulated gastric fluid test fluid (3g of NaCl dissolved in 900ml of 0.1N HCl) at 37± 0.5^0C. The number of gelibeads adhering to the tissue was counted and recored at every 30 minutes interval up to a period of 6 hours. The equipment was stopped after 6 hours and the total no. of gelibeads adhering was counted. The mucoadhesive test was conducted three times [17].

In-vitro dissolution studies for MFN loaded Mucoadhesive Gelibeads

The dissolution test apparatus tank was maintained a simulated temperature at 37± 0.5^0C with the constant rotation speed of 50 rpm. The Simulated gastric fluid (SMG) with the pH 1.2 is used as a dissolution medium. Drug loaded floating Gelibeads formulations equivalent to 100mg of Metformin was slowly spread over the in the dissolution medium fixed with a paddle. Sample was collected at a specified predetermined time interval and to maintain the sink conditions it was replaced with the fresh dissolution medium (Table No-8). The sample was analyzed spectrophotometrically [18].

Results and Discussion

Mucoadhesive Gelibeads of okra gum based Metformin Hydrochloride were prepared by Ionotropic gelation technique and various evaluation parameters were assessed, with a view to obtain oral controlled released of Metformin Hydrochloride for the treatment of diabetes mellitus. Solubility characteristics of Metformin Hydrochloride were performed with different solvents and depicted.

To check the compatibility of the drug with various polymers, IR spectra of drugs, polymers and combinations are shown in Fig No.4-6. The characteristics absorption peaks of Metformin Hydrochloride were obtained. The phytochemical test for the isolated okra mucilage was subjected to identification and purity test. It is shown in Tab. No-2. In the present work, total six mucoadhesive microsphere formulations and were prepared and designated as MFN M1 to MFN F6, the detailed composition is shown in Table No.3-6. The prepared mucoadhesive gelibeads were then subjected to micromeritic study, angle of repose, scanning electron microscopy, drug entrapment efficiency, *in-vitro* wash off test,*in-vitro* byuoncy test, *in- vitro* dissolution and stability studies. Acceptable range of angle of repose is 22º61' to 31º60'. All the formulations showed an angle of repose within the range as shown in Tab. No.3. Formulations MFMA1 to MFN MA6 showed an angle of repose in the acceptable range, which indicates a good flow property. The drug entrapment efficiency of Mucoadhesive microsphere formulations were in the range between 78 % to 91.25%. The results of drug entrapment efficiency are shown in Tab. 7. *In-vitro* wash off study was performed for mucoadhesive gelibeads MFNMA1 to MFNMA6 in 0.1N HCl. It has shown good mucoadhesive property and it is shown in Tab.8. The dissolution studies were conducted for mucoadhesive and floating gelibeads at pH 1.2 dissolution mediumTab No- 8.

The results of the in-vitro dissolution studies of formulation MFN MA1 to MFN MA6 is shown in Table No -9.

Morphology of the mucoadhesive and floating gelibeads were investigated by Optical Microscopy and it was found to be spherical in shape.

Summary

The prime aim of the research is to formulate seaweed alginate okra gum mucilage composite mucoadhesive and floating gelibeads and perform the analysis of Metformin Hydrochloride using a validated FT-IR and UV spectroscopic methods as a novel and green technique Okra gum was was isolated from *A.esculentus* by Hot water extraction method and characterized using chemical methods. Six mucoadhesive and floating gelibeads formulations were prepared by using ionotropic gelation method. The formulations were designed based on the difference in the drug polymer concentration as one parameter and variation in the percentage of the cross linking agent calcium chloride was at 3.0 and 5% w/v solutions. The gelibeads were then characterized for their flow, content, yield, swelling and entrapment efficiency. The mucodhsive gelibeads were tested for its mucoadhesive property by using *in vitro* wash off test.

Conclusion

Blends of *Abelmoshus esculentus* gum and sodium alginate are promising polymer combination for the preparation of controlled-release site specific dosage forms. The mixture of the Okra gum and sodium alginate produced gelibeads with controlled release properties. The gelibead formulation containing 1:1 ratio of Okra gum and sodium alginate respectively produced gelibeads with comparable controlled release when correlated and compared commercial metformin HCl tablet dosage forms.

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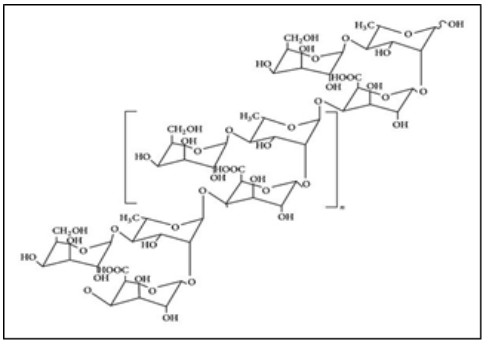

Fig 1: Structure of Okra Gum derived from *A. esculentus*

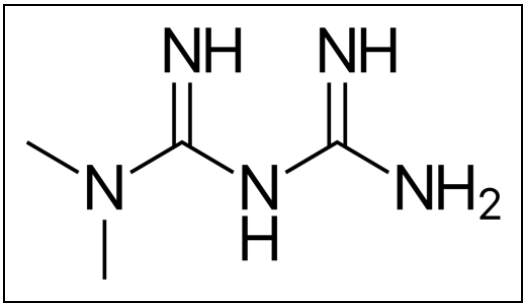

Fig 2: Structure of Metformin Hydrochloride

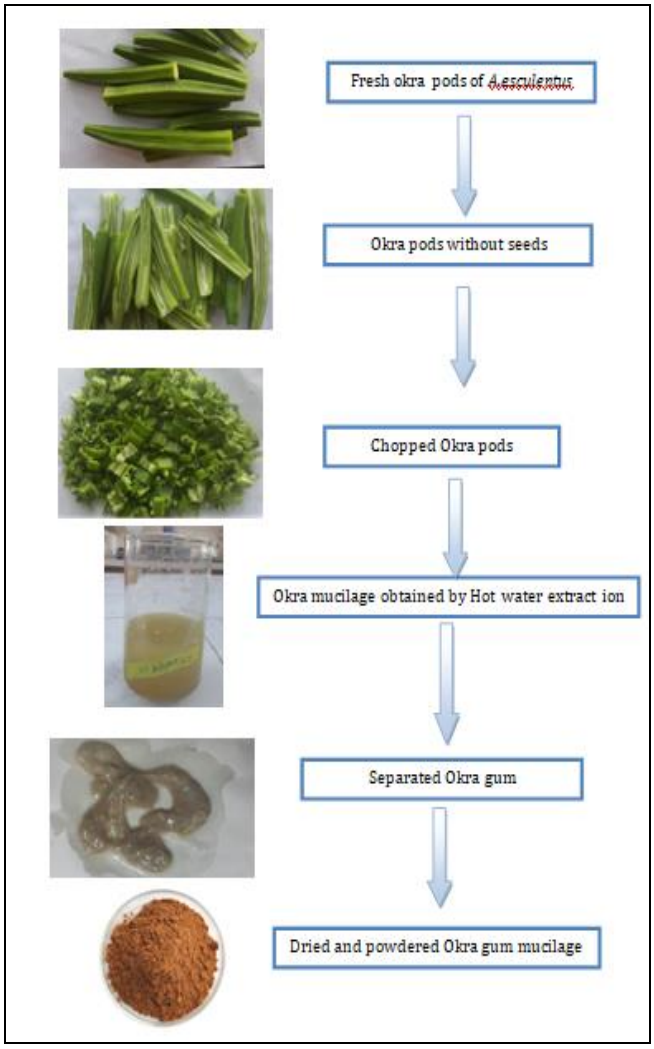

Fig 3: Graphical scheme for isolation of Okra gum

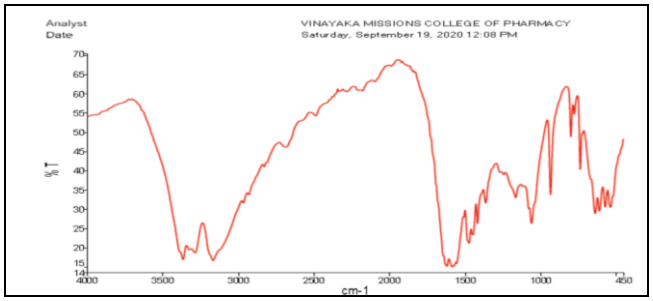

Fig 4: FT-IR spectrum of Metformin Hydrochloride

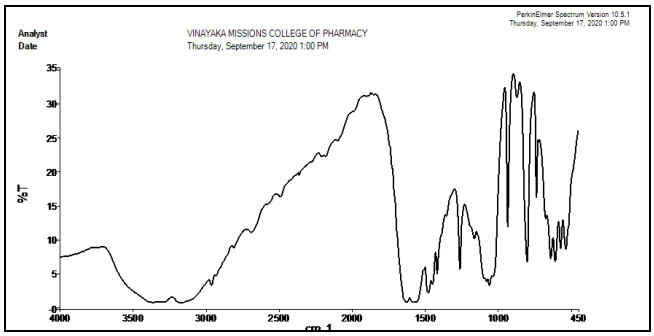

Fig 5: FT-IR spectrum of Metformin Hydrochloride + Sodium alginate

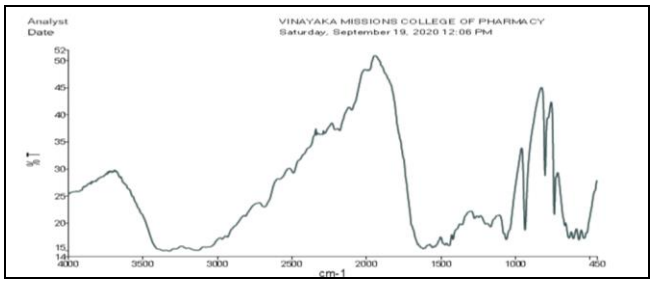

Fig 6: FT-IR spectrum of Metformin Hydrochloride + Sodium alginate + Okra gum mucialage

Fig 7: Formulation of microsphere by ionotropic gelation

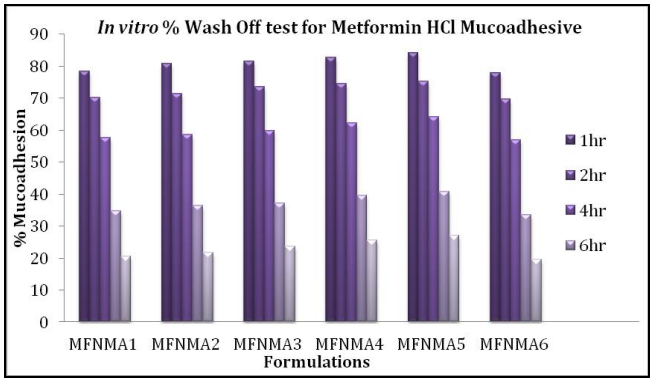

Fig 8: *In Vitro* washoff test for the Mucoadhesive Gelibeads MFNMA1-MFNM6

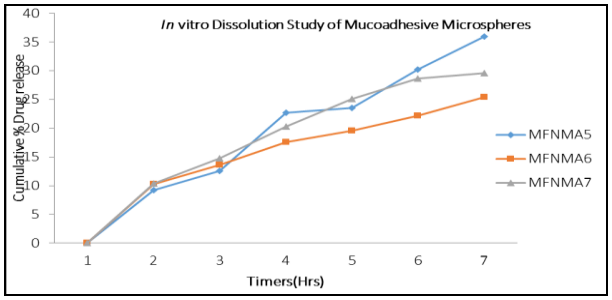

Fig 9: Dissolution Profile for Mucoadhesive Gelibeads formulations

Fig 10: Wet Metformin HCl Mucoadhesive Gelibeads MFNMA5

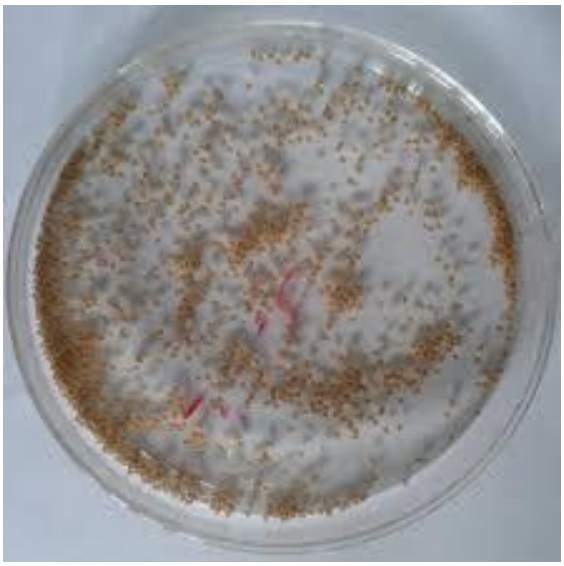

Fig 11: Dry Metformin HCl Mucoadhesive Gelibeads MFNMA5

Table 1: Physicochemical properties of *Abelmoshus esculentus* Okra gum

Parameter	Result
Yield (%)	28.48
Colour	Brown
Odour	Characteristic odour
Taste	Slightly bland
Texture	Slightly gritty
Moisture content (%)	13.62 ± 0.40
Ph	4.00 ± 0.10
Total ash (% w/w)	5.25 ± 0.14
Acid insoluble ash (% w/w)	3.25 ± 0.05

Table 2: Determination of purity of isolated Okra Gum

S. No.	Test	Present/absent
1.	Carbohydrates	+
2.	Hexose Sugar	+
3.	Monosaccharides	-
4.	Proteins	-
5.	Fats and oils	-
6.	Tannins and Phenolic Compounds	-
7.	Alkaloids	-
8.	Amino acids	-
9.	Mucilage	+
10.	Gums	-
+ Present, - absent		

Table 3: Formulations design of Formulations MFNMA1-MFNMA6

Formulation	Drug (mg)	Okra gum (mg)	Drug: Polymer ratio	Sodium alginate (% w/v)	Calcium chloride (%w/v)
MFNMA1	500	250	1.0 : 0.5	2	3
MFNMA2	500	500	1.0 : 1.0	2	3
MFNMA3	500	750	1.0 : 1.5	2	3
MFNMA4	500	250	1.0 : 0.5	2	5
MFNMA5	500	500	1.0 : 1.0	2	5
MFNMA6	500	750	1.0 : 1.5	2	5

Table 4: Data for Angle of repose of mucoadhesive Gelibeads (MFNMA1-MFNMA6)

S. No	Metformin HCl Mucoadhesive Gelibeads (MFNMA1-MFNMA6)	
	Formulation	Angle of repose
1	MFNMA1	25º 39’
2	MFNMA2	25 º23’
3	MFNMA3	26 º51’
4	MFNMA4	22º 56’
5	MFNMA5	22º 24’
6	MFNMA6	25º 10’

Table 5: Data for bulk density

S. No	Formulation	Bulk Density
1.	MFNMA1	0.624
2.	MFNMA2	0.624
3.	MFNMA3	0.596
4.	MFNMA4	0.610
5.	MFNMA5	0.622
6.	MFNMA6	0.590

Table 6: Data for percentage yield of Metformin loaded Mucoadhesive Gelibeads.

Formulation	Percentage yield
$MFNMA_1$	90.12
$MFNMA_2$	88.90
$MFNMA_3$	90.95
$MFNMA_4$	86.53
$MFNMA_5$	95.16
$MFNMA_6$	94.53

Table 7: Data for percentage entrapment efficiency

Formulation	Entrapment efficiency (%w/w)
$MFNMA_1$	93.64
$MFNMA_2$	90.12
$MFNMA_3$	88.90
$MFNMA_4$	88.34
$MFNMA_5$	96.22
$MFNMA_6$	94.87

Table 8: In vitro wash-off test for mucoadhesion in 0.1N HCl MFNMA1-MFNMA6

Formulation	Mean percentage of Gelibeads adhering to tissue in 0.1N HCL				
	1hr	2hr	4hr	6hr	8hr
$MFNMA_1$	80.7	71.4	58.6	36.4	21.8
$MFNMA_2$	81.6	73.5	59.7	37.1	23.7
$MFNMA_3$	82.8	74.6	62.3	39.6	25.6
$MFNMA_4$	77.9	69.6	56.8	33.4	19.6
$MFNMA_5$	84.1	75.2	64.1	40.8	27.1
$MFNMA_6$	79.6	71.8	57.9	34.6	20.2

Table 9: *In Vitro* Dissolution Profile for Formulation MFNMA1-MFNMA6

Time (Hrs)	Cumulative % drug release		
	MFNMA4	MFNMA5	MFNMA6
1	10.28	9.24	10.39
2	13.59	12.59	14.78
3	17.54	22.68	20.28
4	19.56	23.58	25.12
5	22.14	30.2	28.65
6	25.47	35.98	29.62

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