Research Article

Formulation, *In-Vitro* Evaluation and Comparative Study of Itopride Hydrochloride Loaded Sustained Release Matrix Tablet Using Okra Mucilage as a Natural Binder

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ABSTRACT

Natural polymers are abundantly available in plants with their wider pharmaceutical applications and are preferred more than some synthetic polymers because of their biodegradable, biocompatible and non-toxic properties. The study aims to formulate Itopride Hydrochloride loaded Sustained Release (SR) matrix tablet from the mucilage extracted from okra plant (*Abelmoschus esculantus*) and carry out the comparative study on the release retardant effect of synthetic binders like HPMC K100M and sodium carboxymethyl cellulose and their combinations. The extraction of the mucilage was carried by the maceration process. The formulation of Itopride loaded SR matrix tablet was carried by moist granulation technique. The micrometric, physiochemical studies and purity tests confirms the suitability of mucilage as an excipient. Pre-compression study suggests good flow property of the powders. The minimum angle of repose was observed in F7 with 29.03±0.6º and F2 exhibited maximum angle of repose with 34.30±0.5º. Carr's index and Hausner's ratio was lower in F1 with 11.56±0.4 and 1.11±0.3 respectively. Drug-excipient interaction study performed using FTIR spectrophotometry suggested no interaction between the drug and excipients. The in-vitro drug release of Itopride Hydrochloride loaded SR tablet up to 12 hours in 0.1 N HCl was conducted and observed to be maximum in F3 with 87.34±5.33% and minimum in F6 with 77±5.65 %. Drug release from the formulations were significant compared to the marketed product of Itopride Hydrochloride ($p<0.05$). The data were analyzed by Tukey post hoc multiple comparison test.

Keywords: Itopride Hydrochloride, Sustained release, Okra mucilage, Moist granulation technique.

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INTRODUCTION

Binders are a major class of excipients used to hold the Active Pharmaceutical Ingredient (API) and inactive excipients together in a cohesive mass which is also called granulating agents and promote size enlargement to help build granules of desired sizes, thereby enhancing the free-flowing qualities of the powder for a solid dosage form, impart plasticity as well as increases inter-particulate bonding strength in the tablet.[13, 25]

Natural polymers are generally obtained from plants and are high molecular weight, water-soluble polymers made of monosaccharide unit joint by a glyosidic bond which has evoked tremendous interest due to their diverse pharmaceutical applications such as viscosity enhancers, stabilizers, disintegrants, solubilizers, emulsifiers, suspending agents, gelling agents, and bio adhesives, binders and are especially useful in the design of novel drug delivery system.[5] Gums and mucilage are plant-derived polymers widely used as pharmaceutical excipients. Gum is a pathological product produced by the plants during injury and is water-soluble while mucilage is a metabolized product which is intracellularly formed without any injury to plants and form slimy masses in contact with water and well-known natural polymers are aloe mucilage, guar gum, karaya gum, bhara gum, sodium alginate, locust bean gum, okra mucilage, and linseed mucilage.[9]

Mucilages have been also used as matrices for sustained and controlled release drugs and are preferred over the synthetic polymers as they are biodegradable, biocompatible and non-toxic, available at low cost, local availability and better patient tolerance as well as public acceptances overcoming the disadvantages of synthetic polymer.[15] Okra mucilage is obtained from fruits of Okra (*Abelmoschus esculentus*), belongs to the Malvaceae family, which is widely grown in a tropical, sub-tropical and warm temperate region and valued for its edible green seeds pods.[11] Okra is a popular health food due to its high fiber, Vitamin-C, folate content and antioxidant activities and commonly known as lady's finger.[19] Okra mucilage contains polysaccharides such as galacturonic acid, galactose, rhamnose, and when extracted in water forms a highly viscous solution.[10] The viscous property of okra is found to be applicable as a retarding polymer in a sustained release tablet.[23,33]

Itopride Hydrochloride (HCl), chemically a benzamide derivative, is a novel prokinetic drug well absorbed from the gastrointestinal tract. It has anti-cholinesterase (AchE) activity as well as dopamine D2 receptor antagonistic activity which is used for the symptomatic treatment of

various gastrointestinal motility disorders like non-ulcer dyspepsia (NUD), gastro-esophageal reflux disease (GERD), emetic, gastritis, functional dyspepsia and biological half-life of the drug is 5-6 hours, 60% bioavailability and increased dosing frequency (50mg t.i.d).[12] Because of short half-life and high dosing frequency in the treatment of chronic disease, it is a suitable candidate for the preparation of sustained-release dosage form.

MATERIALS AND METHODS

Itopride Hydrochloride (API) and Hydroxypropyl methylcellulose (HPMC K100M) were gifted from Biogain Remedies Pvt. Ltd. (Patthardanda, Rupandehi). Other excipients as Microcrystalline cellulose (MCC), Sodium carboxymethyl cellulose (Na-CMC), Magnesium stearate, Talc were available in the laboratory. All the chemicals used in analytical grade.

Extraction and isolation of mucilage from okra

Okra (*Hibiscus esculantus*) were collected, carefully washed to remove dirt and debris and dried under shade for 24 hours, which was further dried at 30–40°C until a constant weight was obtained. The size was reduced through a grinder and then passed through sieve no. 22 which was finally stored in an airtight container for further use. Figure 1 depicts the okra mucilage extract before drying and after drying. Extraction of mucilage was carried out in two steps:[9,28]

Step 1: Extraction of mucilage: 20 grams of powdered was mixed with 500ml of distilled water and allowed to stand for 24 hours followed by heating under reflux condenser at 60°C for approximately 2 hours. The concentrated solution was filtrated through a muslin cloth and allowed to cool at room temperature.

Step 2: Isolation of Mucilage: Extracted mucilage was isolated with an equal volume of acetone and filtered through a muslin cloth. Mucilage thus obtained was further dried to constant weight at 35–45°C in a hot air oven. Hard mucilage cake was ground and sieved through sieve # 22, stored in a desiccator for further use.

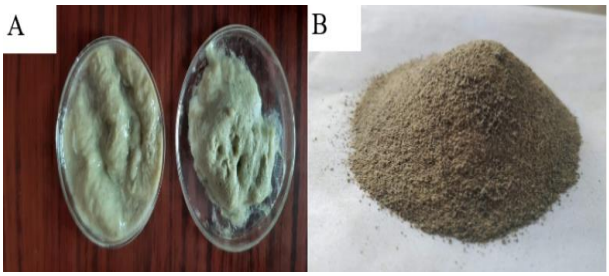

Figure 1: Okra mucilage extract before drying (A) and after drying (B).

Formulation of sustained-release tablets of Itopride Hydrochloride:

Sustained-release tablets of Itopride Hydrochloride were prepared by the moist granulation method. The formulation design of Itopride HCl loaded SR matrix tablet is depicted in Table 1. Itopride HCl, HPMC K100M, NaCMC, Okra extract, and diluents MCC of the required quantity were weighed accurately. Drugs and excipients were mixed and granulated by the addition of a small quantity of granulating solvent (water) and were allowed to dry in tray dryer at 60°C for 30min to obtain dried granules. Dry granules were passed through the sieve to obtained uniform size granules and blended with lubricant and glidant. Finally, the mixture was compressed using a multistation tablet compression machine.[31]

Table 1: Formulation design of Itopride HCl loaded SR matrix tablet

S. No.	Chemicals	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	ItoprideHCL	50	50	50	50	50	50	50	50	50
2	HPMC K100M	45	–	–	22.5	–	30	–	15	–
3	Okra mucilage	–	45	–	22.5	22.5	15	30	30	15
4	NaCMC	–	–	45	–	22.5	–	15	–	30
5	Magnesium stearate	3	3	3	3	3	3	3	3	3
6	Talc	3	3	3	3	3	3	3	3	3
7	MCC	199	199	199	199	199	199	199	199	199
9	Total	300	300	300	300	300	300	300	300	300

Characterization

Preliminary confirmatory test of mucilage

Molisch's test

Dried mucilage powder was mixed in molisch's reagent followed by the addition of conc. H_2SO_4 on the side of the test tube. The presence of violet-green color at the junction of two layers confirms the presence of carbohydrates. [21]

Ruthenium test

A small amount of extract was mounted on the slide with a ruthenium red solution and observed under a microscope. The development of pink color indicates the presence of mucilage.[8,32]

Iodine test

To the dried mucilage powder, 1ml of 0.2 N iodine solution was added. The development of no color indicates the presence of polysaccharides.[15]

Purity test of mucilage

Wagner's test

A small amount of the dried extract was stirred with 5ml of dilute hydrochloric acid and filtered. To a few ml of the filtrate, few drops of Wagner's reagent were added from the side of the test tube. The presence of reddish-brown precipitate indicates the presence of alkaloids.[30]

Bontrager's test

In this test, the extract is hydrolyzed with conc. HCl for 2 hours on a water bath, filtered and to the filtrate 3ml of chloroform, was added shook properly. The chloroform layer and 10% ammonia was added. The presence of pink color indicates the presence of glycosides.[21]

Lead acetate tests

A small amount of extract was dissolved in distilled water and 3ml of 10% lead acetate was added. The presence of bulky white precipitate indicates the presence of flavonoid compound.[3]

Ferric chloride test

A small amount of extract was dissolved in 5ml distilled water. To this few drops of neutral 5%, ferric chloride was added. The presence of a dark green color indicates the presence of a phenolic compound.[3]

Biuret test

A small amount of extract was dissolved in distilled water, and filter. To a few ml of filtrate, 2% of copper sulfate solution, was added then 1ml of ethanol (95%) was added followed by the addition of excess potassium hydroxide pellets. The presence of pink color in an ethanoic layer indicates the presence of protein.[3]

Ninhydrin test

Two drops of ninhydrin solution were added to the filtrate. The presence of purple color indicates the presence of amino acid.[3]

Foam test

The extract was diluted in distilled water and volume was made up to 20ml. The cylinder was shaken for 15minutes. The presence of a layer of foam up to 2cm indicates the presence of saponins.[3]

Physiochemical Characterization mucilage

Solubility

One part of dry mucilage powder was taken and was shaken in different solvents including methanol, ethanol, hot water, and cold water for the determination of solubility behavior of the mucilage.[6]

pH of mucilage

One gram of mucilage was weighed and dissolved in water separately to get a 1%w/v solution. The pH of the solution was determined by using a digital pH meter.[6]

Swelling index

Accurately weighed (1g) powdered mucilage was taken in 25ml of the graduated cylinder and the initial volume was noted. Two ml of 95% alcohol was added and the desired volume was maintained with distilled water and allowed to stand for 24 hours at room temperature. The swelling index will be calculated using the following formula.[9]

$$\text{swelling index} = \frac{\text{final volume} - \text{initial volume}}{\text{initial volume}} \times 100$$

Loss on drying

The moisture content of mucilage was determined by loss on drying method. Accurately weighed 1g sample was heated at 105°C to get a constant weight in a hot air oven and percent loss of moisture on drying was calculated using the following formula:[29]

$$\text{LOD}(\%) = \frac{\text{Weight of water in mucilage}}{\text{Weight of dry sample}} \times 100$$

Ash value

3gm of the sample was taken in finely clean silica crucible and ignited for 4 hours with gradually increasing in temperature up to 450°C using muffle furnace to make it dull red hot. The crucible was cooled and weighed. The procedure was repeated to get constant weight. The percentage of total ash was calculated as.[7]

$$\text{Total ash value} = \frac{\text{weight of ash}}{\text{weight of mucilage}} \times 100$$

Viscosity

The viscosity of okra mucilage was determined using Ostwald viscometer and calculated using the following formula:[9]

$$s = w \times \frac{t_s \rho_s}{t_w \rho_w}$$

Where,

s=viscosity of the solution,

w=viscosity of water,

t=time

ρ_s=density

Micrometric properties of mucilage powder

Angle of repose

The angle of repose was determined by the funnel method. The mucilage powder was passed through the funnel freely on to the surface which was adjusted to a certain height. The diameter of the powder cone was measured and the angle of repose was calculated using the following equation.[7]

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

Where "θ" is the angle of repose, "h" is the height of the cone, and "r" is the radius of the cone base.

Bulk density and tapped density

5 gm of the powder was transferred into a 25ml of graduated measuring cylinder and the initial volume (V_1) was noted. Then, the powder was subjected to tapping from a height of 2.5cm until the constant volume was attained. The final volume (V_2) was noted and the experiment was run in triplicate. The bulk density was calculated as a ratio of the weight of powder taken with bulk volume while tapped density was estimated as a ratio of powder weight with tapped volume.[9]

Hausner's ratio

The Hausner's ratio was calculated as the ratio of the tapped density to the bulk density of the mucilage powder.[29]

$$\text{Hausner's ratio} = \frac{\text{tapped density}}{\text{bulk density}}$$

Carr'sindex

Carr'sindex of the powder was measured as the ratio of the difference in tapped and bulk density to tapped density.[24]

$$\text{Carr's index} = \frac{\text{tapped density} - \text{loose density}}{\text{tapped density}} \times 100$$

Micrometric properties of granules

Angle of repose

The angle of repose of granules was determined by the fixed funnel method.[26] Accurately weighed 5gm of granules was allowed to flow through the funnel freely onto the surface. The diameter of the powder cone was measured and the experiment was carried out in triplicate. The angle of repose was calculated using the following equation:

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

Where "θ" is the angle of repose, "h" is the height of the cone, and "r" is the radius of the cone base.

Tapped density and Bulk density

Bulk density was calculated as the ratio of powder weight with bulk volume. While tapped density was measured as the ratio of powder weight with tapped volume.[4]

Compressibility index

The compressibility index of the granules was determined by Carr's compressibility index.[24] It was calculated by using the following formula:

$$\text{Carr's index} = \frac{\text{tapped bulk density - loose bulk density}}{\text{tapped bulk density}} \times 100$$

Powder with carr's index value below 15% is usually considered to have good flow characteristics, while above 25% is considered to have poor flowability.

Hausner's ratio

Hausner's ratio is an indirect index of ease of powder flow. It was estimated using the following formula:[24]

$$\text{Hausner's ratio} = \frac{\text{tapped density}}{\text{bulk density}}$$

A decent flow is shown by a Hausner's ratio higher than 1.25, and a weak flow maybe 1.5.

Drug-excipient compatibility study

FTIR spectrum of Itopride HCl alone and its mixture with other excipients like HPMC K100M, Okra Extract, NaCMC was recorded. A mixture of the drug and excipients in an equal ratio was stored in 40°C and 75% relative humidity for 30 days. FTIR of drug and mixture was estimated in terms of the vibrational frequencies in the IR range from 2000-400 cm^{-1}using the FTIR spectrophotometer. The IR spectrum thus obtained was compared with the spectrum of the pure drug. [27]

Post-compression evaluation

Thickness

The tablet thickness from all nine formulations was determined by using Vernier caliper. Ten tablets were taken for tests and the average thickness was estimated. Variation in tablet thickness might result in the problems associated with coating and packaging.[23]

Hardness

Hardness testing determines the tablet's ability to withstand mechanical stress during handling. The hardness of the tablets was determined by using Pfizer hardness tester in triplicate. It was expressed in kg/cm^2. Ten tablets were chosen randomly and the average hardness was estimated. The %-deviation in the hardness of the individual tablets to average value was accounted.[16]

Friability test

Friability test determines the tablet's ability to resist the chipping or breaking under conditions of storage, transportation, and handling before usage. Friability refers to the loss in weight of tablets in the containers due to the removal of fines from the tablet surface. The friability of tablets was determined by using Roche friabillator which was operated at 25 rpm for 4 min with a fall height of 6 inches.[14] The difference in the tablet weight before and after the friability test was recorded. Percentage friability was obtained by using the following formula:

$$\%\text{friability} = \frac{\text{initial weight-final weight}}{\text{initial weight}} \times 100$$

Weight variation

Twenty tablets from each batch were weighed and the average weight was determined. The weight variation of the tablet was estimated using the following equation. [1]

$$\text{weight variation} = \frac{\text{Individual weight-average weight}}{\text{average weight}} \times 100$$

Drug content

Ten tablets from each formulation were taken and powdered. Powder equivalent to 50mg of drug was weighed accurately and dissolved in 100ml of 0.1 N HCl. The resultant solution was filtered. 10ml of the filtrate was further diluted with 100ml of 0.1N HCl. The absorbance of the diluted solution was measured spectrophotometrically at 258nm.[1]

***In-Vitro* drug release study**

In- vitro dissolution study was conducted using USP type 2 dissolution testing apparatus in 0.1N HCl at 37±0.5°C rotating at 75rpm for 12 hours. Aliquots of dissolution medium (5ml) were withdrawn at specified time intervals. The withdrawn sample was filtered and 1ml of the filtrate sample was pipetted and diluted to 10ml using the same medium. The in vitro%-release of the drug at different time intervals was determined spectrophotometrically at 258 nm.[22]

Statistical Analysis

All the experiments were run in triplicate and results were expressed as mean ±SD. Statistical analysis was carried out using graph pad prism version 7 software (Graph pad software Inc., La Jolla, CA). The data were analyzed by Tukey's post hoc multiple comparison test; statistical significance was predefined at $p<0.05$.

RESULT AND DISCUSSION

Extraction and Characterization of Mucilage

Percentage yield and organoleptic property

The percentage yield of the mucilage was found to be 8%. Mucilage exhibited light brown in appearance with a characteristic odor.

Confirmatory test of mucilage

The results on the preliminary confirmatory test of mucilage are depicted in Table 1. The study suggests positive results for molisch's test indicating the presence of carbohydrates and the Ruthenium test indicating the extract to be mucilage as depicted in Figure 1. No color was developed in the iodine test which attributing the presence of polysaccharide.

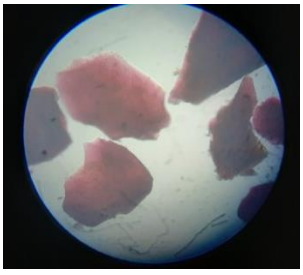

Figure 1: Ruthenium test confirming the presence of mucilage

Table 1: Summary result of confirmatory and purity test of mucilage

Tests	Results
Molisch's test (Carbohydrate)	+
Ruthenium test (Mucilage)	+
Iodine test (Polysaccharide)	+
Alkaloids	–
Glycosides	–
Phenolic compound	–
Flavonoids	+
Proteins	–
Amino acids	–
Saponins	–

Purity test of Mucilage

The result of the purity test of mucilage is depicted in Table 1. Phytochemical screening test for purity of mucilage suggests the presence of flavonoids while other phytochemical constituents like alkaloids, glycosides, phenolic compounds, proteins, amino acids, and saponins were not present in mucilage as depicted in Figure 2.

Figure 2: Phytochemical test confirming the purity of okra extract

Physiochemical characterization of mucilage:

The results on the study of physicochemical characterization of mucilage are depicted in Table 2. The observed pH of the mucilage was neutral (pH 6.5) indicating the mucilage to be less irritating in GIT. [15] The swelling index and the viscosity of the extract were found to be 80 and 267c.p. respectively. The higher viscous property of okra mucilage can be used as a release retardant in the formulation of the sustained-release dosage form.[23] Solubility study suggests the extract to be slightly soluble in acidic medium, insoluble in methanol and acetone, and forms a viscous solution with water.

Table 2: Summary result of Physiochemical characterization of mucilage

S. no.	Parameters	Observation
1	pH (1% solution)	6.5
2	Swelling index	80
3	%LOD	8.8%
4	Ash value	5.12%
5	Viscosity (1% solution)	267Cp

Micrometric properties of the extract

Various micrometric studies were performed on the okra mucilage extract. Angle of repose of the extract powder was 28.36±0.02 ºC, bulk density, and the tapped density value with 0.69±0.03 gm/ml and 0.80±0.01 gm/ml respectively. Hausner's ratio and the compressibility index value were within the considerable range with 1.16±0.01 and 13.75±0.02 respectively, indicating good flow property of the powder extract.[15]

Micrometric properties of powder

Angle of repose

Angle of repose of all nine formulations was found within the considerable range indicating the good flow properties of the granules. The minimum angle of repose was found in F7 with 29.03±0.6º. While the maximum angle of repose was found in F2 with 34.30±0.5º.

Bulk density and Tapped density

The maximum bulk density with 0.55±0.2 gm/ml was found in F4 and minimum bulk density with 0.50±0.02g/ml was found in F7. While F1 exhibited minimum tapped density with 0.57±0.2 g/ml, F4 exhibited maximum tapped density with 0.64±0.3 g/ml.

Carr's index and Hausner's ratio

Carr's index and Hausner's ratio of all the formulations were within the considerable range attributing good compressible character of the powder. The result on the carr's index and Hausner's ratio values are depicted in Table 3. The maximum carr's index with 16.50±0.40 was observed in F5 while minimum carr's index value with11.56±0.4 was observed in F1. Formulation F1 exhibited minimum Hausner's ratio value with 1.11±0.03. While the maximum Hausner's ratio with 1.19±0.01 was observed in F3.

Table 3: Summary results of micrometric properties of the powder (n=3)

Formulation no.	Angle of repose (θ)	Bulk density (gm/ml)	Tapped density (gm/ml)	Carr's index	Hausner's ratio
F1	30.36±0.7	0.51±0.01	0.57±0.2	11.56±0.4	1.11±0.03
F2	34.30±0.5	0.51±0.5	0.60±0.3	16.15±0.5	1.17±0.02
F3	30.77±0.8	0.51±0.4	0.61±0.2	15.10±0.4	1.19±0.01
F4	29.51±0.8	0.55±0.2	0.64±0.3	14.24±0.2	1.16±0.04
F5	34.20±0.9	0.50±0.3	0.59±0.2	16.50±0.4	1.18±0.02
F6	29.90±0.8	0.52±0.1	0.59±0.3	12.44±0.5	1.13±0.02
F7	29.03±0.6	0.50±0.02	0.57±0.3	12.37±0.5	1.14±0.02
F8	30.11±0.9	0.53±0.3	0.61±0.4	14.01±0.5	1.15±0.01
F9	33.5±0.7	0.51±0.3	0.60±0.3	15.35±0.5	1.17±0.03

Drug-excipient compatibility study

Earlier studies suggested that the IR spectra of Itopride HCl displayed the characteristics peak at 1651.12 cm^{-1}, 1581.68 cm^{-1}, 1543.10 cm^{-1} because of C=O bending. 1504.53 cm^{-1} attributable to the C=C aromatic structure and 1234.48 cm^{-1} attributable to the C-N aromatic structure.[2] The sample drug Itopride HCl exhibited the characteristic peak at 1651.07 cm^{-1} and 1543 cm^{-1} owing to C=O bending. 1504.48 cm^{-1} attributable to the C=C aromatic structure and 1235 cm^{-1} attributable to the C-N aromatic structure. IR spectrum of a mixture of Itopride HCl and the different excipients were compared with the spectrum of the pure drug. The IR spectrum of pure drug Itopride HCl and a mixture of Itopride and okra mucilage is depicted in Figure 3. Similarly, the IR spectrum of a mixture of Itopride HCl and HPMC K100M and mixture of Itopride HCl and Na-CMC is depicted in the Figure 4. However, Figure 5 depicts the IR spectrum of a mixture of Itopride HCl, HPMC K100M and okra mucilage and, a mixture of Itopride HCl, Na-CMC, and okra mucilage. Drug-excipient interaction study suggests no significant changes in the peaks of the functional groups in the drug excipient mixture assuring no significant interactions.

Post-compression evaluation

Hardness and Thickness

The hardness of the tablets from all nine formulations was measured using Pfizer hardness tester. Maximum hardness was observed with 7.50±0.11 kg/cm^2in F2. While F8 exhibited minimum hardness with 6.32±0.12 kg/cm^2.

The variation in the hardness can be attributable to the differences in concentration of okra extract as a binder.The thickness of the tablet was minimum with 4.66±0.02 mm in F2. While maximum thickness with 4.9±0.07 mm was observed in F8.

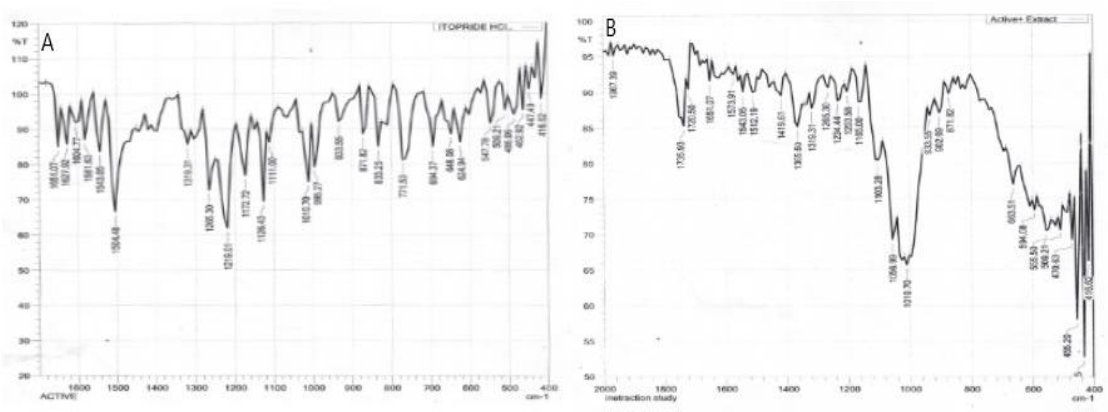

Figure 3: FTIR spectrum of pure drug Itopride HCl (A) and mixture of Itopride HCl and okra extract (B)

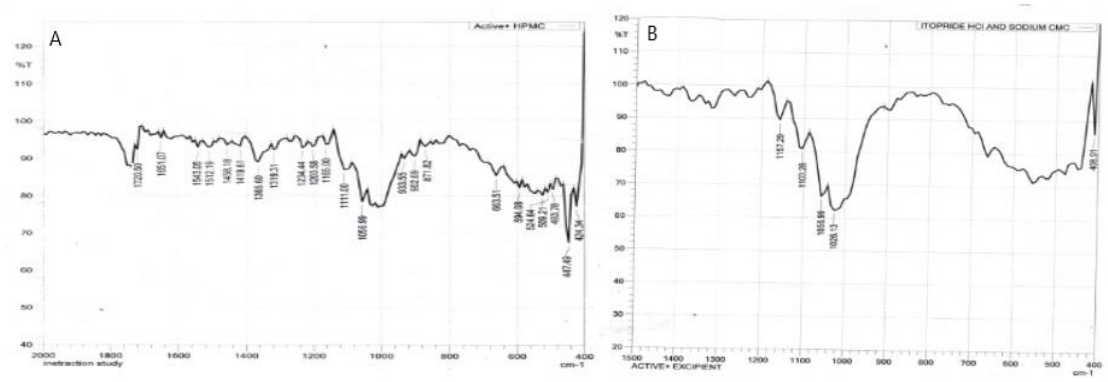

Figure 4: FTIR spectrum of Itopride HCl and HPMC K100M mixture (A) and Itopride HCl and NaCMC mixture (B)

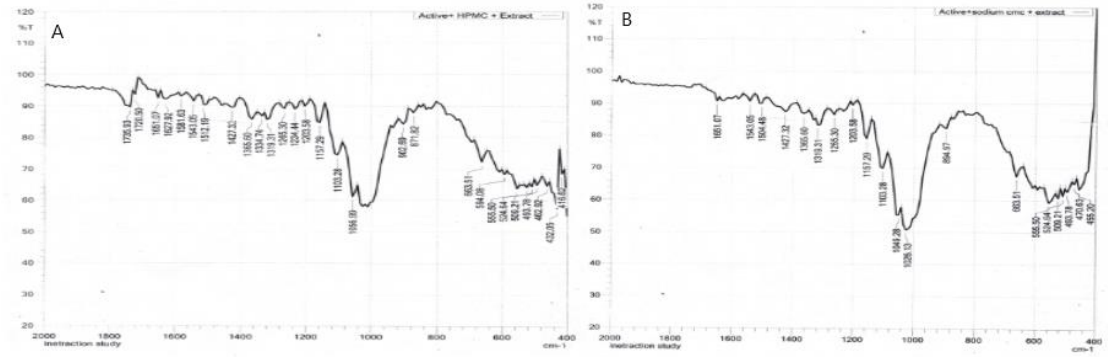

Figure 5: FTIR spectrum of mixture of Itopride HCl, HPMC K100M and extract (A) and Itopride HCl, NaCMC and extract

Friability and Weight variation

The result of the Friability test suggests all the formulation be within the acceptable limit. The maximum friability of 0.50% was observed in F9 while, friability was minimum in F6 with 0.29%. Weight variation of all nine formulations was carried out and the results were observed within the considerable range. The minimum average weight with 299±1.18 mg was found in F2 while the maximum average weight with 301.3±2.55 mg was observed in F3.

Drug content

The drug content of all the formulations was within the acceptable limit. The results on the drug content of the formulations are depicted on the Table 4. Drug content was carried out in each formulation and the result is illustrated in table no.8. Minimum Drug content with 97.5±0.05% is observed in F9. Formulation F5 exhibited maximum drug content with 99.20±0.43%.

Table 4: Summary result of post-compression study of the formulations

Formulation No.	Mean weight (mg)	Mean thickness (mm)	Hardness (kg/cm²)	Friability (%)	Drug content (%)
F1	300.5±2.30	4.86±0.03	6.80±0.04	0.42	98.5±0.15
F2	299±1.18	4.66±0.02	7.50±0.11	0.33	98.60±0.56
F3	301.3±2.55	4.84±0.07	6.37±0.08	0.36	98.4±0.66
F4	300.2±1.43	4.78±0.02	6.50±0.02	0.45	97.80±0.85
F5	300.65±1.53	4.68±0.01	6.67±0.04	0.34	99.20±0.43
F6	300.15±1.66	4.70±0.03	7.42±0.10	0.29	99.05±0.75
F7	299.9±1.51	4.84±0.01	6.82±0.06	0.42	96.8±0.68
F8	300.25±1.48	4.9±0.07	6.32±0.12	0.4	98.20±0.48
F9	300.6±1.30	4.88±0.01	7.20±0.05	0.50	97.50±0.05

In-Vitro drug release study

In vitro drug release study suggests maximum cumulative drug release with 87.34±5.33 % was observed in F3. The higher cumulative drug release might be due to the higher solubility and presence of monovalent cation like sodium leading to reduced swelling and gelling of the formulations. [17] The minimum cumulative drug release with 77±5.65 % was observed in F6. The minimum drug release might be due to the combined effect of the minimum concentration of okra with HPMC K100M increasing gelling strength and retarding the drug release compared to other formulation.[17,18] The result of the in vitro drug dissolution is depicted in Table 5. The comparative in vitro drug release profile of F1, F2 and F3 is depicted in Figure 6. While, comparative in vitro drug release profile of F4, F5, F6 is depicted in Figure 7. Similarly, Figure 8 depicts the comparative in vitro drug release profile of F7, F8, F9 and marketed product.

Table 5: Cumulative % drug release of formulations and Marketed Product (n=3)

Time (hrs.)	F1	F2	F3	F4	F5	F6	F7	F8	F9	M
0	0 ^{a}	0 ^{a}	0 ^{a}	0 ^{a}	0 ^{a}	0 ^{a}	0 ^{a}	0 ^{a}	0 ^{a}	0^{a}
0.5	10.46 ± 1.33^{b}	11.46 ± 1.65 ^{b}	12.32± 1.25 ^{b}	10.74± 1.57 ^{b}	11.82± 4.66 ^{b}	10.28± 1.50 ^{b}	12.11± 2.19 ^{b}	11.12± 2.32 ^{b}	11.64± 1.56 ^{b}	46.20± 1.34 ^{a}
1	17.20± 1.56 ^{b}	19.07± 2.75 ^{b}	21.83± 2.34 ^{b}	17.85± 2.65 ^{b}	21.03± 3.19 ^{b}	16.40± 2.12 ^{b}	21.27± 2.33 ^{b}	18.37± 3.45 ^{b}	20.14± 1.43 ^{b}	61.8 ± 2.45 ^{a}
2	26.70 ± 1.95 ^{b}	28.98± 2.56 ^{b}	30.05± 2.98 ^{b}	27.46± 2.18 ^{b}	29.66± 3.78 ^{b}	26.38± 2.65 ^{b}	29.93± 2.68 ^{b}	28.24± 4.67 ^{b}	29.30± 2.48 ^{b}	73.10± 5.45 ^{a}
3	31.95 ± 2.28 ^{b}	33.72± 2.43 ^{b}	34.88± 3.21 ^{b}	32.36± 2.89 ^{b}	34.13± 4.17 ^{b}	31.54± 3.15 ^{b}	34.62± 3.16 ^{b}	33.09± 4.34 ^{b}	33.99± 4.32 ^{b}	82.03± 6.33 ^{a}
4	37.24± 2.30 ^{b}	38.66± 2.67 ^{b}	40.64± 3.86 ^{b}	37.65± 3.10 ^{b}	39.82± 4.59 ^{b}	37.22± 3.58 ^{b}	40.11± 3.44 ^{b}	38.22± 5.66 ^{b}	39.78± 3.86 ^{b}	92.41± 4.22 ^{a}
5	45.30± 3.23 ^{b}	47.47± 3.78 ^{b}	48.92± 2.15 ^{b}	46.44± 3.77 ^{b}	48.01± 5.21 ^{b}	44.62± 4.17 ^{b}	48.76± 2.98 ^{b}	46.83± 3.46 ^{b}	47.98± 3.54 ^{b}	98.08± 3.76 ^{a}
6	52.44± 4.54 ^{b}	53.56± 3.32 ^{b}	55.76± 4.13 ^{b}	52.82± 4.15 ^{b}	54.96± 6.10 ^{b}	51.08± 4.49 ^{b}	55.22± 4.12 ^{b}	53.37± 6.04 ^{b}	54.46± 5.55 ^{b}	99.05± 2.53 ^{a}
7	57.46± 4.97 ^{b}	59.13± 3.66 ^{b}	60.99± 4.37 ^{b}	58.0 ± 4.19 ^{b}	60.4 ± 6.37 ^{b}	56.7±5.05 ^{b}	60.5±4.47 ^{b}	58.7±5.06 ^{b}	59.6±4.75 ^{b}	98.0 ± 4.44 ^{a}
8	62.97± 5.25 ^{b}	65.53± 4.77 ^{b}	68.03± 5.23 ^{b}	63.44± 5.28 ^{b}	66.96± 6.35 ^{b}	62.33± 5.28 ^{b}	67.20± 6.35 ^{b}	64.97± 5.82 ^{b}	66.32± 5.34 ^{b}	96.23± 3.86 ^{a}
9	68.03± 5.65 ^{a}	70.56± 5.05 ^{a}	73.30± 5.68 ^{b}	68.52± 6.69 ^{a}	72.04± 6.40 ^{b}	67.86± 5.93 ^{a}	72.67± 5.66 ^{a}	69.30± 4.67 ^{a}	71.25± 2.67 ^{a}	95.45± 2.65 ^{a}
10	72.35± 3.76 ^{b}	75.07± 5.22 ^{a}	77.95± 6.18 ^{a}	73.22± 2.27 ^{a}	76.88± 5.21 ^{a}	71.90± 6.25 ^{a}	77.30± 5.87 ^{a}	74.16± 3.78 ^{a}	76.23± 6.50 ^{a}	94.32± 3.39 ^{a}
11	75.23± 3.45 ^{a}	78.68± 5.58 ^{a}	81.86± 4.25 ^{a}	76.49± 2.41 ^{a}	79.96± 5.64 ^{a}	74.82± 6.79 ^{a}	80.39± 6.45 ^{a}	77.60± 3.55 ^{a}	79.16± 3.33 ^{a}	93.89± 3.54 ^{a}
12	78.29± 4.56 ^{a}	82.00± 5.87 ^{a}	87.34± 5.33 ^{a}	80.02± 2.58 ^{a}	84.56± 2.31 ^{a}	77.00± 5.65 ^{a}	85.24± 2.34 ^{a}	81.54± 3.76 ^{a}	83.00± 4.53 ^{a}	92.70± 1.86 ^{a}

The values are expressed as mean ± SD. The different letter superscript within the cumulative % are significantly different ($p<0.05$).

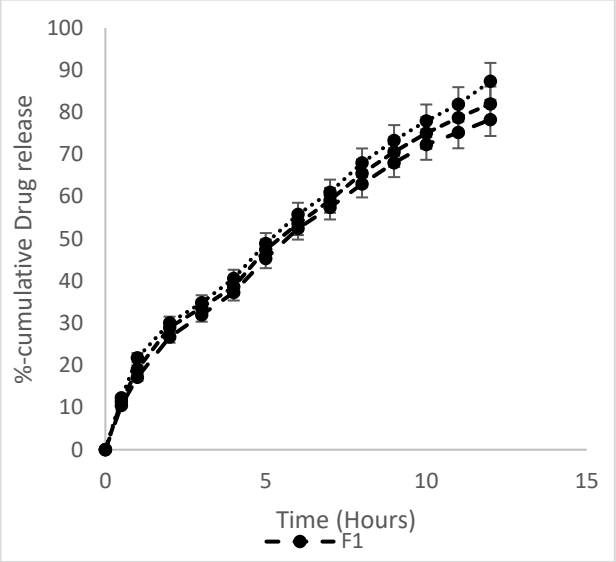

Figure 6: Comparison of the in vitro drug release profile of F1, F2, F3

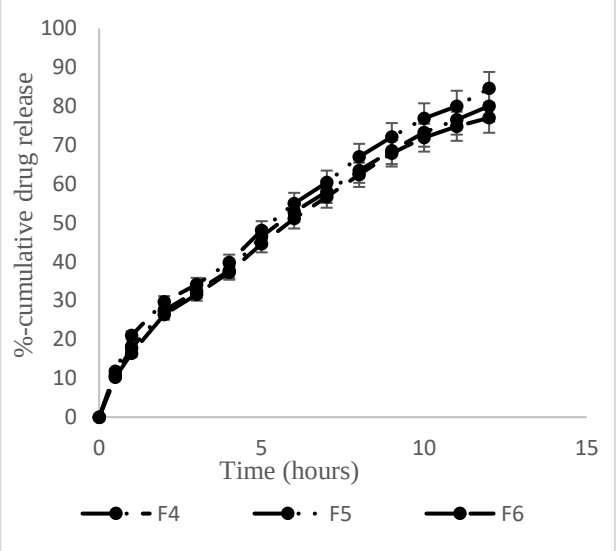

Figure 7: Comparison of in vitro drug release profile of F4, F5, F6

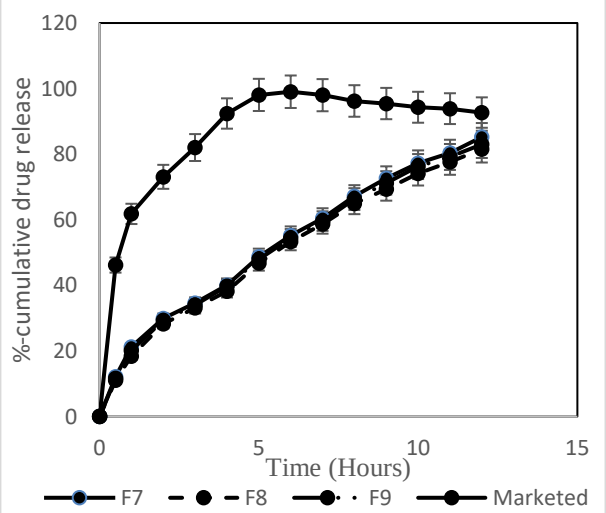

Figure 8: Comparison of in vitro drug release profile of F7, F8, F9, and Marketed product

Previous studies suggest that mucilage used in the formulation of tablets swells to form a gel layer resulting in the lower drug release rate but at the higher concentration mucilage swells resulting in higher drug release due to the bursteffect.[20] While HPMC K100M exhibits sustained release behavior due to its swelling and hydration property resulting in the formation of immediate surface barrier around the tablet matrix eliminating the burst release

The cumulative percentage of drug release of all formulations was significantly retarded compared to the marketed formulation ($p<0.05$) exhibiting excellent sustained-release property up to 9 hours. However, after 9hours the release of the drug from a maximum number of formulations was not found to be significant ($p>0.05$) compared to the marketed product. This might be due to the complete release of drugs from the marketed formulation after 10 hours. and a decrease in the concentration of drug concentration after each sampling in an attempt of maintaining the sink condition.

CONCLUSION

Itopride HCl loaded sustained release tablet formulations using natural and synthetic superdisintegrants were successfully prepared by moist granulation method. The extracted mucilage exhibited good flow property and did not show any interaction with Itopride HCl. Formulation F3 exhibited greater cumulative in vitro drug release with 85.56±5.33 % while, F6 exhibited minimum cumulative drug release with 77±5.65 % at 12 hrs. The use of the okra mucilage extract in optimum concentration and along with the combination of the synthetic polymer can retard the release for an optimum period.

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