Formulation and Evaluation of Metformin Sustained Release Matrix Tablet using Okra (*Abelmoschus Esculentus L.*) Polysaccharide

P D Tawari, M J. Umekar, J B. Taksande *

Department of Pharmaceutics, Shrimati Kishoritai Bhoyar College of Pharmacy, Kamptee, Nagpur (M.S.), India-441 002

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*Corresponding Author
Email ID: jbtaksande@rediffmail.com

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ABSTRACT
Present investigation was carried out to study the sustain property of okra polysaccharide extracted from fresh okra fruits. Extracted okra polysaccharide was characterized for its physicochemical properties such as solubility, pH, moisture content, viscosity and infrared study using FTIR. Presence of polysaccharide in extract was confirmed by phytochemical tests. Sustained release matrix tablets of metformin hydrochloride were prepared by using different proportion of extracted polysaccharide as sustained release matrix excipient using wet granulation method. Formulated tablets were evaluated for post compression parameters such as diameter, hardness, thickness, friability, weight variation swelling index and in-vitro drug dissolution study. Drug – polymer compatibility study was determined using FTIR spectroscopy. Results indicated the suitability of extracted polysaccharide as a tablet excipient and no interaction between the drug and the polysaccharide. Formulated tablets showed hardness in the range of 6.97 – 8.28 kg/cm², content uniformity of all the batches was in the range of 98.21-100.03 % showing uniformity in drug content. High value of swelling index revealed the high swelling ability of matrix tablet of metformin HCl using okra polysaccharide. Results of drug release study showed that formulation containing 23.33 % w/w of okra polysaccharide released 99.81% of drug after 14 hours.

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1. INTRODUCTION
Natural polysaccharides obtained from plants are useful that could be specifically used in different pharmaceutical formulations. In the present era, they have been extracted irrigated crop production giving polysaccharides which can be useful in the pharmaceutical preparations as well as in food and other processing industries’. Polysaccharides have diverse pharmaceutical applications such as diluents, binders, disintegrants in tablet, thickener in oral liquid, protective colloids in suspensions and gelling agent in gels \(^2,3\). Okra polysaccharide obtained from the pods of *Abelmoschus esculentus* is presently being studied as a hydrophilic polymer in formation of various pharmaceutical dosage forms such as tablets \(^4,5\). Okra gum obtained from the fruits of *Abelmoschus esculentus*, is a polysaccharide consisting of D-galactose, L-rhamnose and L-galacturonic acid \(^6\). Okra gum had been evaluated as binder in tablet dosage formulation \(^7,8\). In okra mucilage galactose, galacturonic acid, rhamnose are present as polysaccharides when comes in contact with water produces highly viscous solution. This property of okra polysaccharides may be useful as a release retarding polymer in the formulation of sustained release tablets \(^9\).

The Okra (*Abelmoschus esculentus*) is a widely cultivated annual plant throughout the tropical and subtropical areas of the world, particularly in India, gives fruits as green pods. Okra is commonly harvested and used thus does not require any toxicology studies. It has been investigated as a binding agent for tablets and has also been shown to produce tablets with good hardness, friability, and drug release profiles \(^9\). Natural materials have advantages over synthetic materials because they are non toxic, less expensive and freely available. It has advantages over most commercial synthetic polymers as it is safe, chemically inert, non irritant, biodegradable, biocompatible, and eco-friendly \(^10\).

Present investigation was carried out to study the sustain property of okra polysaccharide extracted from fresh okra fruits. In the present work, Okra polysaccharide was extracted, characterized and evaluated for its sustained-release properties using Metformin as a model drug. Metformin hydrochloride is an orally administered biguanide, which is widely used in the management of type-II diabetes \(^11\).
It is a hydrophilic drug and is slowly and incompletely absorbed from the gastrointestinal tract, and the absolute bioavailability is reported to be of 50-60% \(^{14,15}\). The compound has relatively short plasma half-life of 1.5-4.5 h and the low absolute bioavailability of 50-60% \(^{14}\). Side effects, short half lives, low bioavailability and the need for the administration two to three times a day when larger doses are required can decrease patient compliance. Sustained release products are needed for metformin to prolong its duration of action and to improve patient compliances. The matrix tablets of metformin HCl were formulated using wet granulation method and evaluated for weight variation, swelling behavior, hardness, friability and in-vitro drug release.

2. MATERIALS AND METHODS

Metformin hydrochloride was procured from Alkem Laboratories, Mumbai, Microcrystalline cellulose (Avicel PH-102), acetone, hydrochloric acid, sodium hydroxide pellets and magnesium stearate was obtained from Loba Chemie Pvt. Ltd. Mumbai, sodium meta-bisulphite, Potassium dihydrogen phosphate and potassium bromide was acquired from Hi-Media Laboratories Pvt. Ltd.

**Extraction method of okra polysaccharide:** About 2 kg of fresh immature fruits of *Abelmoschus esculentus* were purchased from a local market. After removal of the seeds, the fresh fruits were sliced, homogenized and extracted with cold water containing 1% (w/v) sodium metabisulphate. The crude mucilage was stirred at 2000 rpm for 10 min and from the supernatant the gum was precipitated using acetone. The precipitated gum was washed several times with acetone; the obtained cream coloured product was dried at 50°C in oven for two days \(^{16}\).

**Characterization of okra polysaccharide**

*Solubility Test:* Solubility of the extracted gum was evaluated qualitatively by stirring 10mg of Okra powder in 10 mL water, acetone, chloroform, and ethanol (1% dispersion). Solubility was determined by visual observation of the solute.

*pH Determination:* 1% wt/vol. dispersion of the sample in water was stirred consistently for 5 minutes and pH was determined using a pH meter.

*Moisture Content:* Moisture content of okra gum powder was conducted by measuring 1 gm of powder using Contech-Mixture Analyzer CB-50, with loss on drying at 105°C.

*Swelling Index:* Swelling index of okra polysaccharide was determined by using modified method. One gram of okra polysaccharide powder was accurately weighed and transferred to a 100 ml stopped measuring cylinder. The initial volume of the powder in the measuring cylinder was noted. The volume was made up to 100 ml mark with distilled water. The cylinder was stoppered, shaken gently and set aside for 24 hr. The volume occupied by the gum sediment was noted after 24 hr. Swelling index was expressed as a percentage and calculate according to the following equation \(^{17}\).

\[
\% \text{ Swelling} = \left( \frac{n_t - n_0}{n_0} \right) \times 100
\]

Where,

- \(n_0\) is the initial height of the powder in graduated cylinder
- \(n_t\) denotes the height occupied by swollen gum after 24 hr

*Viscosity:* Viscosity of okra gum at 1% and 0.5% concentrations was performed using the Brookfield viscometer DV-E Viscometer. The higher the viscosity of the gum, the more sticky it is and this provides more tensile strength which may help in sustaining the drug release from tablet.

*Fourier Transform Infrared (FTIR):* The FTIR spectroscopy method was used for the confirmation of the prepared Okra polysaccharide as well as to study the compatibility between drug and polymer used in the study. The FTIR study was carried out by KBr disc method. Okra polysaccharide was dried in hot air oven at 50°C for 2 hours. The samples were prepared by mixing it thoroughly with potassium bromide. This physical mixture was compressed under of 10 Ton/nm\(^2\) and converted in a circular disc. This disc was then placed in a scanning slot of IR Spectrophotometer and scanned at range from 400 to 4000 cm\(^{-1}\) to obtain FTIR of metformin HCl. The spectrum was then compared with the spectrum of reference standard \(^{18}\). Same procedure was followed for the analysis of drug and physical mixture of drug and polymer.

*Phytochemical Examination:* Chemical tests were performed to confirm the presence of polysaccharide \(^{19}\).

*Molisch's test:* 100 mg dried okra polysaccharide in warm water + Molisch's reagent + conc. H\(_2\)SO\(_4\) on the side of a test tube.

*Ruthenium test:* A small quantity of dried okra polysaccharide powder was mounting on a slide with ruthenium red solution, and observed it under microscope.

*Iodine test:* 100 mg dried okra polysaccharide + 1 ml 0.2 N iodine solution.

**Formulation of metformin HCl Matrix tablets**

The metformin HCl sustained release matrix tablets were prepared by wet granulation method. The granules were prepared using drug, excipients and extracted okra polysaccharide in concentrations ranging from 6.66 % w/w to 26.66 % w/w as mentioned in tablet. The moisten damp mass was prepared and passed through sieve no. 16 and obtained granules were dried at 60°C for 30 min. Magnesium stearate was mixed with dried granules. The uniformly mixed blend was compressed into 750 mg of tablets using rotary press tablet compression machine. The tablets were stored in tightly closed containers.
Table 1. Composition of matrix tablet of metformin HCl using Okra polysaccharide

<table>
<thead>
<tr>
<th>Ingredients</th>
<th>Formulation Code</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metformin hydrochloride</td>
<td>F1</td>
</tr>
<tr>
<td>Okra polysaccharide</td>
<td>F2</td>
</tr>
<tr>
<td>Micro crystalline cellulose</td>
<td>F3</td>
</tr>
<tr>
<td>Magnesium stearate</td>
<td>F4</td>
</tr>
<tr>
<td>Total weight</td>
<td>750</td>
</tr>
</tbody>
</table>

Pre-compression assessment of granules

Granules prepared for all formulations were evaluated for pre-compression parameters as angle of repose, bulk density, tapped density, Hausner’s ratio, and Carr’s consolidation index.

Post-compression evaluation of metformin HCl Tablets

**Thickness and diameter:** The thickness and diameter of tablets with each formulation were measured using Campbell Electronic DHT-250 Thermonik. Average of tablets was determined and reported as mean ± standard deviation.

**Weight variation:** The weight variation test ensures the uniformity in the weight of the prepared tablets in a batch. The total weight of 20 tablets from each formulation was determined and the average weight was calculated. The individual weight of the tablets was also determined accurately and the weight variation was calculated as specified in IP. Results are reported as mean ± standard deviation.

**Hardness:** Hardness or crushing strength is the force required to break a tablet in a diametric compression which was measured using Campbell Electronic DHT-250 Thermonik. It is expressed in kg/cm². The hardness of tablets \( n = 5 \) was determined using a. The average hardness of tablets was reported as mean ± standard deviation.

**Friability:** The friability test was determined using a Roche Friabilator. 10 tablets from each formulation were weighed and placed in Roche Friabilator rotated at 25 rpm for 4 minutes (100 revolutions). The tablets were then dedusted and weighed again \( W \). The % friability was calculated as

\[
% F = \left[1 - \left(\frac{W}{W_0}\right)\right] \times 100
\]

Where,

- \( % F \) = Friability in percentage,
- \( W_0 \) = Initial weight of tablet,
- \( W \) = Weight of tablets after revolution.

**Swelling index:** This method was used with slight modification. Tablets were weighed individually and dispersed in 900 mL of pH 1.2 hydrochloric acid and 6.8 pH phosphate buffers separately at 37.0 ± 0.5°C and 50 rpm rotation. At 30-minute, 1-hour, 2-hour, 3-hour, and 4-hour intervals, tablets were withdrawn and dabbed with filter paper to absorb excess buffer solution and then weighed again. Percentage swelling of tablets was expressed as the following:

\[
SR = \left(\frac{W_g}{W_0 - W_0}/W_0\right) \times 100
\]

Where,

- \( SR \) = swelling ratio,
- \( Wo \) = initial weight of tablet,
- \( Wg \) = final weight of tablet.

In vitro dissolution studies: The release rate of tablets was determined using US Pharmacopeia 29 (USP29) Dissolution Testing Apparatus 2 (paddle method). The dissolution test was performed using 900 ml of 1.2 pH HCl initially for 2 hour, at 37 ± 1°C and 50 rpm, later it was replaced with the pH 6.8 phosphate buffer and study was continued further for 12 hours. A sample (5 ml) of the solution was withdrawn from the dissolution apparatus at selected time intervals, where withdrawn samples were replaced with fresh dissolution medium to maintain sink condition. Samples were filtered through a 0.45μ membrane filter and absorbance was measured at 232 nm using a UV/visible spectrophotometer. The cumulative drug release was then calculated. The study was performed in triplicate. The optimized formulation was also compared with marketed formulation of metformin HCl for drug release study.

Drug release kinetics: To investigate the drug release kinetics of all formulations, data obtained from in vitro release study was analyzed according to the zero order model, first order model, Higuchi’s model, Hixson-Crowell model, and Korsmeyer-Peppas model.

2. RESULTS AND DISCUSSION

Characterization of okra polysaccharide: Okra polysaccharide was extracted according to the procedure and was characterized for its various physical and chemical attributes.

Solubility study: Okra powder was shown to be sparingly soluble in water and insoluble in acetone, ethanol, and chloroform. An increase in solubility was observed when temperature was applied. However, okra polysaccharide produced clumped gum in acetone and this indicated that acetone is a good precipitating and drying agent to produce dried okra. Okra powder was observed to swell and form viscous dispersion when dispersed in water. The slightly soluble behaviour of okra polysaccharide is useful in this formulation as the swell able and viscous dispersion represents a strong matrix polymeric system that is able to control the release of highly soluble metformin hydrochloride drug in the stomach. The pH of okra polysaccharide is 6.8. Okra polysaccharide is known to have maximum viscosity at a neutral ph range, which helps in the retarding effect for the development of sustained release tablets. Neutral ph also causes minimum irritation to the gastrointestinal tract and is suitable for uncoated tablets.
pH determination: The pH of Okra gum was found to be 6.84±0.35. Okra gum is known to have maximum viscosity at a neutral pH range, which helps in the retarding effect for the development of sustained release tablet.

Moisture content: Moisture content of okra polysaccharide is 14.83%, indicating that okra polysaccharide contains bound moisture to the tablet. This is due to the polymer adsorption sites that are able to bind water molecules to the polysaccharide structure via hydrogen bond which leads to a larger permeability of hydrophilic materials. When okra particles are brought into close proximity, the water sorption will interact, resulting in the formation of a strong inter particulate attraction between the particles. Bound moisture will affect the compressibility of tablets by formation of moisture film on the particles upon applied pressure from the tablet compression machine. This layer of moisture may also lubricate the powder and allow easy flow of tablets by reducing friction on the die wall during tablet ejection.

Viscosity: The viscosity of okra polysaccharide 1% solution is higher (230.84 cps) compared to the viscosity of okra polysaccharide at a lower concentration (0.5% solution) which is 65.36 cps. This indicates that okra polysaccharide has higher viscosity at a higher concentration. The higher the viscosity of the gum, the more sticky it is and this produces tablets with slower drug release and better tensile strength.

Swelling index: The swelling ratio of mucilage, determined in distilled water, was observed to be 119.33±0.57. There was a significant change in swelling by the end of the study, which indicated that the mucilage had excellent swelling properties.

FTIR: FTIR Spectrum of extracted Okra polysaccharide depicted in figure 1(B) showed peak at 2358.94 due to C≡N Stretching of alkynes group, 1510.26 cm⁻¹ due to -N=O asymmetric stretching of nitro compound, 1290.38 cm⁻¹ due to C=N Stretching of aromatic and 1101.35 due to C-H Stretching of aliphatic. FTIR Spectrum of drug (figure 1(C)) showed peak at 2493.96 due to -C≡C- Stretching of alkynes group, 2358.94 due to C≡N Stretching alkynes, 1510.26 due to -N=O asymmetric stretching nitro compound, 937.40 due to O-N bending carboxylic acid.

The interpretation of FTIR spectra of metformin HCl and okra polysaccharide revealed no significant change in the principle and prominent peak of metformin HCl and thus considered to be compatible with Okra polysaccharide.
Post-compression evaluation of metformin HCl tablets

The matrix tablets of metformin HCl were prepared by using okra polysaccharide as polymer in different polymer concentration and studies for their drug release. The formulated tablets were evaluated for friability, hardness, thickness, diameter, weight variation, and drug content. The results are depicted in table no. 4. All the formulation batches (F1 to F7) were uniform in properties signifying no significant weight variation having sufficient hardness in the range of 6.97 – 8.28 kg/cm² indicating uniform formulation of tablets. The weight loss in the friability test of all the formulations was less than 0.92 % i.e. within the permissible limits as specified in IP 2014. The content uniformity of all the batches was in the range of 98.21-100.03 % showing uniformity in drug content.

Swelling index: In study of tablet's swelling index as depicted in Figure no. 2, the weight of tablets prepared with Okra polysaccharide was found to increase up to 5 to 6 hours and decreased at the further hours. This illustrates that Okra polysaccharide was able to absorb water significantly and swell with further erosion of swelled matrix. Swelling of tablet controls and sustains drug release. The swelling index of formulations was found to be in the range of 49 to 67 and was maximum for the batch F6 containing 23.33 % w/w of okra polysaccharide.

Table 4. Post compression characterization of matrix tablets metformin HCl

<table>
<thead>
<tr>
<th>Formulation code</th>
<th>Hardness* (kg/cm²)</th>
<th>Thickness* (mm)</th>
<th>Diameter* (mm)</th>
<th>Friability† (%)</th>
<th>Weight Variation (gm)#</th>
<th>Drug content (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>6.97±0.41</td>
<td>4.06±0.01</td>
<td>14.02±0.98</td>
<td>0.20±0.0.9</td>
<td>0.749±0.01</td>
<td>99.01±0.07</td>
</tr>
<tr>
<td>F2</td>
<td>7.28±0.34</td>
<td>4.04±0.08</td>
<td>14.05±0.05</td>
<td>0.29±0.04</td>
<td>0.750±0.08</td>
<td>98.21±0.26</td>
</tr>
<tr>
<td>F3</td>
<td>7.30±0.46</td>
<td>4.03±0.04</td>
<td>14.09±0.28</td>
<td>0.72±0.04</td>
<td>0.750±0.04</td>
<td>99.24±0.51</td>
</tr>
<tr>
<td>F4</td>
<td>7.11±0.09</td>
<td>4.07±0.02</td>
<td>14.07±0.06</td>
<td>0.92±0.02</td>
<td>0.749±0.08</td>
<td>99.1±0.08</td>
</tr>
<tr>
<td>F5</td>
<td>8.28±0.09</td>
<td>4.09±0.01</td>
<td>14.03±0.02</td>
<td>0.20±0.07</td>
<td>0.749±0.15</td>
<td>99.4±0.14</td>
</tr>
<tr>
<td>F6</td>
<td>8.21±0.17</td>
<td>4.04±0.08</td>
<td>14.02±0.19</td>
<td>0.74±0.01</td>
<td>0.750±0.09</td>
<td>100.03±0.08</td>
</tr>
<tr>
<td>F7</td>
<td>7.26±0.17</td>
<td>4.1±0.05</td>
<td>14.04±0.25</td>
<td>0.55±0.10</td>
<td>0.749±0.12</td>
<td>99.4±0.05</td>
</tr>
</tbody>
</table>

Mean ± S.D. *n=3, †n=10, #n=20

In vitro drug dissolution studies: Results of in vitro drug dissolution studies are revealed in Figure no. 3. To study the effect of polymer concentration on drug release profile, different formulations containing various percentages of Okra polysaccharide were used.

The drug release was found to retard with the increase in concentration of polysaccharide in the formulation. By increasing the polymer concentration a viscous gel layer is formed resisting to erosion and the diffusion of the drug is controlled and sustained for more than 14 hrs coating 23.33 % w/w of Okra polysaccharide in formulation.

The formulations F4, F5, and F7 containing 16.66 %, 20.0 %, and 26.66 % w/w polysaccharide were able to sustain the drug release up to 12 hrs. The swollen matrix of polymer retains more water until the shearing in the dissolution medium disentangle the polymer and further erosion of the polymer take place. It prolongs the release of drug from the polymer matrix. In addition the release of drug of formulation F6 was also compared with marketed formulation of metformin HCl. Results are illustrated in figure 4 indicated that formulation prepared with okra polysaccharide (F6) sustains the release of drug similar to that of the marketed preparation of metformin HCl.
Drug Release Kinetics: The release data were fitted to kinetic models in order to investigate the drug release kinetics. It was found that the in vitro drug release of optimized formulation (F6) was best fitted to the Higuchi's kinetic model, as the plot showed the highest linearity ($R^2=0.983$). The results of release kinetics studies indicate that the drug release is controlled by diffusion principle. The tablets swell well if immersed in dissolution medium and sustains the diffusion of drug from the tablets matrix. To verify the diffusion mechanism, the data were fitted into Korsmeyer-Peppas equation. The release exponent ($n$) of Korsmeyer–Peppas equation was found to be $0.989$ for optimized F6 formulation indicating the non-Fickian or anomalous diffusion mechanism of drug release.

3. CONCLUSIONS

Metformin HCl sustained release matrix tablets were prepared using Okra polysaccharide as a sustained release matrix excipient. The formulated tablets were evaluated and the results indicate that as the concentration of polysaccharide increased, drug release was retarded due to increase in the swelling index and strength of the polymer matrix when comes in contact with dissolution medium. Thus it can be concluded that okra polysaccharide obtained from fresh fruits of Okra is an efficient sustained release matrix former used for preparation of sustained release metformin HCl tablets.

5. REFERENCE


