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Formulation and Evaluation of Sustained Release Metformin Hydrochloride Matrix Tablet Using Natural Polysaccharide

Dharmendra Solanki[1*], Surendra kumar Jain[2], Sujata Mahapatra[3]
1. Charak Institute of Pharmacy, Mandleshwar, M.P, India
2. Sagar Institute of Research and Technology, Bhopal, M.P, India
3. Khallikote College, Berhampur,Orissa, India.

ABSTRACT

The aim of this investigation was to develop and optimize Metformin Hydrochloride matrix tablets for sustained release application. The sustained release matrix tablet of Metformin Hydrochloride was prepared by wet granulation technique using Tamarind pulp polysaccharide. The polysaccharides obtained after extracted from natural source and evaluated for their colour, viscosity and pH. The prepared tablet was evaluated for their hardness, friability, drug content, *In vitro* dissolution, swelling studies. *In vitro* drug release profiles of Metformin Hydrochloride Tablet using Tamarind pulp polysaccharide formulation release of drug from the Tablet exhibited a sustained & controlled pattern over an extended time period. .The tablet formulation TF-1 was found to release the drug of about 95% after 12 hrs, The tablet formulation TF-5 was found to release the drug of about 70% after 12 hrs, thus concluded to have sustained drug release for longer period of time in sustained and controlled pattern when compared to other tablet formulations. Using Higuchi's Model and the Korsmeyer equation, the drug release mechanism from the sustained release tablets was found to be Anomalous (non-Fickian) diffusion. Compatibility study confirmed that interactions do not exist between the drug and polymer.

Keywords: Metformin Hydrochloride, Tamarind pulp Polysaccharide, matrix tablet, Sustained Release. Swelling index.

*Corresponding Author Email: dharmendrasolanki29@gmail.com
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INTRODUCTION

Sustained-release oral delivery systems are designed to achieve therapeutically effective concentrations of drug in the systemic circulation over an extended period of time. Possible therapeutic benefits of a properly designed SR dosage form include low cost, simple processing, improved efficacy, reduced adverse events, flexibility in terms of the range of release profiles attainable, increased convenience and patient compliance.[1-2] Polysaccharides are regarded as key ingredients for the production of bio-based materials in life sciences (e.g., food, cosmetics, medical devices, and pharmaceutics). The biodegradability and biocompatibility of these biopolymers, coupled to the large variety of chemical functionalities they encompass, make them promising carriers for drug delivery systems. Polysaccharides are the polymers of monosaccharide's (sugar). They are found in abundance, have wide availability, are inexpensive and are generally regarded as safe (GRAS). Natural polysaccharides are now extensively used for the development of solid dosage forms for delivery of drug to the colon. Use of naturally occurring polysaccharides is attracting lot of attention for drug targeting to the colon since these polymers of monosaccharide are found in abundance, have wide availability, inexpensive and are available in a variety of structures with varied properties. They can be easily modified chemically and biochemically and are highly stable, safe, non-toxic, hydrophilic, gel forming and biodegradable.[3-5] Metformin hydrochloride is 1, 1-dimethyl biguanide hydrochloride, which is white, crystalline; hygroscopic powder and highly water soluble anti-hyperglycemic (anti-diabetic) agent used in the treatment of type II *i.e.* non-insulin-dependent diabetes mellitus. Its relatively low (50-60 %) bioavailability together with short and variable biological half-life (0.9-2.6 h) require repeated administrations of high doses to maintain effective plasma blood concentrations, thus reducing patient compliance and/or enhancing the incidence of side effects. It has been reported that its absorption is proximal small intestines.[6-7] Therefore, sustained release dosage forms are developed to avoid repeated administration. Hence, sustained release tablets are formulated to achieve an extended action for a time period of 12 hrs. The objective of present investigation is to prepare and evaluate sustained release matrix dosage form of Metformin Hydrochloride using natural polysaccharide which will help to sustain the drug release in the GIT.

MATERIAL AND METHOD

Materials

Fresh young Tamrind fruit were bought from local market for the extraction of the polysaccharide. Metformin was received as a gift sample from Yarrow Chem. Products, Mumbai. Lactose

monohydrate, Magnesium stearate and other excipients used to prepare the tablets were of standard pharmaceutical grade and all other chemical reagents used were of analytical grade.

Method

Extraction and evaluation of polysaccharides[8]

The natural polysaccharides from the respective natural source (Tamrind fruit) were extracted following the method described elsewhere. In this method, 250 gm natural material obtained from the source were soaked in double distilled water and boiled for 5 hrs in a water bath until slurry was formed. The slurry was cooled and kept in refrigerator overnight so that most of the undisclosed portion was settled out. The upper clear solution was decanted off and centrifuged at 500 rpm for 20 minutes. The supernatant was concentrated at 60°C on a water bath until the volume reduced to one third of its original volume. Solution was cooled down to the room temperature and was poured into thrice the volume of acetone by continuous stirring. The precipitate was washed repeatedly with acetone and dried at 50°C under vacuum. The dried material was powdered and kept in desiccators.

Colour:

After complete extraction and drying the polysaccharides were evaluated for colour by visualization.

pH:

A 1%w/v solution of the polysaccharides were prepared and its pH were measured in digital pH meter.[9]

Viscosity:

The viscosity of 1% w/v solution of the polysaccharides were measured in Ostwald viscometer.[10]

Preparation of Matrix Tablets [11-12]

Tablets containing Metformin Hydrochloride were prepared by wet granulation technique using the formula given in the table 1 and lactose as filler. Different tablets formulations were prepared by wet granulation method. All the powders were passed though #60 sieve. This is accomplished by adding a liquid binder or an adhesive to the powder mixture, passing the wetted mass through a screen of the desired mesh size, drying the granulation and then passing through a second screen of smaller mesh to reduce further the size of the granules. Metformin Hydrochloride controlled release tablets were prepared with natural polysaccharide and other additives. Metformin Hydrochloride and, lactose were mixed together, and granulate it with the natural polysaccharide solution until a wet mass was obtained. Then the coherent mass was passed through #16 and the granules were dried at 40 + 2 °C for 2 hours. Dried granules were passed through #20 and

lubricated it with magnesium stearate and talc was added to the granules. Then the lubricated granules were compressed into tablets using tablet punching machine. The compressed tablets were dedusted and evaluated for various tablet properties.

Table 1 Formulation of Metformin Hydrochloride Tablets Using Tamrind pulp Polysaccharides (TPP)

Ingredient	TF1	TF2	TF3	TF4	TF5
Drug Metformin Hydrochloride	500	500	500	500	500
Lactose Monohydrate	117.6	104.8	92	79.2	66.4
Tamarind pulp polysaccharide	12.8	25.6	38.4	51.2	64.0
Talc	6.4	6.4	6.4	6.4	6.4
Magnesium Stearate	3.2	3.2	3.2	3.2	3.2
Total Weight	**640**	**640**	**640**	**640**	**640**

All quantities were in milligrams.

All the batches contained 1% w/w talc and 0.5% w/w magnesium stearate

Evaluation of prepared matrix tablet of Metformin Hydrochloride

Pre-compression characteristics [13-15]

All the formulation prepared was evaluated for Angle of repose, Bulk density, and Compressibility index.

Post-compression characteristics [16-19]

All the formulation prepared was evaluated for Weight variation test, Thickness and diameter, Hardness and Friability test.

Drug content [20]

Five tablets were weighed individually and powdered. The powder equivalent to average weight of tablets was weighed and drug was extracted in Phosphate buffer pH 6.8, the drug content was determined measuring the absorbance at 233 nm after suitable dilution using a UV- Vis double beam spectrophotometer Shimadzu 1800, Japan.

***In vitro* dissolution study of tablet** [21]

The *in vitro* release of Metformin Hydrochloride from the formulated tablets was carried out in Tablet dissolution tester USP- Electro lab USP- TDT- 08L using 900 ml of dissolution medium maintained at 37.0 ±0.5°C and a stirring rate of 100 rpm. Six tablets from each formulation were tested individually in simulated gastric fluid (pH 1.2) for the first 2 h and in phosphate buffer (pH 6.8) for the following 10 h. At every 1 h interval, samples of 5 ml were withdrawn from the dissolution medium and replaced with fresh medium to maintain the volume constant. After filtration and appropriate dilution, the amount of DS resent in each sample was determined spectrophotometrically at 233 nm.

***In vitro* drug release kinetic study of tablet [22-23]**

To examine the drug release kinetics and mechanism, the cumulative release data were fitted to models representing zero order (Q v/s t), first order [Log(Q0-Q) v/st], Higuchi's square root of time (Q v/s t1/2) and Korsmeyer Peppas double log plot (log Q v/s log t) respectively, where Q is the cumulative percentage of drug released at time t and (Q0-Q) is the cumulative percentage of drug remaining after time t. In short, the results obtained from in vitro release studies were plotted in four kinetics models of data treatment as follows:

- Cumulative percentage drug release Vs. Time (zero order rate kinetics)
- Log cumulative percentage drug retained Vs. Time (first order rate kinetics)
- Cumulative percentage drug release Vs. √T (Higuchi's classical diffusion equation)
- Log of cumulative percentage drug release Vs. log Time (Peppas exponential equation)

Swelling Index [24]

The swelling index of tablets was determined in pH 6.8 phosphate buffer at room temperature. The swollen weight of the tablets was determined at predefined time intervals. The swelling index (SI) was calculated by the following equation:

$$\text{SI}\ (\%) = \frac{(\text{Weight of Swollen Tablet} - \text{Initial Weight of Tablet})}{(\text{Initial Weight of Tablet})} \times 100$$

Compatibility Studies [25]

Compatibility with excipients was confirmed by FTIR studies. The pure drug and its formulations along with excipients were subjected to IR studies. In the present study, the potassium bromide disc (pellet) method was employed for the same and compares the pure drug peak with combination of drug and polymer peak.

RESULTS AND DISCUSSION

Characterization of natural polysaccharides

The polysaccharides obtained after extraction Cremish white in colour. The viscosity were found to be 12.46 cp for Tamarind polysaccharide, The pH were found to be 6.2 for Tamarind pulp polysaccharide

Pre-Compression Characterization of Metformin Hydrochloride Matrix Tablet

The angle of repose for the formulated blend was carried out and the results were shown in table 2 It concludes all the formulations blend was found to be in the range from 21-26 its indicate well to passable flow of granules. Compressibility index was found in the range from 9.14 % -22.21 % indicating the powder blend has the excellent to good flow property for compression.

Table 2 Pre-Compression Characterization of Metformin Hydrochloride Matrix Tablet

Batch No.	Bulk Density (gm/ml)	Tapped Density (gm/ml)	Carr's Index (%)	Housner Ratio	Angle of Repose (°)
TF-1	0.614	0.789	22.21	1.28	26
TF-2	0.668	0.726	15.42	1.08	22
TF-3	0.699	0.776	9.92	1.11	21
TF-4	0.621	0.712	12.78	1.14	24
TF-5	0.656	0.722	9.14	1.10	23

Post-compression characterization of Metformin Hydrochloride matrix tablet

Microscopic examinations of all the tablets formulations were found to be circular shape with no cracks. The measured hardness of tablets of each batch ranged between 4.02 to 6.06 kg/cm^2 (Table 3). This ensures good handling characteristics of all batches. The % friability was less than 1% in all the formulations ensuring that the tablets were mechanically stable. The percentage weight variations for all formulations were tabulated in Table 3**.** All the formulated tablets passed weight variation test as the % weight variation was within the Pharmacopoeia limits of ±7.5% of the weight. The weights of all the tablets were found to be uniform with low standard deviation values.

Drug Content (%)

The drug content for all the formulated tablets was found to 98.86% to 99.76 % of Metformin Hydrochloride. It complies with official specifications. The results were shown in Table 3

Table 3: Post-compression characterization of Metformin Hydrochloride matrix tablet

Batch No.	Weight Variation (%) (n=20)	Hardness kg/cm2 (n=3)	Friability (%) (n=20)	Drug Content (%) (n=3)
TF-1	0.13	4.02	0.47	99.16
TF-2	0.20	4.51	0.38	99.76
TF-3	0.26	5.01	0.21	99.10
TF-4	0.63	5.58	0.19	99.17
TF-5	0.43	6.06	0.11	98.86

where n is number of Tablets.

***In vitro* drug release study**

In vitro drug release profiles of the prepared Metformin Hydrochloride tablets were studied. The release data obtained from all the formulations TF-1, TF-2, TF-3, TF-4, TF-5 were mentioned in Figure.1. The release of drug from the Tablet exhibited a sustained & controlled pattern over an extended time period. The tablet formulation TF-1 was found to release the drug of about 95% after 12 hrs, The tablet formulation TF-5 was found to release the drug of about 70% after 12 hrs, thus concluded to have sustained drug release for longer period of time in sustained and controlled pattern.

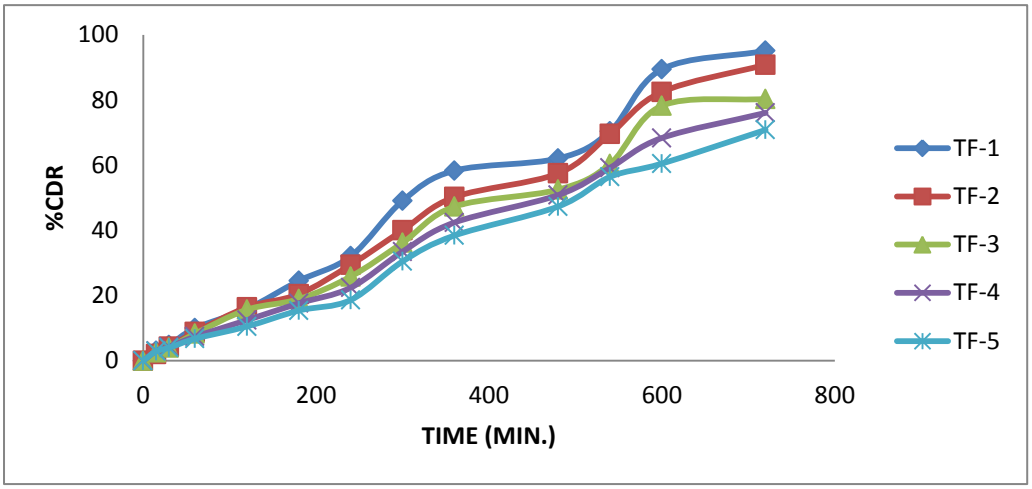


Figure. 1: *In vitro* Release Data for Formulation using Tamarind pulp polysaccharide

Kinetic Modeling for Drug Release

In vitro release data obtained for all the formulations are tabulated in table 4 and shows cumulative percentage drug released. The cumulative percentage drug release data obtained were fitted to zero order, first order, Higuchi's square root of time and Korsemeyer-Peppas equations to understand the mechanism of drug release from the matrix tablet. The slopes and the regression coefficient of determinations (r^2) were listed in table. From the in vitro release data it is evident that the formulations viz formulations from TF-1 to TF-3 shows 'n' values in the range from 0.992 to 0.996, this indicated Non Fickian diffusion mechanism. TF-4 and TF-5 shows 'n' values more than 1, which indicates case II transport for these formulations.

Table 4: Regression co-Efficient (r^2) of different kinetic models and diffusion exponent (n) of Peppas model

Batch No	Zero Order	First Order	Higuchi Matrix	Peppas Plot	
				r^2	'n' value
TF-1	0.9823	0.9461	0.8785	0.9846	0.922
TF-2	0.9934	0.9466	0.8649	0.9934	0.996
TF-3	0.9850	0.9540	0.8644	0.9853	0.974
TF-4	0.9941	0.9637	0.8625	0.9941	1.004
TF-5	0.9923	0.9627	0.8503	0.9928	1.040

Swelling Index study

The results of the swelling study in terms of swelling index (%) are presented in the following figure. 2.

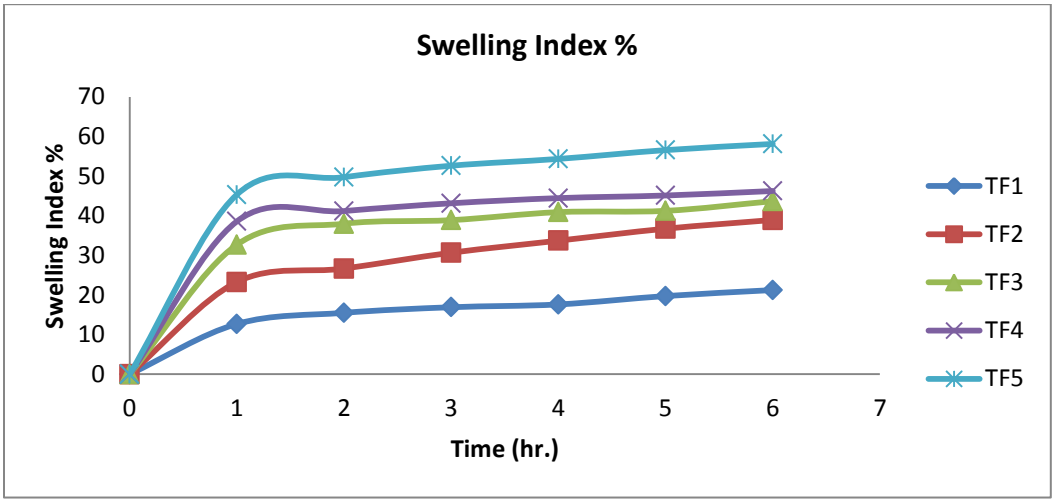
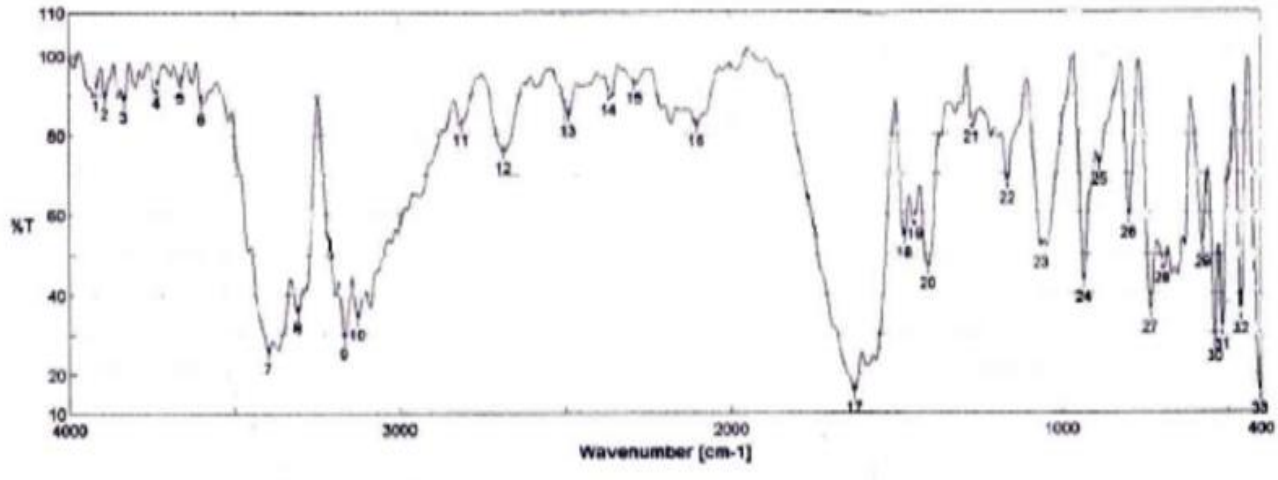


Figure 2- Swelling index of formulations containing Tamarind pulp polysaccharide

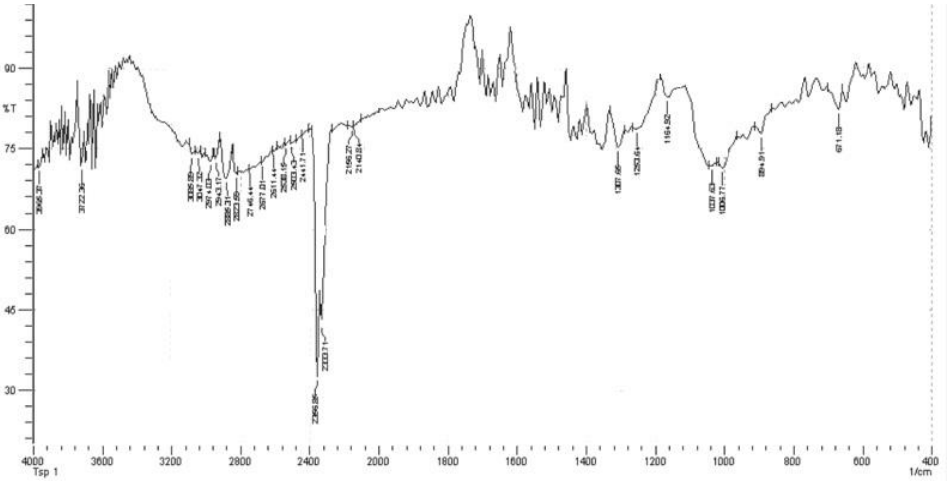
Drug Polymer Compatability Study

Fourier Transform Infrared Spectroscopy (FTIR)

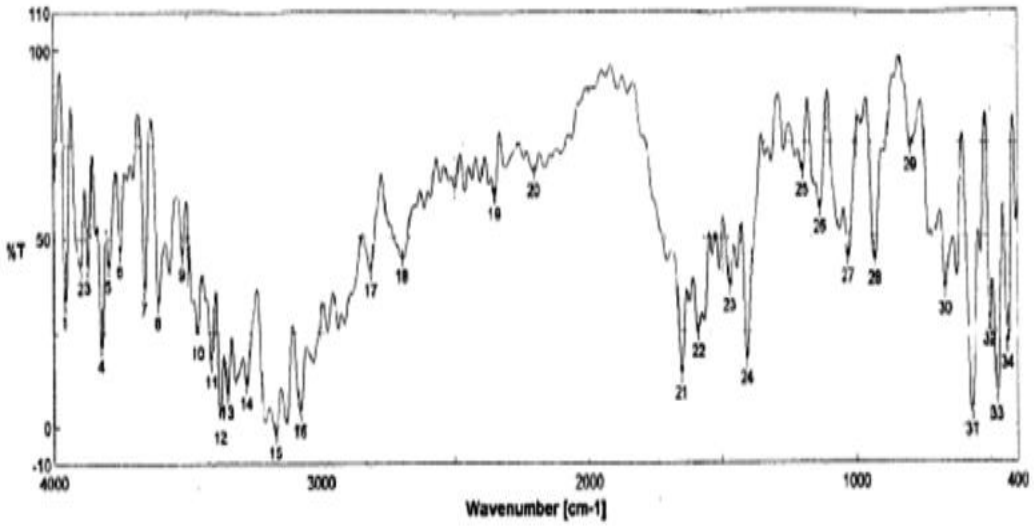
Compatibility study of drug and Polysaccharide was conducted by employing I.R. Spectral studies. The IR spectrum of Metformin Hydrochloride, Tamarind pulp polysaccharide and their physical mixtures are shown in Figure. The following characteristic peaks were observed with Metformin Hydrochloride as well as the formulations containing Tamarind pulp polysaccharide and Metformin Hydrochloride. C=N- (stretching) 1629.55, 1655.59, 1669 cm-1, C-N- (stretching) 1061.62, 1029.48, 1030.77 cm-1, N-H- (stretching) 3397.96, 3378.67, 3394.1 cm-1. As the identical principle peaks were observed in all the cases, Hence it shall be confirmed that interactions do not exist between the drug and polymer.



(a)



(b)



(c)

Figure 3: FTIR spectra showing (a) Metformin Hydrochloride (b) Tamarind pulp polysaccharide (c) physical mixtures of drug and polysaccharide

CONCLUSION

The present investigation was carried out to develop sustained delivery of Metformin Hydrochloride for an effective and safe therapy by using three natural polymers i.e. Tamarind pulp polysaccharide. From this present study it can be concluded that: The drug content was uniform in all the formulations of tablets prepared. The low values of standard deviation indicate uniform distribution of drug within the matrices. Infrared spectroscopic indicated that the drug is compatible with the polymers. From all above parameters it is concluded Tamarind pulp polysaccharide are suitable polymer for the modify the release property of Metformin Hydrochloride by preparing sustained release matrix tablet.

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