ORIGINAL ARTICLE

Butea monosperma Gum as Matrix Former for Oral Sustained Release Matrix Tablet

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Abstract

Context: There is need to develop cheap and effective natural excipient that can be used as an alternative in pharmaceutical formulation due to their non-toxicity, easy availability, biodegradability, and biocompatibility. **Aims:** The purpose of this research was to develop and evaluate sustained release matrix tablets of metoprolol tartrate based on natural gum exudates of *Butea monosperma*. **Materials and Methods:** *B. monosperma* gum was characterized for its properties such as compressibility index, angle of repose, viscosity, and moisture content. The interaction between the gum and metoprolol tartrate was studied through differential scanning calorimetry and Fourier transform infrared spectroscopy. Matrix tablets were prepared by wet granulation method with different concentrations of *B. monosperma* gum and guar gum and evaluated for their physical properties such as weight variation, hardness, friability, and content uniformity. A dissolution study was conducted to characterize the release mechanism from the matrix system, and data were fitted to various kinetic models. **Results:** The mechanism of drug release from both types of matrix tablets was found to be anomalous type. The F5 batch prepared using *B. monosperma* gum shows 92.45% release in 24 h. **Conclusions:** *B. monosperma* gum could be used as drug release retardant in sustained release matrix systems.

Key words: *Butea monosperma* gum, guar gum, hydrophilic matrix tablets, sustained release

INTRODUCTION

Polysaccharide hydrocolloids such as mucilages, gums, and glucans are abundant in nature and commonly found in many plants.[1] They are useful as tablet binders, disintegrants, emulsifiers, suspending agents, stabilizing agents, thickening agents, and as matrix polymer.[2,3] This increased interest in natural polysaccharides is due to their non-toxicity, easy availability, biodegradability, and biocompatibility.[4,5] Oral matrix tablets are the most frequently manufactured and used system because of their technological simplicity, ease of fabrication and convenience.[6,7]

Butea monosperma (palasa) is a fast growing, medium sized tree belonging to *Fabaceae* family, native to Asia tropical, Asia temperate and Australasian region.[8] The gum was obtained from the bark of the tree *B. monosperma*. Structural studies on *B. monosperma gums* reveal the presence of leukocyanidin, procyanidin, gallic acid, and mucilaginous material.[9] This gum is a dried astringent juice obtained from incisions in the stem of the tree. The juice exuded by the bark hardens into brittle ruby colored gum beads.[10] Literature revealed that the acute toxicity study of methanolic extract of *B. monosperma* gum showed no mortality or toxic reaction at fixed dose of 2000 mg/kg body weight. Hence, *B. monosperma* gum can be used in formulation.[11,12] Recent studies on *B. monosperma* gum exudates have shown that it is useful as a binding agent in tablet formulations.[13] Metoprolol tartrate is a cardioselective beta-blocker, with its incomplete oral bioavailability, short half-life, and multiple daily dosing, is appropriate for a formulation in a once-a-day extended-release dosage form.[14,15]

This study was aimed to evaluate the feasibility of using *B. monosperma* gum as matrix material for sustained

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Received: 10-09-2016
Revised: 24-09-2016
Accepted: 02-10-2016

release of drugs. *B. monosperma gum* based matrix tablets were prepared using metoprolol tartrate as a model drug and compared with matrix tablets prepared using guar gum (generally recognized as safe excipient).[16]

MATERIALS AND METHODS

Materials

The leaves, gum of *B. monosperma* plant were collected from the local region of Aurangabad Maharashtra, India, in the month of December - February and it was authenticated by Dr. Arvind Dhabe from the Department of Botany, Dr. Babasaheb Ambedkar Marathwada University Aurangabad. Voucher specimen, accession No. 0571 was deposited in the herbarium of Department of Botany, Dr. BAMU, Aurangabad. Microcrystalline cellulose (Avicel PH 101, Sigma-Aldrich), metoprolol tartrate (Lupin, Aurangabad), and guar gum (Research lab fine chem. Industries, Mumbai) were procured from different sources. All other chemicals and reagents used were of analytical grade.

Extraction of gum from *B. monosperma*

The gum was extrudated from the *B. monosperma* plant after incision at bark and thick dark brown crystalline material collected after successive interval from the same plant and in the same season. Then, collected gum was dried, ground, and passed through sieve No 80. This powdered gum from *B. monosperma* plant was stirred in distilled water for 6-8 h at room temperature then filtered to remove the impurities. Then, gum was extracted with alcohol. This precipitated gum was filtered through muslin cloth, and gum was isolated and dried in oven at 45°C till it completely dried. The powdered gum was passed through 80# sieve and it was weighed to calculate yield.[13,17]

Characterization of *B. monosperma* gum

The physicochemical properties and phytochemical analysis of gum were performed as per Indian Pharmacopoeia and British Pharmacopoeia.[18,19] The properties such as moisture content, Ash content, solubility, microbiological properties, pH, specific gravity, loss on drying, viscosity, and compressibility index were determined.[20] For identification of separated gum, biochemical tests were performed such as Molisch's test, ruthenium test, and iodine test.[21]

Preformulation study of model drug

Preformulation studies including purity of drug candidate, its identification, melting point, solubility, and calibration curve were evaluated. Characterizations of drug studies were done according to Indian Pharmacopoeia.[18]

Compatibility study

The compatibility of *B. monosperma* gum with the model drug was established through differential scanning calorimetry (DSC) and Fourier transform infrared (FTIR) studies.[22,23]

FTIR spectroscopy

FTIR spectrum for the dried *B. monosperma* gum alone, metoprolol tartrate alone, and gum-metoprolol tartrate mixture (1:1) were recorded with FTIR spectrophotometer (Shimadzu, Japan). The sample was prepared by using potassium bromide and scanned for absorbance 4000-400/cm^{-1}.[23]

DSC studies

For each analysis, about 8 mg of the sample was taken into the aluminum sample pan and sealed. Empty aluminum pan was used as a reference, and the thermogram (Shimadzu, Japan) was then recorded for *B. monosperma* gum alone, metoprolol tartrate, and gum-metoprolol tartrate mixture (1:1).[24,25]

X-ray diffraction studies (XRD)

XRD of pure *B. monosperma* gum were carried out to access the crystallinity of gum and it was recorded using diffractogram (XPERT-PRO).[26]

Preparation of metoprolol tartrate matrix tablet

Matrix tablets containing metoprolol tartrate were prepared by wet granulation method taking different proportions of *B. monosperma* gum and Guar [Table 1]. The weighed amount (200 mg) of the drug and polymers were blended and passed through sieves No. 250. The powders were granulated with 9:1 isopropyl alcohol and water mixture. The wet mass was passed through sieve No. 30 and dried overnight at 50°C in tray drier. The dried granules were subjected to dry screening trough sieve No. 22. The granules were lubricated with 1% magnesium stearate and 1% talc and compressed at 19.6 kN using 11 mm round, concave punches and dies in 12 stations mini press II MT tableting machine (Karnavati Engineering, India). [27,28]

Characterization test of tablets

The prepared matrix tablets were evaluated for official and non-official test for tablets like weight variation, crushing strength (Monsanto hardness tester), friability (Roche friabilator, India), thickness and content uniformity. Water uptake studies, drug release mechanism, and other physical properties of *B. monosperma gum* based matrix tablets were compared with guar gum based formulations.[29]

Drug content

Drug content in tablets was determined by pulverizing 20 tablets, and powder quantity equivalent to 100 mg of drug was

Table 1: Formulations of different batches of metoprolol tartrate matrix tablets

Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8
Metoprolol tartrate	200	200	200	200	200	200	200	200
B. monosperma gum	40	80	120	160	200	-	-	-
Guar gum	-	-	-	-	-	40	120	200
Lactose	20	20	20	20	-	20	20	-
Microcrystalline cellulose	162	122	82	42	22	162	82	22
Magnesium stearate	4	4	4	4	4	4	4	4
Talc	4	4	4	4	4	4	4	4
Total	430	430	430	430	430	430	430	430

B. monosperma: Butea monosperma

dissolved in 100 ml distilled water. After suitable dilution, it was analyzed (ultraviolet (UV)-spectrophotometer, Shimadzu, Japan) at 223 nm wave length.

Water uptake

Each tablet was initially weighed (W1) and then placed in a beaker containing 250 ml of distilled water maintained at 37°C ± 0.5°C in a dissolution rate test apparatus TDT-08T (Electrolab, Mumbai).[30] The paddles were rotated at 50 rpm and tablets were removed from the medium at different time intervals (up to 12 h), dried between two filter papers to remove surface water and re-weighed (W2). The percentage water uptake was determined using the following equation.

$$\% \text{ Water uptake} = W2 - W1/W1 \times 100$$

In vitro release

The *in vitro* drug release study was conducted using USP dissolution rate test apparatus, Type-I (Labindia, India) at 37°C ± 0.5°C. Dissolution medium was 900 ml of phosphate buffer pH 6.8 and the agitation speed was maintained at 50 rpm. 5 ml of the sample was withdrawn at a predetermined time interval and replaced immediately with equal volumes of prewarmed dissolution media. The withdrawn samples were filtered through 0.45 µm membrane filter, diluted suitably and analyzed spectrophotometrically at 223 nm using UV-visible spectrophotometer (Shimadzu, Japan).[31,32]

Release kinetics

The release data obtained from *in vitro* dissolution studies were fitted to various kinetic equations to find out the mechanism of drug release from the matrix tablets. The kinetic models used include zero-order equation, first-order equation, Higuchi equation, Hixson-Crowel cube root law, and Korsemeyer–Peppas equation. Correlation coefficients were determined from the plots which assessed fitness of the data into various kinetic models. The rate constants, for respective models, were also calculated from slope. To compare the effects of polymers on the drug release, a model independent method of release profile comparison was also performed.[33,34]

Stability of matrix tablet

To study the effect of temperature and humidity on the tablets, matrix tablets were stored at 40°C ± 2°C and 75% ± 5% RH in humidity chamber (Standard Model, Thermolab, India). After 3 months, percent content of the drug was determined and FTIR spectrum along with DSC thermogram was recorded to observe any effect caused on the tablets by the exposure to humidity and temperature.[35]

RESULTS AND DISCUSSION

Characterization of *B. monosperma* gum

The purified *B. monosperma* gum was pale white in color, odorless and slowly soluble in water yielding viscous solution. The percentage yield of the purified gum was found to be 45.00% (w/w). It was characterized for its physicochemical properties. The results are shown in Table 2.

Pharmacopeial limit for moisture content of natural gums such as acacia and tragacanth has been set at ≤15.0%.[36] The moisture content of the *B. monosperma* gum was found to be within the limit. The value of Carr's index and angle of repose indicates that *B. monosperma gum* possesses a fairly good flow property and compressibility but not good enough to be used as direct compression excipient.[37]

The values of Carr's index below 20% shows good compressibility and above it show poor compressibility. Therefore, wet granulation method was followed in the preparation of the matrix tablets.

Preformulation study of metoprolol tartrate

Physical appearance: The drug was found to be white in color and crystalline in nature which complies with the reported.

Solubility: Very soluble in water; freely soluble in ethanol (95%), in chloroform pH: 2% w/v solution of drug shows pH 6.9.

Melting point: The average melting point of metoprolol tartrate was determined by capillary method and was found to be 135°C, which is in good agreement with reported melting point (131-136°C).

UV absorption spectrum of metoprolol tartrate

The UV spectrum of metoprolol tartrate was obtained, and the λ_{max} was found to be 223 nm which complies with the reported as shown in Figure 1. From the preformulation study of drug, it was found that the drug obtained is of good quality.

FTIR spectroscopy

FTIR spectroscopy was performed to assess the compatibility of metoprolol tartrate with *B. monosperma gum*. The FTIR spectra of metoprolol tartrate, *B. monosperma gum* and metoprolol tartrate - *B. monosperma gum* admixture were depicted in Figure 2. The FTIR spectrum of metoprolol tartrate - *B. monosperma gum* mixture showed all the characteristic peaks of metoprolol tartrate which signifies that there are no significant chemical interactions. Further, all the characteristic peaks of metoprolol tartrate are also observed when the FTIR spectrum was recorded for matrix tablets after 3 months storage under accelerated conditions.

Table 2: Physicochemical properties of *B. monosperma* gum

Parameter	Observations
Moisture content (%)	8.8±0.53
Total cash value	4.1±0.3
Carr's index (%)	21.01
Angle of repose	34.63
Solubility at 10°C	Partially soluble in water and ethanol, Insoluble in chloroform, ether and acetone
Loss on drying (%)	6.5±0.121
Swelling index	9
Viscosity	2.35
pH	7.5

B. monosperma: Butea monosperma

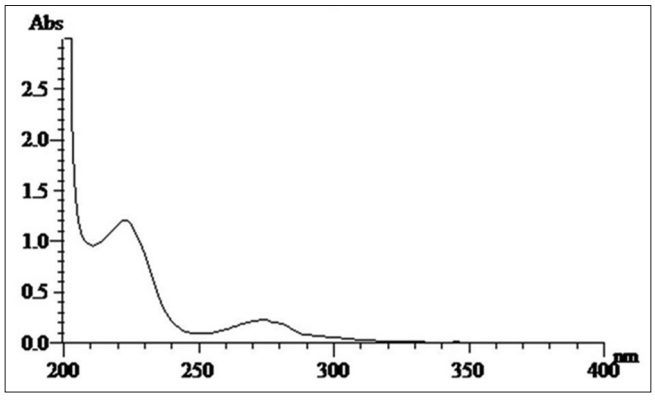

Figure 1: Ultraviolet absorption spectrum of metoprolol tartrate in phosphate buffered saline pH 6.8

DSC analysis

DSC thermograms were given in Figure 3. DSC trace for metoprolol tartrate showed a sharp endothermic peak at 139.53°C and was in accordance with the reported. It was observed that there was no considerable change in the endothermic values of metoprolol tartrate when it was mixed with *B. monosperma* gum and other excipients. Further, after 3 months storage under accelerated condition, there was no significant change in the endothermic characteristics of the drug and this support the absence of interaction between the drug and polymer as shown by IR spectra results.

XRD

The X-ray diffraction pattern of the bulk metallic glasses shown in Figure 4 from it can be seen that *B. monosperma* gum shown peak at 12.90, 19.861, 21.390, 27.260, 75.70. The peaks were diffused; it indicates amorphous nature of gum.

Effect of polymers on physical properties of matrix tablets

Wet granulation method followed in the preparation of granules significantly improve the flow properties as all the batches of formulations showed Carr's index of <15 which indicate good powder flow. The granule was characterized for various properties [Tables 3 and 4].

Results show that all the formulations are within the limit of weight variation and content uniformity. There is no statistical difference ($P = 0.170$, *B. monosperma* gum; $P = 0.172$, guar gum) in weight variation and content uniformity between different batches. All these results showed that *B. monosperma gum* and guar gum produced good quality matrix tablets as per standard specified in pharmacopeia.

Mechanical properties of pharmaceutical tablets are quantifiable by hardness and friability of the tablets. The crushing strength shows that *B. monosperma* gum matrix tablets have a good strength. There is significant decrease ($P \leq 0.001$) in the crushing strength while friability is increased when the concentration of *B. monosperma* gum is increased. A similar trend was also observed with guar gum based matrix tablet formulations. Friability study shows that in all the formulations including *B. monosperma* gum and

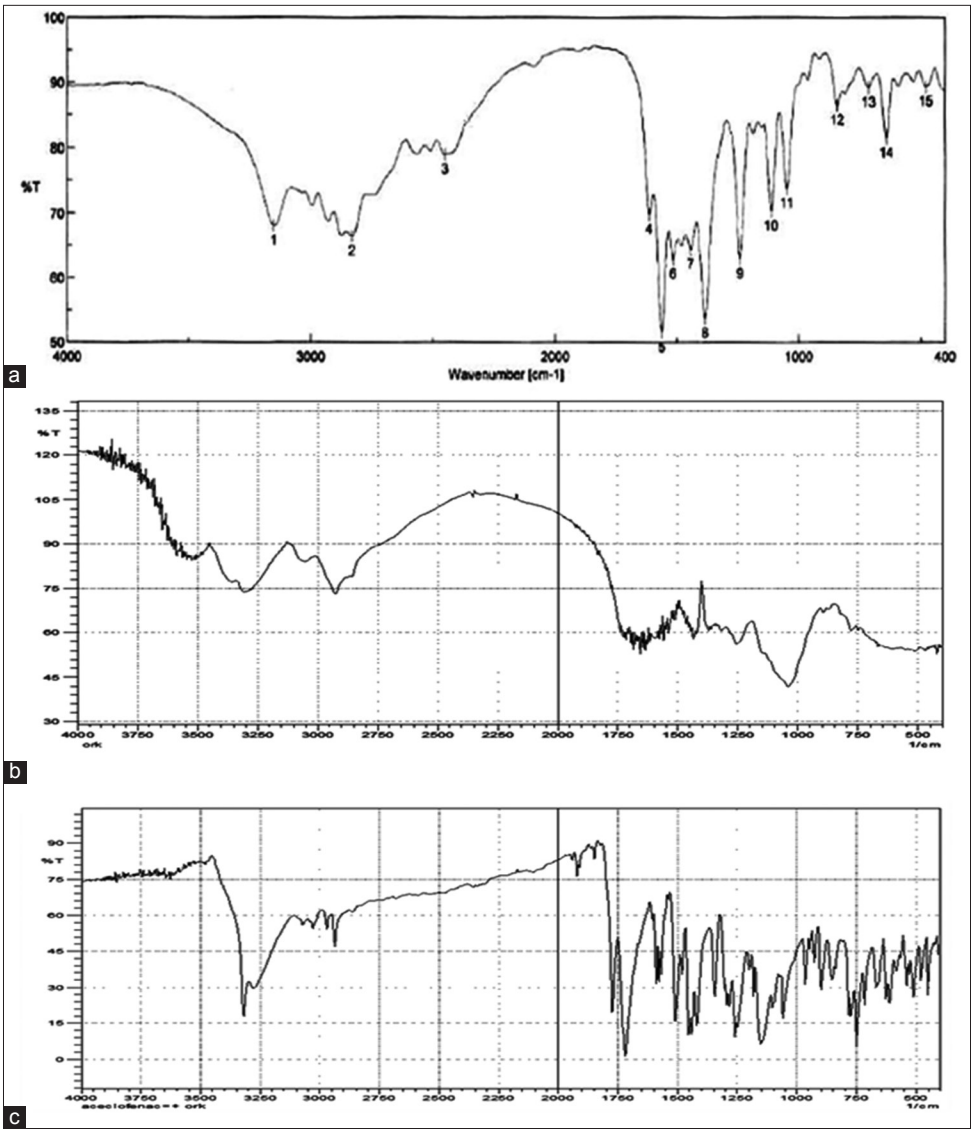

Figure 2: Fourier transform infrared of (a) metoprolol tartrate drug, (b) *Butea monosperma* gum and (c) physical mixture of metoprolol tartrate drug and *Butea monosperma* gum

Table 3: Precompressional characterization of granules obtained from *B. monosperma* gum

Batch	Bulk density (g/cm³)	Tapped density (g/cm³)	Carr's index (%)	Hausner ratio	Angle of repose (°)
F1	0.250	0.292	14.4	1.168	26.82
F2	0.274	0.306	10.5	1.116	28.39
F3	0.269	0.340	20.89	1.263	30.25
F4	0.272	0.313	13.15	1.151	32.49
F5	0.267	0.290	8.152	1.088	30.24
F6	0.276	0.312	11.47	1.129	29.50
F7	0.34	0.36	14.7	1.05	28.45
F8	0.431	0.500	13.76	1.16	20.8

B. monosperma: Butea monosperma

guar gum matrix tablets increase in the concentration of polymers results in increase in friability; however, all the batches were within the limit of 1% friability suggested in the Indian Pharmacopeia.

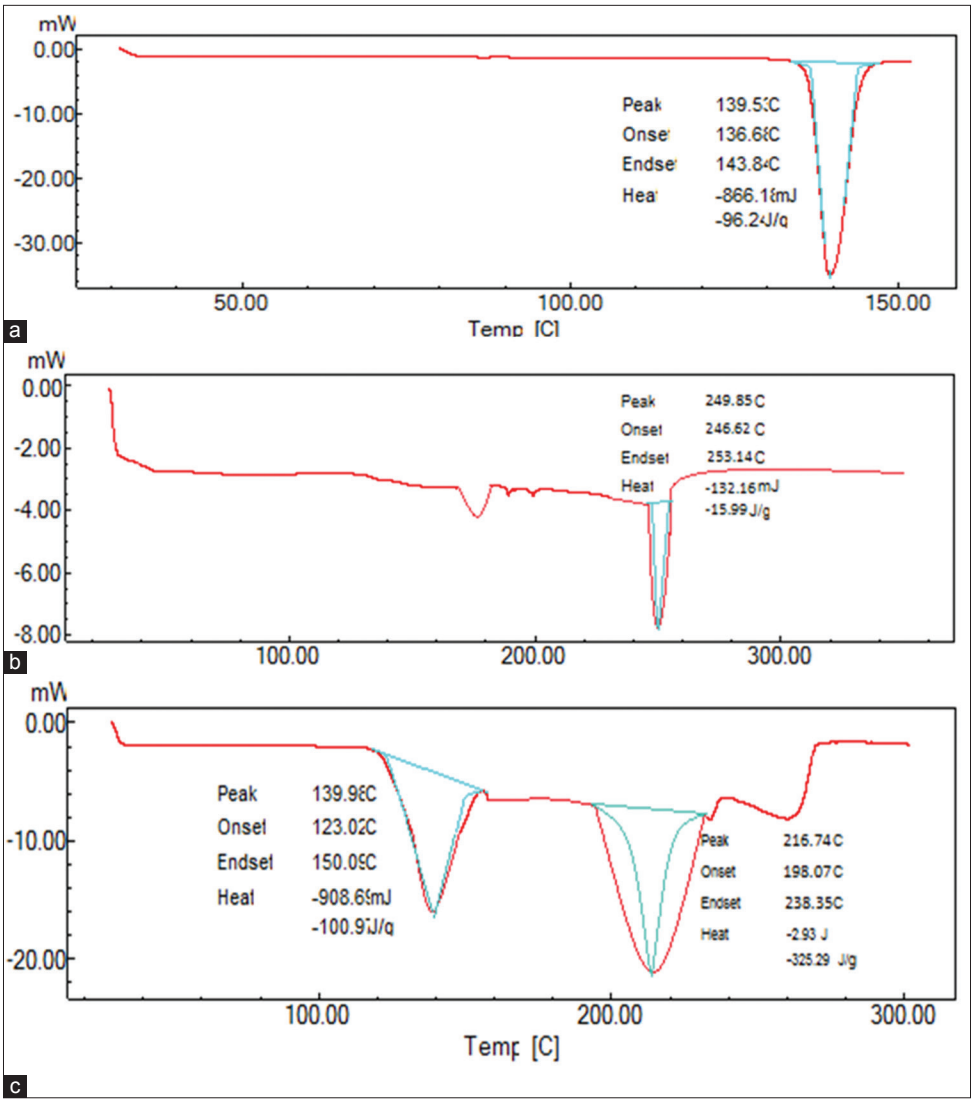

Figure 3: Differential scanning calorimetry thermograms of (a) pure metoprolol tartrate drug, (b) *Butea monosperma* gum and (c) physical mixture of metoprolol tartrate drug and *Butea monosperma* gum

Table 4: Evaluation of matrix tablets prepared with *B. monosperma* gum and guar gum

Batch	Wt variation (mg)	Hardness (kg/cm²)*	Friability (%w/w)*	Thickness (mm)*	Uniformity of content
F1	429.9±0.78	8.13±0.15	0.12	3.59±0.02	98.92±0.88
F2	430±1.01	7.63±0.07	0.12	3.68±0.01	96.25±0.75
F3	429.5±1.96	7.5±0.15	0.14	3.62±0.017	98.02±0.22
F4	429.2±1.86	7.3±0.20	0.20	3.59±0.020	95.82±0.78
F5	430.4±1.91	6.5±0.20	0.23	3.63±0.03	96.22±0.96
F6	428.3±2.50	8.23±0.25	0.13	3.61±0.015	97.08±0.64
F7	430.85±1.94	8.03±0.02	0.18	3.66±0.03	97.26±0.86
F8	429.33±2.02	7.66±0.15	0.26	3.61	96.22±0.96

*Results are mean of three observations±SD. *B. monosperma: Butea monosperma*, SD: Standard deviation

Water uptake

Water uptake study was performed to observe the swelling behavior and erosion characteristics of the matrix tablets. *B. monosperma* gum based formulations exhibit higher water uptake than Guar gum based tablets which result in rapid increase in the weight. *B. monosperma* gum based formulations showed sign of erosion after 2-5 h depending

on the amount of the *B. monosperma* gum.[38,39] Guar gum based formulations showed slow water uptake and steady hydration for 3-7 h depending on the polymer concentration. Faster water uptake leads to increased osmotic force and polymer chain relaxation and this result in erosion of the tablets.

In vitro drug release

The *in vitro* drug release profiles of sustained release matrix tablets containing *B. monosperma* gum and guar gum are depicted in Figure 5. Hydration and swelling of the polymers take place which was correlated with the level of the polymers in the formulations. In the *B. monosperma* gum based formulations, release of metoprolol tartrate in the 1st h varies between 15.2% in F1 and 12.69% in F5 while it was between 13.2% in F6 and 18.4% in F8 guar gum based formulations. The release of drug extended from 8 h in F1 to more than 12 h in F4 in the case of *B. monosperma* gum matrix tablets. The dissolution of F5 Batch of the *B. monosperma* gum and F7 of guar gum was observed optimum.[40,41]

At the end of the dissolution study, formulations containing *B. monosperma* gum were found to be more eroded than guar gum based formulations. It was observed from the dissolution study that *B. monosperma* gum was able to sustain the release of the drug, and the rate and amount of drug release can be sustained by varying the amount of the polymer added to the formulations.

Release kinetics

The release kinetics from matrices composed of *B. monosperma* gum (F5) or guar gum (F7) was analyzed through various equations, and the release kinetic table was prepared as shown in Table 5.

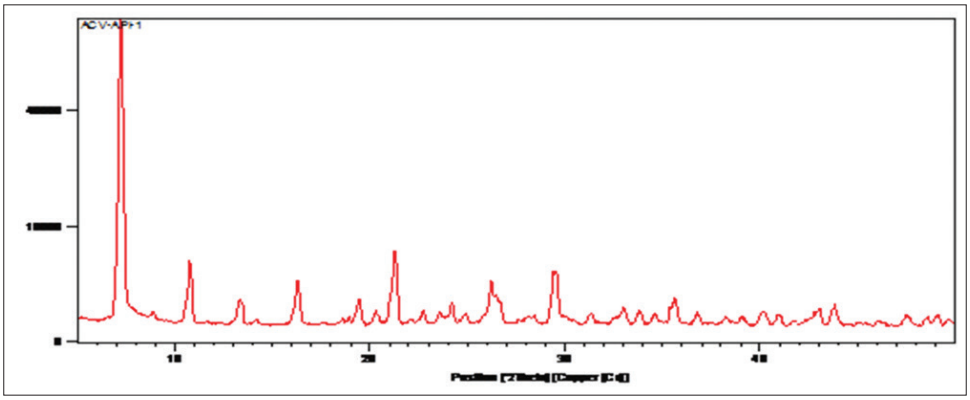

Figure 4: X-ray diffraction pattern of *Butea monosperma* gum

Table 4: Evaluation of matrix tablets prepared with *B. monosperma* gum and guar gum

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F1	429.9±0.78	8.13±0.15	0.12	3.59±0.02	98.92±0.88
F2	430±1.01	7.63±0.07	0.12	3.68±0.01	96.25±0.75
F3	429.5±1.96	7.5±0.15	0.14	3.62±0.017	98.02±0.22
F4	429.2±1.86	7.3±0.20	0.20	3.59±0.020	95.82±0.78
F5	430.4±1.91	6.5±0.20	0.23	3.63±0.03	96.22±0.96
F6	428.3±2.50	8.23±0.25	0.13	3.61±0.015	97.08±0.64
F7	430.85±1.94	8.03±0.02	0.18	3.66±0.03	97.26±0.86
F8	429.33±2.02	7.66±0.15	0.26	3.61	96.22±0.96

*Results are mean of three observations±SD. *B. monosperma: Butea monosperma*, SD: Standard deviation

Table 5: Release Kinetics study of matrices composed of *B. monosperma* gum or guar gum

Batch	Zero order		1st order		Matrix		Peppas		Hix. Crow	
	R^2	k	R^2	k	R^2	k	R^2	k	R^2	k
F5	0.965	4.224	0.966	−0.093	0.956	15.868	0.976	9.903	0.990	−0.022
F7	0.939	4.381	0.979	−0.095	0.979	16.758	0.999	11.480	0.996	−0.023

B. monosperma: Butea monosperma

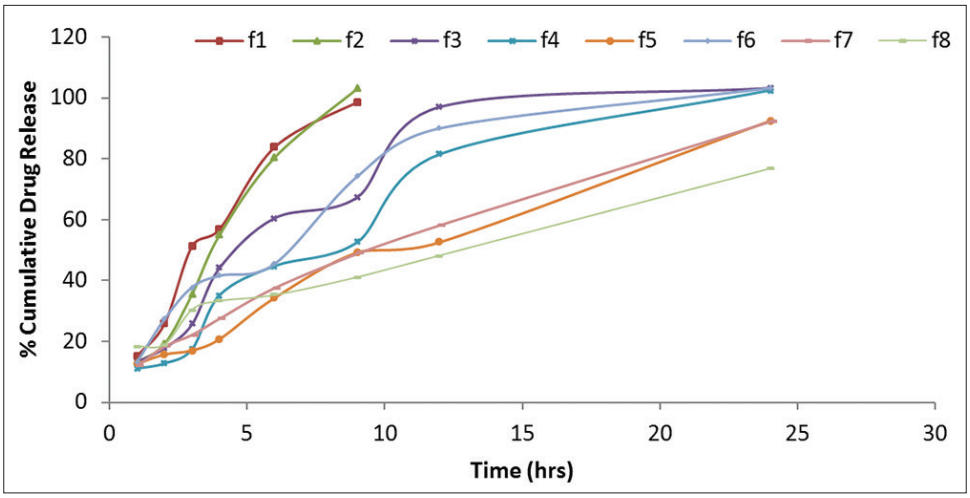

Figure 5: Dissolution release profiles of sustained release matrix tablets containing *Butea monosperma* gum and guar gum

The correlation coefficients (r^2) for F5 for first order release kinetics was found slightly higher (r = 0.966) when compared to that of zero order kinetics (r = 0.965) indicating that the drug release from the formulation followed the first order. Evaluation of release kinetics and application of best fit by correlation coefficient shows that *B. monosperma* gum releases the drug following Hixon-Crowel model and approaches zero-order with increase in concentration.

The correlation coefficients (r^2) for guar gum based formulations were reported to sustain release of drugs by first-order kinetics which may be true for the present study as well. The correlation coefficient for formulations containing guar gum (F7) for the first order release kinetics was found higher (r = 0.979) when compared to that of zero order kinetics (r = 0.939) indicates that first-order and Higuchi equations seemed to be a better fit than other equations.

The release exponent "*n*" calculated from the Korsemeyer-Peppas equation, shows for F5 batch was found to be 0.6753 and for guar gum (F7) 0.652. It can be suggested that the release mechanism was non-Fickian, anomalous transport where release is dependent on both drug diffusion as well as polymer relaxation.

Stability studies

The results of accelerated stability studies indicated that there was no significant change in the matrix tablets. The drug content was found to be within 99.56% ± 5% for all the formulations at the end of the 90 days. FTIR and DSC analysis also suggested that there was no significant degradation or changes taking place in the matrix tablets during the study period.

CONCLUSION

Sustained release matrix tablets formulations of gum exudates from *B. monosperma* were prepared by wet granulation method and its properties were evaluated and compared with guar gum based formulations. Drug release from the *B. monosperma* gum was found to be dependent on the polymer concentration and determination of release mechanism by Korsemeyer-Peppas model indicated that drug release was anomalous, where drug release is dependent on drug diffusion. It was observed that by increasing the amount of *B. monosperma* gum, sustained release of metoprolol tartrate for more than 24 h can be achieved indicating its suitability as release retardant in sustained release formulation.

ACKNOWLEDGMENT

We express our sincere gratitude to Principal, Shree Bhagwan College of Pharmacy, Aurangabad for providing facilities.

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Source of Support: Nil. **Conflict of Interest:** None declared.