FORMULATION AND CHARACTERIZATION OF SUSTAINED RELEASE TABLET USING MARDI GUM

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ABSTRACT

Objective: The present research work was to develop and evaluate alprazolam sustained release tablet using Mardi gum, a comparative study on binding properties of gum and hydroxypropyl methylcellulose (HPMC) was performed.

Methods: Formulation of alprazolam tablets (f1–f6) was done by direct compression method using 15%, 30%, and 45% concentration of gum as a natural binder, and HPMC was used as synthetic matrix forming agent. Microcrystalline cellulose was used as diluents, talc, and magnesium stearate as a lubricant and PVP K30 as the binder. The formulated batches were evaluated for parameters such as tablet thickness, % friability, hardness, weight variation, and *in vitro* drug release characteristics. The release information was fitted into different dynamics models to decide the release mechanism of the drug.

Results: The results showed that all the parameters of the developed tablets (f1–f6) were in fulfillment with pharmacopeia limits. *In vitro*, drug release studies showed that formulation f1 had most controlled and sustained manner releaser with maximum drug release of 97.89±0.52% in 18 h with comparison to f2–f4 and f6 drug release is 98.12±0.55%, 97.24±0.57%, 98.16±0.74%, and 97.26±0.35%, respectively, in 16 h and f5 giving 97.89±0.85% release in 14 h.

Conclusion: On the basis of obtained result, it can be concluded that Mardi gum can be used to sustain the drug release as a natural polymer in tablet dosage form.

Keywords: Alprazolam, Mardi gum, Matrix tablets, Natural polymer, Sustain.

INTRODUCTION

Sustained release delivery system is increasingly being used in the treatment of acute and chronic diseases as they maintain the concentration of drug in plasma above the minimum effective concentration to and below the minimum toxic level for an extended period of time [1,2]. The development of sustained release drug delivery systems has broad been a major area of research in the pharmaceutical industry. Sustained release drug delivery design involves the exploitation of physical and polymer chemistry to dosage form design to formulate well-characterized and reproducible units that control drug delivery into the body within the specification of the required drug delivery profile [3]. Nature provides a noteworthy collection of polymeric materials that have been finding very attractive applications in the biomedical field, as they are well known to perform a varied set of functions in their inhabitant environment [4]. Gadchiroli of Vidarbha region in Maharashtra state is one of the nature surrounding areas, which is well-known forest area having tree with gummy exudates. In the present study, sustained release tablets of alprazolam using exudates from the tree of *Terminalia tomentosa* were prepared to see its application as a release retardant. Sustained release tablets were prepared using natural gum Mardi and synthetic polymer hydroxypropyl methylcellulose (HPMC) by employing a direct compression method. The objective of the work was to explore a novel natural binding agent and to formulate sustained released tablets of alprazolam so as to reduce its frequent administration and to improve patient compliance. Hence, the novelty of the proposed work is the use of Mardi gum as the matrix forming agent to delay the release of the drug.

METHODS

Material alprazolam obtained as a gift sample from Lake Chemicals Pvt. Ltd., Bengaluru, and microcrystalline cellulose pH 102, talc, magnesium stearate, and PVP K30 were obtained as a gift sample from Relief Lab Pvt. Ltd., Kalmeshwar, and HPMC from Loba Chemie Pvt. Ltd., Mumbai, India. All other chemicals used were of analytical grade.

Collection and purification of gum exudates
As the authors described elsewhere, gums were collected from the plants of *T. tomentosa* (Mardi), Mardi was subjected to the stress by making incisions on the trunk in the 1st week of January, and gum was collected in the month of February and March. Collected gum exudates were treated with petroleum ether and chloroform (to remove pigments and chlorophyll) and then carefully washed with distilled water, dried under shade for 24 h, further dried at 30–40°C until a constant weight was obtained. The size was reduced through the grinder. Powdered gum passed through sieve no. #22 and stored in an airtight container for further use. The gums were then precipitated from the solution using acetone. The precipitate was separated, dried in the oven at 50°C, and stored in a tightly closed container for future use as a binder in formulating matrix tablets [5].

Characterization of drug and excipients
An infrared spectrum was taken by scanning the samples of pure drug and the polymers individually over a wavenumber range of 4000–400 cm^{-1} using Fourier transform infrared spectrophotometer (FT-IR, Shimadzu 8400S, Shimadzu, Japan). The change in spectra of the drug in the presence of polymer was investigated which indicates the physical interaction of the drug molecule with the polymer [6].

Preparation of alprazolam tablet
The sustained release matrix tablet of alprazolam was prepared using the direct compression method. A variety of concentrations 15%, 30%, and 45% of natural and synthetic polymers was used. Total seven

formulations were developed using constant 200 mg of alprazolam with amounts of excipients. The polymers being used in the formulation are HPMC and Mardi gum from *T. tomentosa* which is given in Table 1.

Pre-compression parameters

The prepared powder blend was evaluated for various parameters such as angle of repose, loose bulk density, tapped bulk density, and compressibility index [7-9].

Post-compression parameters

All prepared matrix tablets were evaluated for their uniformity of hardness, weight, friability, and thickness according to official methods. Tablet hardness was determined for 10 tablets using a Monsanto tablet

Table 1: Composition of tablet

Ingredients	Batch					
	F1	F2	F3	F4	F5	F6
Alprazolam (mg)	3	3	3	3	3	3
Gum (mg)	30	60	90	-	-	-
Hydroxypropyl methylcellulose (mg)	-	-	-	30	60	90
Microcrystalline cellulose (mg)	153	123	93	153	123	93
PVP K30 (mg)	10	10	10	10	10	10
Talc (mg)	2	2	2	2	2	2
Mg stearate (mg)	2	2	2	2	2	2

hardness tester; thickness was measured by Vernier caliper. Friability was determined by Roche friabilator. The weight variation was determined by taking 20 tablets using an electronic balance all ridings noted in triplicate [10].

Drug content was determined by taking 50 mg equivalent weighed of alprazolam in tablet powder which was accurately weighted and transferred into a 100 ml volumetric flask. At first, 10 ml of phosphate buffer (pH 6.8) was added and shaken for 10 min. After that, the volume was made up to 100 ml with buffer. Subsequently, the solution in the volumetric flask was filtered, and 1 ml of the filtrate was diluted and analyzed at 255 nm using a UV–visible spectrophotometer (Shimadzu, Japan). The drug content of each sample was estimated from their standard curve.

***In vitro* dissolution studies**

In vitro dissolution studies of tablets were studied in USP XXIII tablet dissolution test apparatus-I (Electrolab) employing a basket stirrer, 500 ml of 0.1 pH buffer was used as a dissolution medium for the first 1 h and replaced with 6.8 phosphate buffer for a specified time which is stirred at 50 rpm. The temperature of the dissolution medium was previously warmed to 37±0.5°C and was maintained throughout the experiment. One tablet was used in each test. Five milliliters sample of dissolution medium was withdrawn by means of a syringe fitted with a pre-filter at known intervals of time (1 h). The sample was analyzed for drug release by measuring the absorbance at 255 nm using UV–visible spectrophotometer Shimadzu-1700 after suitable dilutions.
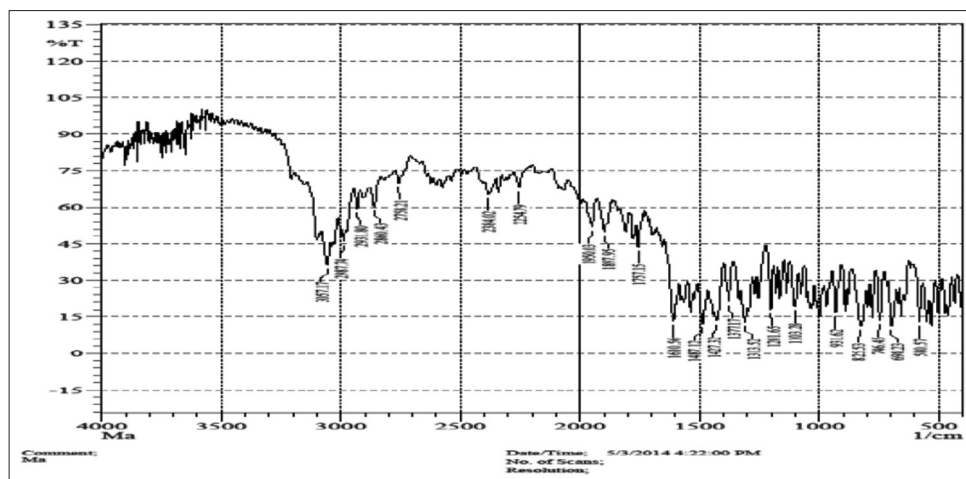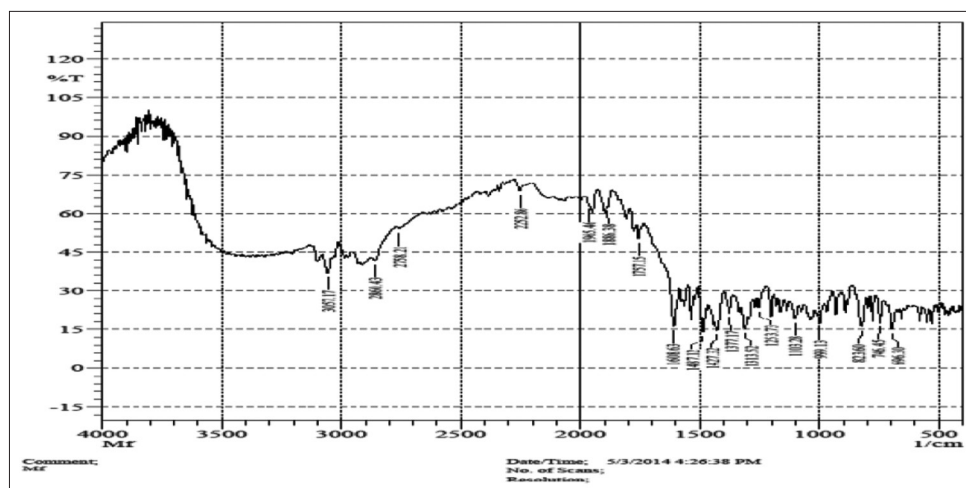

Fig. 1: FTIR spectrum of alprazolam

Fig. 2: FTIR spectrum of alprazolam with polymers blends

The volume withdrawn at each interval was replaced with the same quantity of dissolution medium [11].

Drug release kinetics

To study the release kinetics, data obtained from *in vitro* drug release studies were plotted in various kinetic models: Zero order as the cumulative amount of drug release versus time, first-order as log cumulative percentage of drug remaining versus time, and Higuchi's model as cumulative percentage of drug released versus square root of time and Korsmeyer–Peppas model, etc.

Uniformity of drug content

The test is mandatory for tablets with 10 mg or less weight of the active ingredient. From each batch, 10 tablets were randomly selected and

Fig. 3: *In vitro* release with Mardi gum

Fig. 4: *In vitro* release with hydroxypropyl methylcellulose

finely powdered, and dissolved in 10 ml of 6.8 phosphate buffer. Sonicate it for 20 min, till the entire drug leached out from the complex, and then the solution was filtered through Whatman filter paper No. 41. From this solution, take 1 ml and diluted up to 100 ml with 6.8 phosphate buffer and the drug content was determined spectrophotometrically at 255 nm for alprazolam.

Stability studies of optimize formulation

The prepared tablets were packed and subjected to stability studies at $40\pm2^{\circ}C/75\pm5\%$ RH and $30\pm2^{\circ}C/60\pm5\%$ RH as per ICH guidelines for a period of 6 months. Samples were withdrawn at 1 month time intervals and evaluated for physical appearance, drug content, and *in vitro* drug release.

RESULTS AND DISCUSSION

Characterization of drug and excipients

To determine possible interaction between the alprazolam drug, Mardi gum, and other excipients used in the formulation, compatibility studies were conducted using FTIR spectroscopy. There was no significant shift in the positions of the wave numbers when compared to that of the pure drug values. Thus, there was no interaction between the drug and other excipients of the formulation. FTIR spectra are shown in Figs. 1 and 2.

Pre-compression parameters

Powder blend prepared for compression of sustained release tablets of alprazolam was evaluated for their flow properties such as the angle of repose, loose bulk density, tapped bulk density, and compressibility index. The results were shown, Table 2. The angle of repose was in the range of 28–30°. The loose bulk densities of the granules were in the range of 0.369–0.398 g/ml. The bulk density was in the range of 0.455–0.472 g/ml, which indicates that the powder was not bulky. The compressibility index was found to be in the range of 15.38462–21.82203.

Post-compression parameters

The results of the physical properties of alprazolam sustained release matrix tablets are presented Table 3. The thickness was measured by Vernier caliper and was ranged between 4.02 ± 0.2 mm and 4.25 ± 0.2 mm. The diameter of tablets was measured by Vernier caliper and was ranged between 8.02 ± 0.02 mm and 8.22 ± 0.05 mm. The hardness of the tablets was measured by Monsanto tester and was controlled between 4.6 kg/cm² and 5.8 kg/cm². The friability was below 1% for all the formulations. The percentage of drug content for f1–f6 was found to be between $98.33\pm0.51\%$ and $99.83\pm0.21\%$ of alprazolam, it complies with the official specification. Thus, all the physical attributes of the prepared tablets of alprazolam were found be practically within control. Weight variations for different
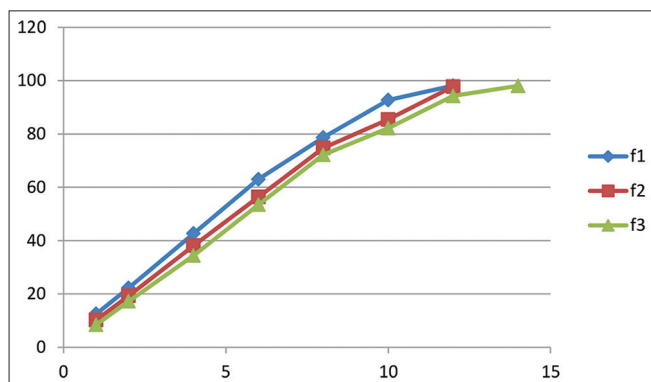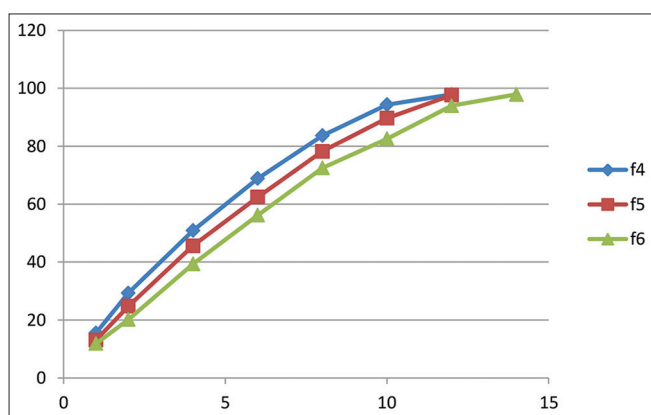
Table 2: Results of the evaluation of powder blends

Formulations	Angle of repose (°)	Bulk density (g/ml)	Tapped density (g/ml)	Carr's index (%)	Hausner ratio
F1	29	0.399	0.469	14.9253	1.1754
F2	30	0.365	0.442	17.4208	1.2109
F3	30	0.389	0.463	15.9827	1.1902
F4	29	0.392	0.465	15.6986	1.1862
F5	29	0.395	0.468	15.5982	1.1848
F6	30	0.385	0.472	18.4322	1.2259

Table 3: Results of post-compression parameters

Formulations	Weight variation (mg)	Friability (%)	Thickness (mm)	Diameter (mm)	Hardness (kg/cm²)	Drug content
F1	206±5	0.658	4.12±0.3	8.02±0.4	5.6	98.53±0.71
F2	208±6	0.478	4.15±0.5	8.09±0.3	5.8	98.43±0.81
F3	208±9	0.689	4.15±0.4	8.02±0.5	5.7	99.13±0.31
F4	206±4	0.478	4.21±0.2	8.09±0.5	5.8	99.83±0.21
F5	205±5	0.698	4.12±0.1	8.22±0.4	5.9	99.13 ±0.41
F6	204±7	0.989	4.23±0.2	8.02±0.2	5.8	98.23±0.81

Table 4: Results of mathematical modeling

Batch	Zero order	1st order	Matrix	Peppas	Hix. Crow	N value K value
F1	0.9672	0.9677	0.9881	0.9990	0.9675	0.6510 0.1026
F2	0.9764	0.9767	0.9838	0.9994	0.9766	0.6926 0.0936
F3	0.9764	0.9767	0.9838	0.9994	0.9766	0.7143 0.0866
F4	0.9694	0.9698	0.9875	0.9994	0.9797	0.7024 0.0909
F5	0.9772	0.9776	0.9830	0.9987	0.9675	0.7340 0.0830
F6	0.9662	0.9667	0.9849	0.9979	0.9765	0.7442 0.0809

formulations were found to be 204±7–210±4 mg. The weight variation is presented, Table 3.

In vitro drug release decreases with an increase in gum concentration. This may be due to the fact that at a higher concentration of gum, there is the formation of the dense matrix which reduces the mobility of drug particles and slow down the dissolution rate [12]. With f3 formulation giving 72.18% release after 8 h and formulation f1 containing 15% Mardi gum showed about 80% release after 8 h. *In vitro* drug release profile of all the formulation batches is shown in Figs. 3 and 4.

The release data as given in Table 4 were fitted to various mathematical models to evaluate the kinetics and mechanism of drug release. The kinetic data of all formulations f1–f6 could be best expressed by the zero-order equation as the plots showed the highest linearity (R^2:0.966–0.977). The n values obtained from Korsmeyer–Peppas plots range from 0.692 to 0.744 indicate that mechanism of release from formulations f1 to f6 was polymer diffusion and erosion (anomalous [non-Fickian] diffusion).

CONCLUSION

The experimental data of the present research work carried out indicated the potential of Mardi gum (*T. tomentosa*) as a release retardant agent in the formulation of sustained release tablets of alprazolam. *In vitro* release studies of formulation f1–f6 showed, formulation f3 containing the maximum amount of gum release the drug in a controlled and sustained manner with the maximum amount of 98.02% drug in 14 h. Hence, it is concluded that Mardi gum (*T. tomentosa*) can be utilized as a natural matrix forming agent in the formulation of sustained released tablets.

AUTHORS' CONTRIBUTIONS

Mangesh Kumare carried out the experiment. Giridhar Shendarkar directed the project.

CONFLICTS OF INTEREST

No conflicts of interest related with this work.

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