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 1.5%, 3.0%, and 4.5% 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 dynamic 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, and f6 drug release is 98.12±0.55%, 97.24±0.57%, 98.16±0.74%, and 97.62±0.35%, respectively, in 16 h and f5 giving 97.89±0.08% 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.
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 hardness tester; thickness was measured by Vernier caliper. Friability 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.

| Ingredients                     | F1  | F2  | F3  | F4  | F5  | F6  |
|---------------------------------|-----|-----|-----|-----|-----|-----|
| Alprazolam (mg)                 | 3   | 3   | 3   | 3   | 3   | 3   |
| Gum (mg)                        | 30  | 60  | 90  | -   | -   | -   |
| Hydroxpropyl 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   |
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 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±2°C/75±5% RH and 30±2°C/60±5% 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±0.51% and 99.83±0.21% 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 formulations are shown in Table 4.
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 (R²:0.966-0.977). 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.

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| Batch | Zero order | I* 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  |

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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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