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Research Article

FORMULATION DEVELOPMENT AND EVALUATION OF ALMOND GUM BASED SUSTAINED RELEASE MATRIX TABLET OF INDOMETHACIN

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ABSTRACT

Objective: The aspiration of the current research involves employing various concentrations of polymer and filler to develop indomethacin sustained release (SR) matrix tablets. The objective of this research work is to reduce dosing frequency thereby increasing patients compliance and enhanced therapeutic activity.

Methods: Polymers such as Almond gum (AG), polyvinylpyrrolidone (PVP), and starch at different concentrations were used for formulating SR polymeric matrix tablets. Evaluation of pre-compression and post-compression parameters was done for both granules and formulated tablets.

Results: Results obtained from pre-compression parameters and post-compression parameters suggested that all the parameters are within the prescribed limits, demonstrating that formulated granules had shown better flow properties. The morphological characteristics of the developed tablet were observed by employing scanning electron microscope where the surface of the tablet was found to be smooth from the *in vitro* dissolution study, combination of AG (30 mg) with PVP (30 mg), and starch used as a filler has sustained the release of drug up to 10 h.

Conclusion: Therefore, developed polymeric matrix tablet exhibited enhanced potency over a conventional tablet by exhibiting an excellent dissolution profile for a period of 10 h.

Keywords: Almond gum, Indomethacin, Starch, Matrix tablet, Sustained release, Polyvinylpyrrolidone.

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INTRODUCTION

In recent times, the introduction of tablets as sustained release (SR) dosage forms has bought a transformation in pharmaceutical technology. Where the drug was sustained for a prolonged duration of time in the systemic circulation by incorporating in polymeric matrices that have a short-term elimination half-life by releasing the drug in a zero-order pattern and developed as a SR dosage forms [1]. These dosage forms offer a number of benefits over an immediate release dosage forms, such as better patient acceptance due to reduce dosing frequency, portability, convenience, negligible side effects and shows enhanced pharmacological and therapeutic effects. The polymers which are widely employed in SR matrices are hydrophilic polymers (cellulosic and non-cellulosic) or hydrophobic polymers (ethyl-cellulose, hypromellose acetate succinate, cellulose acetate propionate, polyvinyl acetate, etc.) [2].

In recent times among other strategies matrix tablets are gaining importance due to its release pattern of the drug, convenient method of formulation, ease of processing, and lesser cost of production. Loading of drug into the polymer matrix can be done by coating or as a bi-layer, either granulation or direct compression can be used to formulate matrix tablet. To choose the appropriate method to formulate matrix tablets rely on the nature of the API and other excipients [3].

Indomethacin (IM) is an nonsteroidal anti-inflammatory drug usually adopted to diminish fever, pain, stiffness in rheumatic disease, and swelling from inflammation. IM inhibits the prostaglandin production; endogenous signaling molecules present these symptoms which were exhibited by inhibiting cyclooxygenase, enzyme that catalyzes the production of prostaglandins [4].

MATERIALS AND METHODS

Materials

IM was purchased from Yarrow Chem product, Mumbai, India; Almond gum &(AG) was obtained from a local certified ayurvedic market and exudates; polyvinylpyrrolidone (PVP-30) SRL, Mumbai India; Starch, Taclum, and Mg-Stearate were obtained from Loba, and Isopropyl alcohol was obtained from Merck Mumbai.

Experimental methods

Preformulation studies

Pre-formulation studies can be termed as the examination of physicochemical characteristics of a drug substance alone. The main reason to perform these studies is to acquire bioavailable and unchanging dosage forms by providing useful information to the formulator.

Development of prolonged release formulation of IM

Wet granulation technique was adopted for formulating the SR matrix tablets. In the current work, SR tablets were formulated by employing varied concentrations of AG along with binder (PVP K30). As shown in Table 1, six preparations of IM were formulated. Ingredients mentioned in Table 1 were weighed, sieved, and finally blended. The obtained blend was then sieved, dried, and compressed [5].

Micromeritic properties

The physical properties of the powder were analyzed for flowability. Carr's index equation was employed to determine the flow property of the powder blend. In this method, using a Scoopula and the mass occupied by the powder was recorded using a 100ml measuring cylinder. Using, well-established formula, that is, weight divided by the volume of the blend,

the bulk density of mixture was measured. Mixture was then allowed to settle by tapping it for a count of 100 times using different cylinders. To measure the tapped density, the process was continued until a constant value was attained. Angle of repose was the most widely used technique for measuring the flowability [by determining the shape of the powder heap]. The formula used to measure the flowability [6].

$\text{Tan}\theta = h/r$

Tablet compression

The talc and mg-stearate were used separately for lubricating the dried granules. Per each tablet, 50 mg of IM equivalent SR granules were weighed, and tablets were compressed using a 10 station lab compressor.

Physical properties of SR tablets

Weight variation

Initially, 20 units were selected randomly which were then weighed individually, and the average was calculated. In comparison with the percentage given in the pharmacopeia, deviation for any two tablets should not be more than the average weight. Weight variation was carried out using digital balance [7,8].

Tablet thickness

In this, 10 tablets were assessed for thickness using electronic Vernier caliper, Mitutoyo, Japan [7,8].

Hardness

Hardness is defined as the resistance of a material to permanent deformation such as indentation, wear, abrasion, and scratch. Monsanto tester was employed for evaluating the hardness of 10 tablets. The two main processes to test the hardness of the tablet: Compression testing and three-point bends testing. The hardness of oral tablets usually varies from 4 to 8 or 10 kg/cm^2 [9].

Friability

Roche friabilator or tumbler test was used for measuring the friability. Friabilator implies the ability of the compressed tablet to deter fracture and breakage during shipping. Friability is illustrated as the percentage of weight reduction due to mechanical action during the test. Tablets were weighed before and after testing and friability can be recorded as a percentage loss on pre-test tablet weight. 10 tablets were evaluated by Roche type friability test apparatus at the rate of 25 rpm for 4 min. The weight difference due to abrasion is the measure of tablet friability; the value is expressed in terms of percentage, minimum weight loss of the compressed tablet should be NMT 1% [9,10].

Drug content

Crushed powder of 20 tablets of the SR formulations was weighed. Powder equivalent to 200 mg of IM was taken in a 100 mL volumetric flask containing pH-7.2 phosphate buffer. Absorbance was measured at 265 nm for the diluted and filtered solutions to estimate the drug content [11,12].

Surface topography of matrix tablet by scanning electron microscope (SEM)

The surface texture of the developed formulations can be investigated using the SEM Hitachi Noran System 7 manufactured by Thermo Fisher Scientific technique. The surface texture of the formulated bi-layer matrix tablet can be determined by employing the SEM technique [13,14].

Dissolution study

Electrolab USP dissolution testing apparatus II (paddle type) was used to evaluate the rate of drug release from matrix tablets. Initially, test was carried out using 750 mL of 0.5N HCL (pH 1.2) for 2 h at 37±0.5°C to which 250 mL of 0.2N phosphate buffer was added, and pH was adjusted to 6.8 for the remaining period of duration (8 h); thus, the test was carried out for time period of 10 h at 37±0.5°C. A sample of 10 mL was withdrawn at regular intervals, was then supplanted with the same volume of fresh pre-warmed dissolution medium. Withdrawn sample was filtered and analyzed spectrophotometrically at wavelength 265 nm [15,16].

Table 1: Composition of IM formulations with different AG concentrations along with starch as filler

Composition	Formulation					
	F1	F2	F3	F4	F5	F6
IM (mg)	50	50	50	50	50	50
AG (mg)	15	20	25	30	35	40
PVP K30 (mg)	0	30	0	30	0	30
Starch (mg)	125	90	115	80	105	70
Talcum (mg)	5	5	5	5	5	5
Magnesium stearate (mg)	5	5	5	5	5	5
IPA (mL)	1	1	1	1	1	1
Total (mg)	200	200	200	200	200	200

IM: Indomethacin, AG: Almond gum, PVP: Polyvinylpyrrolidone

RESULTS AND DISCUSSION

Micromeritic properties of granules

As described earlier matrix dosage forms were prepared using wet granulation method. Granulation is the key step in the formulation of SR matrix tablet. The properties of the granules were assessed and depicted in Table 2.

Table 2: Micromeritic properties of granules

Formulation code	Angle of repose	Loose bulk density (g/mL)	Tapped bulk density (g/mL)	Compressibility index (%)
F1	24.02±0.05	0.41±01	0.551±0.05	15.01±0.21
F2	25.01±0.03	0.446±03	0.531±0.03	15.08±0.13
F3	24.21±0.14	0.413±0.2	0.502±0.09	12.07±0.17
F4	24.13±0.09	0.458±0.09	0.518±0.02	11.09±0.23
F5	24.01±0.04	0.436±0.08	0.508±0.04	14.02±0.26
F6	24.23±0.05	0.414±0.05	0.519±0.01	12.09±0.17

Table 3: Physical properties of the tablet

Formulation code	Weight variation	Hardness	Thickness	Friability	Drug content
F1	201±2.26	5.2±0.12	4.5±0.15	0.48±0.12	98.03±0.12
F2	199±2.37	4.3±0.04	4.4±0.12	0.53±0.12	97.09±0.12
F3	199±3.42	5.2±0.03	4.6±0.08	0.41±0.02	97.07±0.03
F4	200±1.06	5.3±0.08	4.4±0.16	0.43±0.05	98.03±0.12
F5	201±1.06	4.3±0.06	4.4±0.09	0.61±0.11	97.09±0.12
F6	199±0.77	4.3±0.12	4.6±0.28	0.55±0.04	94.03±0.12

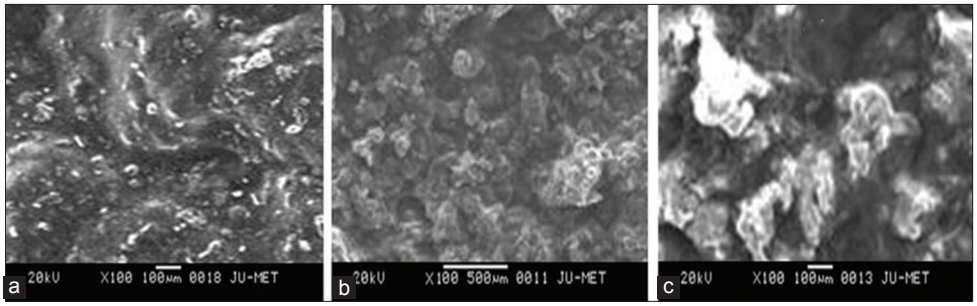

Fig. 1: Surface of sustained release layer of indomethacin (a) after 1 h, (b) after 4 h, and (c) after 8 h of dissolution investigated by SEM

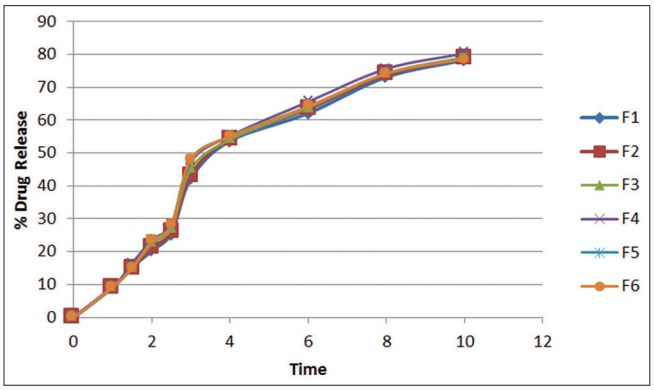

Fig. 2: Dissolution study of formulated indomethacin matrix tablets

Bulk density

The bulk density values ranged from 0.41±01 to 0.458±0.09 (Table 2) suggesting that the obtained results were within the prescribed limits.

Tapped density

The values for the tapped density were within the range of 0.502±0.09–0.551±0.05 (Table 2) assuring the free flow of granules.

Angle of repose

The results were ranged between 24.01±0.04 and 25.01±0.03 (Table 2) that is <30° which assures excellent flow properties of the powder.

Compressibility index

The values obtained were found to fall in the range of 11.09±0.23–15.08±0.13 (Table 2). These observations suggested that the granules of all batches have showed good flow characters, and hence, were suitable for compression into matrix tablets.

Physical properties of matrix tablet

Formulated SR tablets of IM were analyzed for post-compression parameters such as weight variation, thickness, hardness, friability, and drug content. The results were depicted in Table 3. From the results, it was evident that values from all the tests were within the limits prescribed by pharmacopeia.

Weight variation

The results from the weight variation varied from 199±0.77 to 201±2.26 and were found to be within the pharmacopeial specifications that is ±7.5% (Table 3).

Tablet thickness

The formulated sustained matrix tablets loaded with IM had showed thickness varying from 4.4±0.09 to 4.6±0.28 (Table 3), and the average value of thickness was found to be within the range ±5% as prescribed by pharmacopeia.

Hardness

The variation in hardness of the formulated sustained matrix tablets loaded with IM was in the range of 4.3±0.04–5.3±0.08 kg (Table 3), suggesting acceptable mechanical strength with a capability to endure mechanical and physical stress circumstances while handling and shipping.

Friability

Decrease in the weight of the sustained matrix formulations due to friability was observed to be in the range of 0.41±0.02%–0.55±0.04% (Table 3), results suggested that formulated tablets were mechanically stable.

Drug content

Drug content values obtained from various formulations were highly uniform and within the range of 94.03±0.12–98.03±0.12 (Table 3). The maximum percentage drug content among various formulations was found to be 98.03±0.12%. The minimum percentage of drug content was found to be 94.03±0.12% for all the batches. All the values of the drug content were within limits specified by pharmacopeia.

Surface topography of matrix tablet by SEM

By employing SEM, the surface morphology of SR layer of matrix tablet was determined. From, Fig. 1 SEM photographs exhibit the intact SR layer of IM after 1 h, 4 h, and 8 h of dissolution study. SEM photomicrograph taken at different time intervals of sustained matrix tablet after the dissolution study presented that the matrix was unimpaired and the matrix had pores throughout its surface. Tablet surface also exhibited erosion of matrix has proportionately enhanced with reference to time as indicated by the photocopies at 2, 4, and 8 h and explaining that there is an increase in the diameter of the pores. The formation of gelling structure was explained by these photomicrographs revealing the probability of swelling of the formulated dosage form (Fig. 1). The release of IM from developed formulation was due to the formation of the pores and gelling structures (due to diffusion and erosion mechanism) on the tablet surface.

Dissolution study

Dissolution of the formulated IM SR matrix tablets takes place by swelling between the polymer networks by which the drug is getting diffused into the dissolution medium. Thus, the release of the active agent from the matrix tablet takes place by the diffusion mechanism. As shown in Fig. 2, formulation F4 had shown the accurate and complete release of the drug by 10 h. From the results, it can be inferred that formulation F4 can be considered as optimized formulation as it had SR of IM up to 10 h [14].

CONCLUSION

Matrix tablets loaded with IM was formulated using wet granulation method to sustain the release of drug for a period of time. The pre-compressional (micromeritics properties) and the post-compressional parameters (physical properties) were found to be within the pharmacopeial limits. From the various formulations F4 with 30 mg

of almond gm, 30 mg of PVP and 80 mg of starch were considered as optimized formulation based on its drug release pattern, i.e., 10 h, which was better when compared with other formulations. SEM photographs of F4 suggested that tablet surface exhibited erosion of matrix with reference to the time at 2, 4, and 8 h, which explains the increase in diameter of the pores and facilitates the drug release from the uniform surface of the matrix tablet. Therefore, it can be concluded that IM matrix tablets can be used for enhancing both the therapeutic efficacy and patient acceptance by reducing the dosing intervals.

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AUTHORS' CONTRIBUTIONS

The author is a faculty in division of pharmaceutics, and the work contributed on faculty development program in the institution.

CONFLICTS OF INTEREST

The author confirms that this article content has no conflicts of interest.

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