FORMULATION AND EVALUATION OF SUSTAINED RELEASE MATRIX TABLETS OF FLURBIPROFEN USING GUAR GUM

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ABSTRACT

Sustained release formulation of Flurbiprofen based on matrix technology was developed and evaluated. It is practically insoluble in water hence suitable to develop sustained release matrix tablet using hydrophilic polymer. Flurbiprofen is a non-steroidal anti-inflammatory drug (NSAID) used extensively in the treatment of rheumatoid arthritis, osteoarthritis and ankylosing spondylitis. It is newer derivative of diclofenac and having less gastrointestinal complication with short biological half-life of 4 hrs, hence developed formulation provides the added advantages of sustained release formulations. The guar gum was utilized in the formulation of matrix tablets containing Flurbiprofen by wet granulation technique and evaluated for drug release characteristics. Formulation was optimized on the basis of acceptable tablet properties (hardness, friability, drug content and weight variations), *in vitro* drug release and stability studies. The *in vitro* release study of matrix tablets were carried out in phosphate buffer pH 7.4 for 12 hr. Among all the formulations, F5 showed 97.22% better controlled release at the end of 12 hr. The results indicated that a decrease in release kinetics of the drug was observed by increasing the polymer concentration. The release data was fitted to various mathematical models such as, Higuchi, Korsmeyer-Peppas, First-order and Zero order to evaluate the kinetics and mechanism of the drug release. The drug release of optimized formulation, F5 follows zero order kinetics and the mechanism was found to be diffusion. The stability studies were carried out according to ICH guidelines which indicate that the selected formulation was stable.

Keywords: *Flurbiprofen, Guar gum, Matrix tablet, Sustained release, Wet granulation.*

INTRODUCTION

Oral route is the most preferred route for administration of drugs. Tablets are the most popular oral formulation available in the market and widely preferred by the patients and physician alike. In long-term therapy for the treatment of chronic disease conditions, conventional formulations are administered in multiple doses and therefore have several disadvantages[1]. The primary benefit of a sustained release dosage form in comparission with conventional dosage form, maintains uniform drug plasma concentration and hence uniform therapeutic effect is achieved. Over the past two decades, sustained release dosage forms have made significant progress in terms of clinical efficacy and patient compliance. Matrix devices due to their chemical inertness, drug embedding ability and drug release character have gained steady popularity for sustaining the release of a drug[2, 3]. Hydrophilic matrices are interesting options for developing an oral sustained release formulation[4]. The drug release from such matrices can be controlled through their physical properties. Polysaccharides are the choice of material among the hydrophilic polymers used, as they are nontoxic and acceptable by the regulating authorities. The various polysaccharides used in drug delivery application are cellulose ethers, xanthan gum, locust bean gum and guar gum[5, 6]. Guar gum is galactomannan, obtained from the ground endosperm of the guar plant, *Cyamopsis tetragonolobus*. It has been investigated as a controlled release carrier and regarded as nontoxic and nonirritant material[7, 8]. Flurbiprofen is non-steroidal anti-inflammatory (NSAID) drug used extensively in the treatment of rheumamatoid arthritis, degenerative joint disease, osteoarthritis, ankylosing spondylitis, acute musculoskeletal disorders, low back pain and allied conditions[9]. Flurbiprofen is newer derivative of diclofenac and having less GIT complications with short biological half-life of 4 hrs and dosing frequency more than one time, makes an ideal candidate for modified release multiple unit preparation. To reduce the frequency of administrations and to improve patient compliances hence flurbiprofen is suitable for making sustain release dosage form[10]. The aim of present study is to design and characterize sustained release matrix tablet of flurbiprofen containing guar gum.

MATERIALS AND METHODS

Materials

Flurbiprofen was obtained as a gift sample from FDA Pharmaceutical Ltd. (India). Guar gum and polyvinyl pyrrolidine (PVP-K-30) were procured from Himedia laboratories Pvt. Ltd, Mumbai, Microcrystalline cellulose (Avicel PH 101), magnesium stearate, talc were purchased from SD Fine chemicals Ltd. Absolute ethanol, diethyl ether and all other chemicals used were of analytical grade.

Preparation of sustained release matrix tablets

Tablet formulations were prepared by wet granulation method. A non-aqueous granulation process was adopted to prepare Flurbiprofen tablets. Granules were prepared as follows. Proportion of excipients with drug was as given in **Table 1**. All ingredients were sifted through sieve no. 60 and microcrystalline cellulose was mixed with flurbiprofen manually and the blend was mixed with guar gum (F1to F6) to form final blend. PVPK 30 was dissolved in PVA (5% w/v) for wet granulation of the final blend. The wet mass was passed through sieve no.16 and wet granules were dried at 50°C in an oven for 30 mins. Dried granules were sized by passing it through sieve no.22 and lubricated with magnesium stearate and talc for 1 min. Tablets was compressed using rotary tablet machine with 12 mm round flat punches.

Table 1: Composition of Flurbiprofen matrix tablets

Ingredient	Formulation					
	F1	F2	F3	F4	F5	F6
Flurbiprofen (mg)	200	200	200	200	200	200
Guar gum (mg)	50	75	100	125	150	175
Microcrystalline cellulose (mg)	222	197	172	147	122	97
PVP K 30 (5%) (mg)	25	25	25	25	25	25
Magnesium stearate (mg)	02	02	02	02	02	02
Talc (mg)	01	01	01	01	01	01

Evaluation parameters of granules

Angle of Repose

Angle of Repose of powder was determined by the funnel method. Accurately weighed powder blend was taken in the funnel. Height of the funnel was adjusted in order to the touch the apex of the powder blend to the tip of the funnel. Powder blend was allowed to flow through the funnel freely on to the surface. Diameter of the powder cone was measured and angle of repose was calculated using the following equation (1) [11, 12]

$$Tan\ \theta = h/r \dots\dots\dots\dots (1)$$

Density

(a) Bulk density (BD)

Weigh accurately 25g of powder, previously passed through 20# sieve and transferred in 100 ml graduated cylinder. Carefully level the powder without compacting and read the unsettled apparent volume (V). Calculate the apparent bulk density in gm/ml by the following equation (2) [11, 12].

$$Bulk\ density = Weight\ of\ powder/\ Bulk\ volume \dots\dots\dots (2)$$

(b) Tapped density (TD)

Weigh accurately 25g of powder, previously passed through 20# sieve and transferred in 100 ml graduated cylinder. Then tap the cylinder containing the sample using tapped density tester, provides a fixed rap of 14 ± 2 mm at a nominal rate of 300 drops per minute. Tap the cylinder for 500 times and 750 times to measure the tapped volume (V) to the nearest graduated units. Calculate the tapped bulk density in gm/ml by the following equation (3) [11, 12].

$$Tapped\ density = Weight\ of\ powder\ /\ Tapped\ volume \dots\dots\dots (3)$$

Carr's Index

Compressibility index of the powder blend was determined by Carr's compressibility index. It is a simple test to evaluate the BD and TD of a powder and the rate at which it packed down.

The formula for Carr's index is as below equation (4) [13, 14].

$$Carr's\ index\ (\%) = [(TD-BD)\times 100]\ /\ TD \dots\dots\dots (4)$$

The physical properties of granules were shown in **Table 2**.

Evaluation of tablets

Thickness

Thickness of the tablets was determined using a vernier caliper (For-bro engineers, Mumbai, India) [15].

Hardness

Hardness of the tablets was determined using a hardness testing apparatus (Monsanto Type, USA). A tablet hardness of about 3-5 kg/cm^2 is considered adequate for mechanical stability[15].

Weight Variation Test

Weight variation was determined using 20 tablets of each formulation, weighed using an electronic balance (Sartorius electronic balance: Model CP-2245, Labtronic), and the test was performed according to the official method[16].

Friability

The friability of the tablets was measured by Roche friabilitor. Tablets of a known weight (W_0) or a sample of tablets are dedusted in a drum for a fixed time (100 revolutions) and weighed (W) again. Percentage friability was calculated from the loss in weight as given in equation (5), the weight loss should not be more than 1% w/w[16].

$$\%\ Friability = (W_0-W)/\ W_0 \times 100 \dots\dots\dots (5)$$

Uniformity of drug content

Weigh accurately quantity of the powdered tablet equivalent to 100mg of the drug was transferred to 100 ml volumetric flask. 50ml of buffer solution of pH-7.4 was added, mixed with the aid of ultrasound for 10 min and volume made upto 100 ml with the same buffer solution. Later mixed solution was filtered through the membrane filter disc with an average pore diameter not greater than 0.45μm. 5 ml of the filtrate was diluted to 100 ml with same buffer solution and examined under UV Spectrophotometer (Shimadzu UV-150, Japan) at 247nm[17].

All prepared matrix tablets were evaluated for its uniformity of weight, hardness; friability and thickness according to official methods were shown in **Table 3.**

In vitro drug release studies

In-vitro drug release studies were carried out using USP XXII dissolution apparatus type 2 (Electrolab, Mumbai, India) at 50 rpm. The dissolution medium consisted of 900ml of pH 7.4 phosphate buffer, maintained at $37\pm0.5°C$[18-21]. Ten milliliters of sample was withdrawn at predetermined time intervals and the volume of the dissolution medium was maintained by adding the same volume of fresh prewarmed buffer every time. The drug release at different time intervals was measured using an UV spectrophotometer (Shimadzu UV-150, Japan) at 247nm[27]. The study was performed for drug release profile.

Characterization of Drug Release Kinetics

For finding out mechanism of drug release from matrix tablet, the dissolution data obtained from the above experiments were treated with the different release kinetic equation[22, 25, 26] and were shown in **Table 4**.

Zero order release equation: $Q = K^0t$

Higuchi's square root of time equation: $Q = K\ H\ t_{1/2}$

Peppas equation: $F = (M_t/M) = Ktn$

Stability Study

The optimized formulation was subjected to stability at $40 \pm 2°C$ and $75 \pm 5\%$ RH for period of three months. Tablet sample was analyzed every month for physical characteristics and drug release profile[23].

RESULT & DISCUSSION

Characterization of granular properties

Granules prepared for compression of matrix tablets were evaluated for their flow properties, the results were shown in Table 2. Angle of repose was in the range $24.32 \pm 1.14°$ to $27.53 \pm 1.16°$, which indicates excellent flow of powders for all formulations. The bulk density of the powder formulation was in the range of 0.452 ± 0.003 to 0.486 ± 0.002gm/cc; the tapped density was in the range of 0.501 ± 0.016 to 0.538 ± 0.009gm/cc, which indicates that the powder was not bulky. The Carr's index was found to be in the range of 9.32 ± 1.63 to 11.84 ± 0.75; indicating good compressibility of the tablet blend. These values indicate that the prepared granules exhibited good flow properties[24].

Table 2: Micromeritic properties of powder blend of different formulation (F1-F6)

Parameter	Formulation					
	F1	F2	F3	F4	F5	F6
Angle of repose (°)	26.21±1.40	26.03±1.25	25.62±1.43	27.53±1.16	26.77±1.39	24.32±1.14
Bulk density (gm/cm³)	0.48±0.00	0.48±0.00	0.46±0.00	0.45±0.00	0.45 ±0.00	0.45 ±0.00
Tapped density (gm/cm³)	0.53±0.00	0.53±0.01	0.51±0.01	0.50±0.01	0.51±0.01	0.50±0.01
(%)Compressibility	9.66±1.33	10.26±0.78	10.27±1.35	9.32±1.63	11.84±0.75	9.78±1.48

Physicochemical evaluation of matrix tablets

Tablets weighing 500mg, diameter of 12mm were obtained and subjected to quality control tests such as hardness, friability and drug content (**Table 3**). The contents of the formulations were found to be uniform, amount of the active ingredient for each of the 10 units were tested, was found within the range of 98.91% – 100.21% and the relative standard deviations were less than 2.0%, indicating uniform mixing. The mean values for hardness were over 5.6 kg/cm² and all the formulations exhibited for friability found to be NMT 0.4%. The punches used for compression were 12mm spherical shaped tablets.

The shape and size of the tablets were found to be within the limit. The hardness of the tablets was found to be in the range of 5.6 ± 0.35 to 6.2 ± 0.10 Kg/cm². Thickness of the tablets was found to be in the range of 3.88 ± 0.32 to 3.93 ± 0.18 mm.

Table 3: Tablet properties of formulation (F1-F6)

Parameter	Formulation					
	F1	F2	F3	F4	F5	F6
Hardness (Kg/cm²)	5.6±0.35	6.1±0.13	5.9±0.24	6.2±0.10	6.1±0.12	5.8±0.14
Thickness (mm)	3.91±0.16	3.88±0.32	3.93±0.18	3.90±0.14	3.89±0.17	3.92±0.21
Friability (%)	0.23±0.36	0.17±0.22	0.36±0.14	0.31±0.21	0.29±0.32	0.18±0.19
Weight variation (mg)	498.2	500.5	499.1	498.9	501.4	500.9
Drug content (%)	99.67	100.21	98.94	99.45	99.31	98.91

In-Vitro Release Study

In-vitro release studies were carried out for all the formulations as per USP XXII tablet dissolution tester employing rotating paddle at 50rpm using 900ml of phosphate buffer of pH 7.4 as dissolution medium. The results were evaluated for 12 hrs for the formulations F1, F2, F3, F4, F5, F6 showed 99.41, 98.72, 99.58, 98.19, 97.22 and 96.35% respectively. This showed that the drug release from the tablet was sustained for 4 to 12 hr. F1 with 10% guar gum showed 99.41% release within 5 hr, where as in formulation F5 with 30% guar gum as a retardant showed 97.22% release upto 12hr. This is mainly due to increasing polymer concentration or increasing path length diffusion. By using the different concentrations of guar gum as a release retardant, drug release from guar gum showed sustained release for 4 to 12hrs by varying the concentration of polymer matrix composition. Formulation F5 and F6 with guar gum showed reasonable release 97.22%, 96.35% respectively. From the above results, it was found that the drug release is depleted as the concentration of guar gum polymer was increased in polymeric matrix composition. Hence, formulation F5 with 30% guar gum was found to be most promising formulation and maintained excellent matrix integrity during the 12hrs study period. Hence formulation F5 was selected as the optimized formulation.

Determination of the release kinetics

The regression coefficient (R^2) value of Zero order, First order, Higuchi's, and Peppas plots for formulation F5 were found to be 0.984, 0.870, 0.971, 0.974. The optimized formulation F5 (0.971) follows Higuchi's plot since the regression coefficient (R^2) is found to be linear, this confirms that the drug release through the matrix was diffusion and slope (*n*) value was found to be 0.761. Thus, non-Fickian diffusion/anomalous was the main mechanism. The regression coefficient (R^2) values of zero order in the optimized formulation F5 was greater than the R^2 values of first order. Thus, the drug release follows zero order kinetics.

The optimized formulation (F5) was subjected to accelerated stability studies according to ICH guidelines by storing at 40ºC/75% RH for 90 days and the results showed that the formulation did not undergo any chemical changes/interaction during the study period.

Table 4: Release kinetic parameters of formulations

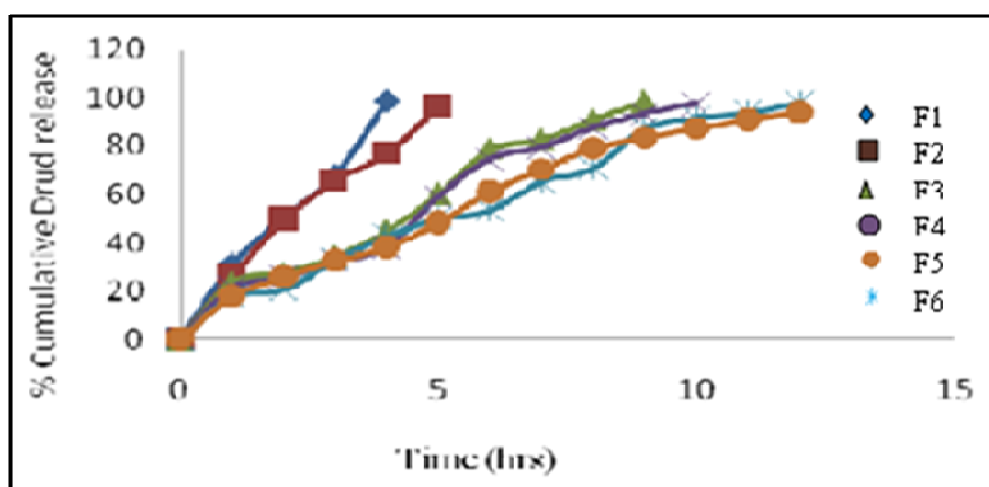| Formulation	Zero order plot R²	First order plot R²	Higuchi plot R²	Korsmeyer plot R²	Slope (n)
F1	0.988	0.735	0.952	0.982	0.807
F2	0.982	0.832	0.991	0.992	0.794
F3	0.979	0.821	0.947	0.936	0.729
F4	0.972	0.899	0.949	0.937	0.756
F5	0.984	0.870	0.971	0.974	0.761
F6	0.973	0.961	0.976	0.981	0.729

Fig. 1: *In-vitro* dissolution profile of F1 to F6 formulations

CONCLUSION

The matrix tablets were found to be significantly effective in sustaining the drug release upto 12hrs, is mainly due to formation of a thick gel structure that delays the drug release from tablet matrix due to diffusion coupled with erosion mechanism. Stability studies revealed that there was no significant change in drug content and dissolution profile of matrix tablets. It can be concluded that stable formulation could be developed by incorporating hydrophilic polymer (Guar gum) in a definite proportion, so that the controlled released profile can be maintained for an extended period.

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