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Preparation and Evaluation of Mouth Dissolving Tablets of Flurbiprofen

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ABSTRACT

The aim of investigation is to develop the effective delivery system for pain management of rheumatic disorders. The mouth dissolving tablets (MDTs) containing flurbiprofen was developed in order to accomplish enhanced solubility leading to better bioavailability profile. Different ratios, of flurbiprofen and Poly ethylene glycol 6000 i.e. 1:1, 1:2, 1:3, 1:4 and 1:5 were selected for the formulation of mouth dissolving tablets system and prepared by direct compression technique.

The prepared batches of mouth dissolving tablets were characterized for thickness, hardness, weight variation, wetting time, disintegration time and drug content. The evaluation data for all batches was satisfactory out of them formulation C3 containing 6% MCC PH- 102 (Avicel) showed the best results with a value of 27.3 sec and 37.1 sec for wetting and disintegration, respectively.

Key words: Flurbiprofen, Poly ethylene glycol 6000, Solid dispersion, MCC PH- 102 (Avicel), mouth dissolving tablets.

1. INTRODUCTION

Rheumatoid arthritis (RA) is an autoimmune disease characterized by joint inflammation accompanied with long lasting severe pain leading to joint destruction or disability. According to the literature reports, this disease markedly influences the population with a contributory percentage of 1% approximately.[1,2] NSAIDs like ibuprofen, aspirin and indomethacin are preferred for pain management in rheumatoid arthritis and acts by blocking prostaglandin synthesis owing to non-selective inhibition of cyclooxygenase enzyme (COX-1& COX-2).[3]The use of these therapeutic agents is restricted due to the associated severe GI distress and ulcers.

Flurbiprofen is a nonsteroidal anti-inflammatory drug in the phenylalkanoic acid derivative family of NSAIDswith proven efficacy for the pain management in RA in human being. Similar to other NSAIDs, flurbiprofen acts by preventing cyclooxygenase from producing prostaglandins which can cause inflammation.The cyclooxygenaseenzyme is responsible for the conversion of arachidonic acid to prostaglandin G2 (PGG2) and PGG2 to prostaglandin H2 (PGH2) in the prostaglandin synthesis pathway. Its high lipophilicity with a log P value of 4.42 rationalizes its lower bioavailability after oral administration due to which frequent dosing is required.[4]These shortcomings may be conquered by the utilization of solubility enhancement technique i.e. solid dispersion and novel formulation approach i.e. mouth dissolving tablets.

Mouth dissolving tablet is a desirable dosage form for patients with problems swallowing tablets or other solid dosage forms. It has advantages over oral solutions including better stability, more accurate dosing, and lower volume and weight. The dosage form can be swallowed as a soft paste or liquid, and suffocation is avoided because there is no physical obstruction when swallowed. Since the tablets disintegrate in the mouth, drugs can be absorbed in the buccal, pharyngeal, and gastric regions.

Thus, rapid drug therapy intervention and increased bioavailability of drugs might be possible. Because pre-gastric drug absorption avoids first pass metabolism; the drug dose can be reduced if a significant amount of the drug is lost through the hepatic metabolism[1].

The present study attempts to enhance the solubility of flurbiprofen by solid dispersion technique with polyethylene glycol 6000 and compressed it as a Mouth dissolving tablet in order to develop an effective treatment for the management of RA.

2. MATERIALS AND METHODS

2.1 Materials

Flurbiprofen was purchased from Taj Pharmaceutical Pvt. Ltd. Valsad, India. Sodium starch glycolate, Crosspovidonewas a kind gift from SD fine chemicals pvt. Ltd. Pune, Maharashtra and MCC PH- 102 (Avicel) was kindly donated by Dishmanpharma. All other chemicals used were of analytical grade.

2.2 Preparation of solid dispersion

Solid dispersion of flurbiprofen and Poly ethylene glycol 6000 was prepared using different ratios i.e. 1:1, 1:2, 1:3, 1:4, 1:5 by conventional solvent evaporation method[5]. Briefly, flurbiprofen and Poly ethylene glycol 6000 were weighed accurately in different ratios and mixed uniformly. This mixture was dissolved in ethanol with continuous stirring and subjected to solvent evaporation by heating at 40^0C. The resultant solid dispersions were dried for 24 hr in descicator. Dried mass was scraped, crushed, pulverized and passed through sieve (# 60).

2.3 Formulation of mouth dissolving tablets using solid dispersion

Solid dispersion of flurbiprofen andPoly ethylene glycol 6000is compressed in to mouth dissolving tablets. The A3 formulation containing 1:3 ratios is selected on the basis of solid dispersion characterization for tablet preparation. Direct compression technique was utilized for the compression of solid dispersion of flurbiprofen and Poly ethylene glycol 6000for the development of mouth dissolving tablets. All ingredients (solid dispersion equivalent to 5 mg flurbiprofen and other excipients) were mixed properly and the blends were passed through sieve (#40). The powder blend was compressed into tablets on a single punch tablet machine using round shape flat punch having diameter of 12 mm (Jyoti Industries, Ambala, India). The tablet weight was adjusted to 130 mg (Table 1). Sodium starchglycollate, crosprovidone sodium and Pregeletenised starch used as disintegrating agent. While aspartame used as diluents and magnesium stearate was used as lubricant.

2.4 Evaluation of mouth dissolving tablets

2.4.1 Thickness and hardness

The tablet thickness was measured using digital verniercaliper. Hardness was determined by Monsanto hardness tester (Jyoti Scientific Labs, Gwalior).

2.4.2 Friability and weight variation

Friability test was carried out on 10 tablets. Initial weight of the tablets was measured and subsequently placed in chamber of friabilator (Roche friabilator) at 25 rpm speed for 4 min. After that tablets were de-dusted, reweighed and % friability was calculated. From each batch twenty tablets weight were noted using electronic balance. Their average weight (W_A) was calculated. Percentage weight variation and average weights of the tablets along with standard deviation values were calculated using formulae given below.

$$\% \text{ Weight variation} = (W_A - W_T) / W_A$$

2.4.3 Wetting time

Another important parameter is wetting time. Five circular tissue papers of 10 cm diameter were placed in a Petri dish of a 10 cm diameter. 10 ml of water containing eosin, a water- soluble dye, was added to Petri dish. A tablet was carefully placed on the surface of the tissue paper. The time required for water to reach upper surface of the tablet is noted as wetting time.

2.4.4 Disintegration time

Disintegration test is determined using the USP XXII type device used to test disintegration comprises six glass tubes that are 3 cm long, open at the top, and held against 10 cm screen at the bottom end of the basket rack assembly. One tablet is placed in each tube and the basket rack is positioned in beaker containing 900 ml of PBS (pH 6.8) at 37±2°C, such that the tablets remain below the surface of the liquid on their upward movement and descend not closer than 2.5cm from the bottom of the beaker. The disintegration time was recorded at the point at which tablet completely disintegrated.

2.4.5 Drug content

Ten tablets were weighed and powdered. An amount of

the powder equivalent to 10 mg of flurbiprofen was dissolved in 100 ml of pH (6.8) phosphate buffer, filtered, diluted suitably and analyzed for drug content at 247 nm using UV Visible spectrophotometer (UV-1800, Shimadzu, Japan).

2.4.6 In vitro drug release study

In vitro drug release studies of all formulations were carried out using paddle type tablet dissolution test apparatus at 50 rpm. The dissolution media, phosphate buffer pH (6.8) was maintained at 37.0±0.5^{0}C. Samples were withdrawn at different intervals, diluted suitably and analysed at 247 nm for cumulative drug release using UV-Visible spectrophotometer (UV-1800, Shimadzu, Japan). The percentage of flurbiprofen dissolved from tablet was calculated.

3. RESULT AND DISCUSSION

3.1 Formulation of mouth dissolving tablets using solid dispersion

From above study of solid dispersion preparation of flurbiprofen with Poly ethylene glycol 6000 it was found that solid dispersion ratio A3 (1:3) has maximum solubility and drug content, is selected for further preparation of mouth dissolving tablets with addition of Superdisintegrants i.e. sodium starch glycollate, crosprovidone sodium and Pregeletenised starch, taken in various ratios to find the optimum concentration of the superdisintegrants required to yield formulation having least wetting time and disintegration time.

3.2 Evaluation of mouth dissolving tablets

The Mouth dissolving tablet of flurbiprofen was evaluated on different parameters which were shown in table 2.

All the prepared tablets are characterized by their size and shape, which found round shape. Friability for all formulations was found to be less than 1 %(acceptable limit). The result shows resistance to loss of weight indicated the tablet ability to withstand abrasion in handling, packaging and shipment. The weight variation was found within the limit as per USP %. The wetting time for all formulations was 56.1 to 44.3 sec for A formulations, 62.6 to 48.3 sec for B formulations and 45.1 to 27.1 sec for C formulation which was sufficient for dissolution and bioavailability of active ingredient. In the present study, all the tablets disintegrated in approximately in 1.5 minutes which was suitable for fast release of active drug ingredient. The porous structure of the tablets is responsible for faster water uptake resulting in fast disintegration. Percentage drug content for various formulations i.e. A1, A2, A3, B1, B2, B3, C1, C2, C3 were found to be 93.29%, 96.95%, 97.38%, 96.55%, 97.84%, 99.25%, 96.86%, 95.72%, 98.51% respectively. The percent drug content was found to be in the USP limits for all formulations. The % drug content for all formulations is represented in table 2.

3.3 *In vitro* drug release study

The release characteristics of mouth dissolving tablets was studied using tablet dissolution test apparatus is paddle type (USP XXII type) at 50 rpm. 900 ml of Phosphate buffer pH (6.8) was used asthe dissolution media at 37±2^{0}C. The cumulative percent drug release of formulations i.e. A1, A2, A3, B1, B2, B3, C1, C2, C3 were 95.31%, 96.44%, 99.04%, 97.11%, 90.20%, 80.48%, 84.12%, 90.32%, 99.22% respectively in 30 minute. All the results of Cumulative percent drug release of all formulations graphically represented in figure 1.

4. CONCLUSION

The method utilized for the preparation of mouth dissolving tablets was simple and reproducible. Mouth dissolving tablets of flurbiprofen prepared with addition of solid dispersion technique by solvent evaporation method with PEG 6000 and superdisintegrants like sodium starch glycollate, crosprovidone sodium and pregeletenised starch. Formulation containing 4% crosprovidone sodium shows least wetting time and disintegration timeWhich indicates that crosprovidone sodium is suitable disintegrate for mouth dissolving tablets.

The results of the study establish the flurbiprofenmouth dissolving tablets as a potential drug delivery system for effective pain management and long term treatment of rheumatoid arthritis.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this paper.

Table 1. List of ingredients used in formulations of mouth dissolving tablets of flurbiprofen

S.No	Ingredients (Mg)	Formulations								
		A1	A2	A3	B1	B2	B3	C1	C2	C3
1	Drug dispersion (eq. to 5 mg of Flurbiprofen)	10	10	10	10	10	10	10	10	10
2	Sodium starch glycollate	2	4	6	-	-	-	-	-	-
3	Pregeletenised starch	-	-	-	2	4	6	-	-	-
4	Crosprovidone	-	-	-	-	-	-	2	4	6
5	Mannitol	70	68	66	70	68	66	70	68	66
6	MCC PH- 102 (Avicel)	40	40	40	40	40	40	40	40	40
7	Aspartame	1	1	1	1	1	1	1	1	1
8	Magnesium stearate	2	2	2	2	2	2	2	2	2
9	Talc	4	4	4	4	4	4	4	4	4
Total Weight		130	130	130	130	130	130	130	130	130

Table 2. Evaluation parameters of various mouth dissolving tablets prepared

Batch	Friability (%)	Wetting time(sec)	Disintegration time (sec)	%Drug content
A1	0.68±0.02	56.1±1.78	91.0±4.18	93.29±0.16
A2	0.52±0.04	47.0±1.09	80.3±3.39	96.95±0.17
A3	0.61±0.02	44.3±1.10	72.1±1.22	97.38±0.05
B1	0.57±0.03	62.6±1.37	75.9±2.43	96.55±0.56
B2	0.61±0.23	52.4±3.08	65.6±2.12	97.84±0.42
B3	0.65±0.18	48.3±1.26	57.4±1.38	99.25±0.29
C1	0.67±0.02	45.1±1.98	55.3±1.94	96.86±0.38
C2	0.53±0.03	33.4±1.30	44.1±1.36	95.72±0.01
C3	0.47±0.10	27.1±1.61	37.3±1.85	98.51±0.44

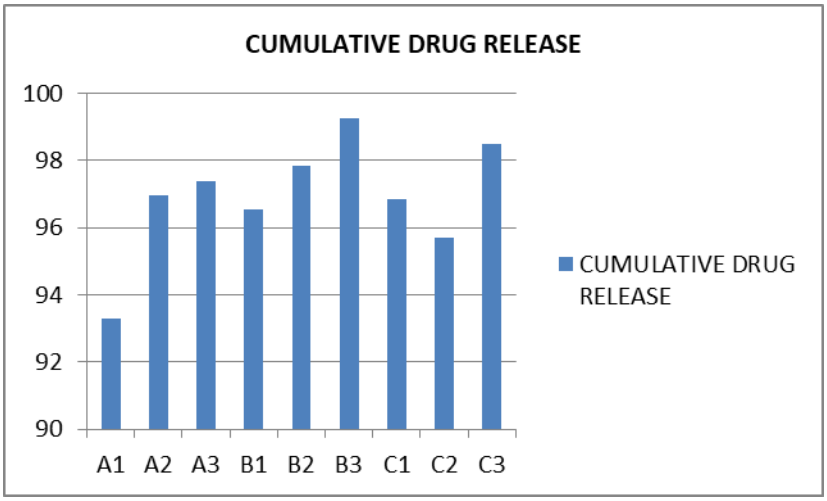

Fig 1. Cumulative % drug releases of various Mouth dissolving tablet formulations

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