WORLD JOURNAL OF PHARMACY AND PHARMACEUTICAL SCIENCES
SJIF Impact Factor 7.421
Volume 8, Issue 3, 1205-1215 Research Article ISSN 2278 – 4357

FORMULATION OF FAST DISSOLVING TABLETS OF MELOXICAM USING SOLID DISPERSION METHOD

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Article Received on
14 Jan. 2019,
Revised on 03 Feb. 2019,
Accepted on 23 Feb. 2019
DOI: 10.20959/wjpps20193-13339

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ABSTRACT

In the present work, an attempt was made to prepare fast dissolving tablets containing meloxicam solid dispersions with the aim to enhance its dissolution rate. Meloxicam solid dispersions (MSDs) with polyvinyl pyrrolidone (PVP) in different ratios were prepared by solvent evaporation method. The MSDs was mixed with other excipients and compressed into tablets by direct compression method. The prepared tablets were evaluated for various pharmaceutical characteristics such as hardness, friability, weight variation, thickness, disintegration time, drug content, and *in vitro* drug release. All the formulated tablets were within the acceptable limits. Among the tablet formulations, formula F-1 containing SD of meloxicam to PVP in ratio of 1:1 showed short disintegration time of almost 34 sec and about 57.92% , 85.76% and 104.62% of drug release after 2, 15 and 30 minutes respectively which was much higher than those tablets prepared without PVP (F-0) and marketed products. It was concluded that the prepared solid dispersions with PVP as a hydrophilic carrier was a suitable method to enhance the dissolution of meloxicam.

KEYWORDS: Meloxicam, solid dispersion, enhanced dissolution, fast dissolving tablets.

INTRODUCTION

Drug delivery through oral route is the most common and preferred route of drug administration for liquid and solid dosage forms. Solid dosage forms are popular because of the stability, ease of administration, accurate dosing, self-medication, pain avoidance and most importantly the patient compliance.[1-3] Although, tablets and capsules are the most popular solid dosage forms but many patients find difficulty in swallowing of these

conventional tablets and hard gelatin capsules. It has been found that this problem has been encountered in all groups of patient especially with pediatric, geriatric patients and mentally retarded persons. Recent advances in novel drug delivery systems (NDDS) aim to enhance safety and efficacy of drug by formulating a convenient dosage form for administration to achieve better patient compliance.[4,5] The bioavailability of drug is dependent on in-vivo disintegration, dissolution and various physiological factors.[6] To fulfill these tasks, pharmaceutical technologists have developed a novel oral dosage form known as Fast dissolving tablets (FDTs). Such a tablets disintegrate rapidly in saliva, usually in seconds, without the need to take water by using suitable diluents and superdisintegrants. Drug dissolution and absorption as well as the onset of clinical effect and drug bioavailability may be significantly greater for FDTs when compared to conventional dosage forms.[7]

Meloxicam is a non-steroidal anti-inflammatory drug (NSAID) belongs to oxicam class and a selective cyclooxygenase-2 (COX-2) inhibitors, widely used in the treatment of osteoarthritis, rheumatoid arthritis, low back pain, primary dysmenorrheal, dental pain. It has comparable efficiency and greater gastric tolerability in comparison to conventional NSAIDs. Meloxicam is practically insoluble in water (12µg/ml). The poor aqueous solubility and wettability leads to poor dissolution and hence, delaying onset of action, thus increasing the aqueous solubility and dissolution of meloxicam is of therapeutic importance.[8,9] To overcome these problems, various techniques have been utilized to improve the solubility/ dissolution rate of poorly water-soluble drugs. Among them, is solid dispersion technique using polymeric water soluble carriers like polyethylene glycols and polyvinyl pyrrolidons.[10-14]

The present investigation was an attempt to improve meloxicam dissolution rate through the formulation of meloxicam solid dispersions with different ratios of polyvinyl pyrrolidone as a hydrophilic carrier by solvent evaporation technique. Furthermore, the Solid dispersions were formulated into fast dissolving tablets which were evaluated and the best formula was compared with the marketed tablets.

MATERIALS AND METHODS

Meloxicam was obtained as a gift sample from RFA pharmaceutical industries; Yemen, polyvinyl pyrrolidone, crosscarmellose sodium, microcrystalline cellulose (MCC), mannitol, talc fine powder and sodium lauryl sulphate (LobaChemie, India), magnesium stearate (Scharlau, EU). All other materials used were of pharmaceutical grade.

Preparation of meloxicam fast dissolving tablets

Solid dispersions of meloxicam with polyvinyl pyrrolidone (PVP) in the proportion 1:1, 1:3 and 1:5 (w/w) were prepared by solvent evaporation method. In this method, accurately weighed quantities of the carrier in the stated proportions were dissolved in methanol. To these solutions, accurately weighed amounts of meloxicam were added and allowed to dissolve and the mixture was mixed thoroughly using magnetic stirrer to obtain a homogeneous dispersion. Then, the solvent was allowed to evaporate at room temperature and the residue was dried at 40°C in a hot air oven for 6 hours. The obtained solid mass in each case was crushed, ground and passed through a 60 mesh and stored in desiccator.

Fast dissolving tablets of meloxicam-PVP solid dispersions were prepared by direct compression method according to the formulae given in table (1). All the ingredients were passed through a 60 mesh separately. Diluents and superdisintegrants were weighed and mixed in geometric order with solid dispersions equivalent to 7.5 mg of drug. Then talc, sodium lauryl sulphate and magnesium stearate which were used as a glidant/lubricant were added to the initial mixture and mixed intimately. The resulting blend was compressed into tablets using single tablet machine and using 9 mm diameter circular punches with flat faces. Four formulations (F-1, F-2, F-3 and F-0) were prepared with a target mass of 200 mg and were stored in a tightly closed container and evaluated for the following characteristics in triplicate.

Table 1: Compositions of fast dissolving tablets of meloxicam.

Ingredients (mg/tablet)	Formulation code			
	F-1	F-2	F-3	F-0
Drug: PVP solid dispersions	7.5:7.5	7.5: 22.5	7.5:37.5	7.5: 0
Crosscarmellose sodium	10	10	10	10
Microcrystalline cellulose	40	40	40	40
Mannitol	128	113	98	135.5
Talc	3	3	3	3
Sodium lauryl sulphate	2	2	2	2
Mg stearate	2	2	2	2
Total weight/tablet (mg)	200	200	200	200

Evaluation of tablets

The physical properties of all prepared tablets were determined according to the UPS30 methods[15]:

***Weight variation*:** Twenty tablets were selected randomly and weighed individually. The individual weights were compared with the average weight for determination of weight variation.

***Thickness, Hardness and Friability*:** the thickness of the tablets was measured using a venire callipers. Monsanto hardness tester was used for the determination the force required to break a tablet. Friability of the tablets was determined using a Roche Friabilator by taking twenty tablets and the equipment was rotated at 25 rpm for 4 min.

***Content uniformity*:** For determining of drug content, ten tablets were weighed and powdered. An amount of the powder equivalent to 7.5 mg of meloxicam was weighed, dissolved in methanol and filtered. The filtrate was diluted suitably by phosphate buffer pH 6.8 and analysed for the content of meloxicam by UV/Visible spectrophotometer at 362 nm (Unico, USA).

***Disintegration time*:** six tablets from each formulation were placed in an Erweka disintegration apparatus , distilled water at 37 ± 0.5°C was used as a disintegration media and the time in second taken for complete disintegration of the tablet with no palpable mass remaining in the apparatus was measured in seconds.

In vitro dissolution studies

The dissolution studies of the prepared tablets were carried out according to USP specifications[15] using USP type II Erweka dissolution apparatus DT-D6. The dissolution medium consisted of 900 ml of pH 6.8 phosphate buffer solution maintained at 37± 0.5°C and stirred at 50 rpm. Aliquot samples (5ml) were withdraw at predetermined time intervals, filtered through a 0.45µm membrane filter and replaced by the same volume of fresh dissolution medium. The samples were analyzed at 362 nm for the amount of the drug dissolved using UV/Vis spectrophotometer.

Comparison between formulated FDTs and marketed product

Difference factor (f_1) and similarity factor (f_2) between the formulated fast dissolving tablets (F-1) that has shown maximum in-vitro dissolution and marketed conventional tablets (Mobic® and Mobitil®) were determined from the data collected in the drug dissolution studies. Difference factor (f_1) is the percentage difference between two curves at each point and is a measurement of the relative error between the two curves. The similarity factor (f_2) is

a logarithmic reciprocal square root transformation of the sum of squared error and is a measurement of the similarity in the percent (%) dissolution between the two curves. The following equations were used to calculate difference factor f_1 and similarity factor f_2.

$$f_1 = \left\{ \frac{\sum_{t=1}^{n} |R_t - T_t|}{\sum_{t=1}^{n} R_t} \right\} X100$$

$$f_2 = 50 \log \left\{ \left(1 + \frac{1}{n} \sum_{i=1}^{n} (R_t - T_t)^2 \right)^{-0.5} X100 \right\}$$

Where (n) is the number of withdrawal points, (R_t) is the reference product dissolved at time t and (T_t) is the percentage of test product dissolved at time t. When the test and reference drug profiles are identical (f_1) is zero and (f_2) is 100 and f_1 increases and f_2 decreases proportionally as the dissimilarity increases. Two dissolution profiles are verified similar if f_1 is between 0 and 15 and if f_2 is between 50 and 100[16,17]

RESULTS AND DISCUSSION

Polyvinyl pyrrolidones (PVPs) are the most widely used carriers to prepare solid dispersions due to their ability to provide the hydrophilic environment to enhance drug dissolution [18]. Therefore, PVP was utilized to prepare meloxicam solid dispersions using solvent evaporation method. Fast dissolving tablets of meloxicam were prepared by direct compression method employing combination of two superdisintergants; croscarmellose sodium and microcrystalline cellulose. A total of three formulations with different amount of PVP and a control formulation without PVP were designed and evaluated.

The physical parameters of the four formulations were presented in table 2. The Uniform weight variation from all formulations was within the acceptable limit as per USP specifications i.e., below ±7.5. Drug content was found to be consistent and uniform and in the acceptable limits in all tablets formulations in the range of 98.8-102.2%. Hardness of tablets was between3.11to3.7 kg/cm^2 which indicated good mechanical strength of all formulations. Friability below 1% was indicated of good mechanical resistance of the tablets. The disintegration time of the tablets containing solid dispersions varied from 34 to 57 seconds and 46 seconds from those tablets prepared without PVP solid dispersion as shown in figure 1. It was observed that although all formulae including that containing only pure drug were disintegrated within one minute but F-1 demonstrated a minimum disintegration time of 34 sec. The decreasing in time of disintegration could be attributed to the effect of the

swelling ability, rapid disintegration, high capillary activity and pronounced hydration of crosscarmelose.[19] A highly compressible microcrystalline cellulose has good wicking and absorbing capacity and provided good dissolution property.[20] Mannitol was included in the formulations for having good aqueous solubility, wetting properties, a negative heat of solution and exhibits a unique cooling and pleasing feeling in the mouth when used in tablets formulation.[21,22]

Table 2: Physical properties of fast dissolving tablets of meloxicam.

Parameters	Formulation code			
	F-1	F-2	F-3	F-0
Weight variation (mg)	201.49	200.25	202.66	199.29
Thickness (mm)	3.2±0.15	3.5±0.26	3.15±0.12	3.11±0.12
Hardness (kg/cm^2)	3.7± 0.93	3.52± 0.67	3.15± 0.50	3.11± 0.89
Friability (%)	0.39±0.01	0.36±0.04	0.32±0.03	0.33±0.04
Drug content %	101.8±0.38	102.2±0.60	99.37±0.16	98.8±0.58
Disintegration time (sec.)	34±3	51±2	57±3	46±2

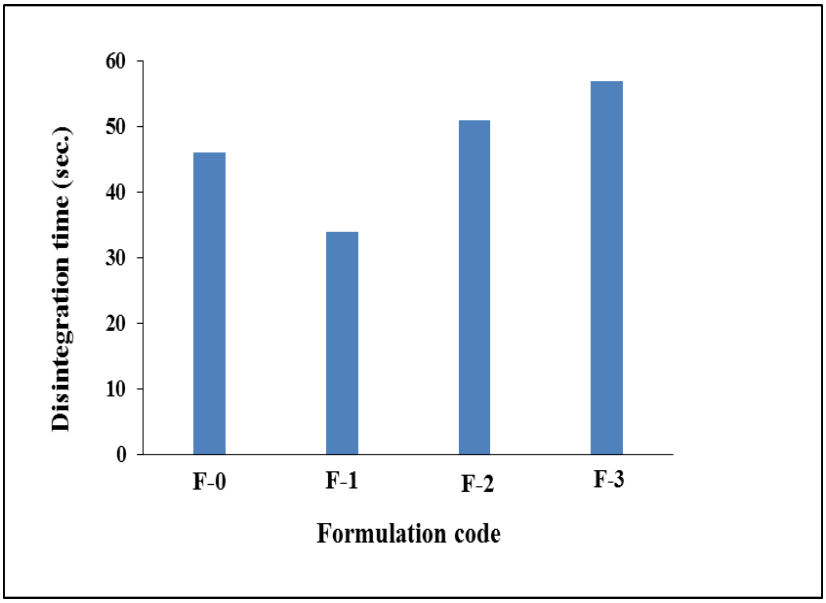

Fig.1: In-vitro disintegration time (in sec) of Meloxicam fast dissolving tablets.

In-vitro dissolution studies

The in-vitro release studies revealed that there was a faster and marked increased in the dissolution rate of meloxicam from formulation F-1 compared to other formulations. Results were depicted in tables 3-4 and figures 2-3. The cumulative percentage of meloxicam released from tablets prepared from 1:1 ratio solid dispersions F-1 was 57.92%, 85.76% and 104.62% after 2, 15 and 30 minutes respectively which was much higher than those tablets prepared without PVP solid dispersions F-0 as well as 18.46%, 47.16% and 71.37% were

released within the same times. The increase in the cumulative % drug release may be attributed to the combined effect of hydrophilic carrier which provided wettability, reduction of particle size which increase the contact area with the dissolution media and amorphization of the drug in the process of solid dispersions[23-25] and due to the rapid disintegration enable by the superdisintegrants which facilitate the drug to be in contact with the media. The obtained results showed the importance of using the drug in the form of solid dispersion to enhance the dissolution. On the other hand, formulation F-1 showed higher dissolution compared to other formulations namely F-2 and F-3. The decreased in the dissolution rates by increasing the amount of PVP may be ascribed to the formation of viscous hydrophilic layer due to a higher content of polymeric carrier around the drug particles and in the diffusion boundary layer adjacent to the dissolving surface of the dispersion generated by the carrier during the dissolution.[26] Overall, the time required to release 50% and 100% of the drug indicate the superiority of solid dispersed tablets over the tablets of pure drug. Finely, the selected formula of meloxicam solid dispersion tablets F-1 was compared with two marketed tablets, Mobic® and Mobitil®, as illustrated in table 4 and figure 3. Results showed better dissolution than the marketed products of meloxicam and completely drug release was achieved from F-1 after 30 minutes whereas 88.6% and 88,9% were released from the two products respectively within the same time. The *in-vitro* release profile of F-1 was compared with conventional tablets and meloxicam-βcd solid dispersed tablets for similarity factor (f_2) and dissimilarity factor (f_1). The values showed that there was no similarity in *in-vitro* dissolution of F-1 with conventional market tablets (Mobic®). Although there was similarity between formulated F-1 tablet and marketed meloxicam-βcd tablet but it was apparently that PVP was more efficient in enhancing the dissolution rate of meloxicam than βcd.

Table 3: Cumulative percentage of meloxicam released from different formulations.

Formulation code	Cumulative % drug released (min.) ±SD			
	t_2	t_{10}	t_{15}	t_{30}
F-1	57.92 ±0.002	74.22 ±0.009	85.76 ±0.024	104.62 ±0.013
F-2	21.95 ±0.007	38.30 ±0.002	49.99 ±0.009	73.35 ±0.012
F-3	16.91±0.012	36.19±0.003	49.17±0.013	71.38±0.005
F-0	18.46 ±0.004	37.35±0.010	47.16 ±0.013	71.37 ±0.018

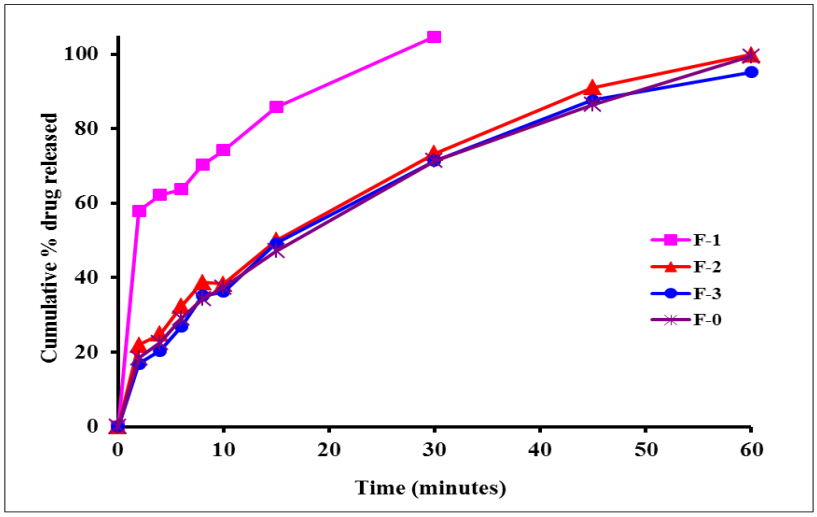

Fig. 2: In-vitro dissolution profiles of meloxicam fast dissolving tablets.

Table 4: Comparison of in-vitro dissolution profiles of meloxicam fast dissolving tablets (F-1) and marketed products.

Time (min.)	Cumulative % drug released ±SD		
	F-1	Mobic®	Mobitil®
0	0	0	0
2	57.92 ±0.002	29.93 ±0.067	49.3 ±0.013
4	62.13 ±0.003	43.79 ±0.023	53.4 ±0.019
6	63.70 ±0.004	55.04 ±0.005	65.3 ±0.009
8	70.28 ±0.012	62.59 ±0.003	69.7 ±0.011
10	74.22 ±0.009	67.50 ±0.001	73.6 ±0.010
15	85.76 ±0.024	73.30 ±0.005	79.6 ±0.002
30	104.62 ±0.013	86.66 ±0.008	88.9 ±0.001
Similarity factor (f_1)		19.24	8.102601
Dissimilarity factor (f_2)		39.84	54.89231

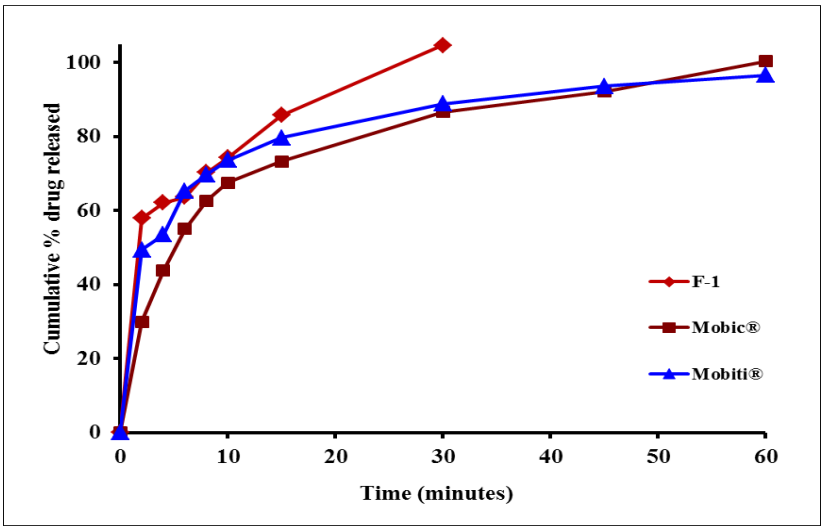

Fig. 3: Comparison of dissolution profiles of fast dissolving tablets of meloxicam (F-1) with marketed products (Mobic® and Mobitil®).

CONCLUSION

It was concluded that solid dispersion approach can be adopted for the formulation of fast dissolving tablets with higher in vitro dissolution for water insoluble drugs like Meloxicam which was achieved with PVP a hydrophilic carrier.

ACKNOWLEDGMENT

The authors acknowledge RFA pharmaceutical industries for the donation of the drug.

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