International Journal of Current Pharmaceutical Research
Vol 2, Issue 3, 2010
ISSN-0975-7066

Research Article

FORMULATION AND DEVELOPMENT OF FAST DISSOLVING MELOXICAM TABLETS BY SOLID DISPERSION TECHNIQUE: FOR THE EFFECTIVE TREATMENT OF DENTAL PAIN

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Received 12 Jan 2010, Revised and Accepted 08 Feb 2010

ABSTRACT

Attempts were made to prepare fast dissolving tablets of Meloxicam by employing solid dispersion technique. Formulations were evaluated for precompressional parameters such as angle of repose, % compressibility and Hausner's ratio. Tablets were subjected to post compressional analysis for the parameters such as hardness, friability, in-vitro disintegration time, wetting time and dissolution. Drug crystalline nature was checked by XRD studies. Stability studies were carried out as per ICH guidelines for three months. The results revealed that tablets prepared by solid dispersion having drug to PVP ratio of 1:4 (P3), yielded the best result in terms of dissolution rate. Stability studies revealed that upon storage tablets prepared by solid dispersion with PVP did not show any change in disintegration time after stability studies.

Keywords: Fast Dissolving Tablets, Meloxicam, Croscarmillose Sodium, Solid Dispersion.

INTRODUCTION

The Oral route of administration still continues to be the most preferred route due to its manifold advantages including ease of ingestion, pain avoidance, versatility and most importantly patient compliance. Therefore, oral solid dosage forms are popular because of ease of administration, accurate dosage, self medication, pain avoidance and most importantly patient compliance. Among the pharmaceutical dosage forms, the conventional tablets seem to be most popular, because of its ease of transportability and comparatively lower manufacturing cost. There are several factors other than physicochemical properties of the drug that may influence the dissolution rate and hence, bioavailability of the drugs forms the solid dosage forms. It has shown that, the dissolution rate of pure drugs can be altered significantly by the proper selection of formulation components as well as processing methods[1].

Meloxicam is a nonsteroidal anti-inflammatory drug of the oxicam class, used to relieve the symptoms of dental pain, arthritis, primary dysmenorrhea, fever and as an analgesic, especially where there is an inflammatory component[2]. Meloxicam inhibits cyclooxygenase (COX) synthesis. This enzyme is responsible for converting arachidonic acid into prostaglandin H2. This is the first step in the synthesis of prostaglandins, which are mediators of inflammation. Meloxicam has been shown, especially at its low therapeutic dose, selectively to inhibit COX-2 over COX-1 [3]. A primary advantage of the oxicam family of drugs is their long half-life which permits once-day dosing[4]. In gastric disease, lower dose of meloxicam is required 7.5 mg/day. Meloxicam is safer then other NSAID's [5]. One of the major problems with the drug is the very low solubility in biological fluids. The rate of dissolution can be increased by increasing the surface area of the drug by solid dispersion method .The dissolution of a drug can also be influenced by the disintegration time of the tablets[6]. Most dental pain can be treated clinically with effective local anesthesia, interventional dental treatment and in the immediate post-treatment phase, by maximizing the use of non-opioid analgesia such as paracetamol and non-steroidal anti-inflammatory drugs such as Meloxicam[7].Hence in the present work Meloxicam fast dissolving tablets were prepared by solid dispersion method using PVP as a carrier for the immediate and effective treatment of dental pain.

MATERIALS AND METHODS

Meloxicam was gifted from Zydus Hetero drugs Ltd. (Hyderabad, India). Croscarmellose sodium Gift sample from Maple biotech Pvt. Ltd, Pune , Microcrystalline cellulose, PVP, Talc and Magnesium stearate were purchased from S.D. Fine chemicals Pvt limited, Mumbai and all other materials were of analytical grade.

METHODS

Preparation of solid dispersions of Meloxicam

Solid dispersions of Meloxicam were prepared by solvent evaporation method. Drug was weighed and taken in a china dish, dissolved in methanol and then carrier (PVP) was added in ratio of 1:1, 1:2, 1:4 and 1:9. The solvent was evaporated at room temperature and dried in hot air oven at 50^0 C for 4 hours. The resultant mass was passed through sieve no. 60 and stored in dessicator.

Preparation of tablets containing solid dispersions of Meloxicam

The solid dispersions equivalent to 7.5 mg of drug were taken. Then mixed with directly compressible diluent and superdisintegrant in a plastic container. Magnesium stearate and aerosil were passed through sieve no. 60, mixed and blended with initial mixture in the plastic container followed by compression of the blend (Table 1).

Evaluation of Meloxicam tablets

All prepared tablets were evaluated for hardness, thickness, friability, disintegration time, wetting time, drug content and stability studies.Pfizer hardness tester was used for the determination of the hardness of the tablets. The tablet was placed in contact between the plungers and the handle was pressed,the force of the fracture was recorded (Fig.1) .The thickness of tablets were recorded during the process of compression using Calipers(Mitotoyo;Japan) .The friability of the tablets was determined using a Roche Friabilator (Electrolab,EF-2 Friabilator) by taking two tablets from each batch and accurately weighed and placed in the Friabilator then operated for 100 revolutions .Then the tablets were dedusted and reweighed .Percentage friability was calculated using the formula,$F= (1-w_o/w)*100$. In the disintegration time study, the tablets were taken and introduced in each tube of disintegration apparatus, and the tablet rack of the disintegration apparatus was positioned into a 1 litre beaker containing 900ml of distilled water and time of disintegration was recorded at 37±2º C. In the wetting time study, a piece of tissue paper folded twice was placed in a petridish (with internal diameter 6.5cm) containing 5ml of distilled water. A tablet was placed on the paper and the time for complete wetting of the tablet was measured in seconds. For drug content analysis a total 10 tablets were weighed and powdered .The powder equivalent to 7.5mg of Meloxicam was taken and dissolved

in phosphate buffer pH 7.4 .After that an aliquot of the filtrate was diluted and analysed spectrophotometrically (UV 1700 Shimadzu Corporation.Japan) at 360 nm . The stability study of the tablets was carried out according to ICH guidelines .The formulations were stored at 40 ±2ºC / 75 ±5%RH for 4 weeks in a stability chamber (Labcare ,Mumbai,India)

Invitro release studies

The invitro dissolution study was carried out in the USP dissolution test apparatus (Electrolab TDT - 08 L Dissolution tester USP) type 2 (paddle). 900 ml of the dissolution medium (Phosphate buffer pH 7.4) was taken in vessel and the temperature was maintained at 37 ± 0.5ºC. The speed of the paddle was set at 50 rpm. 5ml of the dissolution medium was withdrawn and the same amount of fresh medium was replenished to the dissolution medium. The sample withdrawn was filtered and diluted with Phosphate buffer pH 7.5 prior to analysis in the UV Spectrophotometer (UV-1700 Shimadzu Corporation, Japan) at 360 nm.

Characterization of Meloxicam tablets

X-ray diffraction studies

X-RD analysis of pure drug Meloxicam, polymer (PVP) and formulation P3 were performed . This was done by measuring the 2 θ ranges from 10-50 on PW 3710 X-ray generator defractometer. The XRD patterns were recorded automatically using rate meter with time per step was 0.500 seconds and scanning speed of 2 θ per minute.

RESULTS AND DISCUSSIONS

The values of pre–compression parameters evaluated were within prescribed limits and indicated a good free flowing property. Results are shown in Table 2. The post compression parameters such as hardness, friability, thickness, disintegration time, wetting time, $t_{50\%}$, $t_{90\%}$ and drug content are shown in Table 3.

Table 1: Formulae used in the preparation of tablets using PVP solid dispersion

Ingredients (mg)	P	P1	P2	P3	P4
Amount of solid Dispersion equivalent to 7.5 mg of drug	27.9	12.66	17.74	28.81	55.13
Lactose	97.60	106.84	101.76	90.69	64.37
MCC	20	20	20	20	20
Croscarmellose Sodium	-	6	6	6	6
Magnesium Stearate	1.5	1.5	1.5	1.5	1.5
Talc	1.5	1.5	1.5	1.5	1.5
Aerosil	1.5	1.5	1.5	1.5	1.5
Tablet Weight	150	150	150	150	150

Table 2: Precompressional parameters

Formulation	Angle of repose(θ) (±SD), n=3	Compressibility (%) (±SD), n=3	Hausner's Ratio (±SD), n=3
P	23.65 ±2.22	16.66 ±4.22	1.37 ±0.06
P1	24.21 ±3.52	29.57 ±0.060	1.32 ±0.05
P2	23.70 ±0.28	23.80 ±1.34	1.31 ±0.02
P3	22.49 ±1.12	23.60 ±2.60	1.35 ±0.04
P4	34.06 ±0.95	27.22 ±1.67	1.32 ±0.03

Note: Values in parenthesis are standard deviation ±SD

Table 3: Post compression parameters, disintegration time, wetting times, dissolution parameters and drug content of tablets

Formulation	Hardness test (kg/cm^2) ±SD, n=6	Friability (%) ±SD, n=10	Thickness (mm) ±SD, n=4	Disintegration time (sec) ±SD, n=6	Wetting time (sec) ±SD, n=6	$t_{50\%}$ (min) ±SD, n=4	$t_{90\%}$ (min) ±SD, n=4	Drug content (%) ±SD, n=6
P	4.50 ±0.28	0.26 ± 0.04	3.5 ± 0.00	420± 10.50	500 ± 7.70	7.42± 0.12	28.33 ± 0.3	99.55±1.97
P1	3.55±0.10	0.30 ± 0.04	3.65± 0.05	48± 2.00	52±3.75	1.34± 0.25	10.07±0.25	100.15±2.20
P2	3.55±0.15	0.32 ±0.02	3.48±0.058	42±3.44	50 ±2.20	1.32±0.14	8.52 ± 0.19	101.15±1.50
P3	3.50 ± 0.20	0.33±0.04	3.50 ± 0.06	50±2.90	60±2.50	1.17±0.40	6.12±0.26	101.0± 1.55
P4	6.05± 0.31	0.33± 0.02	3.50±0.06	420±5.50	500± 8.50	18.34±0 .32	41.15± 0.22	99.00±3.00

Note: Values in parenthesis are standard deviation (±SD)

Table 4 : Tablet parameters after stability studies

Formulation	Disintegration time(sec) (±SD), n=6	Thickness (mm) (±SD), n=4	Drug content (%) (±SD), n=6
P	450 ±10.15	3.50 ±0.052	99.00±0.62
P1	50.00±6.33	3.62±0.050	96.00 ±0.72
P2	44.00±4.11	3.45±0.051	95.36±1.35
P3	48.00±3.92	3.48±0.062	94.72±0.72
P4	490.0±4.56	3.38±0.039	97.62±1.55

In all the formulations, the hardness test indicates good mechanical strength. Friability of all formulations were less than 1%, which indicated that the tablets had a good mechanical resistance. Drug content was found to be high (≥ 101.55 %) and uniform in all the formulations.

The tablets were subjected for evaluation of invitro disintegration time and it was observed that formulations P1, P2, P3 disintegrated rapidly while P and P4 did not disintegrated in the specified limit of time for fast dissolving tablets .This may be due to more hardness of the tablets as PVP act as strong binder at higher level within the tablets. During compression, the carrier could plasticize, soften or melt, filling the pores within tablets and thus making them non disintegrating. It is also possible that the soften and melted carrier may coat the disintegrant and other ingredients used in the tablets ,and such a coating along with reduction of porosity of tablets make disintegration difficult . Wetting time of formulations P and P4 were significantly higher than other formulations .The dissolution of Meloxicam from the formulations is shown in Fig 2 .The results were compiled in Table 3. The dissolution rate of tablets prepared with solid dispersion in the ratio1:1, 1:2,1:4 (P1,P2,P3) with PVP increased significantly (P< 0.05) than formulation P(control) . This may be due to the use of Croscarmellose sodium, which causes swelling to 4-8 folds in 10 seconds[8] and due to particle size reduction and improved wettability[9]. In addition to micronization, conversion of drug to amorphous form during the preparation might have also contributed to the increased dissolution rates observed with the solid dispersions[10]. However tablets prepared in the ratio 1:9 (P4) did not further enhance the dissolution rate unlike solid dispersions. In practice the effect of micronization is often disappointing, especially when the drugs are encapsulated or tabletted[11,12] . This phenomenon was attributed to the agglomeration tendency of micronized, poorly soluble, hydrophobic drugs, which effect results in a decreased effective surface area for dissolution[13].

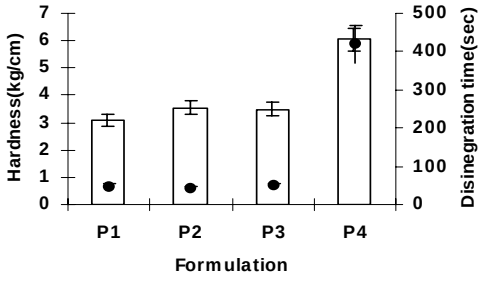


Fig. 1: Hardness and Disintegration time of tablets prepared with PVP (P1, P2, P3, P4) solid Dispersion

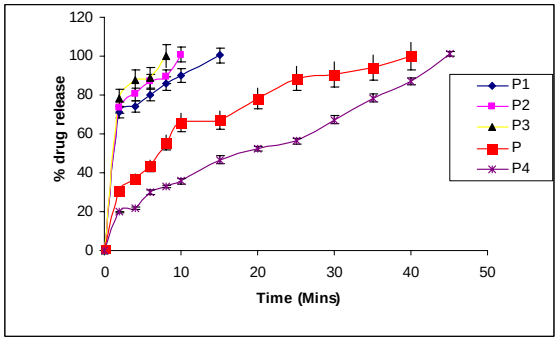
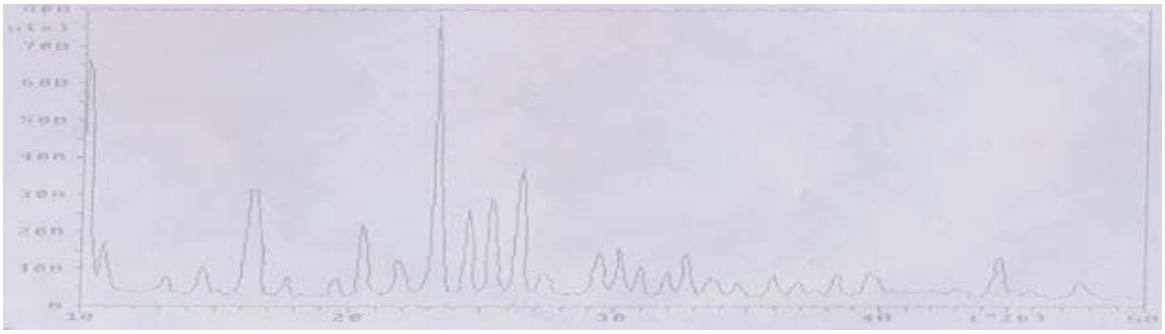


Fig. 2: Dissolution profiles of formulations containing PVP solid dispersions

A



B

C

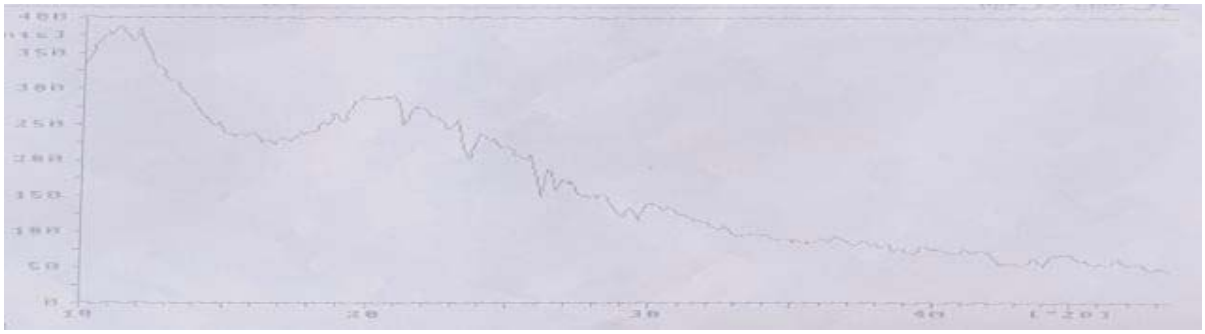


Fig. 3: XRD Patterns of Pure Meloxicam (A), PVP (B) and Meloxicam solid dispersion with PVP (C)

X-ray diffraction pattern

XRD patterns of pure drug, polymer and formulation P3 are shown in Fig.3. XRD patterns of pure Meloxicam a crystalline material show the characteristic peaks at 2θ 10.30, 10.38, 10.87, 13.26, 14.69, 16.22, 17.75, 20.43, 23.44, 24.43, 25.49, 26.42, 27.58, 29.23, 31.90, 33.81, 36.89, 39.50, 43.19, 44.65 and 47.67. However the XRD patterns of its solid dispersion in PVP (P3) shown the typical profiles of amorphous material as observed from the values. A peak corresponding to Meloxicam crystals completely disappeared in formulation P3 .This indicates that, the drug was dispersed in amorphous form in the formulation.

The stability study for all the formulations were carried out according to the ICH guidelines at 40 ± 2º C / 75 ±5% RH for 4 weeks, by storing the tablets in a stability chamber (Labcare, Mumbai, India) . No change was observed in the disintegration time of all the formulations. No significant change in the thickness was observed in all the formulations and drug content of all formulations was within the acceptable limits. Results are shown in Table 4.

CONCLUSION

The major problem of Meloxicam is its very low solubility in biological fluids. The results revealed that it is possible to enhance the dissolution rate of Meloxicam by increasing the surface area of the drug by solid dispersion method. Tablets prepared by PVP solid dispersion of ratio 1:4 (P3) yielded best results in terms of dissolution rate and such fast release tablets are more essential in severe dental pains and the adopted technique was found to be economical and industrially feasible.

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