Advance Research in Pharmaceuticals and Biologicals
(A Peer Reviewed International Journal for Pharmaceutical and Allied Research)
ISSN 2250-0774 USA CODEN: ARPBGZ

FORMULATION AND INVITRO EVALUATION OF IMMEDIATE RELEASE MELOXICAM TABLETS

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Received : 21/01/2014 **Revised : 01/02/2014** **Accepted : 09/02/2014**

ABSTRACT:
The main objective of the present study was to formulate stable immediate release Meloxicam tablets matching in invitro dissolution with the marketed formualtion. Meloxicam is a poorly soluble drug. The present works focused on improving the dissolution of Meloxicam with the aid of sodium citrate as alkalizing agent and superdisintegrants. Tablets were manufactured by wet granulation method. The use of superdisintegrants reduced the disintegration time but did not improve the dissolution of Meloxicam. Since Meloxicam is soluble in alkaline media, trials were taken with different concentrations of sodium citrate as alkalizing agent and the dissolution profiles were compared with that of marketed formulation. It was found that the dissolution profile of trial T7 which was formulated with Meloxicam and Sodium citrate 1:1.5 ratio was similar to marketed formulation. Based on the results it was concluded that an alkalizing agent is required to improve the dissolution of Meloxicam. The 7.5mg strength was formulated by common blend approach, with formula similar to optimized formula of 15mg tablets. The dissolution profile of 7.5 mg strength was compared with 15mg strength and the results were found to be satisfactory.

Keywords: Formulation**,** Optimization, Immediate Release Tablet, Meloxicam

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INTRODUCTION

The oral route is the most preferred route of administering drugs for systemic effect due to its simplicity, versatility, convenience, ease of ingestion, pain avoidance, versatility and most importantly patient compliance[1]. Tablets are the most common oral dosage forms. The tablet dosage form is preferred to other oral dosage forms since one accurate dose of the drug can be easily administered[2].

Clinically, nonsteroidal anti-inflammatory drugs (NSAIDs) are the most frequently prescribed by physicians for inflammatory disorders[3]. Meloxicam is a non-steroidal anti-inflammatory drug (NSAID) of the oxicam family, with anti-inflammatory, analgesic and antipyretic properties. Meloxicam is safer than other NSAIDs[4]. The mode of action is inhibition of the biosynthesis of prostaglandins, known inflammation mediators. Meloxicam is indicated for short-term symptomatic treatment of exacerbations of osteoarthrosis and long-term symptomatic treatment of rheumatoid arthritis or ankylosing spondylitis. Meloxicam is chemically described as [4–hydroxy–2–methyl–N-(5–methyl-1, 3–thiazol–2-yl)-2H-1,2 benzothiazine-3-carboxamide1,1-dioxide][5]. The structure of Meloxicam is given in fig 1:

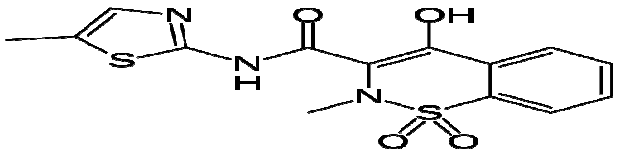

Fig. 1: Structure of Meloxicam

Its empirical formula is $C_{14}H_{13}N_3O_4S_2$. Meloxicam is a yellow solid drug, practically insoluble in water, with higher solubility observed in strong bases. It is very slightly soluble in methanol. Meloxicam has an apparent partition coefficient (log P) app=0.1 in n-octanol/buffer pH 7.4. Meloxicam has pKa values of 1.1 and 4.2[6]. Meloxicam has a low solubility in aqueous media and low dissolution rate[7]. Meloxicam is well absorbed from the gastrointestinal tract, which is reflected by a high absolute bioavailability of about 90% following oral administration (capsule). It is, therefore, considered a class II drug as per Biopharmaceutics classification system.

The objective of the present study was to develop stable oral immediate release Meloxicam tablets with dissolution profile similar to that of marketed formulation. Immediate release tablets are those intended to be swallowed whole and to disintegrate and release their medicaments rapidly in the gastrointestinal tract (GIT). Superdisintegrants are more effective at lower concentrations typically 1- 10 % by weight relative to the total weight of the dosage unit with greater disintegrating efficiency and mechanical strength. Different commonly used superdisintegrants are: 1. Modified Starches- Sodium Carboxymethyl Starch (Sodium Starch Glycolate) 2. Cross-linked polyvinylpyrrolidone (crosspovidone) 3. Modified Cellulose (croscarmellose sodium)[8]. Various formulations of Meloxicam tablets 15mg were prepared using the above mentioned superdisintegrants and the invitro dissolution profiles of the formulations were compared with that of marketed formulation 15mg. It was found that by increasing the concentration of superdisintegrants alone did not improve the dissolution profile. Since Meloxicam is soluble in alkaline pH, trials were taken with different concentrations of sodium citrate as alkalizing agent to improve the solubility of Meloxicam. The formulation trials were also evaluated for inprocess parameters like bulk density, tapped density, compressibility index, Hausner's ratio and parameters for finished product like average weight, weight variation, tablet thickness, friability, hardness, disintegration time and drug content. The invitro dissolution profiles were compared with the marketed formulation 15g as per the BP method. Based on the dissolution results, the formula was optimized for 15mg tablets. The lower strength 7.5mg was formulated by common blend approach as that of optimized formula for 15mg strength and its dissolution profile was compared with that of 15mg strength[8].

MATERIALS AND METHODS

Meloxicam was procured from Sekhsaria Chemicals limited. Other ingredients in the formulation included Lactose monohydrate, Microcrystalline Cellulose (Avicel PH101), Povidone (Kollidon 30), Pregelatinised maize starch (Starch 1500), Crospovidone (Polyplasdone XL), Croscarmellose sodium (Ac-Di-Sol), Sodium starch glycollate (Primogel) and Magnesium stearate.

Meloxicam is extremely sticky in nature and hence wet granulation method was selected. Trials were taken with different superdisintegrants and different concentrations of sodium citrate to match the dissolution profile with the marketed formulation. Composition of various trials of Meloxicam tablets 15mg are given in Table 1.

Table 1: Compostion of formulation trials of Meloxicam tablets 15mg

Ingredients	Mg/tablet							
	T1	T2	T3	T4	T5	T6	T7	T8
DRY MIX								
Meloxicam	15.0	15.0	15.0	15.0	15.0	15.0	15.0	15.0
Microcrystalline Cellulose	86.0	86.0	86.0	86.0	78.5	71.0	63.5	56.0
Lactose monohydrate	34.0	34.0	34.0	34.0	34.0	34.0	34.0	34.0
Sodium Starch Glycollate	6.0	---	---	---	---	---	---	---
Croscarmellose Sodium	---	6.0	---	---	---	---	---	---
Crospovidone	---	---	6.0	3.0	3.0	3.0	3.0	3.0
Sodium citrate	---	---	---	---	7.5	15.0	22.5	30.0
WET GRANULATION								
Povidone	6.0	6.0	6.0	6.0	6.0	6.0	6.0	6.0
Purified water	q.s	qs	qs	qs	qs	qs	qs	qs
LUBRICATION								
Crospovidone	---	---	---	3.0	3.0	3.0	3.0	3.0
Magnesium stearate	3.0	3.0	3.0	3.0	3.0	3.0	3.0	3.0
CORE WEIGHT	150	150	150	150	150	150	150	150

MANUFACTURING PROCESS

Meloxicam, Microcrystalline Cellulose, Lactose monohydrate, Sodium citrate and superdisintegrant were sifted through 40# mesh using a vibratory sifter. The sifted raw materials were loaded into rapid mixer granulator and mixed for 15 minutes with impeller at slow speed and chopper off. Povidone was dissolved in purified water was added slowly to the dry mix over a period of 5 minutes with impeller at slow speed and chopper off. The granules were kneaded for 5 minutes with impeller at fast speed and chopper at slow speed. The granules were dried in a fluid bed dryer with inlet temperature between 55°C to 65°C till the LOD was between 2.5 to 3.5%. The dried granules were then sifted through 20# mesh using a vibratory sifter. The

retentions were milled using multimill fitted with 1.5 mm screen in knife forward direction at medium speed. The granules were then loaded into octagonal blender. Crosspovidone was sifted through 40# and added to sized granules in blender and mixed for 5 minutes. Magnesium stearate was sifted through 30# mesh and added to the sized granules and mixed for 3 minutes at slow speed. The lubricated granules were then compressed using 7.5mm circular standard concave plain punches on Rimek 10 station single rotary "B" tooling machine at an average weight of 150mg and hardness between 70-100 N.

Formulation Trials T1 to T4: Trials T1, T2 and T3 were taken with different superdisintegrants, each used at 4% w/w Sodium starch glycolate (Primogel) (T1), Croscarmellose sodium (Ac-Di-Sol) (T2) and Polyplasdone XL (T3). Trial T4 was taken with 4% of Polyplasdone XL10 with 2% of superdisintegrant intragranular and remaining part was added extragranular. Primogel has an average particle size of 60 microns. Ac-Di-Sol has an average particle size of 45 microns. Polplasdone has average particle size of 110 to 140 microns. The dissolution profile of all these trials were slower compared to marketed formulation, Mobic 15mg.

Formulation Trials T5 to T8: The disintegration time of trials T1 to T4 was less than 3 minutes but the dissolution of the trials was not matching with marketed formulation due to poor solubility of Meloxicam. Trials T5, T6, T7 and T8 were taken with different concentrations of sodium citrate as alkalizing agent to increase the solubility of Meloxicam. The ratio of Meloxicam : Sodium citrate being 1:0.5 in T5, 1:1 in T6, 1:1.5 in T7 and 1:2 in T8. Among these 4 trials, the dissolution profile of trial T7 was similar to marketed formulation (BP Method). Two dissolution profiles are considered to be similar if the dissimilarity factor F1 lies between 0 to 15 and similarity factor F2 lies between 50 to 100.

Formulation Trials of 7.5mg Strength: Among the trials taken for Meloxicam tablets 15mg, Trial T7, in which Meloxicam: Sodium citrate was 1:1.5 was concluded as optimized formulation. The 7.5mg tablets were compressed from the granules of 15mg strength (T7) at average weight of 75 mg using 6.0 mm circular standard concave plain punches. This was common blend approach. The dissolution profile of 7.5mg (A1) was similar to 15mg strength (T7). The CDER guidance states that, to claim biowaivers for lower strengths of a dosage form, an important criteria is that the dissolution profiles of the lower strengths should be similar to that of the highest strength. The dissolution profile of 7.5mg strength was similar to 15mg strength.

Evaluation of in process parameters of granules

The lubricated granules were evaluated for loss on drying, bulk density, tapped density, compressibility index, Hausner's ratio and particle size distribution. Loss on drying was determined at 105°C for 5 minutes using IR moisture analyzer. Bulk density and tapped density was estimated using Bulk density apparatus (Electro lab, Mumbai, India).

EVALUATION OF TABLETS

The finished tablets were tested as per standard procedure.

Average Weight: 20 tablets were weighed together and the average weight was determined.

Weight Variation: Twenty tablets were randomly selected from each batch and individually weighed. The average weight and standard deviation of 20 tablets was calculated.

Thickness: Ten tablets were randomly selected from each batch and their thickness was measured by using digital vernier caliper. The average thickness and standard deviation was determined.

Hardness: The hardness was determined for 10 tablets of each batch by using Erweka tablet hardness tester. The average hardness and standard deviation was determined.

Friability: Twenty tablets were weighed and placed in the Electrolab friabilator and apparatus was rotated at 25 rpm for 4 minutes. After revolutions the tablets were dedusted and weighed again. The percentage friability was measured using the formula,

$$\% F = \{1-(Wt/W)\} \times 100$$

Where, % F = friability in percentage
W = Initial weight of tablet
Wt = weight of tablets after revolution.

Disintegration time: The disintegration test was done on 6 units using the apparatus as per British pharmacopoeia method.

Assay of tablets: The assay of Meloxicam in tablets was estimated as per the British pharmacopoeia method.

Chromatographic conditions

Mode: Liquid chromatography
Detector: UV 254 nm
Column: 10-mm x 4.0-cm; 10-µm packing.

Procedure:

1. 20 tablets were powdered and weight equivalent to 30 mg of Meloxicam was moistened with 10 ml of 1M sodium hydroxide. 80 ml of methanol was added and mixed and volume was made upto 100ml
2. 2 volumes of solution (1) was diluted to 100 volumes

with methanol. 1 volume was diluted to 10 volumes with methanol.
3. 15 mg of meloxicam impurity standard BPCRS was dissolved in 5 ml of 1M sodium hydroxide. 30 ml of methanol was added and mixed and volume was made to 50 ml.

Mobile phase: 370 volumes of a mixture of 650 volumes of methanol and 100 volumes of propan-2-ol and 630 volumes of a 0.20% w/v solution of di-ammonium hydrogen orthophosphate adjusted to pH 7.0 with dilute orthophosphoric acid.

In-Vitro Dissolution Studies: In Vitro dissolution study was carried out as per British pharmacopoeia method.
Number of units: 6
Medium: Buffer; 900 ml, pH 7.5
Apparatus 2: 50 rpm.
Time: 45 min

Procedure:
(1) The absorbance of the filtered sample was measured at 362 nm using dissolution medium in the reference cell.
(2) The absorbance of the standard solution prepared by dissolving 30 mg of meloxicam BPCRS in 5 ml of methanol, adding 1 ml of 0.1M sodium hydroxide and adding sufficient dissolution medium to produce 100 ml was measured.

RESULTS AND DISCUSSION

The lubricated granules were evaluated for in process parameters like loss on drying, bulk density, tapped density, compressibility index and Hausner's ratio. These results were found to be satisfactory and are presented in Table 2.

Table 2: Evaluation of inprocess parameters of lubricated granules of formulation trials

S.No.	Parameters	T1	T2	T3	T4	T5	T6	T7	T8
1	Loss on drying(% w/w)	3.2	2.8	2.9	3.4	3.1	2.7	2.8	2.8
2	Bulk density (g/cc)	0.556	0.532	0.581	0.543	0.521	0.510	0.562	0.554
3	Tapped density (g/cc)	0.658	0.625	0.694	0.641	0.610	0.595	0.638	0.652
4	Compressibility Index	15.55	14.89	16.27	15.22	14.58	14.29	13.59	14.58
5	Hausner's ratio	1.18	1.17	1.19	1.18	1.17	1.17	1.19	1.14
6	Particle Size	Cumulative % retained							
	20#	10.36	8.52	12.65	10.68	7.54	9.52	9.41	10.22
	30#	15.94	14.83	15.97	14.89	15.61	17.32	16.74	16.47
	40#	38.62	40.58	45.62	40.36	38.42	34.86	38.42	40.98
	60#	53.68	51.62	52.48	51.28	54.32	49.58	53.64	57.64
	80#	68.92	63.52	62.80	64.35	68.27	65.76	67.42	66.48
	100#	75.21	70.46	75.24	76.58	75.84	72.84	75.16	76.32

The tablets after compression were evaluated for parameters like average weight, weight variation, hardness, thickness, disintegration time and friability. The results were satisfactory and are presented in Table 3.

Table 3: Evaluation of Meloxicam tablets 15mg

S.No	Parameter	Specification	T1	T2	T3	T4	T5	T6	T7	T8
1	Average weight	150.0 mg ±2.0% (147.0-153.0 mg)	148.9	151.5	149.4	152.4	148.4	150.5	151.5	150.8
2	Weight variation	150.0 mg ±7.5% (138.8-161.3 mg)	141.5 - 151.6	145.6 - 156.4	142.8-157.7	145.2-155.5	146.5-156.6	148.5-153.7	143.2-155.8	142.2 - 157.8
3	Hardness	70-100 N	77 - 92	82-95	78 -91	78 -39	75 -95	79- 95	72- 95	76-92
4	Disintegration time	NMT 15 minutes	2'55'	2'45'	2'30'	2'15'	2'22'	2'25'	2'32'	2'35'
5	Thickness	3.50±0.20 mm (3.30 to 3.70 mm)	3.38-3.62	3.43-3.58	3.45-3.61	3.41-3.61	3.42-3.56	3.43-3.59	3.48-3.65	3.51-3.61
6	Friability	NMT 1% w/w	0.22	0.31	0.29	0.22	0.28	0.27	0.21	0.24

Table 4: Evaluation of Meloxicam tablets 7.5mg

S.No	Parameters	Specifications	Results
1	Average weight	75.0 mg ±2.0% (73.50 to 76.50 mg)	76.2
2	Weight variation	75.0mg ±10.0%(67.50 to 82.50 mg)	71.5 - 78.4
3	Hardness	40-70 N	45 - 63
4	Disintegration time	NMT 15 minutes	2'25''
5	Thickness	2.50±0.20 mm (2.30 to 2.70 mm)	2.45 - 2.65
6	Friability	NMT 1.0%w/w	0.22

Invitro dissolution profiles of tablets: The dissolution profiles of Meloxicam tablets 15mg were compared with marketed formulation Mobic 15mg (BP Method). The results are presented in Table 5.

Table 5: Comparative dissolution profiles of formulation trials (15mg) vs marketed formulation Mobic 15mg

Time (mins)	% drug release in pH 7.5 buffer								
	Mobic 15mg	T1	T2	T3	T4	T5	T6	T7	T8
5	30.8	12.8	14.7	13.8	14.9	23.6	28.4	30.2	33.2
10	40.7	20.5	22.8	24.1	25.7	31.7	37.2	41.7	43.5
15	52.8	32.4	34.8	33.8	35.7	42.5	49.7	53.8	56.4
20	68.1	42.9	43.9	44.7	44.4	54.4	63.8	67.5	70.4
30	79.4	54.8	52.7	55.4	56.8	63.9	70.5	79.7	81.4
45	85.7	68.2	67.4	69.7	68.4	74.5	78.9	87.2	88.7
60	92.5	77.4	78.4	79.7	78.9	84.5	88.7	93.4	94.5
F1		31.3	30.1	28.6	27.8	16.2	7.3	0.8	4.0
F2		34.5	35.2	36.3	36.9	48.2	63.9	93.4	77.5

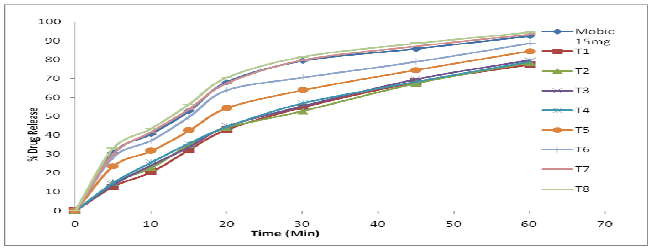

Fig. 2: Comparative dissolution profiles of formulation trials (15mg) vs marketed formulation Mobic 15mg in pH 7.5 buffer

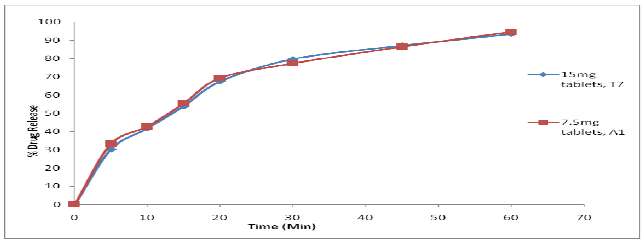

Fig. 3: Comparative dissolution profiles of formulation trials T7 (15mg) vs formulation trial A1(7.5mg) in pH 7.5 buffer

The dissolution profile of 7.5mg strength was similar to 15mg tablets (Trial T7) in pH 7.5 buffer. The results are presented in Table 6.

Table 6: Comparative dissolution profiles of formulation trials A1(7.5mg) vs formulation trial T7 (15mg) in pH 7.5 buffer

Time (Minutes)	% Drug Release in pH 7.5 buffer	
	15 mg (T7)	7.5 mg (A1)
5	30.2	33.2
10	41.7	42.8
15	53.8	55.4
20	67.5	69.4
30	79.7	77.4
45	87.2	86.5
60	93.4	94.6
F1		2.1
F2		82.6

CONCLUSION

Meloxicam tablets 7.5mg and 15mg were formulated by wet granulation method. A prerequisite to demonstrate bioequivalence of generic formulation with that of marketed formulation is that the dissolution profile of generic formulation should be similar to marketed formulation. The bioavailability of the drug is influenced by the solubility of the drug from the dosage form. Three different superdisintegrants, crospovidone, croscarmellose sodium and sodium starch glycolate were selected for matching the dissolution profile with the marketed formulation. Trials taken with different superdisintegrants reduced the disintegration time of the tablets, but did not improve the dissolution. Since Meloxicam is soluble in alkaline pH, an alkalizing agent, sodium citrate was necessary to improve the dissolution of Meloxicam. The dissolution profile of trial T7, which contained Meloxicam and Sodium citrate in 1:1.5 ratio was similar to marketed formulation Mobic 15mg. The 7.5mg tablets were formulated based on common blend approach to Trial T7 of 15mg tablets. The dissolution profiles of 7.5mg strength was similar to 15mg strength, which is an essential criteria to claim biowaivers for lower strengths of generic formulation. The inprocess and finished product quality control parameters of all strengths were found to be satisfactory. Thus it can be concluded that the formulations of Meloxicam tablets 7.5mg and 15mg are suitable for intended use.

Acknowledgement

The authors are thankful to the management of Microlabs Limited, Hosur, Tamilnadu, India for providing the necessary facilities to carry out the research work.

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