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ENHANCEMENT OF DISSOLUTION RATE OF MELOXICAM USING SUPER DISINTEGRATING AGENTS AND SOLID DISPERSION TECHNIQUE

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ABSTRACT
The aim of the research is to enhance the dissolution rate of meloxicam using superdisintegrants and solid dispersion technique, to know the effect of super disintegrants on the dissolution rate of meloxicam by selecting the best super disintegrant among SSG, CMS, CP by preparing the solid dispersion of meloxicam using PEG 4000 as carrier, to know the effect of combination of solid dispersion technique and superdisintegrants on dissolution rate of meloxicam. Meloxicam is a nonsteroidal anti-inflammatory drug (NSAID) with analgesic and fever reducer effects. It is a derivative of oxicam, closely related to piroxicam, and falls in theenolic acid group of NSAIDs. It was developed by Boehringer-Ingelheim. Meloxicam starts to relieve pain about 30–60 minutes after administration. Meloxicam inhibits cyclooxygenase (COX), the enzyme responsible for converting arachidonic acid into prostaglandin H_2—the first step in the synthesis of prostaglandins, which are mediators of inflammation. To enhance the dissolution rate and its bioavailability, meloxicam is formulated into capsules using super disintegrating agents (SSG, CMS, and CP) and solid dispersion technique. All the formulations are suitable for development of hard capsules of Meloxicam. Compared to all formulations of F-series, F7 was found to yield best results in terms of *in vitro* dissolution rate. In A-series formulations, A1 shows increased drug release patterns with the fastest in vitro dissolution rate followed by CMS then SSG. The study concluded that the formulation prepared using A- series and F- series, A1 and F7 exhibits better dissolution rate at high concentration of super disintegrating agents.

KEYWORDS: Dissolution, Meloxicam, Super Disintegrating Agents, Solid Dispersion Technique, Non-Steroidal Anti-Inflammatory Drug (NSAID).

INTRODUCTION
Dissolution is pharmaceutically defined as the rate of mass transfer from a solid surface into the dissolution medium or solvent under standardized conditions of liquid/solid interface, temperature and solvent composition. More than 40% NCEs (new chemical entities) developed in pharmaceutical industry are practically insoluble in water[1]. These poor water soluble drugs having slow drug absorption leads to inadequate and variable bioavailability and gastrointestinal mucosal toxicity. For orally administered drugs solubility is the most important one rate limiting parameter to achieve their desired concentration in systemic circulation for pharmacological response. Problem of solubility is a major challenge for formulation scientist[2]. The improvement of drug solubility thereby its oral bio-availability remains one of the most challenging aspects of drug development process especially for oral-drug delivery system. There are numerous approaches available and reported in literature to enhance the solubility of poorly water-soluble drugs. The techniques are chosen on the basis of certain aspects such as properties of drug under consideration, nature of excipients to be selected, and nature of intended dosage

form. The poor solubility and low dissolution rate of poorly water soluble drugs in the aqueous gastrointestinal fluids often cause insufficient bioavailability.[3-5] The bioavailability may be enhanced by increasing the solubility and dissolution rate of the drug in the gastro-intestinal fluids.[6]

Meloxicam has been shown, especially at its low therapeutic doses, selectively to inhibit COX-2 over COX-1. Meloxicam concentrations in synovial fluid range from 40% to 50% of those in plasma. The free fraction in synovial fluid is 2.5 times higher than in plasma, due to the lower albumin content in synovial fluid as compared to plasma.[7,8] The significance of this penetration is unknown, but it may account for the fact that it performs exceptionally well in treatment of arthritis in animal models. Meloxicam is a poor water soluble drug, having slow drug absorption which leads to inadequate and variable bioavailability and gastrointestinal mucosal toxicity. For orally administered drugs solubility is the most important one rate limiting parameter to achieve their desired concentration in systemic circulation for pharmacological response.[9-10]

Particle size reduction like micronization and nanosuspension, modification of the crystal habit like polymorphs, amorphous form and cocrystallization, drug dispersion in carriers like eutectic mixtures, solid dispersions, solid solutions and cryogenic techniques. Change of P^H, use of buffer, derivatization, complexation, and salt formation.[11,12] Supercritical fluid process, use of adjuvants like super disintegrating agent, surfactant, solubilizers, cosolvency, hydrotrophy, and novel excipients. Disintegrants are agents added to tablet and some encapsulated formulations to promote the breakup of the tablet and capsule "slugs' into smaller fragments in an aqueous environment there by increasing the available surface area and promoting a more rapid release of the drug substance.[13] Disintegrants are an essential component to tablet formulations. The ability to interact strongly with water is essential to disintegrant function. Combinations of swelling and/or wicking and/or deformation are the mechanisms of disintegrant action[14]. A disintegrant used in granulated formulation processes can be more effective if used both "intragranularly" and "extragranularly" thereby acting to break the tablet up into granules and having the granules further disintegrate to release the drug substance into solution.[15]

MATERIALS AND METHODS

Materials

A gift sample of Meloxicam was obtained from Dr. Reddy's Lab, Crospovidone (CP), Croscarmellose sodium (CMS) from Aurobindo Pharmaceuticals Ltd and Sodium starch glycolate (SSG), Methanol, Talc, Sodium hydroxide, Potassium dihydrogen phosphate, Magnesium stearate, PEG 4000 from SD Fine Chem. Ltd. were used. Capsule filling machine (Secor), USP basket dissolution apparatus (Veego), UV-VisibleSpectrophotometer (Shimadzu) were the equipments used.

Methods

Analytical method used for the estimation of drug

The UV spectrophotometer analytical method was developed for Meloxicam using a double beam Schimadzu UVspectrophotomer

Preparation of phosphate buffer pH 7.4

Dissolved 27.22 g of monobasic potassium phosphate in water and diluted to 1000 ml with water. In 50 ml of above solution added 39.1 ml of 0.2 M sodium hydroxide solution and added water to make up 200 ml.

Procedure for estimatingλmax:

The required quantity of drug was dissolved in few ml of methanol and diluted with phosphate buffer pH7.4 to get 10 µg/ml solutions and scanned for maximum absorbance in UV spectrophotometer between a wavelength ranges of 200 to 400 nm against phosphate buffer pH 7.4 as blank. In this study, meloxicam showed a maximum absorbance (λmax) at 363 nm. The value was confirmed by repeating procedure three times.

Procedure for establishing of the calibration curve

The required quantity of drug was dissolved in phosphate buffer 7.4 to get a stock solution of 100 µg/ml solution from which serial dilutions were made in order to get 5 µg/ml, 10 µg/ml, 15 µg/ml, 20 µg/ml, 30 µg/ml, 40 µg/ml solutions. The absorbance of these solutions was measured at 363 nm by using double beam UV spectrophotometer against a blank of phosphate buffer pH 7.4. The calibration curve of Meloxicam is shown in Figure 1.

Table 1: Composition of different formulations

S. No.	Ingredients (mg/capsule)	Formulation code						
		F1	F2	F3	F4	F5	F6	F7
1	Meloxicam	7.5	7.5	7.5	7.5	7.5	7.5	7.5
2	Sodiumstarch glycolate	-	2	5	-	-	-	-
3	Croscarmellose sodium	-	-	-	2	5	-	-
4	Crospovidone	-	-	-	-	-	2	5
5	Lactose	up to 100	up to 100	up to 100	up to 100	up to 100	up to 100	up to 100
6	Talc	0.02	0.02	0.02	0.02	0.02	0.02	0.02
7	Magnesium stearate	0.01	0.01	0.01	0.01	0.01	0.01	0.01

Table 2: Composition of different formulations with meloxicam solid dispersions and superdisintegrants

S. No.	Ingredients (mg/capsule)	Formulation code		
		A1	A2	A3
1	Meloxicam solid dispersion (1:3)	30	30	30
2	Croscarmellose sodium	-	-	5
3	Crospovidone	5	2	-
4	Lactose	up to 100	up to 100	up to 100
5	Talc	0.02	0.02	0.02
6	Magnesium stearate	0.01	0.01	0.01

Evaluation

Determination of drug release using different concentrations of super disintegrants:

Hard gelatin capsules of formulation of F- series were prepared using different super disintegrating agents like SSG, CMS, CP and their composition are shown in the table. All the materials i.e. meloxicam, super disintegrating agents (of varying concentrations), lactose, talc, magnesium stearate are mixed in a mortar to get a uniform mixture. These formulations containing super disintegrating agents are filled in hard gelatin capsules using capsule filling machine. A separate formulation without any super disintegrating agent is also prepared and filled into capsules. These capsules are subjected to dissolution test and samples of each formulation are collected at different time intervals and are measured for its absorbance using UV spectrophotometer for the estimation of percentage drug release. The formulations with best absorbance values are selected and formulated along with a water soluble carrier into solid dispersion.

Evaluation of Solid Dispersions

Solid dispersions are prepared using Melting or fusion method, involves the preparation of physical mixture of a drug and a water-soluble carrier i.e., PEG 4000 in ratios 1:1, 1:2, 1:3 and heating it directly until it melted. The melted mixture is then solidified rapidly in an ice-bath under vigorous stirring. The final solid mass is crushed, pulverized and sieved. Best Solid dispersionwas selected and forumulatedwith the best selected super disintegranting agents and filled into capsules. These capsules are subjected to dissolution test and samples of each formulation are collected at different time intervals and are measured for its absorbance using UV spectrophotometer for the estimation of percentage drug release.

RESULTS AND DISCUSSION

The absorbance of 10 µg/mL solution of Meloxicam was measured at 200 nm to 400 nm. The maximum wavelength of Meloxicam was found to be 363 nm and is shown in Table 3 and depicted in Figure 2.

Table 3: Determination of λmax of Meloxicam by UV spectrophotometry

Wavelength (nm)	Absorbance
200	0.471
210	1.198
220	0.689
230	0.686
240	0.821
250	1.092
260	1.388
270	1.441
280	1.144
290	0.756
300	0.486
310	0.349
320	0.342
330	0.450
340	0.617
350	0.776
360	0.850
361	0.851
362	0.864
363	0.868
364	0.864
365	0.834
366	0.835
367	0.818
368	0.823
369	0.834
370	0.818
380	0.692
390	0.486
400	0.298

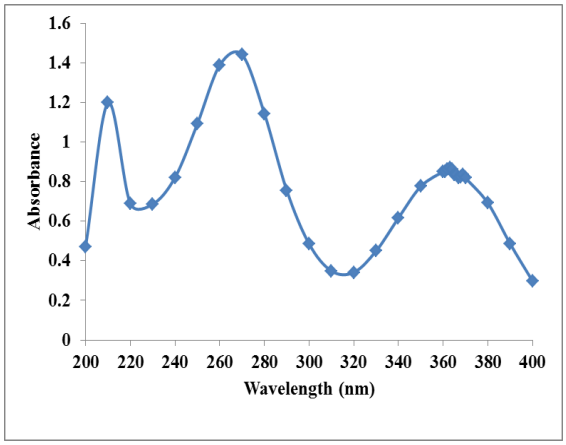

Figure 1: Determination of λmax of Meloxicam by UV spectrophotometry

Standard graph of Meloxicam phosphate buffer pH 7.4:

The absorbance of different concentrations of Meloxicam was measured using UV-Visible spectrophotometer at 363 nm. The results are shown in Table and depicted in Figure 2.

Table 2: Calibration curve of Meloxicam.

S. No.	Concentration (µg/mL)	Absorbance (nm)
1.	5	0.177
2.	10	0.225
3.	15	0.423
4.	20	0.526
5.	30	0.811
6.	40	1.23

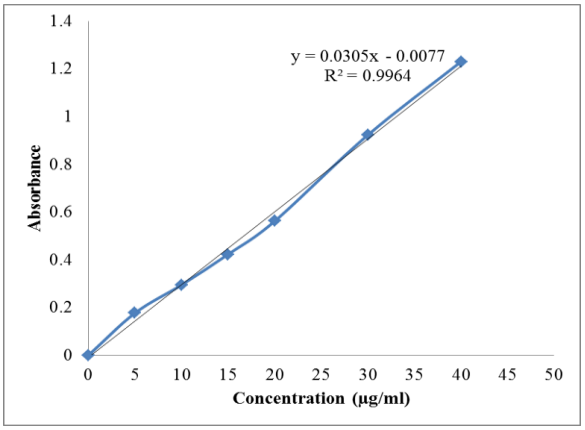

Figure 3: Standard Graph of meloxicam.

Effect of Disintegrating Agents on Dissolution rate of Meloxicam

The superdisintegrants alleviate most of the problems associated with long disintegration time; Formulas F1–F7 were prepared to study the effect of type of superdisintegrants, SSG, Croscarmellose sodium (Ac-Di-Sol) and crospovidone, on the in vitro dissolution time of the prepared Meoxicam hard gelatin capsules. The results shown in Table 4 indicate that crospovidone is the strongest among other superdisintegrants, which results in the fastest in vitro dispersion time followed by CMS then SSG.

F7>F6>F4>F5>F4>F3>F2

Table 4: Cumulative % drug release of different.

Time (min)	Cumulative % drug release						
	F1	F2	F3	F4	F5	F6	F7
10	20.57	28.55	39.58	46.45	52.40	49.57	48.63
30	46.06	56.79	66.31	77.63	73.44	65.97	68.12
60	69.52	74.77	83.69	87.04	92.54	92.67	95.3

Formulations containing superdisintegrants

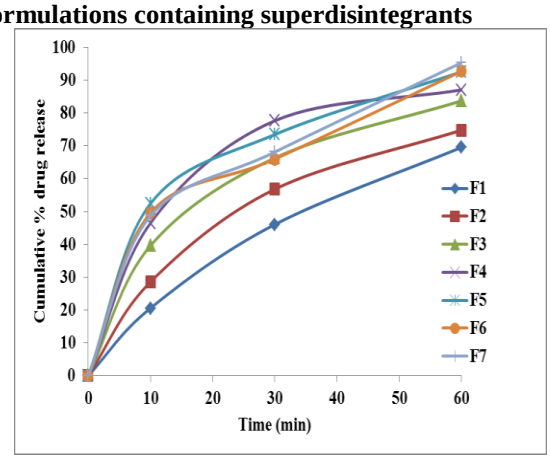

Figure 4: Cumulative % drug release of different formulations containing superdisintegrants

Effect of Solid Dispersions and Disintegrating Agents on Dissolution rate of Meloxicam

The melting or fusion method, was employed in the preparation of Solid dispersions by mixing the physical mixture of a drug and a water-soluble carrier, PEG 4000 in different ratios i.e.1:1, 1:2, 1:3 and heating it directly until melted. The melted mixture is then solidified rapidly in an ice-bath under vigorous stirring. The final solid mass is crushed, pulverized, sieved. It is then formulated into capsules with the best selected super disintegrating agents i.e., CMS 5%, CP 2%, CP 5% from the above results. Capsules are subjected to dissolution test for the estimation of percentage drug release. The results shown in Table 5 indicate that 5% crospovidone along with PEG 4000 (1:3) is the strongest among other superdisintegrants, which results in the fastest in vitro dispersion time followed by CMS then SSG.

Table 5: Cumulative % drug release of solid dispersions.

Time (min)	Cumulative % drug release		
	A1	A2	A3
	1:3	1:2	1:1
10	21.18	22.07	21.83
20	65.88	45.78	36.15
30	80.24	71.69	53.20

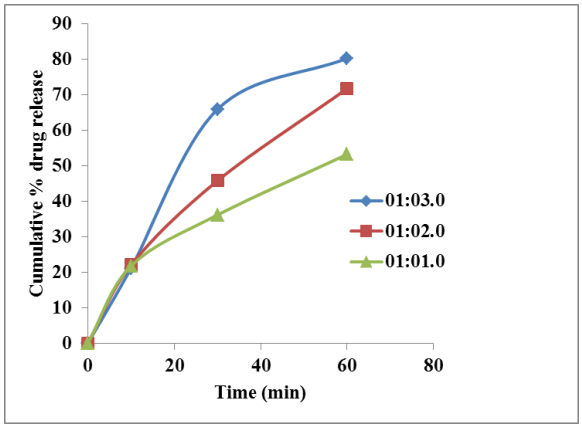

Figure 5: Cumulative % drug release of solid dispersions

Table 6: Cumulative % drug release of meloxicam solid dispersions in combination with superdisintegrants

Time (min)	Cumulative % drug release		
	A1	A2	A3
10	34.54	31.22	35.92
30	78.82	63.49	71.26
45	96.23	91.06	92.23

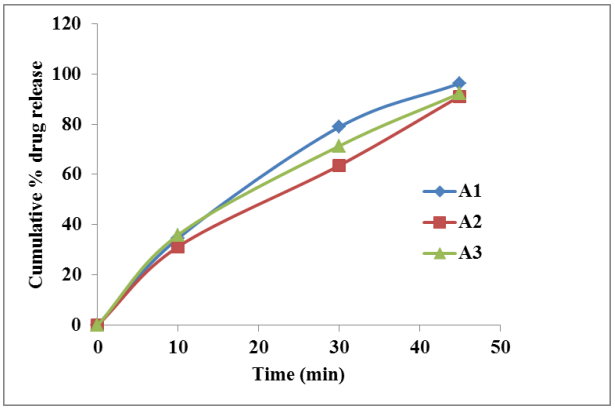

Figure 5: Cumulative % drug release of meloxicam solid dispersions in combination with superdisintegrants

CONCLUSION

Meloxicam is a poor water soluble drug, having slow drug absorption which leads to inadequate and variable bioavailability and gastrointestinal mucosal toxicity. For orally administered drugs solubility is the most important one rate limiting parameter to achieve their desired concentration in systemic circulation for pharmacological response. To enhance the dissolution rate and its bioavailability, meloxicam is formulated into capsules using super disintegrating agents (SSG, CMS, and CP) and solid dispersion technique. From the results of *in vitro* dissolution rate, it was concluded that all the formulations are suitable for development of hard capsules of Meloxicam. Compared to all formulations of F-series, F7 was found to yield best results in terms of *in vitro* dissolution rate. In A-series formulations, A1 shows increased drug release patterns with the fastest in vitro dissolution rate followed by CMS then SSG. The study concluded that the formulation prepared using A- series and F- series, A1 and F7 exhibits better dissolution rate at high concentration of super disintegrating agents.

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