

Design and development of spherical agglomerated crystals loaded fast dissolving tablets for enhancing the solubility of meloxicam

K. Ashok^{1,2}, M.V. Nagabhushanam³

¹ Research scholar, ² Associate Professor, ³ Principal & Professor

¹ Department of Pharmaceutics, QIS College of Pharmacy
Ongole-523001

Author for correspondence: K. Ashok

Research scholar, Department of pharmaceutics,
Acharya Nagarjuna University, Nagarjunanagar-522510

Abstract:

In the present work an attempt was done to study the effect of different carriers on the solubility and dissolution rate of Meloxicam poorly water soluble COX-2 inhibitor, by spherically agglomeration using methanol, water and dichloromethane as good solvent, poor solvent and bridging liquid, respectively. The quasi-emulsion solvent diffusion technique was used as a method for spherical agglomeration. Spherical agglomeration of Meloxicam were prepared by using Poloxomer -F338 and Gelucire 48/16 in the ratio of 1:0.5, 1:0.75, 1:1. The agglomerates were subjected to various physicochemical evaluations such as practical yield, drug content, solubility, flow properties, average particle size, scanning electron microscopy and dissolution studies. The optical electron microscopy studies showed that the agglomerates possesses a good spherical shape. This study, demonstrated that the successful development of directly compressible spherical agglomerates of Meloxicam prepared with selected carriers enhances the *in-vitro* dissolution property of Meloxicam, which could provide rapid onset of action and potentially increases oral bioavailability. To study the influence of co-processed superdisintegrants on performance of Meloxicam Fast dissolving tablets, a set of three formulations (F₇, F₈, F₉) were prepared using co-processed superdisintegrants (Croscarmallose sodium:Crospovidone) in three different ratios 1:1, 1:2, 1:3 respectively. The formulation prepared with co-processed superdisintegrants (Croscarmallose sodium:Crospovidone) in 1:3 ratio (F₉) was offered relatively rapid release of Meloxicam when compared with other ratios employed in this investigation.

Key words: Meloxicam, Poloxomer -F338, Gelucire 48/16, spherically agglomeration

INTRODUCTION

Meloxicam is a COX-2 inhibitor used to treat joint diseases such as osteoarthritis, rheumatoid arthritis and other musculoskeletal disorders. It is practically insoluble in water, leading to poor dissolution, variations in bioavailability, and gastric irritation on oral administration. Its solubility increases significantly with an increase in pH. It is a white crystalline powder to off-white crystalline powder and has poor flow properties and undesirable dissolution properties. As such it needs enhancement in the dissolution rate and bioavailability to derive its maximum therapeutic efficacy. Therefore, in the present study, an attempt has been made to increase solubility of Meloxicam by spherically agglomeration technique¹⁻² The resultant crystals can be designated as spherical agglomerates. Spherical crystallization is an effective alternative to improve dissolution rate of drugs. This can be achieved by various methods such as spherical agglomeration, quasi-emulsion solvent diffusion and neutralization methods. Many of the drugs, evolving from these techniques, can be categorized as class II drugs according to Biopharmaceutical classification system. These drugs are poorly water soluble, but once they are dissolved they easily absorbed through the gastrointestinal membrane. Therefore, bioavailability after oral administration can be improved by enhancement of the dissolution rate. One of the approaches dissolution rate is use of spherical crystallization technique.³⁻⁶

MATERIALS AND METHODS

Meloxicam was obtained from Dr.Reddy's labs, Hyderabad,India. Poloxomer -F338 and Gelucire 48/16 were purchased from SD fine Chemicals Ltd,Mumbai. All other materials used were of analytical grade.

Preparation of Spherically Agglomerates:

All spherical agglomerates were obtained by the quasi emulsion solvent diffusion method ⁷. Spherical agglomerates were prepared with and without stabilizers by spherical crystallization technique. The stabilizers composition was given in Table 1. Meloxicam (1.0 g) was dissolved in good solvent N,N-dimethylformamide (25.0 mL). The bridging liquid chloroform (12.5 mL) was added to it. The resulting solution was then poured drop wise in to the poor solvent distilled water (100 mL) containing different surfactant like, Poloxamer -F338 and Gelucire 48/16 with a stirring rate of 500 rpm using propeller type agitator (Remi Motors Ltd., Mumbai, India) at room temperature ⁸. After agitating the system for 30 minutes, the prepared agglomerates were collected by filtration through whatmann filter paper no.42.

Evaluation of spherical agglomerates:

a) Particle size determination: Particle size determination was carried out using optical microscopy with a calibrated eye piece micrometer and stage micrometer by taking a small quantity of formulation on slide⁸. About 100 spherical agglomerates size was measured individually, average was taken and their size range and mean diameter frequency was calculated. Average Particle size is calculated by the following formula,

$$\text{Average Particle size} = \sum d^n / n$$

b) Drug Content Estimation:

The percentage drug content in spherical agglomerates was estimated by dissolving spherical agglomerates equivalent to 100 mg of Meloxicam in methanol, mixed thoroughly by shaking and the volume was made up to the mark within 6.8 pH phosphate buffer. The solution was filtered and the filtrate was diluted suitably with 6.8 pH phosphate buffer and absorbance was measured at 372 nm using UV/Visible spectrophotometer ⁹.

c) Dissolution studies of agglomerates:

In-vitro dissolution studies of pure drug and spherical agglomerates were carried out for 60 minutes using USP Dissolution test apparatus type II (Lab India DISSO 2000, eight stages) at 50 rpm. Spherical agglomerates equivalent to 100 mg of Meloxicam was used for dissolution study at $37 \pm 0.5^{\circ} \text{C}$ in 900ml of 6.8 pH phosphate buffer as dissolution medium. Aliquot equal to 5 ml was withdrawn at regular time intervals (10, 20, 30, 40, 50, 60 min), an equal volume of fresh dissolution medium was replaced to maintain the sink condition and aliquots were measured at 372 nm UV/Visible spectrophotometer. $DE_{30\%}$, T_{50} , T_{90} and k^{-1} values were calculated from dissolution data ¹⁰.

Preparation of Meloxicam tablets : To study the influence of co-processed superdisintegrants on performance of Meloxicam Fast dissolving tablets, a set of three formulations (F₇, F₈, F₉) were prepared using co-processed superdisintegrants (Croscarmallose sodium:Croscopovidone) in three different ratios 1:1, 1:2, 1:3 respectively. Tablets were made from blends by direct compression method. All the ingredients (shown in Table 3) were mixed ¹¹. The resulting blend was lubricated with magnesium stearate and compressed into tablets using the Cadmach single punch (round shaped, 7 mm thick) machine.

EVALUATION OF MELOXICAM TABLETS

a) Weight variation test ¹²: Weight variation test was done by weighing 20 tablets individually, calculating the average weight and comparing the individual tablet weight to the average weight.

b) Drug content ¹³ : Twenty tablets were powdered, and powder equivalent to 100 mg of Meloxicam was accurately weighed and transferred into a 100 ml volumetric flask. Initially, 5 ml methanol was added and shaken for 10 min. Then, the volume was made up to 100 ml with 6.8 phosphate buffer. The solution in the volumetric flask was filtered, diluted suitably and analyzed spectrophotometrically at 372nm.

c) Disintegration Time ¹⁴: The disintegration time was determined in distilled water at $37 \pm 0.5^{\circ} \text{C}$ using disintegration test apparatus USP ED-2L (Electro lab, Mumbai).

d) Friability ¹⁴: Roche friabilator was used to determine the friability. Pre weighed tablets were placed in friabilator and rotated at a speed of 25 rpm for 4 minutes or up to 100 revolutions. The tablets are dropped from a distance of 6 inches in each revolution. The tablets were then reweighed after removal of fines and the percentage of weight loss was calculated.

$$\% \text{ friability} = \frac{\text{Weight before friabilation} - \text{Weight after friabilation}}{\text{Weight before friabilation}} \times 100$$

e) Hardness¹⁴: Hardness of the tablet was determined using the Monsanto hardness tester. The lower plunger was placed in contact with the tablet and a zero reading was taken. The plunger was then forced against a spring by tuning threaded bolts until the tablet fractured. Then the final reading was recorded. The hardness was computed by deducting the initial pressure from the final pressure.

f) Wetting Time¹⁴: The wetting time of the tablets can be measured using a simple procedure. Five circular tissue papers of 10 cm diameter are placed in a petridish with a 10 cm diameter. 10 mL of water-containing amaranth a water soluble dye is added to petridish. A tablet is carefully placed on the surface of the tissue paper. The time required for water to reach upper surface of the tablet is noted as a wetting time.

g) In vitro dispersion time¹⁴: Tablet was added to 10 ml of phosphate buffer solution pH 6.8 (pH of saliva) at $37 \pm 0.5^\circ\text{C}$. Time required for complete dispersion of tablet was measured.

h) Fineness of dispersion¹⁴: This test was performed by placing two tablets in 100 ml of water and stirring it gently, until the tablets get completely disintegrated. Then the dispersion is passed through a sieve screen with a nominal mesh aperture of $710 \mu\text{m}$.

j) Dissolution studies¹⁴: Dissolution studies for Meloxicam fast dissolving tablets were performed in pH 6.8 phosphate buffer using USP dissolution test apparatus (Electrolab, Mumbai, India) with a paddle stirrer. The paddles are allowed to rotate at speed of 100 rpm. The dissolution medium was maintained at a temperature of $37 \pm 0.5^\circ\text{C}$ and samples are withdrawn at an interval of every 5 min the volume of the withdrawn samples are replaced by fresh dissolution medium in order to kept the volume of the dissolution medium as constant. The withdrawn samples are filtered and absorbance was measured at absorption maxima of 372 nm using UV-visible spectrophotometer.

k) In-vitro dissolution kinetic studies¹⁴: The drug release data were plotted and tested with zero order (cumulative % drug released Vs time), First order (Log % remained Vs time). The in vitro dissolution kinetic parameters, dissolution rate constants (K), correlation coefficient (r), the times (t_{50}) for 50 % drug released (half-life) and dissolution efficiency [D.E.] were calculated. From the slopes of linear plots, the dissolution rates were calculated.

l) FTIR (Fourier Transform Infra-red Spectroscopy) Studies¹⁵: Infrared (IR) spectroscopy studies of Meloxicam and its optimized formulations with PVP and cross povidone were recorded in a FTIR spectrophotometer (Thermo-IR 200) Potassium bromide pellet method was employed and background spectrum was collected under identical conditions. The spectrum for each sample showed the wavelength of absorbed light which is a characteristic of the chemical bonds in the sample. Each spectrum was derived from 16 single average scans collected in the region of $400 - 4000 \text{ cm}^{-1}$ at a spectral resolution of 2 cm^{-1} .

RESULTS AND DISCUSSION:

Spherical agglomerates of Meloxicam were prepared by quasi emulsion solvent diffusion method (QESD) using a three solvent system. It involves good solvent, poor solvent and a bridging liquid. The selection of these solvents depends on the miscibility of the solvents and the solubility of drug in individual solvent. Accordingly methanol, dichloromethane, water were selected as a good solvent, bridging liquid, and poor solvent, respectively. Meloxicam is highly soluble in methanol, but poorly soluble in water. Also it is soluble in dichloromethane which is immiscible in water. Hence, this solvent system was used in the present study. In QESD method, when good solvent solution of drug plus bridging liquid were poured in the poor solvent (containing different carriers) under agitation, quasi emulsion droplets of bridging liquid and good solvent were produced. Then the good solvent diffuses gradually out of the emulsion droplet into the outer poor solvent phase. The counter-diffusion of the poor solvent into the droplets induces the crystallization of the drug within the droplet due to the decrease in solubility of the drug in the droplet containing the poor solvent. The bridging liquid wets the crystal surface to cause binding and promotes the formation of liquid bridges between the drug crystals to form spherical agglomerates. The spherically agglomerated crystals are formed by coalescence of these dispersed crystals. In the present study effect of different polymers on solubility and dissolution rate of spherical agglomerates of Meloxicam were studied. Incorporation of polymer during agglomeration significantly enhanced the dissolution. Mixing of drug with a carrier results in greater wetting and increase surface available for dissolution by reducing interfacial tension between the hydrophilic drug and dissolution media. It was noted that drug carrier system sink immediately, while pure drug keeps floating on the surface for a longer time interval. The cumulative percentage of drug released from different agglomerates was increased in the following order: Meloxicam spherical agglomerates prepared with Poloxamer -F338 > Meloxicam spherical agglomerates prepared with Gelucire 48/16. Among all the formulations prepared, spherical agglomerates prepared Meloxicam and Poloxamer -F338 in 1:1 ratio showed highest drug release in 60 minutes.

To study the influence of co-processed superdisintegrants on performance of Meloxicam Fast dissolving tablets, a set of three formulations (F₇, F₈, F₉) were prepared using co-processed superdisintegrants (Croscarmallose sodium: Crospovidone) in three different ratios 1:1, 1:2, 1:3 respectively. The dissolution rate followed first-order kinetics as the graphs drawn between log % drug unreleased vs time were found to be linear. The dissolution rate of Meloxicam was found to be effected by nature of the superdisintegrant used in the preparation of tablets. The formulation prepared with co-processed superdisintegrants (Croscarmallose

sodium:Crospovidone) in 1:3 ratio (F₉) was offered relatively rapid release of Meloxicam when compared with other ratios employed in this investigation.

Table 1: Composition of Meloxicam Spherical Agglomerates

Ingredients	F1	F2	F3	F4	F5	F6
Meloxicam(g)	1	1	1	1	1	1
Poloxomer -F338 (g)	0.5	0.75	1			
Gelucire 48/16 (g)				0.5	0.75	1
N,N-dimethylformamide	25	25	25	25	25	25
Dichloromethane(ml)	12.5	12.5	12.5	12.5	12.5	12.5
Water (ml)	62.5	62.5	62.5	62.5	62.5	62.5

Table 2: Particle size and % of Drug content of Meloxicam spherical agglomerates

Formulation	Particle size(μm)	% of Drug content
F1	256	0.0636
F2	278	0.0747
F3	294	0.0866
F4	312	0.0563
F5	334	0.0649
F6	356	0.0758

Table 3: In-vitro dissolution kinetics of Meloxicam spherical crystals prepared with different carriers.

S.No.	Formulation	T ₅₀ (min)	T ₉₀ (min)	DE ₃₀ (%)	K (min ⁻¹)	Correlation coefficient values	
						Zero Order	First order
1	F ₁	20.2	67.1	35.43	0.034	0.9466	0.9870
2	F ₂	17.2	57.0	39.51	0.040	0.9250	0.9836
3	F ₃	15.4	51.2	41.49	0.044	0.9135	0.9768
4	F ₄	23.5	78.0	32.14	0.029	0.9544	0.9919
5	F ₅	22.0	73.1	34.34	0.032	0.9480	0.9888
6	F ₆	19.6	65.2	36.09	0.035	0.9438	0.9857

Table 4: Composition of ingredients for Meloxicam fast dissolving tablets

S.No	Ingredients	F ₇	F ₈	F ₉
1	Meloxicam crystals prepared with Poloxomer -F338 in 1:1 ratio	15	15	15

2	Croscarmallose sodium+ Crospovidone	5	5	5
3	Micro crystalline cellulose	76	76	76
4	Talc	2	2	2
5	Magnesium streate	2	2	2
	Total weight	100	100	100

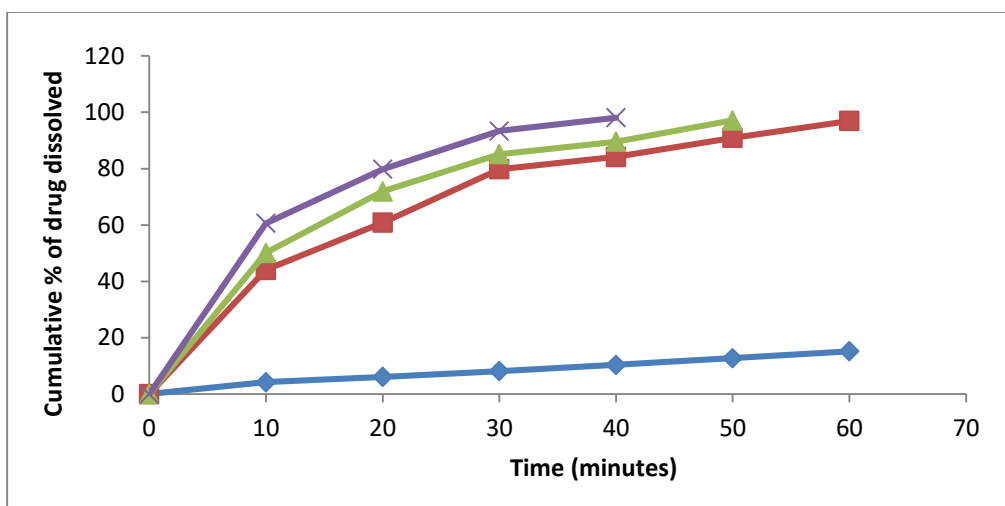
Table 5: Physical parameters of Meloxicam fast dissolving tablets

S.No.	Parameters	F ₇	F ₈	F ₉
1	Average weight (mg)	99±0.3	99±0.1	100±0.2
2	Drug content(%)	98.54	99.8 1	99.19
3	Disintegration time (sec)	163	147	125
4	Friability(%)	0.44	0.28	0.13
5	Hardness(kg/sqcm)	4.2	4.2	3.8
6	Wetting time (sec)	117	112	92
7	In-vitro dispersion time (min)	223	202	152
8	Fineness of dispersion	pass	pass	pass

Table 6: In-vitro dissolution kinetics of Meloxicam fast dissolving tablets

S.No.	Formulation	T ₅₀ (min)	T ₉₀ (min)	DE ₁₅ (%)	K (min ⁻¹)	Correlation coefficient values	
						Zero Order	First order
1	F ₇	6.0	20.1	48.78	0.115	0.8493	0.9751
2	F ₈	4.7	15.6	56.37	0.148	0.8268	0.9762
3	F ₉	3.1	10.3	66.31	0.222	0.8049	0.9833

Figure 1: In-vitro dissolution profile of Meloxicam fast dissolving tablets with co-processed superdisintegrants



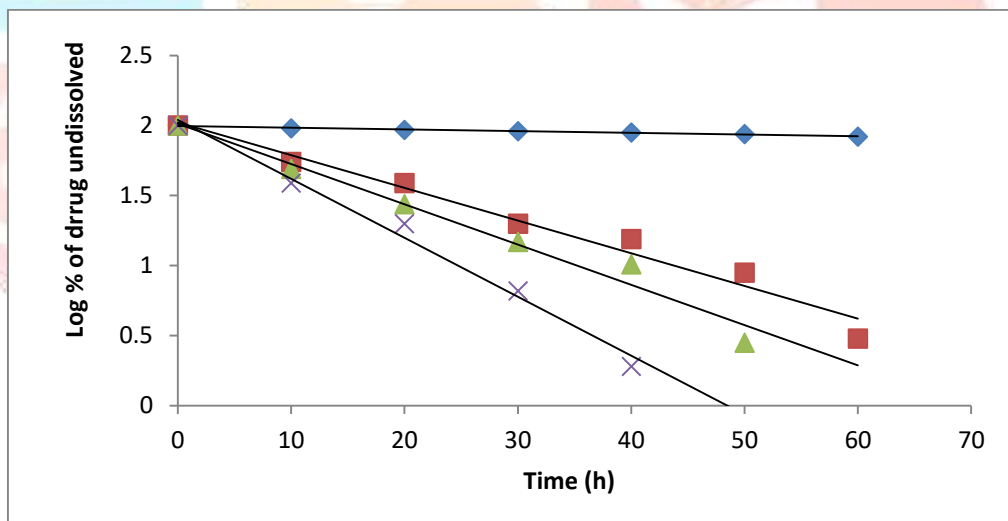
(-♦-) Meloxicam pure drug

(-■-) Meloxicam tablets prepared with crospovidone and croscarmallosesodium in 1:1 ratio by coprocessing technique

(-▲-) Meloxicam tablets prepared with crospovidone and croscarmallosesodium in 1:2 ratio by coprocessing technique

(-×-) Meloxicam tablets prepared with crospovidone and croscarmallosesodium in 1:3 ratio by coprocessing technique

Figure 2: First order plots of Meloxicam tablets with coprocessed superdisintegrants



(-♦-) Meloxicam pure drug

(-■-) Meloxicam tablets prepared with sodium starch glycolate

(-▲-) Meloxicam tablets prepared with croscarmallosesodium

(-×-) Meloxicam tablets prepared with crospovidone

CONCLUSION: Present study concluded that spherical agglomerates prepared by the quasi emulsion solvent diffusion method showed an improvement in the solubility, dissolution rate, compactibility, wettability, flowability and bioavailability. These spherical agglomerates also showed excellent physico-chemical characters as compared with plain drug which indicates that the spherical agglomerates can suitable for directly compressible tablet process.

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