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Enhancement of Dissolution and Anti- inflammatory Activity of Meloxicam by Spherical Agglomeration Technique

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Abstract

Spherical crystallization is the novel agglomeration technique that can transform directly the fine crystals in to spherical shape. This technique of particle design of drugs emerged as one of the areas of active research industry and gained great interest in the formulation and manufacturing of pharmaceutical dosage forms. The poor aqueous solubility of meloxicam was modified by spherical agglomeration technique. The objective of the present study is to improve the dissolution rate and to transform the meloxicam crystals in to spherical agglomerates. The agglomerates are prepared by neutralization method of agglomeration. The obtained agglomerates of meloxicam were spherical and dissolution rates were faster than conventional crystals. Spherical agglomerates were characterized by differential scanning calorimetry, Infrared spectroscopy, X-ray diffractometry and scanning electron microscopy. The DSC results indicated that decrease in melting enthalpy related to disorder in the crystalline content. XRD studies showed changes in crystallinity and the IR spectroscopy revealed that there was no chemical change with pure drug. The pharmacodynamic activity revealed that the optimized spherical agglomerates provided a rapid anti inflammatory activity.

Key words: Anti inflammatory activity, bridging solvent, crystals, dissolution Meloxicam, spherical agglomerates.

INTRODUCTION

Novel method development to increase the dissolution of drugs with inherent poor aqueous solubility is of great challenge in solid dosage formulation development. Mechanical micronization of crystalline drugs and agglomeration of drugs during the crystallization process are the techniques commonly used to improve the bioavailability of poorly soluble drugs. To overcome this problem, Kawashima et.al developed a spherical crystallization technique that led to improving the flow properties, solubility and dissolution rate [1]

Spherical agglomeration is a novel agglomeration technique involving agglomerate formation based on addition of bridging solvent. It is the particle engineering technique by which crystallization and agglomeration can be carried out simultaneously in one step [2].

Kawasima et.al developed spherical agglomeration as a method of novel particulate design. In typical spherical agglomeration method the drug dissolved in a good solvent is poured in a poor solvent under controlled condition of agitation with the addition of bridging solvent, which wets the crystal surface to form agglomerate [3, 4].

Spherical agglomeration is a process of formation of aggregates of crystals which are held together by liquid bridges of bridging solvent. The bridging liquid should be immiscible in the suspending medium but capable of cementing the particles to be agglomerated. The obtained particles so designed to improve the bulk density, flow properties, compressibility, cohesivity, solubility and dissolution rate [3, 5].

Spherical agglomeration is carried by four methods (a) Spherical agglomeration method (b) Quassi emulsion solvent diffusion method (C) Ammonia diffusion method (d) Neutralization method [6].

Meloxicam is a pale yellow powder, practically insoluble in water soluble in strong acids and alkalis. Based on its solubility neutralization method is selected for the preparation of spherical agglomerates [7].

Meloxicam is a potent COX -2 preferential anti inflammatory agent with less frequency of gastro intestinal adverse effects. Meloxicam is a class-II drug as per the biopharmaceutical classification and the poor solubility and wettability of meloxicam leads to poor dissolutions and hence variations in bioavailability. The objective of the present work is to enhance dissolution of meloxicam by spherical agglomeration technique by neutralization method [8].

MATERIALS AND METHODS

Meloxicam was a gift sample of Dr. Reddy's Laboratory, Hyderabad. Di ethyl ether was procured from Merck, Mumbai, India. All chemicals used were of analytical grade.

Preparation of spherical agglomerates

In a crystallization vessel as described by Kawasima et.al. Meloxicam was dissolved in 1N sodium hydroxide which has neutralized by 1N hydrochloric acid with agitation using a four blade turbine type agitator at 300r.p.m.The system was thermally controlled at a temperature of 40±1º c. After the crystallization of meloxicam diethyl ether was added as a bridging solvent and the system was agitated for 15min.at a temperature of 20±1°C.The obtained agglomerates were separated by filtration and dried at 60ºC for 24 hours. The method has been optimized by monitoring the variables such as agitator speed, time of agitation, temperature, addition of bridging solvent [4, 6].

EVALUATION STUDIES

Solubility studies

Solubility studies were carried out by taking excess quantity of drug and its agglomerates in a series of screw capped vials .The vials were rotated in rotary shaker at25ºc for 24 hrs. Then the samples were withdrawn and filtered through a sintered glass filter. The concentration of drug in a saturated solution was determined by UV spectrophotometer. The study was performed in triplicate [9].

Drug content in spherical agglomerates

The content of meloxicam in agglomerates was analyzed on schimadzu HPLC consisting of auto injector, diode array detector as per the method mentioned in B.P. The drug content was determined by using the mobile phase of di ammonium hydrogen phosphate with the mixture of methanol and iso propanol. The pH is maintained 7.0.The liquid chromatogram was equipped with at 354 nm, using Kromosil containing octa decyl silane as a packing material. Inject about 10µl of standard preparation and test preparation in to the chromatogram and the response of peak was measured [10].

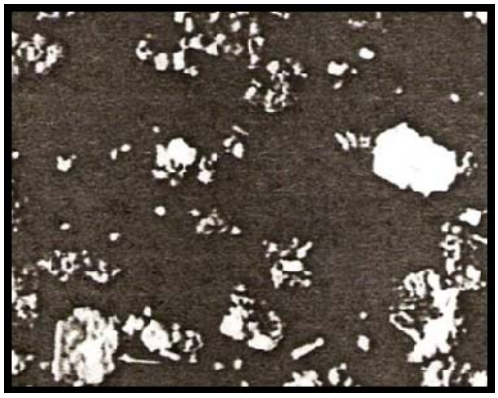
Dissolution studies

In vitro dissolution of meloxicam and its agglomerates (equivalent to 15mg of meloxicam) was carried out using USP dissolution apparatus (type-2). The dissolution medium was 0.5% sodium lauryl sulphate at 37±0.5ºc and stirred at 100 r.p.m. The samples were withdrawn at predetermined intervals and replaced with fresh medium. The samples were filtered and analyzed using double beam spectrophotometer (Systronics) at 360nm [11, 12].

PHYSICO CHEMICAL CHARACTERISATION

Optical microscopy and Particle size analysis

The microscopic observation of agglomerates was performed using optical microscope (Leica microscope, Germany) equipped with a video camera. The external morphology of spherical agglomerates was analyzed using a scanning electron microscopy (Model JSM 840A, Joel, Japan).



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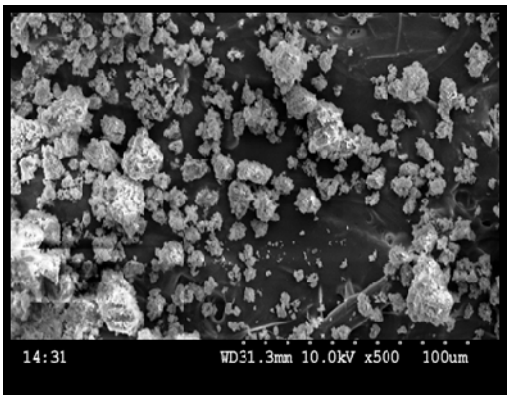
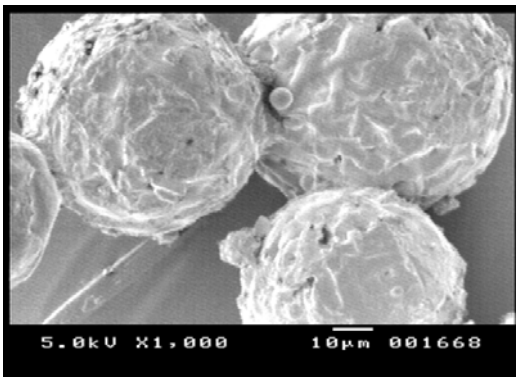


2(a)Low



2(b) High

Fig-1: Microscopy of meloxicam spherical agglomerates (1) Hot stage microscopy (2) Scanning electron photo micrograph under low and high magnification

X-ray diffraction

X-ray diffraction pattern of meloxicam and its agglomerates were obtained using diffractometer

(Seifer 3003TT) using cu k α radiation at 30ma and 450kv. The angular range was set from 0-60° with a step of 0.003. The relative intensity and inter planar distance corresponding to 2θ values were obtained and compared with the plain drug. [13].

Differential thermal analysis

Differential scanning calorimetry thermo grams of sample were recorded in Mettler Toledo Analyzer. The instrument was calibrated with indium as a standard. Accurately weighed 2.5 mg of samples were placed in aluminium sample pan. Thermo grams were obtained by heating the sample from 35°c to 400ºc.The agglomerate scan was compared with drug for melting point and enthalpy of fusion [14].

Fourier Transform Infra Red Spectroscopy

The FTIR spectra of meloxicam and its agglomerates were taken using a Schimadzu model 8033. Meloxicam and its agglomerates were dispersed in KBr powder and pellet was made by applying 6000kg\cm² pressure. The spectra of agglomerates are compared with the pure drug.

***In vivo* Anti-inflammatory studies**

The anti inflammatory studies of spherical agglomerates were evaluated by carrageenan induced rat hind paw odema studies. The protocol for experiment was designed and approval of Institutional Animal Ethical Committee (registration number CPCSEA 154\1999) was taken. A male Wistar rats with a body weight of 170-200gm are divided in to 3 groups of 6 each were fasted overnight prior to the experiment but water was allowed *ad libitum*. Then the standard group received 3mg\kg of meloxicam and the test group received agglomerates at an equivalent weight of 3mg\kg. After 1 hour the oedema was induced by sub plantar injection of 0.1 ml of 1% carrageenan injection in to the right hind paw of each rat. After 1hr of drug treatment paw volume were measured at predetermined intervals of after the injection of carrageenan using plethysmograph. ANOVA test was used to test the significance [15].

RESULTS AND DISCUSSIONS

Solubility profile of meloxicam and its crystalline forms in water at 25˚c was found to be 0.014mg/ml and for agglomerates a significant increase of 0.120mg/ml was observed.

Microscopic evaluation of meloxicam shows irregular crystals as compared to agglomerates which were roughly spherical, elongated masses with excellent free flowing ability. The agglomerates are poly dispersed with wide distribution of particle size.

Dissolution studies

Meloxicam agglomerates showed remarkable increase in dissolution compared to plain drug. However the crystals obtained without bridging solvent does not showed any enhancement in dissolution rate. The reason for this faster dissolution could be linked to the better wettability of the spherical agglomerates. From the above results it was concluded that addition of bridging solvent had significant effect on enhancement of dissolution.

Content of meloxicam

The content of meloxicam in spherical agglomerates was assayed by High pressure liquid chromatography. The assay value was found to be 94% to 96% of the theoretical values.

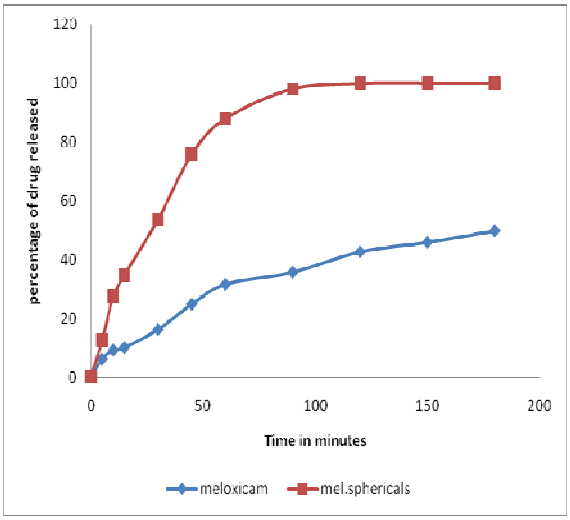


FIG-2: Dissolution profile of meloxicam and its agglomerates

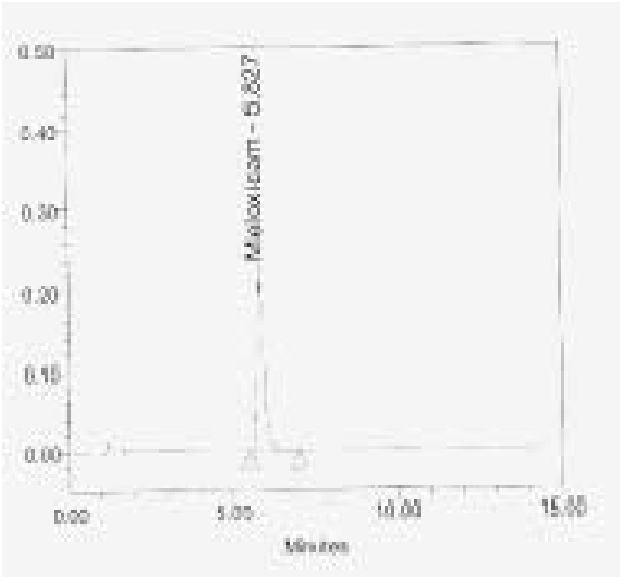


FIG-3: Content of meloxicam in agglomerates by HPLC

PHYSICO CHEMICAL CHARACTERISATION

X-ray diffraction

The x-ray diffraction scan of meloxicam and its crystals showed decreased intensity of peaks due to its dilution. The d-values of meloxicam and its agglomerates are varying in diffractomers proves the formation of polymorphs which has taken place due to the incorporation of bridging solvent, varied temperature conditions. The decreased intensity of peaks resembles the decreased crystallinity of agglomerates which may be contributing the enhancement of dissolution rate.

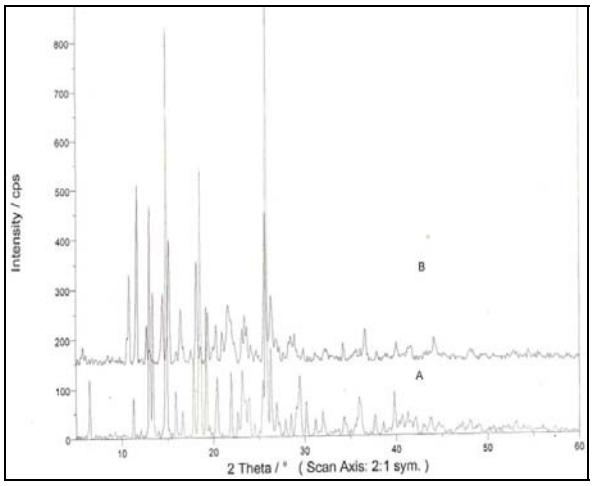


FIG-4: X- Ray diffraction spectra of meloxicam and its agglomerates.

FIG-5: Differential scanning calorimetry of meloxicam with its agglomerates.

Thermal analysis

The differential scan of meloxicam agglomerates shows a sharp endothermic peak at 254.75°c and this peak is due to the melting of the crystalline form of meloxicam thus indicating that the meloxicam did not undergo any crystal modification. The temperature range of agglomerates was showing the slight variations as the nature of crystals might have affected by the solvent. The melting point of agglomerates with decreased enthalpy (-306.87mJ) indicating decreased crystallinity.

FTIR spectroscopy

The IR spectra of meloxicam are showing similar finger print as that of pure meloxicam. The spectra of melocicam agglomerates shows a strong peak at 2856 indicating CH– stretching of CH_3, 1065 indicates sulphoxide group, A sharp peak at 3057 indicates an aromatic ring,1618 carboximide group,1526 NH bending which is relevant to spectra of meloxicam.

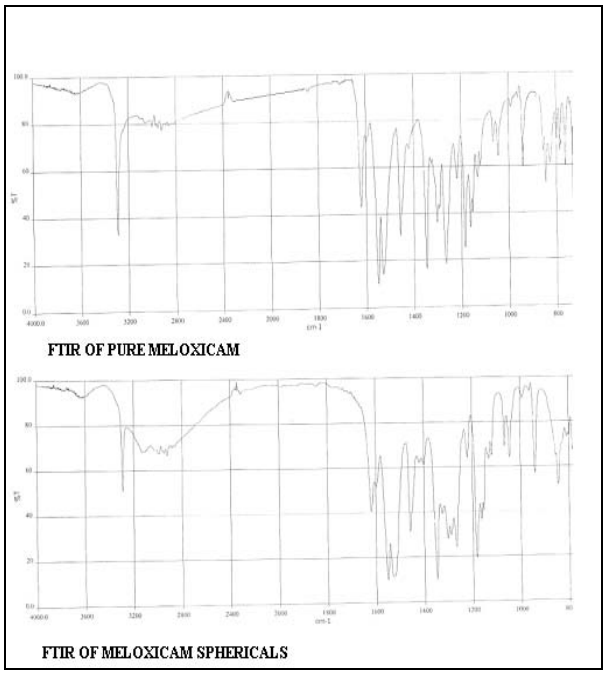


FIG-6: FTIR spectra of meloxicam with its agglomerates.

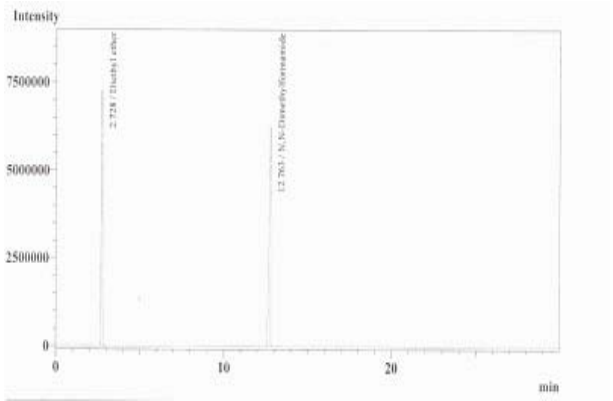


FIG-7: Residual solvent level in agglomerates by gas chromatography

ANTI INFLAMMATORY ACTIVITY

The anti inflammatory activity of spherical agglomerates in comparison with pure drug was evaluated on the basis of ability to inhibit the edema produced in hind paw after challenging with carrageenan. The spherical agglomerates of meloxicam showed faster onset of action as compared to pure drug. A peak of inhibition of 48.67% was observed after 2 hour for agglomerates and respectively meloxicam showed inhibition of 32.02%. The difference was significant and showing a significance with a *p* value less than 0.005% (p= 0.03780), indicating that the agglomerates showed an improvement in rate and extent of absorption.

CONCLUSION

The present study spherical agglomerates of meloxicam are prepared by neutralization method. The agglomerates exhibited improved dissolution rate and anti inflammatory activity than the pure meloxicam. From these results we can conclude that this technique may be applicable for producing oral solid dosage forms of meloxicam with improved dissolution rate.

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