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ORIGINAL ARTICLE

Optimization, Fabrication and Characterization of Novel Meloxicam-Loaded Surface Attached Solid Dispersions to Ameliorate its Aqueous Solubility and Dissolution Employing Spray-Drying Technique

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ABSTRACT

Objective: To formulate unmodified crystalline meloxicam solid dispersions by the use of surfactants and polymer. This polymeric particulate system is named as meloxicam-loaded surface attached solid dispersion (MSDs).

Methodology: This experimental study was conducted at Lab of Physical and Industrial Pharmacy, Hanyang University, South Korea. The duration of this study was around seven months. The first phase of this study (optimization and fabrication) was completed within 3 months, while, solubility, dissolution and physicochemical characterization was completed in next 4 months. These surfaces attached solid dispersions were prepared by using spray drying technology. Moreover, HPMC and SLS were used as hydrophilic carriers. Various MSDs were prepared using carriers/drug, and were evaluated for aqueous solubility and dissolution studies.

Results: Amongst different formulation prepared, MSDs3 having Meloxicam/HPMC/SLS in a (1:0.5:0.5) gave the highest solubility and dissolution (i.e. from 0.25 ±0.17ug/ml of meloxicam to 153 ±5.3ug/ml). Moreover, dissolution was enhanced from 2.96 ±0.55% to 47 ±1.07% at 15 minutes. Furthermore, physicochemical characterization was performed by scanning electron microscopy (SEM), differential scanning calorimetry (DSC) and powder X-ray diffraction (PXRD).

Conclusion: In conclusion we can predict a better solubility and dissolution of meloxicam in surface attached solid dispersion.

Keywords: Meloxicam, solubility enhancement, spray drying, surface attached, solid dispersion

INTRODUCTION

Meloxicam is an active pharmaceutical ingredient (API) that belongs to non-steroidal anti-inflammatory drugs (NSAIDs). Patients suffering from osteoarthritis and other types of inflammatory diseases are commonly prescribed with meloxicam.[1] Often, this drug is ordered for management of postoperative pain and fever. As an analgesic and anti-inflammatory medicine, it shows lesser problems of gastric and local tissue irritations as compared to its primitive analogues. Moreover, meloxicam is considered to be more specific and effective in inhibiting cyclooxygenase enzyme system.[2-4] Organoleptically, meloxicam appears to be a pastel yellow solid powder. But intrinsically the drug is practically insoluble in aqueous media.[4-5] Therefore, biopharmaceutics classification system had in fixed meloxicam as class-II drug. Which means the drug is low soluble but high permeable. It is known scientifically that, drugs administered orally undergo absorption through biological membranes.[6-8] However, before absorption the drug had to undergo dissolution in order to release the active ingredient in the gastric fluids. Therefore, it is considered that to produce its pharmacodynamics and pharmacokinetic effects the drug needs to be soluble in fluids that a human body possesses. Hence, ameliorating the solubility of meloxicam is required in order to achieve its brilliant therapeutic effects.[9-10]

Scientists had previously researched a number of solubilities improving techniques in order to overcome the poor aqueous solubility of drugs. Namely, lipid nanoparticles, self-emulsifying drug delivery system, micellization, inclusion complexes, salt formation and nano-suspensions.[11-15] Solid dispersion is considered as one of the prominent solubility enhancing technique. Moreover, for the sake of preparing solid dispersion, spray-drying is ordinarily employed. Firstly, to prepare a solid dispersion all the ingredients are dissolved or suspended in some compatible solvent. Then, this mixture is subjected into spray dryer to evaporate the solvent. The fabricated solid dispersion not only enhances wettability and dispersibility, but also prevents the drug from aggregation and agglomeration. This results in an improvement of solubility and dissolution profile in aqueous system, and ultimately enhancement in bioavailability of drug.[11,16] There are a number of preparatory methods for solid dispersion like, kneading technique, solvent evaporation, solvent wetted, and melting technique. However, these methods may have some advantages but some disadvantages as well. Like, solvent wetted and solvent evaporation methods often used substantial amount of organic solvent. Simultaneously, a larger amount consists of hydrophilic excipients as well. These methods might convert the drug into amorphous form which can alter drug stability too. Furthermore, melting technique is a conventional and effortless approach but high temperatures could menace the drug stability.[16-19]

In this research to avoid the usual problem associated with the above said methods, meloxicam-loaded surface attached solid dispersion (MSDs) with aqueous solvent was prepared employing spray drying technique. The method allows fabricating the solid dispersion without altering the crystalline structure of the active ingredient. Moreover, the method also significantly improved the dissolution profile and aqueous solubility. This could be due to the neighboring of hydrophilic carriers onto the drug particles. The MSDs were prepared by utilizing HPMC and SLS, which were used as polymer and surfactant, respectively. The addition of surfactant with polymer can possibly reduce the larger hydrophobic agglomerates of the drug. The physicochemical investigation was done by powder X-ray diffraction (PXRD). Furthermore, scanning electron microscopy (SEM) was done to analyze morphology, whereas, differential scanning calorimetry (DSC) was done to check thermal aspects of formulation. Lastly, the solubility and dissolution profile of the fabricated formulation was also evaluated in contrast to the pure meloxicam.

MATERIALS AND METHODS

This experimental study was conducted at Lab of Physical and Industrial Pharmacy, Hanyang University, South Korea. The duration of this study was around seven months. The first phase of this study (optimization and fabrication) was completed within 3 months, while, solubility, dissolution and physicochemical characterization was completed in next 4 months. HPMC was acquired from shin-Etsu Company (Tokyo, Japan). Meloxicam and Sodium lauryl sulfate (SLS) (supplied by Hanmi Pharm.co Republic of Korea). All additional solvents and chemical materials were of reagent grade.

Solubility of Meloxicam: Solubility of meloxicam was evaluated in aqueous medium. A surplus amount of drug was placed in 2ml

Eppendorf tube (EP tube) containing water. It was then vortexed and mixed. Further, the EP tubes were positioned vertically in shaking water bath at 100 RPM, 25^0 C for five days. The samples were then centrifuged at 5,000 Xg for 5 minutes (HSIC smart; Gangneung, Republic of Korea). After centrifugation, dilution (with Acetonitrile) and filtration (with 0.45um syringe filter) of the aliquot (0.5 ml) was carried out. Filtered samples were quantified for meloxicam concentration by using the HPLC system (Agilent 1260 infinity, Agilent technologies Santa Clara, CA, USA), which was furnished with C18, reverse phase, 0.5µm column. The mobile phase comprised of acetonitrile and 50mM of phosphate buffer (pH 2.1) at volume ratio of 70%:30%. The peak was obtained at 256 nm and retention time was 2.7 minutes. The injection volume was kept at 20µl.

Fabrication of meloxicam-loaded surface attached solid dispersion (MSDs): The MSDs were formulated by taking API/excipients ratio (1:1) employing a Büchi B-290 nozzle type mini spray dryer (Labortechnik AG, Flawil, Switzerland). Firstly, several proportions of hydrophilic carriers (HPMC/SLS) were solubilized in aqueous medium up to an extent to obtain a clear solution. To this solution, meloxicam powder (1gm) was incorporated with continuous stirring. Table 1 enunciates the different formulations of MSDs prepared. The resultant suspensions were subjected to spray dryer with uninterrupted stirring through peristaltic pump which was set at a flow rate of 7 ml/min. The temperature conditions of the spray dryer were set to be at 115^0 C and $60\text{-}70^0$ C for inlet and outlet, respectively. Pressure of spraying air in pneumatic nozzle was affixed at 4 kg/cm^2 and aspirator was set at 100%. Finally, the dried MSDs were acquired from collecting chamber.

Meloxicam drug content: A precise amount of MSDs equivalent to 10 mg of meloxicam was taken to conduct drug content. The powder was thoroughly dissolved in 100 ml organic solvent. Magnetic stirring was employed for this mixing. This was done at ambient temperature. The aliquot from the prepared solution was then assayed at 256 nm in triplicate opting HPLC method as described in previous section. The amount of drug incorporated in solid dispersion was determined using the formula: Cd = Ca/Ct * 100. Where, Ct is the theoretical concentration, Cd is the drug content and Ca is tangible content of the drug in solid dispersion; determined by the HPLC.

Dissolution: Test for dissolution profile was conducted by means of the USP apparatus II (Vision® Classic 6TM, Hanson Research Co.; Los Angeles, CA, USA). Individually, meloxicam formulation and drug powder were retained in a blank hard gelatin capsule. Afterwards, each packed capsule was placed into a sinker and submerged in the dissolution apparatus containing dissolution medium. The rotation of the paddle in dissolution apparatus was set at 100 RPM. The apparatus was set at 37°C ±0.5 °C. The dissolution medium was composed of 900ml of 7.4 phosphate buffer. Aliquots (1ml) were collected at preset time breaks. Furthermore, these withdrawn samples were clarified using 0.45 µm and quantified by means of HPLC method.

Morphological characterization: Scanning electron microscopy (SEM) is usually employed to evaluate morphological characteristics of fabricated formulations. In this study, the examination was accomplished using SEM (S-4800, Hitachi Tokyo, Japan). Furthermore, the formulations were placed on the top of double side adhesive carbon tape, which was then afterwards secured on brass disc. Moreover, testers were coated in platinum for four minutes using EMI Tech Ion Sputter (K575K), in order to make it electrically conducted. Condition for coating was set as 8 $x10^{-3}$ mbar pressure, 15mA current and finally the turbo speed was set at 100%.

Thermal characterization: Differential scanning calorimeter (DSC Q20, TA Instruments; New Castle, Delaware, USA) was employed in this research for thermal representation of meloxicam powder, HPMC, SLS, physical mixture and MSDs. This was done by placing samples (5mg approx.) in an aluminum pan. This pan after sealing was exposed to heating in DSC at a temperature array of 45-300°C. Moreover, the heating rate was set at a rise of 20°C/min, while flow of nitrogen was purged at 25 ml/min.

Structural Aspects: The crystallinity of prepared MSDs and pure drug meloxicam was examined by Rigaku X-ray diffractometer (D/MAX-2500 PC, Rigaku Corporation; Tokyo, Japan). Powder X-ray diffraction investigation was accomplished by means of Cu Kα1 monochromatic radiation at 100 mA current and the voltage of the instrument was 40 kV. The powder-XRD configurations were attained in the range of 5°-50°C with 2θ scanning mode, an angular stride of 0.02°/second and 10°/minute scan speed.

RESULTS

The ratios of drug, polymer and surfactant (Meloxicam/ HPMC/SLS) incorporated in different formulations prepared in this research are depicted in table: 1. Moreover, each fabricated formulation presented a specific enhancement in aqueous solubility and dissolution as compared to pure drug powder of meloxicam (Figs. 1 and 2), respectively.

The morphology of the fabricated MSDs which has shown the highest solubility and dissolution versus meloxicam powder was analyzed through scanning electron microscopy (SEM). The micrographs of SEM are shown in Figure 3. Whereas, further evaluation for thermal characterization is depicted as DSC and PXRD in figure 4 and 5, respectively.

Table 1: Composition of MSDs prepared

Constituents	MSDs 1	MSDs 2	MSDs 3	MSDs 4	MSDs 5
Meloxicam	1	1	1	1	1
HPMC 4000	1	0.75	0.5	0.25	0.125
SLS	0	0.25	0.5	0.75	0.375

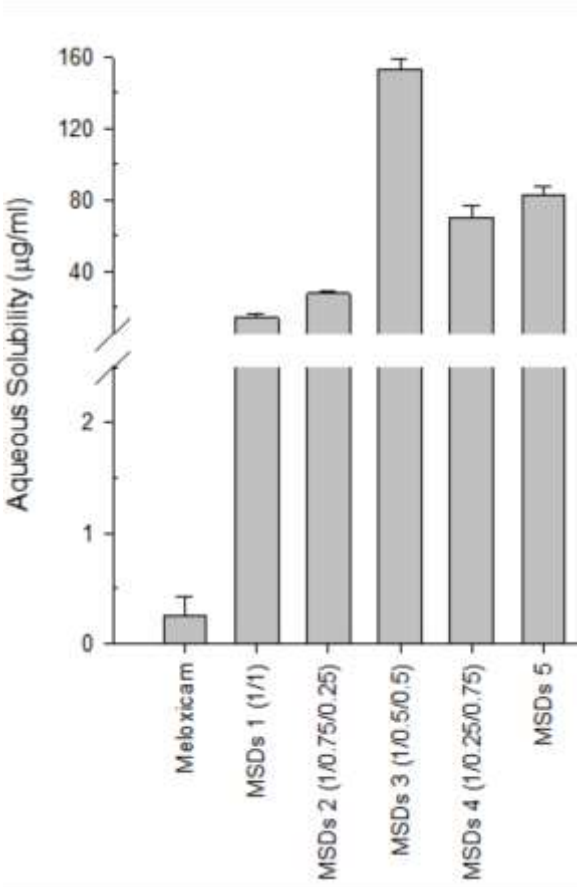

Figure 1: Aqueous solubility of meloxicam and MSDs

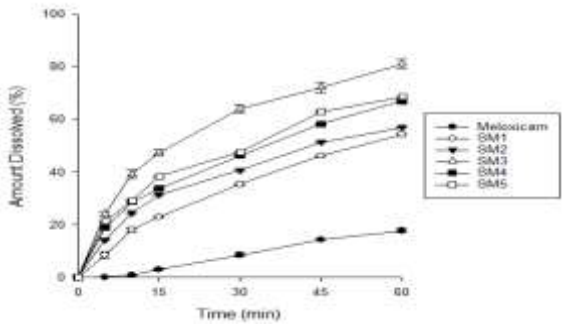

Figure 2: Dissolution Profile of meloxicam and MSDs

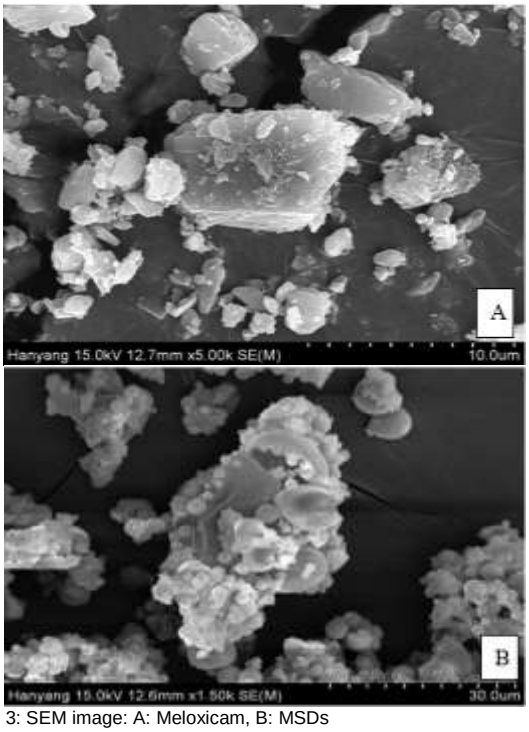

Figure 3: SEM image: A: Meloxicam, B: MSDs

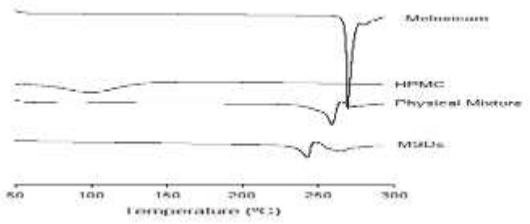

Figure 4: DSC of meloxicam, HPMC, Physical mixture and MSDs

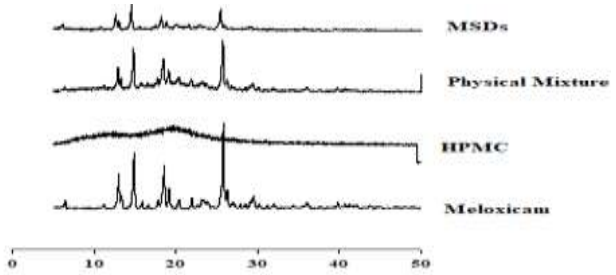

Figure 5: PXRD of meloxicam, Physical mixture, HPMC and MSDs

DISCUSSION

Solid dispersions which are molecular mixtures of drug and carriers were prepared in this research employing spray drying technique. The novel feature of this research was to enhance the solubility of poorly aqueous soluble drug meloxicam by consuming HPMC and SLS as carriers. The carriers were chosen due to their effects in enhancing solubility of poorly aqueous soluble active ingredients. Moreover, the use of aqueous medium as vehicle instead of organic solvent was also a prominent feature.[20-23]

Largely, solid dispersions are prepared by solubilization of API/Carriers in organic solvents, which are dried for final product or by melting of the said ingredients by heating.[24,25] The solid dispersions formulated from these methods, mostly convert the drug to amorphous form. Furthermore, these methods also require a generous amount of hydrophilic carriers for the generation of solid dispersions.[26-28] Conversely, in this research a nominal and optimized quantity of excipients were employed for fabrication of meloxicam loaded surface attached solid dispersion (MSDs). For the preparation of MSDs firstly, hydrophilic carriers that is HPMC and SLS were completely solubilized in aqueous solvent. Furthermore, the meloxicam in crystalline form was dispersed in this solution. This dispersion of API/carriers was then subjected to spray drying to obtain a solid dispersion in which the dissolved carriers were attached onto the surface of crystalline drug that is meloxicam. Hence, MSDs with improved aqueous solubility and dissolution of the meloxicam were produced. The formulation obtained, consisted of water as a solvent in place of organic solvent. Thus, the MSDs were free from organic solvent vulnerabilities, which often ascend in solid dispersions prepared from conventional solvent evaporation techniques.[29,30]

The ratios of drug, polymer and surfactant (Meloxicam/ HPMC/SLS) incorporated in different formulations prepared in this research are depicted in table: 1. Moreover, each fabricated formulation presented a specific enhancement in aqueous solubility and dissolution as compared to pure drug powder of meloxicam (Figs. 1 and 2), respectively. It was observed that amongst all the formulation MSDs3 with a weight ratio of Meloxicam/HPMC/SLS (1/0.5/0.5) enhanced the aqueous solubility to an extreme level as compared to drug powder and other formulations as well (153.45 ±5.36 vs. 0.25 ±0.17 µg/ml). Likewise, the dissolution profile (Fig. 2) represents that MSDs3 ameliorated the dissolution of meloxicam at 15 minutes by ~ 13 folds (47.46 ±1.07 vs 2.96 ±0.55%). In comparison to Ismail et al., results the present study showed more than 100 fold increase in solubility of meloxicam in MSDs.[32] Furthermore, the reason of improvement in aqueous solubility and dissolution was due to the attachment of hydrophilic carriers (HPMC/SLS) on the surface of the crystalline lattice of the drug.[31] This connection of carriers with the drug resulted in fabrication of a novel meloxicam-loaded surface attached solid dispersion. Hence, it can be said that the attachment of hydrophilic carriers improved the wetting of the drug within solid dispersion.

The morphology of the fabricated MSDs which has shown the highest solubility and dissolution versus meloxicam powder was analyzed through scanning electron microscopy (SEM). The micrographs of SEM are shown in Figure 3. It can be seen from fig. 3A that the drug is in crystalline form. Similarly, fig. 3B depicts the morphology of MSDs which exhibits that the hydrophilic carriers are adsorbed on to the surface of crystalline lattice of the drug. This confirms that the drug was in crystalline form in the fabricated solid dispersion. Furthermore, it is evident in figure 4 that the meloxicam is depicting a sharp endotherm at its melting point. Similarly, the MSDs also showed endotherm peak confirming that the drug was not converted into amorphous form. Simultaneously, the figure 5 is representing PXRD. It can be observed that pure meloxicam powder is showing characteristics peak pattern which is confirming its crystalline nature. Likewise, the peak pattern was also observed in MSDs confirming that the drug was not converted to amorphous form. Nevertheless, the enhancement in solubility and dissolution was due to the improvement in wettability of

meloxicam inside this formulation, which was owed to the carriers that were attached onto the surface of crystalline drug.

CONCLUSION

The present research involved the fabrication of an economical pharmaceutical formulation, which was not only free from hazards of organic solvents, but also consumed an optimized quantity of ingredients as compared to other solubility enhancing techniques. The prepared MSDs containing crystalline meloxicam, HPMC and SLS (1/0.5/0.5 w/w/w) can be considered as a potential candidate to overcome the poor aqueous and dissolution behavior of meloxicam. However, it can be suggested that to perform in-vivo studies in order to establish a connection to oral bioavailability of the active ingredient

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