
Formulation and Dissolution Properties of Meloxicam Solid Dispersion Incorporated Suppositories

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β -Cyclodextrin complexes of meloxicam were prepared by solvent evaporation technique in different ratios to enhance the solubility of the drug. The complex was characterized by infrared spectroscopy and differential scanning calorimetry studies. There was no interaction between drug and carrier. Based on physical characters and *in vitro* drug release pattern, 1:3 drug-carrier ratio was selected as ideal batch for suppositories. A water-soluble base, polyethylene glycol, was selected as ideal base for the preparation of suppositories. The suppositories were prepared by moulding technique. The ideal batch of solid dispersion was incorporated into suppository base. The prepared suppositories were characterized for hardness, melting point, disintegration time and drug content. All these properties were found to be ideal. The *in vitro* drug release pattern was determined by rotating dialysis bag method. The *in vitro* release of meloxicam from its solid dispersion incorporated suppositories was significantly improved when compared to the intact bulk drug incorporated suppositories.

Non-steroidal antiinflammatory drugs are used extensively in the community for a variety of musculoskeletal conditions and still provide the main stay of therapy for inflammatory forms of arthritis and non-rheumatic conditions like acute and chronic pain. Meloxicam is a selective COX-2 inhibitor belonging to oxicam class, developed for the treatment of rheumatoid arthritis, osteoarthritis and ankylosing spondylitis¹. The solubility of meloxicam is very low in acidic environments, which may delay its absorption from the GIT and thereby its onset of action. Meloxicam is associated with gastrointestinal and renal adverse effects¹.

Cyclodextrins are oligosaccharides, which have received increasing attention in the pharmaceutical field because of their ability to form inclusion complexes with many lipophilic drugs, thus changing their physicochemical and biopharmaceutical properties². Among the cyclodextrins, β -cyclodextrin (BCD) is the most widely studied compound for

drug complexation². Meloxicam is practically insoluble in water and as such, its oral absorption is dissolution-dependent. The poor aqueous solubility of the drug gives rise to difficulties in the pharmaceutical formulation of dosage forms and may lead to a variable bioavailability. The objective of the present study was to investigate the dissolution behavior of meloxicam from the solid dispersion-incorporated suppositories, which may avoid the gastrointestinal problems of meloxicam.

MATERIALS AND METHODS

Meloxicam was a gift sample from Unichem Labs, Mumbai. β -Cyclodextrin, PEG 4000 and PEG 1000, all of AR grade, were purchased from SD Fine Chemicals, Chennai. All the other chemicals used in the present study were of AR grade.

Preparation of solid dispersions:

The inclusion complexes were prepared using solvent evaporation technique². The required amount of meloxicam

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and β -cyclodextrin in 1:1, 1:2, 1:3, 1:4 and 1:5 ratios were dissolved in N, N-dimethyl formamide (DMF) and allowed to stand overnight. The solvent from the solutions was removed at temperature of 60° under vacuum until the solid dispersion was dry. The complete evaporation of DMF was confirmed by gas chromatography (Hewlett Packard, Series, II) with a flame ionization detector³. The dried mass was pulverized, passed through sieve no. 60 and stored in desiccator until used for further studies.

Preparation of physical mixtures:

The physical mixtures of meloxicam and β -cyclodextrin in 1:1, 1:2, 1:3, 1:4 and 1:5 ratios were obtained by mixing pulverized powders of drug and carrier together with the help of a spatula.

Characterization of solid dispersions:

The prepared solid dispersions were evaluated for drug carrier interaction using differential scanning calorimetry (DSC, Sieko, DSC-220C) and FTIR (Perkin-Elmer) spectral studies. For DSC studies, the samples were sealed in aluminium pans and the DSC thermograms were recorded at a heating rate of 10°/min from 30°-300°. FTIR spectrum was taken between 4000-400 cm⁻¹ using KBr disc of the sample. The solid dispersions were also characterized for appearance. The displacement value of solid dispersions and pure drug was determined by a procedure described by Carter⁵.

In vitro dissolution studies for solid dispersions:

The USP dissolution apparatus (Type II) was used for evaluation of *in vitro* release profile of solid dispersions⁴. The dissolution medium was 900 ml phosphate buffer of pH 7.4 kept at 37±0.1°. The drug or physical mixture or solid dispersion was filled in empty capsules and then kept in the basket of dissolution apparatus, which was then rotated at 50 rpm. Samples of 5 ml were withdrawn at specified time intervals and analyzed spectrophotometrically at 347.6 nm. Withdrawn samples were replaced by fresh buffer solution.

Preparation of suppositories:

Suppositories were prepared by moulding method⁵. A combination of PEG-1000 and PEG-4000 in the ratio of 75:25 was used as ideal base for suppositories. Intact meloxicam or its solid dispersion was added to the water-soluble base melt at 50° and thoroughly mixed. The molten mass was poured into suppository mould of 1 g capacity. The suppositories formed were then refrigerated until use for further studies.

Physical characteristics of suppositories:

Physical characteristics such as hardness, melting point, disintegration time and drug content were measured. The hardness of a cylindrical portion (8 mm thickness) of suppository, which was obtained by cutting the middle portion of the suppository, was measured in its diameter direction by using a Monsanto hardness tester. Melting was measured by capillary method. The disintegration time was measured by using tablet disintegration apparatus. For determination of drug content, the solid dispersion incorporated suppositories were dissolved in 50 ml buffer of pH 7.4 by stirring slowly at 37° for 1 h. After 1 h, the solution was filtered and the filtrate was diluted suitably and the absorbance was measured against blank at 347.6 nm.

In vitro release profile for suppositories:

In vitro release studies for the suppositories were carried out by dialysis bag method⁶. A solid dispersion loaded suppository was placed in a dialysis bag and it was held in position in the dissolution fluid by a heavy clamp with the stirring element (paddle), which was rotated at 50 rpm. The sampling was done at different time intervals over a period of 4 h, filtered, diluted and the absorbance was measured at 347.6 nm against the blank prepared by using dummy suppository. The same procedure was followed for pure drug loaded suppositories also.

Stability testing:

Each suppository, in its final packing, was kept for 6 w at refrigeration temperature (4°). After 6 w of storage, the suppository was dissolved in phosphate buffer of pH 7.4 by slow stirring for 1 h. Then, the sample was withdrawn and diluted suitably using the same buffer solution. The drug content was determined by spectrophotometry at 347.6 nm against blank prepared using dummy suppository.

RESULTS AND DISCUSSION

Five batches of solid dispersions and physical mixtures corresponding to drug-carrier ratios of 1:1, 1:2, 1:3, 1:4 and 1:5 were prepared and characterized by FTIR and DSC for drug-carrier interactions. There was no interaction between drug and BCD. Physical appearance of solid dispersions prepared in the proportion of 1:1 and 1:2 showed deep yellowish colour, whereas the other batches were slightly yellowish in colour. Hence, it was concluded that as the proportion of BCD increases, the colour of solid dispersion decreases. This is important because colour appearance is one of the important organoleptic properties of suppositories as

TABLE 1: PHYSICAL CHARACTERISTICS OF MELOXICAM INCORPORATED SOLID DISPERSIONS.

Drug-Carrier Ratio	% Yield	Appearance
1:1	82.0	Yellowish
1:2	73.2	Yellowish
1:3	74.5	Slight Yellowish
1:4	77.8	Slight Yellowish
1:5	80.1	Slight Yellowish

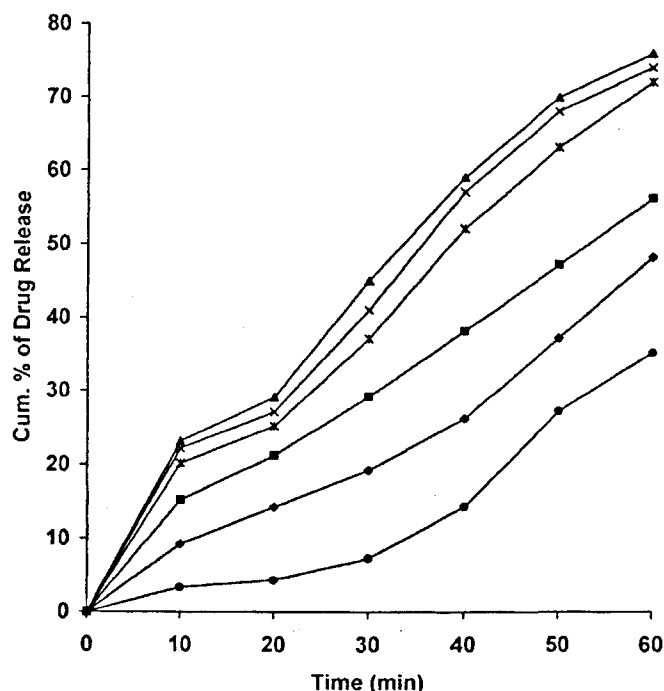


Fig. 1: *In vitro* dissolution profile of meloxicam from solid dispersions.

Dissolution of meloxicam from different batches of solid dispersions such as 1:1 (-◆-), 1:2 (-■-), 1:3 (-▲-), 1:4 (-×-), 1:5 (-*-) and pure drug (-●-) using USP dissolution apparatus (type II).

shown in Table 1.

The *in vitro* release studies of different batches of solid dispersions are shown in fig. 1. The solid dispersions showed improved dissolution when compared with physical mixtures and pure drug. Among the solid dispersions prepared 1:3 ratio showed greater solubility than the others and it showed 75.54% release over an hour. The solid dispersion prepared with 1:4 ratio showed nearest rate of release with 1:3 ratio.

In case of 1:5, the release was less than 1:4. This may be because of over-saturation of BCD with drug. After reaching the saturation stage, BCD often results in decreased availability². The drug-BCD complex cannot permeate the membrane and hence, an excess of BCD will decrease the availability of free drug molecules at the membrane surface. Based on above data, solid dispersions prepared with 1:3 drug-carrier ratio was selected as ideal batch for incorporation into suppositories. The displacement values for solid dispersion and pure drug were determined and for pure drug, it was found to be 2.3, whereas for solid dispersion, it was found to be 2.7.

The solid dispersion incorporated suppositories were prepared by moulding technique using PEG 1000 and PEG 4000 in percentage proportion of 75:25, respectively. The physical characteristics of suppositories were satisfactory (Table 2). Pitting and fissuring were not observed and the drug content was found to be uniform in the suppositories.

The melting point of the loaded suppositories was observed by open capillary tube method. It was found that the melting points of solid dispersion loaded, drug loaded and dummy suppositories did not change. All the suppositories melted in the optimum temperature of 36.5-37.5°. The mechanical strength of ideal batch of suppositories was found to be 1.3-1.4 kg/cm². The drug content was analyzed at 347.6 nm spectrophotometrically and was found to be 14.05 mg per suppository.

The *in vitro* dissolution studies were performed by dialysis bag method over a period 4 h and the results are shown in fig. 2. At the end of 4 h, 94.79% of drug was released from solid dispersion loaded suppositories with a C_{50%} of 47 min whereas pure drug loaded suppositories released 50% of drug in 167 min. At the end of 4 h, pure drug loaded suppositories released only 69.7% of drug. The results proved that the solid dispersion incorporated suppositories

TABLE 2: PHYSICAL CHARACTERISTICS OF SUPPOSITORIES.

Parameter	Behaviour
Melting Point	36.5-37.5°
Surface Fractures	Absent
Mechanical Strength	1.3-1.4 kg/cm ²
Disintegration Time	Fully dissolved within 6 min
Drug Content	14.051 mg/g of suppository

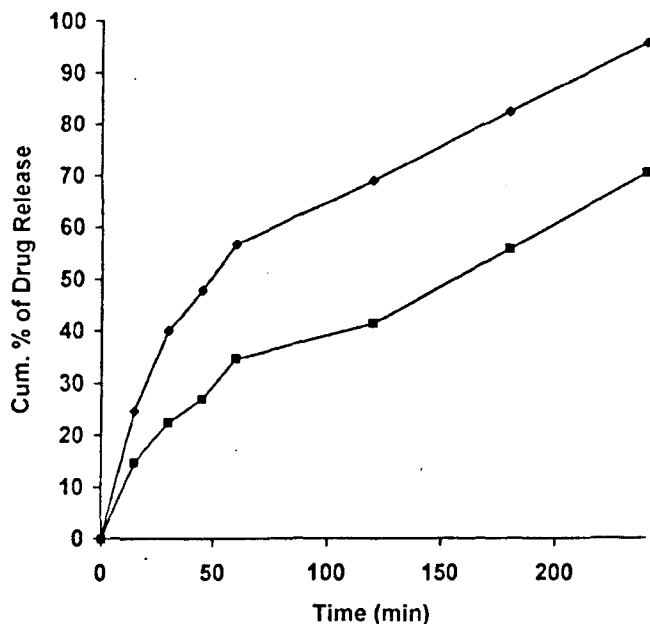


Fig. 2: *In vitro* dissolution profile of meloxicam suppositories.

Dissolution of suppositories containing meloxicam solid dispersions (-♦-) and suppositories containing pure drug (-■-) was determined using dialysis bag method.

were better in releasing the drug than the pure drug loaded suppositories.

The results of stability studies showed that there was no significant change in drug content, physical characters and dissolution profile of suppositories after storing them for 6 w at refrigeration temperature. Meloxicam was stable in a water-soluble suppository when incorporated in the solid dispersion form and physical characteristics such as hardness, melting point were satisfactory for practical use. The *in vitro* dissolution of meloxicam solid dispersion incorporated water-soluble suppositories was greatly improved when compared with those of intact meloxicam incorporated water-soluble suppositories. From the above results, it may be concluded that suppositories were better for improvement of dissolution of meloxicam and also to overcome the gastric side effects of the drug.

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