Beta-Cyclodextrin and Maltodextrin Based Solid Dispersion of Meloxicam to Enhance the Solubility of Meloxicam; Formulation and *In-vitro* Evaluation

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Summary: The purpose of the current study was to enhance the solubility of the meloxicam (MLX) by preparing complex with *β*-Cyclodextrin (CD) and maltodextrin (MD). Dextrins have the ability to capture the drug inside their cavities without forming any chemical bonding. Three (3) formulations, each of solid dispersion (SD) and physical mixture (PM) were prepared by using different drug to polymer ratios (1:4, 1:6 and 1:8) followed by evaluation for micromeritic properties, drug contents, and *in vitro* drug release studies, scanning electron microscopy (SEM), differential scanning calorimetry (DSC) and x-ray diffraction (XRD) studies. Chemical compatibility of the ingredients was evaluated by using Fourier transform infrared spectroscopy (FTIR). Results of conducted studies exposed excellent flow properties of SDs as well as prepared PMs, with reasonable amount of loaded drug, i.e. >90%. SEM showed a bit irregular surface while XRD suggested crystalline behavior of pure drug, which was masked after its conversion into SDs and PMs based on dextrins. Solubility of the MLX was increased significantly form its initial extent of solubility i.e. 12.5 µg/ml in pure form to 786.72 µg/ml in the form of SD ($p<0.05$), advocating suitability of materials and methods for solubility enhancement of MLX.

Keywords: *β*-Cyclodextrin; Maltodextrin; Solid dispersion; Kneading technique; Polymeric materials.

Introduction

Clinically, non-steroidal anti-inflammatory drugs (NSAIDs) are the most frequently prescribed by physicians for inflammatory disorders. Meloxicam [4-hydroxy-2methyl-N- (5-methyl-2-thiazolyl)-2H-1,2-benzothiazine-3- carboxamide1,1-dioxide] (Figure 1), is one of the most commonly prescribed NSAIDs for the treatment of various inflammatory conditions such as rheumatoid arthritis, osteoarthritis, low back pain [1]. Although, it has excellent bioavailability (89%) but its poor aqueous solubility makes absorption and dissolution rate-limited, thus delaying onset of action. Hydrophilic, modified and unmodified[2] polymeric materials have various application in the development of drug delivery systems as well as in the enhancement of solubility of poorly water soluble drugs and hence; bioavailability [2, 3]. Cyclodextrins (CDs) are a family of cyclic oligosaccharides with a hydrophilic outer surface and a lipophilic central cavity. CD molecules are relatively larger in structure with a number of hydrogen donors and acceptors and, thus, in general, they do not permeate lipophilic membranes. In the pharmaceutical industry, CDs have been used mainly as complexing agents to increase aqueous solubility of poorly soluble drugs and to increase their bioavailability and stability. Currently, there are approximately 30 different pharmaceutical products are available worldwide in the market containing drug/CD complexes. Maltodextrins (MDs) are complex mixtures of high and low molecular weight carbohydrates, obtained by acid and/or enzymatic hydrolysis of starch. They contain linear amylose and branched amylopectin degradation products and are considered as d-glucose polymers, joined by α-(1,4) and α-(1,6) linkages. MDs are endowed with the capability to form complexes with various classes of compounds usually of the host–guest type. Complex formation depends on the size of the complex forming molecule and is believed to require a conformational change from a flexible coil to a helix form in the presence of the guest molecule [4].

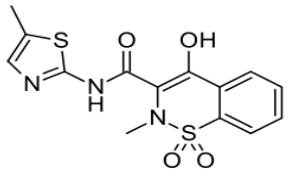

Fig. 1: Structural formula of Meloxicam.

The purpose of the current study was to enhance the solubility of water insoluble drug, MLX by using *β*-CD and MD as solubility enhancers. Solid dispersion was prepared by Kneading technique using different drug to polymer ratio. Moreover,

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effect of varying concentrations of the carriers on the extent of solubility was also evaluated.

Experimental

Materials

MLX was gifted by Pharmedic Laboratories Lahore Pakistan. *β*-CD and MD were purchased from Merck Germany. Sodium hydroxide (NaOH), dihydrogen potassium phosphate (KH_2PO_4), methanol (Sigma Aldrich) and distilled water were taken from research laboratories of The University of Lahore. All the chemicals, used in the project were of analytical grades.

Methods

Preparation of Binary System

PMs and SDs were prepared by mixing accurate weight of MLX with *β*-CD, MD in the drug: polymer ratios of 1:4, 1:6 and 1:8 for 30 min using mortar and pestle (Table-1). The physical mixture was triturated using a small volume of methanol containing 0.1M solution of NaOH (9:1) to give a dense paste. Prepared paste was subjected to the process of kneading for 30 min, and subsequent drying at the temperature 45°C in a hot air oven (DHIAN Lab Tech Korea). Dried material was pulverized, passed through sieve no 40, stored in a vacuum desiccator for 24h, and then passed through sieve no 80. Sieved mass was collected, weighed and stored in well closed container at room temperature [5].

Evaluation of physical mixture and solid dispersion

Micromeritics

Bulk density

Bulk density was measured by using method 1 of United States Pharmacopeia, 2006. The measured amount of powder/solid dispersion was added to a graduated cylinder of 100ml capacity. Without tapping the cylinder, the powder was flattened and apparent volume V was noted to the adjacent graduated unit. Then by using the following equation, the bulk density was measured in g/ml.

$$\text{Bulk density} = M\frac{\square}{Vb}\square\square\square$$

where M =mass of the powder and V=volume of the material

Table-1: Compositions of MLX containing SDs and PMs of MLX with varying concentrations of *β*-CD and MD

Formulations Code	Solid Dispersion		Physical mixture	
	MLX: *β-CD*	MLX:MD	MLX: *β-CD*	MLX:MD
CDF1	1:4	--	--	--
CDF2	1:6	--	--	--
CDF3	1:8	--	--	--
MDF1	--	1:4	--	--
MDF2	--	1:6	--	--
MDF3	--	1:8	--	--
PMCD1	--	--	1:4	--
PMCD2	--	--	1:6	--
PMCD3	--	--	1:8	--
PMMD1	--	--	--	1:4
PMMD2	--	--	--	1:6
PMMD3	--	--	--	1:8

Tapped density

The powder/solid dispersion was shifted to a graduated glass cylinder (readable to 2 ml) having filling capacity of 100ml. The apparent volume of the material without compressing (V) was noted. After that tapping was done until a constant volume was achieved. Tapped volume Vt was noted. The following equation was used to compute the tap density in g/ml.

$$\text{Tapped density} = M\frac{\square}{\square}Vt$$

where M= mass of the material and Vt= tapped volume

Compressibility index

It is an easy and commonly used method to assess the flow properties of the materials. Compressibility index of the powder/solid dispersion was determined by using the following equation;

$$\text{Compressibility Index} = \frac{100(Vi - Vt)}{Vi}$$

where V_i =initial volume and V_t = tapped volume

Hausner's Ratio

Hausner's ratio is another vital parameter to determine the flow properties of powder and granules. Following equation was used to calculate the Hausner's ratio;

$$\text{Hausner's ratio} = \frac{Vo}{Vf}$$

where Vo =initial volume and Vf = final tapped volume.

I.P (Indian Pharmacopoeia) limits describes that if the values are 1.00-1.11 the flow is excellent, good when values are 1.1-1.18, fair, when 1.19-1.25, passable when 1.26-1.34, poor when 1.35-1.45 and very poor when the values are >1.50 [6].

Angle of repose

Fixed funnel and cone method was used to measure the angle of repose. Piece of paper has been positioned on a flat surface. A glass funnel was fixed over it with the help of a clump in such a way that the difference between its tip and paper was 20mm. Very carefully; the prepared SDs and PMs were transferred on the flat surface through the funnel to form a heap until the cone thus formed was touching the tip of the funnel. Height and diameter of the heap were measured and the angle of repose was calculated as [7];

$$\tan \emptyset = \frac{2h}{D}$$

where

h=height of the powder cone and D= mean diameter of the powder cone

If the values are <20 then flow is excellent, 25-30 good, 30-40 passable and >40 shows very poor flow [8].

Percentage yield of MLX containing PMs and SDs

The percentage yield of each formulation was calculated according to the total weight obtained after passing the mass through sieve no 80 and the sum of the total mass of the drug and carriers used for the preparation of solid dispersion. Percentage yield was determined by the equation;

$$\% \text{ Yield} = \left[\frac{a}{b+c} \times 100\right]$$

where 'a' is the weight of solid dispersion passed through sieve no 60, 'b' was the weight of meloxicam for solid dispersion and 'c' is the weight of carrier (CD and MD).

Calibration curve of MLX

5mg of MLX were weighed accurately and transferred to a volumetric flask having capacity of 50cm^3. Small volume of methanolic phosphate buffer of pH 6.8 was added to dissolve the drug and the final volume was made up to 50ml. The concentration of MLX in this stock solution was 100µg/ml, which was taken as the stock solution. Different dilutions of concentrations, ranging from 1µg/ml-10µg/ml were prepared and analyzed by spectrophotometer (Double beam UV-visible spectrophotometer, PG Instruments T80, UK) at 365nm.

Drug contents (%)

PMs and SDs were evaluated for drug contents. Each formulations containing approximately 10mg of the MLX was taken and added to the volumetric flask containing suitable volume of methanolic phosphate buffer of pH 6.8. Percentage drug contents were evaluated using a double beam UV-visible spectrophotometer at 365nm [9].

Phase solubility studies

The study was accomplished by using the process adopted by Higuchi and Connors. Excess quantity of MLX (20mg) was poured in a round bottom flask containing 20ml distilled water. The flasks were wrapped and subjected to continuous shaking at 37°C for 96h on a mechanical shaker [10]. Furthermore, samples were filtered through a 0.22µm membrane filter, diluted and analyzed by spectrophotometer at 365nm (Figure 2).

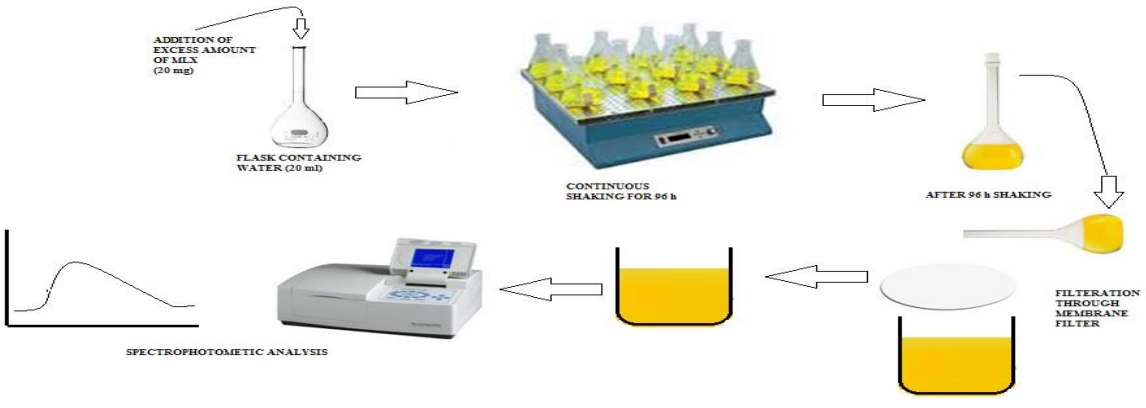

Fig. 2: Schematic diagram of phase solubility studies of MLX containing solid dispersions and physical mixtures.

In-vitro dissolution studies

Pure MLX, PMs and SDs of drug and carrier were subjected to i*n vitro* dissolution studies. Distilled water was used as dissolution medium and USP paddle method II was used for dispersed powder technique [5]. A sample containing 7.5mg of MLX was added to 500ml dissolution medium. Working conditions were maintained at 50 rpm and 37°C±0.5for 60min. 5ml aliquots were drawn after every 10min and equal volume of fresh dissolution medium was poured in the vessels to maintain the constant volume of dissolution medium. Withdrawn samples were filtered through membrane filter of 0.22µm pore size and analyzed by spectrophotometer (specification already mentioned) at 365nm [11] and drug release was calculated by equation; [7];

$$\% \text{ Drug Release} = \frac{\text{A(sample)}}{\text{A(standard)}} \times 100$$

where A is the absorbance.

Mechanism and pattern of drug release

Both model dependent and model independent approaches were applied to assess the mechanism and pattern of the drug release. Model dependent approach includes,

Zero order models

$Q_1=Q_0+k_ot$

where k_o is the release rate constant Qt is the amount of drug released at any time interval

1st order model

$\log Q_t = \log Q_0 + K_1 t/1.303$

k_1, is the 1st order release rate constant Q_t, is the amount of drug released at any time interval

Higuchi model

$F_t=K_Ht^{1/2}$

K_H, is release rate constant for Higuchi model

Korsmeyer Peppas model

$M^t/M^0=kKPtn$

Kkp, is release rate constant for Korsmeyer peppas model, M^t/M^0 is the amount of drug released in time t and infinity n, is the diffusion constant.

While the model independent approach includes;

Similarity factor and Difference factors

$$f_2 = 50\ log\left\{\left[1+\frac{1}{n}\sum_{t=1}^{a}(R_t-T_t)^2\right]^{-0.5}\times 100\right\}$$

$$f_1 = \frac{\sum[R_t - T_t]}{\sum R_t} \times 100$$

where f_1 is difference factor, f_2 is the similarity factor and, R_t is amount of reference drug at different time interval and T_t are the percent test drug dissolved at various times.

Statistical analysis

The enhancement in solubility of MLX and dissolution profile of MLX using *β*-CD and MD with respect to pure MLX was analyzed using analysis of variance (ANOVA) at 95% confidence interval by using Graph Pad prism.

Surface morphology studies

The surface morphology of the prepared solid dispersion was studied by scanning electron microscopy (SEM having specifications already mentioned). The small amount of the material was placed over the stage and photographs were taken using a lens by 1000X magnification power.

X-ray Diffractometry (XRD)

XRD was studied to observe the change in crystallinity of the MLX in PMs as well as in SDs using X-Rays Diffractometer (JDX-3532 JEOL Japan). The investigational environment were maintained as, tube voltage was 45 kV, tube current 40 mA and scanning angle 2θ was 5–50º [12].

Differential scanning calorimetry (DSC)

Pure MLX, PMs and SDs were subjected to DSC studies using differential scanning calorimeter (DSC-60A Thermal analyzer, Shimadzu Japan). Sample weight of 7mg was wrapped in the aluminum pan and heated in the temperature range of 35°C to 300°C at the rate of 10°C/min and provided with Nitrogen containing atmosphere at the flow rate of 25ml/min [12].

Fourier Transformed Infra-Red Spectroscopy (FTIR)

FTIR studies were performed to insure the compatibility of the ingredients. Sample of pure MLX, *β*-CD, MD, prepared SDs and PMs were analyzed by using Agilent Carry 360 FTIR (Agilent Carry 360 FTIR, United States) and scanning of the samples were performed in the range of 500 cm^{-1} to 4000 cm^{-1} [13].

Results and Discussions

Physicochemical properties of MLX containing PMs and SDs

Micrometrics of PMs and SDs

Micrometric studies of SDs as well as PMs showed good to excellent flow properties.

Bulk density (ρ_b)

Values of ρ_b were 0.35±0.21 to 0.39±0.09, 0.32±0.08 to 0.37±0.12, 0.33±0.05 to 0.35±0.02 and 0.33±0.12 to 0.37±0.11, for *β*-CD based SDs, MD based SDs, *β*-CD based PMs and MD based PMs respectively (Table 2). *β*-CD has been already used by Dhandapani, Nagasamy V and Amged AE in solid dispersions of Cefixime and their excellent flow properties were observed [14].

Tapped density (ρ_t)

Values of ρt were 0.39±0.11 to 0.43±0.03for *β*-CD based SDs, 0.37±0.13 to 0.41±0.06 for MD based SDs, 0.39±0.01 to 0.43±0.18 for *β*-CD based PMs and 0.41±0.15 to 0.45±0.07 MD based PMs respectively (Table 2). Mahmood *et al* in 2016 has prepared complex of Acyclovir with *β*-CD and results of the flow-ability were comparable to that obtained in current study [15].

Compressibility index (C.I)

Least values of C.I (09.3±1.12) was shown by CDF3 and the highest value was achieved in CDF1 amongst *β*-CD based SDs. Amongst, PMs based on *β*-CD the highest value of C.I was 11.9±1.13 shown by CDF1 and the lowest value (9.3±1.12) has been obtained from CDF3. Similarly MD based SDs have shown C.I values 10.2±1.13 to 12.8±1.11 and PMs based on MD have shown 18.6±1.41 to 21.7±1.44.Results of stated parameter were suggesting better flow properties of solid dispersions as compared to physical mixtures. It may be due to the presence of less voids in SDs as they were passed through the kneading process and in more compact form as compared to the PMs. The results of C.I were comparable to those reported by Daravath B and Tadikonda RR in their studies in 2014 where they made attempt to prepare SDs of Meclizine Hydrochloride using MD as carrier (Table 2) [16].

Hausner's Ratio

Values of hausner's ratio were in the range of 1.10±0.04 to 1.13±0.03 for *β*-CD based SDs, which have been found better than those of *β*-CD based PMs (1.12±0.03 to 1.15±0.05). These values were 1.11±0.03 to 1.14±0.03 and 1.22±0.02 to 1.27±0.03 for MD based SDs and MPs respectively. The outcome of the study were comparable to the findings of Noolkar *et al* obtained in 2013 during their attempt to enhance the solubility of MLX by SDs with CD [17].Values of hausner's ratio for SDs were comparatively low suggesting there better flow as compared to PMs. It might be due to the existence of greater intra particle spaces in PMs (Table 2).

Angle of repose

It also showed similar findings of flow properties. Formulated SDs better flow properties in the range of excellent to good flow-ability and the findings of current study were better than those obtained by Mowafaq M *et al* in 2009 [5]. CDF3 has proven to be the superior amongst all the prepared formulations with least value of angle of repose (25.32±0.58) falling in the category of excellent flow-ability. Values for rest of the formulations were 28.21±0.61, 26.42±0.54, 29.21±0.53, 28.31±0.57, 26.87±0.49, 32.71±0.67, 31.92±0.54, 31.19±0.62, 32.58±0.56, 32.11±0.43, 31.33±0.47 for CDF1, CDF2, MDF1, MDF2, MDF3, PMCD1, PMCD2, PMCD3, PMMD1, PMMD2 and PMMD3 respectively. SDs showed comparatively better flow properties which may be attributed due to their better symmetry in shapes of the particles than the particles of PMs (Table 2).

Percentage yield of MLX containing PMs and SDs

Percentage yields obtained in the range of 89 to 95% for *β*-CD based SDs and 88 to 93% for MD based SDs. However, values of percentage yield for PMs of MLX with *β*-CD and MD were somewhat better ranging from 88 to 96%. It may be due to the wastage of some material for SDs during kneading of the material and shifting from pestle mortar to sieve. However, the results were comparable to those obtained by Ghareeb*et al* in 2009 [5].

Table-2: Micrometric studies including bulk density, tapped density, compressibility index, hausner's ratio and angle of repose of PMs and SDs of MLX

Formulation	Bulk density (g/ml)	Tapped density (g/ml)	Compressibility index (%)	Hausner's ratio	Angle of repose (°)
CDF1	0.37±0.11	0.42±0.12	11.9±1.43	1.13±0.03	28.21±0.61
CDF2	0.35±0.21	0.39±0.11	10.3±1.09	1.11±0.04	26.42±0.54
CDF3	0.39±0.09	0.43±0.03	09.3±1.12	1.10±0.04	25.32±0.58
MDF1	0.35±0.10	0.41±0.06	12.8±1.11	1.14±0.03	29.21±0.53
MDF2	0.32±0.08	0.39±0.11	12.1±1.38	1.13±0.01	28.31±0.57
MDF3	0.37±0.12	0.37±0.13	10.2±1.13	1.11±0.03	26.87±0.49
PMCD1	0.33±0.05	0.42±0.17	13.5±1.18	1.15±0.05	32.71±0.67
PMCD2	0.35±0.02	0.44±0.18	11.9±1.23	1.13±0.04	31.92±0.54
PMCD3	0.34±0.03	0.46±0.01	11.3±1.48	1.12±0.03	31.19±0.62
PMMD1	0.37±0.11	0.41±0.15	21.7±1.44	1.27±0.03	32.58±0.56
PMMD2	0.36±0.14	0.43±0.19	19.5±1.31	1.24±0.02	32.11±0.43
PMMD3	0.33±0.12	0.45±0.07	18.6±1.41	1.22±0.02	31.33±0.47

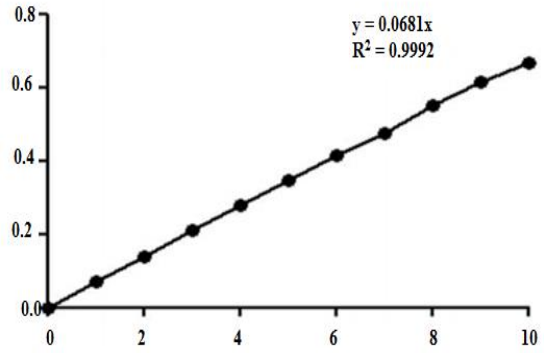

Fig. 3: Calibration curve of MLX showing good linearity in the concentration range of 2-10µg/ml for the evaluation of % drug contents of SDs and PMs of MLX.

Drug contents (%)

Drug contents were 94.16±1.86 to 101.37±1.39%, well with-in the required limits following United States Pharmacopoeia recommendations. Highest amount of MLX was entrapped by CDF3 (101.37±1.39%) while PMMD1 was able to capture only 95.17±1.03 % of the drug. Drug contents entrapped by SDs of MLX with *β*-CD were 97.14 to 101.37% and the results were better as compared to reported by Ghosh A and his co-worker in their study while using *β*-CD for the solubility enhancement of Silymarin [18]. Various researchers have reported the admirable drug loading ability of *β*-CD [19] (Table 3).

Phase solubility studies

Phase solubility of the MLX was greatly improved from 12.5 µg/ml to 786.72 µg/ml (Figure 4). It was the indication that dextrins are quite capable of enhancing the solubility of drugs, like MLX. A common trend was observed that solubility was greatly linked with the concentrations of the carriers. As illustrated in figure 4, the maximum solubility which was 786.72 µg/ml has been achieved by using the ratios 1:8 of MLX and *β*-CD. Although MPs have also increased the solubility of MLX but results were more significant with those of SDs prepared by *β*-CD in the 1:8 drug to polymer ratio (CDF3). A significant difference between the solubility of pure MLX and prepared formulations was observed which may be attributed to the formation of hydrophilic diffusion layer around the drug particles imparting the necessary contact with water molecules for solubilization [20].

Table-3: Percent drug contents obtained from different formulations containing MLX.

Serial Number	Formulations	% Drug contents
1	CDF1	97.14±1.05
2	CDF2	99.01±2.03
3	CDF3	101.03±1.39
4	MDF1	95.16±1.86
5	MDF2	95.37±2.03
6	MDF3	96.24±1.55
7	PMCD1	96.11±1.03
8	PMCD2	97.23±1.19
9	PMCD3	99.56±1.36
10	PMMD1	95.17±1.03
11	PMMD2	96.32±1.25
12	PMMD3	97.51±1.42

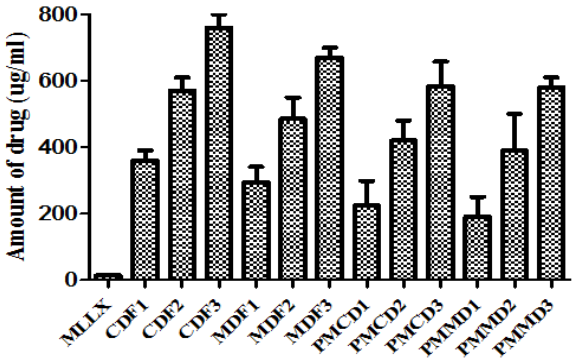

Fig. 4: Phase solubility of MLX using varying concentration, of β-CD and MD.

In vitro dissolution studies

CDF3 has found to be the best of all prepared formulations either they were PMs or SDs.

It was also evident from the i*n vitro* dissolution studies where CDF3, prepared by using *β*-CD in the ratio 1:8 to the drug, has released maximum drug during 1 h of dissolution studies. It has released about 58.21% of the drug in initial 15 min of the studies, which were extended to about 99.98 % at the end of the dissolution process. SDs prepared with MD have released 73.94% to 84.45% and PMs with *β*-CD and MD, released 80.09% to 91.57% and 77.01% to 90.21% respectively (Figure 5). The stated results were comparable to those obtained by Yousaf *et al* in 2016 while using *β*-CD for the solubility enhancement of Fenofibrate [21]. As the concentration of carrier in SDs as well as in PMs increased, the rates of the drugs release were also increased. Better drug release profiles were shown by the formulations with comparatively greater concentration of the carrier, confirmed a close relationship of dissolution rate with the concentration of the carriers.

Mechanism and pattern of drug release

Release mechanism was observed by applying different kinetic models and it was found that excluding CDF2, MDF2, MDF3 and PMMD3, all other formulations including SDs and PMs based on *β*-CD and MD followed korsmeyer peppas model, suggesting diffusion type of drug release pattern (Table 4).

Similarity factor and Difference factors

Higher dissolution rates, showed by the formulations with comparatively greater concentration of the carrier, confirmed a close relationship of dissolution rate with the concentration of the carriers. When % release of pure drug was compared with the % release of drug from drug-carrier complex (CDF3, MDF3M PMCD3 and PMMD3), they showed smaller values of the similarity index (f_2=7, 10, 9 and 9 respectively). However, significant difference was found while calculating the difference factor (f_1) 1393, 1191, 1259 and 1249 respectively. It was also confirmed by applying one way ANOVA with 95% confidence interval. A significant difference was observed with p value 0.0005.

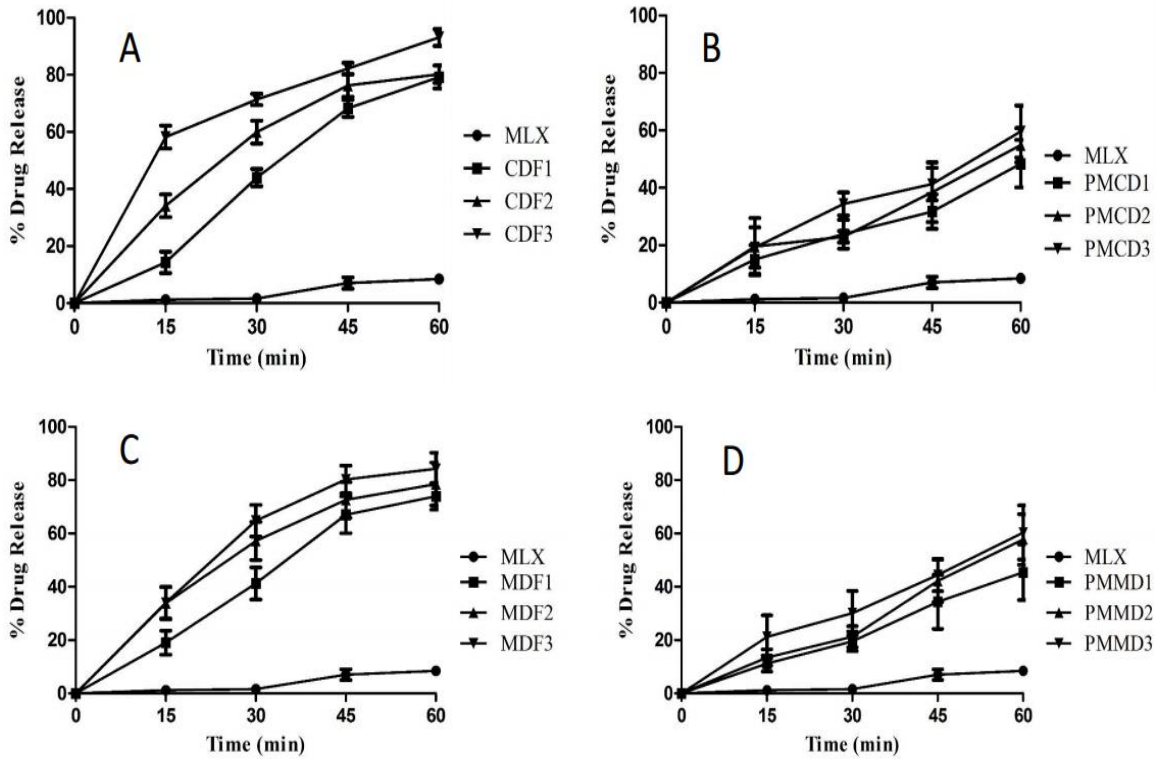

Fig. 5: Graphs showing release of MLX solid dispersion of β-*CD* (A), SD of MD (B), PM of drug and β-*CD* (C) and PM of drug and MD.

Table-4: Application of kinetic models on release data.

Kinetic Models		MLX	CD F1	CD F2	CD F3	MD F1	MD F2	MD F3	PM CD1	PM CD2	PM CD3	PM MD1	PM MD2	PM MD3
Zero order	K_O	0.144	1.387	1.564	1.822	1.331	1.513	1.651	1.400	1.536	1.680	1.332	1.651	1.743
	R^2	0.930	0.961	0.613	1.239	0.952	0.641	0.639	0.941	0.854	0.049	0.952	0.816	0.730
1st order	K_1	0.001	0.022	0.030	0.046	0.021	0.028	0.033	0.023	0.027	0.035	0.020	0.031	0.036
	R^2	0.923	0.892	0.985	0.835	0.932	0.992	0.973	0.967	0.974	0.827	0.882	0.842	0.930
Hixon- crowel	K_{CH}	0.000	0.006	0.008	0.012	0.006	0.008	0.009	0.007	0.008	0.009	0.006	0.009	0.010
	R^2	0.925	0.931	0.956	0.592	0.959	0.957	0.967	0.986	0.985	0.715	0.918	0.882	0.961
Higuchi model	K_H	0.926	9.127	10.62	12.59	8.829	10.27	11.20	9.361	10.33	11.50	8.740	11.04	11.78
	R^2	0.650	0.760	0.938	0.820	0.808	0.955	0.915	0.883	0.916	0.922	0.738	0.755	0.873
Korsmeyer- peppas Model	kK_P	0.034	1.360	8.197	22.64	2.019	7.775	8.166	3.236	5.099	14.20	1.123	3.656	6.968
	N	1.373	1.005	0.570	0.342	0.892	0.574	0.585	0.783	0.689	0.443	1.044	0.795	0.640
	R^2	0.976	0.962	0.949	0.992	0.961	0.968	0.931	0.987	0.976	0.934	0.953	0.852	0.909

Statistical analysis

Enhancement in the solubility of MLX was also confirmed by applying one way ANOVA with 95% confidence interval and a significant difference between the solubility of pure MLX and formulations was observed with p value 0.0005. Results of previous studies have strength the claim of the study as many researchers have reported a significant influence of *β*-CD and MD on the solubility of poorly water soluble drugs.

Surface morphology studies

SEM images taken at 1000X showed evenly mixed complex of both MLX and carrier (Figure 5) with amorphous characteristics. The existence of a smaller amount of drug, evenly and finely distributed or adhered to the surface of the polymer was detected in the solid dispersions. Stated figure was evident of the presence of drug and polymers in the state of solid solution where most of the of the drug particles were appeared to be dissolved in the polymer [16]. The results agreed to the findings of DSC and XRD studies. Apparently, the particles of solid dispersions were seemed more symmetrical than PMs.

XRD studies

The XRD diffraction pattern of MLX showed intensive peaks demonstrating crystallinity of the drug, which was diminished in the complex of the drug and carriers indicating the transformation of crystalline to amorphous nature of the MLX (Figure 6). It may be among one of the reason of enhanced dissolution rates of MLX[16].

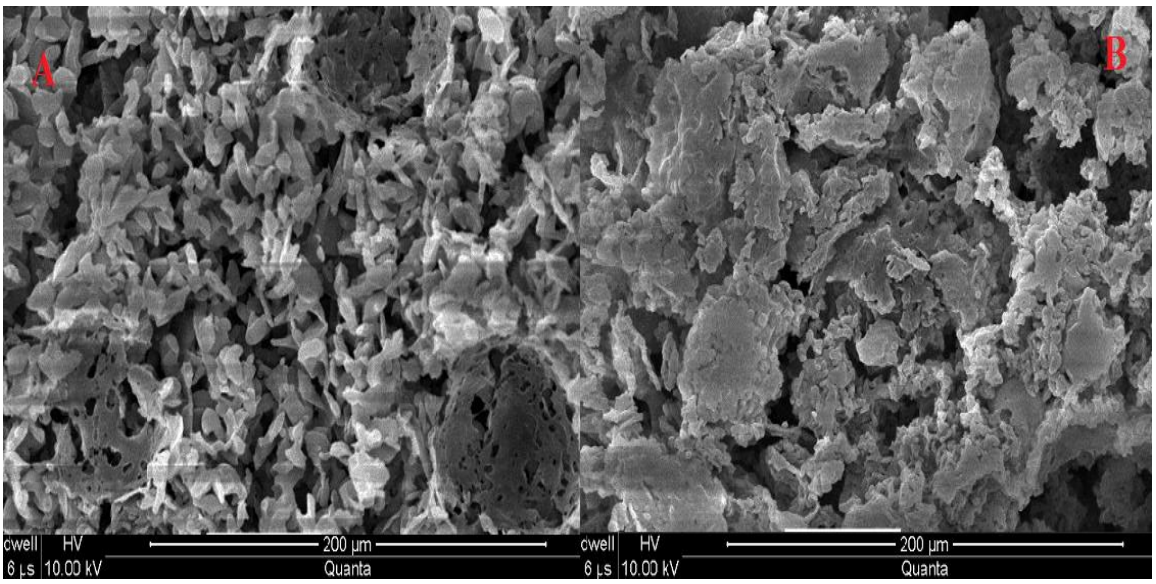

Fig. 5: Scanning microscopic image of Solid Dispersion (A) and Physical Mixture (B) of MLX with β-*CD.*

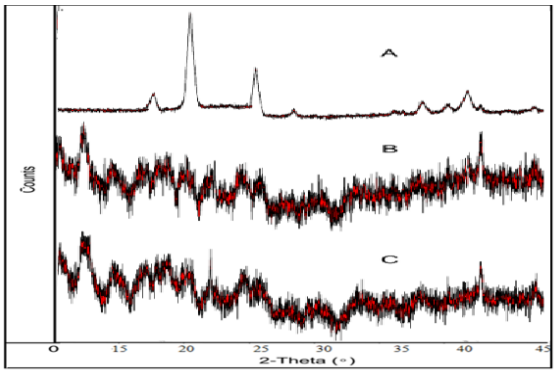

Fig. 6: XRD of pure MLX (A), Prepared PMs (B) and SDs (C).

DSC studies

DSC thermographs were recorded for MLX, *β*-CD, PMs of *β*-CD and MLX, and SDs of *β*-CD and MLX.MLX showed an endothermic peak at about 257.46 ºC[1]and a broader thermogram for *β*-CD at 139.32ºC. Thermogram of PM showed that both *β*-CD and MLX retain their characteristics showing endothermic peaks at 133.48 ºC and 253.16 ºC respectively. However, there was a single endothermic thermogram was observed for SDs at about 130.28 ºC, indicating that MLX is completely captured by particles of *β*-CD (Figure 7).

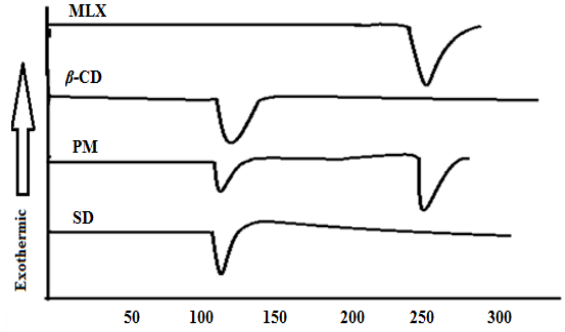

Fig. 7: DSC thermographs showing spectrum of MLX (A), β-*CD* (B), PM (C) and SD (D).

FTIR studies

MLX showed a sharp and intense principle absorption peak at 3283 cm^{-1}, which suggested the stretching of secondary amine (N-H). At 1616 cm^{-1} scissoring vibration of NH_2 and at 1548 cm^{-1} C=N stretch was observed. C-H wagging was seen at 1261 cm^{-1} and at 1161 cm^{-1}, S=O stretching has been observed. Peak at 710 cm^{-1} described the rocking of C-H group. *β*-CD showed a broad and an intense band at 3281 cm^{-1} due to O-H stretching vibration, while vibration due to CH and CH_2 appeared at 2952 cm^{-1} similarly MD showed a strong band at 3274 cm^{-1} due to O-H stretching and at 2924 cm^{-1} vibrations were due to the presence of CH and CH_2. Characteristic peak of MLX in solid dispersion with *β*-CD and MD maintained with a negligible variation at 3286 cm^{-1} and 3284 cm^{-1} respectively. Vibrations due to CH and CH_2 were at 2923 in complex of MLX with *β*-CD and for MLX with MD at 2920. These results were the evidence of chemical compatibility of carriers and drug as all the characteristics peaks of relevant materials were present in individual as well as in prepared formulations (Figure 8).

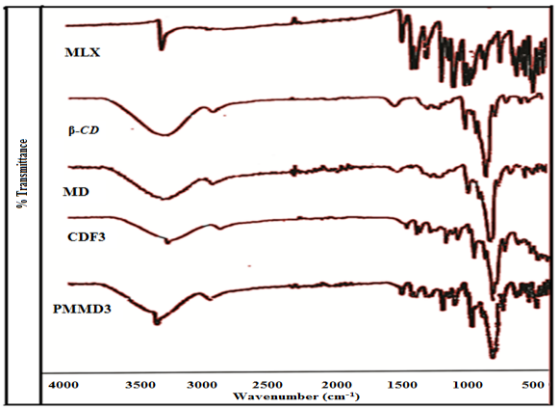

Fig. 8: FTIR spectrum of pure MLX (A), *β*-CD(B), MD (C), CDF3 of MLX with *β*-CD (D), PM of MLX with MD (E)

Conclusion

Results of solubility studies showed a satisfactory increase in the solubility of meloxicam, when it was complexed with carriers, β-Cyclodextrin and maltodextrin. It was confirmed by ANOVA that showed a significant difference of solubility between pure drug and solid complexes of drug and polymers. Dissolution studies showed swift and fast dissolution of the drug from all complexes when compared with pure meloxicam. Hence, it was concluded that both β-Cyclodextrin and maltodextrin could be effectively used to enhance the solubility of meloxicam.

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Conflict of interest

Authors have nothing to disclose.

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