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FORMULATION STUDIES ON CYCLODEXTRIN COMPLEXES OF MELOXICAM

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Abstract

β-Cyclodextrin (β-CD) and HP-β-Cyclodextrin (HP-β-CD) inclusion complexes of meloxicam (M) exhibited higher dissolution rates and dissolution efficiency values than the corresponding un-complexed drug. The feasibility of formulating the β-cyclodextrin and HP-β-cyclodextrin complexes of meloxicam (1:3) into tablet dosage forms is evaluated. Solid inclusion complexes of meloxicam prepared by kneading method were formulated into tablets by wet granulation and direct compression methods. All the tablets formulated employing β-cyclodextrin and HP-β-cyclodextrin complexes of meloxicam gave rapid and higher dissolution rates of when compared to that of meloxicam plain tablets. All the prepared tablets fulfilled the official (I.P.) disintegration time specification of uncoated tablets. Overall, tablets prepared by direct compression method disintegrate rapidly when compared to those prepared by wet granulation method. Analysis of dissolution data as per zero-order and first – order kinetic models indicated that the dissolution of meloxicam from all the tablets followed first-order kinetics. In both direct compression and wet granulation methods, tablets formulated employing cyclodextrin complexes (MT2, MT3, MT5, MT6) gave higher rates of dissolution (K_1) and dissolution efficiency (DE_{30}) values when compared

to the corresponding tablets formulated with meloxicam as such (MT1, MT4). Among all the meloxicam tablets formulated, formulation MT2, which is based on M- βCD (1:3) kneaded complex, gave highest dissolution. A 25.66 fold increase in the dissolution rate of meloxicam was observed with MT2 when compared to its plain tablets (MT1).

Key words: Meloxicam, Cyclodextrin Complexes, Dissolution rate, Solubility; Kneading Method.

INTRODUCTION

The poor dissolution characteristics of relatively insoluble drugs have long been a problem to Pharmaceutical Industry. A number of modern drugs are poorly soluble in water and aqueous fluids. Their absorption and bioavailability require improvement in the dissolution rate and efficiency. Among the various methods for improving the dissolution rate and bioavailability , cyclodextrin complexation was found to be very successful with a number of poorly soluble drugs such as Rofecoxib[1], Nimesulide[2], Ciprofloxacin[3], Tolbutamide[4], Paracetamol[5], Diclofenac sodium[6] etc. Cyclodextrins such HP-β cyclodextrin[7-15], γ-cyclodextrin[16,14,17], α, β, hydroxy propyl-β-cyclodextrin, α-cyclodextrin[18,16], Triacetyl-β- cyclodextrin , Methylated-β cyclodextrin[19], Hydroxy ethyl-β-cyclodextrin[20] etc., are used for preparing cyclodextrin complexes. Most of the Non-steroidal anti inflammatory drugs belong to class II category under Biopharmaceutical classification system (BCS) i.e., they are inherently highly permeable through biological membranes, but exhibit low aqueous solubility. They need enhancement in solubility and dissolution rate for improving their oral bioavailability. In the present investigation studies were carried out on cyclodextrin complexes of meloxicam for enhancing the dissolution rate. meloxicam, is a highly potent drug of enolic acid class and is a non-steroidal anti-inflammatory drug (NSAID) [21]. It is indicated for the treatment of

rheumatoid arthritis, osteoarthritis and other joint diseases.. The usual dose by mouth is 7.5 to 15 mg daily as a single dose. Meloxicam is absorbed from gastro intestinal tract. Rate of absorption and/or extent of bioavailability for such insoluble hydrophobic drug is controlled by rate of dissolution in gastro-intestinal fluids[22]. Cyclodextrin complexes of meloxicam were prepared employing kneading method for enhancing the dissolution rate and bioavailability of meloxicam.

MATERIALS AND METHODS

Meloxicam was a gift sample from M/s.Sun Pharma Ind. Ltd, Mumbai. β cyclodextrin was a gift sample from SA Pharmaceuticals. Lactose, potato starch, talc, magnesium stearate were procured from commercial sources. All other materials used were of pharmacopoeial grade.

PREPARATION OF CYCLODEXTRIN COMPLEXES

Solid complexes of meloxicam and β-cyclodextrin, HP- β-cyclodextrin were prepared in 1:3 ratio employing kneading method.

Kneading Method

Meloxicam and β-cyclodextrin, meloxicam-HP- β-cyclodextrin were triturated in a mortar with a small volume of a solvent blend of water-methanol (3:2). The thick slurry was kneaded for 45 min and then dried at 55 ^{o} C until dry. The dried mass was pulverized and sieved through mesh No.120.

Estimation of meloxicam in cyclodextrin complexes

A spectrophotometric method based on the measurement of absorbance at 365 nm in phosphate buffer pH 7.4 was used in the present study for the estimation of meloxicam[23]. The method was validated for reproducibility, accuracy, precision and linearity by analyzing six individually weighed samples of meloxicam. The stock solution of meloxicam was subsequently diluted to a series of

dilution containing 2,4,6,8 and 10 $\mu g/ml$ of solution, using phosphate buffer pH 7.4. The absorbance of these solutions was measured in UV-VIS spectrophotometer (ELICO SL-159). The method obeyed Beer's law in the concentration range of 0-10 $\mu g/ml$. 100 mg of inclusion complex was taken in a 50 ml volumetric flask. Methanol about 40 ml was added and mixed thoroughly. The contents were repeatedly warmed in a hot bath while mixing to dissolve the drug in the solvent. The solution was made up to volume with methanol. The solution was then suitably diluted with phosphate buffer pH 7.4 and assayed at 365 nm for meloxicam by the spectrophotometric method. The results are given in Table 1.

Table 1. Meloxicam Content of various Solid Inclusion Complexes of Meloxicam -β-CD , Meloxicam-HP-β-CD Prepared by Kneading Method

CD Complex	Percent Meloxicam Content ($\bar{x}$ ± s.d., n =3)
	Kneading Method
M-β CD (1:3)	24.85± 0.05 (0.20)
M-HP-β CD (1:3)	24.90 ± 0.07 (0.29)

Figures in parentheses are coefficient of variation (C.V.) values

PREPARATION OF TABLETS

Solid inclusion complexes prepared by kneading method were formulated into tablets. Both direct compression and wet granulation methods were tried for the preparation of tablets. In the case of direct compression, microcrystalline cellulose (PH 200), a directly compressible vehicle was added to improve the flow character of the CD complexes. Croscarmellose sodium (4%) was used as the disintegrant. In the case of wet granulation method, gelatinized starch was used as binding agent. Tablets each containing 10 mg of meloxicam were prepared as per the formulae given in Table 2.

Table 2. Formulae of meloxicam Tablets Prepared employing its Cyclodextrin Complexes

Sl. No.	Ingredient (mg/tablet)	Formulation					
		MT1	MT2	MT3	MT4	MT5	MT6
1.	Meloxicam	15	-	-	15	-	-
2.	M-β-CD(1:3)	-	45	-	-	45	-
3.	M-HPβCD(1:3)	-	-	45	-	-	45
4.	MCC PH 200	163	133	133	-	-	-
5.	Lactose	-	-	-	158	128	128
6.	Starch (as mucilage)	-	-	-	5	5	5
7.	Ac-Di-Sol	12	12	12	12	12	12
8.	Talc	5	5	5	5	5	5
9.	MagnesiumStearate	5	5	5	5	5	5
	Total Weight (mg)	200	200	200	200	200	200

Direct Compression Method

All ingredients were blended thoroughly in a closed dry plastic container. The blend of powders was compressed into tablets to a hardness of 6-8 kg/sq.cm on a 'Cadmach' single punch tablet machine. In each case 50 tablets were prepared.

Wet Granulation Method

Meloxicam or its cyclodextrin complex and half the amount of disintegrant were mixed thoroughly in a mortar to obtain a uniform blend. Starch paste was then added in small amounts while mixing the powder blend thoroughly. Sufficient binding agent was added (to get 3% starch concentration in the formulae) and mixed to obtain a dough mass. The mass was then passed through sieve No.12 to obtain wet granules. The granules were dried at 60^0 C for about 4 hours. The dried granules were

again passed through sieve No.16. Talc, magnesium stearate and the remaining amount of disintegrant were then added to dry granules and blended thoroughly. The granules were compressed into tablets on a 'Cadmach' single punch tablet machine to a hardness of 6-8 kg/sq.cm.

Evaluation of meloxicam tablets

The tablets were evaluated for hardness, friability, disintegration, content of active ingredient and dissolution rate. Disintegration times were determined in 'Thermonic' tablet disintegration test machine (USP) using distilled water as the fluid. Hardness of the tablets was tested using a 'Monsanto' hardness tester. Friability of the tablets was determined in a 'Roche' friabilator. The results are given in Table 3.

Table 3 : Drug Content, Hardness, Friability and Disintegration Times of Tablets prepared Employing meloxicam and its cyclodextrin Complexes

Tablet Formulation	Drug Content (mg/tablet)	Hardness (kg/sq.cm)	Friability (%)	Disintegration Time (min)
MT1	15.51	4.5	0.58	4.0
MT2	15.09	5.5	0.63	4.2
MT3	14.95	5.8	0.72	4.0
MT4	15.02	5.0	0.32	5.0
MT5	14.98	4.5	0.43	7.3
MT6	14.82	5.0	0.52	7.2

Content of Active Ingredient

From each batch ten tablets were weighed, powdered and mixed thoroughly. Four samples of tablet powder, each equivalent to 10 mg drug were weighed accurately and taken in a boiling test tube. Meloxicam present in the tablet powder was extracted with 4 x 10 ml quantities of methanol and extracts were collected into 100 ml volumetric flask. The volume was made up to the mark with

methanol. The solution was subsequently diluted and assayed for meloxicam at 365 nm by the UV spectrophotometric method. The results are given in Table 3.

Dissolution Rate Study

Dissolution rate of meloxicam-CD tablets was studied using an USP XXIII 6 station dissolution rate test apparatus (Electro Lab) with a paddle stirrer. The dissolution rate was studied in 900 ml of phosphate buffer pH 7.4 at a speed of 50 rpm and a temperature of 37 ^{0}C ± 1^0 C. Samples of dissolution medium (5ml) were withdrawn through a filter (0.45µ) at different time intervals, suitably diluted, and assayed for meloxicam at 365 nm. The dissolution medium withdrawn at each sampling time is replaced with fresh drug-free dissolution fluid. The dissolution experiments were conducted in triplicate. The dissolution profiles of various tablets are shown in Table 4 and dissolution plots are shown in Fig I. First order dissolution plots of the tablets are shown in Fig II.

Table 4: Dissolution Profiles of meloxicam Tablets Formulated Employing its Cyclodextrin complexes Prepared by Direct Compression Method (MT1, MT2,MT3) and Wet Granulation Method (MT4, MT5,MT6)

Time (min)	**Percent MELOXICAM Dissolved ($\bar{x}$ ± s.d., n=3)**					
	MT1	**MT2**	**MT3**	**MT4**	**MT5**	**MT6**
5	5.72 ± 0.57	69.62 ± 0.88	20.92 ± 0.3	2.36 ± 0.54	21.4 ± 0.2	10.87 ± 0.82
10	10.26 ±0.76	83.66 ± 0.96	39.23 ± 0.3	3.36 ± 0.75	38.24± 0.4	18.86 ± 0.44
20	15.82± 0.13	95.26 ± 0.55	45.58 ± 0.8	9.79 ± 0.36	52.1 ± 0.8	30.68 ± 0.38
30	30.00± 0.28	100.1 ± 0.89	59.24± 0.2	15.78 ± 0.5	62.4 ± 0.3	53.28 ± 0.85
45	36.31 ± 0.73	-	66.12 ± 0.6	21.01 ± 0.7	79.8 ± 0.5	67.59 ± 0.44
60	41.49 ± 0.84	-	72.50 ± 0.8	32.08 ± 0.9	86.1 ± 0.9	80.7 ± 0.4
90	46.30 ± 0.52	-	84.2 ± 0.77	36.13 ± 0.3	94.4 ± 0.7	92.0± 0.33
120	51.27 ± 0.89	-	92.6 ± 0.33	43.22 ± 0.7	100 ± 0.8	100.08 ± 0.8

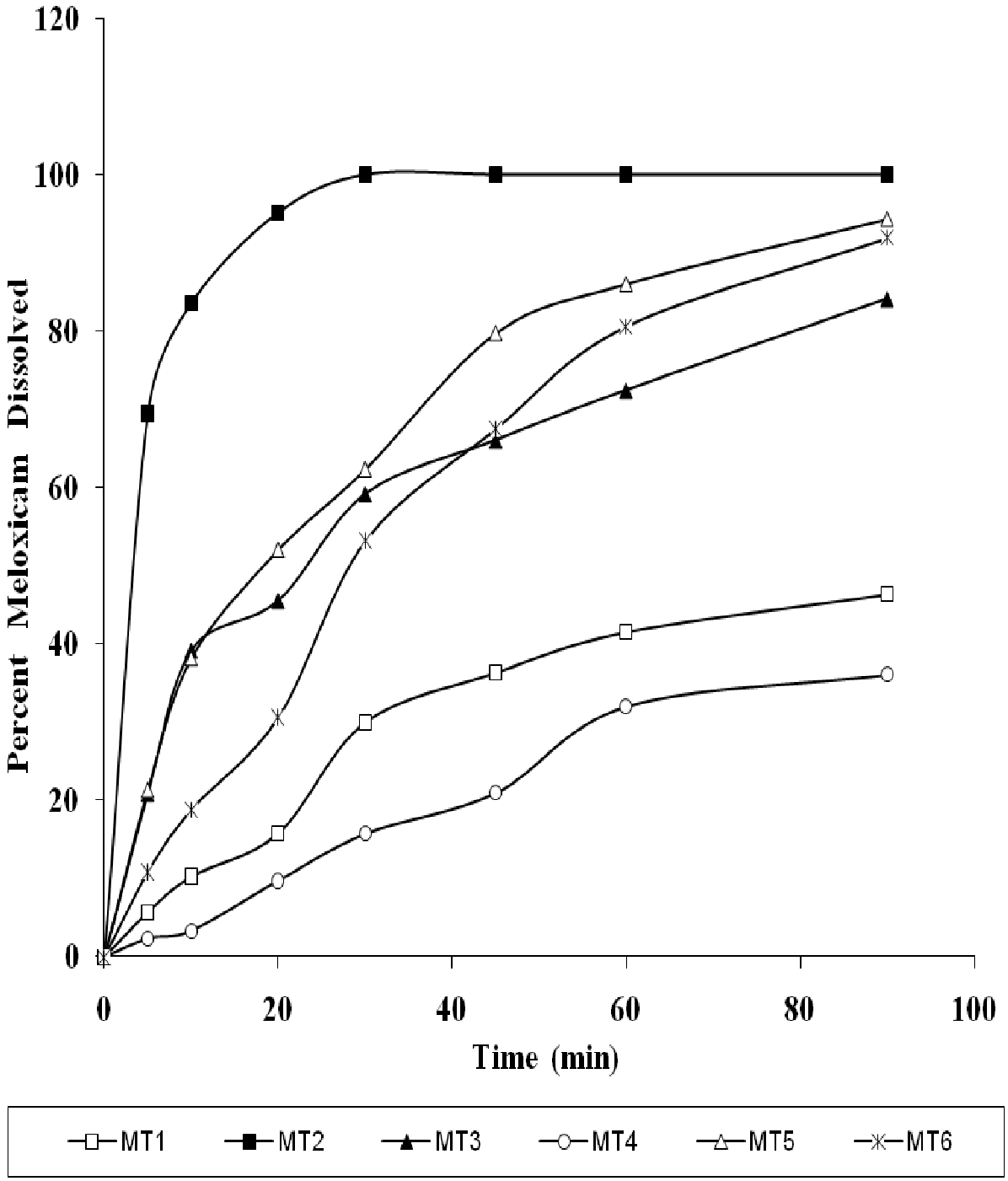

Fig. I: Dissolution profiles of meloxicam Tablets prepared by Direct Compression and Wet Granulation Methods

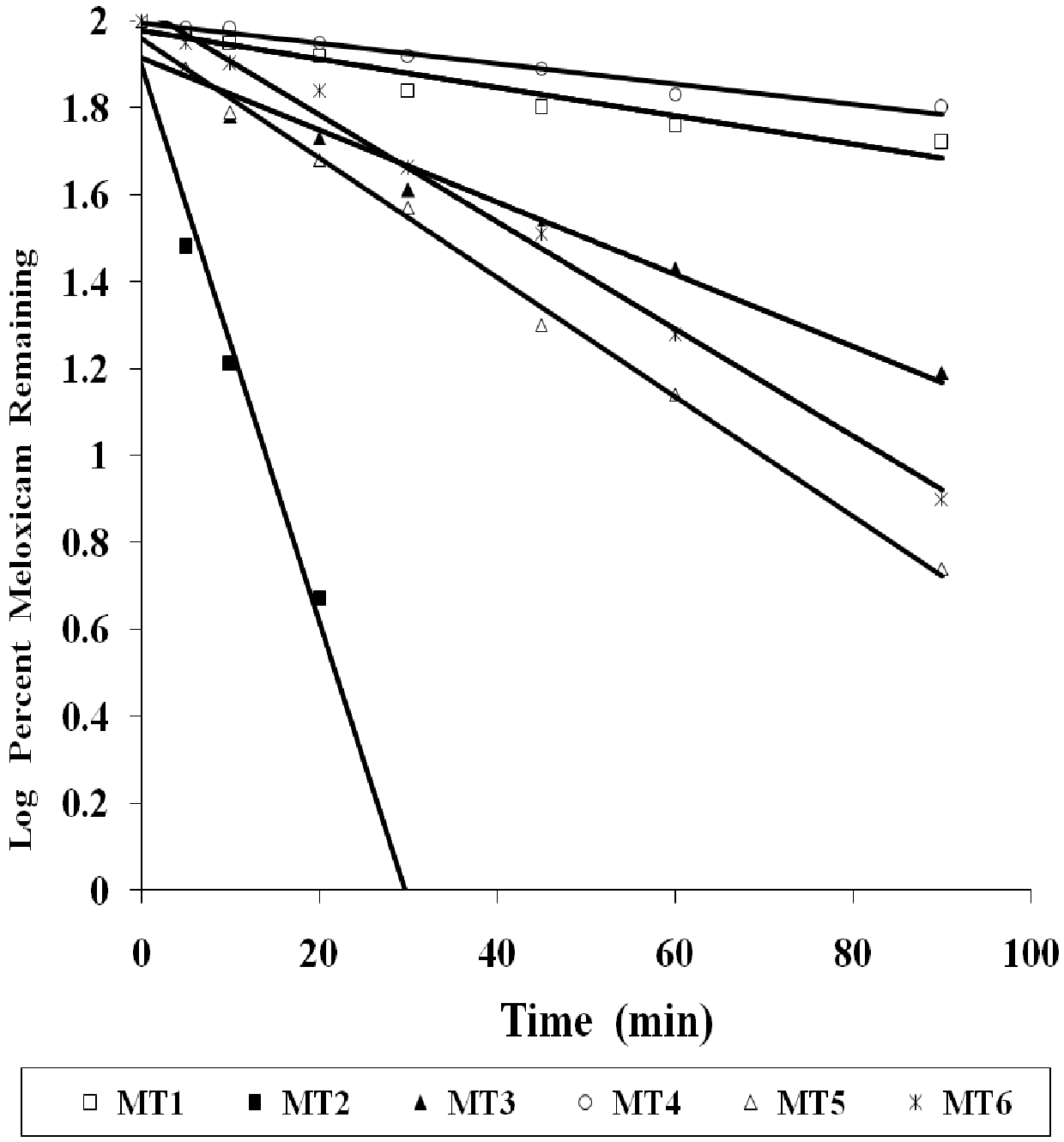

Fig.II: First order dissolution plots of meloxicam Tablets prepared by Direct Compression and Wet Granulation Methods

RESULTS AND DISCUSSION

The dissolution rate and dissolution efficiency of meloxicam could be enhanced several times by the cyclodextrin complexation using kneading method. The inclusion complexes formed are quite stable. A marked increase in the aqueous solubility of meloxicam was obtained by β CD and HP- β CD complexation. β CD complexes prepared by kneading method gave higher enhancement in the dissolution rate of the meloxicam. Tablets prepared by direct compression method disintegrate rapidly when compared to those prepared by wet granulation method. Tablet formulations developed in the present study are quite stable with regard to various physical characters such as hardness, friability, disintegration and dissolution rate. Analysis of dissolution data as per zero-order and first-order kinetic models indicated that the dissolution of meloxicam from all the tablets followed first order kinetics. Co-relation coefficient values (r) are shown in Table 5. In both direct compression and wet granulation methods, tablets formulated employing cyclodextrin complexes (MT2, MT3, MT5, MT6) gave higher rates of dissolution (K_1) and dissolution efficiency (DE_{30}) values when compared to the tablets formulated with meloxicam as such (MT1, MT4). Tablets formulated employing βCD complexes (MT2, MT5) gave higher dissolution than those formulated with HP-βCD complexes (MT3,MT6). The lower dissolution observed with the tablets formulated employing HP-βCD complexes may be due to dry binding nature of HP- β -CD. Among all the meloxicam-CD tablets formulated, formulation MT2 which is based on M-βCD (1:3) kneaded complex, gave highest dissolution rate of meloxicam. A 25.66 fold increase in the dissolution rate of meloxicam was observed with MT2 when compared to formulation MT1. All dissolution parameters (K_1, DE_{30},T_{50},T_{90}) indicated rapid and higher dissolution rates of meloxicam from tablets

formulated employing its cyclodextrin complexes when compared to plain tablets, MT1, MT4 and the values are shown in Table 6.

Table 5 : Correlation Coefficient (r) values in the analysis of Dissolution data of M-CD Tablets as per Zero-order and First-order Kinetics

Formulation	Correlation Coefficient (r)	
	Zero-order	First order
MT1	0.931	0.957
MT2	0.795	0.986
MT3	0.903	0.890
MT4	0.976	0.987
MT5	0.891	0.997
MT6	0.943	0.997

Table 6 : Dissolution Parameters of Tablets Formulated Employing meloxicam and its Cyclodextrin Complexes

Formulation	Dissolution Parameter			
	T_{50} (min)	T_{90} (min)	DE_{30} (%)	K_1 (min^{-1})
MT1	114.55	> 120	15.43	0.012
MT2	3.52	18	82.29	0.308
MT3	19.91	112	40.02	0.029
MT4	> 120	> 120	8.15	0.006
MT5	13.95	83	42.94	0.032
MT6	28.03	86	28.5	0.026

CONCLUSIONS

Among the two cyclodextrins, βCD complexes were found to be more suitable for tablet formulation by both direct compression and wet granulation methods.

Thus, cyclodextrin complexation employing kneading method is recommended as an effective and efficient technique for enhancing the dissolution rate, dissolution efficiency of meloxicam.

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