FORMULATION AND EVALUATION OF MOUTH DISSOLVING TABLET OF MELOXICAM HAVING IMPROVED SOLUBILITY

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ABSTRACT

Meloxicam is an anti-inflammatory drug used in osteoarthritis, primary dysmenorrhoea, acute pain and dental pains. The major problem of meloxicam is its very low solubility in biological fluids. The current aim of our work was to prepare meloxicam loaded solid dispersion using β-cyclodextrin and various grades of PEG which were further compressed into tablets as such fast release tablets are more essential in severe pains. Tablet with drug: polymer of ratio 1:2 yielded best results in terms of dissolution rate. Optimized mouth dispersing tablets of meloxicam were prepared after complexation of meloxicam with β-CD. Dissolution of meloxicam from the tested formulations was fast, which can probably be attributed to its complexation with β-CD. Furthermore, using β-CD facilitated the pharmaceutical preparation of the tablets. In particular, it enhances the compression behavior since it has contributed to good mechanical properties of the tablets when employed in the direct compression technique.

Keywords: Meloxicam, superdisintegrants, solid dispersion, cyclodextrin

INTRODUCTION

Drugs are more frequently taken by oral administration. Although a few drugs taken orally are intended to be dissolved within the mouth, the vast majority of drugs taken orally are swallowed[1]. Immediate release tablet are very quickly after administration. Basic approach used in development is the use of superdisintegrants which provide rapid disintegration of tablet after administration.[2] Fast disintegrating tablets are gaining prominence as new drug delivery system. These dosage forms dissolve or disintegrate in the oral cavity within a minute without the need of water or chewing.[3]

The center for drug evaluation and research (CDER), US FDA defined oral disintegrating tablets (ODT) as "a solid dosage form containing medicinal substances, which disintegrates rapidly, usually within a matter of seconds, when placed upon the tongue." A fast-dissolving drug delivery system, in most cases, is a tablet that dissolves or disintegrates in the oral cavity without the need of water or chewing. These are also called melt-in-mouth tablets; rapid melts porous tablets, oro-dispersible, quick dissolving or rapid disintegrating tablets[4-6].

In this research, meloxicam (COX-2 inhibitor) is chosen as a drug candidate, which is widely prescribed in the elderly patients for osteoarthritis and dental pain. Drug is insoluble in water hence delay the absorption and onset of action. Hence it was felt to formulate this drug into mouth dissolving film. The present work aims to formulate and evaluate the mouth dissolving tablet-containing meloxicam with improved solubility using solid dispersion technique. The term solid dispersion refers to a group of solid products consisting of at least two different components: A hydrophilic matrix and a hydrophobic drug. The matrix can be either crystalline or amorphous. The drug can be dispersed molecularly, in amorphous particles (clusters) or in crystalline particles. In solid dispersion a poorly soluble drug is dispersed in a highly soluble solid hydrophilic matrix, which enhances the dissolution of the drug which can yield eutectic (non-molecular level mixing) or solid solution (molecular level mixing) products[7].

MATERIALS AND METHODOLOGY

Meloxicam was obtained as a gift sample from PIL, Haridwar. All the other chemicals and polymers used in the study were of analytical grade.

Characterization of Meloxicam

The drug meloxicam and excipients were characterized for their orgenoleptic properties, melting point, spectral analysis and solubility. Spectral analysis of drug was performed in phosphate buffer pH 7.4 at

λmax of 362.5 nm. Solubility of drug was determined in various solvents such as distilled water, PBS pH 7.4 and 0.1N NaOH[8].

Preparation of Meloxicam Solid Dispersion

A) Melting Method: Drug and carrier were mixed using mortar and pestle to accomplish a homogenous dispersion the mixture was heated at or above the melting point of the entire component. It was then cooled to acquire congealed mass. It was crushed and sieved through sieve no. 80 and stored in the desiccators until its further use. Following drug polymer ratio was used for solid dispersion.

Table 1: Batches of Solid Dispersion (Drug: Polymer)

S. No.	Polymer	Meloxicam : Polymer Ratio		
		I	II	III
1	PEG-4000	1:2	1:4	1:9
2	PEG-6000	1:2	1:4	1:9
3	PEG-8000	1:2	1:4	1:9

Complexation Method: ***Kneading Method-*** Meloxicam with polymer β – cyclodextrin in different ratios (1:2, 1:4 and 1:9) is added to the mortar and triturated with small quantity of Hydroalcoholic solution (water and etanol in 1:1) to prepare a slurry. Slowly the drug is incorporated into the slurry with constant trituration. The prepared slurry is then air dried at 25^0C for 24hrs. The resultant product is pulverized and passed through sieve no. 80 and stored in dessicator.

Table 2: Batches of Solid Dispersion (Drug: Polymer)

S. No.	Polymer	Meloxicam : Polymer Ratio		
		I	II	III
1	β – cyclodextrin	1:2	1:4	1:9

EVALUATION OF SOLID DISPERSION

Saturation solubility of Meloxicam solid dispersion

The saturation solubility of Meloxicam were checked in surfactants and co surfactants like PEG 4000, PEG 6000, PEG 8000, 0.1N NaOH, PBS pH-7.4 . The solid dispersion will be added in small increments with stirring until saturation level exists. The flask will be kept at 37°C/100 rpm in orbital

shaker for 48 hrs. After that above mixture was kept in centrifuge machine for centrifugation process at 1500 rpm for 20min.the supernatant liquid was removed and dilute with phosphate buffer pH-7.4 and absorbance was checked at 362.5 nm.

Dissolution study of meloxicam solid dispersion: The dissolution study of meloxicam Solid dispersion was done in Six station USP Type II Dissolution Testing Apparatus (Paddle) at 50 rpm in phosphate buffer pH-7.4 at 37°C ± 0.5°C and samples were analysed at λmax of 362.5 nm

Pre-compressional Parameters

Bulk Density (D_b): It is the ratio of total mass of powder to the bulk volume of powder. It was measured by pouring the weighed powder (passed through standard sieve # 20) into a measuring cylinder and the initial volume was noted. This initial volume is called the bulk volume. From this, the bulk density is calculated according to the formula mentioned below. It expressed in g/cc and is given by $Db = M/ V_{b;}$ Where M is the mass of powder and V_b is the bulk volume of the powder[10].

Tapped Density (D_t): It is the ratio of total mass of the powder to the tapped volume of the powder. Volume was measured by tapping the powder for specified times and the tapped volume was noted in a tapped density apparatus. It is expressed in g/ml and is given by Dt = M / Vt; Where M is the mass of powder Vt is the tapped volume of the powder.

Compressibilty index: It indicates powder flow properties. It is expressed in percentage and is given as I= (Dt- Db/Dt)*100

Hausner's ratio: Hausner's ratio is an indirect index of ease of powder flow. It is calculated by the following formula Dt/Db; where, Dt is the tapped density and Db is the bulk density. Lower hausner's ratio (<1.25) indicates better flow properties than higher ones (>1.25).

Angle of Repose (θ): Angle of repose was determined by using funnel method. The accurately weighed blend was taken in a funnel. The blend was poured through funnel .The diameter and height of the powder cone was measured and angle of repose was calculated using the equation, tan θ=h/r, where h and r are the height and radius of the powder cone.

Preparation of mouth dispersing tablet of meloxicam[11]: All the materials were passed through 60 # screens prior to mixing. Meloxicam Solid dispersion, sodium starch glycolate, mannitol, talc, magnesium stearate, menthol were mixed using a glass mortar and pestle. All the materials were

directly compressible so this uniformly mixed blend was compressed into tablets using concave face round tooling on a 12-station rotary tablet machine[10].

Table 3: Batches of Tablet Formulation

Ingredient (in mg)	**T1**	**T2**	**T3**	**T4**
Meloxicam S .D.	22.5	22.5	22.5	22.5
Menthol	-	12	6	12
Sodium starch glycolate	12	6	12	12
Magnesium stearate	1.2	1.2	1.2	1.2
Talc	1.2	1.2	1.2	1.2
D-Mannitol	q.s.	q.s.	q.s.	q.s.

Post compression parameters

Weight variation test: Weight variation test was done by weighing 20 tablets individually, by using analytical balance. Calculating the average weight and comparing the individual tablet weight to the average weight.

Tablet thickness: The thickness was measured by placing tablet between two arms of the Varnier calipers. 5 tablets were taken and their thickness was measured.

Tablet hardness: The tablet hardness, which is the force required to break a tablet in a diametric compression force. The hardness tester used in the study was Monsanto hardness tester, which applies force to the tablet diametrically with the help of an inbuilt spring.

Tablet friability: The friability of the tablets was measured in a Roche friabilator. Tablets of a known weight (W_o) or a sample of 20 tablets are placed in a drum for a fixed time (100 revolutions) and weighed (W) again. Percentage friability was calculated by the ratio of loss in weight to initial weight. The weight loss should not be more than 1 %. Determination was made in triplicate.

Wetting time: The wetting time of the tablets was measured by using a simple procedure. Five circular tissue papers of 10 cm diameter was placed in a Petridish with a 10 cm diameter. Ten millimeters of water- containing Eosin, a water-soluble dye, was added to Petridish. A tablet was carefully placed on the surface of the tissue papers. The time required for water to reach upper surface of the tablet was noted as a wetting time.

Water absorption ratio (%): A piece of tissue paper folded twice was placed in a small petridish (Internal Diameter = 6.5 cm) containing 6 ml of water. A tablet was placed on the paper and the time required for complete wetting was then measured. The water absorption ratio (R) was determined using the equation, R = 100 (Wa -Wb) / Wb; Where Wb is the weight of the tablet before water absorption and Wa is the weight of the tablet after water absorption.

***In-vitro* disintegration test:** The test was carried out on 6 tablets using Tablet disintegration tester, distilled water at 37ºC ± 2ºC was used as a disintegration media and the time in second taken for complete disintegration was measured in seconds.

***In-vitro* dissolution study:** The release rate of Meloxicam from mouth dispersing tablets was determined using United State Pharmacopoeia (USP) dissolution testing apparatus II (paddle method). The dissolution test was performed using 900 ml of phosphate buffer pH 7.4 as a dissolution medium, at 37±0.5^{0}C and 50 rpm. A sample (1 ml) of the solution was withdrawn from the dissolution apparatus at 15, 30, 45, 60, 75, 90, 105, 120 min The samples were filtered through a whatman filter paper. Absorbance of these solutions was measured at 362.5 nm using a UV spectrophotometer. Cumulative percentage of drug release was calculated using an equation obtained from a standard curve.

Drug Content: Three tablets from each batch (T1, T2, T3 and T4) were weighed and powdered separately. An Amount of powder equivalent to 7.5 mg of Meloxicam was dissolved in 100 ml of pH 7.4 phosphate buffer, filtered, diluted suitably and analyzed for drug content at 362.5 nm using a UV spectrophotometer.

Drug release kinetic studies: *In vitro* release data obtained was analyzed using various kinetic models to describe the mode of drug release from the developed formulations.

Results and Discussion

Characterization of meloxicam

Description:-Meloxicam is a pastel yellow solid, practically insoluble in water, with higher solubility observed in strong acids and bases. It is very slightly soluble in methanol.

Melting point-: Melting point of Meloxicam was found to be 252^{0}C – 254^{0}C.

Spectroscopic Study: IR Spectra of Meoxicam was obtained as shown in figure 1.

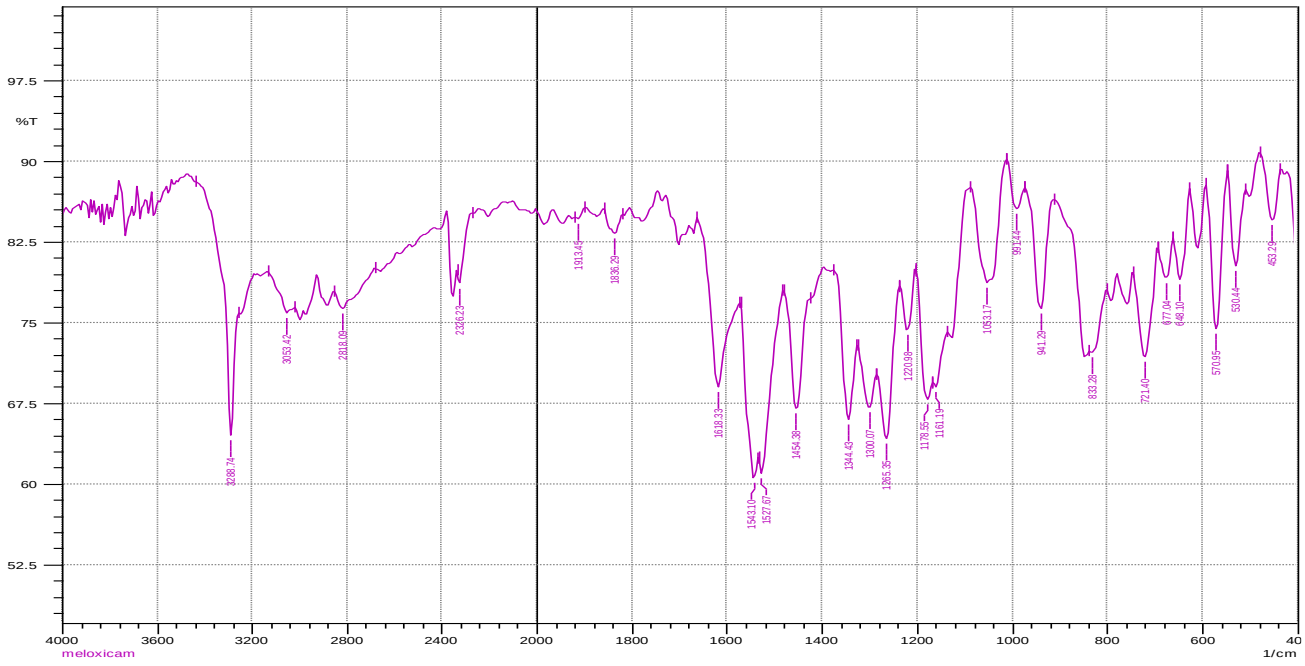

Figure 1: IR spectra of meloxicam

UV Spectrophotometric Analysis

λ max of the procured sample of the Meloxicam was observed at the 262.5nm. Standard curve of the drug was prepared at the observed λ max.

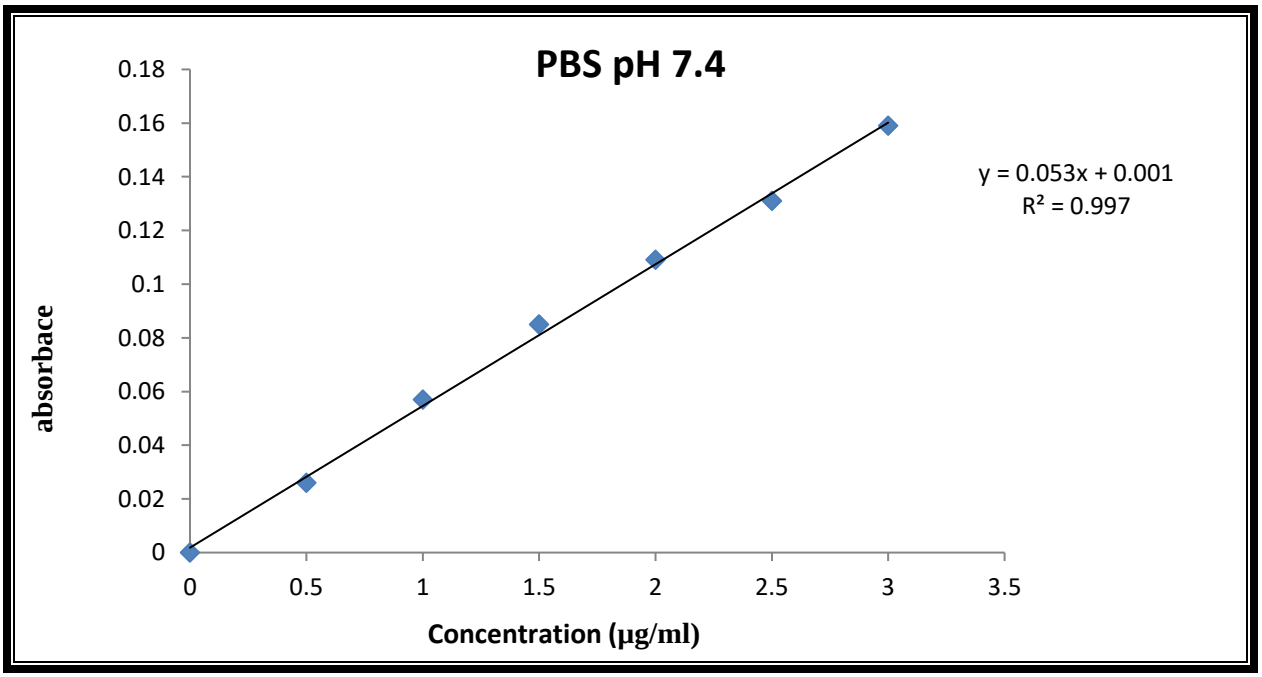

Figure 2: Standard curve of meloxicam in phosphate buffer pH 7.4

Saturation solubility of pure meloxicam: Saturation solubility of pure meloxicam in various solvents is as given in table 4.

Table 4: Saturation solubility of pure meloxicam

S. No.	Solvent	Solubility (mg/ml)
1	0.1 N NaOH	60.2
2	PBS pH 7.4	8.5
3	Distilled water	7.4

Evaluation of Solid Dispersion

Saturation solubility of meloxicam solid dispersions: As shown in table 5, It was found that the Solid Dispersions prepared from β – cyclodextrin showed marked increase in solubility than those with PEG.

Table 5: Saturation solubility of solid dispersion

S. No	Solid dispersion		Solubility ± SD (mg/ml)	
	PEG-4000		**PBS pH-7.4**	**0.1 N NaOH**
1	1:2	X	30.43±0.60	61.42±0.95
	1:4	Y	31.20±0.86	58.91±0.92
	1:9	Z	36.2±0.55	59.18±0.73
2	**PEG-6000**			
	1:2	X	49.01±0.43	66.30±0.42
	1:4	Y	44.47±0.40	59.92±0.42
	1:9	Z	39.77±0.60	66.29±0.45
3	**PEG-8000**			
	1:2	X	27.04±0.16	50.59±0.54
	1:4	Y	44.47±6.16	65.56±0.51
	1:9	Z	42.09±0.62	44.82±0.76
4	**β – cyclodextrin**			
	1:2	X	61.31±0.75	74.35±0.55
	1:4	Y	40.78±0.75	62.18±0.40
	1:9	Z	60.22±0.68	56.6±0.52

Dissolution study (% Drug release): Dissolution profile of formulation SD1 – SD12 is given in table 6,7 and shown in figure 3 & 4. After performing dissolution study of all the batches of solid dispersion it was concluded that SD10 gives good dissolution rate of upto 93% drug release after 120 minutes as compared to other batches of solid dispersion[12,13]**.**

Table 6: Percent drug release of dissolution profile of meloxicam (SD1 to SD6)

Time point (min)	SD1±SD	SD2±SD	SD3±SD	SD4±SD	SD5±SD	SD6±SD
0	0	0	0	0	0	0
15	54.70±2.0	50.08±0.2	57.01±0.8	77.78±0.8	75.47±2.1	66.24±3.5
30	66.09±3.2	47.72±3.0	59.25±1.5	79.99±5.9	77.67±1.2	70.77±4.6
45	68.32±1.2	59.12±2.0	59.18±3.5	73.00±4.1	79.91±3.4	70.70±1.8
60	63.65±1.1	61.35±3.2	63.72±3.8	75.22±3.1	79.82±2.6	72.92±0.9
75	63.57±1.0	65.87±5.2	65.94±4.2	79.73±4.1	84.32±2.6	88.92±3.6
90	63.57±3.0	54.58±0.9	58.99±2.9	79.64±1.6	81.93±1.6	75.20±0.8
105	70.38±0.9	63.50±1.6	61.21±1.4	79.55±3.6	79.55±2.4	79.55±2.9

Table 7: Percent drug release of dissolution profile of meloxicam (SD7 to SD12)

Time point (min)	SD7±SD	SD8±SD	SD9±SD	SD10±SD	SD11±SD	SD12±SD
0	0	0	0	0	0	0
15	49.85±0.8	52.39±0.4	63.93±5.1	87.01±1.5	75.47±2.5	58.93±2.5
30	50.03±1.2	63.86±1.5	75.38±2.5	89.21±3.2	79.99±2.3	70.77±2.4
45	52.28±4.5	59.18±2.8	68.39±3.1	93.72±2.5	86.81±1.9	73.00±1.5
60	49.92±1.5	75.22±3.6	68.32±2.5	91.32±1.5	75.22±1.6	75.22±0.9
75	52.16±4.5	75.13±2.4	63.65±2.3	88.73±1.4	82.02±0.6	79.73±1.5
90	56.69±1.9	68.16±2.0	70.46±0.9	88.82±0.8	77.34±0.4	75.05±1.8
105	61.21±0.5	54.33±0.3	65.8±1.5	93.30±4.0	74.96±1.5	72.67±3.2
120	58.85±3.2	74.88±3.4	74.88±0.4	93.20±1.4	86.33±3.4	79.46±0.5

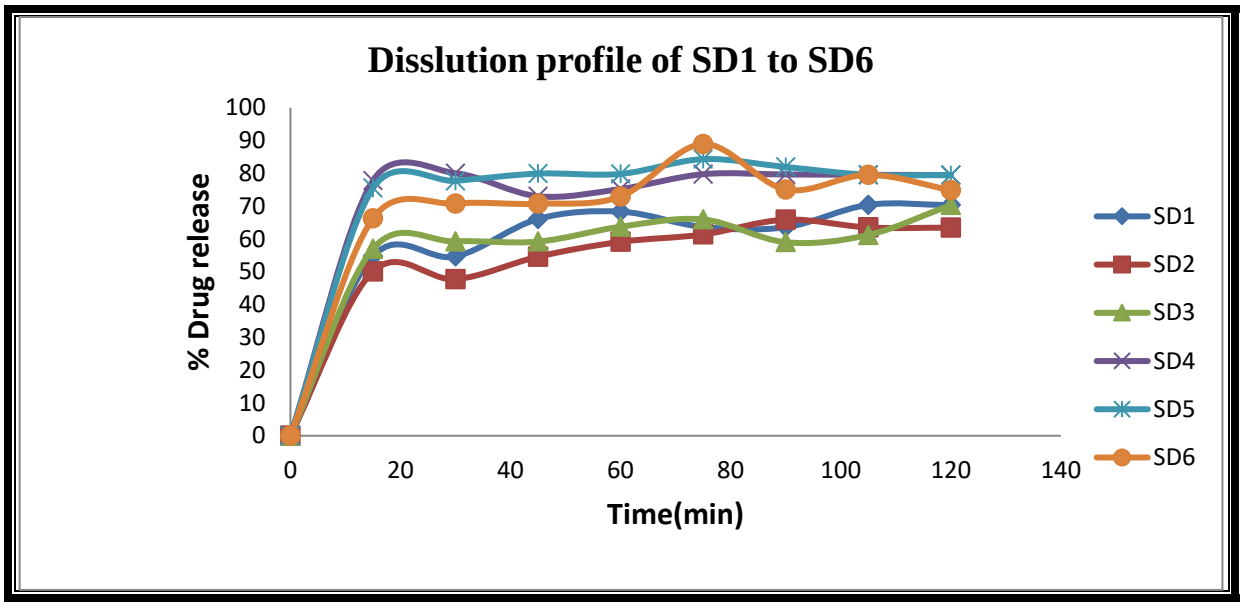

Figure 3: Dissolution profile of SD1- SD6

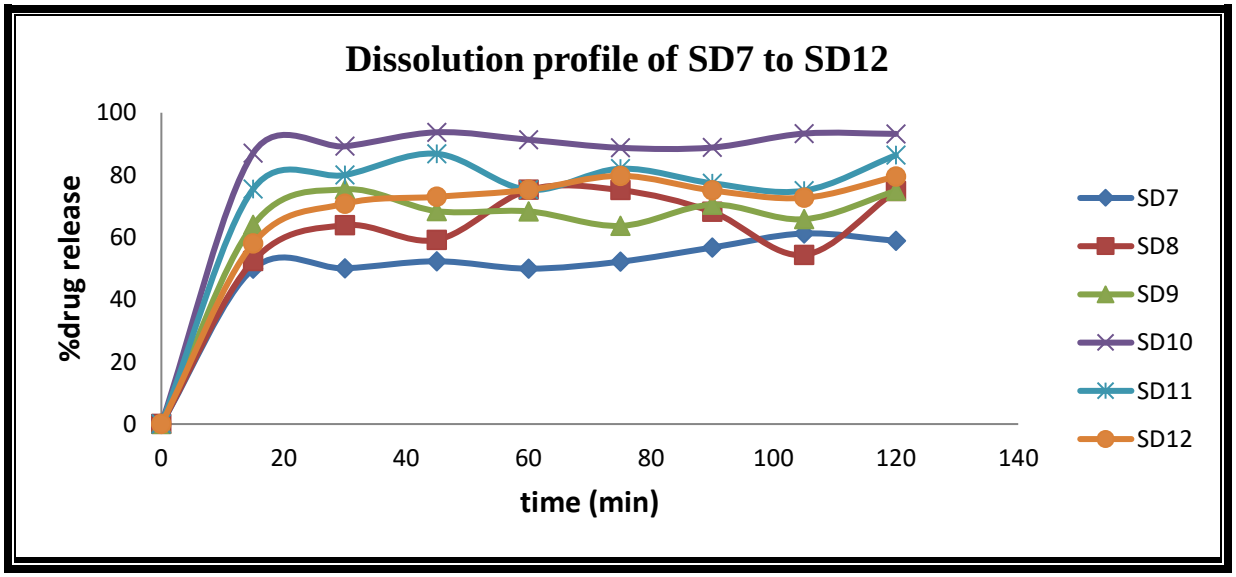

Figure 4: Dissolution Study of SD7 – SD12

Pre-Compression Parameters: Angle of repose was nearly same for all the formulations and was less than 25º which indicates less interparticle friction between the microparticles and their high potential to flow. Carr's index and Hausner's ratio were calculated for all the formulations where the Carr's index value showed that the formulation T4 had Fair Passable flow properties while T1, T2 and T3 showed the poor flow ability. The result for the pre compression parameters is given in table no 7.

Table 8: Pre compression parameters

Formulation	Angle of repose(θ) (±SD)	Compressibility (%) (±SD)	Hausner's Ratio (±SD)
T1	24.21 ±3.52	29.57 ±0.060	1.32 ±0.05
T2	23.70 ±0.28	23.80 ±1.34	1.31 ±0.02
T3	22.49 ±1.12	23.60 ±2.60	1.35 ±0.04
T4	23.53±0.15	24.45±1.07	1.21±0.02

Post-Compression parameters: Tablet thickness was almost uniform in all the formulations. The thickness varies between 3.48±0.05 to 3.65± 0.05mm. The prepared tablets in all the formulations possessed good mechanical strength with the sufficient hardness in the range of 3.45±0.23 to 3.55±0.15 kg/sq cm. Friability values lied below 1% were an indicate good mechanical resistance. Formulation T4 showed the less friable than other. All the tablets passed the weight variation test and was within the pharmacopoeial limits of ±7.5 of the weight variation was found between 149.25 to 150.47 which was in pharmacopoeial limit. The drug content of all formulation was found between 99.37±1.55 to 101.15±1.50 of meloxicam which was within the limits. The wetting time was performed for all the formulation. The values lie between 50 to 60 sec. *In vitro* dispersion time for all formulations varied between 32 to 64 sec. The result of water absorption ratio (%) and *in vitro* disintegration time(sec) lied between (27 to 52) and (42 to 50), respectively. The result for the post compression parameters is given in table 9.

Table 9: Post compression parameter

Batches	Hardness Test (kg/cm^2) ±SD	Weight Variation (mg)	Friability (%) ±SD	Thickness (mm) ±SD	Disinte-gration Time (sec) ±SD	Water Absorption Ratio	*In-vitro* dispersion time (sec)	Wetting time (sec) ±SD	Drug content (%)±SD
T1	3.55±0.10	150.38	0.29±0.04	3.65±0.05	48±2.00	30	64	52±3.75	100.15±2.20
T2	3.55±0.15	149.71	0.30±0.04	3.48±0.05	42±3.44	27	52	50 ±2.20	101.15±1.50
T3	3.50±0.20	149.25	0.32±0.02	3.50±0.06	50±2.90	38	44	60±2.50	99.37±1.55
T4	3.45±0.23	150.47	0.28±0.03	3.52±0.05	41±2.41	52	32	52±3.75	100.15±2.20

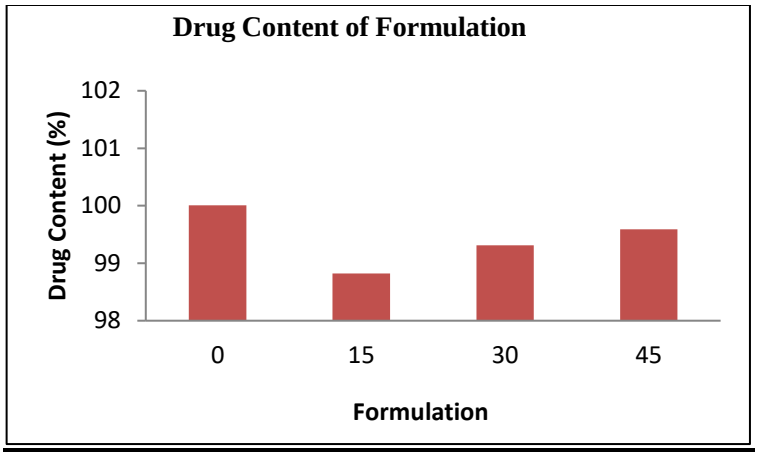

Figure 5: Drug content (%) of the formulation T1-T4

***In-vitro* dissolution study (%drug release):** *In vitro* drug dissolution data obtained for the different formulations was analyzed (Table 10) by using various mathematical drug release kinetic models such as zero order, first order, Higuchi release kinetics and Korsmeyer-Peppas release kinetics to ascertain the mechanism of drug release from the prepared mouth dispersible tablets of meloxicam.

Table 10: Dissolution profile of tablet T1, T2, T3 and T4

Time min	Average % Drug release			
	T1	T2	T3	T4
0	0	0	0	0
15	45.19 ± 2.9	35.90 ± 3.7	39.00 ± 3.2	79.31±2.8
30	55.70 ± 1.7	39.94 ± 2.7	42.40 ± 1.9	83.83±1.4
45	58.61 ± 2.5	46.96 ± 1.8	48.64 ± 1.5	89.11±2.6
60	60.87 ± 3.1	50.37 ± 4.2	54.12 ± 3.2	86.72±1.7
75	62.10 ± 2.3	53.00 ± 1.9	57.41 ± 2.6	90.44±1.3
90	62.81 ± 1.5	66.62 ± 0.7	60.31 ± 3.2	93.41±1.7
105	73.47 ± 2.7	56.49 ± 0.9	62.70 ± 1.6	92.53±1.3
120	75.61 ± 3.1	59.14 ± 1.9	65.35 ± 1.9	93.96± 1.3

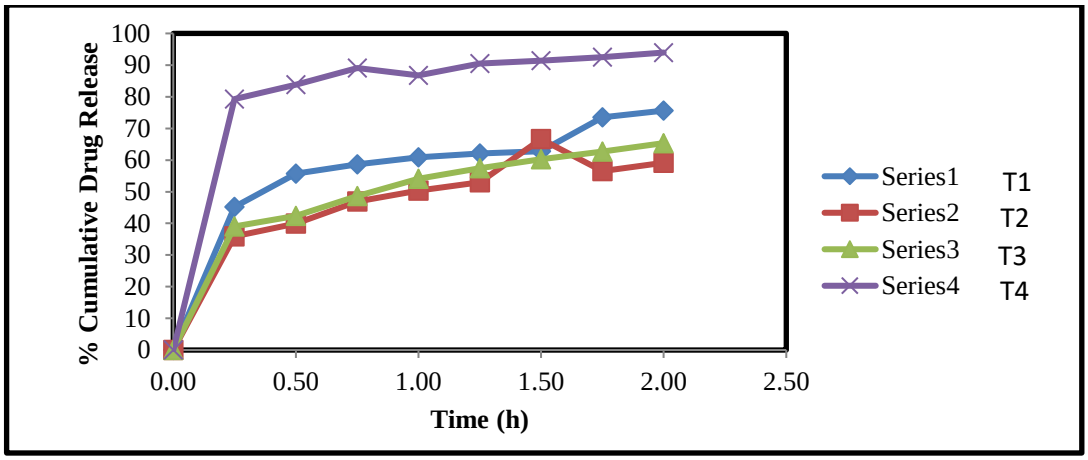

Figure 6: Zero order release kinetics

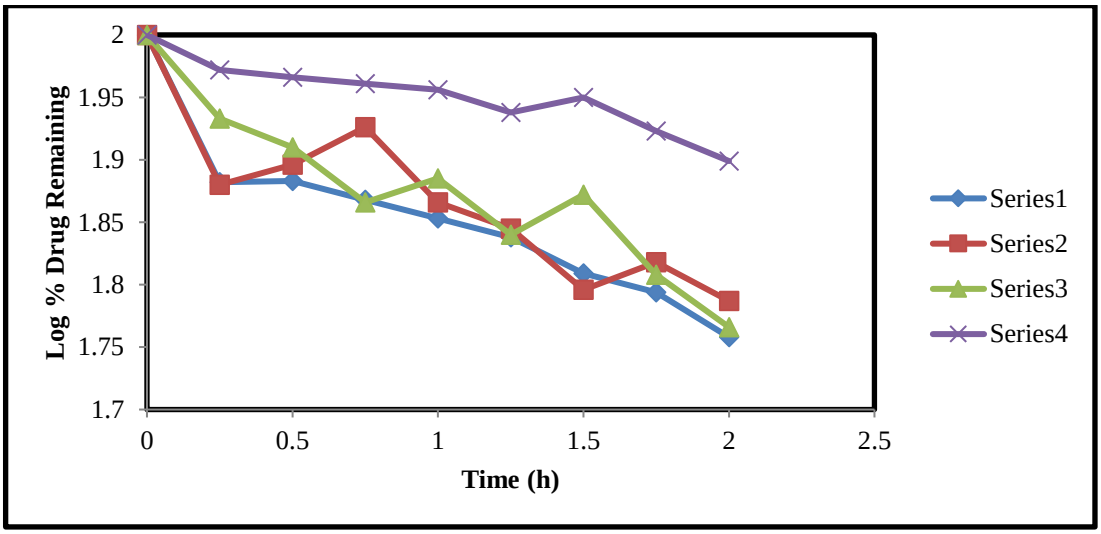

Figure 7: First order release kinetics

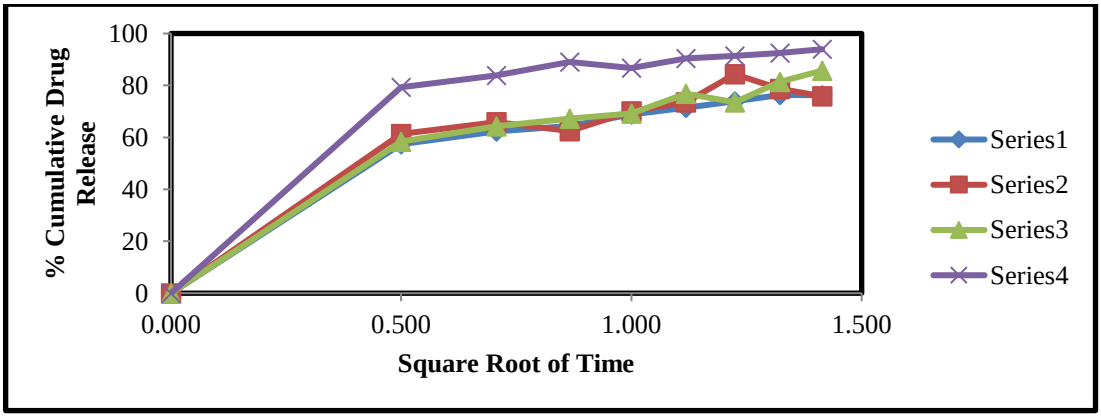

Figure 8: Higuchi release kinetics

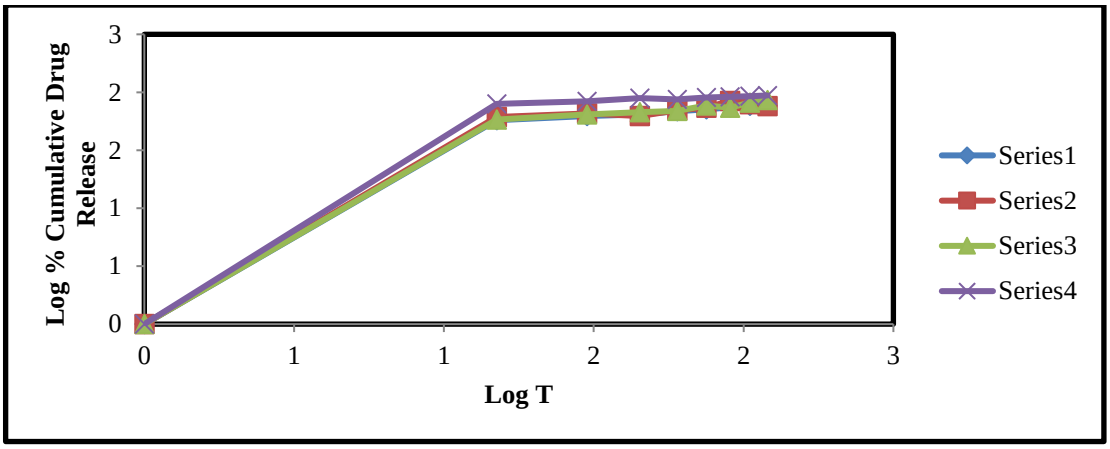

Figure 9: Korsmeyer – Peppas release kinetics release kinetics

Drug release mechanism table of all the mouth dispersible tablets of the Meloxicam (T1 to T4)

Table 11: Drug release mechanism table of all the mouth dispersible tablets of the meloxicam (T1 to T4)

Formulations	Zero Order release	First Order Release	Higuchi release Kinetics	Korsmeyer Peppas release		Best fit model	Release mechanism
	R^2	R^2	R^2	R^2	n value		
T1	0.675	0.866	0.819	0.857	0.873	First Order	Non Fickian
T2	0.704	0.794	0.792	0.852	0.879	First Order	Non Fickian
T3	0.738	0.875	0.854	0.865	0.887	First Order	Non Fickian
T4	0.437	0.894	0.711	0.833	0.911	First Order	Supercase II

In all Formulations T1, T2, T3 and T4 first order release kinetics model was found to be best fit model. The n value obtained from the Korsmeyer Peppas kinetics model or curve is known as the release exponent and is indicate the mechanism of drug release. The value of n for all the formulations T1 , T2 and T3 lies in between the 0.45 to 0.89 which indicate that the release mechanism was non Fickian or anomalous transport mechanism which means both diffusion and erosion mechanism are involved in drug release process. And the value of n for formulation T4 found higher than 0.89 which indicate that the release mechanism was Supercase II which is a hypothetical mechanism of the drug.

CONCLUSION

After preparation of meloxicam solid dispersion by using different drug and polymer concentration the solubility of the drug is increased as compared to solubility of pure drug. β-cyclodextrin complexes indicated more solublization of Meloxicam than PEG-4000 PEG-6000 PEG-8000. Saturation solubility of solid dispersion and inclusion complexes of meloxicam showed improved solubility and dissolution rate. Thus β-cyclodextrin can be used to increase the solubility of other less soluble drugs by complex formation.

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