DEVELOPMENT OF MELOXICAM FORMULATIONS UTILIZING TERNARY COMPLEXATION FOR SOLUBILITY ENHANCEMENT

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ABSTRACT

Meloxicam (an oxicam derivative), a relatively new cyclo-oxygenase inhibitor, is a member of enolic acid group of non-steroidal anti-inflammatory drugs. It is generally used in the treatment of rheumatoid arthritis, osteoarthritis and other joint pains. Meloxicam is practically insoluble in water (8µg/ml), which directly influences the $C_{max,}$ T_{max}, as well as the bioavailability of the drug. In the present study, an attempt has been made to improve the dissolution of Meloxicam by preparation of its solid dispersion using β-cyclodextrin blended with various water soluble polymer carriers i.e., HPMC (methocel IH), methylcellulose (400cps), PVP K30, HPMC (K_4M), HPMC (50cps). It is reported that when small amount of water soluble polymer is added to β-cyclodextrin, its nature of solubilization significantly increases due to increase in the apparent complex stability constant. Phase solubility studies were carried out to evaluate the solubilizing power of β-cyclodextrin along with various water soluble polymers. The solid dispersion was prepared and formulated into tablets and suspension, which were evaluated on the basis of various official tests. All the studies suggest that formulations of Meloxicam utilizing solid dispersion technique significantly enhances solubility (90 µg/ml**)** of the drug and results in superior formulations of the drug by using β-cyclodextrin blended with 0.12% w/w HPMC (Methocel IH). Ternary complexation is a valuable tool for solubility enhancement of drugs.

Keywords: Solid dispersion, solubilization, β-cyclodextrin, phase solubility

INTRODUCTION

Cyclodextrins and their derivatives play an important role in improving the therapeutic efficacy of drugs with poor solubility and/or stability problems (Ahuja *et al*., 2005). They are capable of alleviating the undesirable properties of drug molecules through the formation of inclusion complexes. However, the exploitation of cyclodextrin in the pharmaceutical area is hindered by problems such as high molecular mass, rather high cost and potential parenteral toxicity. Strengthening the complexation and solubilization efficacy of cyclodextrin is a possible tool to reduce their amount in pharmaceutical formulations. Among the strategies proposed toward this aim is the addition of suitable auxiliary substances, which can be a valuable approach to increase cyclodextrin solubilizing capacity by multi-component complex formation (Rangasamy *et al*., 2008).

It has been reported that, addition of some water soluble polymers can strongly enhance the cyclodextrin solubilizing power towards basic drugs, as a result of the combined effect of salt formation and inclusion complexation (Chawla *et al.,* 2008 and Cirri *et al.,* 2004). For instance, the addition of small amounts of polyvinyl pyrrolidone (PVP) to the Naproxen-HPβ-CD system improved the complexing and solubilizing efficiencies of HPβ-CD. Likewise, solubilization and dissolution of Glyburide, Celecoxib and so on with HPβ-CD also increased in the presence of hydrophilic polymers (Cirri *et al.,* 2009, Quan *et al.,* 2009, Inamdar *et al.,* 2008, Gurusamy *et al*., 2006).

Meloxicam (MC), (4-hydroxy-2-methyl-*N*-_5-methyl-2-thiazolyl_-*H*-1, 2 benzothiazine-3-caboxamide 1, 1-dioxide), is a potent non-steroidal anti-inflammatory drug. It is practically insoluble in water (8µg/ml) (Luger *et al*., 1996). Its poor solubility and wettability leads to difficulties in formulating oral and parenteral formulations resulting in variations in bioavailability. Work has been done on binary system of MC/β-CD (Baboota *et al.,* 2002, Naidu *et al.* 2004). Analysis of phase solubility diagrams indicated that β- and HP-β-CD form 1:2 MC/β-CD type complexes with MC while α- and γ-CD form only 1:1 complexes. The fact that the overall 1:2 MC/β-CD type complex formation constant was found significantly higher for β-CD than for HP-β-CD, combined with further spectroscopic studies, indicate that β-CD favors inclusion of the neutral enol form over the zwitterions (Abdoh *et al.,* 2007). Molecular modeling was also used to investigate the interaction between MC and β-CD. The dominant driving force for the complexation was evidently Van der Waals force with very little electrostatic contribution (Obaidat *et al.,* 2009).

The present work was aimed at investigating the role of various water soluble polymers along with β-cyclodextrin in improving the dissolution properties of MC and its bioavailability.

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MATERIAL AND METHODS

Materials

Meloxicam was supplied as gift sample by Sun Pharma. (Gujarat), HPMC (K4M), HPMC (Methocel, IH) and PVP K30 were obtained from "The Dow Chemical Company, Midland, MI USA" and HPMC (50cPs) purchased from S.D. Fine Chem. Ltd., Mumbai. Other chemicals used were of analytical grade.

Phase solubility studies

Excess amount of Meloxicam (50 mg) was added to 10 ml of phosphate buffer solution containing increasing amount of the polymer (0.05, 0.12, 0.25% w/w respectively) which was HPMC (Methocel IH) in sealed glass containers. Suspensions were vigorously stirred at 37 ± 0.5°C for two days. When equilibrium was reached (2 days), samples were filtered through a polycarbonate membrane (0.45µm, Millipore, Billerica, MA) and suitably diluted. Samples were analyzed spectro-photometrically at 354 nm (UV-1700, Shimadzu, Japan). Drug content was calculated from the standard curve of Meloxicam and the polymer ratio was optimized at 0.12% w/w for purpose of comparison. HPMC (K4M), HPMC (Methocel, IH), PVP K30 and HPMC (50cPs) were each taken in a concentration of 0.12% w/w for incorporation into 8 gm of β-CD and similar study repeated for phase solubility studies (table 1).

Phase solubility diagrams were plotted, and the apparent stability constants (Kc) were calculated according to the following formula:

$$Kc = \alpha/Sm\ (1-\alpha)$$

Where 'Sm' represents the solubility of Meloxicam and 'α' represents the slope of straight line (El-Maradny *et al*., 2008).

Phase solubility graph of the drug with different polymers inclusion complexes has been shown in fig. 1, where phase solubility profile of Meloxicam is shown as a function of increasing concentration of the polymer. The pH dependent solubility profile of the drug was used for further optimization by using alkalified alcohol and chloroform as solvents in the preparation of solid dispersion of the drug. Solid dispersions have been used to increase the bioavailability of drugs by various workers (Rane *et al*., 2007 and Shah *et al*., 2009).

Solubility in co-solvent

The co-solvent system in the present study includes chloroform and glycerol. For determination of solubility, excess of the drug (50mg) was placed in contact with 10ml of solvent in sealed glass tubes. Suspensions were vigorously stirred at 37 ± 0.5°C for 2 days, till equilibrium was reached. The samples were filtered through a polycarbonate membrane (0.45 µm, Millipore, Billerica, MA). The concentration of the drug in the saturated solution was determined by UV spectroscopy, after appropriate dilution with selected solutions. Solubility of MC was 11µg/ml in chloroform whereas when only water was used as solvent, the solubility was 8µg/ml. When pure glycerol was used as solvent, the drug solubility was found to be 9.4µg/ml.

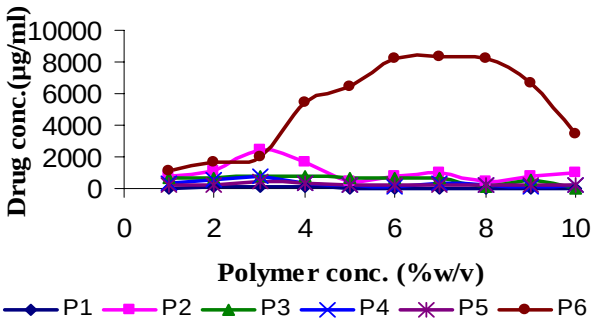

Fig. 1: Phase solubility graph of Meloxicam with β- CD and other hydriphillic polymer.
P1= MC- β-CD, **P2**= MC- β-CD + 0.12% w/w Methylcellulose, **P3**= MC- β-CD + 0.12% w/w PVP K_{30}, **P4**= MC- β-CD + 0.12% w/w HPMC (K4M), **P5**= MC- β-CD + 0.12% w/w (HPMC 50cPs), **P6**= MC- β-CD + 0.12% w/w HPMC (Methocel IH).

Preparation of Solid dispersion of Meloxicam (by using MC + β-CD + 0.12% w/w HPMC (Methocel, IH), Polymer)

Preparation of Physical mixture of Meloxicam: Weighed amount of Meloxicam (MC) and polymer β-CD + 0.12% w/w HPMC (Methocel, IH), were mixed in a glass mortar for 5 minutes using geometrical dilution in the required ratio. The resultant product was passed through a sieve of 80 mesh size.

Preparation of solid dispersion by solvent evaporation method: Solid dispersions of Meloxicam were prepared by solvent evaporation method by using two different solvents:

Using Chloroform: Three different MC carrier ratios (1:1, 1:2, 1:3), were used. The respective amounts of carrier were dissolved in chloroform (30ml) and MC was added in parts with continuous stirring. The solvent was then completely evaporated at 40-45°C with continuous stirring to obtain dry granules. The dry granules so obtained were passed through sieve no. 80 and dried further at room temperature (25°C) for 24 h.

Using ethanol (alkalified): MC was mixed with different carrier ratios (1:1, 1:2, 1:3), the respective carrier was dissolved in alkalified ethanol (alkalified by using 0.1 N NaOH) 20 ml. and MC was added in parts with continuous stirring. The solvent was then completely evaporated at 40-45°C with continuous stirring to obtain dry granules. The granules so obtained were passed through sieve no. 80 and dried further at room temperature (25°C) for 24 h.

Selection of solid dispersion for tablet formulation

The formulated solid dispersions were checked for solubility. 50 mg. of the preparation was added to 10 ml of pH 7.4 phosphate buffer solution in sealed glass container and stirred at 37±0.5°C for 2 days. When equilibrium was reached (2 days), samples were filtered through a polycarbonate membrane (0.45 µm, Millipore, Billerica, MA). The concentration of the drug in the saturated solution was determined by UV spectroscopy, after appropriate dilution with water. This gave the aqueous solubility of the drug (table 2).

*Preparation of granules of solid dispersion of Meloxicam***:** Granules for tableting were prepared by two methods: Direct compression & Wet granulation.

Preparation of Meloxicam tablets using solid dispersions of the drug: Solid dispersions having equivalent dose 7.5 mg in granular form was utilized for the preparation of tablets by direct compression (utilizing G1), and wet granulation (utilizing G2). The granules were fed into the die of 10- station tablets machine (Karnavati-minipress-1, India), using circular punches with flat faces of 8mm. diameter, at a compression pressure of 6 tons.

The machine setting was adjusted to produce tablets of 150 mg. Thus, four types of tablets were developed for the purpose of comparison.

(a) Plain Meloxicam tablets (Batch A)
(b) Direct compression tablets (Batch B)
(c) Direct compression (with SLS) (Batch C)
(d) Wet granulation (Batch D)

Characterization of Meloxicam tablets

The formulated tablets were characterized on the basis of all official tests (i.e. friability, wetting time, *in-vitro* dissolution etc). Results are recorded in table 3.

Table 1: Optimization of concentration of polymer HPMC (Methocel IH) in β-CD for enhanced solubility of Meloxicam.

S. No.	Conc. of β-CD + %w/w Polymer*	Drug solubility in β-CD + 0.05%w/w HPMC (Methocel IH) (µg/ml)	Drug solubility in β-CD + 0.12%w/w HPMC (Methocel IH) (µg/ml)	Drug solubility in β-CD + 0.25%w/w HPMC (Methocel IH) (µg/ml)
1.	1.	1050	1100	1100
2.	2.	1600	1700	1660
3.	3.	1800	2000	1980
4.	4.	4400	5500	4400
5.	5.	5500	6400	2000
6.	6.	7700	8200	3000
7.	7.	6700	8300	5500
8.	8.	6400	8200	3500
9.	9.	4400	6700	6600
10.	10.	3000	3500	4800

Table 2: Aqueous solubility of Meloxicam in physical mixture.

S. No.	Compound	Product Nomen-clature	Nature of Product	Solubility (µg/ml) (n=3 ± SD)	Apparent stability Constant (Kc)	Correlation Coefficient (R^2)	Type of phase solubility diagram*
1.	Pure MC	P0	Yellow crystalline powder	8.0 ±0.4	----	----	----
2.	MC- β-CD	P1	Yellowish granules	10 ±0.3	271 M^{-1}	0.937	A_L
3.	MC- β-CD + 0.12% w/w Methylcellulose	P2	Yellowish white powder	80 ±1.7	631 M^{-1}	0.498	A_L
4.	MC- β-CD + 0.12% w/w PVP K_{30}	P3	Yellowish white powder	20 ±0.5	570 M^{-1}	0.970	A_L
5.	MC- β-CD + 0.12% w/w HPMC (K4M)	P4	Yellowish white powder	16 ±1.1	445 M^{-1}	0.039	A_N
6.	MC- β-CD + 0.12% w/w (HPMC 50cPs)	P5	Yellowish white powder	13 ±0.7	439 M^{-1}	0.820	A_N
7.	MC- β-CD + 0.12% w/w HPMC (Methocel IH)	P6	Yellowish white powder	90 ±1.2	943 M^{-1}	0.970	A_L

*A_L linear increase of drug solubility as function of the polymer concentration, A_N negatively deviating isotherms

In vitro dissolution studies of Meloxicam tablets

Dissolution test was carried out in USP XX dissolution apparatus, using 900ml. of pH 7.4 phosphate buffer solutions at 100 rpm and maintained at 37 ± 0.5°C. The samples (10ml.) were withdrawn at the interval of 10, 20, 30, 40, 50, 60, and 90 minutes and replaced with equal quantity of dissolution medium. Samples were filtered through a polycarbonate membrane (0.45 µm, Millipore, Billerica, MA). The amount of drug dissolved was determined spectrophotometrically at 354 nm. A mean of three readings was taken in each case. The percent drug release was computed at each sampling interval. For comparison purposes, reference MC tablets and marketed tablets of MC of two brands coded as 1 and 2, were evaluated for drug release. The cumulative percent drug released for different batches of tablets has been shown in fig. 2.

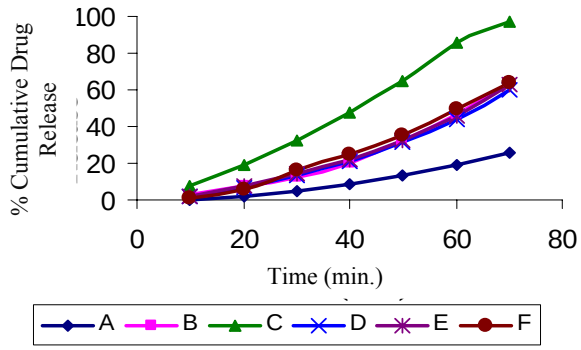

Fig. 2: *In vitro* dissolution profile from different batches of Meloxicam tablets.

Preparation of Meloxicam suspension

No work has been reported on the application of solid dispersion of MC in suspension formulation. In present study, the solid dispersion was used in formulations of MC suspension with an objective of improving the physical stability and dissolution rate of MC suspension.

Suspensions containing 7.5 mg of Meloxicam in 5 ml were prepared as per formula given in table 4.

Method

1- Required amount of water was weighed in an appropriate container, suspending agent was dispersed using a shear mixture universal motor (Remi Motors, Mumbai, India) until a viscous solution of the suspending polymer was formed.
2- Accurately weighed quantity of MC and its solid dispersion (1:3) were taken in two different mortars and it was levigated with small portion of suspending polymer solution as per details mentioned in table 4.
3- When a smooth paste was formed, the remaining suspending polymer solution was added in divided portions while triturating the contents.
4- Sodium saccharine, glycerin and tween-80 were added while mixing.
5- Other ingredients were added one after another and mixed till suspension was obtained which was transferred to a measuring cylinder and volume adjusted.

Evaluation of suspensions

The formulated suspensions were evaluated for various parameters like particle size, pH, sedimentation rate, sedimentation volume, viscosity, and specific gravity as recorded in table 5.

In vitro dissolution study

Dissolution rate of MC from various suspensions was studied using USP XXI dissolution rate test apparatus employing a paddle stirrer. In 900 ml of phosphate buffer pH 7.4, a sample of suspension equivalent to 7.5 mg. of Meloxicam (5ml.) was taken. A speed of 50 rpm and temperature of 37 ± 1°C were employed in each test.

A 10 ml aliquot of dissolution medium was withdrawn at different intervals of time through a filter of size 0.45 µm, suitably diluted and assayed spectrophotometrically at 354 nm for Meloxicam content (fig. 3).

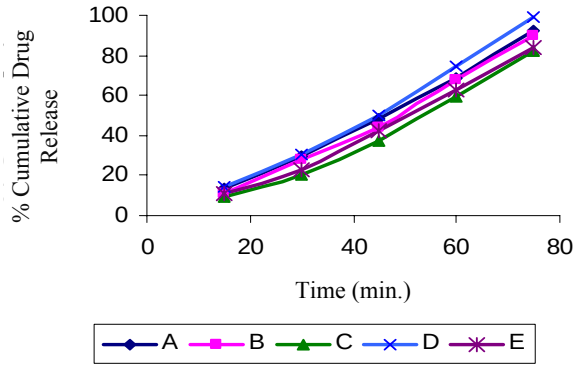

Fig. 3: Cummulative % drug release from different batches of Meloxicam suspension.

RESULTS

MC showed significant enhancement in aqueous solubility with an increase in the pH. Since MC is an acidic drug, the solubility enhancement with increasing pH showed that it dissociated into more than one ionizable group in alkaline medium. Through the study, appropriate concentration for the polymer in β-CD was optimized as 0.12% w/v (tables 1 and 2), since it showed linear as well good solubility enhancement of MC. This concentration was taken for optimization of the other polymers for blending into β-CD. The aqueous solubility of Meloxicam in the inclusion complex with hydrophilic polymers was found to be in following rank order:

Table 3: Evaluation parameters of tablets

S. No.	Parameters	Plain Meloxicam (Batch A)	Direct compression (Batch B)	Direct compression (with SLS) (Batch C)	Wet granulation (Batch D)	Marketed tab. 1 (Batch E)	Marketed tab. 2 (Batch F)
1.	Friability (%)*	3.3 ± 0.11	0.35 ± 0.01	0.38 ± 0.01	0.24 ± 0.04	0.40 ± 0.02	0.82 ± 0.03
2.	Hardness (Kg/cm^2)*	1.0 ± 0.40	3.0 ± 0.57	2.8 ± 0.25	3.4 ± 0.30	1.2 ± 0.11	2.0 ± 0.10
3.	Wetting time(min.)*	30 ± 0.45	45 ± 0.9	27 ± 0.8	60 ± 1.4	32 ± 1.6	10 ± 0.7
4.	Water absorption ratio (%)*	53.36± 0.45	47.62 ± 0.31	54.01 ± 0.13	44.58± 0.31	51.35 ± 0.18	80 ± 0.62
5.	Disintegration time (min)*	1 ± 0.5	7 ± 0.5	4.5 ± 0.6	8 ± 0.8	3 ± 1.2	10 ± 0.1
6.	Weight variation	Failed	Pass	Pass	Failed	---	---

'*' - n=3 ± SD

Table 4: Formulation of different batches of suspensions

S. No.	Ingredients	Batch A %w/v	Batch B %w/v	Batch C %w/v	Batch D %w/v	Batch E %w/v	Batch F %w/v
1.	Plain meloxicam	----	---	---	---	---	0.15
2.	Solid dispersion (1:3)	0.6	0.6	0.6	0.6	0.6	---
3.	Methylcellulose	1.0	---	---	0.5	0.5	0.5
4.	Sodium carboxy methyl cellulose	---	1.0	---	0.5	---	0.5
5.	Colloidal CMC	----	---	1.0	---	0.5	---
6.	Tween-80	0.10	0.10	0.10	0.10	0.10	0.10
7.	Glycerin 99% U.S.P	5.0	5.0	5.0	5.0	5.0	5.0
8.	Saccharine sodium U.S.P.	0.16	0.16	0.16	0.16	0.16	0.16
9.	Methyl paraben N.F.	0.10	0.10	0.10	0.10	0.10	0.10
10.	Propyl paraben N.F.	0.02	0.02	0.02	0.02	0.02	0.02
11.	Flavours (quantity sufficient)	(q.s.)	(q.s.)	(q.s.)	(q.s.)	(q.s.)	(q.s.)
12.	Deionized purified water up to	100 ml	100 ml	100 ml	100 ml	100 ml	100 ml

Table 5: Evaluation of different batches of suspensions

S. No.	Parameter	Batch A	Batch B	Batch C	Batch D	Batch E	Batch F
1.	Particle size (μm)*	15.5 ± 6.2	14.60 ± 5.6	20.3 ± 8.5	9.45 ± 10.6	19.8 ± 2.3	11.8 ± 12.2
2.	pH*	7.42 ± 1.2	7.46 ± 0.32	7.47 ± 1.8	7.64 ± 2.3	7.43 ± 0.9	6.56 ± 1.5
3.	Sedimentation rate (cm/sec)	0.006	---	0.29	---	0.03	0.0008
4.	Sedimentation volume	0.11	1.0	1.3	1.0	0.12	0.5
5.	Viscosity (poise)*	50 ± 1.50	180 ± 1.00	20 ± 2.08	80 ± 1.52	30 ± 1.42	60 ± 1.04
6.	Specific gravity(g/cm^3)	0.979	0.951	0.976	0.984	0.978	0.983

'*' - n=3 ± SD

HPMC (Methocel)>methyl cellulose>PVP K30>HPMC K4M>HPMC 50cPs>inclusion complex with no polymer

From table 3, it is clear that maximum solubility and apparent stability constant of MC were found in P6 [MC-β-CD + 0.12% w/w HPMC (Methocel)] physical mixture (90 μg/ml), and minimum solubility and apparent stability constant of MC reported in P1 [MC-β-CD] physical mixture. The values of apparent stability constant lie within the range of 100-1000 M^{-1}, which is believed to indicate an ideal value. Due to an approximately twelve fold increase in solubility of the drug in product P6 [β-CD + 0.12% w/w HPMC (Methocel, IH), this ternary system was used for preparation of solid dispersion of the drug.

Solubility of MC is significantly enhanced by chloroform as a co-solvent (11μg/ml) whereas when only water was used as solvent, the solubility was less (8μg/ml). When pure glycerol was used as solvent, the drug solubility was 9.4μg/ml.

Since the solubility of the drug was found maximum in 1:3 solid dispersion in which alkalified ethanol has been used, this ratio was taken for the formulation of tablets for the present study. Batch C of the tablets was found to be the best formulation based on characterization and also on the *in vitro* dissolution profile.

In case of Meloxicam suspension, from table 5 it is clear that Batch D has a minimum particle size of 9.45 μm and in batch B & D sedimentation dose not occurs. Thus it can be concluded that batch B and D are physically more stable than other batches. The results of viscosity measurement also supported the finding that Batch B and D are more stable suspensions. The dissolution profile of different suspensions showed that maximum drug

(99.5%) was released from Batch D indicating Batch D to be the superior formulation.

DISCUSSION

Meloxicam was found to be soluble in organic solvents and having poor bioavailability. The aim of the present study was to enhance the dissolution rate of meloxicam (MC), a practically water-insoluble drug by preparation of solid dispersion using a hydrophilic polymer The phase solubility studies were carried out in phosphate buffer solution containing fixed amount of the polymer (0.12% w/w). Figure 1 shows solubility of MC in the inclusion complex with hydrophilic polymers was found to be higher in the case of HPMC; it may be due to formation of soluble complexes and/or co solvent effect of carrier. MC is a hydrophobic drug so its solubility is more in chloroform in comparison to water and glycerol.

Solubility of the drug was found maximum in 1:3 solid dispersion in which alkalified ethanol has been used as solvent because meloxicam is carrying various polar sites such as oxygen, nitrogen, and sulphur. These sites must have a role to form hydrogen bond in alkalified ethanol. So this ratio was taken for further study.

The dissolution profile of various tablets formulated (batch A, B, C, D, E, F) showed that among the tablets formulated batch C gave higher dissolution of medicament due to presence of SLS, which was act as the solubility modifier.

The suspension of MC (Batch D) containing the equal ratio of methyl cellulose and sodium carboxymethyl cellulose exhibited a low sedimentation volume, higher viscosity and dissolution whereas the formulation (batch C) containing the lower level of methyl cellulose and carboxymethyl cellulose displayed an increased sedimentation volume, decreased viscosity and dissolution. On the basis of release profile and other parameter batch D was found to be the superior formulation.

CONCLUSION

From the above study, it is clear that maximum solubility and apparent stability constant of MC were found in P6 [MC- β-CD + 0.12% w/w HPMC (Methocel)] physical mixture, and minimum solubility and apparent stability constant of MC reported in P1 [MC- β-CD] physical mixture. Thus, it can be concluded that P1, which is a binary complex of MC, has lower aqueous solubility than P6 which is a ternary complex. This proves that ternary complexes have better potential for solubility enhancement than binary complexes and is in sync with the findings of other workers (El-Maradny *et al.* 2008). Due to better solubility of the drug in product P6 [β-CD + 0.12% w/w HPMC (Methocel, IH), this polymer was used for preparation of solid dispersion of the drug. All the above studies suggest that tablets and suspension of MC utilizing solid dispersion technique enhances solubility as well as the as the bioavailability of the drug and other such formulations of the drug can be planned as future scope.

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