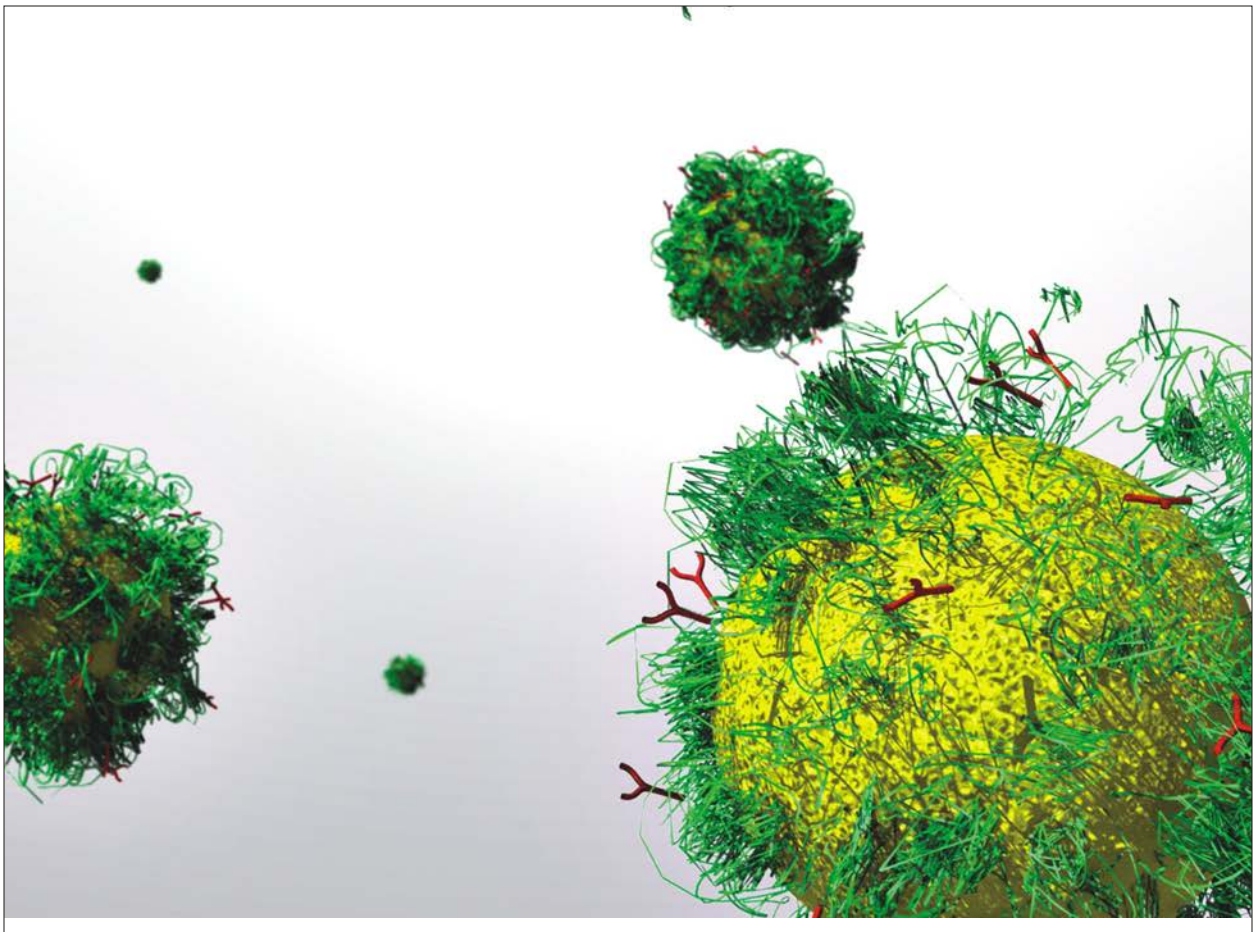

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Enhancement of Complexation Efficiency of Meloxicam Using Binary and Ternary Solid Systems: Formulation Considerations

[1]Lokesh Kumar Bhati, [2]Gaurav Tiwari, [3]Ruchi Tiwari and [3]Vijay Kumar
[1]Department of Pharmaceutical Sciences, Bhagwant University, Ajmer, Rajasthan, India
[2]Pranveer Singh Institute of Technology, Kalpi Road, Bhauti, Kanpur, 208020 (UP), India
[3]National Botanical Research Institute, Lucknow, Uttar Pradesh, India

Corresponding Author: Lokesh Kumar, Department of Pharmaceutics, Rajiv Academy for Pharmacy, P.O. Chattikara, Mathura-281 001 (UP), India Tel: +91-9310850456

ABSTRACT

Investigation on binary and ternary systems of β-cyclodextrin (β-CD) and hydroxypropyl-β cyclodextrin (HPβ-CD) with Polyvinylpyrrolidone (PVP) on the solubility of Meloxicam (MX) was studied. Phase solubility analysis with PVP K-30 v was used to investigate interactions in aqueous solution between MX and the carrier, either alone or in combination. Equimolar MX and both CDs solid systems, in the presence or the absence of 0.4% (w/w) PVP, were prepared by kneading, co-evaporation or freeze-drying and characterized by differential scanning calorimetry, X-ray powder diffraction analysis, scanning electron microscopy, infrared spectroscopy and dissolution studies. The combined use of PVP and CDs resulted in a synergistic increasing effect of the aqueous solubility of MX. The phenomenon was interpreted in terms of the strongest complexation capacity of CDs towards MX. The positive effect of PVP K30 also reflected on MX dissolution rates from solid preparations, because all ternary systems, with exception of physical mixtures, dissolved faster than the corresponding MX-CDs binary systems the results of solid state studies accounted for the occurrence of stronger interaction in ternary than in binary systems.

Key words: Meloxicam, β-cyclodextrin, hydroxy propyl-β cyclodextrin, PVP K30, binary and ternary systems

INTRODUCTION

Solubility of poorly soluble drugs in order to improve their pharmaceutical and biological availability still remains one of the major technological problems. The absorption of such compounds when presented in the crystalline state to the gastrointestinal tract is typically dissolution rate-limited and the drugs are typically BCS class II or class IV compounds. Class IV compounds which have low membrane permeability as well as poor aqueous solubility, are often poor candidates for development, unless the dose is expected to be low. The rate and extent of absorption of class II compounds is highly dependent on the performance of the formulated product. These drugs can be successfully formulated for oral administration, but care needs to be taken with formulation design to ensure consistent bioavailability. Complexation is one of several ways to favorably enhance the physiochemical properties of pharmaceutical compounds. It may be defined as the reversible association of a substrate and ligand to form a new species. Although the classification of complexation is somewhat arbitrary, the differentiation is usually based on the type of interactions and species involved e.g., Metal complex, molecular complex, inclusion complexes and

ion exchange compounds. Cyclodextrins (CDs) are classical example of compounds that form inclusion complex (Swarbrick and Boylan, 2002). These complexes are formed when a "guest" molecule is partially or fully included inside a "host" molecule e.g., CD with no covalent bonding. When inclusion complexes are formed, the physiochemical parameter of the guest molecule is disguised or altered and improvement in the molecule's solubility, stability, taste, safety, bioavailability etc. are commonly seen. Since variety of reasons like cost, production capability and toxicology etc. affect the incorporation of drug in formulation. Therefore, it is desirable to develop methods or techniques to enhance the efficiency of drug CD complexation. But the amount of β-CD that can be used in most pharmaceutical formulation is limited due to various reasons such as high molecular weight, relatively low water solubility and possible parenteral toxicity. Hence, in order to reduce the desirable drug solubilization certain suitable auxiliary substance can be used to significantly increase the solubilization and complexing abilities of β-CD and can provide a suitable approach to overcome the problems with drug β-CD complexes (Mura *et al.*, 2003).

CD is a non reducing crystalline, water soluble, cyclic oligosaccharide. Three naturally occurring CDs are α-CD, β-CD, γ-CD. The entire hydroxyl group in CDs is oriented to outside the ring while glycoside oxygen and two ring of the non exchangeable hydrogen atoms are directed towards the interior of the cavity. This combination gives CD a hydrophobic inner cavity and a hydrophillic exterior. The hydrophobic internal cavity provides the capability to form inclusion complexes with a variety of "guest" hydrophobic molecules (e.g., aromatics, alcohols, halides, fatty acids esters etc.) (Redenti *et al.*, 2000; Mura *et al.*, 2001). The most common CDs are α, β and γ CD having six (α), seven (β), or eight (γ) anhydrous glucose units in the ring structure among them β-CD are most commonly used. Natural CDs have relatively low solubility, both in water and organic solvents which thus limits their uses in pharmaceutical formulations (Uekama *et al.*, 1998). Recently, various kinds of CD derivatives have been prepared so as to extend the physicochemical properties and inclusion capacity of natural CD as novel drug carriers. CDs have been playing a very important role in formulation of poorly water soluble drugs by improving drugs solubility and dissolution through inclusion complexation or solid dispersion, by acting as hydrophilic carriers for drugs with in adequate molecular characteristics for complexation or as tablet dissolution enhancers for drug with high dose. Recently, a number of CD derivatives and CD polymers have been prepared to obtain better inclusion abilities than parent CD. The natural CD and their synthetic derivatives have been successfully utilized to improve various drug properties, such as solubility, dissolution and release rates, stability, or bioavailability (Valero and Esteban, 2004).

The natural cyclodextrins, in particular β-cyclodextrin, have limited aqueous solubility and their complex formation with lipophilic drugs often results in precipitation of solid drug/cyclodextrin complexes. Thus, the solubility of β-cyclodextrin in water is only about 18.5 mg mL^{-1} at room temperature. Various water-soluble cyclodextrin derivatives have been synthesized. Cyclodextrins have been shown to be able to enhance the aqueous solubility of Class II and Class IV drugs. Although, natural cyclodextrins have lower aqueous solubility than the cyclodextrin derivatives, their solubility is frequently sufficient to prevent dissolution rate-limited drug absorption from the gastrointestinal tract, i.e., to move drugs from Class II to Class I. Furthermore, the molecular weights of the natural cyclodextrins are much lower than those of their derivatives. Replacing the cyclodextrin derivatives with their parent cyclodextrins will reduce the formulation bulk which is the main obstacle of usage of cyclodextrins in solid dosage forms. For solid oral dosage forms, there are three requirements: First, the dose/solubility ratio has to be equal to or below 250 mL. In other words, the aqueous solubility of the drug/cyclodextrin complex has to be sufficient in the

gastrointestinal tract. Second, the upper limit in dosage size is about 800 mg. Due to excipient's requirements; only about 700 mg of a complex (or about 50 to 150 mg of drug) can be included in a conventional tablet. Third, drug dissolution rate from the tablets has to be rapid to prevent dissolution rate-limited absorption (Loftsson *et al.*, 1994; Ganzerli *et al.*, 1996; Loftsson and Brewster, 1996; Loftsson and Fee, 2006).

PVP has a molecular weight ranging from 10,000 to 700,000. It is soluble in solvents like water, ethanol, chloroform and isopropyl alcohol. PVP is not suitable for preparation of solid dispersion prepared by melting method because it melts at a very high temperature above 275°C, where it becomes decomposed. The effect of molecular weight of PVP on the rate of dissolution of a drug is more consistent than for PEG. An increase in viscosity of PVP solution due to an increase in molecular weight decreases diffusion of drug molecules from the surface of viscous materials into the dissolution medium. Lower molecular weight PVP has a short swelling time prior to dissolution resulting in an increase in dissolution rate of the polymer and drug. The addition of surfactants to dissolution medium lowers the interfacial tension between the drug and the dissolution medium and promotes the wetting of the drug. Thereby, they enhance the solubility and dissolution of drugs. Ternary systems have higher dissolution rates than binary dispersion system (Row *et al.*, 2006).

MATERIALS AND METHODS

Materials: Meloxicam (MX) was supplied by Sun pharma, Goa, India. 2-Hydroxy Propyl β-cyclodextrin (HPβ-CD) was gifted by Hi Media laboratories, Mumbai, India. β-cyclodextrin (β-CD) was obtained from S-merk, Mumbai. Sodium starch glycolate was generously gifted by Magnus Pharmaceuticals, Ahmedabad, India. Lactose was purchased from Merck India Limited, Mumbai. Other chemicals were of analytical grade. Double distilled water was used throughout the studies.

Methods

Solubility study of pure drug with different concentration of polymers: Excess amount of drug (20 mg) was added to 25 mL conical flask containing different percentage of weighed amount of PVP K-30 and 10 mL of distilled water then placed in a mechanical shaker at 37±5°C for 72 h. At the end of 72 h samples were filtered through the whatman filter paper. A 1 mL of filtered samples were suitably diluted and analyzed at 362 nm.

Phase solubility studies: Excess amount of drug was added to 10 mL of distilled water containing increasing concentration of Cyclodextrins (CDs) and in another conical flask fixed polymer concentration (0.4% w/v for PVP K-30) was added, flasks were then placed in a mechanical shaker at 37±5°C for 72 h. Samples were filtered through the whatman filter paper. A 1 mL of filtered samples were suitably diluted and analyzed at 362 nm (Bhatia and Seedher, 2007).

Preparation of binary and ternary solid systems

Physical mixing: The physical mixtures of drug and CDs in 1:1 molar ratio was obtained by mixing individual components that had previously been sifted (75-150 μm) together with a spatula. For a ternary system 0.4% PVP K30 was added along with drug and CD same procedure was followed (Swarbrick and Boylan, 2002).

Kneading method: A physical mixture of drug and CDs in 1:1 molar ratio was triturated in a mortar with a small volume of water-methanol (1:1, v/v) solution. The thick slurry was kneaded for

45 min and then dried at 45°C until dryness. The dried mass was pulverized and sieved then a (75-150 μm) granulometric sieve fraction was collected. For a ternary system 0.4% PVP K30 was added along with drug and CD same procedure was followed.

Co-evaporation method: The aqueous solution of CDs was added to a solution of drug dissolved in liquid ammonia. The resulting mixture was stirred for 1 h and evaporated at a temperature of 45°C until dried. The dried mass was pulverized and sieved and a granulometric (75-150 μm) sieve fraction was collected. For a ternary system aqueous solution of CD and PVP K30 (0.4%) was added to a solution of drug dissolved in liquid ammonia and rest of procedure is same as Naidu *et al.* (2004).

Freeze drying method: Freeze drying product was prepared by dissolving an equimolar mixture of drug and CD or drug: CD: PVP K30 in distilled water and shaken for 24 h. Ammonia solution (25%v/v) was added to it drop wise till a clear solution was obtained. The solution was frozen overnight in petri dishes at -45°C and lyophilized in a freeze drier at -45°C for 48 h. Secondary drying was carried out at room temperature (Govindarajan and Nagarsenkar, 2004). Formulation code was presented in Table 1.

Determination of drug content: 10 mg of each solid dispersions were accurately weighed and dissolved in 10 ml of volumetric flask with phosphate buffer (pH 7.4), filtered and 1 mL of sample was diluted with phosphate buffer (pH 7.4) up to 10 mL and assayed spectrophotometrically for MX at 363 nm using calibration curve based on standard solutions in phosphate buffer (pH 7.4). Results were expressed both as the drug content (mg incorporated drug) and percent incorporation (actual amount of drug in solid dispersions vs initially added amount). The studies were conducted in triplicate.

***In vitro* drug release studies:** *In vitro* dissolution was performed using USP XXVII Apparatus I in 900 mL of phosphate buffer (pH 7.4) at an agitation rate of 50 rpm. The temperature of medium was maintained at 37±0.5°C. 7.5 mg of drug or its equivalent weight of the

Table 1: Formulation of MX binary and ternary solid systems

Formulation code	Drug (g)	β-CD (g)	Hpβ-CD (g)	PVP K-30 %(w/w)
F 1 (PM)	0.351	1.135	-	-
F 2 (KN)	0.351	1.135	-	-
F 3 (CS)	0.351	1.135	-	-
F 4 (FD)	0.351	1.135	-	-
F 5 (PM)	0.351	1.135	-	0.4
F 6 (KN)	0.351	1.135	-	0.4
F 7 (CS)	0.351	1.135	-	0.4
F 8 (FD)	0.351	1.135	-	0.4
F 9 (PM)	0.351	-	1.380	-
F 10 (KN)	0.351	-	1.380	-
F 11(CS)	0.351	-	1.380	-
F 12 (FD)	0.351	-	1.380	-
F 13 (PM)	0.351	-	1.380	0.4
F 14 (KN)	0.351	-	1.380	0.4
F 15 (CS)	0.351	-	1.380	0.4
F 16 (FD)	0.351	-	1.380	0.4

prepared solid system was taken and analyzed for dissolution. Tablets prepared with selected F16, its corresponding F13 and MX was also analyzed for dissolution. A 5.0 ml sample was withdrawn at specific time points over a 2 h period and equal volume of fresh dissolution medium was used to maintain a constant volume. The aliquot samples were filtered and the drug concentration was determined by Ultraviolet (UV) method at 363 nm (Gao *et al.*, 2006). In order to determine the difference between the release patterns of binary and ternary systems and MX, one way ANOVA was applied with the help of INSTAT SOFTWARE.

***In vitro* permeation studies:** A piece of cellophane membrane was stretched over the end of an open-ended glass tube. The tube was immersed in a 400 mL beaker containing 100 mL of phosphate buffer (pH 7.4) and kept in vertical position so that the membrane was just below the surface of the buffer solution. The surface area available for diffusion was 2.51 cm^2. The tube (donar) and beaker (receptor) were maintained at 37°C shaken in a magnetic stirrer. A 3 mL aliquot of saturated buffer solution (pH 7.4) of drug as a pure drug or solid system prepared by FD was inserted into the tube. At time intervals (up to 7 h). Sample 5 mL were removed from the receptor and analyzed spectrophotometrically at 363 nm (El-Badry and Fathy, 2006).

Characterization of solid dispersion systems FTIR spectroscopy: Infrared spectra were obtained using a shimadzu FTIR-8400 spectrometer (Shimadzu, Japan). The samples were previously ground and mixed thoroughly with KBr, an infrared transparent matrix. The KBr disks were prepared by compressing the powder. The 20 scans were executed at a resolution of 1 cm^{-1} (from 4000-400 cm^{-1}).

Differential scanning calorimetry: Thermograms of pure materials, their treated components and all binary and ternary systems were recorded on a Perkin-Elmer (Pyris Diamond) model differential scanning calorimeter (DSC, Tokyo, Japan). About 10 mg of samples were sealed in aluminum pans and an empty aluminum pan was used as reference. The experiment was carried out under nitrogen flow (20 mL min^{-1}) at scanning rate of 10°C min^{-1} in the range of 30 to 300°C.

X-ray powder diffractometry: Diffraction patterns of drug, physical mixtures, kneading, co-evaporation and freeze drying product and polymers were recorded with a D-8 advance SRD-BRUKER (GERMAN). A voltage of 40 kV and a current of 30 mA for the generator were used, with Cu as the tube anode material. The solids were exposed to Cu-Kα radiation (α1=1.54060 Å and α2=1.54439 Å, with a α1/α2 ratio of 0.5), over a range of 2θ angles from 10 to 30°C, at an angular speed of 1° (2θ) per min.

Scanning electron microscopy: The surface morphology of pure materials, their treated counterparts and all binary and ternary systems were examined by scanning electron microscope (LEO 435 VP, UK). The samples were fixed on a brass stub using double-sided tape and then gold coated in vacuum by a sputter coater. The pictures were then taken at an excitation voltage of 20 kV.

Preparation of tablets: The 7.5 mg of MX or F16 or F13 equivalent to 7.5 mg along with Maize starch (5.0% w/w), Sodium starch glycolate (2.0% w/w), Magnesium stearate (0.2% w/w), Talc

Table 2: Composition of tablet formulation

Ingredients	TMX (mg)	TF16 (mg)
Meloxicam	7.5	37.12
Maize starch (5.0% w/w)	7.5	7.50
Sodium starch glycolate (2.0% w/w)	3.0	3.00
Magnesium stearate (0.2% w/w)	0.3	0.30
Talc (1%)	1.5	1.50
Directly compressed lactose (q.s)	150.0	150.00

(1%) and directly compressed lactose (q.s) were blended in double cone blender (HICON, India). Table 2 shows composition of tablet formulation. The powder blends were compressed by direct compression method using electrically operated single punch tablet machine (10 mm die diameter, Jindal Scientific Industries Pvt. Ltd., India).

Stability studies: A three month accelerated stability test was carried out after preparation in which F16 tablets were kept in an oven at a temperature of 40±1°C and a relative humidity of 75%. The physical appearance, drug content, release profile and hardness of the tablets were determined at the end of 1, 2 and 3 months, respectively and compared with that of freshly prepared F16 tablet (Cui and Jug, 2003).

RESULTS AND DISCUSSION

Solubility and phase solubility studies: Solubility studies of MX in binary and ternary systems with β-CD, HPβ-CD and polymer in distilled water at 37°C showed that PVP K30 was effective polymer in improving MX solubility. When, the polymer was used in combination with β-CD, HPβ-CD, a clear synergistic effect on MX solubility enhancement was found in presence of PVP K30. In fact, by dividing the drug solubility in the MX-β-CD-PVP K30, MX-HPβ-CD-PVP K30 a 13.48, 18.58 fold increasing solubility was found, whereas in the case of MX-β-CD, MX-HPβ-CD binary system at pH 5.8, the corresponding increasing solubility was only 1.65, 2.99-fold. Moreover, the drug solubility in the ternary system was higher than the one calculated by adding the solubilities in the presence of CD (at the same pH 5.8) and polymer separately. The synergistic effect in drug solubility improvement exhibited by PVP K30 in ternary systems with β-CD, HPβ-CD seems to indicate a specific involvement of PVP K30 in the molecular assembly of a ternary complex, probably by establishing electrostatic interactions with the amino group of MX and hydrogen bonds with the hydroxyl groups of CDs. On the basis of these results, the ternary system with PVP K30 was selected for further investigations. Phase-solubility studies of MX in binary and ternary systems with β-CD, HPβ-CD and PVP K30 were then performed to obtain more information about the drug solubilization mechanism and the multicomponent complex formation. Solubility diagrams obtained by adding increasing amounts of β-CD, HPβ-CD to excess amounts of MX or MX-PVP K30 mixture were both of A_L type according to the Higuchi classification (Higuchi and Connors, 1965), showing a linear increase of drug solubility, indicative of the formation of soluble complexes (Fig. 1). A summary of the findings of the phase solubility studies is shown in Table 3. The solubility calculated for MX in distilled water (pH 5.8) was 10.02 μg mL^{-1} at 37°C. The solubility of MX increased linearly with an increase in the concentration of CDs, giving A_L type solubility diagrams. The increase in solubility in the systems is due to one or more molecular interactions between MX and CDs to form distinct species or complexes. The solubilizing efficiency of Hpβ-CD was higher than the β-CD. The cavity size of the HPβ-CD seems to be optimal for

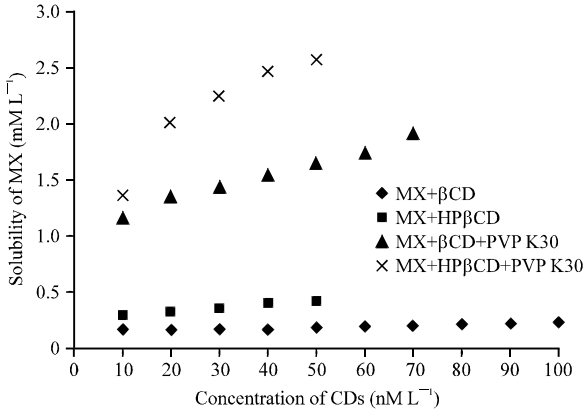

Fig. 1: Phase solubility study of MX with CDs and with CD and screened concentration of PVP K30 (0.4%, w/v) in distilled water (pH 5.8)

Table 3: Summary of MX-CDs phase solubility studies

Sample	Slope	Stability constant via intrinsic solubility	Complexation efficiency	D:CD	Increase in bulk formulation (mg)
MX+β-CD	0.019	137.01	0.019	1:52.54	1268.84
MX+Hpβ-CD	0.033	244.25	0.034	1:30.41	894.05
MX+β-CD+PVP	0.120	960.00	0.136	1:8.35	201.65
MX+HPβ-CD+PVP	0.161	3152.00	0.192	1:6.20	182.28

D: Drug, CD: Cyclodextrin

entrapment of MX molecule and consequently provides the greatest solubilization effect. The apparent stability constants ($K_{1:1}$) were calculated for these complexes from phase solubility diagrams according to the following Equation:

$$k_{1:1} = \text{slope}/S_0(1 - \text{slope})$$

where, S_0 is intrinsic solubility

The stability constant values calculated were 1352±1.25, 960±1.15 M^{-1}, respectively, for HP**β**-CD and **β**-CD. The larger constant that was observed with HP**β**-CD indicated that MX interacted more strongly with the HP**β**-CD.

Determination of drug content: The actual drug content of solid systems was estimated in the range of 84.25 to 93.56% (Table 4). The drug content was found to be uniform in all solid dispersions and was in good agreement with theoretical drug content.

***In vitro* drug release study of solid systems:** The dissolution rate of MX in the form of solid systems was examined in phosphate buffer pH 7.4. The dissolution of pure MX was extremely low, with only 56% of drug release during 120 min of dissolution run in phosphate buffer (pH 7.4). This might be attributed to poor wettability and particle agglomeration during the run that caused the powder to float on the surface of dissolution medium. The mean dissolution curves of MX from various binary systems with **β**-CD/HP**β**-CD and ternary systems of MX with **β**-CD/HP**β**-CD and PVP K30 was carried out. The increase in dissolution rate was higher for the ternary than the

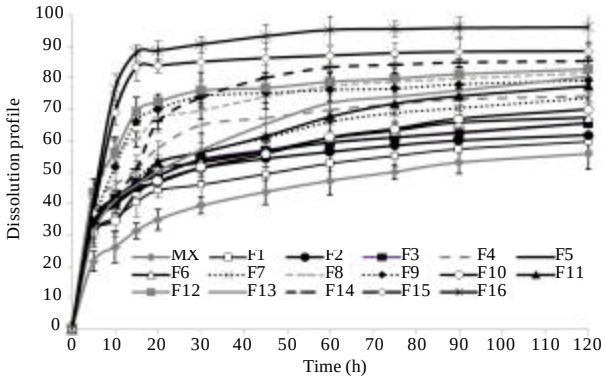

Fig. 2: Comparative dissolution profiles of MX and Solid systems in phosphate buffer (pH 7.4)

Table 4: Model independent parameters of solid systems

Formulation code	Drug content*	$t_{50\%}$(h)	$PD_{30\ min}$	$PD_{2\ h}$	$Rdr_{2\ h}$	$\%DE_{2\ h}$
MX	-	45.0	39.57	56.00	-	54.02
F 1	20.4±0.0576	36.0	46.13	59.73	1.06	59.17
F 2	20.3±0.0581	33.5	51.33	61.86	1.10	61.85
F 3	20.6±0.0531	28.5	54.13	65.65	1.17	64.97
F 4	20.5±0.0432	15.0	65.06	74.26	1.32	74.00
F 5	19.8±0.6003	27.5	54.00	65.60	1.16	63.56
F 6	20.1±0.0523	26.0	53.06	67.46	1.20	65.50
F 7	20.0±0.0402	24.0	56.66	73.60	1.31	72.98
F 8	20.5±0.0521	10.5	69.60	81.73	1.46	80.19
F 9	20.4±0.0576	24.5	51.60	70.00	1.25	69.58
F 10	20.3±0.0581	21.0	56.40	77.46	1.38	76.23
F 11	20.6±0.0531	19.0	74.26	79.33	1.42	78.84
F 12	20.5±0.0432	9.0	76.13	82.93	1.49	82.15
F 15	19.8±0.6003	22.0	65.33	80.53	1.44	79.67
F 16	20.1±0.0523	17.0	73.86	85.46	1.52	83.51
F 17	20.0±0.0402	16.0	85.20	88.53	1.58	87.56
F 18	20.5±0.0521	8.0	90.80	96.26	1.71	94.16

PD: % drug released, Rdr: Relative dissolution rate, DE: dissolution efficiency, * Average of three determination

respective binary compositions, especially for CS and FD preparations (Fig. 2). Due to the very strong affinity of MX for **β**-CD and HP**β**-CD, it is reasonable to assume that MX-**β**-CD, MX-HP**β**-CD interaction in, KN, Cell Suspensions (CS) and FD ternary products occur in a similar way as in the binary systems. Therefore, in ternary preparations the molecules of the MX-**β**-CD, MX-HP**β**-CD inclusion complexes were supposed to be present in a more or less intimate dispersed state within the PVP matrix through interactions between the exterior of the complex and PVP and this state could be responsible for the higher dissolution rates with respect to binary preparations. The results in terms of dissolution efficiency at 2 h ($\%DE_{2h}$) and percent of active ingredient dissolved at 30 min (PD_{30}) were presented in Table 4. DE is defined as the area under the dissolution curve up to the time, t expressed as a percentage of the area of the rectangle described by 100% dissolution in the same time. In the present investigation $DE_{2\ h}$ values were calculated from the dissolution data of each product and used for comparison. The $DE_{2\ h}$ and DP_{30} values of the binary and ternary systems

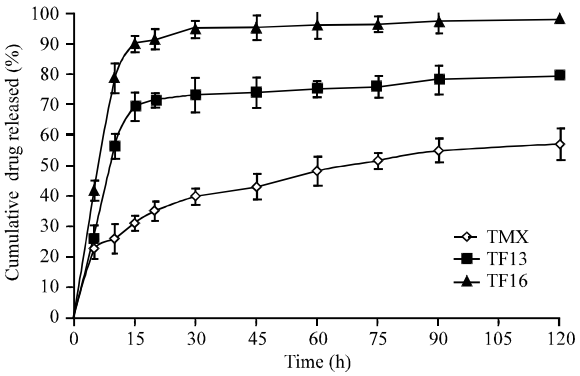

Fig. 3: Comparative drug release profiles of prepared tablets of MX, F13 and F16 in phosphate buffer pH 7.4

Table 5: Drug content and dissolution parameters of tablet formulations

Formulations	Actual drug content*	$t_{50\%}$ (h)	Max dissolved drug (%) (plateau)	DE_{2h}(%)
TMX	97.33±0.09	0.25	56.69	55.98
TF13	95.33±0.02	1.50	79.26	71.53
TF16	96.53±0.07	8.00	97.56	93.98

*: Average of three determinations

that were prepared by the co-evaporation and the freeze drying methods were relatively high in ternary system when compared with the values from the physical mixtures and MX alone. This may be due to less crystallinity of the MX-CD co-evaporation and the freeze drying product than that of physical mixtures and MX alone. Overall the ternary system of HPβ-CD with PVP (F16) (FD) product shows the best dissolution of all the formulation of the β-CD and HPβ-CD. In order to determine the difference between the release patterns of binary and ternary systems and MX, one way ANOVA was applied. From the result obtained, it was found that F_{cal} was greater than F_{tab} (11.15>2.31). So, it can be concluded that alternate hypothesis was accepted which means that there was significant difference between the release patterns of different formulation.

Tablets prepared by incorporating F16 displayed higher dissolution rate than tablets prepared by F13 (Fig. 3). Drug release data revealed that t 50% was 8h and dissolution efficiency up to 2 h is 93.98% in F16 tablet (Table 5). The kinetic analysis of the dissolution curves exhibited better fit for the zero order equation with regression value of 0.9952 for F16 and 0.9828 for F16 tablets while the data fitted to other mathematical models showed poor linearity with experimental data which indicated that drug release from the formulation was independent of the drug concentration.

***In vitro* permeation study:** The total amount of the drug permeated (μg cm^{-2}) through the cellophane membrane (M.W cut off 12000-14000) was investigated in open-ended glass tube as a function of time during the course of 7 h. The results indicated that cellophane membrane was permeable to MX. The permeation rate of the drug from its saturated solution, in phosphate buffer pH 7.4 across the membrane was calculated from the slope of graph. Among both of the complexing agent with the drug, HPβ-CD ternary system showed the pronounced and maximum permeation rate (Fig. 4) which could be attributed to the increasing amount of MX dissolved and hence, drug availability at the surface of the membrane resulting in high concentration gradient. So, Hp β-CD

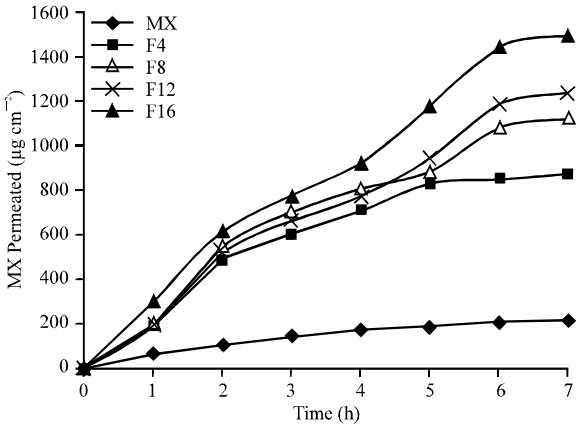

Fig. 4: Permeation release profile of selected Solid systems

and PVP K30 has an improving effect on the properties of MX as the solubility, dissolution rate and permeation through cellophane membrane and this improving effect was dependent as the fraction of HP**β**-CD and the method of preparation. Solid dispersions prepared by FD were superior in dissolving MX than that prepared through other methods.

Solid state studies: The physical state of drug in polymer matrices was studied by Fourier-transformed infrared spectroscopy (FT-IR) spectra, powder X-ray diffraction patterns (XRD), Differential Scanning Calorimetry (DSC) thermograms and Scanning Electron Microscopy (SEM). Physical mixtures with the same composition of solid dispersions were tested as a reference. Infrared spectra in the NH stretching region of MX and the various equimolar MX-**β**-CD, MX-HP**β**-CD systems, either with or without 0.4% (w/w) PVP K30, were presented in Fig. 5. Independently, the presence or the absence of PVP K30, the characteristic absorption bands of the pure drug at 3519 and 3288 cm^{-1} were maintained in physical mixture (PM) and kneading (KN) preparations, though an increase in intensity was observed in ternary systems. A marked modification of the absorption pattern was instead seen for CS and FD products, where the typical NH stretching band at 3288 cm^{-1} appeared strongly broader (binary systems) or totally disappeared (ternary system). This can be probably due to inclusion complexation of MX into the HP**β**-CD cavity. The thermograms of MX and PM showed a sharp endothermic peak at 254°C corresponding to its melting point. However, the thermogram of CS (Co-evaporated MX) in ternary system of both **β**-CD and HP**β**-CD showed melting endothermic peak at 251, 252°C. This may be due to dehydration which may be due to the occluded water during the evaporation process which is present in the liquid ammonia. For **β**-CD preparation of ternary freeze drying product there is decrease reduction of endothermic peaks i.e., 240°C and in case of freeze drying product with HP**β**-CD, endothermic peak of MX was disappeared (Fig. 6) and its intensity was very much diminished, it is due to its maximal/complete complex formation. Power X-ray diffractometry is a useful method for the detection of cyclodextrin complexation in powder or microcrystalline states. The diffraction pattern of the complex should be clearly distinct from that of the superimposition of each of the components if a true inclusion complex has been formed. Crystallinity was determined by comparing some

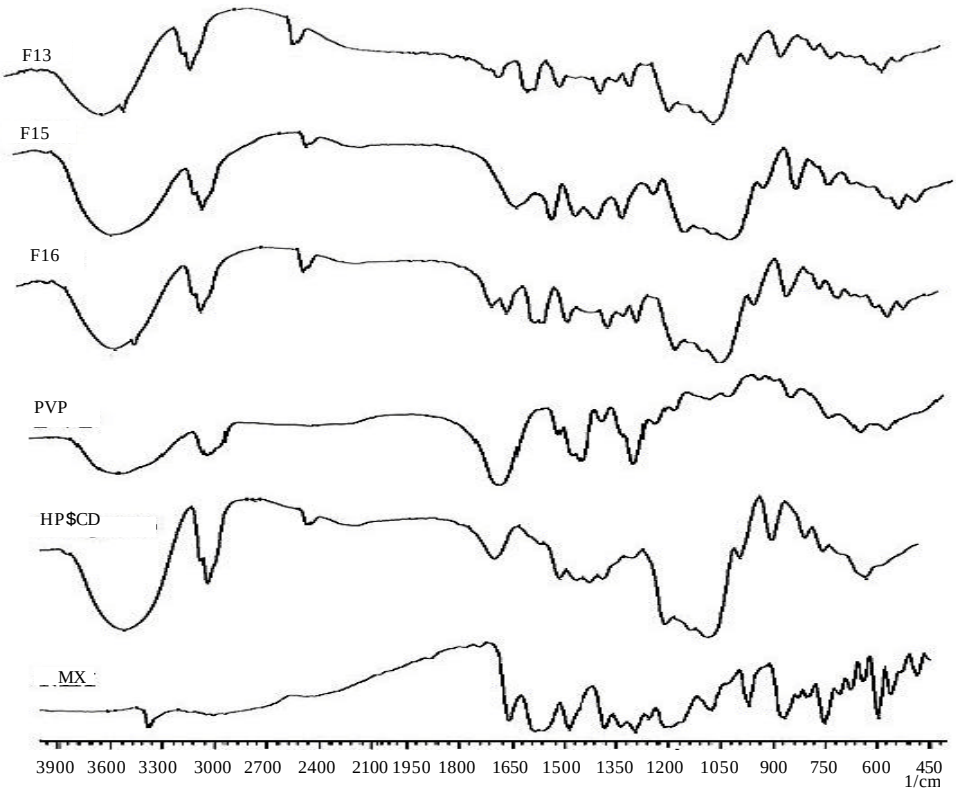

Fig. 5: FT-IR Spectra of pure components and optimized solid systems

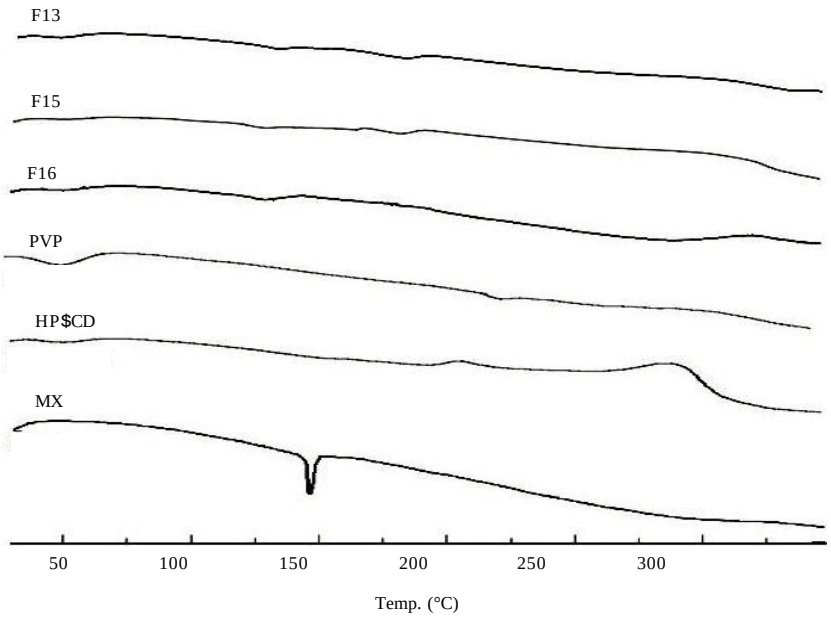

Fig. 6: Comparative DSC Thermograms of Pure Components and optimized solid systems

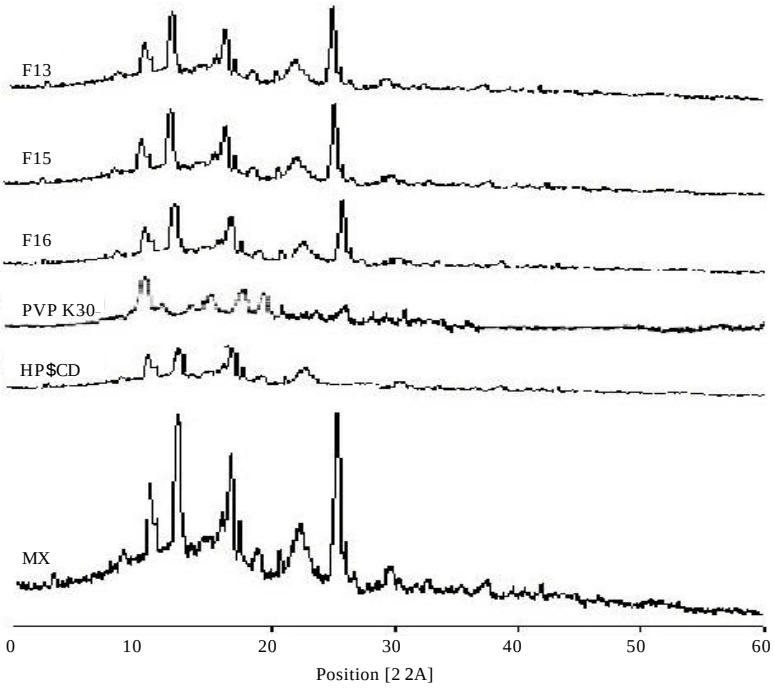

Fig. 7: Powder X-Ray Diffraction Patterns of Pure Components and optimized solid systems

representative peak heights in the diffraction patterns of the binary and ternary systems with those of a reference (Fig. 7). The relationship used for the calculation of crystallinity was as:

$$\text{Relative Degree of Crystallinity (RDC)} = I_{sam}/I_{ref}$$

where, Isam is the peak height of the sample under investigation and Iref is the peak height at the same angle for the reference with the highest intensity. Pure drug peak at 25.8°C (2θ) was used for calculating RDC of co-evaporated and freeze drying method for binary and ternary systems. The RDC values of corresponding pattern similar to that of pure MX but with relatively less intense peaks. However, the peak intensities of the binary systems were lower than the ternary system. The diffraction patterns indicated the presence of MX in a crystalline state. These results suggested that no alteration was produced in the crystal structure of MX, but that crystallinity was modified, since the peak position (angle of diffraction) was an indication of crystal structure and the peak heights in a diffractogram was measure of the sample crystallinity from the RDC values. It is seen that when pure MX was considered as reference sample, a decrement in crystallinity was observed in all of the MX-βCD and MX-HPβCD 1:1 M binary and ternary system. Scanning Electron Microscopy (SEM) was used to study the microscopic aspects of the raw materials i.e., CDs and drug substances and the products obtained by different methods of preparation like KN, CS and FD. Even if there is a clear difference in crystallization state of the raw materials and the products, this study was inadequate to affirm inclusion complexation, but nevertheless help to assess the existence of a single component in the preparations obtained. The commercial MX particles were in the form of prismatic crystals with a relatively well-defined outline. The commercial β-CD particles were irregular spherical shaped with well-developed faces. The HPβ-CD particles were

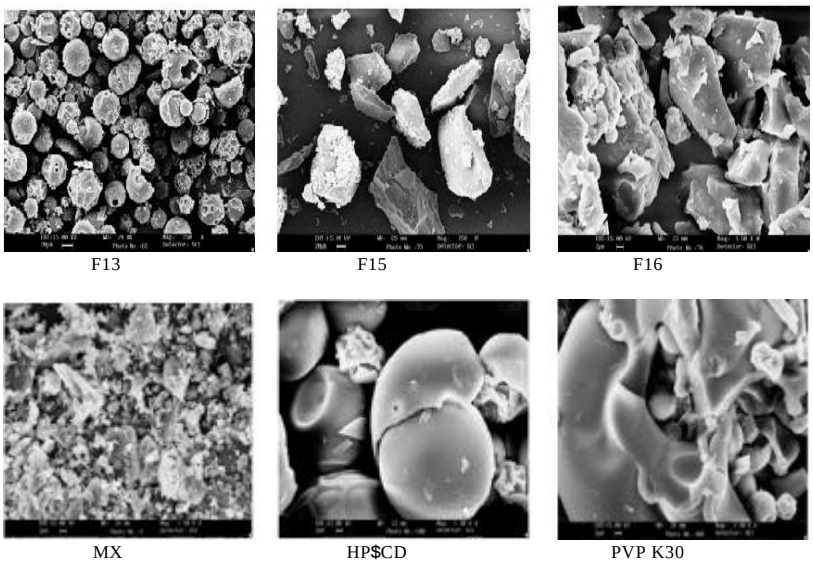

Fig. 8: SEM Images of Pure Components and optimized solid systems

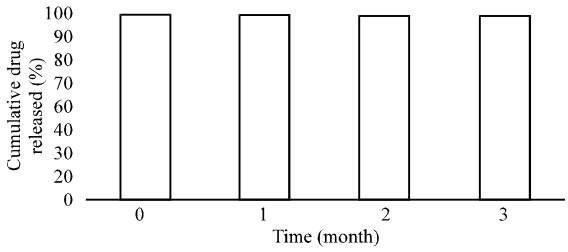

Fig. 9: Comparative graph showing the ageing effect on % dissolved for F16

large in shape as compare to the **β**-CD particles in irregular circular in shape. The smaller particles were adhered to surfaces of larger ones i.e., kneaded sample displayed similar appearance. Where as the CS particles were well-developed sphere in shape, where smaller particles were adhered to surfaces of larger ones (Fig. 8). But in case of F16 formulation, the prismatic particles were adhere to the irregular circular particles which is clearly shown and different from the physical mixture.

Stability studies: The stability data of ternary freeze dried tablets (F16 tablets) were presented in Fig. 9. The results obtained in stability test showed that the drug content, hardness and release rate of MX from F16 tablet formulation stored at a temperature of 40°C±1°C and a relative humidity of 75% was unchanged during three months of accelerating condition storage. It was indicated that solid system incorporated in tablet formulation was stable, probably due to the fact that the stable excipients such as, Sodium starch glycolate, Magnesium stearate and Lactose were employed in preparation process of tablets; another reason was that the excipients contributed towards protecting the dispersion state of the drug.

CONCLUSION

The study demonstrated the possibility of significantly improving the dissolution performance of MX by simultaneous complexation with cyclodextrin. The importance of proper selection of the most suitable counter ion to adequately improve the cyclodextrin - complexation efficiency has been pointed out. PVP showed a synergistic effect when used in combination with Hpβ-CD. Phase solubility experiments demonstrated that the ternary system with PVP (pH 5.8) exhibited a stability constant 12.9 times greater than the binary complex. The drug solubility in the presence of 50 mM HPβ-CD was about 6.23 times higher than that in the binary system. Results confirmed that the strong increase in the drug solubility shown by HPβ-CD ternary system with PVP. Solid state demonstrated that freeze drying technique was suitable for obtaining solid homogeneous equimolar MX-HPβ-CD-PVP complexes. These systems could be useful for formulating fast-dissolving drug solid dosage form able to assure rapid onset of analgesic action and improved bioavailability. To illustrate the behavior of class II drugs, the dose/solubility ratio of MX has been calculated. Its aqueous solubility of 3.7575 ìg/ml at 37°C combined with a dose of 7.5 mg, resulted in D/S of 1.996 L. On the basis of MX D/S ratio and distribution coefficient of log P = 1.904, it is reasonable to assume that MX falls under class II of BCS. Practically water insoluble drugs like MX with high D/S ratio have motivated the development of drug delivery technologies to overcome the obstacle to its solubilization through either chemical or mechanical modification of the environment surrounding the drug molecule or physically altering the macromolecular characteristics of aggregated drug particles.

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