Bulletin of Pharmaceutical Research 2015;5(3):101-7
An Official Publication of Association of Pharmacy Professionals
ISSN: 2249-6041 (Print); ISSN: 2249-9245 (Online)

RESEARCH PAPER

PREPARATION AND CHARACTERIZATION OF LORNOXICAM SOLID SYSTEMS USING CYCLODEXTRINS FOR IMPROVED BIOAVAILABILITY

P. Radhika[1]*, M.V. Nagabhushanam[2] and M. Venkata Ramana[3]

[1]*Department of Pharmaceutics, Moonray Institute of Pharmaceutical Sciences, Mahabubnagar- 509 216, Telangana, India*
[2]*Department of Pharmaceutical Management and Regulatory Affairs, Hindu college of Pharmacy, Guntur-522 002, Andhra Pradesh, India*
[3]*Department of Pharmaceutics, GBN Institute of Pharmacy, Ghatkesar, Ranga Reddy-501 301, Hyderabad, Telangana, India*

**E-mail*: radhipadarthy@gmail.com
Tel.: +91 9550954863.

Received: Dec 20, 2015 / Revised: Dec 29, 2015 / Accepted: Dec 30, 2015

The specific objectives of the investigation was to enhance the dissolution rate and bioavailability of the NSAID (lornoxicam), by Cyclodextrin complexation and to study the complexation of the selected NSAID with α-CD, β-CD and HP-β-CD. The DSC, SEM, and XRD studies indicated a reduction in crystallanity and partial amorphization of the lornoxicam because of the formation of inclusion complexes with cyclodextrins. Drugs formed inclusion complexes with β-CD, HP-β-CD, and α-CD at a 1:1 M ratio in solution. The complexes formed were quite stable. The solubility and dissolution rate of all the anti inflammatory drugs studied were markedly enhanced by complexation with α-CD, β-CD and HP-β-CD. Studies concluded that all ternary systems, showed significantly better dissolution parameters than that of the corresponding binary systems.

Key words: Lornoxicam, Cyclodextrins, Complexation, Dissolution rate, Binary systems, Ternary system.

INTRODUCTION

A number of modern drugs are poorly soluble in water and aqueous fluids. As such their absorption and bioavailability often require an improvement or an increase in the dissolution rate and efficiency (Noyes and Whitney, 1897). When poor availability is caused by dissolution rate limited absorption, improvements in the dissolution rate characteristics of the dosage form usually result in an increase in the rate and extent of the drug absorption. The major advantage of this approach is its relative accessibility and the fact that by keeping the molecular structure of the drug intact, no need will arise to conduct new and very expensive clinical studies. Many approaches have been used by researchers to enhance *in vitro* dissolution properties of poorly soluble drugs including solid dispersion (Rascnack and Muller 2002; Vijaya Kumar and Mishra 2006; Ye *et al* 2007; Malleswara Rao *et al* 2008; Patil et al, 2009; Sachan and Pushkar 2011; Patel *et al* 2015) and complexation (Miajaya *et al* 1995; Loftsson and Brewster, 1996; Endo *et al* 1997; Dahiya and Tayde 2013).

NSAIDs belong to Class II category under Biopharmaceutics Classification System (BCS) *i.e.* they are inherently highly permeable through biological membranes, but exhibit low aqueous solubility (Galia *et al* 1998). As such their oral bioavailability and efficacy are severely limited by their poor aqueous solubility and dissolution. They need enhancement in solubility and dissolution rate for improving their oral

bioavailability. Lornoxicam, which is poorly soluble in aqueous fluids, were included in the investigation and studies are carried out on these poorly soluble drugs to enhance their dissolution rate and oral bioavailability.

MATERIALS

Lornoxicam was obtained as gift sample from M/s Sigma Laboratories Ltd, Mumbai. Methanol (Qualigens Fine Chemicals, Mumbai), Distilled water (triple distilled water), 0.1 N HCl (Qualigens Fine Chemicals, Mumbai). Hydroxypropyl methylcellulose (HPMC), Polyethylene glycol (PEG 6000), Polyvinyl pyrrolidone PVP K30 were purchased from Sigma Chemical Company and *α*-, *β*- and Hydroxypropyl-*β*-cyclodextrins were obtained as gift sample from SA Pharmaceuticals.

METHODS

Preparation of solid complexes

In each case solid complexes of drug and cyclodextrin were prepared in 1:1, 1:2 ratios by three methods, kneading, coevaporation and physical mixture (Miyazawa *et al* 1995).

Kneading method

Drug and cyclodextrin with or without auxiliary substances (PEG, PVP, HPMC) were triturated in a mortar with a small volume of water. After wetting the mixture in a mortar, the thick slurry was kneaded for 45 min and then, dried at 55°C until dry. The dried mass was pulverized, sieved through sieve no. 120 and stored in desiccators till further use.

Co-evaporation method

Drug with or without auxiliary substances (PEG, PVP, HPMC) was dissolved in methanol, stirred the solution. The solvent was removed at reduced pressure in rotary evaporator at 45° C for 3 h and dried mass was pulverized, sieved through sieve no. 120 and stored in desiccators till further use.

Physical mixture

The physical mixtures were prepared by gently mixing drug, cyclodextrin with or without auxiliary substance (PEG, PVP and HPMC) in a mortar with pestle for 10 min. These mixtures were passed through a sieve no. 120 and stored in desiccators till further use.

Drug content studies

All formulations were subjected to drug content analysis using UV spectrophotometric method.

Dissolution rate studies

Dissolution rate of drug from the CD complexes in each case was studied using USP XXIII - 6 station dissolution rate test apparatus (Electro Lab) with a paddle stirrer at specified 50 rpm and a temperature of 37±1°C (Rasenack and Muller, 2002; Patil *et al* 2009).

RESULTS AND DISCUSSION

Solid binary and ternary systems were successfully prepared and evaluated. Results of drug content analysis of solid systems were in good agreement with theoretical drug content (**Tables 1**-**3**).

Table 1. Results of drug content studies of binary and ternary solid complexes prepared with *α*-CD and auxiliary compounds

CD Complex	Percent lornoxicam content (mean±s.d.)		
	Kneading method	Co-evaporation method	Physical mixture
L-*α*-CD (1:1)	49.98±0.23(0.34)	49.97±0.76(0.45)	49.93±0.82(0.97)
L-*α*-CD:PEG (1:1:0.2)	45.44±0.34(0.45)	45.40±0.28(0.87)	45.35±0.83(0.67)
L-*α*-CD:PVP (1:1:0.2)	45.56±0.56(0.78)	44.99±0.78(0.60)	45.09±0.94(0.49)
L-*α*-CD:HPMC (1:1:0.2)	45.54±0.61(0.89)	45.40±0.71(0.98)	44.97±0.95(0.67)
L-*α*-CD (1:2)	33.34±0.28(0.76)	33.32±0.98(0.65)	33.30±0.71(0.69)
L-*α*-CD:PEG (1:2:0.3)	30.29±0.45(0.87)	30.31±0.88(0.61)	29.99±0.67(0.78)
L-*α*-CD:PVP (1:2:0.3)	30.23±0.76(0.65)	30.29±0.23(0.76)	30.28±0.45(0.89)
L-*α*-CD:HPMC (1:2:0.3)	30.29±0.77(0.54)	30.28±0.76(0.54)	30.27±0.55(0.49)

Table 2. Results of drug content studies of binary and ternary solid complexes prepared with β-CD and auxiliary compounds

CD Complex	Percent lornoxicam content (mean±s.d.)		
	Kneading method	Co-evaporation method	Physical mixture
L-β-CD (1:1)	49.97±0.78(0.52)	50.03±0.73(0.78)	50.93±0.90(0.78)
L-β-CD:PEG (1:1:0.2)	45.41±0.91(0.87)	45.44±0.39(0.67)	44.95±0.86(0.78)
L-β-CD:PVP (1:1:0.2)	45.55±0.89(0.49)	44.90±0.49(0.90)	45.89±0.72(0.78)
L-β-CD:HPMC (1:1:0.2)	45.50±0.23(0.54)	45.50±0.58(0.57)	45.97±0.77(0.76)
L-β-CD (1:2)	33.29±0.45(0.98)	33.30±0.60(0.87)	33.28±0.67(0.67)
L-β-CD:PEG (1:2:0.3)	30.28±0.98(0.45)	30.29±0.59(0.59)	30.20±0.57(0.54)
L-β-CD:PVP (1:2:0.3)	30.13±0.76(0.87)	30.39±0.90(0.50)	30.38±0.65(0.76)
L-β-CD:HPMC (1:2:0.3)	30.27±0.76(0.39)	30.29±0.34(0.59)	30.29±0.90(0.90)

Table 3. Results of drug content studies of binary and ternary solid complexes prepared with HP-β-CD and auxiliary compounds

CD Complex	Percent lornoxicam content (mean±s.d.)		
	Kneading method	Co-evaporation method	Physical mixture
L-HP-β-CD (1:1)	49.97±0.65(0.34)	50.09±0.61(0.54)	49.97±0.54(0.78)
L-HP-β-CD:PEG (1:1:0.2)	45.39±0.23(0.49)	45.44±0.19(0.59)	45.23±0.43(0.90)
L-HP-β-CD:PVP (1:1:0.2)	45.45±0.45(0.44)	44.89±0.93(0.98)	45.89±0.87(0.98)
L-HP-β-CD:HPMC (1:1:0.2)	45.35±0.78(0.67)	45.50±0.45(0.58)	44.78±0.98(0.67)
L-HP-β-CD (1:2)	33.23±0.81(0.56)	33.30±0.85(0.69)	33.29±0.76(0.90)
L-HP-β-CD:PEG (1:2:0.3)	30.31±0.29(0.80)	30.25±0.28(0.90)	30.09±0.71(0.90)
L-HP-β-CD:PVP (1:2:0.3)	30.22±0.87(0.60)	30.28±0.19(0.76)	30.31±0.92(0.67)
L-HP-β-CD:HPMC (1:2:0.3)	30.39±0.76(0.87)	30.38±0.69(0.56)	30.29±0.65(0.65)

Comparative dissolution parameters of all solid complexes prepared with HPBCD by kneading method is summarized in **Table 4.**

CD complexation of lornoxicam exhibited several times higher dissolution rates and DE_{30} values when compared to the uncomplexed drug. CD complexes prepared by kneading method gave higher enhancement in the dissolution rate of the drug than the one prepared by co-evaporation method.

Overall, HP-β-CD complexes gave higher dissolution rates than that of complexes prepared with α-CD (**Figure 1, 2**).

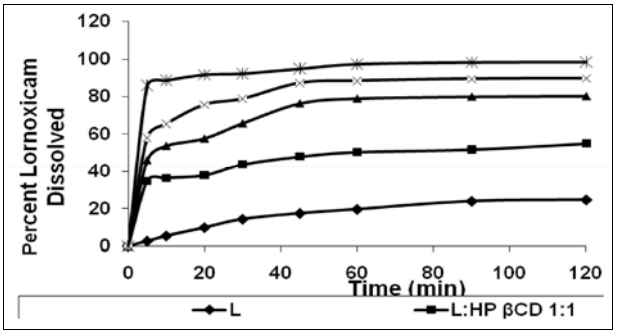

Fig. 1. Comparative dissolution profiles of lornoxicam and its HP-β-cyclodextrin binary complexes prepared by kneading method

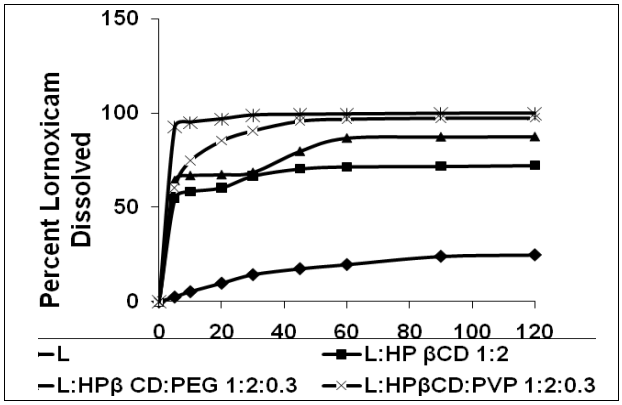

Fig. 2. Comparative dissolution profiles of lornoxicam and its HP-*β*-cyclodextrin ternary complexes prepared by kneading method

FT-IR spectra showed reduced absorption bands which suggest physical interaction between drugs and cyclodextrins. Since there is no total disappearance of the bands, it can be said that there is no chemical reaction between drug and the CDs (**Figure 3, 4**). The higher dissolution rates and DE_{30} values observed with cyclodextrin-CD complexes are due to the solubilizing effect of cyclodextrins by forming inclusion complexes with drugs in water. DSC (**Figure 5-6**) and XRD (**Figure 7-8**) studies indicated a reduction in crystallinity and partial amorphization of the lornoxicam because of the formation of inclusion complexes with cyclodextrins (Hancock and Zografi, 1997).

Table 4. Summary of dissolution parameters of lornoxicam-cyclodextrin binary and ternary complexes prepared by kneading method

Sr. No.	CD Complex	$DP_{5\ MIN}$	$RD_{r\ 5min}$	% Dissolved in 10 min	DE_{30}	K_1 (min^{-1})	Increase in K_1 (No. of folds)
1.	Lornoxicam	2.53	-	5.36	7.39	0.0043	-
2.	L:*β*-CD 1:1	26.4	10.42	28.32	26.96	0.034	8.03
3.	L:*β*-CD 1:2	48.76	19.26	63.67	57.07	0.103	24.10
4.	L:*β*-CD:PEG 1:1:0.2	40.90	16.15	42.21	41.06	0.055	12.79
5.	L:*β*-CD:PEG 1:2:0.3	58.41	23.07	68.92	60.24	0.117	27.21
6.	L:*β*-CD:PVP 1:1:0.2	63.40	25.04	68.74	63.24	0.110	25.71
7.	L:*β*-CD:PVP 1:2:0.3	72.74	28.71	80.81	74.29	0.145	38.56
8.	L:*β*-CD:HPMC 1:1:0.2	82.74	32.66	87.95	83.77	0.246	57.31
9.	L:*β*-CD:HPMC 1:2:0.3	90.62	35.78	92.21	89.08	0.345	80.23
10.	L:*α*-CD 1:1	20.31	8.01	20.74	19.25	0.025	5.89
11.	L:*α*-CD 1:2	30.62	12.08	37.81	34.90	0.048	11.24
12.	L:*α*-CD:PEG 1:1:0.2	39.78	15.68	47.52	46.55	0.064	14.99
13.	L:*α*-CD:PEG 1:2:0.3	45.65	18.01	52.31	49.54	0.076	17.67
14.	L:*α*-CD:PVP 1:1:0.2	56.74	22.39	65.74	63.05	0.108	25.17
15.	L:*α*-CD:PVP 1:2:0.3	60.21	23.77	68.44	54.00	0.115	26.78
16.	L:*α*-CD:HPMC 1:1:0.2	73.85	29.15	80.23	75.01	0.163	38.03
17.	L:*α*-CD:HPMC 1:2:0.3	82.31	32.5	86.74	81.06	0.202	47.13
18.	L:HP-*β*-CD 1:1	34.87	13.74	36.45	33.93	0.046	10.71
19.	L:HP-*β*-CD 1:2	52.96	20.89	57.87	54.85	0.092	21.39

20.	L:HP-β-CD:PEG 1:1:0.2	54.65	21.59	58.32	53.76	0.087	20.23
21.	L:HP-β-CD:PEG 1:2:0.3	64.21	25.35	66.87	61.24	0.113	26.27
22	L:HP-β-CD:PVP 1:1:0.2	58.11	22.95	75.41	71.52	0.195	45.40
23.	L:HP-β-CD:PVP 1:2:0.3	60.32	23.82	83.54	76.04	0.182	42.30
24.	L:HP-β-CD: HPMC 1:1:0.2	85.84	36.57	91.52	84.06	0.249	57.67
25.	L:HP-β-CD: HPMC 1:2:0.3	92.63	33.89	94.96	86.77	0.347	80.69

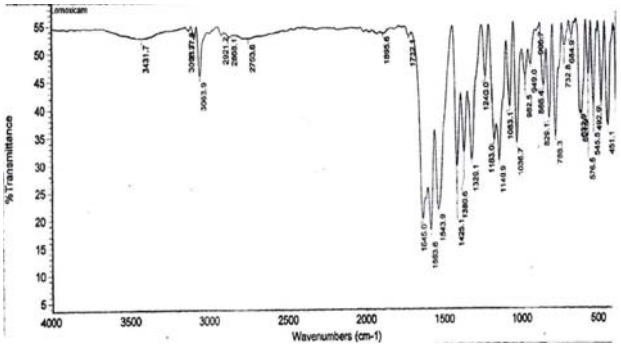

Fig. 3. IR spectra of lornoxicam

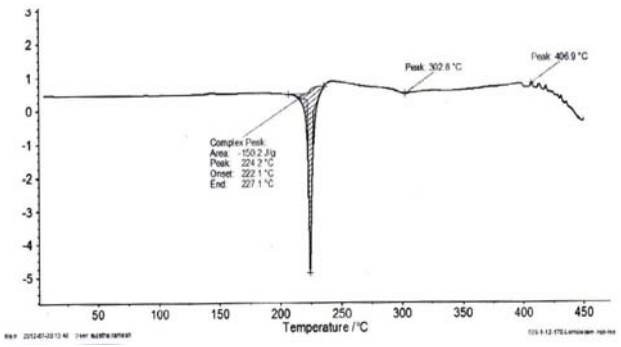

Fig. 5. DSC spectra of lornoxicam

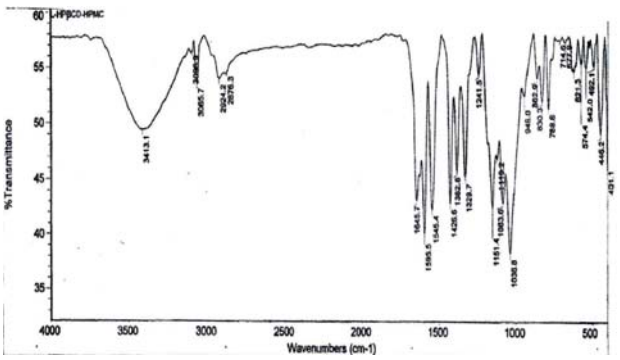

Fig. 4. IR spectra of lornoxicam:HP-β-CD-HPMC

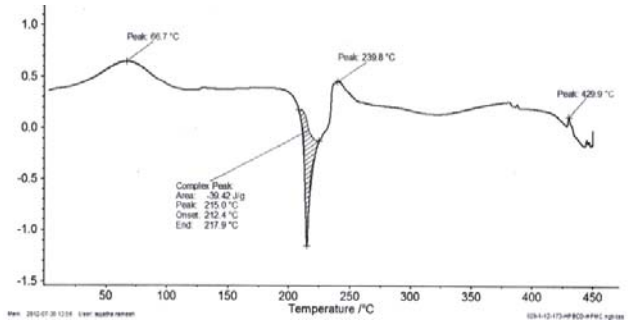

Fig. 6. DSC spectra of lornoxicam:HP-β-CD-HPMC

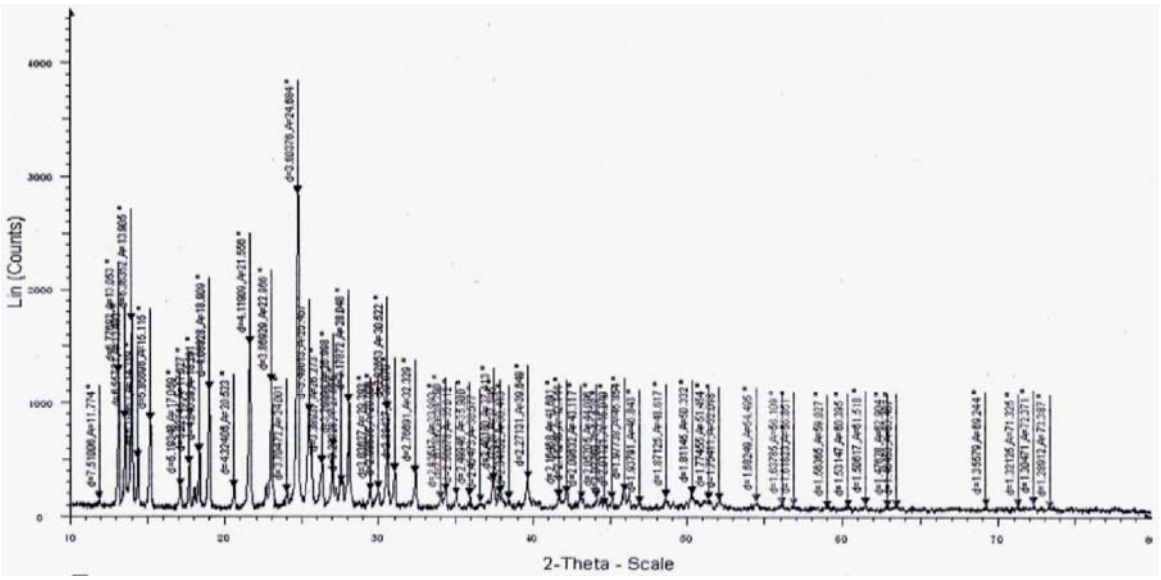

Fig. 7. XRD spectra of lornoxicam

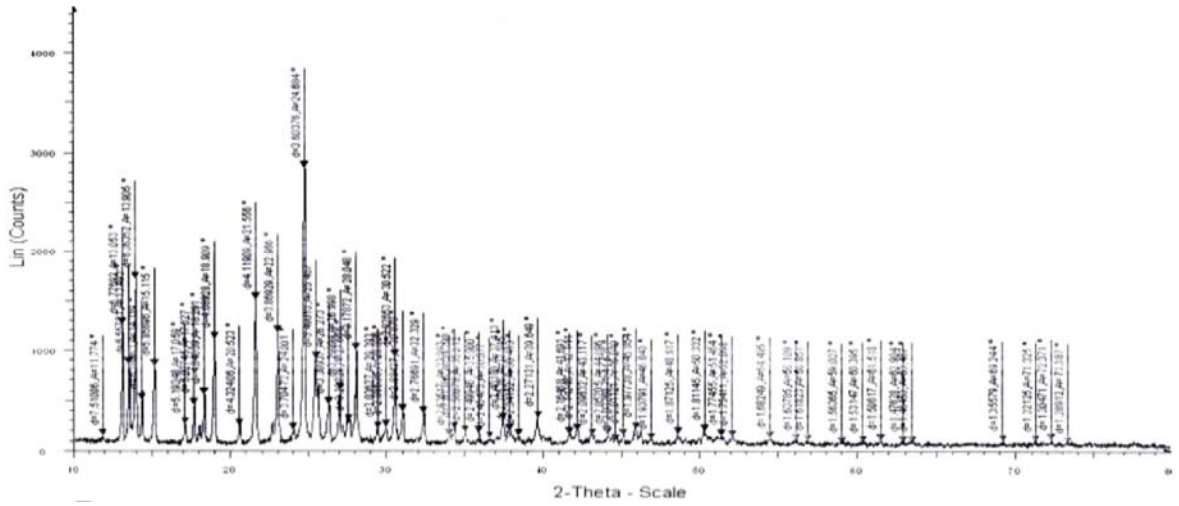

Fig. 8. XRD spectra of lornoxicam:HP-*β*-CD-HPMC

The solubility and dissolution rate of all the anti inflammatory drugs studied were markedly enhanced by complexation with *α*-CD, *β*-CD and HP-*β*-CD. Drugs formed inclusion complexes with βCD, HP-*β*-CD, and *α*-CD at a 1:1 M ratio in solution. The complexes formed are quite stable. SEM images further supported the results of DSC, XRD and FTIR studies (**Figure 9**).

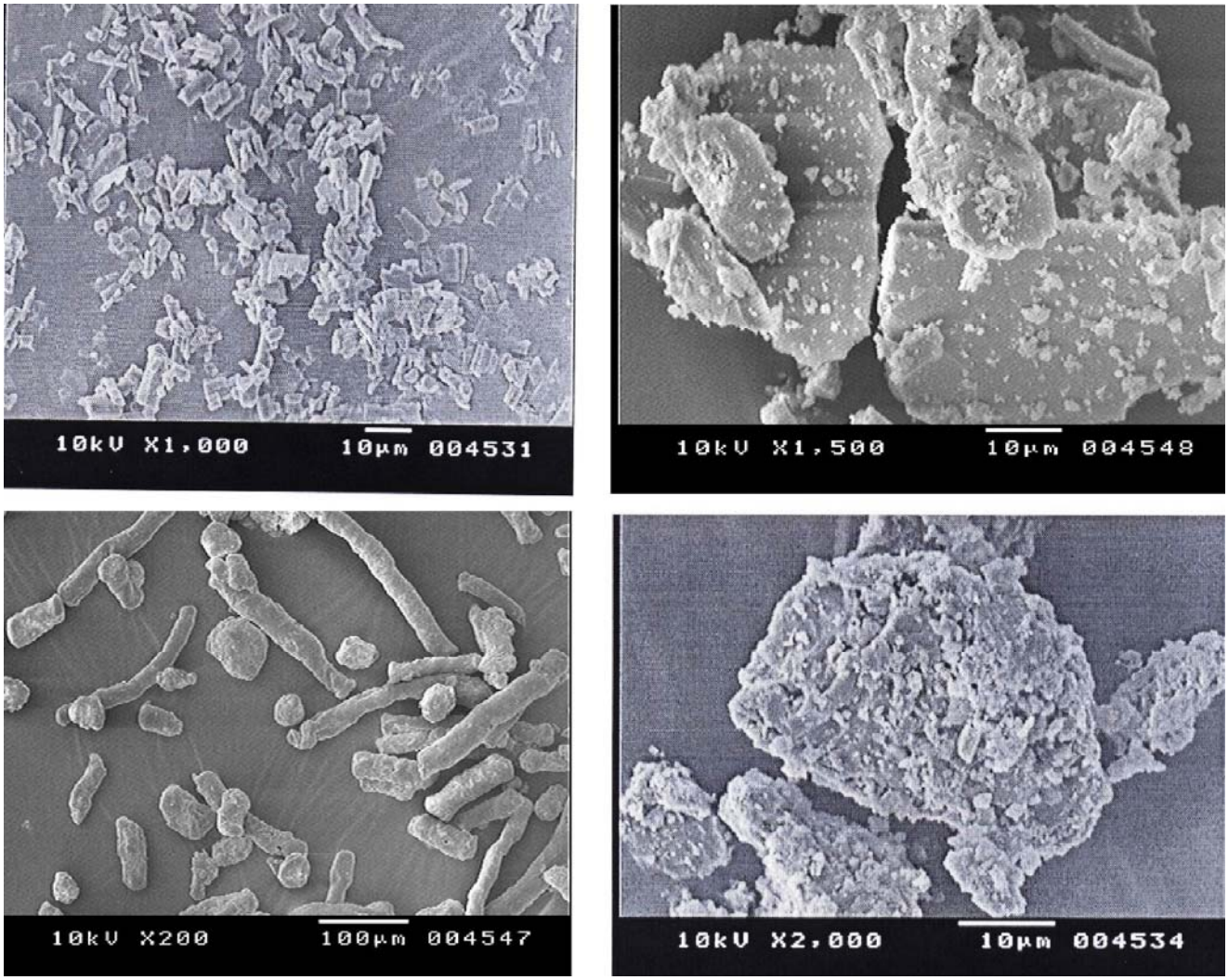

Fig 9. SEM images of (i) Lornoxicam (ii) HP-*β*-CD (iii) HPMC (iv) Lornoxicam:HP-*β*-CD-HPMC

CONCLUSION

All ternary systems, showed significantly better dissolution parameters than the corresponding binary systems. Ternary kneaded products were significantly more effective in terms of dissolution efficiency, percent dissolved in 10 min, DE 30 values. Statistical analysis of all dissolution parameters showed that for all the systems the rank order in terms of both dissolution efficiency, percent dissolved in 10 min relative dissolution rate was always: kneading > co-evaporation > physical mixture.

REFERENCES

Dahiya S, Tayde P. Binary and ternary solid systems of carvedilol with 2-hydroxypropyl-*β*-cyclodextrin and PVP K30. *Bull. Pharm. Res.* 2013;3(3):128-34.

Endo T, Nagase H, Ueda H, Kobayashi S, Nagai T. Isolation, purification, and characterization of Cyclomaltodecaose (curly epsilon-Cyclodextrin), Cyclomaltoundecaose (zeta-Cyclodextrin) and Cyclomaltotridecaose (é-Cyclo-dextrin). *Chem. Pharm. Bull.* (Tokyo) 1997;45:532-6.

Galia E, Nicolaides E, Horter D, Lobenberg R, Reppas C, Dressman JB. Evaluation of various dissolution media for predicting *in vivo* performance of class I and II drugs. *Pharm. Res.*1998;15(5):698-705. [DOI: 10.1023/A:1011910801212]

Hancock BC, Zografi G. Characteristics and significance of the amorphous state in pharmaceutical systems. *J. Pharm. Sci.* 1997;86(1):1-12. [DOI: 10.1021/js9601896]

Loftsson T, Brewster ME. Pharmaceutical applications of cyclodextrins. I. Drug solubilization and stabilization. *J. Pharm. Sci.* 1996;85(10):1017-25. [DOI: 10.1021/js950534b]

Malleswara Rao VSN, T Shyam, B Appa Rao, Y Srinivasa Rao. Formulation and characterization of meloxicam solid dispersions. *The Indian Pharmacist* 2008;7(70)67-70.

Miyazawa H, Ueda H, Nagase H, Endo T, Kobayashi S, Nagai T. Physicochemical properties and inclusion complex formation of δ-cyclodextrin. *Eur. J. Pharm. Sci.* 1995;3(3):153-62. [DOI: 10.1016/0928-0987(95)00006-Y]

Noyes AA, Whitney WR The rate of solution of solid substances in their own solutions. *J. Am. Chem. Soc.* 1897;19(12):930-4. [DOI: 10.1021/ja02086a003]

Patel TB, Patel LD, Patel TR, Suhagia BN. Artificial neural network as tool for quality by design in formulation development of solid dispersion of fenofibrate. *Bull. Pharm. Res.* 2015;5(1):20-7.

Patil SR, Ravikumar MB, Paschapur MS, Malleswara Rao VSN. Enhancement of dissolution rate of aceclofenac by solid dispersion technique. *Int. J. PharmaTech Res.* 2009;1(4):1198-1204.

Rasenack N, Muller BW. Dissolution rate enhancement by in situ micronization of poorly water-soluble drugs. *Pharm. Res.* 2002;19(12):1894-900. [DOI: 10.1023/A:1021410028371]

Sachan NK, Pushkar S. Solid dispersions: An industrially feasible alternative approach to formulate brick dust molecules. *Bull. Pharm. Res.* 2011;1(1):75-87.

van Drooge DJ, Hinrichs WL,Visser MR, Frijlink HW. Characterization of the molecular distribution of drugs in glassy solid dispersions at the nano-meter scale, using differential scanning calorimetry and gravimetric water vapour sorption techniques. *Int. J. Pharm.* 2006;310(1-2):220-9. [DOI: 10.1016/j.ijpharm.2005.12.007]

Vijaya Kumar SG, Mishra DN. Preparation and evaluation of solid dispersion of meloxicam with skimmed milk. *Yakugaku Zasshi.* 2006;126(2):93-7.

Ye G, Wang S, Heng PW, Chen L, Wang C. Development and optimization of solid dispersion containing pellets of itraconazole prepared by high shear pelletization. *Int. J. Pharm.* 2007;337(1-2):80-7. [DOI: 10.1016/j.ijpharm.2006.12.028]

*****