

## Preparation and Characterization of Domperidone Inclusion Complexes with Cyclodextrin: Influence of Preparation Method

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### Abstract

Domperidone is a widely used antiemetic, poorly water soluble drug, erratically absorbed in stomach and possess several dissolution-related problems thus it has poor bioavailability. Solubility of a drug plays a very important role in dissolution and hence absorption of drug which ultimately affects its bioavailability. Hence, by considering the facts related to drug, attempts have been made to formulate inclusion complexes using methylated  $\beta$ -cyclodextrin and also to study the effect of preparation method. Inclusion complexes were prepared using methylated  $\beta$ -cyclodextrin in 1:1 and 1:2 molar ratios. Kneading, ultrasonification and physical mixture method were used for preparation of inclusion complexes. All the inclusion complexes were characterized using FTIR, DSC and XRD. The solubility and dissolution results revealed that there was a considerable increase in solubility and dissolution of all inclusion complexes as compared to pure drug. It was highest in case of methylated  $\beta$ -cyclodextrin in 1:1 molar ratio using ultrasonification method (USM1). Stability study revealed that all complexes were stable for a period of three months.

**Keywords:** Domperidone; Methylated cyclodextrin; Inclusion complexes; Solubility.

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### Introduction

Aqueous solubility is one of the key determinants in development of new chemical entities as successful drugs (1). Drugs with poor water solubility typically have low bioavailability and/or tend to be highly crystalline. As shown, cyclodextrins (CDs) are water soluble and form inclusion complexes with a polar molecules or functional groups in water insoluble compounds. The resulting complex hides most of the hydrophobic functionality in the interior cavity of the cyclodextrin while the hydrophilic hydroxyl groups on its external surface remain exposed

to the environment (2). Cyclodextrins comprise a family of three well-known industrially produced major, and several rare, minor cyclic oligosaccharides. The three major CDs are crystalline, homogeneous, nonhygroscopic substances, which are torus-like macro-rings built up from glucopyranose units. The  $\alpha$ -cyclodextrin (Schardinger's  $\alpha$ -dextrin, cyclomaltohexaose, cyclohexaglucan, cyclohexaamylose,  $\alpha$ -CD, ACD, C6A) comprises six glucopyranose units,  $\beta$ -cyclodextrin (Schardinger's  $\beta$ -dextrin, cyclomaltoheptaose, cycloheptaglucan, cycloheptaamylose,  $\beta$ -CD, BCD, C7A) comprises seven such units and  $\gamma$ -cyclodextrin (Schardinger's  $\gamma$ -dextrin, cyclomaltooctaose, cyclooctaglucan, cyclooctaamylose,  $\gamma$ -CD, GCD, C8A) comprises eight such units (3).

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Domperidone ( $C_{22}H_{24}ClN_5O_2$ ) is a widely used antiemetic, poorly water soluble drug, erratically absorbed in stomach and possess several dissolution-related problems thus it has poor bioavailability (15%). From an economic point of view, low oral bioavailability results in wasting of a large portion of an oral dose and adds to the cost of drug therapy, especially when the drug is an expensive one and also more exposure of drug to body. The approach of complexation has been frequently used to increase the aqueous solubility and dissolution rate of water insoluble and slightly soluble drugs in an effort to increase oral bioavailability. However, in certain instances, this approach can be used to increase drug stability e.g. 13-cis-retinoic (4) and disoxaril (5), to control drug release rate e.g. nicardipine (6), vinpocetine (7) and fentanyl(8), to improve organoleptic properties and finally to maximize the gastrointestinal tolerance by reducing drug irritation after oral administration. Generally speaking, cyclodextrins are potential carriers for achieving such objectives.

Consequently, the rationale of this study was to improve the therapeutic efficacy of domperidone utilizing the approach of inclusion complexation of the drug in cyclodextrins.

## Experimental

### Materials

Domperidone was kindly donated by IPCA Laboratories, and Ratlam,  $\beta$ -Cyclodextrin ( $\beta$ -CD) and methylated  $\beta$ -cyclodextrin (M- $\beta$ -CD) were kind gifts from Roquette Fereres, France. All other chemicals used in the study were of analytical grade and used as received.

### Methods

#### *Phase solubility studies*

Phase solubility studies were performed according to the method reported by Higuchi and Connors (9-12). An excess amount of Domperidone (10 mg) was added to 10 mL of distilled water containing rising amounts of  $\beta$ -CD and M- $\beta$ -CD solutions at various concentrations (0.001-0.01 M) in 10-mL screw capped bottles. The contents were stirred at 37°C for 72 h on a rotary flask shaker. After equilibrium, the samples were filtered through Whatman filter

paper no. 42 and absorbances were recorded at 284 nm using a 2401-PC UV spectrophotometer (Shimadzu Corporation, Japan), if necessary, after suitable dilution. The apparent stability constant was calculated from the initial straight portion of the phase solubility diagram using the following equation:

$$K 1 : 1 = \frac{\text{Slope}}{S(1 - \text{Slope})} m - 1$$

where,

S = solubility of drug without cyclodextrin

M = molar concentration

K = apparent stability constant

Slope is calculated from regression equation.

#### *Preparation of inclusion complexes*

Domperidone inclusion complexes were prepared with M- $\beta$ -CD in different ratio (1:1 and 1:2) as follows:

a) The mixture was transferred to mortar and kneaded for 45 min using alcohol-water mixture in ratio 1:1, sufficient solvent was added to maintain paste like consistency (13).

b) The mixture was transferred to beaker using alcohol-water mixture in ratio 1:1, sufficient solvent was added to maintain paste like consistency. The resulting paste was then ultrasonicated for 6 h. During ultrasonication, paste-like consistency was maintained using alcohol-water (14).

c) Physical mixtures were prepared by simply blending domperidone and CDs with 1:1 molar ratio uniformly in a mortar (15).

Then prepared complexes were dried and passed through sieve no. 100. The prepared complexes were stored in glass vials and used for further studies.

#### *Infrared spectroscopy*

The FT-IR spectra of pure drug, pure M- $\beta$ -CD, physical mixtures and all formulations were taken by preparing KBr pellets using 8400S FTIR spectrophotometer (Shimadzu Corporation, Japan). The condition used was as follows: pressure, 6-8 tons; die size, 13mm; scanning range, 4000-500  $cm^{-1}$ )

#### *X-Ray diffraction studies*

The structural, crystal and physical state

characterization were studied using X-Ray diffraction for pure drug, M- $\beta$ -CD, physical mixtures and all inclusion complexes. Powder X-ray diffractometry was carried out with X-ray powder diffraction system, PAN Analytical Spectris Pvt. Ltd., Singapore using copper target, a voltage of 40 kV and a current of 30 mA. The scanning was done over  $2\theta$  range of  $5^\circ$  to  $60^\circ$ . This study was performed at Department of Physics, RTM Nagpur University, Nagpur.

#### *Differential scanning calorimetry*

Differential scanning calorimetry studies were performed for pure drug, pure cyclodextrins, physical mixtures and inclusion complexes. The DSC study was carried out with METTLER DSC 30S, Mettler Toledo India Pvt. Ltd., Switzerland, using crucible Al 40  $\mu$ L, at of  $10^\circ\text{C}/\text{min}$  heating rate, under nitrogen environment. The temperature range used was  $0\text{-}400^\circ\text{C}$ . This study was performed at Sophisticated Analytical Instrument Facility, RTM Nagpur University, Nagpur.

#### *UV interference*

Scanning of inclusion complexes were performed to evaluate whether there is any interference in UV detection of inclusion complexes compared to control (drug) which can depict the drug polymer interaction, if any (16). The UV interference of each inclusion complexes was determined using powder equivalent to 10 mg of domperidone and was dissolved in 20 mL of 0.1-M HCl using the mechanical shaker for 20 min and to the solution obtained 0.1-M HCl was added and volume made to 50 mL. The solution was then filtered through Whatman filter paper No.42 and required dilutions were made and finally dilutions were scanned.

#### *Drug content*

The percent drug content of each inclusion complexes were determined using powder equivalent to 10 mg domperidone and was dissolved in 20 mL 0.1-M HCl using the mechanical shaker for 20 min. To the solution obtained, 0.1-M HCl was added and volume was made to 50 mL. The solution was then filtered through Whatman filter paper no.42 and required

dilutions were made and absorbance was taken at 284.20 nm.

#### *Solubility studies*

The solubility of domperidone, as bulk drug, and its inclusion complexes were determined in 0.1-M HCl and distilled water. Inclusion complexes equivalent to 10 mg of drug was taken and to this, 10 mL of the respective medium was added in 100 mL stoppered volumetric flasks and shaken for 24 h at room temperature ( $25^\circ\text{C}$ ) on a mechanical shaker (15). After 24 h, samples were filtered through Whatman filter paper No.42 and aliquots were suitably diluted for estimation.

#### *Dissolution studies*

The dissolution studies on pure drug and inclusion complexes (equivalent to 10 mg of drug) were performed. The condition of dissolution test was as follows: medium, 900 mL 0.1-M HCl (pH 1.2); speed, 100 rpm; temperature,  $37 \pm 0.5^\circ\text{C}$ ; apparatus, USP type II rotating paddle. During dissolution study, 10-mL aliquot was withdrawn at different time intervals from 5 to 60 min and replaced with equal volume of fresh medium. The withdrawn samples were filtered through Whatman filter paper no.42 and absorbance were measured at 284.20 nm against 0.1-M HCl blank.

Cumulative percent drug dissolved was found out at each time interval and graph was plotted between cumulative percent drug dissolved and time in min.

#### *Stability studies*

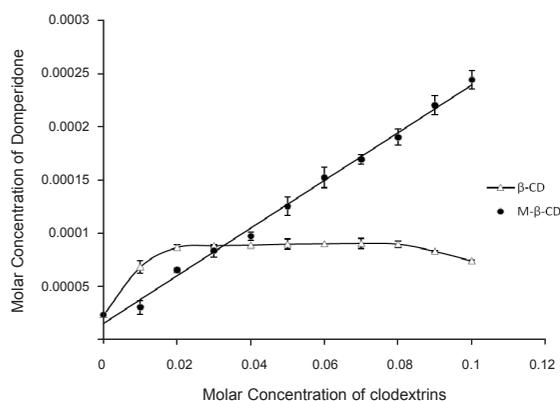
The inclusion complex stability study was carried out at two conditions:

- i)  $25 \pm 2^\circ\text{C}$  and  $75\% \pm 5\%$  relative humidity (RH).
- ii)  $40 \pm 2^\circ\text{C}$  and  $75\% \pm 5\%$  RH for the period of three months (17).

The inclusion complexes were placed in amber coloured bottles and put at above specified conditions for 3 months. After every month, inclusion complexes were analyzed for drug content.

#### *Statistical analysis*

All studies were performed in triplicate and values were expressed as mean $\pm$ SD. The



**Figure 1.** Phase solubility studies of domperidone.

data were analysed by one-way analysis of variance (ANOVA) followed by Dunnett test or by Unpaired Student 't' test. A value of  $P < 0.05$  was considered as significant. Graph Pad InStat (Demo Version) was used for analysis of data.

### Results and Discussion

The phase solubility study is useful for investigating an inclusion complexation of drug with cyclodextrin and its derivatives in distilled water because it gives not only the solubilising ability of host molecules but also the stability constant of complexes with the help of phase solubility curve. From the phase solubility study (Figure 1), it was observed that solubility increases when concentration of CDs rises.  $\beta$ -CD showed  $B_s$  type phase solubility curve, indicating a limited solubility. Over 0.01-0.03 M of  $\beta$ -CD concentration, the solubility of domperidone was suddenly increased linearly due to the formation of soluble complexes. As the ascending portion of the phase solubility diagram may be considered as  $A_L$  type phase solubility diagram, it is possible to determine the complex stoichiometry. At the  $\beta$ -CD concentration value of 0.05 M, the solubility limit of this complexes is reached and so further addition of  $\beta$ -CD results in precipitation of the complexes. From 0.08 M  $\beta$ -CD concentration, domperidone solubility decreased to reach a plateau. These observations suggest that  $\beta$ -CD concentration above 0.08 M forms another complex with a different stoichiometry (probably 1:2) and shown lowest



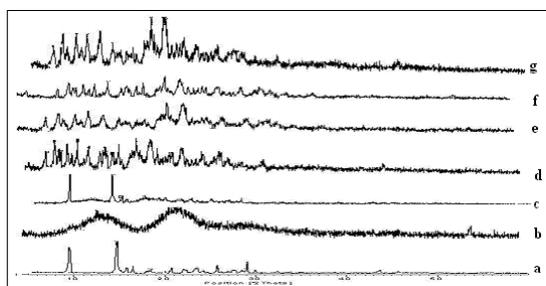
**Figure 2.** FTIR spectra of (a) domperidone; (b) M- $\beta$ -CD and the corresponding drug-carrier molar ratio; (c) physical mixtures 1:1 (PMM1); (d) kneaded 1:1 (KNM1); (e) kneaded 1:2 (KNM2); (f) ultrasonification 1:1 (USM1); (g) ultrasonification 1:2 (USM2).

solubility, as reported by Pascal et al. (10). The stability constant ( $K_s$ ) of the 1:1 complex of drug with  $\beta$ -CD was calculated by the ascending part of the diagram in  $B_s$  type solubility diagram and it was found to be 3.19.

From these it could be concluded that  $\beta$ -CD is not the proper carrier for increasing solubility. Hence,  $\beta$ -CD was not taken for further study.

From the phase solubility study, it was observed that M- $\beta$ -CD shows  $A_L$  type phase solubility curve, indicating improved solubility. This fact is well supported by Challa et al. (18). Solubility of domperidone increased in all medium in a linear fashion with increased concentration of M- $\beta$ -CD and showed  $A_L$  type phase solubility curve indicating that soluble complexes were formed and no precipitation was observed. The stability constant ( $K_s$ ) of the 1:1 complex of drug with M- $\beta$ -CD was calculated from the slope of straight line in  $A_L$  type solubility diagram and was found to be  $96.05 \text{ M}^{-1}$ .  $K_s$  values obtained are adequate for the formation of inclusion complexes which may contribute improving the bioavailability of poorly water soluble drugs.

The FT-IR of pure drug was characterized by N-H stretching at  $3122 \text{ cm}^{-1}$  and C=O stretching at  $1714.60 \text{ cm}^{-1}$ , indicating the presence of -CONH group, asymmetric C-H stretching at  $2937.38 \text{ cm}^{-1}$  symmetric C-H stretching at  $2817.81 \text{ cm}^{-1}$ , N-H deformation at  $1693.38 \text{ cm}^{-1}$ , aromatic C-H stretching at  $3024.18 \text{ cm}^{-1}$  and C=C at  $1622.02 \text{ cm}^{-1}$ . The FT-IR of pure M- $\beta$ -CD was characterized by OH stretching at  $3442.70 \text{ cm}^{-1}$  and  $3300.84 \text{ cm}^{-1}$ , aliphatic

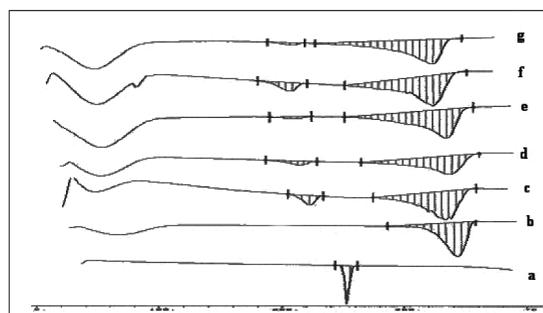


**Figure 3.** X-Ray diffraction pattern (a) domperidone; (b) M-β-CD and the corresponding drug-carrier molar ratio; (c) physical mixtures 1:1 (PMM1); (d) kneaded 1:1 (KNM1); (e) kneaded 1:2 (KNM2); (f) ultrasonification 1:1 (USM1); (g) ultrasonification 1:2 (USM2).

C-H stretching at  $3471\text{--}3332\text{ cm}^{-1}$  and C-O-C stretching at  $1159.14\text{ cm}^{-1}$ . In all the inclusion complexes the prominent and characteristics peaks of domperidone are appeared indicating intactness of drug in complexes (Figure 2).

The X-Ray diffraction pattern of domperidone exhibited sharp, highly intense and less diffused peaks indicating the crystalline nature of drug. The X-Ray diffraction pattern of physical mixture of domperidone with M-β-CD was simply a superimposition of each component with peaks of both domperidone and carriers, however, with lower intensity. The kneaded and ultrasonicated inclusion complexes showed less intense and highly diffused peaks of drug which was very poor in reflections which testified to a reduced ordering of crystal lattice, indicating formation of amorphous solid state. The extent of crystallinity influences the dissolution of the drug. An amorphous, less crystalline and metastable form as compared to pure drug dissolves at a faster rate because of high internal energy and greater molecular motion which enhance the thermodynamic property as compared to crystalline materials. In the prepared inclusion complexes there was a reduction in crystallinity of the drug as compared to pure sample reflecting that the drug was dispersed in the polymer and hence increased in the solubility as compared to pure drug (Figure 3).

The thermal curve of domperidone ( $T_{\text{peak}} = 251.6^{\circ}\text{C}$ ,  $\Delta H = 150.9\text{ J/g}$ ) indicated its crystalline anhydrous state. Marked reduction of area, broadening and down shifting of

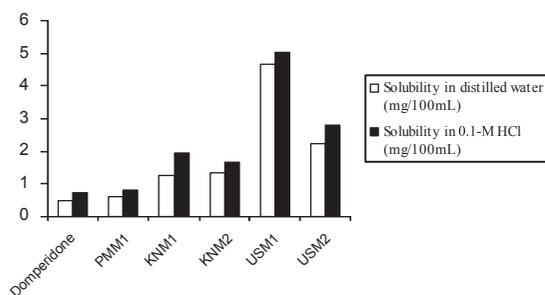


**Figure 4.** DSC curves (a) domperidone; (b) M-β-CD and the corresponding drug-carrier molar ratio; (c) physical mixtures 1:1 (PMM1); (d) kneaded 1:1 (KNM1); (e) kneaded 1:2 (KNM2); (f) ultrasonification 1:1 (USM1); (g) ultrasonification 1:2 (USM2).

peak temperature of drug melting endotherm ( $T_{\text{peak}} = 246.7^{\circ}\text{C}$ ,  $\Delta H = 31.4\text{ J/g}$ ), was observed in physical mixture with M-β-CD, indicative of a more evident loss of drug crystallinity. In all the inclusion complexes, the drug melting endotherm broadened and shifted to lower temperature passing from physical mixture ( $T_{\text{peak}} = 246.7^{\circ}\text{C}$ ,  $\Delta H = 31.4\text{ J/g}$ ) to ultrasonification 1:1 ( $T_{\text{peak}} = 240.9^{\circ}\text{C}$ ,  $\Delta H = 28.6\text{ J/g}$ ), ultrasonification 1:2 ( $T_{\text{peak}} = 240.7^{\circ}\text{C}$ ,  $\Delta H = 12.6\text{ J/g}$ ), kneaded 1:1 ( $T_{\text{peak}} = 237.6^{\circ}\text{C}$ ,  $\Delta H = 24.3\text{ J/g}$ ) and kneaded 1:2 ( $T_{\text{peak}} = 236.3^{\circ}\text{C}$ ,  $\Delta H = 7.8\text{ J/g}$ ). In all the inclusion complexes, the drug endothermal effect further broadened and was almost hidden by the dehydration band of the carrier and it finally disappeared in the ultrasonification 1:1 and 1:2 (Figure 4). This last phenomenon was attributable to both inclusion complexes formation and/or drug amorphization (19).

In order to study the possibility of any drug polymer interaction, the scanning of the various inclusion complexes were carried out in 0.1-M HCl and scanning results indicated that there was no interference or shifting of  $\lambda_{\text{max}}$  of domperidone which reflects no drug polymer interaction. Drug content of all inclusion complexes were in the range of 78.94%–88.43%. This indicates the proper loading of drug in inclusion complexes and effectiveness of kneading method and ultrasonification. The drug content of inclusion complexes are as shown in (Table 1).

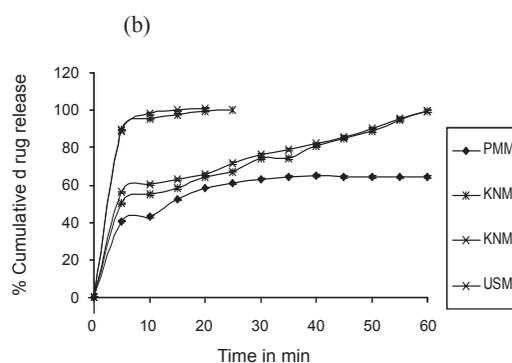
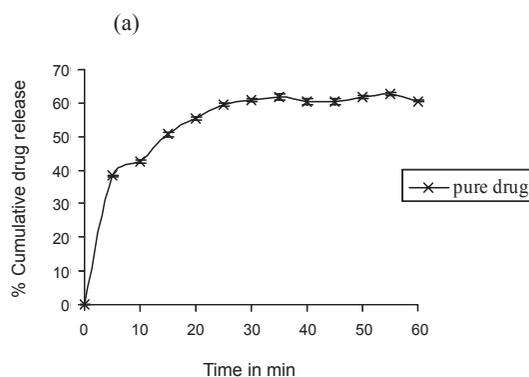
The solubility of all inclusion complexes was studied in distilled water and 0.1-M HCl.



**Figure 5.** Solubility of domperidone and the corresponding drug-carrier inclusion complexes in distilled water as well as 0.1-M HCl

The data indicated (Figure 5) that solubility increased in all cases but highest increase was found in inclusion complexes prepared by M-β-CD prepared in 1:1 ratio (USM1).

It is evident at a glance that all system with CDs exhibited better dissolution properties than pure drug alone. Statistically significant differences in term of dissolution were found in all the domperidone-M-β-CD inclusions. The greater ability of M-β-CD in domperidone amorphization could explain the better dissolution properties of the drug. As for the influence of the preparation method, an analog trend was observed with both CDs; the greatest improvement of drug dissolution was obtained with ultrasonification product, followed in order by kneading and finally by physical mixture. The increased dissolution rate (physical mixture) is attributable both to improvement in drug wettability and to formation of readily soluble complexes in dissolution medium. Further improvement obtained with kneading and ultrasonification could be explained by the more intimate contact between drug and carrier and the decrease of drug crystallinity, as well as a phenomenon of at least partial drug inclusion complexation. On the contrary, the influence of the preparation method was clearly more marked in case of product with M-β-CD, where kneaded and ultrasonification product showed an increase in dissolution efficiency of 90% or 110% (Figure 6), in comparison to corresponding physical mixture. The best performance of these product seemed to confirm that drug inclusion



**Figure 6.** a) Dissolution studies of pure drug; b) dissolution studies of various inclusion complexes prepared with M-β-CD.

complexation occurred substantially only in such systems, thus allowing to obtain the highest dissolution improvement. Dissolution data of inclusion complexes also indicated that there was an increase in dissolution as compared to pure drug, and maximum increase was observed in case of inclusion complexes USM1. Statistical analysis of data considering USM1 as control batch showed considerable significant difference ( $P < 0.05$ ).

The result of stability study indicated that the inclusion complex USM1 was stable and there was no significant changes observed in the drug content ( $P > 0.05$ ).

In conclusion, inclusion complexes of domperidone prepared with M-β-CD showed improved dissolution behaviour as compared to plain drug. Amongst all complexes prepared with M-β-CD, complexes USM1 (1:1 M) prepared by ultrasonification showed a statistically

significant increase in solubility and dissolution ( $P < 0.01$ ).

### Acknowledgements

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### References

- (1) Thorsteinn L, Dagny H, Mar Masson . Evaluation of cyclodextrin solubilization of drugs. *Int. J. Pharm.* (2005) 302: 18-28.
- (2) Cyclodextrin for Pharmaceutical Application [Editorial]. Technical brochure of wacker-chemie GmbH, international specialty product (2002)
- (3) Jozset S. Past, present and future of cyclodextrin research. *Pure Appl. Chem.* (2004) 76: 1825-1845.
- (4) Yap KL, Liu X and Thenmozhiyal JC. Characterization of the 13-*cis*-retinoic acid/cyclodextrin inclusion complexes by phase solubility, photostability, physicochemical and computational analysis. *Eur. J. Pharm. Sci.* (2005) 25: 49-56.
- (5) Ventura CA, Giannone I, Musumeci T, Pignatello R, Ragni L, Landolfi C, Milanese C, Paolino D and Puglisi G. Physico-chemical characterization of disoxaril-dimethyl- $\beta$ -cyclodextrin inclusion complex and *in vitro* permeation studies. *Eur. J. Med. Chem.* (2006) 41: 233-240.
- (6) Fernandes CM, Ramos P and Baptista V. Hydrophilic and hydrophobic cyclodextrins in a new sustained release oral formulation of nicardipine: *in vitro* evaluation and bioavailability studies in rabbits. *J. Control. Rel.* (2003) 88: 127-134.
- (7) Ribeiro LS, Ferreira DC, Francisco JB and Veiga FJ. Physicochemical investigation of the effects of water-soluble polymers on vinpocetine complexation with  $\beta$ -cyclodextrin and its sulfobutyl ether derivative in solution and solid state. *Eur. J. Pharm. Biopharm.* (2003) 20: 253-266.
- (8) Holvoet C, Vercammena JP, Heyden YV, Gabriëls M and Camuc F. Preparation and in-vitro release rate of fentanyl-cyclodextrin complexes for prolonged action in epidural analgesia. *Int. J. Pharm.* (2003) 265: 13-26.
- (9) Jose RM, Maria LAB and Juan MG. Nuclear magnetic resonance investigation of the inclusion complexation of gliclazide with  $\beta$ - cyclodextrin. *J. Pharm. Sci.* (1997) 86: 72-75.
- (10) Pascal B, Maud G, Georges D, Adelin A, Valery B, Bruno P, Geraldine A, Luc D and Brigitte E. The effect of cyclodextrin on the aqueous solubility of new MMP inhibitors: phase solubility. H-NMR spectroscopy and molecular modeling studies, preparation and stability study of nebulizable solution. *J. Pharm. Sci.* (2005) 8: 164-175.
- (11) Liu X, Lin H, Thenmozhiyal JC, Chan S and Paul HC. Inclusion of acitretin into cyclodextrins: Phase solubility, Photostability, and physicochemical characterization. *J. Pharm. Sci.* (2003) 92: 2449-2457.
- (12) Mourya VK, Saini TR, Balasubramaniyam V, Shete JS and Jadhav GS. Molecular inclusion of sparfloxacin with hydroxypropylbetacyclodextrin. *Indian J. Pharm. Sci.* (2002) 64: 568-572.
- (13) Wen X, Tan F, Jing Z and Liu Z. Preparation and study the 1:2 inclusion complex of carvedilol with cyclodextrin. *J. Pharm. Biomed. Anal.* (2004) 34: 517-523.
- (14) Liu L and Zhu S. Preparation and characterization of inclusion complexes of prazosin hydrochloride with cyclodextrin and hydroxypropyl-cyclodextrin. *J. Pharm. Biomed. Anal.* (2006) 40: 122-127.
- (15) Yap KL, Liu X and Thenmozhiyal JC. Characterization of the 13-*cis*-retinoic acid/cyclodextrin inclusion complexes by phase solubility, photostability, physicochemical and computational analysis. *Eur. J. Pharm. Sci.* (2005) 25: 49-56.
- (16) Chowdhary KPR and Madhusudhan P. Studies on preparation and evaluation of solvent deposited systems of piroxicam. *Indian J. Pharm. Sci.* (1990) 52: 32-33.
- (17) Cartensen JT. *Drug Stability: Principle and Practice*. 2<sup>nd</sup> ed. Marcel Dekker, New York (1995) 538-550.
- (18) Challa R, Ahuja A and Khar RK. 2005. Cyclodextrins in drug delivery: an updated review. *AAPS Pharm. Sci. Tech.*, 2(4) 82-99.
- (19) Mura P, Faucci MT, Manderioli A, Bramanti G and Parrini PL. 1999. Thermal behaviour and dissolution properties of naproxen from binary and ternary solid dispersions. *Drug Dev. Ind. Pharm.*, 25, 257-264.