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Ibuprofen-β-cyclodextrin Inclusion Complexes: Evaluation of Different Complexation Methods

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The objective of this research work was to investigate the influence of temperature on the optimization process of the formation of inclusion complexes, preparation and characterization of inclusion complexes between ibuprofen (IBF) and β-cyclodextrin (β-CD), and the evaluation of different complexation methods. Inclusion complexes in the solid powdered forms were prepared by homogenous coprecipitation-evaporation (CE), coprecipitation-centrifugation (CC), spray drying (SD), and freeze drying (FD) methods. Scanning electron microscopy (SEM), differential scanning calorimetry (DSC), x-ray diffractometry and IR absorption spectroscopy were exploited to characterize the solid complexes. *In vitro* dissolution experiments were conducted in distilled water using the USP XXII paddle method. The f_2-metric technique was employed for the determination of equivalency between the dissolution profiles through multiple linear regression computer soft ware program. Temperature was found to have an important role in the optimization process of the complex formation. A marked difference in the properties of the complexes was observed due to their methods of preparation. In general, the solubility and dissolution rates of the complexes formed were greatly enhanced over that of the physical mixture, which, in turn, could demonstrate higher dissolution rates than those displayed by the pure drug. The freeze drying method was found to provide with the highest dissolution rates among the methods used in this investigation.

Key words: Ibuprofen, β-cyclodextrin, inclusion complexes, temperature, different complexation methods

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Introduction

Complexation by cyclodextrins, especially the most commonly available β-cyclodextrin (β-CD), is widely used to increase the solubilities of drug molecules which have limited solubilities in water (Mc.Donal *et al.*, 1996; Peri *et al.*, 1994; Labenderia *et al.*, 1993; Amdidoch *et al.*, 1989). This is due to the particular structure of β-CD that imparts interesting physico-chemical properties by molecular encapsulation of a wide variety of drugs into its interior hydrophobic cavity, resulting in the enhancement of water solubility and dissolution rate of the drugs (Sanghavi *et al.*, 1993). Because of these abilities, β-CD has been widely used in the pharmaceutical field.

Different methods are being used to prepare inclusion complexes of a variety of drugs in order to improve their solubility and dissolution rates e.g. coprecipitation (Labenderia *et al.*, 1993; Sherif *et al.*, 1996; Loftsson *et al.*, 1996), kneading (Palmieri *et al.*, 1993), SD (Boymond *et al.*, 1994) and FD (Labenderia *et al.*, 1993 and Nagarsenkar *et al.*, 1996) methods.

Phase solubility analysis has been among the preliminary requirements towards the optimization of the development into inclusion complexes of the drugs. This process has been used by many researchers for the determination of the exact molar ratios in which the drugs could make complexes with β-CD (Peri *et al.*, 1994 and Labenderia *et al.*, 1993., however, as far as our knowledge is concerned, there has been little available information concerning the influence of temperature on the ability of molecular encapsulation of the drugs by the β-CD cavity.

The objective of this study was to investigate the influence of temperature on the optimization process of the formation of inclusion complexes, preparation and characterization of IBF/β-CD inclusion complexes, and the evaluation of different complexation methods, with respect to improvement in the dissolution rates of IBF.

Materials and Methods

The materials used were ibuprofen (Xin Hua Pharmaceutical Factory Shandong, China), and β-CD (Central Chemical Factory, Shanghai, China). All other reagents used were of analytical grade.

Phase Solubility Studies: The phase solubility studies were conducted according to the method of Higuchi and Connors (1965), three samples were made (a) at room temperature (b) shaken and retained at 37° C (C) shaken at 37° C and retained at room temperature. Excess amounts of IBF (100mg) were added to aqueous solutions (100ml) containing various concentrations of β-CD. Samples in air-tight containers were shaken in a thermostatically controlled mechanical shaker (Guo Hua C. T.Z. 82, China) for 24hr. and then retained for another 24hr. period in order to attain the equilibrium. Finally, samples of 5ml were carefully filtered (0.8 μm) and analyzed spectrophotometrically (model 752-C, The 3rd Analytical Instrument Factory, Shanghai, China) at 264nm.

Preparation of Inclusion Complexes: As determined from the phase solubility studies, the molar ratios of IBF and β-CD required for the complex formation were 2:3 and 1:3 at 37°C and at room temperature, respectively; therefore, complexes were prepared using these two molar proportions of the constituents.

(A) Coprecipitation-evaporation (CE) Method: The homogeneous CE method (Puglisi *et al.*, 1990) was used to prepare a 1:3 and a 2:3 inclusion complex between IBF and β-CD using the appropriate, respective molar ratios of the two ingredients. IBF was dissolved in a minimum volume of ethanol (C_2H_5OH) to which the required moles of β-CD, dissolved in distilled water, were gradually added. The mixtures were stirred at a rate of 400 rpm for 24 hr. using a constant velocity electric stirrer (Especial Medical Instruments Factory Shanghai, China), and then slowly evaporated on a boiling water bath. The precipitated complex was dried at 60° C for about 4hr., pulverized, sieved (# 100 mesh), and finally stored in a desicator till further use.

(B) Coprecipitation-centrifugation (CC) Method: IBF and β-CD in their molar ratio of 2:3 were treated as above, however, centrifugation was performed instead of evaporation using a centrifuge (Medical Analytical Instruments Factory, Shanghai, China) at 1500 rpm for 1 hr to obtain the sedimented complex. Later on the sedimented complex was collected by decanting the supernatant liquid and the solid mass thus obtained was treated as above to get the dry sample. Inclusion complex 1:3 was not prepared by this method.

(C) Spray Drying (SD) Method: For preparing the molar ratios of 1:3 and 2:3, the required molar quantity of IBF was dissolved in minimum volume of C_2H_5OH and the respective molar solutions of β-CD were added into it with constant stirring, which was continued for 24 hr. Later on the solution was filtered (0.8 μm) and then spray dried, employing Buchi B-191 Mini Spray Dryer (Switzerland) with the process parameters adjusted as; inlet temperature at 125° C, outlet temperature at 60°C, aspirator at 91% and the pump at 24%. An off-white powdered complex, with a poor yield (76.68 %), was obtained which was stored in a desicator till further use.

(D) Freeze Drying (FD) Method: IBF and β-CD in 1:3 and 2:3 molar ratios were dissolved in 0.14 % aqueous ammonium hydroxide (NaOH) (because IBF is a slightly water-soluble drug). The solution was filtered (0.8symbol μm) and then freeze dried in a freeze dryer (Heto F D 2.5) and this mass was kept in a desicator for three days and finally treated as described above. No trace of ammonium ions (NH^+_4) were detected in the complex, using the Nesselarization method (Labenderia *et al.*, 1993).

Physical mixtures of IBF and β-CD (1:3 and 2:3) were also prepared by gradually mixing the two components, passed through # 100 mesh sieve, dried in an oven at 60 °C for 4hr., and stored in a desicator.

Characterization And Evaluation Methods: The particle shape and topography were studied by Scanning Electron Microscopy(SEM) (ISI-SX-40, Akashi, Japan). The samples for SEM were mounted on sample stubs with double-sided adhesive tape and vacuum coated with gold.

Differential Scanning Calorimetric (DSC) patterns were determined using a differential scanning calorimeter (DSC-25 Mettler, Switzerland). Each sample was heated between 50 and 200°C, with a scanning rate of 10°C min^{-1}.

Powder x-ray diffraction patterns of the ingredients and the products were carried out using Rigako model D/MAX-RC diffractometer (Japan) with Cu-Kμ radiation (λ= 1.5406 A°), voltage 40 KV, current 50 mA, at a scanning rate of 3° min^{-1}.

Infra Red (IR) absorption studies of pure IBF, β-CD, their physical mixture, and the inclusion complexes were prepared by CE, CC, SD and FD methods, were carried out using Perkin-Elmer model 983 IR spectrophotometer (USA), according to the KBr disk method.

***In vitro* Dissolution Rate Studies:** *In vitro* dissolution studies of IBF powder , IBF-β-CD physical mixtures, and the inclusion complexes prepared by the above mentioned methods were

conducted using USP XXII paddle method, with model ZRS -4 Intelligent Dissolution Tester (Tianjin University Radio Factory, Tianjin, China) at a speed of 100 rpm. The dissolution medium was distilled water (900 ml) and the bath temperature was maintained at 37± 0.1°C. A powdered sample (pure IBF, physical mixture, or the respective inclusion complex) equivalent to 15 mg of IBF was introduced into the dissolution medium. At suitable intervals, samples of 5 ml were taken and immediately replaced with equal volume of fresh dissolution medium (distilled water maintained at 37± 0.1°C to maintain a constant volume for the drug dissolution. The withdrawn samples were filtered (0.45μ) and analyzed spectrophotometrically at 264 nm (752-C The 3rd Analytical Instrument Factory, Shanghai, China).

Determination of Dissolution Equivalency: The use of f_2-metric equation (Moore and Flanner, 1966) was made, which has recently been recommended for use by the US FDA (Us Federal Register, 1995) when determining the equivalence of dissolution profiles;

$$f_2 = 50 \text{ Log}\{[1 + 1/n\sum_{t=1}^{n} (R_t - T_t)^2]^{-0.5} \times 100\}$$

where R_t and T_t represent the release profiles data from the reference and test formulations at time t. f_2 = 100 when test and reference profiles are identical and decreases as the level of dissimilarity increases. The US FDA has suggested that f_2 values between 50 and 100 constitute identical behavior. f_2-metric values were computed by linear regression analysis, fitting the release profiles data from the reference and test formulations in the above equation, using a computer software program True Basic here-Version 2.03 (True Basic Inc., USA).

Results and Discussion

Phase Solubility Studies: The phase solubility diagram of the samples a, b and c is shown in Fig. 1. In all the three cases the IBF-β-CD system exhibited the Bs-type of solubility curves (Higuchi and Conners, 1965), suggesting that the molar ratio for the complex formation is not 1:1 but as calculated from their respective solubility data, it was 1:3 for the samples described above in (a) while 2:3 for those of the (b), and (c). The changes in the stoichiometric ratios of the two components at different temperatures could be attributed to the influence of temperature leading towards the conclusion that molecular encapsulation capability of β-CD cavities could be increased at higher temperatures. The possible explanations for this effect can be:
(a) changes could have occurred in the geometric compatibility between IBF molecules and β-CD cavities e.g. at higher temperatures the sizes of the elongated IBF molecules in the liquid system would have been reduced because of breaking down of the water structure around those parts which are going to be included in the cavities of β-CD and due to transport of some water molecules into the solution (Cramar *et al.*, 1967). In this way the IBF molecules would be able to find complete accommodation in the cavities of the host molecules and become amenable to the formation of a complex having higher molar ratio of the drug (Lengyel *et al.*, 1981), and (b) breaking down of water structure inside the β-CD ring and removal of some molecules from the ring at higher temperatures, resulting in increasing the capacity and consequently, the capability of β-CD cavities to accommodate more molecules of IBF (Cramar *et al.*, 1967).

Scanning Electron Microscopy (SEM): Fig. 2 shows the scanning electron photomicrographs of all complexes studied. Analysis of the SEM revealed that the large polyhedral crystalline forms of β-CD and the elongated crystals of IBF, clearly visible in the physical mixture, were transformed to more amorphous ones in case of the inclusion complexes, demonstrating a totally different picture from those of the pure components and the physical mixture. This indicates that some type of interaction(s) might have occurred during the complexation process.

Differential Scanning Calorimetry (DSC): Fig. 3 shows that the DSC thermograms of IBF, β-CD, their physical mixture and the inclusion complexes, while their recorded DSC melting points are given in Table 1. The sharp endothermic peaks of the pure IBF at 76.4°C is of very high intensity, showing the crystalline form of IBF (Fig. 3a). The thermogram of the physical mixture (Fig. 3c) demonstrated both the peaks due to free IBF as well as β-CD, with some changes in the characteristics of the peaks shown by the individual components, for example the endothermic peak representing the free IBF was of reduced intensity and was shifted towards lower temperature (72.7 °C). At the same time the second peak representing β-CD, originally at 147.6 °C (Fig. 3b) has been shifted to 137.6 °C along with some apparent changes in its intensity. These results led us to the conclusion that some type of interactions did occur between IBF and β-CD, even in the physical mixture of the two components. Most probably, this could be due to the processing (mixing, sieving, heating of samples for DSC analysis, etc.) of the physical mixture. In support there is another study (Nakai, 1086) describing the interactions which took place between β-CD and some drugs, even by simply grinding the components with one another. However, in the DSC thermogram for IBF-β-CD inclusion complex the fusion peak of free IBF was absent from the thermograms, indicating that all of the IBF was engaged in the complexation leading to the formation of inclusion complexes in which IBF is protected by the β-CD ring molecule. This not only confirms the interactions between IBF and β-CD but at the same time the formation of real complexes is also confirmed, with clearly different structures than that of the physical mixture (Szejtli, 1982).

Table 1: Recorded DSC Melting Points of Various Samples

Sample	Formulation	1st Peak	2nd Peak
a	Pure Ibuprofen	76.4	---------
b	Pure β-CD	147.6	---------
c	IBF-β-CD physical mixture	72.7	137.6
d	IBF-β-CD CE inclusion complex (1:3)	169.0	---------
e	IBF-β-CD CE inclusion complex (2:3)	144.3	---------
f	IBF-β-CD CC inclusion complex (2:3)	141.0	---------
g	IBF-β-CD SD complex (1:3)	160.5	---------
h	IBF-β-CD SD complex (2:3)	157.7	---------
I	IBF-β-CD FD complex (1:3)	163.0	---------
j	IBF-β-CD FD complex (2:3)	154.6	---------

X-ray Diffraction Patterns: Fig. 4 shows the x-ray diffraction patterns of the all complexes. Significantly different x-rays diffraction patterns are to be expected if an inclusion complex is formed, because crystal structure will be changed (Green *et al.*, 1991). It was seen that most of the diffraction patterns of the physical mixture were simply superimposition or summation of the drug and β-CD, with similar sharp peaks, much similar d (interplanar distance) values, and other characteristics as that of the pure components. Nevertheless, some changes like peak locations, reduction in peak intensities, and small differences in the d values were observed in the diffractograms of the physical mixture (Table 2), indicating the possibility of some types of interactions between β-CD and IBF. On the other hand, the investigation of changes in peaks locations, appearances, disappearances and the relative intensity of the peaks of the inclusion complexes demonstrated somewhat diffused diffraction patterns with clear cut differences than those of the physical mixture and the individual constituents. Moreover the d values of the inclusion complexes were totally different from that of IBF and β-CD (Table 2), which further strengthens the evidence that complexation did occur between ibuprofen

Table 2: Powder x-ray diffraction of IBF, β-CD, their physical mixture and the inclusion complexes, expressed as 2θ, peak intensity, width, interplanar distance, and relative diffraction intensity.

SamplSample	2 θ	Peak Intensity (cps)	Width (deg)	Interplanar Dist. (d)	Rel. Diffr. Int. (I/I_o)
IBF	6.060	51870	0.360	14.573	1.00
	12.180	18564	0.360	7.261	0.36
	16.500	11025	0.480	5.368	0.21
	24.520	11342	0.390	3.628	0.22
β-CD	12.440	4389	0.390	3.628	0.22
	18.800	2322	0.540	4.71	0.53
	19.480	2849	0.570	4.553	0.65
	2 0.800	2238	0.570	4.267	0.51
IBF-β-CD.	6.520	3721	0.330	14.430	0.84
Phys.Mixt.	12.440	4439	0.660	7.110	1.00
	19.460	3452	0.450	4.558	0.78
	20.820	2099	0.600	4.263	0.47
IBF-β-CD	6.520	1681	-------	13.713	0.12
CE Complex	12.220	856	0.360	7.237	0.16
	17.160	3157	0.240	4.881	0.58
	17.840	5448	0.420	4.968	1.00
IBF-β -CD	6.560	823	0.450	13.463	0.53
SD	11.480	1256	0.450	7.702	0.82
Complex	17.540	1541	0.570	5.052	1.00
	19.960	683	-------	4.445	0.44
IBF-β-CD	6.580	767	0.510	13.422	0.42
FD	11.600	1416	0.420	7.622	0.78
Complex	7.640	1812	0.750	5.024	1.00
	19.880	719	--------	4.462	0.40

Table 3: f_2-metric values for the determination of equivalency between the release profiles from different formulations

Formulation	f_2-metric values*	f_2-metric values**	1:3 vs. 2:3 formulations	f_2-metric values***
Phy.mixture (1:3)	32.5169	------	physical mixtures	98.7589
Phy.mixture (2:3)	30.2891	------		
CC complex (1:3)	------	------	------	------
CC complex (2:3)	18.8721	41.4675		
CE complex (1:3)	12.4288	------	CE complexes	97.3170
CE complex (2:3)	12.2801	------		
SD complex (1:3)	13.3538	77.8815	SD complexes	87.8104
SD complex (2:3)	12.8373	86.1856		
FD complex (1:3)	9.0767	51.1080	FD complexes	77.6392
FD complex (2:3)	8.5020	47.9172		

* f_2-metric values for the release profiles of IBF control (reference) vs. different formulations (tests)
** f_2-metric values for the release profiles of CE 1:3 or 2:3 (reference) vs. different formulations with their respective IBF-β-CD ratios (tests).
*** f_2-metric values for the release profiles of different formulations with IBF-β-CD ratios 1:3 (references) vs. IBF-β-CD ratios 2:3(tests)

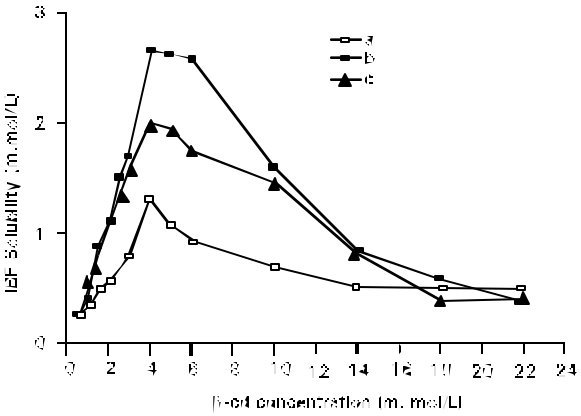

Fig. 1: Phase solubilty diagram of IBF-β-CD systems (a) Samples shaken and retained at room temperature (23° C), (b) Samples shaken and retained at 37° C, and (C) Samples shaken at 37 ° C and retained at 23° C.

and β-CD. The x-ray diffraction patterns further showed that the crystalline peaks in the diffractograms of the inclusion complexes were broader and of much reduced intensities, indicating the amorphous nature of the complexes. These results are in accordance with those, previously, revealed by the SEM. This could be attributed to the molecular encapsulation of the IBF molecules by the interior hydrophobic cavity of the β-CD leading to the inhibition or retardation of IBF crystallization (Najib *et al.*, 1985; Hassegawa *et al.*, 1986).

Infra Red (IR) Spectral Studies: The IR spectra of all complexs studies shown in Fig. 5. The IR spectrum of IBF showed the most prominent and the characteristic sharp band due to the C = O stretching vibrations of carboxylic acid group(-COOH) at 1730 cm^{-1} (Fig. 5a). The same peak with almost similar sharpness and exactly the same location was also exhibited by the spectrum for the physical mixture of IBF and β-CD, however, the intensity of the peak seemed to be reduced, because of the probable interactions between the two components of the mixture. On the other hand Fig. 5 (c-f), the spectra for the inclusion complexes indicated that this

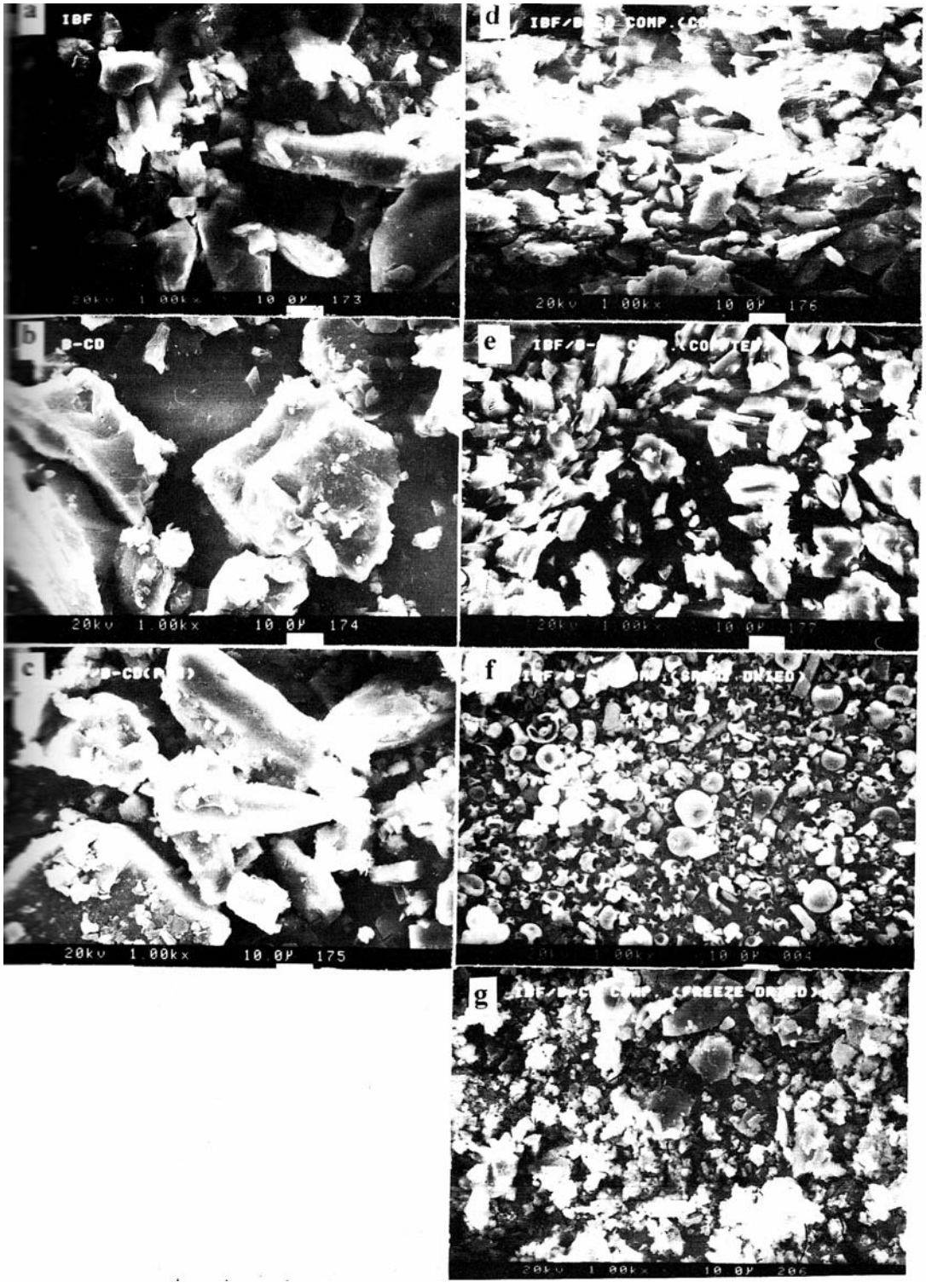

Fig. 2: Scanning electron photomicrographs of (a) IBF, (b) β-CD, (c) their physical mixture (2:3) and the complexes (2:3) prepared by (d) CE, (e) CC, (f) SD, and (g) FD methods.

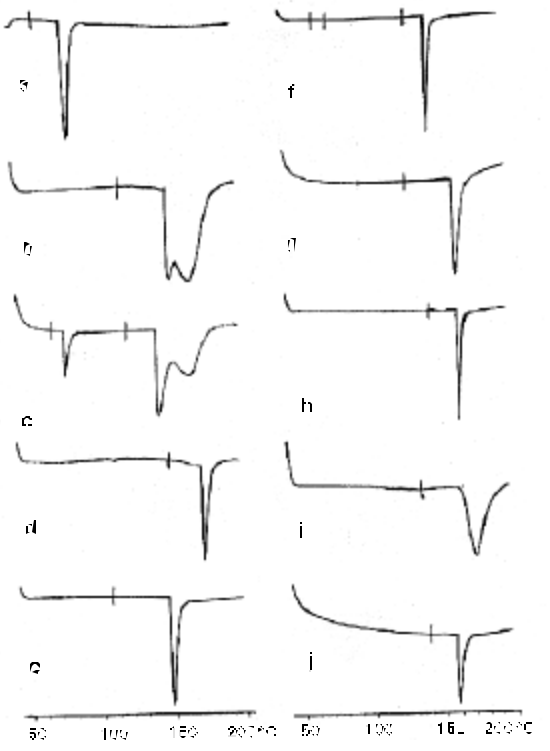

Fig. 3: DSC thermograms of (a) IBF, (b) β-CD, (c) their physical mixture, and inclusion complexes prepared by the methods of (d) CE 1:3 and (e) CE 2:3; (f) CC 2:3; (g) 1:3 and (h) SD 2:3; and (I) FD 1:3 and (j) FD 2:3.

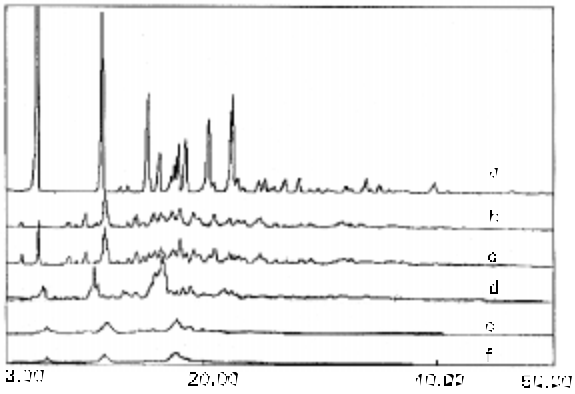

Fig. 4: X-ray diffractograms of (a) IBF, (b) β-CD, (C) physical mixture of IBF and β-CD, and IBF-β-CD inclusion complexes prepared by (d) CE, (e) SD, and (f) fD methods.

band of IBF spectrum had been reduced considerably and shifted from 1730 cm^{-1} to the lower wave numbers in case of the SD complex (1715 cm^{-1}) and the in CE complex (1706 cm^{-1}), while in case of the FD complex it was completely absent. These results suggested the existence of

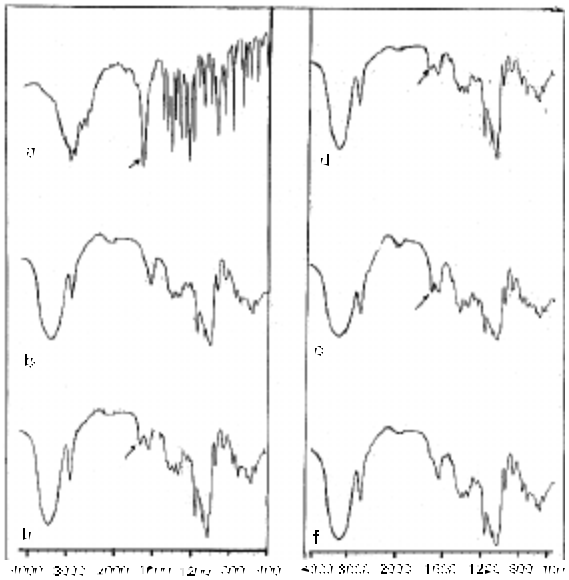

Fig. 5: IR spectra of (a) IBF, (b) β-CD (c) Physical mixture of IBF and β-CD, and IBF-β-CD inclusion complexes prepared by (d) CE, (e) SD, and (f) FD methods.

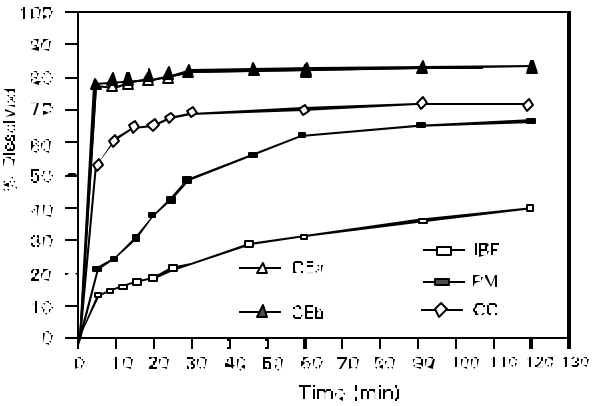

Fig. 6: Dissolution profiles of IBF-β-Cd physical mixture (pM), and inclusion complexes prepared by the methods of copercipitation-centrifugation 1:3 (CC), and coprecipitation-evaporation 1:3 (CEa), 2:3 (CEb).

some stronger types of interactions between IBF and *β*-CD, which could be due to the breaking down of intermolecular hydrogen bonding of IBF and establishment of weaker forces in the complex system (Vromans *et al*, 1989) and /or because of the restriction of the C = O group of IBF into the *β*-CD cavity, resulting in complete absence of the band or a shift of the wave number of the stretching vibrations due to C = O to a lower wave number (Sanghavi *et al.*, 1993).

***In vitro* Dissolution Rate Studies:** Fig. 6 shows the dissolution profiles of IBF, its physical mixture with *β*-CD and their inclusion complexes prepared by CE and CC methods, while the dissolution profiles of the complexes prepared by SD and

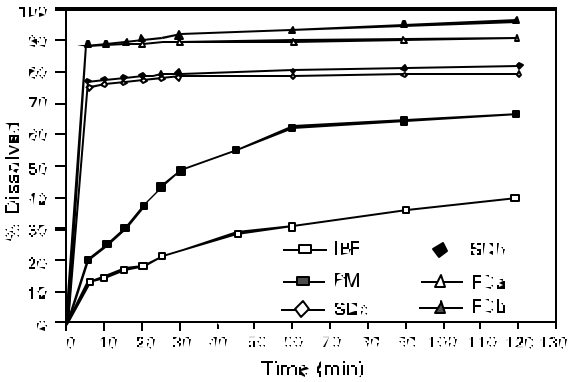

Fig. 7: Dissolution profiles of IBF, IBF-β-CD physical mixture (PM), and inclusion complexes prepared by the method of spray drying 1:3 (SDa), 2:3 (SDb), and freeze drying 1:3 (FDa), 2:3 (FDb)

FD methods are presented in Fig. 7. It was found that after 2 hr. of the dissolution testing about 96.5, 91.2; 83.6, 83.2; 82.0, 79.7; and 71.4% of IBF was dissolved from the FD complex 2:3, 1:3; CE complex 2:3, 1:3; SD complex 2:3, 1:3; and CC complex 2:3, respectively. Dissolution rate of the physical mixture (66.4 %) also demonstrated improvements over the free drug (about 39.6 %), but it had much lower initial as well as apparent dissolution rates when compared to those from the inclusion complexes. This could be due to some probable interactions between IBF and β-CD, which might have caused improved wettability, increased surface area, the molecular dispersion characters, etc. (Vromans *et al.*, 1989). To determine the dissolution equivalency or differences, the dissolution profiles of IBF, IBF-β-CD, their physical mixtures, and the inclusion complexes prepared by different methods were inspected visually as well as by employing the f-metric technique. The f_2-metric values computed for this purpose are shown in Table 3 which clarifies the significance of differences between the dissolution profiles from the reference and test formulations.

From this investigation concluded that Phase solubility analysis is the preliminary and the most important process for the optimization of the development into inclusion complexes of the drugs and temperature was found to have an important role and pronounced influence on this process of optimization. The solubility and dissolution rates of all the complexes studied were greatly enhanced over that of the physical mixture, which, in turn, could demonstrate higher dissolution rates than those displayed by the pure drug. The improvement in solubility and dissolution rate was attributed to complexation and amorphization. Moreover, keeping into consideration the higher doses of IBF in various formulations, inclusion complex 2:3 would be preferred from formulation point of view.

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