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Research article

Solubilization of some COX-2 Inhibitors through 2-HPβCD comparison with hydrotropic solubilization

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Abstract

In this study solubility of some COX-2 inhibitors (rofecoxib, celecoxib and meloxicam), was enhanced by complexing with 2-hydroxy propylene-β-cyclodextrin (2-HPβCD). HPβCD is a new derivative of β-CD, presents improved safety and solubility properties compared to the parent β-CD. The objective of this study was to prepare aqueous solution of these drugs that could be suitable for the parenteral formulations. In order to elucidate the problem of mechanism of solubilization various solution properties of hydrotropes such as viscosity, specific gravity, surface tension, refractive index, specific conductance of common hydrotropes (viz., nicotinamide, sodium salicylate and sodium benzoate) solutions were studied at 25 $\pm 2^{O}$Con the basis of earlier studies and compared with HPβCD solutions. The solubility enhancement of these drugs by HPβCD and hydrotropes was observed in decreasing order as HPβ-CD >NE>SB>SS with rofecoxib, HPβ-CD> NE>SB>SS with celecoxib but it was HPβ-CD >SB>SS>NE with meloxicam. The results indicate that the enhanced solubility of the drugs in presence of hydrotropes in low concentration is due to weak ionic interaction. At higher concentrations, the formation of molecular aggregation seems to be the possible mechanism of solubilization. When drugs are added to the HPβ-CD solution then these drugs dissolve through formation of some inclusion complexes. The stability constant (Kc) of HPβ-CD complex with the drugs was determined using solubility and spectral shift methods.

Keywords: COX-2 Inhibitors, hydrotropic solubilization, solubilization.

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1. Introduction

Cyclodextrins are cyclic oligosaccahride, which have been recognized as useful pharmaceutical excipient. The molecular structure of these glucose derivatives generates a hydrophilic exterior surface and a hydrophobic cavity interior. As such CD can interact with appropriate sized molecule to result in the formation of inclusion complex. These complexes offer a variety of physicochemical advantages. including the possibility for increased water solubility, solution stability and bioavailability. Originally only the natural CDs were used, but due to problem encountered with the aqueous solubility and renal toxicity of β-CD, derivatives of these CDs with increased solubility properties have been developed**.**

CDs are known to form inclusion complex with various drugs molecule and utilized successfully for improvement of drug properties such as solubility, stability and bioavailability (16). Since change of physico chemical and biological properties of a drug are dependent on the magnitude of the stability constant of CD complex, it is important for the prediction or simulation of the property change to determine accurately these parameters (17). There are many methods for determining the stability constant of CD complexes, using techniques such as solubility(18), potentiometry (19), HPLC(20). Kinetic (21), and spectroscopic (22)

Hydrotropy is the term originally put forward by Neuberg [1] to describe the increase in the solubility of a solute by the addition of fairly high concentration of alkali metal salts of various organic acids. Saleh et al., [2] made an attempt to extend the definition of hydrotropic agent to include cationic and non-ionic organic compounds bearing the essential structural features of Neuberg's hydrotropes. There is a controversy concerning the mechanism by which hydrotropes act. Winsor [3] considered hydrotropy a solubilization phenomenon while Ueda [4-6] proposed the formation of molecular complexes at low concentration of hydroptopes and a 'salting in' effect at high concentration. Further, various forms of molecular interactions between insoluble compounds and hydrotrope molecules have been reported [7,8]. The mechanisms proposed so far fall short of giving an overall explanation of hydrotropy and a well-defined mechanism is of interest. Hydrotropic solubilization of nifedepine [9,10], ibuprofen [11], carbazepamine [12] nalidixic acid have been reported.

Rofecoxib [8,9], celecoxib [10-12] and meloxicam [13-15], are non-steroidal anti-inflammatory analgesic drug that inhibit the activity of the enzyme "cyclooxygenase"' which is responsible for the formation of prostaglandin that cause inflammation, swelling, pain and fever. These are practically insoluble in water that precludes their use in various formulations, specially the parenteral one. For parenteral formulations, it is mandatory to obtain a clear solution of drugs. To fulfill this requirement, the aqueous solubility of the experimental drug has to be increased. In this present study, the aqueous solubility was increased by solubilizing the drugs through HPβCD as well as by hydrotropes. The influence of structural variation in a hydrotrope molecule on solubilization pattern of rofecoxib, celecoxib and meloxicam, has been studied to gain an insight into the mechanism of solubilization. The chemical structure of drugs and various hydrotropes used in the study are shown in fig 1.

Material and method

Material: Rofecoxib was obtained as a gift sample from Wokchardt Pharmaceutical Ltd. India, Lupin Laboratories, India, provided meloxicam and celecoxib as a gift sample. Sodium Benzoate, sodium salicylate and nicotinamide were procured from Loba Chemie, Mumbai, India, 2-hydroxy propylene-β-cyclodextrin was obtained as the gift sample from

Method

Estimation of drugs

In the present study, UV spectrophotometric method was used for the estimation of rofecoxib celecoxib and meloxicam. The calibration curve of rofecoxib was prepared using methanol at 268 nm using double beam spectrophotometer **(**Shimadzu UV-2101PC, UV-VIS scanning spectrophotometer**,** Japan), A solution (100μg/ml) of rofecoxib was prepared by dissolving the drug in 20 ml of methanol. The mixture was sonicated for 20 minutes. After making up the final volume this solution was used to construct the calibration curve. The calibration curves for celecoxib and meloxicam were prepared in the same manner in methanol by measuring the maximum absorbance at 252 and 362 nm respectively.

Solubility studies

Excess quantities of rofecoxib, celecoxib and meloxicam were added to 15 ml screw capped glass vials containing fixed volumes (10 ml) of different aqueous solutions such as distilled water, buffers of pH1.2 to 10.0 and hydrotropic solutions of different concentrations (0.4 to 2.0 M) in water. These vials were shaken mechanically in a mechanical shaker (Elico Pvt. Ltd., Mumbai, India) at 25 $\pm$0.5^{O}C and 37 $\pm$0.5^{O}C in a constant temperature water bath for 24 hr. These mixtures allowed to equilibrate for next 24 hrs and then centrifuged for 3 minutes at 2000 rpm .The supernatant of each vials were filtered through Whatman filter paper no 41. Filtrate were diluted with suitable quantity of water and analyzed spectrophotometrically at 268 nm, 252 nm and 362 nm for rofecoxib, celecoxib and meloxicam respectively. The solubility determination was carried out in triplicate.

Properties of hydrotropic solutions

In order to interpret the probable mechanism of solubilization, UV spectral studies of these drugs were performed in different hydrotropic solutions to study the possible spectroscopic

changes in the structures on the drugs in the presence of hydrotropes. The various solution properties of hydrotropes such as pH, viscosity, specific gravity, surface tension, refractive index and conductance were also studied in an attempt to reason out the increase in the solubility of these drugs in the hydrotropes concentration [30].

UV spectra of drug in hydro trope solutions

The UV spectral studies were carried out to study the possible spectroscopic change in the structure of the drug in presence of different hydrotropes so as to access into the possible mechanism of solubilization. For the study, an excess amount of drug (rofecoxib/ celecoxib/ meloxicam) was added to 0.4 to 2.0 M solutions of different hydrotropes solutions (10 ml each) contained in screw capped glass vials and shaken for 12 hrs. The contents were filtered through Whatman filter paper no 41, suitably diluted with water and scanned over UV range (190- 500 nm) against respective blanks.

Determination of stability constant of the complex

Phase solubility studies

Solubility studies were performed according to the method reported by Higuchi and Connors [16]. Excess meloxicam was added to 30 *ml* of purified water (pH-6.8) containing various concentration of βCD (0.002 M to 0.01M) taken in a series of 100 *ml* volumetric flasks and the mixture were shaken for 24 hours at room temperature (25^{o}C) on a shaker (GPM 150). Then they were kept aside to achieve the equilibrium. The aliquots were then filtered through Whatman filter paper No 41. Then filtered samples were diluted suitably and assayed for meloxicam, by measuring the absorbance at 352 nm, against blanks prepared by the respective concentration of βCD in water so as to cancel any absorbance that may be exhibited by βCD molecules. The mixture was shaken till three consecutive samples estimated same amount of drug.

Spectroscopic studies

Formation complex between meloxicam and βCD was also studied by Spectroscopic method. The concentration of the drug in these studies was $3.18x10^{-5}$ M where as βCD concentration was increased from 0.002 to 0.01M. The UV spectra of drug were recorded on a Shimadzu UV-2101PC, UV-VIS scanning spectrophotometer. The change in the absorbance of the drug on the addition of various concentration of the complexing agent, were measured at 352 nm to evaluate the stability constant of a complex by spectrophotometric method also.

Results and discussion

To find out the influence of pH on the solubility of RXB, CXB and MXM, the pH dependent solubility studies were carried out using phosphate buffer of different pH ranging from 1.2 to 10.0. (Higuchi 1961. and Ueda, 1960) at 25 ±1 ^{O}C. The solubility of RXB was found to decreases on increasing the pH. While there was no significant effect of pH on solubility of CXB. Whereas the solubility of MXM increases (23 folds) as on increasing the pH. This exhibits the pH dependence solubility of drug in following manner MXM > RXB >CXB. The results also indicate that MXM and CXB are soluble more at alkaline pH than acidic pH. This may be due to acidic nature of the drugs. RXB is more soluble at acidic pH range, which may be due to the basic nature of the drug fig 2 to 4.

The equilibrium solubility of RXB, CXB and MXM was determined at 25±1^{O}C (room temperature) and at 37±1^{O}C (to simulate body temperature at normal condition). The solubility data of RXB CXB and MXM in different hydrotropic and HPβCD solutions are shown in table 1. The solubility enhancement ratios at 25±1^{O}C for all drugs are given in table 2. It appears from the data that the solubility increases up to 22 times in sodium bicarbonate (SB), 21 times in sodium salicylate (SS), 23 times in nicotinamide (NE) and 160 times in 2-hydrooxy propyl β-cyclodextrin (HP-β-CD) solutions in case of RXB, while CXB solubility increases up to 22 times in SB, 17 times in SS, 24 times in NE and 380 times in HPβCD and MXM solubility increases up to 29 times in SB, 13 times in SS, 10 times in NE and 351 times in HPβCD at 25±1^{O}C. The solubility of these drugs in HP-β-CD were compared with regular hydrotropes, it was found that the solubility of RXB, CXB and MXM increases to 160 fold, 380 fold and 351 fold

respectively. It is evident from the solubility studies that the solubility is increased by increasing temperature, i.e. from 25±1^{O}C to 37±1^{O}C. On the basis of solubility studies the solubilizing power of different hydrotropes and HP βCD could be ranked for various drugs as;

For rofecoxib	HP βCD	>NE	>SB	>SS
	160.07	22.98	21.91	21.33
For celecoxib:	HP βCD	>NE	>SB	>SS
	380.23	24.48	22.79	17.08
For meloxicam:	HP βCD	>SB	>SS	>NE
	351.65	25.61	12.86	9.63

A detailed perusal of solubility data reveals that initially the solubility was increased linearly with increase in the concentration of hydrotropes or HPβCD in the solution, which attributed some kind of complex formation (Saleh, 1974; Badwan, 1983) while there occur abrupt positive deviation at one particular concentration of each hydrotropes after which the solubility increases many fold which s in consistent with Jain and Patel (1988) and Poochikian and Cradock (1979). While in case of HPβCD, the drug solubility is linearly increased with the increased concentration of the HPBCD in the solution.

To explain the mechanism of solubilization of RXB, CXB and MXM in presence of structurally different hydrotropes, it is necessary to have the basic understanding of chemical structures of drug and hydrotropes.HP-β-cyclodextrin contains 4.5 degree of substitution for hydroxy propyl groups. In hydroxy propyl moiety the propylene group is responsible for non-polar bonding (London force of attraction) with non-polar portion (aromatic ring) of RXB. The hydrogen of primary and secondary groups of hydroxy propyl βcyclodextrin (HPβCD) is responsible for H bonding with all 'O' in sulphonyl furonyl ketonic oxygens of the RXB, thus H bonding and non-polar bonding help HPβCD to solubilize RXB.

Niacinamide offers its aromatic ring for non-polar bonding (London force of attraction) for solubilization of non- polar structure (aromatic ring) of the RXB. Heteroatoms like O and N of niacinamide joined with methyl hydrogen being acidic in nature in RXB. But compared to HPβCD it offers insignificant sites for solubilization. Hence it has around 14.36% solubilizing power when compared to HPβCD.

Sodium benzoate contain aromatic ring, which helps for bonding with non-polar portion (aromatic ring) of RXB and then dissolves it. The heteroatoms on sodium benzoate i e., O is responsible for bonding with methyl H of RXB. It has also around 13.68% solubilizing power when compared to HPβCD.

Sodium salicylate also has its aromatic ring for non-polar binding (London force of attraction) with aromatic rings of RXB. Sodium salicylate has intra molecular H bonding hence its heteroatom O poorly contributes for H bonding with methyl H of RXB. So it could offer only13.32% solubilizing power than that of HPβCD.

Similarly, typical molecular arrangement and high degree of substitution for hydroxy propyl groups, the non-polar bonding (London force of attraction) between propylene groups of hydroxy propyl moiety of HP-β-cyclodextrin and non-polar portion (aromatic ring) of CXB and H bonding between hydrogen of primary and secondary groups of hydroxy propyl β-cyclodextrin (HPβCD) and heteroatoms like N, S and O of CXB, allowing it for aqueous solubility.

Niacinamide offers its aromatic ring for non-polar bonding (London force of attraction) for solubilization of non-polar structure (aromatic ring) of the CXB. H of amide group of niacinamide joins with S/O/N of sulfonamide group of CXB, which is responsible of aqueous solubility. When compared to HPβCD it was found that it offers insignificant sites for solubilization. Hence, it has around 6.44% solubilizing power when compared to HPβCD.

Sodium benzoate contain aromatic ring, which helps for bonding with non-polar portion (aromatic ring) of CXB and then dissolves it. The heteroatoms on sodium benzoate i e., O is responsible for bonding with H of sulfonamide group present in CXB. It has 6.04 % solubilizing power when compared to HP-β-CD.

Sodium salicylate also has its aromatic ring for non-polar (London force of attraction) with aromatic rings of CXB. Sodium salicylate has intra molecular H bonding hence its heteroatom O poorly contributes for H bonding with H of sulfonamide of CXB. So it could offer only 4.49% solubilizing power than that of HP-β-CD.

Similarly, meloxicam exhibits non-polar bonding (London force of attraction) and H bonding with hydroxy propyl β-cyclodextrin (HP-β-CD) between their non-polar moieties and H, N, S and O groups.

Niacinamide offers its aromatic ring for non-polar bonding (London force of attraction) for solubilization of non-polar structure (aromatic ring) of the MXM. Heteroatoms like O and N of niacinamide joined with H of methyl, phenolic, thiazole ring and NH group of MXM thus assist in solubility. When compared to HPβCD it was found that it offers insignificant sites for solubilization. Hence, it has only 2.73% solubilizing power when compared to HPβCD.

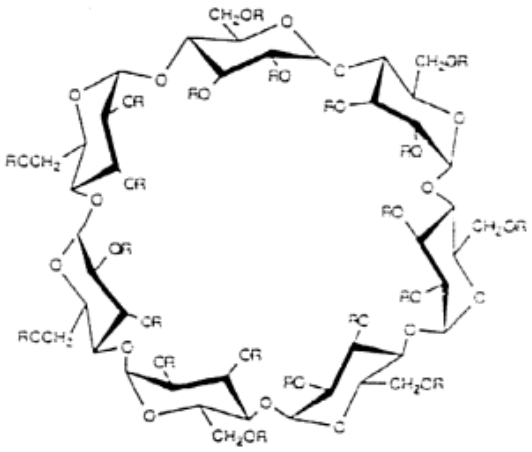
Sodium benzoate contain aromatic ring, which helps for bonding with non-polar portion (aromatic ring) of CXB and then dissolves it. The heteroatoms on sodium benzoate i e., O is responsible for bonding with H methyl, phenolic, thiazole ring and NH group of MXM. It has 3.65 % solubilizing power when compared to HPβCD.

Sodium salicylate also has its aromatic ring for non-polar bonding (London force of attraction) with aromatic rings of MXM. Sodium salicylate has intra molecular H bonding hence its heteroatom O poorly contributes for H bonding with H methyl, phenolic, thiazole rings and NH group of MXM. So it could offer only 7.28% solubilizing power than that of HPβCD.

Therefore it could be concluded that HPβCD has significant solubilizing power for all three drugs i.e. RBX, CXB and MXM. A shift in the λ_{max} of drug and hydrotropes is an indicative of such interaction (table 3). The bathochromic or hypsochromic shifts occur with all the systems, this may be due to electronic change in drug molecules. There is no ground to assume any complex formation of new chromophores (appearance of new peak) or merging of two peaks to generate a common peak. Similarly, HP-β-CD, also forms inclusion complex with drug molecules. Thereby the inclusion complex, which forms with β-CD or with HP-β-CD, is only a physical combination not a chemical one.

The stability constant Kc of drug(s):βCD and drug(s): HPβCD were calculated from linear plot of the phase solubility diagrams according to the equation Kc=Slope/So*(1-slope). The stability constants of drug and HPβCD complex were found to be 210.71 M^{-1}, 221.58 M^{-1} and 287.13 $M^{-1}$for RXB, CXB and MXM respectively fig 5 to 7. The UV spectra of drug(s) solution in the presence of increasing molar concentration of β-CD were studied and revealed that the changes in peak intensity could be resulted from changes in the solvent microenvironment upon inclusion of the solute. The observed reduction in peak intensity may result from the transfer of the guest molecule from water to the HPβCD cavity (Ismail, 1991), because the molar absorptivities of the complex and drug differed at the same wavelength. Therefore, using spectral data, the stability constants were determined by the double reciprocal plots (Connors and Mollica, 1966). The plot between 1/ΔA and

1/(HPβCD) is linear indicating the presence of a 1:1 M complex. The apparent 1:1M stability constant (Kc) was estimated from the Benesi-Hildebrand equation. (Benesi, and Hildebrand, 1949). The Kc values by spectral shift method with HPβCD were calculated to be 4.16 M^{-1}, 8.644 M^{-1} and 36.85 $M^{-1}$for RXB, CBX and MXM, respectively. The double reciprocal curves for all these three drugs are graphically reported in fig 8 to 9.



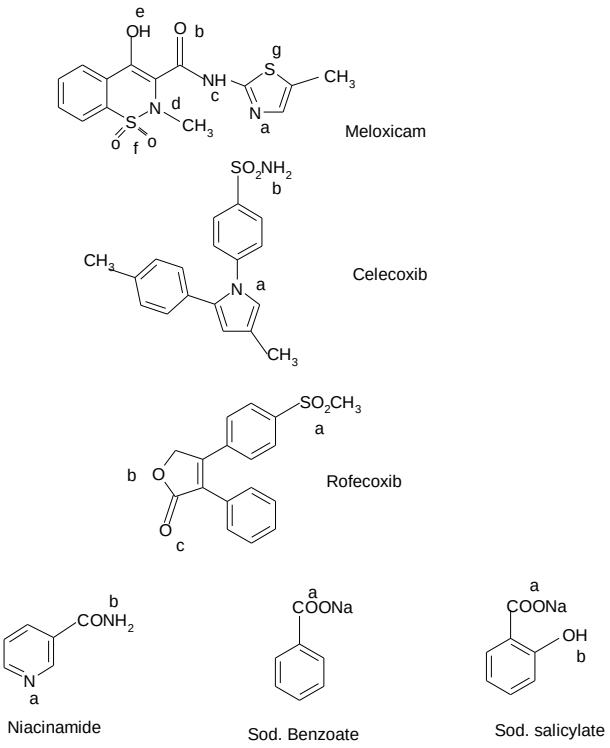
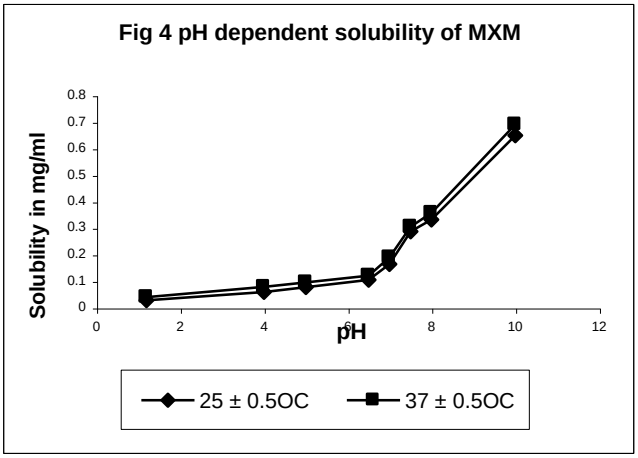
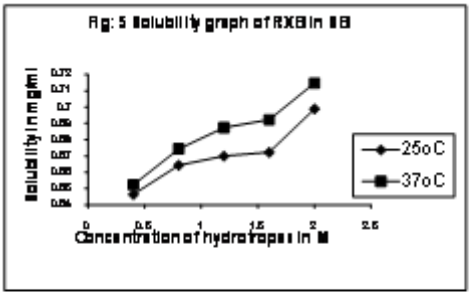
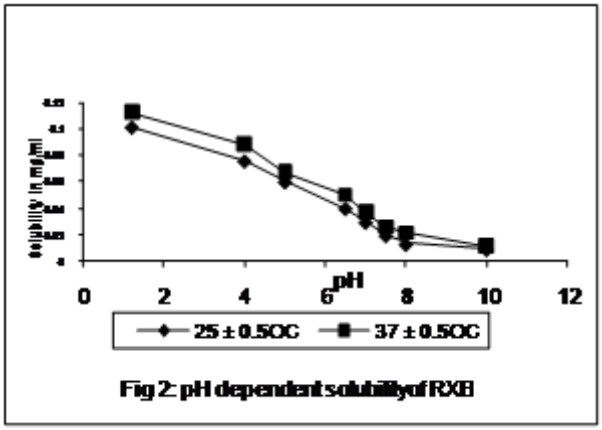
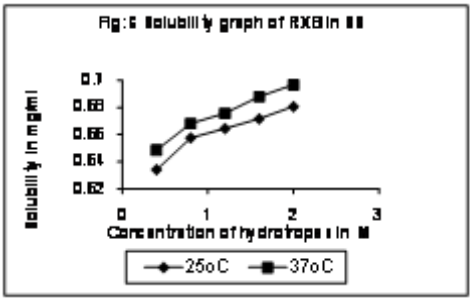


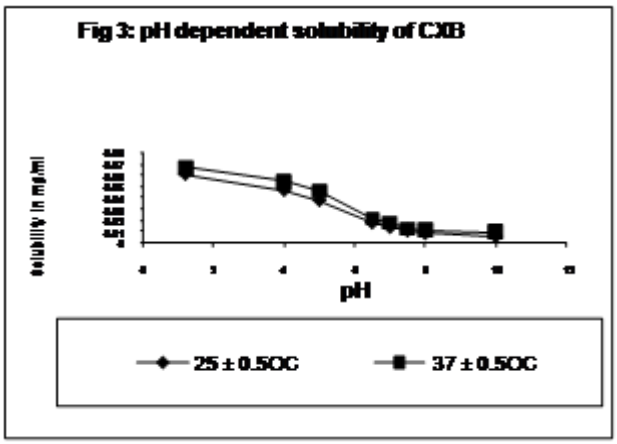
Fig 1. Structure of different drugs and hydrotropes

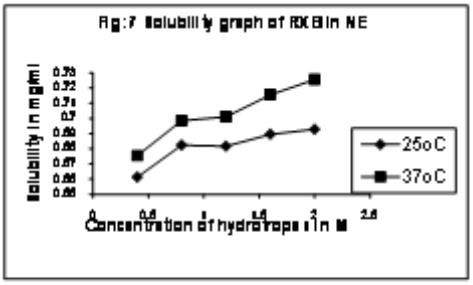












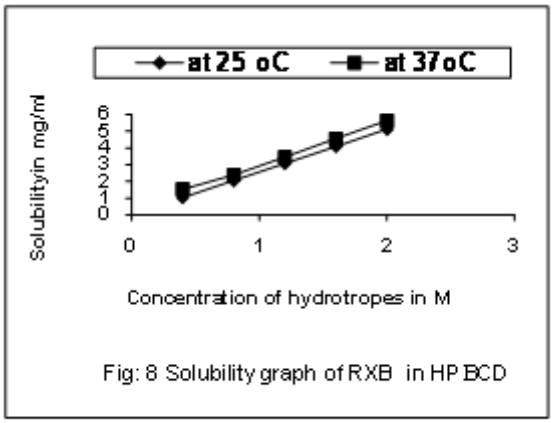
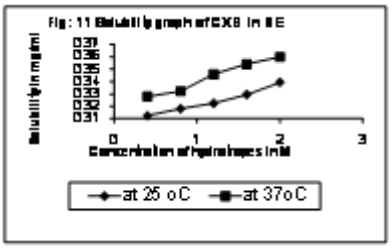


Fig: 8 Solubility graph of RXB in HP BCD



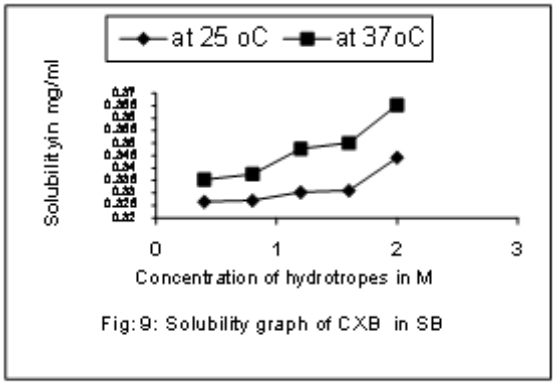
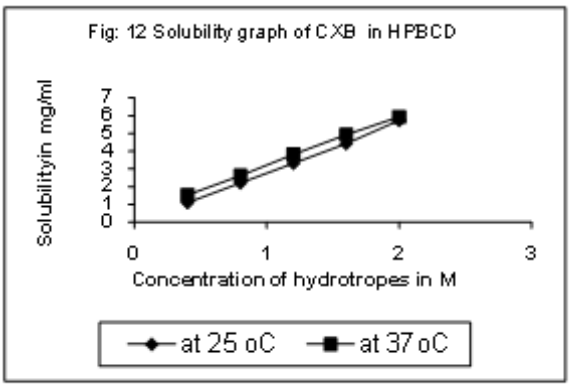
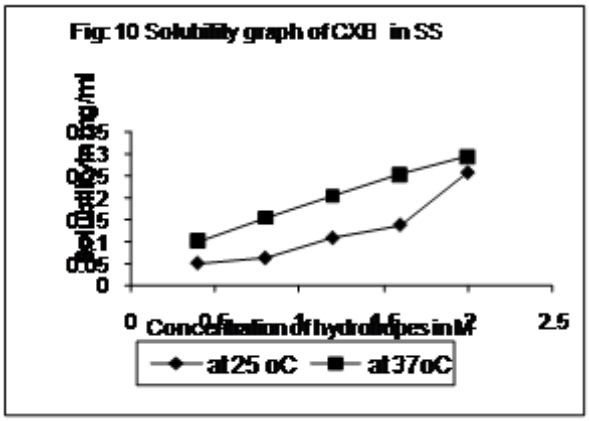
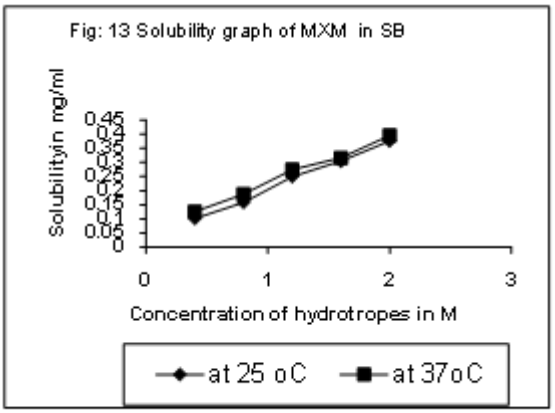
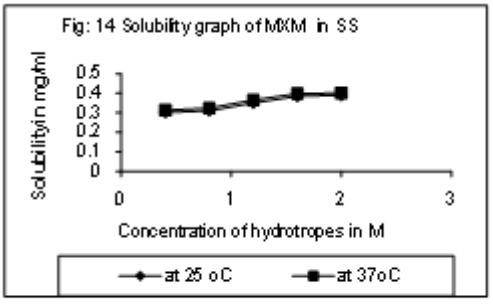


Fig: 9: Solubility graph of CXB in SB









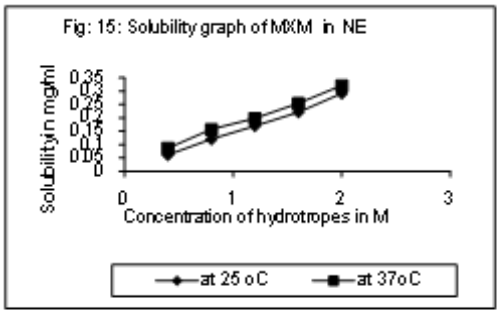


Fig: 15: Solubility graph of MXM in NE
Solubility in mg/ml
Concentration of hydrotropes in M
at 25 oC
at 37oC

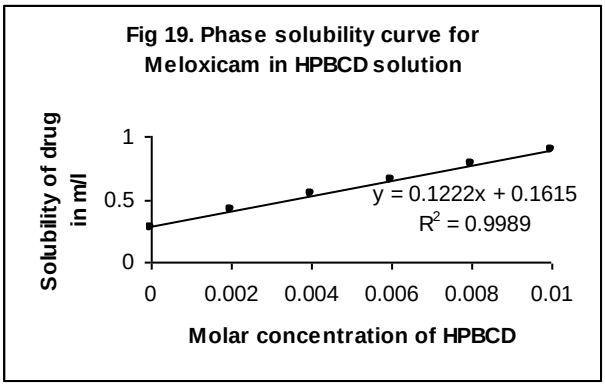


Fig 19. Phase solubility curve for Meloxicam in HPBCD solution
Solubility of drug in m/l
y = 0.1222x + 0.1615
R2 = 0.9989
Molar concentration of HPBCD

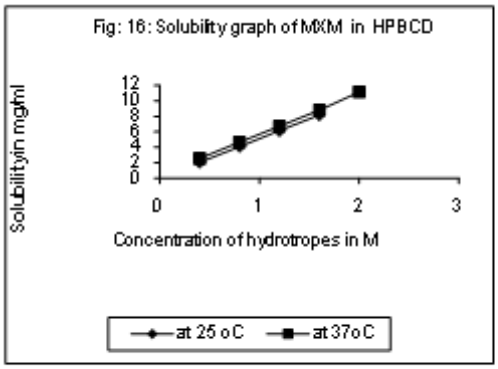


Fig: 16: Solubility graph of MXM in HPBCD
Solubility in mg/ml
Concentration of hydrotropes in M
at 25 oC
at 37oC

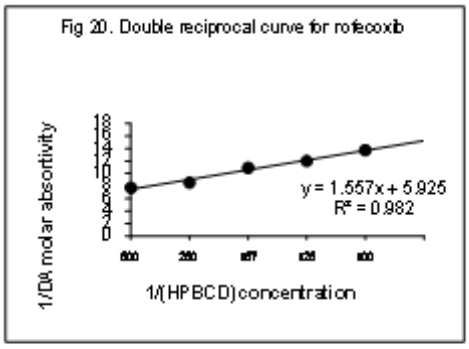


Fig 20. Double reciprocal curve for rofecoxib
1/DA molar absortivity
y = 1.557x + 5.925
R2 = 0.982
1/(HPBCD) concentration

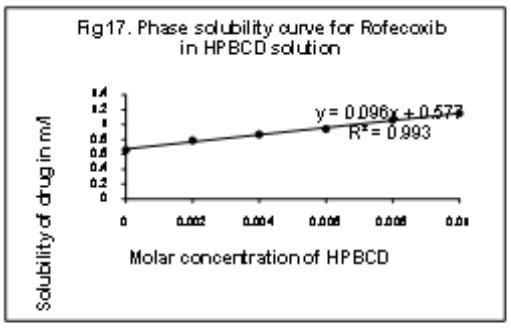


Fig 17. Phase solubility curve for Rofecoxib in HPBCD solution
Solubility of drug in m/l
y = 0.096x + 0.573
R2 = 0.993
Molar concentration of HPBCD

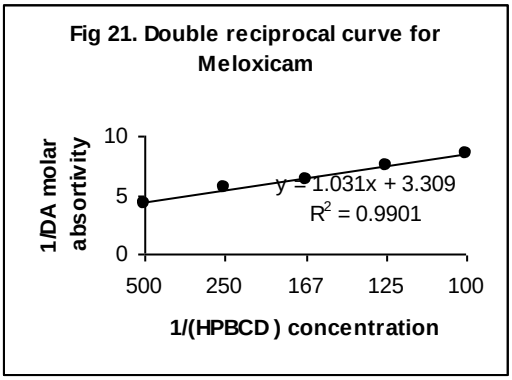


Fig 21. Double reciprocal curve for Meloxicam
1/DA molar absortivity
y = 1.031x + 3.309
R2 = 0.9901
1/(HPBCD) concentration

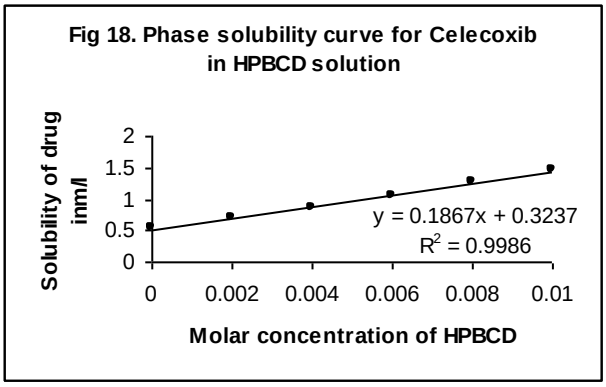


Fig 18. Phase solubility curve for Celecoxib in HPBCD solution
Solubility of drug in m/l
y = 0.1867x + 0.3237
R2 = 0.9986
Molar concentration of HPBCD

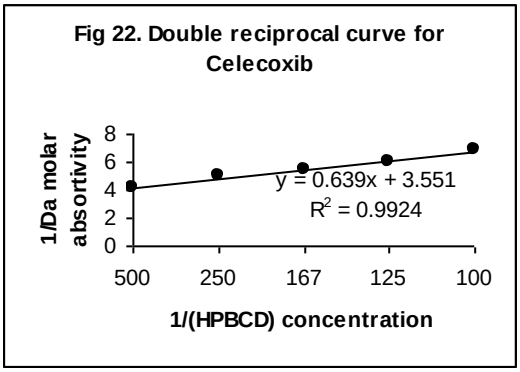


Fig 22. Double reciprocal curve for Celecoxib
1/Da molar absortivity
y = 0.639x + 3.551
R2 = 0.9924
1/(HPBCD) concentration

Table 3: Solubility-enhancement ratios of drugs in hydrotropic solutions

Drugs	Hydrotropes		Concentrations of the Hydrotropes in M				
			0.4	0.8	1.2	1.6	2.0
RXB	SB	25 ± 0.5^{O}C	20.266	20.827	21.003	21.075	21.912
		37 ± 0.5^{O}C	20.451	21.141	21.548	21.702	22.407
	SS	25 ± 0.5^{O}C	19.817	20.614	20.831	21.056	21.338
		37 ± 0.5^{O}C	20.335	20.948	21.185	21.570	21.843
	NE	25 ± 0.5^{O}C	20.733	21.397	21.618	21.369	22.975
		37 ± 0.5^{O}C	21.050	21.903	21.981	22.439	23.379
CXB	SB	25 ± 0.5^{O}C	21.625	21.625	21.656	21.874	21.920
		37 ± 0.5^{O}C	22.212	22.35	23.033	23.185	24.198
	SS	25 ± 0.5^{O}C	3.318	4.099	7.146	8.139	17.079
		37 ± 0.5^{O}C	6.785	10.245	13.556	16.828	19.503
	NE	25 ± 0.5^{O}C	20.695	21.066	21.658	22.477	24.476
		37 ± 0.5^{O}C	21.709	21.993	22.900	23.450	25.158
MXM	SB	25 ± 0.5^{O}C	3.356	5.238	8.251	10.046	25.610
		37 ± 0.5^{O}C	4.152	6.182	9.059	12.413	28.660
	SS	25 ± 0.5^{O}C	9.983	10.274	11.564	12.692	12.855
		37 ± 0.5^{O}C	10.314	10.669	12.059	13.158	13.241
	NE	25 ± 0.5^{O}C	2.063	3.984	5.624	7.314	9.630
		37 ± 0.5^{O}C	2.885	5.195	6.558	8.386	10.607

n=3 SS= Sodium salicylate, SB= sodium bicarbonate, NE= Nicotinamide,

Table 4: UV spectral analysis for RXB, CXB and MXM

SN	System	Peaks (λmax) nm	
		Hydrotropes	Drugs
1	RXB/water	-	268
2	CXB /water	-	252
3	MXM /water	-	362
4	RXB/Methanol	-	276
5	CXB /methanol	-	262
6	MXM /methanol	-	364
7	SB /water	224	-

8	SS /water	296	-
9	NE /water	260	-
10	HPBCD /water	192	-
11	RXB/SB 0.4M	232.5	260,285
12	RXB/SB 0.8M	244	262.285.5
13	RXB/SB 1.2M	240	263.283
14	RXB/SB 1.6M	246	263.5, 289.5
15	RXB/SB 2.0M	246	265,289.5
16	RXB/SS 0.4M	248	265,284.5,305,
17	RXB/SS 0.8M	250	268,286.5,307.5
18	RXB/SS 1.2M	248	270,288,307.5
19	RXB/SS 1.6M	249	268,291.5,306.5
20	RXB/SS 2.0M	249	266.5,291,307.5
21	RXB/NE 0.4M	246	261.316.5,
22	RXB/NE0.8M	249	259.5,319
23	RXB/NE 1.2M	252.5	261.5,318
24	RXB/NE 1.6M	252	261,318.5
25	CXB/NE 2.0M	254	262.5,319
26	CXB/SB 0.4M	243.5	254,284,
27	CXB/SB 0.8M	239.5	254.5,285.5
28	CXB/SB 1.2M	243.5	250.5, 289,
29	CXB/SB 1.6M	243.5	253,291,
30	CXB/SB 2.0M	243	254.5,293
31	CXB/SS 0.4M	291	247,316,332
32	CXB/SS 0.8M	293.5	251,313,332
34	CXB/SS 1.2M	291	250,317,333
35	CXB/SS 1.6M	291	253,318,334
36	CXB/SS 2.0M	291	250.5,317.5,334
37	CXB/NE 0.4M	260	247.5,314
38	CXB/NE0.8M	265	249,318
39	CXB/NE 1.2M	263	250.5,319.5
40	CXB/NE 1.6M	261.5	250.5,318.5
41	CXB/NE 2.0M	262	256,315.5
42	MXM/SB 0.4M	224	237.5,268.5
43	MXM/SB 0.8M	237.5	244,268,315
44	MXM/SB 1.2M	237.5	250,285,319
45	MXM/SB 1.6M	239	275,285.5,315
46	MXM/SB 2.0M	237	281,292,316
47	MXM/SS 0.4M	238	247,262,336
48	MXM/SS 0.8M	247.5	253,264,356
49	MXM/SS 1.2M	253.5	257,275,392
50	MXM/SS 1.6M	255	258,268.5,387
51	MXM/SS 2.0M	251	263,265,394
52	MXM/NE 0.4M	263	291,306,
53	MXM/NE0.8M	270	298.5,308.5
54	MXM/NE 1.2M	269.5	297.5,310.5
55	MXM/NE 1.6M	271	300,316
56	MXM/NE 2.0M	275.5	301,315

RXB= Rofecoxib, CXB= Celecoxib, MXM= Meloxicam, SS= Sodium salicylate, SB= sodium bicarbonate, NE= Nicotinamide,

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