COMPARATIVE EVALUATION OF CO-CRYSTALLIZATION METHODS FOR SOLUBILITY ENHANCEMENTOF POORLY WATER SOLUBLE DRUG OF BCS CLASS II

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INTRODUCTION

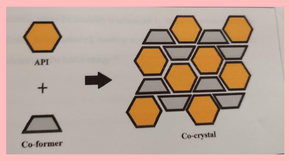
Co-crystallization is a process of formation of co-crystals by the mixture of API and crystal conformer to form a co-crystal formation.

Drugs with low water solubility are predisposed to poor and variable oral bioavailability and therefore to variability in clinical response that might be overcome through an appropriate formulation of the drug.

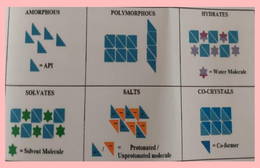
The polymorphic solids exhibit different physiological properties. Polymorphism has acheived significance during recent years due to the fact that different polymorphs of a same drug exhibit different solubilities.

Piroxicam is a non steroidal anti inflamatory drug{NSAID} It is indicated for acute or long-term use in the signs and symptoms of osteoarthitis and rheumatoid arthritis.

According to the biopharmaceutic Drug Classification system [bcs]piroxicam is a class 2 drug,characterized by low solubility -high permeability.



The main motivation to explore co-crystals of pharmaceuticals is to potentially modiy their physical properties,primarily solubility and dissolutionrates,bioavailability and physical stability.

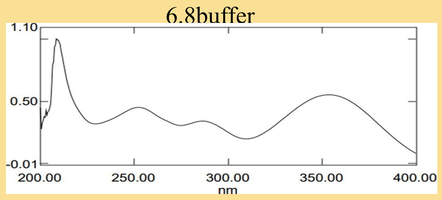


MATERIALS & METHODS

Sl. no	Materials
1.	Piroxicam
2.	Benzoic acid
3.	PABA
4.	Citric acid
5.	Ethanol
6.	Acetone
7.	Acetonitrile

❖ Standardisation of drug estimation by ultraviolet spectroscopy

- Preparation of 6.8pH buffer solution
- Determination of absorbance maxima
- Calibration curve of Pirixicam in 6.8buffer



❖Preparation of co-crystals

- Selection of solvents
- Investigation of co-formers
- Selection of Co-formers
- Based on Hansen Solubility Parameter

Sl no	Co-former	Ratio
1	Benzoic acid	1:6
2	Citric acid	1:4
3	PABA	1:3

❖Preparation of piroxicam co-crystals

- The ratio drug-co-former ratio employed for the preparation ofco-crystals

❖METHODS

- Solvent evaporation method
- Slow coolig method

❖Charaterization of co-crystals

- Melting point
- Estimation of drug content in co-crystals
- Aqueous solubility studies
- In-vitro dissolution studies

RESULTS

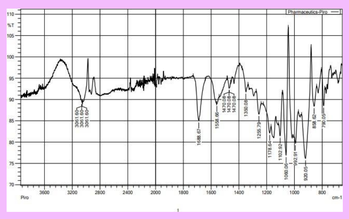
MP of Piroxicam API

Sample	Melting point of the drug in °C				
	Trial 1	Trial 2	Trial 3	Average	SD
Piroxicam	197.5	197.8	197.7	197.6	± 0.1527

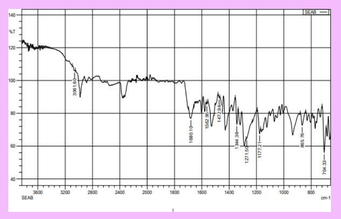
Sl no	Solvent and method	co-former	Melting point of piroxicam / co-former °C Literature value	Melting points of piroxicam co-crystals °C with decomposition	
				Average	± SD
1	Ethanol Solvent evaporation	Benzoic acid	122.3	121.6	± 1.5
		Citric acid	153	151.8	± 0.9
		PABA	187	184.4	± 0.5
2	Ethanol Slow cooling	Benzoic acid	122.3	121.7	± 0.5
		Citric acid	153	151.9	± 0.4
		PABA	187	185.1	± 1.20
3	Acetone Solvent evaporation	Benzoic acid	122.3	122.7	± 0.4
		Citric acid	153	152.7	± 0.49
		PABA	187	186.1	± 0.15
4	Acetone Slow cooling	Benzoic acid	122.3	123.5	± 0.4
		Citric acid	153	153.09	± 1.49
		PABA	187	186.4	± 0.7
5	Acetonitrile Solvent evaporation	Benzoic acid	122.3	122.9	± 0.1
		Citric acid	153	151.5	± 1.3
		PABA	187	186.3	± 0.5
6	Acetonitrile Slow cooling	Benzoic acid	122.3	123.2	± 0.55
		Citric acid	153	152.33	± 0.5
		PABA	187	186.2	± 1.2

Sl no	Solvent and method	co-former	% drug content ± SD
1	Ethanol Solvent evaporation	Benzoic acid	96.60 ± 0.585
		Citric acid	72.16 ± 2.528
		PABA	82.21 ± 0.984
2	Ethanol Slow cooling	Benzoic acid	96.9 ± 0.8
		Citric acid	73.96 ± 0.8
		PABA	84.3 ± 0.95
3	Acetone Solvent evaporation	Benzoic acid	99.96 ± 0.2
		Citric acid	96.96 ± 0.8
		PABA	93.3 ± 0.4
4	Acetone Slow cooling	Benzoic acid	100.3 ± 0.45
		Citric acid	98.3 ± 0.45
		PABA	99.96± 0.2
5	Acetonitrile Solvent evaporation	Benzoic acid	94.3 ± 0.95
		Citric acid	93.2 ± 0.2
		PABA	94.9 ± 1.21
6	Acetonitrile Slow cooling	Benzoic acid	95.23 ± 0.89
		Citric acid	93.86 ± 0.5
		PABA	95.23 ± 0.45

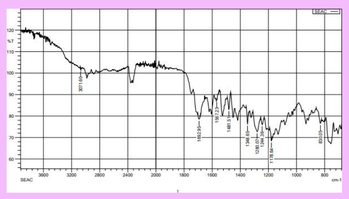
FTIR of piroxicam solvent evaporation method



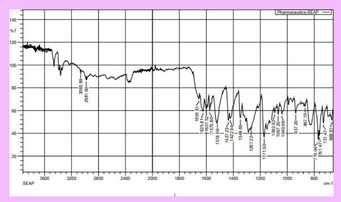
Piroxicam-Benzoic acid



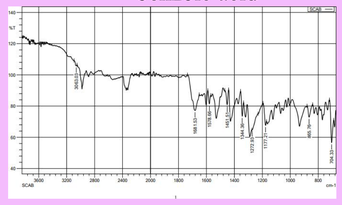
Piroxicam-Citric acid



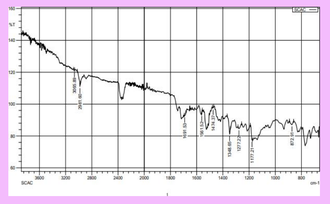
Piroxicam-PABA



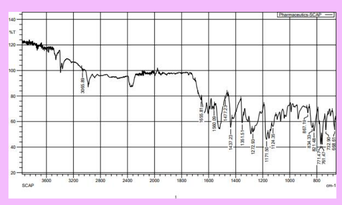
FTIR Slow cooling method benzoic acid



Piroxicam-citric acid

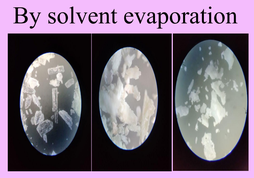


Piroxicam-PABA



Images of co-crystals by slow cooling method

By solvent evaporation



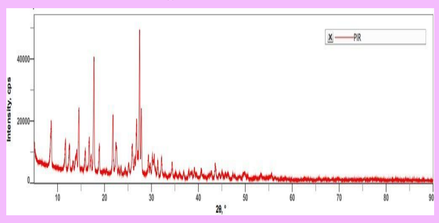
Dissolution of piroxicam by solvent evaporation and slow cooling method

Time	Abs	Concin µg/ml	Conc inmg/ml	Concin10 ml	Conc in900 ml	CLA	CDR	%CDR
0	0	0	0	0	0	0	0	0
10	0.163	3.0697	0.00306	0.00613	5.5254	0	5.52549	38.911
20	0.206	3.9262	0.00392	0.0078	7.0673	0.00613	7.0734	49.813
30	0.228	4.3645	0.00436	0.00872	7.8561	0.01399	7.87016	55.423
40	0.245	4.70318	0.00470	0.00940	8.46573	0.02272	8.48845	59.7778
50	0.268	5.16135	0.00516	0.01032	9.29043	0.03212	9.32256	65.6518
60	0.297	5.73904	0.0057	0.01147	10.3302	0.04245	10.3727	73.0473

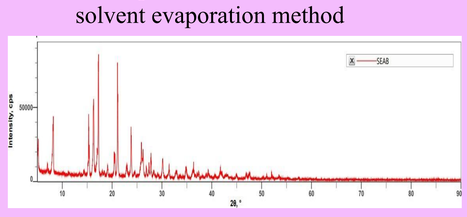
Dissolution of piroxicam by slow cooling method

Time	Abs	Concin µg/ml	Conc inmg/ml	Conc in10 ml	Conc in900 ml	CLA	CDR	%CDR
0	0	0	0	0	0	0	0	0
10	0.173	3.28884	0.00328	0.00657		0	5.91992	41.689
20	0.205	3.90637		0.00781	7.03147	0.00657	7.03805	49.5637
30	0.235	4.50398	0.00450	0.00900	8.10717	0.01439	8.1215	57.19
40	0.249	4.78286	0.00478	0.00956	8.60916	0.02339	8.63256	60.7926
50	0.280	5.40039	0.00540	0.01080	9.72071	0.0329	9.75368	68.6878
60	0.308	5.95816	0.00595	0.01191	10.7247	0.04376	10.7684	75.8342

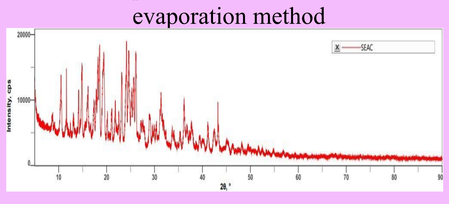
XRD of piroxicam API



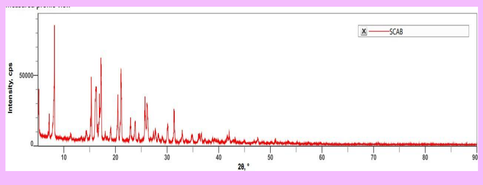
XRD of piroxicam benzoic acid solvent evaporation method



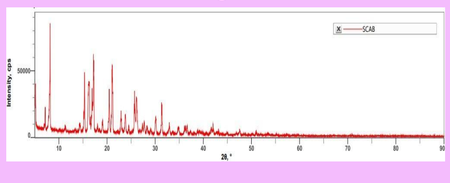
XRD of piroxicam citric acid solvent evaporation method



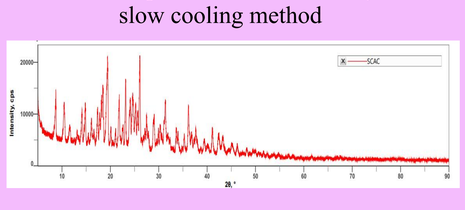
XRD of piroxicam PABA



XRD of piroxicam benzoic acid by slow cooling method



XRD of piroxicam citric acid by slow cooling method



CONCLUSIONS

- UV analytical method was developed for piroxicam in a 6.8 pH buffer solution. The λmax 353 nm was used as analytical wavelength and Beer Lambert's law obeyed inthe range of 2 to 20 µg/ml (R2 = 0.996).
- Piroxicam co-crystal s approach was used to modify the physicochemical properties of piroxicam.
- Hansen's solubility parameter was calculated for twenty-one co-formers out of which three co-formers were used in preparing the co-crystals by two methods of co- crystallization with three different solvents. Out of which one type of co-crystal produced by a particular solvent was selected for instrumental methods of analysis.
- The melting points of piroxicam co-crystals indicated variations in the melting range, suggesting the possible formation of co-crystals.
- The dissolution of piroxicam alone and the various co-crystals prepared by two different methods in the 6.8 pH buffer were attempted. All the co-crystals showed improved dissolution rate compared to piroxicam API.
- The results of FTIR showed significant changes in their bands in prepared piroxicam co-crystals.
- XRD pattern of the piroxicam co-crystals indicated the presence of additional peaks.
- The topography of all the co-crystals are not smooth due to the presence of co- former on their surface

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