Research Article

Solubility and Pre formulation Studies of Non Micronized Piroxicam SEDDS

***Surya N. Singh[1,2], U. K. Patil[2,3]**

1. Product Development Lab, ACG-Associated Capsules Pvt. Ltd., Kandivli (west)-Mumbai-400067 Maharastra, India.
2. Institute of Pharmaceutical Sciences and Research Center, Bhagwant University, Ajmer-305004, India.
3. People's Institute of Pharmacy and Research Center, Bhopal-462037, Madhya Pradesh, India.

ABSTRACT

Piroxicam is a poorly soluble, highly permeable drug and is characterized by a slow and gradual absorption via the oral route and this causes a delayed onset of therapeutic effect. Thus, plain piroxicam preparations are not indicated for analgesia. The results of the in vivo study revealed that the GL dosage form would be advantageous with regards to rapid onset of action, especially in various painful conditions where an acute analgesic effect is desired.

The poor dissolution rate of water-insoluble drugs is still a major problem confronting the pharmaceutical industry. There are several techniques to enhance the dissolution of poorly soluble drugs. Among them, the technique of liquisolid compacts is a promising technique towards such a novel aim.

Hence in the present study, it was attempted to formulate Piroxicam in the form of self emulsifying drug delivery system (SEDDS) technique. Preformulation studies were performed to check the compatibility of drug and excepient for the preparation of formulation. Compatibility study, brittleness and softness study, solubility study, phase solubility were performed. Hence it was concluded that SEDDS of Non Micronized piroxicam could be formulated. The aim of this research article is to understand and overcome the challenges of physicochemical and physical properties of liquid excipients with different type of hard capsules and to shorten expensive development phase and to reduce time to market. To facilitate the development of novel drug delivery systems, the demand for new liquid excipients have been increased. The quality of finished formulation depends not only on the active principles and production processes, but also on the performance of the liquid excipients.

Keywords: Non Micronized Piroxicam, compatibility study, brittleness and softness study, solubility study, phase solubility

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***Address for correspondence:**
Surya N. Singh,
Product Development Lab, ACG-Associated Capsules Pvt. Ltd., Kandivli (west), Mumbai-400067 Maharashtra, India.
E-mail: isurya1981@gmail.com

INTRODUCTION

Piroxicam is a member of the oxicam group of non-steroidal anti-inflammatory drugs (NSAIDs). NSAIDs are widely used for rheumatoid arthritis, osteoarthritis, and a variety of other acute and chronic musculoskeletal disorders, dysmenorrhea, and as ordinary analgesics [1,2]. According to the Biopharmaceutic Drug Classification System (BCS) proposed by Amidon et al. [3], piroxicam is a class 2 drug with low solubility and high permeability. Its pharmacokinetic pattern is characterized by slow and gradual absorption.

In early development phase, excipients compatibility studies are the first formulation development step, providing a rational basis for identification of low-risk excipients with physical and chemical compatibility to the drug substances [4]. Drug excipient compatibility studies [5] are critical for well-formulated final dosage forms where the drug may be in direct contact with one or more excipients during process scale-up from clinical trials through commercial to consumer. Performing these studies at the early development stage has the potential to both accelerate drug development and minimize the risk of drug product stability failure or regulatory delays and the ability to understand and

overcome challenging physicochemical and physical properties of liquid excipients with different type of capsules to prevent costly development delays [6].

The impact of liquid excipients on mechanical properties of hard capsules must be considered when developing liquid fill formulations [6,7]. Different liquid excipients behave differently in hard capsules based on the material of construction of hard capsule shells. Hence it is imperative to evaluate the effect of various solvents in different hard capsules like Capsules from Type B gelatine, capsules from Fish gelatine and hypromellose capsules. Usually small amounts of hydrophilic solvents, which are filled into hard capsules in order to improve the solubility or dissolution of the active drug. It is known that such solvents may cause either brittleness or softening of the hard capsule shell [8]. Depending on the composition of a liquid formulation, it may take a long time e.g. several months before one can visually observe changes (i.e. leaking or deformation) in the mechanical properties of the capsules [5,9].

Tensile strength testing machines have been widely used to study the mechanical properties of polymers [10]. A non-destructive texture analysis was described by Kuentz and Rothlisberger (2002) for determination of the optimal amount of water in liquid-filled hard gelatine capsules [11]. The potential advantage of this method is that the capsules can be re-analyzed at later time points, which is advantageous especially in an early development stage where little drug material is available and capsules must be hand filled. However, the prerequisite is that the properties of capsules will not be affected by the analysis.

MATERIALS AND METHODS

MATERIALS

Propylene Glycol(PG), Polyethylene Glycol(PEG 600),Polyethylene Glycol(PEG 400),Sorbitol 70%,Tween-20, Tween-80,Span-80 was purchased from SD fine-chem Ltd, Triethyl Citrate was purchased from Alfa Aesar a Johnson Matthey company, Transcutol-P, Capryol-90, Capryol PGMC, Labrasol,Lauroglycol-90, Labrafil M2125C, Labrafil M 1944CS, Lauroglycol FCC, Labrafac PG (Gattefosse make) were provided by Colorcon Asia Private Ltd, Oleic Acid was purchased from New Modern Chemical corporation, Mustard Oil was purchased from P.P Pvt. Ltd, Coconut oil was purchased from Parachute, Acconon were obtained from Abitec, USA.

COMPATIBILITY STUDY OF HARD CAPSULES

Capsules - Liquid excipients compatibility study

Compatibility study is the most critical part of any pre-formulation testing of intended dosage form and it is necessary that it shall be carried out even before any formulation development trials of new drug or new formulation of existing drug [12]. This is required to be carried out for the following reasons:

- Formulation stability studies are time consuming and expensive
- Need to minimize the number of model formulations
- Provide rational basis for selection of excipients used in formulations

Objective of Liquid excipients compatibility study with hard capsules

- To find out the excipients that is compatible with the hard capsules.
- To find out and eliminate those excipients which are incompatible and affect the stability of the capsules and formulation.
- To find out the excipients that can stabilize the unstable formulations and hard capsules.
- To assign a relative risk level to each excipients within a function.
- To optimize the liquid excipients proportion in a mixture.
- To design and develop a selective and stability indicating analytical method to determine the impurities, wherein the dosage strength difference is very large.

For compatibility study of hard capsule with liquid excipients, capsules were filled with individual hydrophilic solvents manually and band sealed. These capsule samples were packed in HDPE container with induction seal under ambient condition and stored at Controlled Room Temperature (25°C/ 60%RH) and at 30°C/60%RH for 7 days. After exposure, these capsules were evaluated for physical stability (softness and brittleness) for preliminary screening purposes.

BRRITTLENESS AND SOFTNESS STUDY BY TEXTURE ANALYSIS

Texture analysis is primarily concerned with measurement of the mechanical property of a product, often a food product, as they relate to its sensory properties detected by humans. Fifty years of texture research has developed a set of definitions relating the sensory properties of a product to the instrumental properties, which can be calculated from the result of a two cycle texture profile analysis test. Texture analyzer perform this test by applying controlled forced to the product and recording its response in the form of force, deformation and time.

For the purpose of texture analysis of hard capsule with hydrophilic solvents, capsules were filled with individual hydrophilic solvents manually without band sealing. All these capsules were filled up to the brim in order to expose the entire inner surface of the shells with different fill materials in order to have better surface contact for reaction to occur. 10 capsule samples each were packed in aluminum pouches under ambient conditions and stored at Controlled Room Temperature (CRT) for 72 hours. After 72 hours exposure, these capsules were emptied by removing the fill material and cleaned by wiping the inner wall with a cotton applicator. These capsules were then subjected for tensile strength analysis using the instrument.

The mechanical properties of hard capsule were studied using AGS-1kNJ Texture Analyzer (SHIMADZU). The instrument is crosshead speed range 0.5 to 500mm/min (0.0197 to 20in/min) with crosshead speed accuracy ±0.5% or ±0.025mm/min (0.001in/min). The instrument is fixed with two short rods (similar to pin used in capsule manufacturing after two rods join together), protruding horizontally from the fixture to accommodate the empty capsule shell. The capsule body or cap is then subjected for the tensile strength testing. Three parameters were measured are maximum stress, break displacement and break stress during the tensile strength testing. All these three parameters were recorded in the system and average value was considered for tabulation and plotting the graph.

SOLUBILITY STUDIES OF PIROXICAM IN DIFFERENT OILS, SURFACTANT AND CO-SURFACTANT

The solubility of piroxicam was examined in different oils, *i.e.,* soyabean oil, mustard oil, castor oil, coconut oil and oleic acid; surfactants, *i.e.,* Tween-20,Tween-80, span-80,acconon,; and co-surfactants, *i.e., n*-butanol and propylene glycol. The equilibrium solubility method was performed as follows. Briefly, an excess amount of piroxicam was added to 10 mL of each solvent (the aforementioned oils, surfactants, and co-surfactants) in 20 mL test tube. The test tube were kept ultrasonic bath as subjected for sonication at 37°C and 40°C for 60min in a thermostatically controlled water bath shaker (Metal power analytical, India). Then, remove the undissolved drug by Whatman filter paper (41, Ashless, circles 125mm, cat No-1441-125 GE Health care UK Limited). Samples of these solutions were then collected and the drug concentration was determined spectrophotometrically at 242 nm against a suitable blank of using an ultraviolet spectrophotometer UV-1601(Shimadzu). All experiments were performed in triplicate.

PHASE SOLUBILITY STUDIES:-

Solubility studies were performed according to a published method (Higuchi & Connors, 1965). An excess amount of pure Piroxicam was placed into each 20 mL test tube, to which were added10mL of various concentration of increasing amount of Acconon and Triethyl Citrate. The test tube were sonicated for 60min at 37°C ± 0.1 or 45°C ± 0.1 (Ultrasonic bath). After 2 days, an aliquot of each mixture was trans-ferred to a 10 mL glass syringe preheated at the appro-priate temperature filtered through a Whatman filter paper(41, Ashless, circles 125mm, cat No-1441-125 GE Health care UK Limited) in ther-mostatic test tubs. About 1 mL of the clear filtrate after appropriate dilution, were allowed to stand in bath at appropriate temperature until analyzed. Concentration of Piroxicam in each aliquot was determined by using an ultraviolet spectrophotometer UV-1601(Shimadzu at 242 nm with reference to a suitable constructed standard curve. ALL Acconon and Triethyl Citrate solution were diluted with methanol than 0.1NHCL. The

apparent stability constants, Ks were calculated from the phase solubility diagrams with the assumption of 1:1 stochiometry, according to the equation

$$Ks = \frac{slope}{S\infty\ (1 - slope)} \quad (1)$$

where So is Piroxicam solubility in the absence of carrier.

RESULTS AND DISCUSSION

COMPATIBILITY STUDY OF HARD CAPSULES

The primary objective behind the compatibility study was to find the most appropriate excipients for the liquid formulation of suitable Active Pharmaceutical Ingredient (API) for a dosage form under consideration. This exercise was carried out to eliminate those excipients, which shall be avoided for particular drug under consideration due to incompatibility with capsule shell. The objective was to select suitable excipients, which may be optimally used with drug in proposed liquid dosage form so that development time can be shortened and enables manufacturing of robust product with process control and without compromising on product quality.

The solvents as shown in **(Table 1)** were taken for the compatibility study with Gelatine (type B), Fish gelatine and Hypromellose hard capsules. Some of the capsules filled with these solvents were showing physical incompatibility due to the reaction with the capsule shell and solvent encapsulated. The physical changes observed were either deformation of capsules, capsule shell was getting softened or brittleness of capsule shell within 24hr at room temperature either due to absorption of moisture or by loosing moisture from the shell. However, it is observed that many of the solvents were compatible with hard capsules at room temperature.

Table 1: Physical Evaluation of Capsule Shells with Various Solvents

Component	Observation		
	Fish gelatine Capsules	**Type B gelatine Capsules**	**Hypromellose Capsules**
Soyabean oil	*	*	*
Castor oil	*	*	*
Mustard oil	*	*	*
Oleic acid	*	*	*
PEG-400	Softened	Softened	Softened
PEG-600	Softened	Softened	Softened
Propylene Glycol	Brittle	Brittle	Brittle
Sorbitol-70%	Slight Soft	Slight Soft	Slight Soft
Tween-80	*	*	*
Tween-20	*	*	*
Labrafac PG	*	*	*
Lauroglycol FCC	*	*	*
Lauroglycol-90	*	*	Slight Soft
Labrafil M2125CS	*	*	*
Labrafil M1944CS	*	*	*
Labrasol	*	*	Slight Soft
Capryal-90	*	*	Cap Brittle
Capryal-PMGC	*	*	Cap Brittle
Transcutol-P	Cap Brittle	Cap Brittle	Brittle
Triethyl Citrate	*	*	Cap Brittle
Acconon	*	*	*
Span-80	*	*	*
Arachis oil	*	*	*

* = No Physical Changes observed

BRRITTLENESS AND SOFTNESS STUDY BY TEXTURE ANALYSIS

It is well known that water content is critical for maintaining the structural and mechanical properties of capsule, and it has been shown that the structural and mechanical properties of hard capsules are a function of relative humidity [13]. Therefore, in order to demonstrate, the proposed texture analysis method could be used to characterize both brittle as well as softness of the capsules. Samples, which were stored under the condition and for the same length of time, were analyzed for elastic stiffness, tensile force and elongation at break by texture analysis.

The mechanical properties of empty hard capsules, as measured using texture analysis are a function of shell water content. As may be seen, both elastic stiffness and tensile force decrease when capsules become softer due to increasing water content. Also, elongation at break increases dramatically (plastic deformation) when capsules contain more water, Conversely lower moisture content in hard capsules will result in an increase in elastic stiffness as well as tensile force. When water content drops the capsules become so brittle that the tensile force and elongation at break start decreasing. The results of the tensile testing on bovine gelatin capsules, fish gelatin capsules and Hypromellose capsules exposed after encapsulating with various solvents. The average value has been considered for the purpose of tabulation and plotting the graph (**Table 2**).

Table 2: Tensile Strength Values of Empty Capsule Shells with Various Solvents

Solvents	Capsules	Max Stress (N/mm2)	Break Displacement (mm)	Break Stress (N/mm2)
Initial	Gelatin	39.53	1.38	39.53
	Fish	39.85	1.41	39.85
	Hypromellose	28.02	1.16	28.02
Triethyl Citrate	Gelatin	51.50	1.98	51.50
	Fish	9.41	1.14	9.41
	Hypromellose	29.26	1.71	28.91
Captex	Gelatin	52.15	1.52	52.15
	Fish	51.39	1.50	51.39
	Hypromellose	27.77	1.29	27.00
Glycerol	Gelatin	1.98	5.84	0.31
	Fish	6.40	2.18	0.30
	Hypromellose	33.97	1.86	33.95
Capryal-PMGC	Gelatin	49.52	1.64	49.52
	Fish	11.25	1.02	11.25
	Hypromellose	29.26	1.71	28.26
PEG-600	Gelatin	39.33	1.08	39.33
	Fish	32.62	0.98	32.62
	Hypromellose	14.99	2.12	14.99
Propylene Glycol	Gelatin	2.78	1.41	2.15
	Fish	6.84	1.52	6.76
	Hypromellose	10.29	2.42	0.44
Transcutal-P	Gelatin	60.88	2.14	60.88
	Fish	59.38	2.13	59.38

	Hypromellose	2.61	0.12	0.23
PEG-400	Gelatin	39.33	2.07	53.53
	Fish	56.99	2.23	56.99
	Hypromellose	25.15	1.77	25.15
Acconon	Gelatin	54.25	1.80	54.24
	Fish	29.57	1.32	29.57
	Hypromellose	12.29	1.36	1.40
Sorbitol-70%	Gelatin	24.09	5.39	0.35
	Fish	31.13	14.08	0.34
	Hypromellose	52.97	1.96	52.97

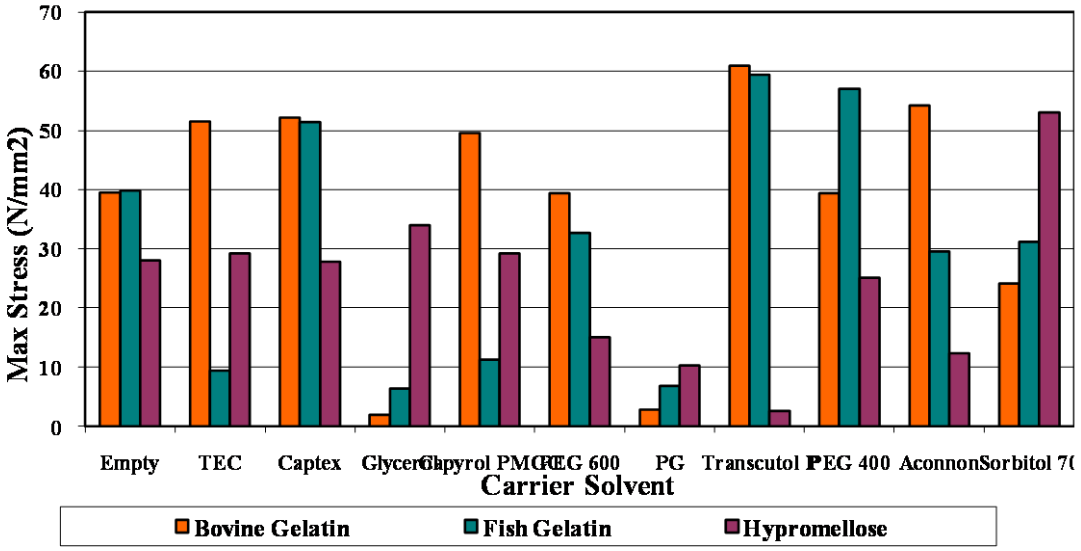

Figure1: Graph of Max Stress

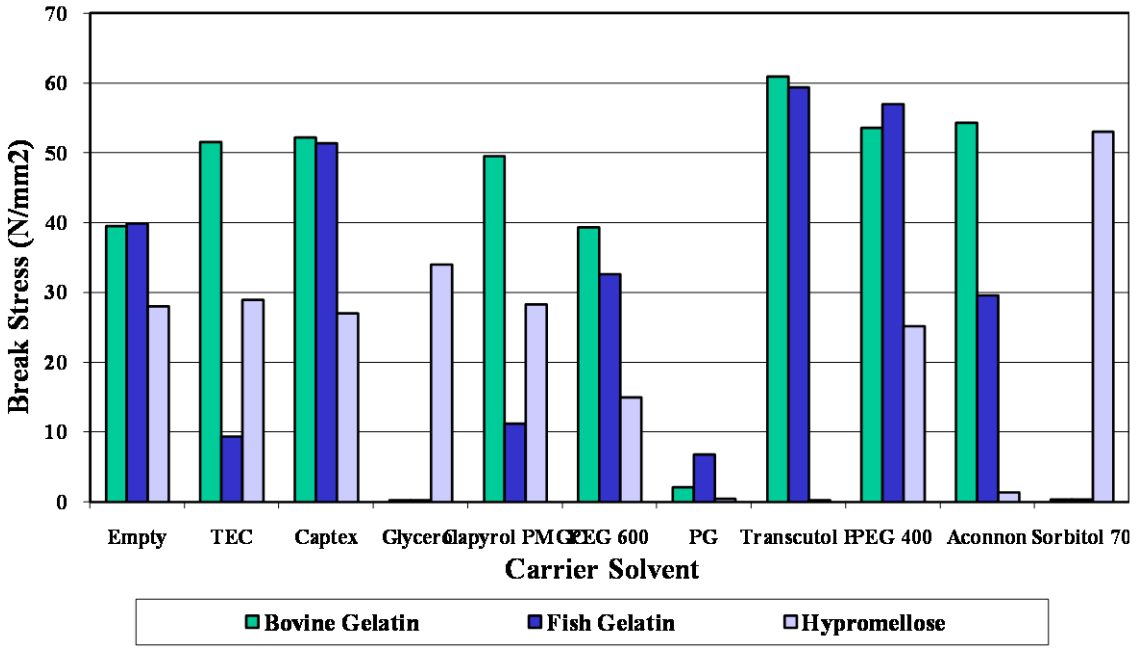

Figure 2: Graph of Break Stress

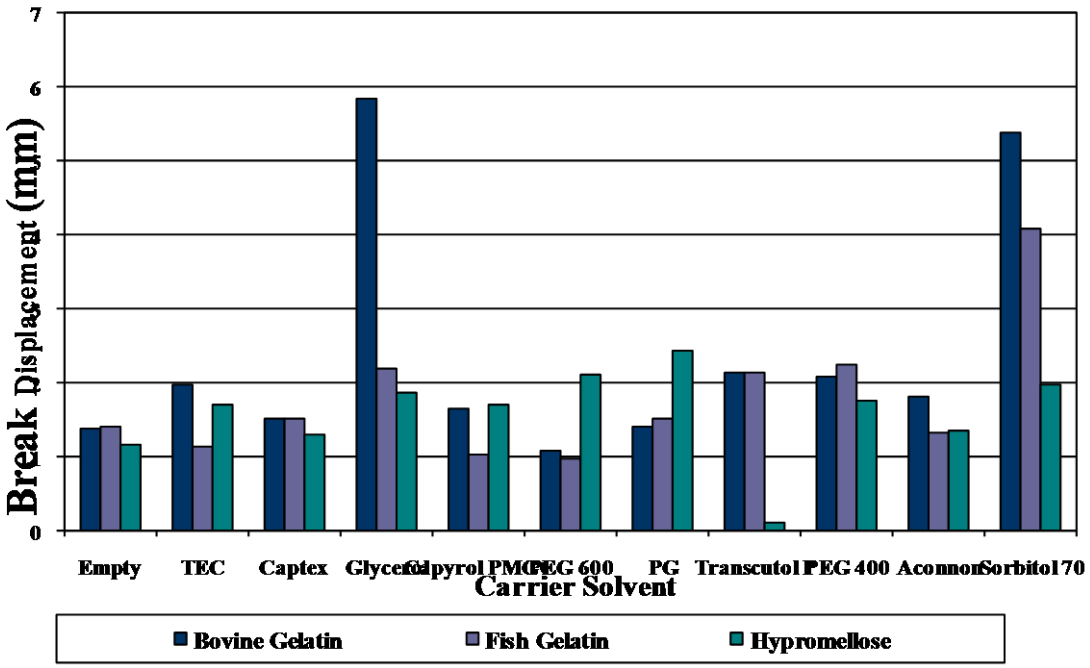

Figure 3: Graph of Break Displacement

SOLUBILITY STUDIES OF PIROXICAM IN DIFFERENT OILS, SURFACTANT AND CO-SURFACTANT

Identifying an appropriate solvent to dissolve Piroxicam and then formulating micro emulsion formulations is crucial because only the dissolved drug can penetrate the skin. In order to screen appropriate solvents for the preparation of micro emulsions, the solubility of Piroxicam in various solvents including oils, surfactants, and co-surfactants was measured and the obtained results were summarized in Table. The solubility of Piroxicam in oleic acid was found to be 12.6 mg/mL. This value was the best among all the investigated oils, but it was still much lower than that of Tween-80, which dissolved Piroxicam of up to 17.8 mg/mL (**Table 3**).

As mentioned above, Piroxicam is known to be water-insoluble. This fact has been proven by the experimental work in this study as water had the lowest solubility with respect to Piroxicam among the investigated solvents. Piroxicam solubility in water was 0.0836 mg/mL (**Table 3),** which equals 0.66%, 0.47%, and 1.3% of Piroxicam solubility in oleic acid, Tween - 80, and propylene glycol, respectively.

These results revealed that the solubility of Piroxicam in oleic acid, Tween-80, and propylene glycol was 150.8, 212.4, and 76.78 times the aqueous solubility of Piroxicam. Therefore, oleic acid was selected as the oil phase, Tween-80 as the surfactant, and propylene glycol as the co-surfactant in this study.

Table 3: Solubility of Piroxicam in different Components

S.NO.	liquid Excipients	Absorbency	mg/ML after dilution	Solubility mg/ML actual
1	PEG 600	0.3341	0.00944	9.438
2	Propylene Glycol	0.0907	0.00256	2.562
3	Transcutol P	0.0345	0.00097	0.975
4	Labrasol	0.0129	0.00036	0.364
5	Lauroglycol FCC	0.1583	0.00447	4.472
6	Lauroglycol 90	0.0178	0.00050	0.503
7	Acconon	0.3742	0.01057	10.571

8	Triethyl Citrate	0.3807	0.01075	10.754
9	Capryal PMGC	0.0063	0.00018	0.178
10	Labrafil M1944 CS	0.0982	0.00277	2.774
11	Arachis Oil	0.0126	0.00036	0.356
12	Purified Water	0.0029	0.00008	0.0836
13	Castor Oil	0.0963	0.00272	2.720
14	Oleic Acid	0.4461	0.01260	12.602
15	Polysorbate 20	0.6303	0.00046	17.805
16	Polysorbate 80	0.6231	0.01760	17.602

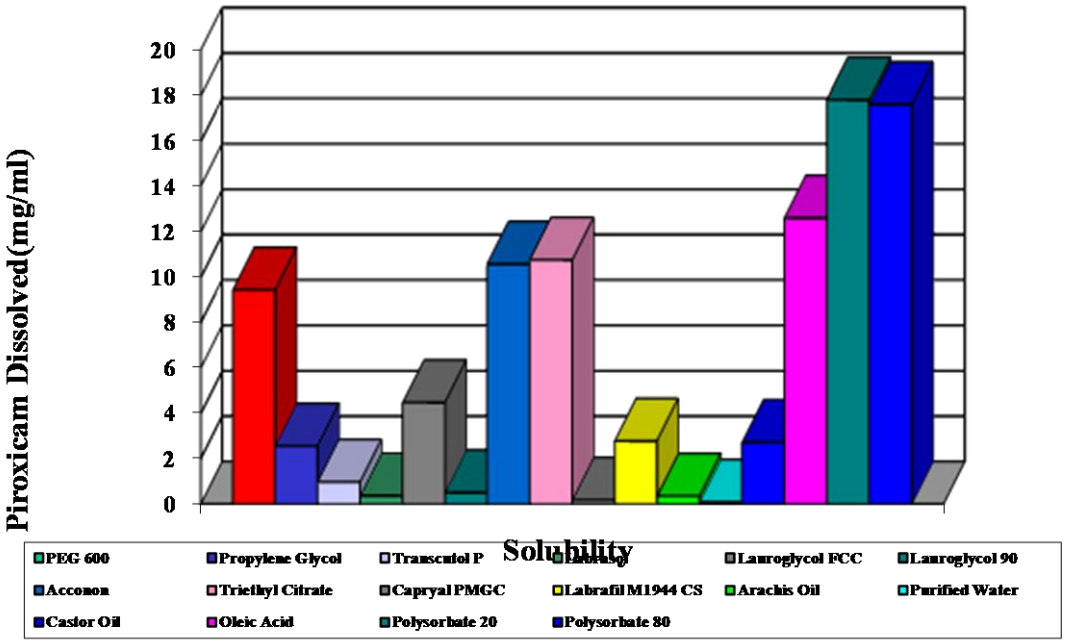

Figure 4: Piroxicam Solubility in Various Carrier Solvent

PHASE SOLUBILITY STUDIES

The solubility of pure Piroxicam in water is poor, but the literature gives no exact data. In this study the solubility of Piroxicam in water was found to be about 0.0836mg/ml. Figure shows the solubility phase diagram representing the effect of increasing the concentrations of Acconon and Triethyl Citrate on the apparent solubility of Piroxicam in water at 37°C and 40°C. Comparing the two polymers, aqueous solutions of Acconon increased the solubility of Piroxicam more than that of Triethyl Citrate. Solubility experiment showed that the concentration of Piroxicam in water at 37°C, 45°C increased as a function of Acconon and Triethyl Citrate concentration. The increase in solubility was linear with respect to the weight fraction of the carrier. The shape of all solubility diagrams followed an all type system (Higuchi & Connors, 1965) where a linear increase of Piroxicam solubility was observed as function of Acconon and Triethyl Citrate concentrations, over the entire concentration range studied.

At 15% concentration of Gelucire 44/14 and TPGS, the increase in Piroxicam solubility was approximately 22 and 27 fold, at 37°C, respectively, and 37-fold for Gelucire 44/14 at 45°C. The apparent solubility constant ($k_{1:1}$) were estimated from the slope of the straight line of the phase-solubility diagram according to equation (1). The increase in solubility of Piroxicam by Acconon and Triethyl Citrate may probably be explained by increased wettability of Piroxicam and micelle solubilisation. Indeed, Acconon and Triethyl Citrate being surfactants cause a decrease of the interfacial tension between the drug and the dissolving solution.

Phase Solubility Study in Triethyl Citrate:

Table 4: At Room Temperature

S.NO.	Concentration	Absorbency	mg/ml after dilution	Solubility mg/ml actual
1	0.50%	0.2408	0.00680	6.80
2	0.63%	0.2896	0.00818	8.18
3	0.83%	0.4408	0.01245	12.45
4	1.25%	0.8704	0.02459	22.71
5	2.50%	1.1011	0.03110	31.10

Table 5: At 40 deg C

S.NO.	Concentration	Absorbency	mg/ml after dilution	Solubility mg/ml actual
1	0.50%	0.2928	0.00827	8.27
2	0.63%	0.3388	0.00957	9.57
3	0.83%	0.4838	0.01367	13.67
4	1.25%	0.9124	0.02577	24.59
5	2.50%	1.1498	0.03248	32.48

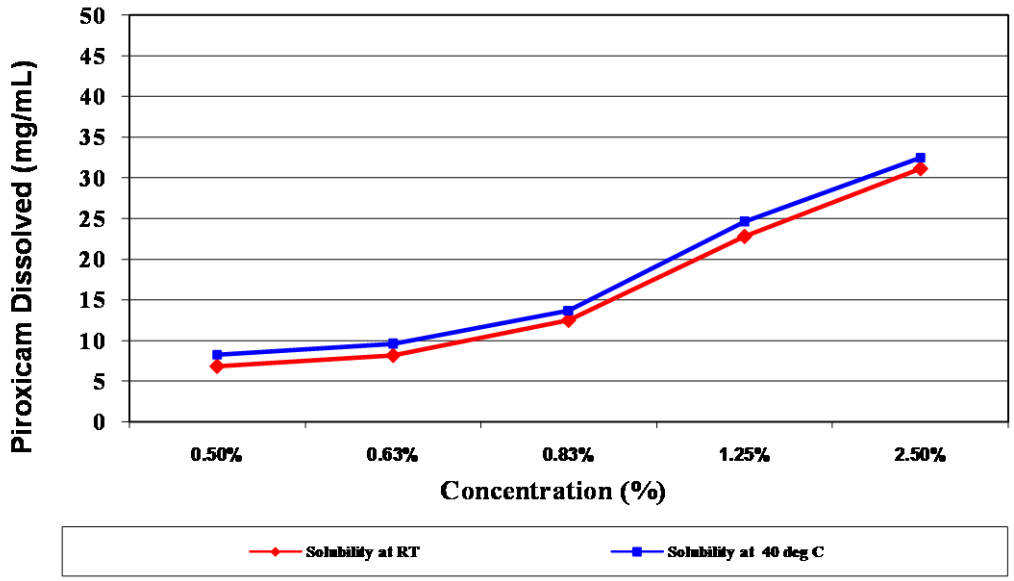

Figure 5: Phase Solubility of Piroxicam in Tri Ethyl Citrate (TEC)

Phase Solubility Study in Acconon MC8-2EP/NP:

Table 6: At Room Temperature:

S.NO.	Concentration	Absorbency	mg/ml after dilution	Solubility mg/ml actual
1	0.50%	0.1975	0.00558	5.58
2	0.63%	0.2698	0.00762	6.86
3	0.83%	0.4225	0.01194	11.94
4	1.25%	0.4606	0.01301	13.01
5	2.50%	0.4815	0.01360	13.60

Table 7: At 40 deg C:

S.NO.	Concentration	Absorbency	mg/ml after dilution	Solubility mg/ml actual
1	0.50%	0.2192	0.00619	6.19
2	0.63%	0.2428	0.00686	7.62
3	0.83%	0.4726	0.01335	13.35
4	1.25%	0.5164	0.01459	14.99
5	2.50%	0.5846	0.01651	16.51

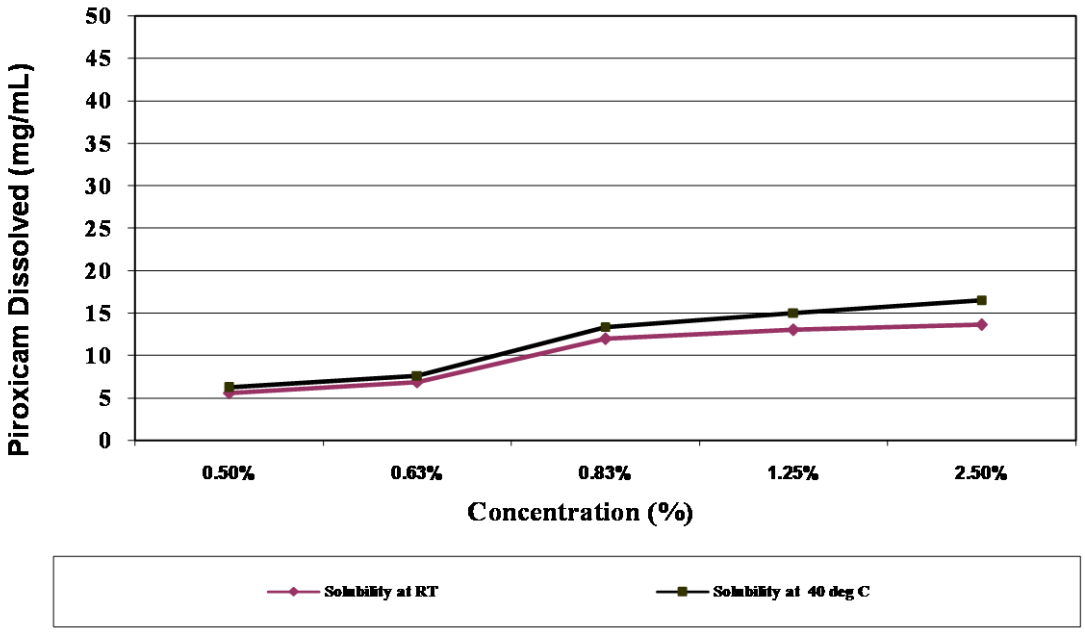

Figure 6: Phase Solubility of Piroxicam in Acconon MC8-2EP/NP

CONCLUSION

The present results of investigation show the suitability of Tri Ethyl Citrate (TEC), Acconon MC8-2EP/NP as the carrier for preparation of Piroxicam SEDDS into hard gelatine capsules. As mentioned above, these substances are widely used as pharmaceutical excipients.

The unique characteristics of liquid excipients and lipid-based delivery systems have presented several challenges during the drug formulation development and achieving desirable physical and chemical stability of the final finished formulation. Solvents and capsule shell interaction which play a major role in capsule product instability, study on such interaction provide a useful tool for excipients screening prior to the initiation of preformulation activities, optimal excipients selection, formulation optimization and long term stability studies. Knowledge of excipients capsule interaction is a necessary prerequisite for the development of liquid dosage forms that are stable. It is believed that this article provides a good perspective to formulators in terms of formulation of Liquid in hard capsule dosage form and overall development pharmaceutics and pharmaceutical technology.

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