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Research Article

Design and Development of Pharmacosome Loaded with Piroxicam to Improve Oral Bioavailability

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Abstract: The design of the present investigation was to prepare Piroxicam bounded pharmacosomes to improve the water solubility, bioavailability and to minimize the gastrointestinal toxicity of Piroxicam. Pharmacosome is a potential approach in vesicular drug delivery systems which exhibits several advantages over conventional vesicular drug delivery systems. Pharmacosomes are phospholipid complexes with a potential to improve bioavailability of poorly water soluble as well as poorly lipophilic drugs. Piroxicam was complexed with soya phosphatidylcholine in various ratios using conventional solvent evaporation technique. In our study, Pharmacosomes thus prepared were subjected to drug solubility, drug content evaluation, surface morphology (by scanning electron microscopy), crystallinity (by X- ray powder diffraction), quality control tests for capsules and *in-vitro* dissolution study. Solubility profile of the prepared complexes was found to be much better than Piroxicam pure drug. This improvement in solubility of the prepared pharmacosomes may result in improved dissolution and lower gastrointestinal toxicity. Drug content was found to be 96.84%w /$_W$ for the optimized Piroxicam phospholipid complex, F_I (Piroxicam: lecithin ratio of 1:1). The pharmacosomes were found to be disc shaped in scanning electron microscopy. X-ray powder diffraction data confirmed the formation of phospholipid complexes. The formulation F_I showed 94.69% drug release while the free Piroxicam showed a total of only 60.42% at the end of 10-hour dissolution study. Thus the solubility and hence the bioavailability of Piroxicam can be increased to a greater extent by complexing it with soya phosphatidylcholine.

Keywords: Piroxicam, Bioavailability, Pharmacosomes, Phospholipid Complex, Solubility.

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1. INTRODUCTION

Pharmacosomes showed unique advantages over liposome and niosome vesicles and served as an alternative to conventional vesicles. As the system is formed by linking a drug (pharmakon) to a carrier (soma), they are termed as pharmacosomes'. They serve as an effective tool to achieve desired therapeutic goals in terms of drug targeting and controlled release of drug. The criterion for the development of the vesicular pharmacosome is dependent on surface and bulk interactions of lipids.[1] The pharmacosomal drug delivery system is advancing as a method used for delivery of various drugs like non-steroidal anti-inflammatory drugs (NSAIDs), cardiovascular drugs, antineoplastic drugs and proteins. Phosphatidylcholine (PC) complex of non-steroidal anti-inflammatory drugs (NSAIDs) improve the permeation of these drugs across the biomembranes and thereby improve their bioavailability to target sites.[1,2]

1.1 Advantages of Pharmacosomes

No leaching of drugs takes place because, the drug is covalently bound to the carrier. Drugs can be delivered directly to the site of infection. Reduces cost of therapy and suitable for both hydrophilic and lipophilic drugs, improves bioavailability especially in case of poorly soluble drugs. Reduction in adverse effects and toxicity. However, the pharmcosmes have the following limitations: Synthesis of a compound depends upon its amphiphilic nature. It requires surface and bulk interaction of lipids with drugs. It requires covalent bonding to protect the leakage of drugs. Pharmacosomes in storage undergo storage fusion and aggregation, as well as chemical hydrolysis. The following materials are essential for the preparation of pharmacosomes. There are three essential components for pharmacosomes (Figure 1)[3,4] preparation. They are drug, solvents and lipids.

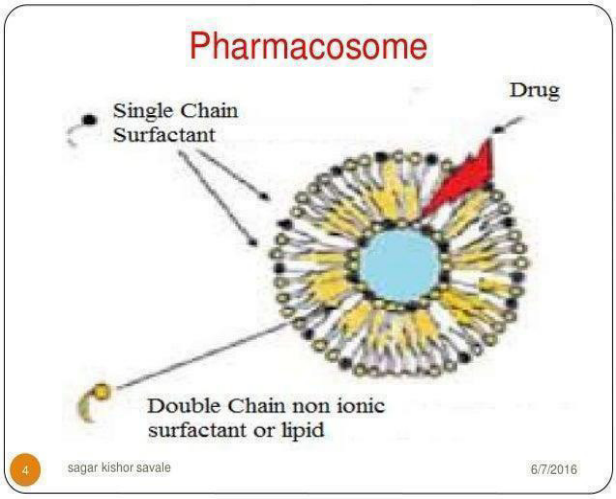

Fig 1: Pharmacosomes

1.2 Formulation of Pharmacosomes [5,6]

There are various methods which have been employed to prepare these vesicles;

1.2.1 Solvent evaporation method

In the solvent evaporation method of preparing the pharmacosomes, the drug is first acidified, so that the active hydrogen might be available for complexation. The drug acid is then extracted into chloroform and subsequently recrystallized. The drug-PC complex is prepared by associating drug acid with PC in various molar ratios. The accurately weighed PC and drug acid are placed in a 100 ml round bottom flask and dissolved in sufficient quantity of dichloromethane. The mixture is then refluxed for one hour. The solvent is then evaporated off under vacuum at 40 °C in a rotary vacuum evaporator. The dried residues are then collected and placed in vacuum desiccator for complete drying.

1.2.2 Hand –shaking method

In the hand-shaking method, a mixture of drug and lipids are dissolved in a volatile organic solvent such as dichloromethane in a round bottom flask. The organic solvent is removed at room temperature using a rotary vacuum evaporator, which leaves a thin film of solid mixture deposited on walls of flask. The dried film can then be hydrated with aqueous media and gives a vesicular suspension.

1.2.3 Ether injection method

In this method, solution containing a drug-lipid complex is slowly injected into a hot aqueous medium through a gauze needle to develop vesicles

1.2.4 Anhydrous co-solvent lyophilisation method

Drug powder and phospholipids dissolved in 1ml of Dimethylsulfoxide (DMSO) containing 5% glacial acetic acid, after that agitates the mixture to get clear liquid. Freeze – dried overnight at condenser temperature. Then the resultant complex flushed with nitrogen and stored at 4°C.

1.2.5 Supercritical fluid process

This method is known as solution enhanced dispersion by complex supercritical fluid. Drug and lipid complex are premixed in a supercritical fluid of carbondioxide, then high supersaturation is obtained by passing through the nozzle

mixture chamber. The turbulent flow of solvent and cabon dioxide results in fast mixing of dispersion leading to the formation of pharmacosomes.

1.2.6 Alternative Approach

An alternative approach for producing pharmacosomes is to synthesize a biodegradable micelle-forming drug conjunct from the hydrophobic drug adriamycin and a polymer composed of polyethylene glycol and polyaspartic acid. This approach provides an advantage that, although micelle can be diluted, the drugs probably not precipitate due to the water solubility of the monomeric drug conjuncts.

1.2.7 Piroxicam

Piroxicam is a non-steroidal anti-inflammatory agent (NSAID) that is well established in treating rheumatoid arthritis and osteoarthritis and used for musculoskeletal disorders, dysmenorrhea, and postoperative pain. Oral administration of this drug on long-term administration is associated with gastrointestinal side effects like ulceration and gastrointestinal bleeding. The drug has poor water solubility, which affect the rate of dissolution in GI fluid, which lead to poor bioavailability. These barriers that are obstacle for therapy can be overcome by making use of the prodrug approach-the pharmacosomes[7,8] Based on the above observations, we formulated pharmacosomes for the oral delivery of Piroxicam and evaluated for its improvement in solubility, drug loading and drug release in this study.

2. MATERIALS AND METHODS

Materials used: Piroxicam (Microlabs, Chennai), Soy lecithin, chloroform (Himedia laboratories), Dichloromethane (Lobachemie, Mumbai), Hydrochloric acid (SD Fine Chem, Mumbai).

2.1 Determination of $\lambda_{max.}$ [9,10]

The stock solution of 1000 µ g/ml was prepared by dissolving 100 mg of pure Piroxicamin 100 ml of pH 7. 4 phosphate buffer, from the stock solution, 10 ml was taken and was further diluted to 100 ml with the buffer solution. The prepared solution was then scanned in a wavelength range of 200-400 nm, to find the IR maximum absorbance. The maximum wavelength was found to be 331nm and was used for further study.

2.2 Preparation of pharmacosomes of piroxicam by solvent evaporation technique. [11,12]

To prepare the pharmacosomes of Piroxicam, it was first acidified, so that the active hydrogen might be available for complexation. Piroxicam acid was prepared by acidification of an aqueous solution of Piroxicam using 0.1N hydrochloric acid. It was then dissolved into chloroform and subsequently recrystallized. Piroxicam-phosphatidylcholine (PC) complex was prepared by associating Piroxicam acid with PC in various molar ratios. The accurately weighed PC and Piroxicam acid were placed in a 100 ml round bottom flask and dissolved in sufficient amount of dichloromethane. The mixture was refluxed for one hour. Then the solvent was evaporated off under vacuum at 40 °C in a rotary vacuum evaporator. The dried residues were collected and placed in vacuum desiccator for three days and then subjected to characterization.

Table1: Formulation table of Piroxicam pharmacosomes

Ingredients	F_1	F_2	F_3	F_4	F_5	F_6	F_7
Piroxicam:Soyalecithin	1:1	1:1.5	1:2	1:2.5	1:3	1:3.5	1:4
Dichloromethane (ml)	20	20	20	20	20	20	20

2.3 Pre formulation studies

2.3.1 Compatibility studies. [13,14]

IR spectra matching was done for detecting any possible chemical interaction between drug and excipient. A physical mixture of drug and excipient was prepared and mixed with the suitable quantity of potassium bromide. About 100 mg of mixture was compressed to form a transparent pellet using a hydraulic press at 6 tons' pressure. It was scanned from 4000 to 400 cm^{-1}in FTIR spectrometer.

2.3.2 Angle of repose

It was determined by the funnel method. A funnel was kept vertically at a specified height and the funnel bottom was closed. Weighed accurately 10 gm of the granules and filled into the funnel. The funnel height was adjusted as the tip of the funnel touches the apex of the heap of powder. The sample was allowed to pass through the funnel freely onto the surface.[15,16] Then the powder cone diameter was measured and angle of repose was calculated by using the following formula:

$$\tan\theta = h/r$$
$$\text{Therefore, } \theta = \tan^{-1}(h/r) \quad (1)$$

Where,
θ =angle of repose
h=height of the cone
r=radius of the cone base

2.3.3 *Bulk density*

The bulk density was determined by pouring pre sieved (#40 mesh) powder into a graduated cylinder via a large funnel and measured the volume and weight.[17] It was calculating m/cm^3 by the formula,

$$\text{Bulk Density}(\delta_0) = M/V_0 \quad (2)$$

Where, M = Mass of sample taken/ weight of sample
V_0=Apparent unstirred volume/ Bulk volume.

2.3.4 *Tapped density*

Tapped density was determined by placing a known amount of powder in graduated cylinder on the mechanical tapper apparatus which was operated for a fixed number of taps (1000) until the powder bed volume had reached a minimum. The tapped density was calculated by using the weight of the sample in the cylinder and that minimum volume.[17] Tapped densities was calculated in gm/cm^3 by the formula,

$$\text{Tapped density } (\delta_t) = (\delta_t) = \left[\frac{M}{V_f}\right]\left[\frac{M}{V_f}\right] \quad (3)$$

Where,
M=Weight of sample.
V_f=Tapped volume.

Compressibility index/ Carr's index

The compressibility index of the powder was determined by using the following formula[17]:

$$\text{Compressibility Index (\%)} = \left[\frac{TBD-LBD}{TBD}\right]X100\left[\frac{TBD-LBD}{TBD}\right]X100 \quad (4)$$

Where, LBD = Loose Bulk Density
TBD=Tapped Bulk Density.

Hausner's ratio

Hausner's ratio was calculated by using the following formula[17]:

$$\text{Hausner's ratio} = \left[\frac{\delta_t}{\delta_o}\right]\left[\frac{\delta_t}{\delta_o}\right] \quad (5)$$

Where, δ_t =Tapped density
δ_0= Bulk density.

2.3.5 *Drug content determination*

For the determination of the drug content in Piroxicam pharmacosome, the complex equivalent to 50 mg Piroxicam was weighed and added in to a volumetric flask with 100ml of PH 7.4 phosphate buffer. Then the volumetric flask was stirred continuously for 24 hr on a magnetic stirrer. At the end of 24 hr, the dilutions were made suitably and it was measured for the drug content at 331nm UV spectrophotometrically.[18,19]

2.3.6 *Solubility determination*

To determine the change in solubility due to complexation, the apparent solubility of Piroxicam and Piroxicam pharmacosome was determined by adding an excess amount of drug and pharmacosomes to 6ml distilled water, 7.4 PH phosphate buffer and n-octanol in screw capped vials. The vials were then shaken at 25 °C for 24 hr in a water bath. After equilibrium had been attained, the saturated solutions obtained were centrifuged to remove the excess drug (15 min, 1000 rpm). The supernatant was filtered immediately and rapidly and diluted suitably with same solvent to prevent crystallization. The filtered and diluted solutions were then analyzed spectrophotometrically at 331 nm.[18]

2.4 Post formulation studies

2.4.1 Weight variation test

Select 20 capsules randomly. Weigh an intact capsule. Open it without losing any part of the shell and remove the contents as completely as possible. Weigh the shell. The difference between the weighing gives the weight of the contents. Repeat the procedure with the remaining 19 capsules. Calculate the average weight. Not more than two of the individual weights deviate from the average weight by more than the percentage deviations how in the table and non-deviates by more than twice that percentage.[14,17]

2.4.2 Disintegration test

This test was done by using disintegration apparatus (Tab machine, Mumbai). Place one capsule in each of the 6 tubes of the basket and add distilled water to each tube. Suspend the assembly in the beaker containing distilled water. The distilled water in that apparatus was maintained at 37±2 °C. The assembly should be raised and lower between 28-32 cycles per minute. The time taken for complete disintegration of the capsule with no palpable mass remaining in the apparatus was measured and recorded.[14,17] If 1 or 2 capsules fail to disintegrate, repeat the test on 12 additional capsules; NLT16 of the total18 capsules tested should disintegrate.

2.5 Dissolution studies

This test was carried out by using USP XXIV dissolution test apparatus Type I (basket apparatus). The stirring speed was maintained at 50 rev/min and the temperature was maintained at 37°C ± 0.5 °C. The release study for the capsules was carried out by keeping the capsules for 10 hr hours in the dissolution medium of Ph 7.4 phosphate buffer solution (900 ml). At predetermined time intervals,10ml of sample was withdrawn and was replaced with 10 ml fresh buffer solution. The absorbance of the sample was measured by using double beam spectrophotometer at 331 nm. The cumulative release of the sample was calculated by using suitable equations with the help of the standard curve.[14,17]

2.5.1 X-Ray Powder Diffraction (XRD) Analysis

The crystalline state of Piroxicam in the different samples was measured using X-ray powder diffraction. Diffraction patterns were obtained on a XRD-6000 diffractometer (Shimadzu,Japan) at CRL, Karunya University, Coimbatore. The powder sample was placed in an aluminium sample holder. The X-ray generator was operated at 40 Kv tube voltages and 30 Ma of tube current, using the Ka lines of copper as the radiation source. The scanning angle ranged from 10 to 90° with a scan speed of 10 °min^{-1} .The drug, phosphatidylcholine and the pharmacosome were analyzed with X-ray diffractions.[15]

2.5.2 Scanning Electron Microscopy(SEM)Analysis

To detect the surface morphology of the prepared pharmacosome, a SEM analysis was performed by Scanning Electron Microscope JSM 6390 (JEOL,Japan). The sample was kept on an SEM stub using double-sided adhesive tape at 50Ma for 6 minutes through a sputter. A scanning electron microscope with a secondary electron detector was used to obtain digital images of the pharmacosomes.[20]

2.5.3 Drug Release Kinetic Analysis[21,22]

To study the release kinetics, data obtained from *in-vitro* drug release studies were plotted in various kinetic models: Zero order (Equation 7) as cumulative amount of drug released vs. time. First order (Equation 8) as log cumulative percentage of drug remaining vs. time Higuchi model (Equation 9) as cumulative percentage of drug released vs. square root of time.

2.6 Stability studies[23,24]

The prepared formulations format with different stability studies was conducted by storing the capsules at40° C ± 2° C, 70% RH ±5% for 45 days. The samples were withdrawn at initial, 30th & 45th day and analyzed suitably for the physical characteristics, drug content and cumulative drug release.

3. RESULTS AND DISCUSSION

1. Calibration curve of piroxicam

The λ_{max} of Piroxicam pure drug was determined by scanning the prepared solution in the wavelength range of 200-400 nm. The maximum wavelength was found to be 331 nm. The linearity of the curve was found in the concentration range of 2-10 µg/ml (Figure 2). A regression coefficient (R_2) value of 0.9989 was obtained.[25]

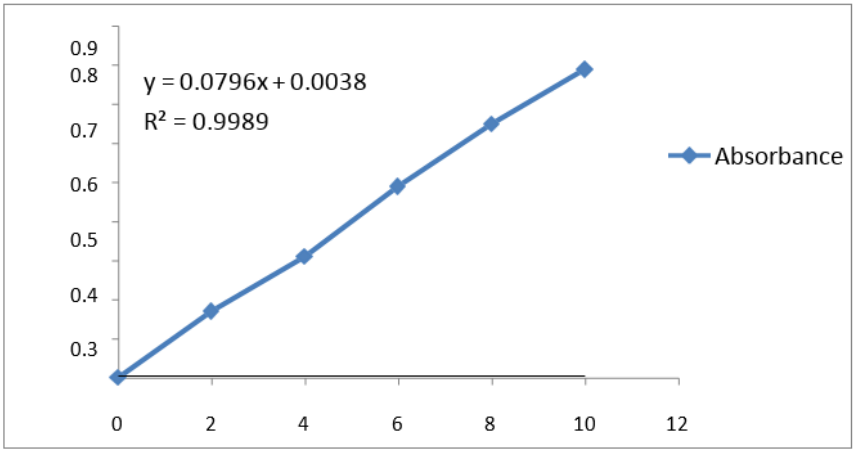

Fig 2: *Calibration curve of Piroxicam*

3.2 Compatibility studies

The IR spectra of pure drug, Piroxicam and the excipient, soya lecithin was analyzed and compared with IR spectra obtained for the mixture. It was found that the spectra of the drug with excipient (Figure 3) showed all the characteristic peaks (Table 2) of Piroxicam suggesting that, there was no compatibility problem between the drug and the excipient.[26]

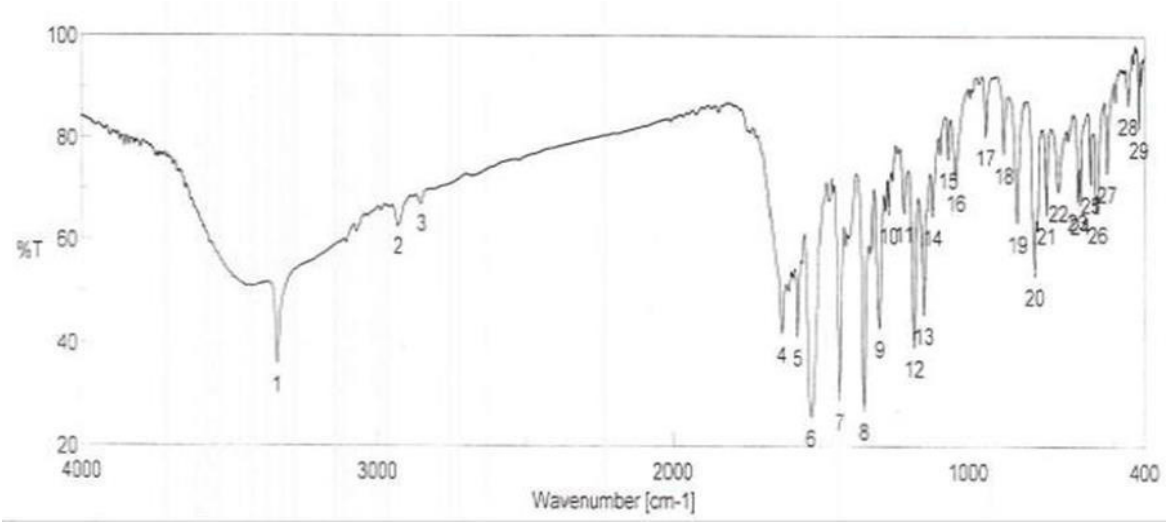

Fig 3: IR Spectra of Piroxicam pure drug

Table2: Characteristic peaks of Piroxicam

SPECIFICATION	WAVE NUMBER – PIROXICAM
C-H Stretching	2976.93
C=N Stretching	1577
N-H Stretching	3338.66
S(=O) 2 Stretching	1350.89
C=O Stretching	1630.04
C-S Stretching	691.355

3.3 Preformulation Studies

The preformulation parameters like angle of repose, bulk density, tapped density, Hausner's ratio and Carr's index were studied to evaluate the flow ability and compressibility of the powder formulations (Table 3).

Table 3: Results of preformulation studies

FORMULATION	ANGLE OF REPOSE	BULK DENSITY (gm/cm)3 (mean±S.D*)	TAPPED DENSITY (gm/cm)3 (mean±S.D*)	HAUSNER'S RATIO	CARR'S INDEX(%)
F1	25°16'	0.555±0.02	0.625±0.02	1.126±0.02	11.20±0.3
F2	27°54'	0.400±0.01	0.454±0.03	1.135±0.02	11.89±0.4
F3	25°83'	0.500±0.01	0.571±0.05	1.143±0.03	12.00±0.3
F4	26°09'	0.434±0.03	0.500±0.04	1.152±0.01	13.20±0.4
F5	29°31'	0.454±0.01	0.526±0.03	1.159±0.04	13.74±0.2
F6	28°57'	0.416±0.02	0.500±0.03	1.201±0.01	16.80±0.5
F7	27°63'	0.500±0.03	0.625±0.02	1.250±0.02	20.00±0.3

standard deviation (n=3)

The above values indicate all samples have good flow character. All the results were within the prescribed limits. F_1 formulation showed the best flow property. This study values showed better flow properties compared to Lohithasu D[27] study who evaluated flow properties of various Piroxicam liguisolid systems.

3.4 Drug content studies

The drug content of Piroxicam in the pharmacosomes was estimated (Table 4) by UV spectrophotometry at 331 nm using Ph 7.4 phosphate buffer.

Table 4: Results of drug content studies

FORMULATION	DRUG CONTENT (%w/w) (mean±S.D*)
F1	96.84±0.6
F2	96.13±0.7
F3	93.39±0.5
F4	93.57±0.6
F5	90.82±0.7
F6	90.05±0.8
F7	88.61±0.8

standard deviation (n=3)

The drug content of Piroxicam in the complexes were found to be in the range of 88.61%- 96.84% indicating the presence of an acceptable amount of drug in the formulations. The pharmacosomes showed a high percentage of drug loading, which is a prime advantage over liposomes. The percentage of drug loading decreased with an increase in the concentration of lipid. The formulation F_1 showed the maximum drug content of 96.84%. The drug content of Piroxicam loaded pharmacosomes can be compared to the study conducted by Lohithasu D [27], where the drug content of various piroxicam liquisolid systems had been reported.

3.5 Solubility studies

The change in solubility of Piroxicam due to complexation was determined (Table 5) by evaluating its solubility in water, Ph 7.4 phosphate buffer and n-octanol solutions and was estimated by UV spectrophotometry at 331 nm.

Table5: Solubility profile in different media

Formulation	Solubility in Water(mg/ml) (mean±S.D*)	Solubility at Ph 7.4 Phosphate Buffer (mg/ml) (mean±S.D*)	Solubility in n-Octanol(mg/ml) (mean±S.D*)
Pure drug	0.143±0.05	0.197±0.06	0.231±0.08
F1	0.789±0.02	5.273±0.05	5.976±0.08
F2	0.781±0.03	5.151±0.06	5.640±0.06
F3	0.652±0.02	4.837±0.07	5.284±0.08
F4	0.694±0.02	3.950±0.08	4.569±0.06
F5	0.528±0.03	3.752±0.08	4.191±0.07
F6	0.573±0.03	3.864±0.07	4.237±0.06
F7	0.617±0.02	4.356±0.06	4.587±0.06

standard deviation (n=3)

The solubility of the Piroxicam pharmacosomes was found to be much higher than the pure drug. The increase in solubility of Piroxicam in the complex can be explained by the solubilisation theory resulted from the formation of micelle in the medium and also by the amorphous nature of the complex. These amphiphilic surfactants (phospholipids) may increase the solubility of the drug by their wetting and dispersion properties. The formulation F1 has the highest degree of solubility. The Solubility acceptance criteria for Piroxicam were similar to the study conducted by Shohin et al.[28]

3.6 Post Formulation Studies

Table6: *Results of post formulation studies*

Formulation	Weight Variation (mg) (mean±S.D*)	Disintegration Time (Sec) (mean±S.D*)
F1	41±3.1	20±20
F2	49±2.8	23±15
F3	62±2.5	27±13
F4	70±3.0	29±14
F5	79±2.7	30±11
F6	91±4.3	35±10
F7	102±3.2	37±12

standard deviation (n=3)

From the values obtained (Table 6), it was observed that the weight variation was within the specified limits and the disintegration time was in the range of 225-256 sec. While Piroxicam fast dissolving tablets showed better disintegration time, obtained in the study conducted by Sachan Anupam et al.[29] compared to the Pharmacosomes loaded Piroxicam drug.

3.7 n-vitro dissolution studies

In-vitro release study was performed for all the formulations for a period of 10hours by using USP XXIV dissolution test apparatus Type I (basket apparatus). The data obtained was used to calculate the percentage cumulative release and plots were drawn by taking times percentage cumulative release.

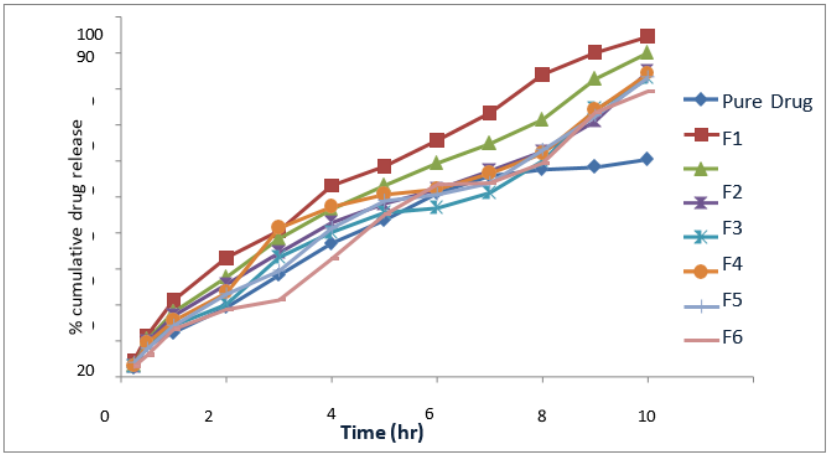

Fig 4: *In-vitro* comparative diffusion profile of pharmacosomes containing

3.8 Piroxicam

The pharmacosomes of Piroxicam showed better dissolution profile than the pure drug (Figure 4). Unlike the free Piroxicam (which showed a total of only 60.42% drug release at the end of the 10 hour), all the formulations showed the percentage cumulative drug release in the range of 79.49 – 94.69 %. The formulation F_1 with drug: soya lecithin ratio of 1:1 showed the maximum release of 94.69 % at the 10^{th} hour. The solid dissolution is a complex process which is affected by various factors like the particle size, crystal habit, surface area, surface energies and wettability. Wetting and dispersion properties of phospholipids (an amphiphilic surfactant) increased the solubility of the drug and hence improved the dissolution profile of the complex. Pharmacosomes loaded piroxicam showed greater dissolution profile comparing to the Piroxicam fast dissolving tablets, obtained in the study conducted by Sachan Anupam et al.[29]

3.9 X-Ray Powder Diffraction (XRD) Analysis

The XRD pattern of the pure drug (Piroxicam), soya lecithin and the selected formulation (F_1) are shown in Fig:5, Fig:6

and Fig: 7. Characteristic diffraction peaks were observed for Piroxicam. On the other hand, the formulation F_1 was characterized by less intensity of the diffraction peak when compared to that of the pure drug. This clearly indicates the reduction in the crystallinity of Piroxicam in the pharmacosome Similarly in the study conducted by Lohithasu D [27], the formulated Piroxicam drug showed reduction in the crystallinity and enhanced the dissolution profile of the formulation.

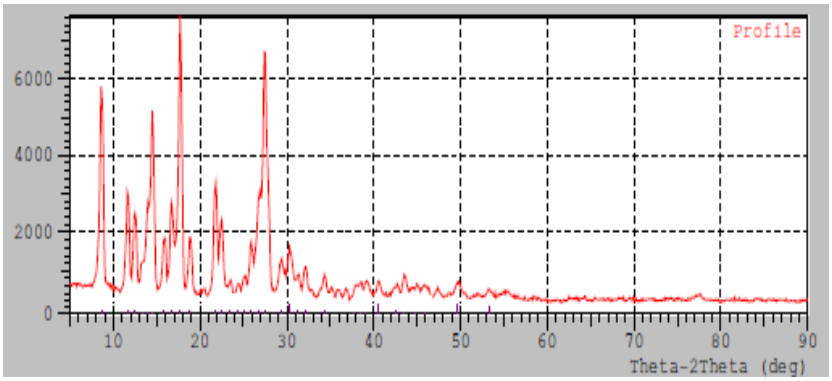

Fig 5 : *XRD p atternofpuredrug(Piroxicam)*

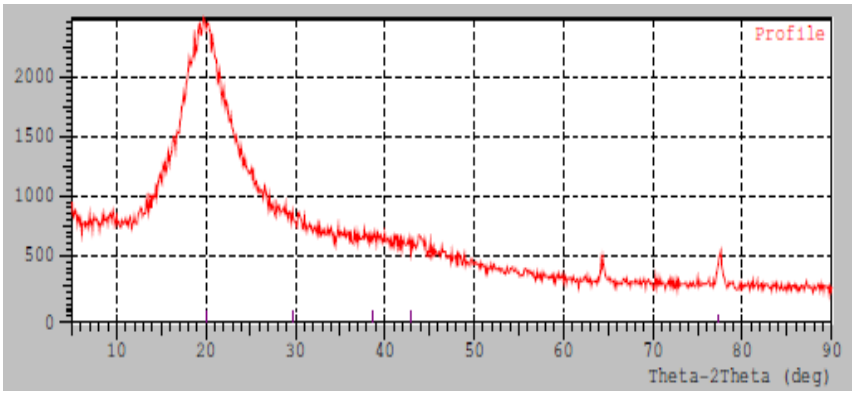

Fig 6 : XRD pattern of soya lecithin

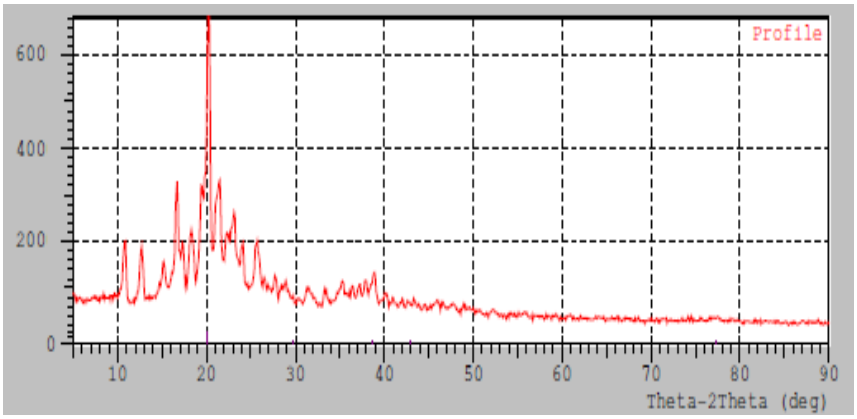

Fig 7 : XRD pattern of Piroxicam pharmacosome (F1)

3.10 Scanning Electron Microscopy (SEM) Analysis

Particle morphology was determined by scanning electron microscopy. The SEM images showed (Figure 8) that the pharmacosomes were disc shaped.

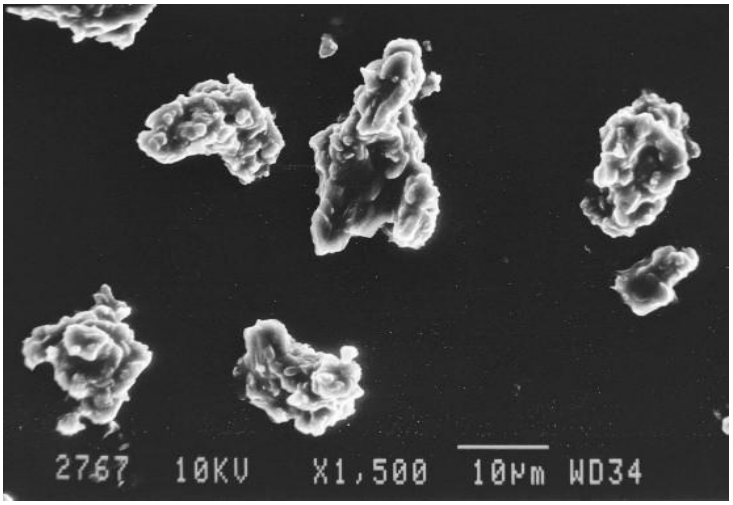

Fig 8 : SEM image of Piroxicam pharmacosome (F_1)

3.11 Release kinetic analysis

Based on the data obtained from the *in-vitro* drug release studies, the best formulation F_1 was analysed for the release kinetic studies. The cumulative release of drug was fitted into various plots like Zero order, First order and Higuchi model to know the pattern of release and Korsmeyer-Peppas model in order to find out the mechanism of release from the prepared pharmacosome (Table 7). The model that best fits the release data is selected based on the regression coefficient value of various models (Fig: 9, Fig: 10, Fig: 11, Fig: 12).

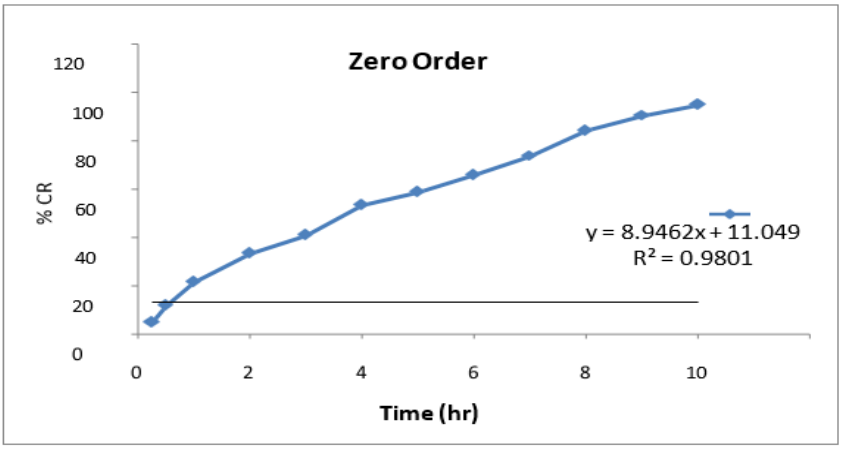

Fig 9 : Zero order plot F1

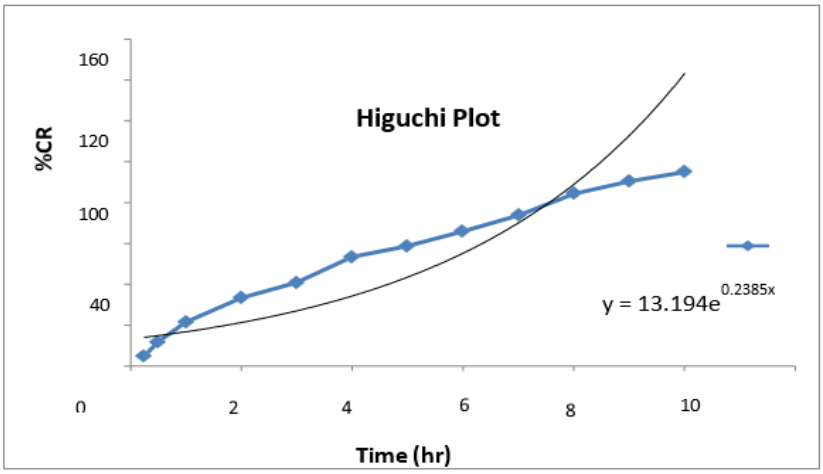

Fig 10 : First order plot of F_1

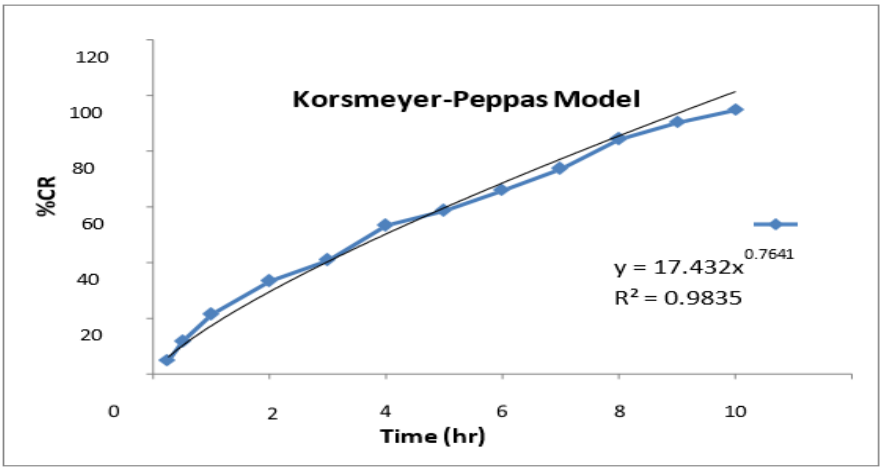

Fig 11 : Higuchi plot of F1

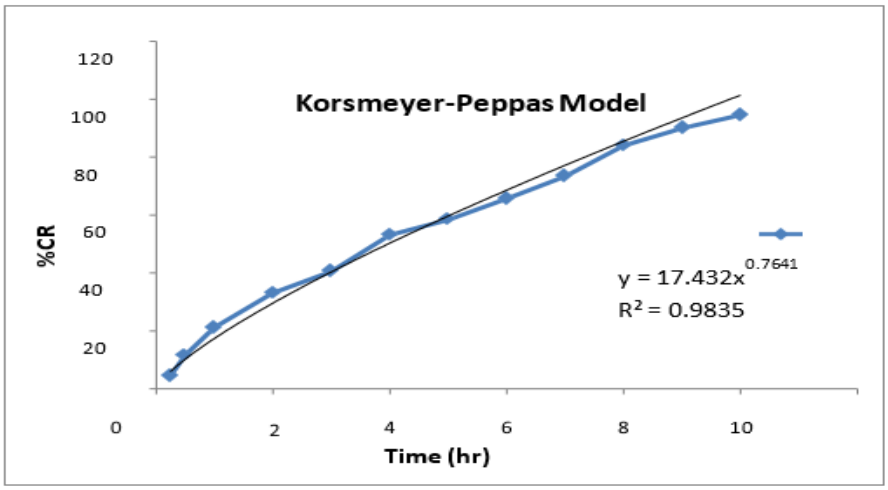

Fig 12 : *Korsmeyer-Peppas model of F_1*

Table7: *Results of kinetic analysis*

Formulation	Zero Order	First Order	Higuchi Model	Korsmeyer-Peppas model	
	R^2	R^2	R^2	N	R^2
F_1	0.9801	0.9172	0.7602	0.7641	0.9835

From the regression coefficient values obtained, it was found out that the formulation follows the near Zero order kinetics. The slope value (n) obtained from Peppas plot was 0.7641, which indicates that the formulation followed a non-Fickian diffusion mechanism of drug release.

1.12. Stability Studies

Stability study of best formulation (F_1) was carried out at an accelerated temperature of 40° ± 2°C and a relative humidity of 70 % ± 5 % RH in a humidity control oven for 45 days [29]. After 45 days the sample was evaluated for the physical appearance, drug content, and *in-vitro* drug release studies. The values areas shown in the Table 8.

2.2.1 Table8: *Stability studies of F_1 formulation*

Sl.no	Parameters	Accelerated Temperature of 40 ± 2°C/RH 70 ±5 %		
		Initial	30thday	45thday
1	Physical appearance	Light Yellow	Light Yellow	Light Yellow
2	Drug content (%)	96.84±1.5	95.97±2	95.41±3.1
3	% of Cumulative release at10th hr	94.69± 3.1	93.78±4.2	93.54±5

standard deviation (n=3)

After 45 days under stability conditions, it was concluded that there was no major changes in the various parameters valuated like physical appearance, percentage drug content and *in-vitro* drug dissolution study of F_1 at 40 ± 2°C. Thus, it can be concluded that, F_1 is stable temperature of 40±2 °C and at a relative humidity of 70±5% for a period of 45 days. In the present study the Piroxicam–phospholipid complexes (pharmacosomes) were prepared by a simple and reproducible method. The physicochemical investigations confirmed that Piroxicam formed a complex with phospholipids with better solubility and dissolution profile. The phospholipid complex of Piroxicam may be of potential use for improving bioavailability. As the phospholipid complexes have also been reported to reduce the GI toxicity of the drugs, the phospholipid complex of Piroxicam may also be useful or minimizing the GI toxicity of Piroxicam. The pharmacosomes may be developed for other NSAIDs with poor bioavailability and GI side effects.

4. CONCLUSION

Thus the formulated pharmacosomes seen to be potential candidate as an oral controlled drug delivery system in this era of novel and controlled drug delivery systems. The developed formulations are expected to improve the patient compliance, form better dosage regimen and provide optimum maintenance therapy to rheumatoid arthritis patients.

5. AUTHOR CONTRIBUTION STATEMENT

The author's responsibilities were as follows – Dr Muthukumar S compiled the overall data. Dr Sankar C analysed the data and included necessary input. Dr Gayathri R developed the work scheme. Mr Manoranjan R collected all necessary data and Mr Mohandass A discussed the methodology. Mr Rajaguru B drafted results. Ms Rajeshwari V and Ms Ardra Krishna PV collected and designed statistical data. Ms Winnine rose designed the manuscript and Mr Gunasekaran M discussed the conclusion.

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7. CONFLICT OF INTEREST

The authors possess no conflict of interest.

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