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Formulation and Evaluation of Selective Cox-2 Inhibitor Loaded Pharmacosomes for the Treatment of Rheumatoid Arthritis

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Abstract

Pharmacosome is a newer novel vesicular approach in the drug delivery system. It reduces toxicity, minimum dosage frequency and has drug entrapment efficiency. In the present research work, an attempt was made to develop pharmacosomal gel from pharmacosomal suspension for topical delivery containing non-steroidal anti-inflammatory drug to treat rheumatoid arthritis. This approach provides the sustained release of drug and thereby reducing the frequency of drug administration and improves patient compliance. Pharmacosomes were prepared by thin film hydration technique/hand shaking method by using soya lecithin as phospholipid in different ratios using different solvents. The prepared pharmacosomes were evaluated for preformualtion parameters. All batches of pharmacosomes were evaluated for entrapment efficiency, drug content and *in vitro* drug release. After evaluation the best formulation was selected for the preparation of pharmacosomal gel. Pharmacosmal gel were prepared by using carbapol 934 and triethanolamine. The prepared gel was evaluated for physical appearance and homogeneity, clarity, pH, viscosity, spreadability, extrudability and drug diffusion data. The study indicated that the pharmacosomal gel of etoricoxib follows sustained release mechanism. It shows better drug release and high entrapment efficiency. The pharmacosome could be prepared in a cost effective and simple manner.

Key words: pharmacosome, etoricoxib, sustained release.

INTRODUCTION

Pharmacosomes are novel vesicular drug delivery system. They are colloidal dispersion of drug covalently bound to lipids. They provide an efficient method for the delivery of drug to the target site. The physicochemical properties depend on drug as well as the lipid. Pharmacosomes may be hexagonal aggregates, ultrafine vesicular and micellar form. Both synthetic and natural drugs which are facing difficulties like low solubility and low permeability can be effectively formulated. Pharmacosomes have been prepared for various NSAIDs, proteins, cardiovascular and antineoplastic drugs. Developing the Pharmacosomes of the drugs has been found to improve the absorption and minimize the gastrointesinal toxicity. Pharmacosomes are amphiphilic complexes of drug with lipids. The amiphiphilic character help to reduce interfacial tension leading to increase in contact area and increase bioavailability of drugs[1 - 6].

Inflammation is the part of the body defence mechanism. It is the process by which the immune system recognizes and removes harmful stimuli and begins healing process. There are two types of inflammation: acute and chronic inflammation. The symptoms of acute inflammation include pain, redness, swelling and heat. Chronic inflammation includes fatigue, chest pain, abdominal pain, rash, fever and joint pain. There are more than 100 different types of arthritis and related conditions. Arthritic joint symptoms include swelling, pain, stiffness and finally decreased range of motion. The most common treatment for rheumatoid arthritis or arthritis include non steroidal anti-inflammatory drugs (NSAIDs), corticosteroids, disease modifying anti- rheumatic drugs (DMARDS), and some biological agents[7, 8].

Oral route is the most preferable route of drug delivery. Treatment with NSAID through oral route is associated with side effects like ulceration and GI bleeding[9]. It's poor water solubility which affect it's dissolution in GI fluid, lead to poor bioavailability. Selective COX- 2 inhibitors should be used in patients at higher risk of peptic ulcer, perforation or bleeds. If selected, they should be administered in the lowest dose for the shortest period of time. Moreover, it should be avoided in patients with history of ischaemic heart disease/hypertension/cardiac failure/cerebrovascular disease etc. In order to avoid this toxicity, cardiovascular risk and for better therapeutic effect, is to be delivered through skin.

Pharmacosomes are novel drug delivery system, resolving so many related problems and issues to the conventional dosage form such as the drug release at the specific site of desired rate for achieving controlled or targeted drug delivery. When handling, there are possibility of leaching as the drug is bounded to the lipid by covalent bonding and also the entrapment efficiency is high. Pharmacosome drug delivery system suitable for both hydrophilic and lipophilic drugs. Pharmacosomes reduce the cost of therapy, adverse effects and toxicity. They improve in the bioavailability of poorly soluble drugs[10, 11].

MATERIALS AND METHODS

Etoricoxib, soyalecithin, dichloromethane, methanol, carbapol934, triethanolamine were obtained from Yarrow Chem products, Mumbai.

Formulation of pharmacosome

Pharmacosomes were formulated by thin - film hydration technique/ hand shaking method. The drug –PC complex was prepared by associating drug acid with PC in various molar ratios. The accurately weighed phosphatidyl choline and drug (etoricoxib) were placed in a 100 ml round bottom flask and dissolved in sufficient amount of solvents like, dichloromethane/ methanol. Then the

solvent was evaporated off under vaccum at 40 ℃ in a rotary vaccum evaporator for 45 minutes at 100 rpm. Then thin film was hydrated using phosphate buffer of pH to get a vesicular suspension. The obtained formulation was sonicated in the sonicator[12].

Formulation of Pharmacosomal Gel

Sufficient quantity of water was taken in a beaker and carbapol 934 was added little by little on continuous stirring by using mechanical stirrer. Then added pharmacosomal suspension and dissolved it well. Pure gel of pharmacosomes was obtained by the addition of triethanolamine[13].

EVALUATIONS OF PHARMACOSOMES

ENTRAPMENT EFFICIENCY

Prepared pharmacosome suspension of approximate 10 ml was taken from total volume and dissolved in 10 ml of phosphate buffer solution of pH 6.8. The mixture was sonicated for 10 min in a bath sonicator and un entrapped drug was separated by centrifuging at 10,000 rpm for 30 minutes. Suitable dilutions were made in supernatant liquid collected with phosphate buffer solution and then analysed spectrophotometically at 233 nm using UV spectrophotometer against phosphate buffer 6.8 as balnk. The percentage drug entrapment was calculated using the following equation[13].

Percentage drug entrapment

$$= \frac{\textbf{Total drug} - \textbf{Drug in supernatent}}{\textbf{Total drug}} \times 100$$

PERCENTAGE YIELD OF PHARMACOSOMES

The prepared pharmacosomes were dried, collected and weighed. The measured weight was divided by the total amount of the drug and ingredients which were used for the preparation of pharmacosomes. The percentage yield was calculated by the equation,

Percentage yield

$$= \frac{\textbf{Actual weight of product}}{\textbf{Total weight}} \times 100$$

DRUG CONTENT

Drug content in the pharmacosome complex was determined by taking a pharmacosomal dispersion equivalent to drug which was dissolved in a medium like phosphate buffer having pH in a volumetric flask. The mixture was shaken for 2 h in a bath sonicator to ensure the complete solubility of drug. Suitable dilutions were made and the resultant mixture was filtered, and analysed spectrophotometrically at 233 nm against phosphate buffer 6.8 as blank[12].

IN VITRO DRUG RELEASE STUDIES

Franz diffusion studies are the general approach for measuring the drug release. According to Food and Drug Administration (FDA) regulations, it is an ideal tool for quality control of the preparations. The system contains a donor and receptor compartments, in which donor compartment contains pharmacosome preparation and the receptor compartment, filled with phosphate buffer medium. A dialysis membrane sandwitched between donor and receptor compartments. 100 ml buffer solution was placed in the receptor compartment. Samples were withdrawn at predetermined intervals like 1, 2, 3, 4, 5 to 10 h and was replaced with an equal volume of fresh buffer solution. The collected samples were filtered, proper dilutions are made and analysed spectrophotometrically using UV spectrophotometer against phosphate buffer 6.8 as blank[13].

DRUG RELEASE KINETICS

Release kinetics of drug from the dosage form was determined by various mathematical models such as zero order, first order, koresmeyer- peppas and higuchi model.

1. Cumulative percent drug released Vs time (zero order plots)
2. Log cumulative percent drug remaining Vs time (first order plots)
3. Cumulative percent drug release Vs square root of time (Higuchi plots)
4. Log cumulative percent drug release Vs log time (korsmeyer – peppas plots)

EVALUATIONS OF PHARMACOSOMAL GEL

PHYSICAL APPEARANCE AND HOMOGENEITY

The physical appearance and homogeneity of the prepared gels were tested by visual observations after the gels have been set in the container. They were tested for their appearance and presence of any aggregates [13].

CLARITY

The clarity of various formulations was determined by visual inspection under black and white background .

pH DETERMINATION

1.0 g gel was accurately weighed and dispersed in 100 ml purified water. The pH of the dispersion was measured using digital pH meter, which was calibrated before use with standard buffer solution at pH 4.0, 7.0 and 9.0. The measurements of pH were done in triplicate and average values were calculated.

VISCOSITY

Brookfield digital viscometer was used for the determination of viscosity and rheological properties of etoricoxib pharmacosomal gel using spindle noT-64. The viscosity of gel was measured at different angular velocities at a temperature of 37°C. A typical run comprised changing of the angular velocity from 0.3 to 2.5 rpm. The averages of the readings were used to calculate the viscosity [13].

SPREADABILITY

Spreadability was determined by assessing the required time to separate the slide by applying force or weight over the slide. Spreadability of the formulation was reported in seconds. Spreadability was calculated using the formula:

$S = M \times {}^{L}/_{T}$

Where S = spreadability

M = weight to upper slide

L = length of glass slide

T = time taken to separate the slide completely from each other [12].

EXTRUDABILITY

To determine extrudability a closed collapsible tube containing formulation was pressed firmly at the crimped end. When the cap was removed, formulation extruded until the pressure dissipated [12, 13].

***IN VITRO* DIFFUSION STUDY**

The *in-vitro* diffusion study of prepared gel was carried out in Franz diffusion cell apparatus. Etoricoxib pharmacosomal gel was spread uniformly on the cellophane membrane which was previously soaked in phosphate buffer and was sandwiched between donor and receptor compartment. 100 ml of phosphate buffer was used as receptor compartment. The temperature was maintained at 37 °C. The whole assembly was fixed on a magnetic stirrer and the solution in the receptor compartment was constantly stirred using magnetic bead at 450 rpm. Sample of 1 ml was withdrawn at various time intervals (15, 30, 45, 60,120,180, 240, 300, 360 and 420 min.) and replacement was done with 1 ml of fresh buffer. The drug concentration on the receptor fluid was determined spectrophotometrically against blank at 233 nm against phosphate buffer 6.8 as blank[13].

Table a: Composition of pharmacosome

Ingredients	Formulation code					
	F1	F2	F3	F4	F5	F6
Etoricoxib (mg)	200	200	200	200	200	200
Soya lecithin (mg)	300	300	400	200	300	400
Dichloromethane (ml)	5	5	5	-	-	-
Methanol (ml)	-	-	-	5	5	5
Phosphate buffer (ml)	q.s	q.s	q.s	q.s	q.s	q.s

RESULTS AND DISCUSSIONS

Fourier-transform infrared spectroscopy

FTIR spectrum of levofloxacin showed all the peaks corresponding to the functional groups present in the structure and there were no additional peaks. The combination spectrum of drug and excipient in figure 1, 2, 3, 4, 5 also showed no change in the peak values corresponding to functional groups of the drug when combined with excipients, indicating that the drug is compatible with the excipients.

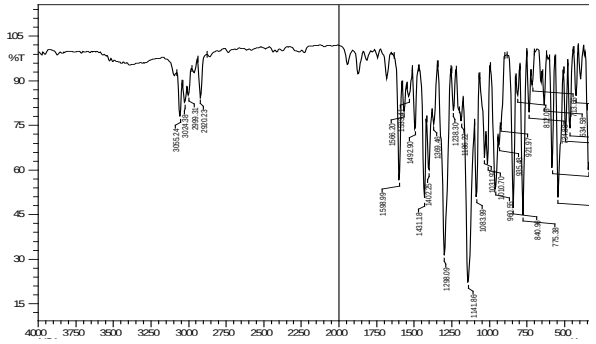

Fig 1: FTIR of Etoricoxib

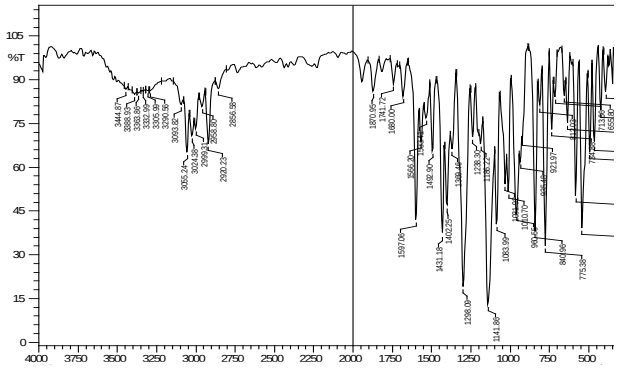

Fig 2: FTIR of drug + soyalecithin

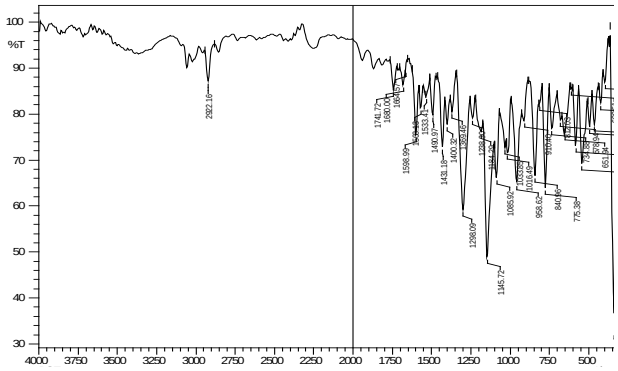

Fig 3: FTIR of drug + soyalecithin + dichloromethane

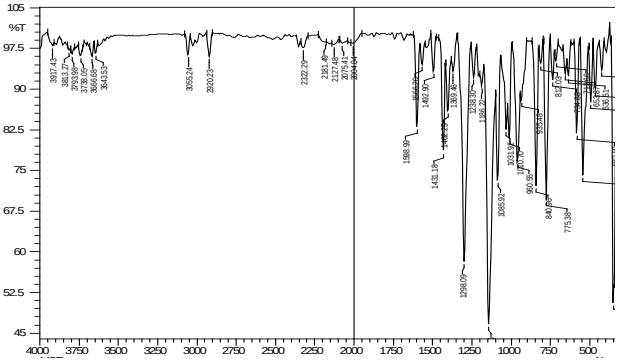

Fig 4: FTIR of drug + soyalecithin + methanol

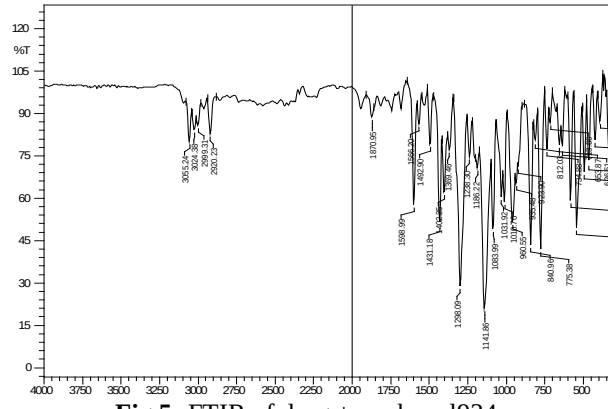

Fig 5: FTIR of drug + carbapol934

FORMULATION DEVELOPMENT

Fig 7: Thin film development and pharmacosome suspension formation using rotary vacuum evaporator.

Fig 8: Pharmacosome suspension of Etoricoxib

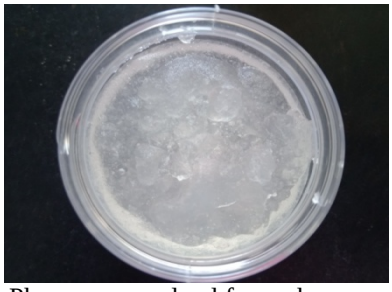

Fig 9: Pharmacosomal gel from pharmacosomal suspension

EVALUATION OF PHARMACOSOMAL SUSPENSION

ENTRAPMENT EFFICIENCY

Percentage entrapment of etoricoxib pharmacosomes were performed and the values were found in the range of 81% to 90.20% as shown in Table b.

Table b: Entrapment efficiency of pharmacosome

Sl no.	Formulation	Entrapment efficiency (%) (Mean±SD)*
1	F1	81± 0.132
2	F2	85.30±0.253
3	F3	90.20±0.141
4	F4	82±0.326
5	F5	85.80±0.214
6	F6	86±0.461

(*=Average mean values of six determinants, SD= Standard deviation)

The entrapment efficiency was found higher in formulation F3. Concentration of lecithin and the nature of solvent are belived to affect in the entrapment efficiency.

PERCENTAGE YIELD

The percentage yield of all formualtions were performed and the values obtained were in the range of 91.32% to 94.91% and were summarized in the Table c.

Table c: Percentage yield of pharmacosome

Formulation code	Percentage yield (%) (Mean±SD)*
F1	92.13±0.132
F2	93.60±0.224
F3	94.91±0.112
F4	91.32±0.461
F5	93.55±0.235
F6	93.93±0.221

(*=Average mean values of six determinants, SD= Standard deviation)

DRUG CONTENT

The drug content of pharmacosomal suspension was determined by UV spectroscopic method at a wavelength of 233 nm against phosphate buffer 6.8 as blank. The percentage drug content of the pharmacosomes were performed. The values obtained were summarized in the Table d.

Table d: Percentage drug content of pharmacosome formulation

Formulation code	Percentage drug content (%)± SD
F1	76.88±0.171
F2	83.12±0.324
F3	91.95±0.216
F4	74.55±0.142
F5	80.52±0.313
F6	89.09±0.272

(*=Average mean values of six determinants, SD= Standard deviation)

IN VITRO DRUG RELEASE STUDIES

In vitro drug release was performed by using franz diffusion model of pharmacosome in different concentration of polymer and solvent. The *in vitro* drug dissolution profile of pharmacosome was performed. The percentage cumulative drug release of all the pharmacosome formulations was summarized in the Table e and the percentage cumulative drug release with time was shown in Figure 10 and 11.

Table e: Data of *in vitro* drug release studies

Sl no.	Time (h)	Percentage drug released (%) ±SD					
		Formulation code					
		F1	F2	F3	F4	F5	F6
1	1	16.40±0.12	18.55±0.34	27.82±0.22	18.03±0.13	17.37±0.37	18.43±0.15
2	2	22.55±0.17	27.82±0.61	38.43±0.34	22.36±0.22	19.20±0.29	26.72±0.48
3	3	28.70±0.20	36.17±0.36	41.08±0.28	31.02±0.51	26.52±0.14	33.22±0.59
4	4	38.96±0.26	40.81±0.58	50.35±0.16	41.84±0.36	31.09±0.54	41.47±0.61
5	5	43.74±0.34	51.94±0.69	53.00±0.54	45.45±0.29	34.75±0.16	47.00±0.36
6	6	49.21±0.42	57.51±0.50	64.93±0.35	51.22±0.27	42.07±0.33	54.38±0.10
7	7	61.51±0.16	65.86±0.36	67.58±0.46	62.77±0.61	47.55±0.47	58.98±0.52
8	8	64.25±0.23	76.99±0.46	72.54±0.41	65.65±0.16	55.78±0.21	63.59±0.24
9	9	71.08±0.32	82.5±0.25	82.16±0.39	71.42±0.34	65.84±0.37	66.45±0.30
10	10	77.92±0.25	85.34±0.14	91.43±0.19	77.20±0.52	74.08±0.25	71.84±0.52

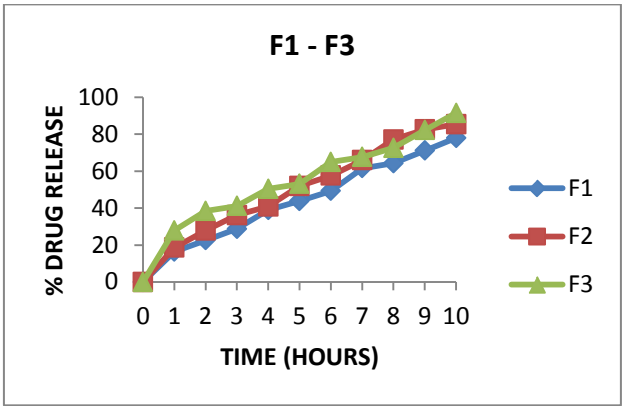

Fig :10 *In vitro* drug release study of formulation F1 – F3

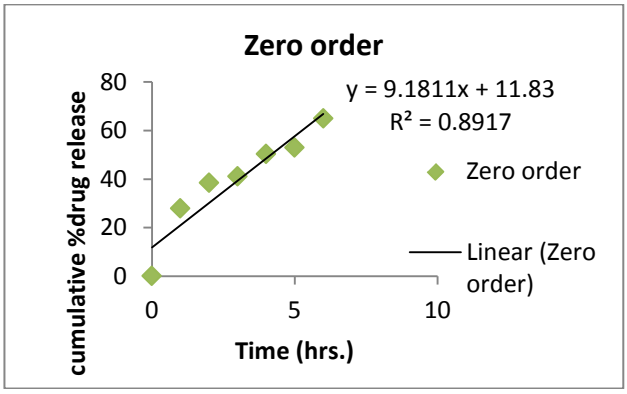

Fig 12: Zero order plot for drug release kinetics of F3 formulation

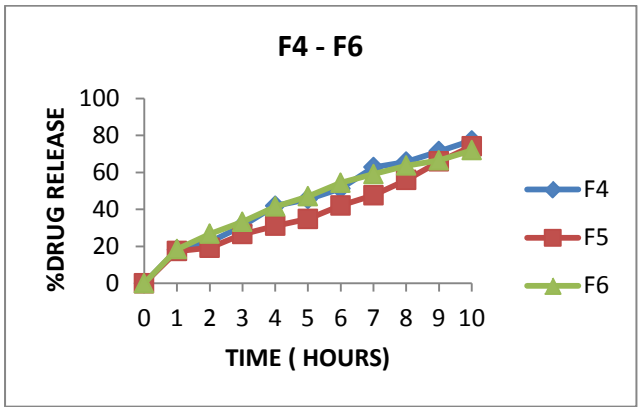

Fig :11 *In vitro* drug release study of formulation F4 –F6

KINETIC MODELLING OF F3

The kinetic study of the optimized formulation F3 were done in an attempt to obtain the release kinetics and to understand release mechanism.

Zero order plot

Graph was plotted between % cumulative drug release v/s time.

Korsmeyer – peppas model

Graph was plotted between log % cumulative drug release v/s time.

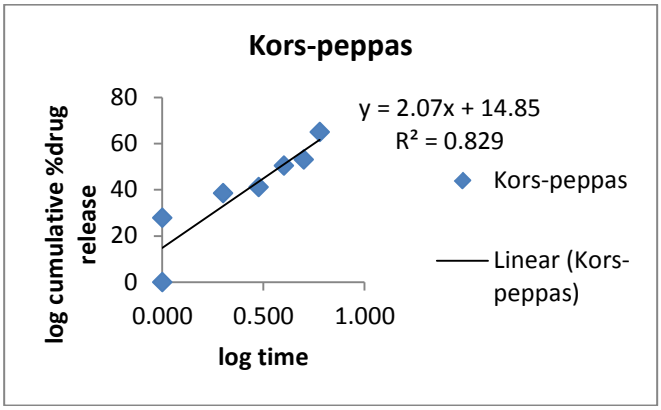

Fig 13: Korsmeyer – peppas plot for drug release kinetics of F3 formulation

First order plot

Graph was plotted between log % cumulative drug remaining v/s time.

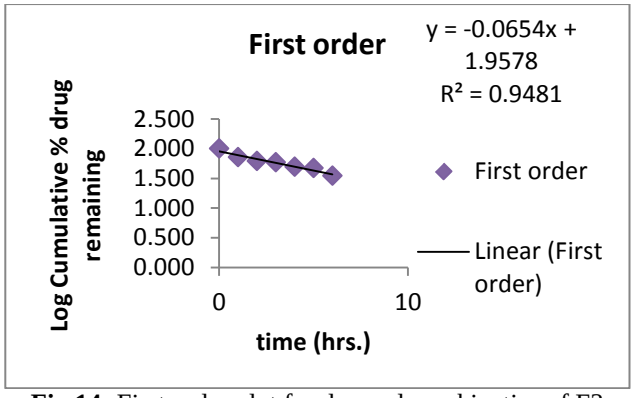

Fig 14: First order plot for drug release kinetics of F3 formulation

Higuchi model

Graph was plotted between % cumulative drug release v/s square root of time.

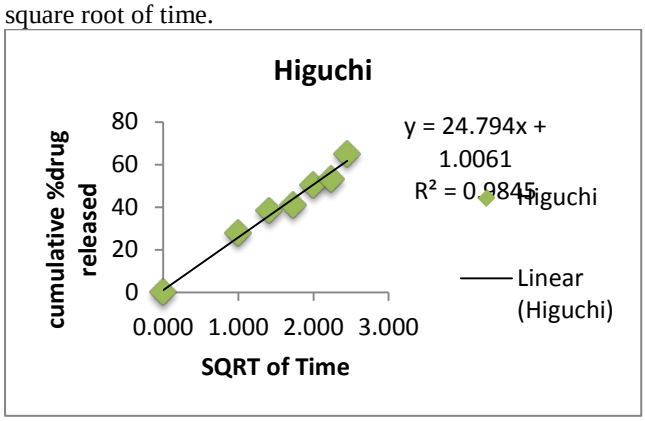

Fig 15: Higuchi order plot for drug release kinetics of F3 formulation

Table f: Kinetic modeling data of optimized pharmacosome F3

Formulation	Zero order	First order	Higuchi	Korsmeyer
F3 (R^2)	0.891	0.948	0.984	0.829

The dissolution profile of optimized formulation F3 was fitted to zero order, first order, higuchi model and korsmeyer peppas model to acertain the kinetic modeling of the drug release. The best fit with highest regression value R^2 was shown in higuchi model 0.984. So the optimized formulation shows diffusion mechanism.

EVALUATION OF PHARMACOSOMAL GEL

PHYSICAL APPEARANCE AND HOMOGENEITY

The physical appearance and homogeneity was determined. The results were shown in Table g .

Table g: Physical appearance and Homogeneity

Formulation code	Colour	Homogeneity	Occlusiveness	Washability
F3	White	Homogenous	Yes	Washable

CLARITY

The clarity was determined, the etoricoxib pharmacosomal gel was found to be turbid.

pH DETERMINATION

The pH was determined. The results were shown in Table h.

Table h: pH of gel

Formulation code	pH (Mean ±SD)*
F3	6.5±0.186
	6.3±0.124
	6.2±0.269

(*=Average mean values of six determinants, SD= Standard deviation)

pH of the optimized formulations were within limits of range of 6.2 – 6.5.

VISCOSITY

The viscosity was determined. The results were shown in Table i.

Table i: Viscosity of gel

Formulation code	Viscosity (cps)
F3	163
	172
	180

The determined viscosity was found in between 163 – 180 cps.

SPREADABILITY

The spreadability was determined. The results were shown in Table j.

Table j: Spreadability of gel

Formulation code	Spreadability (Mean ±SD)*
F3	0.201±0.131
	0.364±0.105
	0.518±0.257

(*=Average mean values of six determinants, SD= Standard deviation)

EXTRUDABILITY

The extrudability was determined. The results were shown in Table k.

Table k: Extrubability of gel

Formulation code	Extrudability
F3	Good
	Good
	Good

***IN VITRO* DIFFUSION STUDY**

The *in vitro* drug diffusion study was determined. The results were shown in Table l.

Table l: *In vitro* drug diffusion study datas of the optimized formulation F3

Sl no.	Time (min)	Percentage drug release (%)
1	0	0
2	15	23.85±0.14
3	30	33.13±0.29
4	45	42.40±0.16
5	60	49.03±0.33
6	120	54.33±0.40
7	180	63.60±0.37
8	240	66.26±0.24
9	300	72.88±0.46
10	360	86.13±0.21
11	420	95.41±0.19

Drug diffused from the pharmacosomal gel was found to be 86.13%. The concentration of soyalecithin, dichloromethane and polymer influenced the drug release to a great extent.

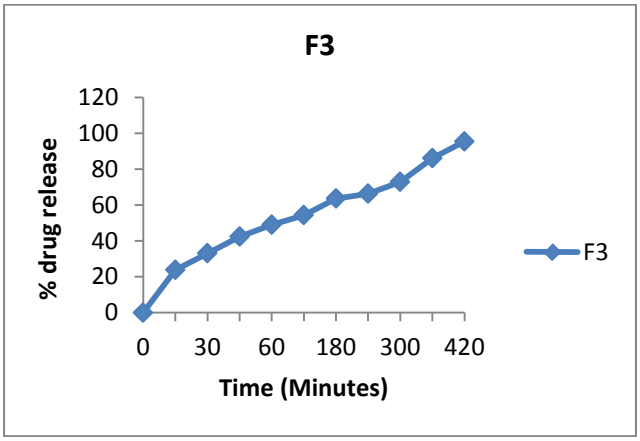

Fig 16: *In vitro* drug diffusion of optimized formulation F3

CONCLUSION

From the present study, an attempt was made to prepare pharmacosomal gel. The pharmacosomal suspension were prepared by thin film hydration method using soya lecithin, dichloromethane and methanol. The prepared pharmacosome suspension was evaluated for organoleptic evaluation, drug entrapment efficiency and *in vitro* drug release studies. The formulation F3 exhibited good entrapment efficiency, drug content and *in vitro* drug release profiles hence, selected as the best formulation. The pharmacosomal gel from the optimized formulation was prepared by using carbapol 934. The prepared pharmacosomal gel was evaluated for viscosity, pH, spreadability, extrudability and *in vitro* drug diffusion. The present research proved that the pharmacosomal gel that will have significant impact in the community, as they followed sustained release mechanism, increase drug release and increased solubility. Hence the objectives of the envisaged research was fulfilled.

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