DESIGN AND DEVELOPMENT OF PHARMACOSOMES FOR ORAL DRUG DELIVERY OF LOSARTAN

A Dissertation Submitted to

THE TAMIL NADU DR. M.G.R. MEDICAL UNIVERSITY

CHENNAI-600032

In partial fulfillment of the requirement for the award of the Degree of

MASTER OF PHARMACY

in

PHARMACEUTICS

OCTOBER-2017

DEPARTMENT OF PHARMACEUTICS,

KMCH COLLEGE OF PHARMACY,

KOVAI ESTATE, KALAPATTI ROAD,

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Submitted by

(Reg. No. 261510902)

Under the Guidance of

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CERTIFICATE

This is to certify that the dissertation work entitled **"DESIGN AND DEVELOPMENT OF PHARMACOSOMES FOR ORAL DELIVERY OF LOSARTAN"** was carried out by **Ms. Kiruthika .S (Reg. No. 261510902)**. The work mentioned in the dissertation was carried out at the Department of Pharmaceutics, KMCH College of Pharmacy, Coimbatore, Tamilnadu, under the guidance of **Mrs.J.Padmapreetha,M.Pharm,** for the partial fulfillment for the degree of Master of Pharmacy during the academic year 2016-2017 and is forwarded to the TamilnaduDr.M.G.R.Medical University,Chennai.

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This research work either in part or full does not constitute any of any thesis /dissertation.

Date: Signature

Place: Coimbatore **GUIDE**

DECLARATION

I do here by declare that to the best of my knowledge and belief ,the dissertation work entitled **"DESIGN AND DEVELOPMENT OF PHARMACOSOMES FOR ORAL DELIVERY OF LOSARTAN"** submitted to the Tamil Nadu Dr. M.G.R. Medical university,Chennai, in the partial fulfillment for the Degree of **Master of Pharmacy** in **Pharmaceutics** was carried out at Department of Pharmaceutics, KMCH College of Pharmacy, Coimbator, during the academic year 2016-2017.

Date: Signature

Place: Coimbatore **(Reg. No.261510902)**

EVALUATION CERTIFICATE

This is to certify that the work embodied in the thesis entitled **"DESIGN AND DEVELOPMENT OF PHARMACOSOMES FOR ORAL DELIVERY OF LOSARTAN"** submitted by **(Reg. No:261510902)** to the Tamil Nadu Dr. M.G.R. Medical university, Chennai, in the partial fulfillment for the Degree of **Master of Pharmacy** in **Pharmaceutics** is a bonafide research work carried out by the candidate during the academic year 2016-2017 at KMCH College of Pharmacy, Coimbatore, Tamilnadu and the same was evaluated by us.

Examination Center: K.M.C.H College of Pharmacy, Coimbatore

Date:

Internal Examiner **External Examiner**

Convener of Examination

ABBREVIATIONS

w/w	Weight by weight
i.e.	That is
Fig	Figure
e.g.	Example
PC	Phosphatidylcholine
HDL	High density lipoprotein
FT-IR	Fourier transform infrared spectroscopy
SEM	Scanning electron microscopy
XRD	X-ray powder diffraction
mg	Milligram
µg	Microgram
°C	Degree centigrade
hr	Hour
ml	Mililiters
rpm	Rotation per minute
min	Minute
nm	Nanometer

rpm	Rotation per minute
min	Minute
vs.	Versus
RH	Relative humidity
ICH	International Council for Harmonisation

ABSTRACT

The design of the present investigation was to prepare Losartan bounded pharmacosomes to improve the water solubility, bioavailability and minimize the toxicity of Losartan. Pharmacosomes is a potential approaches in vesicular drug system which exhibits several advantages over conventional vesicular drug delivery systems. Pharmacosomes are phosphilipid complexes with a potential to improve bioavailability of poorly water soluble as well as poorly lipophilic drugs. Losartan was complexed with soya phosphatidylcholine in various ratio using conventional solvent evaporation technique. 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 complex was found to be much better than Losartan pure drug. The improvement in solubility of the prepared pharmacosomes may be result in improved dissolution and lower gastrointestinal toxicity. Drug content was found to be 96.83% w/w for the optimized Losartan phospholipid complex F_1 (Losartan: lecithin ratio of 1:1). The pharmacosomes were found to be disc shaped in scanning electron microscopy. X-ray powder diffraction data confirmed the formulation of phospholipid complex. The formulation F_1 showed 94.69% drug release while the free Losartan showed data of only 60.42% at the end of 10 hours dissolution study. Thus the solubility and hence the bioavailability of Losartan can be increased to a greater extend by complexing it with soya phosphatidylcholine.

Key words: Losartan, Bioavailability, pharmacosomes, phospholipid complex, solubility.

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Above all I dedicate myself before the unfailing presence of **God Almighty** throughout the way of my success.

Reg. no: 261510902

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My Beloved Parents ,

Sisters & Friends

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PHARMACOSOMES

Pharmacosomes bear unique advantages over liposome and noisome vesicles and serve as an alternative to conventional vesicles. They are the colloidal dispersions of drugs covalently bound to lipids. Depending upon the chemical structure of the drug-lipid complex they may exist as ultrafine vesicular, micellar, or hexagonal aggregates. 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 desire 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.[8]

Any drug possessing an active hydrogen atom can be esterified into the lipid, with or without spacer chain that strongly result in the formation of an amphiphilic compound, which facilitates better penetration in to the target site. The prodrug conjoins with hydrophilic and lipophilic properties, thus acquires amphiphilic characters. The amphiphilic characters help pharmacosomes to reduce the interfacial tension and at higher contraction exhibits mesomorphic behavior. This decrease in the interfacial tension leads to an increase in the contact area, thereby increasing the bioavailability of drug.[9]

The phospholipids, when placed in water form micelles or are organized as lipid bilayers with the hydrophobic tails lined up against one another and the hydrophilic head-group facing the water on both sides. These unique features make phospholipids most suitable to be used as excipients for poorly water soluble drugs. Thus, the enhanced solubility of lipophilic drugs from lipid-based systems will not necessarily arise directly from the administered lipid, but most likely from the intra-luminal processing to which it is subjected before it get absorbed.[10]

The pharmacosomal drug delivery system is advancing as a method used for delivery of various drug like non-steroidal anti-inflammatory drugs (NSAIDs), cardiovascular drugs, antineoplastic drugs and proteins. A drug possessing a free carboxyl group or an active hydrogen atom can be esterified to the hydroxyl group of a lipid molecule, thereby producing an amphiphilic pordrug. Phosphatidylcholine (PC) complex of non-steroidal anti-inflammatory drugs (NSAIDs) improve the permeation of these drugs across the biomembranes and thereby improving their bioavailability to target sites. GI safety of NSAIDs has been reported to be improved upon complexation or any other interaction

with phospholipid. The phospholipid (acting as surfactant) provide a protective hydrophobic cover on the surface of the mucus to protect the GI tissue.[8]

ADVANTAGE OF PHARMACOSOMES[9]

1. As the drug is covalently bound to lipid, membrane fluidity has no effect on release rate, but depends upon the phase-transition temperature of the drug-lipid complex.
2. No leaching of drug takes place because the drug is covalently bound to the carrier.
3. Drugs can be delivered directly to the site of infection.
4. Drug release from pharmacosomes is generally governed by hydrolysis (including enzymatic).
5. Their degradation velocity into active drug molecule, after absorption depends on their size and functional groups of the drug molecules, the chain length of the lipids, and spacer.
6. Reduced cost of therapy
7. Suitable for both hydrophilic and lipophilic drugs. The aqueous solution of these amphiphiles exhibits concentration dependant aggregation.
8. High and predetermined entrapment efficiency as the drug and the carrier are covalently linked together.
9. Volume of inclusion does not influence the entrapment efficiency.
10. No need of removing the free un-entrapped drug from the formulation which is required in case of liposomes.
11. Improves bioavailability especially in case of poorly soluble drugs.
12. Reduction in adverse effect and toxicity.

ADVANTAGES OF PHARMACOSOMES OVER CONVENTIONAL VESICULAR SYSTEM[10]

1. In case of pharmacosomes, volume of inclusion does not influence the entrapment efficiency. On the other hand, in case of lipsomes, the volume of inclusion has great influence on entrapment efficiency.
2. In pharmacosomes, the membrane fluidity depends upon the phase transition temperature of drug-lipid complex but it has no effect on release rate because the drug-lipid composition is one of the crucial factors that decided its

membrane fluidity, which affect the rate of drug release and physical stability of the system.

3. Drug release from pharmacosomes is by hydrolysis (including enzymatic) unlike lipsomes the release of drug is by diffusion through bilayer, desorption from the surface of degradation of lipsomes.
4. Unlike lipsomes in pharmacosomes there is no need of following the tedious, time consuming step for removing the free, un-entrapped drug from the formulation.
5. In liposomes there are chance of sedimentation and leaching of drug, but in pharmacosomes the incident of leakage of drug does not take place because the drug is covalently linked to the carrier.

SALIENT FEATURES OF PHARMACOSOMES [11]

1. Entrapment efficiency is not only high but predetermined, because drug itself in conjugation with lipids from vesicles.
2. There is no need of following the tedious, time-consuming step for removing the free, un-entrapped drug from the formulation.
3. Since the drug is covalently linked, loss due to leakage of drug, does not take place. However, loss may occur by hydrolysis.
4. No problem of drug incorporation into the lipids.
5. In pharmocosome, the encaptured volume and drug-bilayer intractions do not influence the entrapment efficiency.
6. In case of pharmacosomes, the membrane fluidity depends upon the phase transcition temperature of the drug lipid complex, but it does not affect release rate since the drug is covalently bound to lipids.
7. Phospholipid transfer/exchange is reduced, and solubilization by HDL is low.
8. The physicochemical stability of the pharmacosomes depends upon the physicochemical properties of the drug-lipid complex.
9. Following absorption, their degradation velocity into active drug molecule depends to great extent on the size and functional groups of drug molecule, the chain length of the lipids, and the spacer. These can be varied relatively precisely for optimized in vivo pharmacokinetics.
10. They can be given orally, topically, extra or intra vascularly.

LIMITATION[11]

1. Synthesis of a compound depends upon its amphiphilic nature.
2. It requires surface and bulk intraction of a lipid with drugs.
3. It requires covalent bonding to protect the leakage of drugs.
4. Pharmacosomes, on storage, undergo fusion and aggregation, as well as chemical hydrolysis.

COMPONENTS USED FOR THE FORMULATION OF PHARMACOSOMES

There are three essential components for pharmacosomes preparation.

Drugs

Drugs containing active hydrogen atom (-COOH, OH, NH2) can be esterified to the lipid, with or without spacer chain and they form amphiphilic complex which in turn facilitate membrane, tissue, cell wall transfer in the organisms.

Solvents

For the preparation of pharmacosomes, the solvents should have high purity and volatile in nature. A solvent with intermediate polarity is selected for pharmacosomes preparation.

Lipids

Phospholipids are the major structure component of biological membranes, where two types of phospholipids such as phosphoglycerides and sphingolipids are generally used. The most common phospholipid is phosphotidyl choline moiety. Phosphotidyl choline is an amphiphilic molecule in which a glycerol bridges links a pair of hydrophobic acyl hydrocarbon chains, with a hydrophilic polar head group phosphocholine. Most commercial lecithin products contain 20% phosphatidylcholine. Lecithins containing phosphatidylcholine can be obtained from vegetables (mainly), animals and microbial sources. Lecithin is also available as a dietary supplement in two forms: as granular

lecithin (oil-free refined lecithin with calcium phosphate as a flow agent); and as capsules containing a dispersion in oil.

FORMULATION OF PHARMACOSOMES[7, 12]

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

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 amount of dichloromethane. The mixture is refluxed for one hour. Then the solvent is evaporated off under vacuum at 40 ° C in a rotary vacuum evaporator. The dried residues are then collected and placed in vacuum dessicator for complete drying.

2. Hand –shaking method

In the hand-shaking method, a mixture of drug and lipids are dissolved in volatile organic solvent such as dichloromethane in a round bottom flask. The organic solvent is removed at room temperature using a rotary vaccum 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.

3. Ether injection method

In this method solution containing drug-lipid complex is slowly injected into a hot aqueous medium through gauze needle and vesicle is formed readily.

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 resultant complex flushed with nitrogen & Stored at 4°C.

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 carbondioxide results in fast mixing of dispersion leading to the formation of pharmacosomes.

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 polyxyethylene glycol and polyaspartic acid. This approach provides an advantage that all though micelle can be diluted, the drugs probably not precipitate due to the water solubility of the monomeric drug conjuncts.

CHARACTERIZATION OF PHARAMACOSOMES [5, 6]

1) FTIR spectroscopy

The formation of the complex can be confirmed by IR spectroscopy comparing the spectrum of the complex with the spectrum of individual components and their mechanical mixture. Stability of pharmacosomes can be evaluated by comparing the spectrum of the complex in solid form with the spectrum of its micro dispersion in water after lyophilization, at different time intervals.

2) Surface Morphology

Surface morphology of the pharmacosomes can be observed with scanning electron microscopy (SEM) or transmission electron microscopy (TEM). The shape and size of the pharmacosomes may be affected by the purity grades of phospholipid and the process variables such as speed of rotation, vacuum applied or the method used. Pharmacosomes prepared by low purity grades of lipids yields a greasy product, which in

turn results in the formation of sticky large aggregates. Pharmacosomes prepared by very high purity grades (>90%) lipids are prone to oxidative degradation, which in turn adversely affect the stability of complexes. Most commonly used phospholipids are of 80% purity.

3) Solubility Studies

Solubility of the drug, phospholipids, their physical mixture and the pharmacosomes can be determined by the shake-flask method where two phases are mutually saturated before use. Equal volume of buffer solution with a different pH(from 2.0 to 7.4) and 1-octanol containing phospholipid complex are mixed properly in the screw capped penicillin bottles and equilibrated under constant shaking at 37°c for 24 hours. After separating the aqueous phase, the concentration of drug in this aqueous phase is determined by HPLC or UV spectrophotometer.

4) X-ray powder diffraction.

It has been performed to determine the degree of crystallinity by using the relative integrated intensity of reflection peaks. The integrated intensity is given by the area under curves of the XRPD patterns and it represents the specimen characteristics.

5) *In-vivo* and *In-vitro* evaluation

Depending upon the expected therapeutic activity of biologically active constituents, models of *in-vivo* and *in-vitro* evaluations are carried out. *In-vitro* dissolution studies can be done with media of different pH in a standard dissolution apparatus to determine the pH in a standard dissolution apparatus to determine the pH dependent dissolution profile.

APPLICATIONS OF PHARMACOSOMES [9, 11]

1. Pharmacosomes demonstrate a wider stability profile and greater shelf life.
2. Pharmacosomes have the capacity to augment drug absorption and its transport.
3. Pharmacosomes can improve the rate of permeation by improving the membrane fluidity. The transition temperature of vesicles in the form of vesicles and micelles

might pose an evident effect on vesicular interaction with biomembrane, hence improving the transfer of drug across membrane.

4. Pharmacosomes have achieved a new level by enhancing therapeutic effects of several drugs like pindolol derivative, toxol, bupronolol acid derivative, cytarabin, amoxicillin, etc.
5. Pharmacosomes, the amphiphilic lipid vesicular system, can be used for the development of novel ophthalmic dosage forms. Amphiphilic prodrug forms pharmacosomes, when diluted with tear, and modify corneal drug transport and release profile.
6. Pharmacosomes have greater degree of selectivity for action on specific target cells.

The oral route of drug administration is the most important route of administering drugs for systemtic effect. About 90% of drug is used to produce systemic effect are administered by oral route. When a new drug is discovered one of the first questions a pharmaceuticst asks is whether or not the drug can be effectivelyadministered for its intended effect by the oral route.

The drug that are administerted orally,solid oral dosage formrepresent the preferred class of products. The reasons for this preference are as follows. Capsule is unit dosage form in which one usual dose of the drug has been accurately filled in the capsules. Liquid dosage forms, such as syrups, suspensions, emulsions, solutions and elixirs are usually designed to contain and dose of medication in 5 to 30 ml and the patient is then asked to measure his or her own medication using teaspoons, tablespoon or other device. Such dosage measurements are typically in error by a factor ranging from 20 to 50% when the drug is self administered by the patients.

LOSARTAN

Losartan is the potassium salt form of losartan, a non-peptide angiotension II antagonist with antihypertensive activity. Angiotensin II, formed from angiotensin I by angiotensin-converting enzyme (ACE), stimulates the adrenal cortex to synthesize and

secret aldosterone, which decrease the excretion of sodium and increase of potassium. Angiotension II also acts as a vasoconstrictor in vascular smooth muscle.

Losartan is an angiotension II receptor antagonist drug used mainly to treat high blood pressure. It is well absorbed oral administration and undergoes significant first-pass metabolism. It may also delay progression of diabetic nephropathy and is associated with a positive clinical outcome in that regard. Lowering high blood pressure helps prevent strokes, heart attacks, and kidney problems. It works by relaxing blood vessels so the blood can flow more easily. It is freely soluble in water and sparingly soluble in ethyl acetate, butyl acetate and cyclohexane, and the solubility in these three solvents varys little with the temperature, which affect it's dissolution in GI fluid and leads to poor bioavailability. The diffusion of drug across lipid membranes and into target cells is accelerated when they are in a complex with phosphatidylcholine.

Based on the above observation, it was concluded to formulate pharmacosomes for the oral delivery of Losartan and evaluated for the improvement in solubility, drug loading and drug release. Findings of the research are included in this thesis.

REVIEW OF LITERATURE

1.Ajay semalty *et al* (2010)., [20] Developed and evaluated pharmacosomes of acelofenac. The pharmacosomes was prepared to recover the water solubility, bioavailability and minimize the gastrointestinal toxicity of acelofenac. Acelofenac was complexed with phosphatidylcholine (80%) in two different ratios (1:1 and 1:2) by the conventional solvent evaporation technique. Pharmacosomes thus prepared were subjected to solubility and content evaluation, SME, XRD, DSC and *in-vitro* dissolution study. Drug content was found to be 91. 88% (w/w) for acelofenac phospholipid complex (1:1) and 89.03 %(w /w) aceclofenac-phospholipid complexes (2:1). The datas obtained from DSC thermograms and XRD confirmed the formation of phospholipid complex. Solubility and dissolution summary of the pharmacosomes was found to be much better than aceclofenac.

2.Savita patil *et al* (2014).,[21] Investigated the *in-vitro* and *ex-vivo* classification of furosemide bounded pharmacosomes thus improving the solubility and permeability of the drug. The furosemide pharmacosomes were prepared by simple solvent evaporation technique. Furosemide bounded pharmacosomes formulation (PMC1 & PMC2) were prepared and compared with pure drug which showed a fivefold increase in the solubility and a significant increase in permeability of furosemide bounded pharmacosomes. *In-vitro* release profile exhibits excellent sustained drug release properties. Prepared furosemide bounded pharmacosomes were confirmed by using differential scanning calorimetry (DSC), X-ray diffraction (XRD) and FT-IR.

3.Harikumar *et al* (2010)., [22] To recover the water solubility, bioavailability and diminish the gastrointestinal toxicity of ketoprofen, its pharmacosomes were planned and developed. Ketoprofen was complexed with phosphatidylcholine in various ratios with conventional solvent evaporation method. Pharmacosomes thus prepared were subjected to solubility and drug content evaluation, scanning electron microscopy, differential scanning calorimetry, X ray powder diffraction, *in-vitro* dissolution and *in-vitro* diffusion

study. Pharmacosomes of ketoprofen were found to be disc shaped with rough surface in SME. Solubility and *in-vitro* dissolution profile of pharmacosomes was found to be 99.8% and showed high percentage of drug loading.DSC thermograms and X ray powder diffraction datas confirmed the formation of phospholipid complex. *In-vitro* diffusion rate of ketoprofen from pharmacosomes was significantly higher. The release experiments clearly indicated sustained release of ketoprofen from pharmacosomal formulation.

4.Han M *et al* (2010).,[23] The 20(S)-photopanaxadiol (Ppd) pharmacosomes was successfully prepared by thin film dispersion and its *in-vitro* stability was studied. The particle size of pharmacosomes was evaluated by dynamic scattering (DLS) and the encapsulation efficiency of ppd pharmacosomes was 80.84±0.53% with a diameter of 100.1nm. in addition, the effect of some factors on the encapsulation efficiency and the particle size such as temperature, alcohol, pH and artificial gastro-intestinal fluids, were also investigated. The selected formulation and technology were simple and practical to prepare ppd pharmacosome.

5.Ajay semalty *et al* (2009)., [24] To improve the water solubility of diclofenac, and also to decrease its gastrointestinal toxicity, the pharmacosomes containing diclofenac were prepared and evaluated for physicochemical analysis. Diclofenac was complexed with phosphatidylcholine (80%) in equimolar ratio, in the presence of the organic solvent dichloromethane, by the conventional solvent evaporation technique. Pharmacosomes thus prepared were evaluated for drug solubility, drug content, surface morphology, phase transition behavior, crystallinity and *in-vitro* dissolution. Pharmacosomes of diclofenac were found to be irregular or disc shaped with rough surface in SEM. Drug content was found to be 96.2±1.1%. DSC thermograms and XRPD data confirmed the formation of the phospholipid complex. Water solubility of the prepared complex was found to be twice than that of the pure drug. The improvement in water solubility of prepared pharmacosomes resulted in improved dissolution and lower gastrointestinal toxicity. Pharmacosomes showed 87.8% while the free diclofenac acid showed a total of only 60.4% drug release at the end of 10 hour dissolution study.

6.Patel R A *et al* (2010)., [25] The pharmacosomes containing the β-blockers bupranolol were designed and developed. The pharmacosomes was then covalently linked to 1, 3-dipalmioyl-2-succinyl-glycerol. The resulting prodrug was amphipathic and dispersed readily in water above 30°c forming a smectic lamellar phase. The dispersion, similar to charged phospholipids showed continuous swelling with increasing water content and so in excess water region, the thermodynamically most stable structure was the unilamellar vesicles which oligomeric vesicles were also formed. Enhanced effect on intraocular pressure in rabbit was observed after incorporation in pharmacosomes.

7.Chauhan N *et al* (2009)., [26] Synthesized various amphipathic liponucletide pharmacosomes, 1-β-D-arabinofuranosylcytosine 5'-diacylglycerols (containing either dimyistoyl distearoyl free fatty acid side chain) and determined the aggregation and morphological characteristics of their sonicated dispersion in relation to change in temperature. The sonication at low temperature gave turbid solutions containing layer bilayer sheets. On raising the temperature, atrastion temperature (tg) was reached at which a stable three dimensional cross-linked network of small interlocking bilayer stacks was formed. Sonication at the temperature close to tg produced small disc-shaped micellar structures. These micelles were shown to exist another aggregational equilibrium consisting of stacking –destacking process. In this study the biological activity was found to be improved after incorporation of drugs (taxol and cytarabin) into pharmacosomes.

8.Vaizoglu et al (2009)., [27] synthesized phospholipid complexes of the drug pindolol via spacer (succinic acid). This prodrug having structural similarity with lysolecithin reduced the interfacial tension between benzene/water and opalescent vesicular dispersion could be obtained by the film method and ether injection method .It was combined with tween-80 and pharmacosomes were prepared by the film method. The *in-vitro* fate was studied in beagle dogs by administering the pharmacosomes and parent drug through oral and intravenous route and determining the plasma concentrations of unchanged pindolol. Plasma drug profile followed the one compartment open compartment open model, indicating rapid hydrolysis in body fluids. Three to five times higher concentrations of unchanged pindolo were observed following intravenous administration of the

pharmacosomes rather than free pindolol. Urine data indicating lowering of renal clearance when administered as pharmacosomes.

9.Peng yue *et al* (2012)., [28] Prepared and characterized geniposide-pharmacosomes (GPPMS) and optimized the process and formulation variables using response methodology. Tetrahydrofuran was used as a reaction medium, geniposide and phospholipids were resolved into the medium, and GP-PMS was formed after the organic solvent was evaporated off under vacuum condition. The process and formulation variables were optimized by central composite design (CCD) of response surface methodology (RSM). The phospholipid-to-drug ratio (X1), reaction temperature (X2) and the drug concentration (X3) were selected as independent variables and the yield (%) of GP 'present as a complex' in the PMS was used as the dependent variable. The physico-chemical properties of the complex obtained by optimal parameters were investigated by means of FT-IR, differential scanning calorimetry, n-octanol /Water partition coefficient (P) and particle size analysis. Multiple linear regression analysis for optimization by CCD revealed than the higher yield of GP 'present as a complex' in the GP-PMS was obtained wherein the optimal setting of XI, X2, X3 are 3, 50°C and mg/ml, respectively. The DSR and IR studies of GP-PMS by the optimal settings demonstrated that GP and phospholipids in the GP-PMS were combined by non-covalent bond, not forming a new compound. GP-PMS significantly increased the lipophilicity of GP, and P of GP-PMS in n-octanol and water was about 20 multiples more than that of GP material. The study concluded that pharmacosomes could be an alternative approach to improve the absorption and permeation of biologically active constituents.

10.Ping A *et al* (2005)., [29] Designed and development didanosine pharmacosomes from 5′-cholesterylsuccinyldideoxinosine (CS-ddl). The lipophilic prodrug of didanosine was prepared using the tetrahydrofuran injection method. Configuration and particle size were observed through TME and AFM, and *in-vivo* behavior of the pharmacosomes was investigated in rats by determination of CS-ddl and ddl in plasma and tissue with HPLC. The ddl pharmacosomes were particles of tube-shape with a particle size of about 200 nm;$t_{1/2}$ of CS-ddl in plasma of rat was 7.64 min, CS-ddl concentrated in liver quickly after

iv administration, its elimination from target tissue was slow, $t_{1/2}$ of CS-ddl in liver was 10 days. The study concluded that the ddl pharmacosomes showed obvious liver targeting and sustained-release effect in the target tissues.

11.Jin Guang *et al* (2005)., [30] Prepared acyclovir pharmacosomes by tetrahydrofuran injection and investigated the various properties. The negatively charged pharmacosomes were nanometer vesicles based on analysis of transmission electron scanning calorimetry. The effects of centrifugation and heating on stability of pharmacosomes were weak. Freezing and lyophilisation disrupted pharmacosomal structure. The amphiphilic pharmacosomes were inserted into rabbit erythrocyte membranes and it led to hemolysis. Plasma protein in blood absorbed pharmacosomes or interfered the interaction with erythrocytes to reduce hemolytic reaction.

12.Zhang Z R *et al* (2001)., [31] Attempted to optimize the preparation of 3′, 5′-dioctanoyl-5-fluro-2′-deoxyuridine pharmacosomes. The study found that the drug-phosphatidylcholine ratio, pluronic F-68 concentration, and glycerol tri stearate concentration have an influence on the mean particle size, entrapment ratio and drug loading. The study also revealed that the pharmacosomes can improve the ability of a drug to cross the blood-brain barrier and act as a promising drug-targeting system for the treatment of central nervous system disorders.

13.Raikhman L M *et al* (2002).,[32] Developed pharmacosomes of ibuprofen to improve the bioavailability as well as to minimize the gastrointestinal toxicity of free ibuprofen. The pharmacosomes of ibuprofen were prepared by conjugation of free ibuprofen with phosphatidylcholine (80%) in two different molar ratios (1:1 and 1:2). The water solubility of ibuprofen pharmacosomes were found to be much better than free ibuprofen. The free ibuprofen showed only 67.96% drug release at the end of 4 hour dissolution study. The study concluded that the solubility and dissolution of ibuprofen can be enhanced by pharmacosomes formulation which could also minimize the gastrointestinal toxicity.

14.Vishal patel *et al* (2011)., [33] Designed, synthesized and characterized a prodrug of glycerol-skeleton lipid prodrug, which was 1-octadecyl-2-fluorouracil-N-acetyl-3-zidovudine phosphoryl glycerol (OFZPG). The study revealed that the prodrug had suitable amphiphilicity. A kind of highly dispersed homogenous suspension system with high concentration was prepared by tetrahydrofuran (THF) injection method. OFZPG pharmacosomes were spheroidal. Antitumor activity of OFZPG pharmacosomes was investigated, in the three human colon cancer cells and it was better than that of 5-FU. The results indicates that the prodrug could degrade to the active compound efficiently, which could play an important role in pharmacodynamic action. OFZPG pharmacosomes played an important role in the antitumor activity.

15.Sharma S *et al* (2010)., [34] An amphiphilic phyto-phospholipid complex were developed in order to enhance the delivery of poorly soluble drug (baicalein). The poor solubility and dissolution rate limits its oral absorption and bioavailability. The baicalein-phospholipid complex (Ba-PLc) was prepared and evaluated for various physico-chemical parameters like drug loading, FT-IR, DSC,X-ray powder diffractometry, scanning electron microscopy, aqueous/n-octanol solubility and dissolution study. In the SME, the phospholipid complex was found to be fluffy and porous with rough surface morphology. FT-IR, DSC and XRD data confirmed the formation of phospholipid complex. The water /n-octanol solubility of baicalein was improved significantly in the complex. The result of the study concluded that the phospholipid complex may be considered as a promising drug delivery system for improving the absorption and overall bioavailability of the baicalein molecule.

16.Shipra Duggal *et al* (2012).,[34] Quercetin(3,3′,4′,5,7-pentahydroxyflavone), which is a polyphenolic flavonoid, shows several biological effects like anti-inflammatory, anti-cancer, anti-proliferative, anti-mutagenic and apoptosis induction, but its use is limited due to its low aqueous solubility. To overcome this limitation, the phospholipids complex of quercetin was developed to improve its aqueous solubility for better absorption through the gastrointestinal tract which may improve its bioavailability. The quercetin-

phospholipid complex prepared were evaluated for various physic-chemical parameters like infra-red spectroscopy, differential scanning calorimetry, X-ray powder diffraction, scanning electron microscopy, solubility studies and *in-vitro* antioxidant activity. The phospholipid complex of quercetin was found to be fluffy and porous with rough surface in SME, FTIR, DSC and XRPD data confirmed the formation of phospholipid complex. The water solubility of quercetin was improved by 12 folds in the prepared complex. There was no statistical difference between the quercetin complex and quercetin in the *in-vitro* anti-oxidant activity, indicating that the process of complexation did not adversely affect the bioactivity of the active ingredient.

17.Yi-Guang *et al* (2007).,[36] The pharmacosomes of cholesterly –adipoyl didanosine (CAD) were prepared and the physical and chemical stability were evaluated. The pharmacosomes were prepared from the previously synthesized lipophilic prodrug of didanosine (CAD) using the tetrahydrofuran (THF) injection method. The morphology and particle size of pharmacosomes were evaluated using TEM and laser particle analyzer. The effects of heat, centrifugation and storage on the physical stability were also investigated. The degradation of prodrug in buffer solutions, carboxyl ester enzyme solution, rat plasma and liver homogenates was also evaluated. The prepared pharmacosomes were spherical vesicles with the size of 122nm and showed good physical stability. The degradation of prodrug was different in various environments. The half-life of CAD in rat liver homogenates was 23 hour.

18.Ajay Semalty *et al* (2010)., [37] Prepared and characterized phospholipid complex of naringenin for effective drug delivery. Naringenin is a flavonoid specific to citrus fruits and possesses anti-inflammatory, anti-carcinogenic, and anti-tumor effects. But due to a lower half-life and rapid clearance from the body, frequent administration of the molecule is required. To improve the bioavailability and prolong its duration in body system, its phospholipid complexes were prepared. Naringenin was complexed with phosphatidylcholine in equimolar ratio, in presence of dichloromethane. The prepared phytosomes were evaluated for various physical parameters like FT-IR spectroscopy, differential scanning calorimetry, X-ray powder diffractometry, solubility, scanning

electron microscopy and the *in-vitro* drug release study. These phospholipid complex of naringenin were found to be irregular and disc shaped with rough surface in SEM. Drug content was found to be 91.7 %(w/w). FTIR,^{1}H NMR, DSR and XRPD data confirmed the formation of phospholipid complex. Water solubility of naringenin improved in the prepared complex. Unlike the free naringenin (which showed a total of only 27% drug release at the end of 10 hours), niringenin complex showed 99.80% release at the end of 10 hour of dissolution study. It was concluded that the phospholipid complex of naringenin is of potential use for improving bioavailability.

19.Prabhu S *et al* (2005).,[38] The study was carried out to prepare novel lipid based formulations of a model drug, piroxicam (PXCM), which is poorly water soluble non-steroidal anti-inflammatory drug (NSAID) using 1,2-dimyristoyl-sn-glycerol-3-phosphatidylcholine (DMPC) phospholipid alone, and in combination with polyethylene glycol (PEG 4600). Lipid-based drug delivery systems were prepared by using conventional method of preparation and were evaluated for the *in-vitro* dissolution behavior, absorption via Caco-2 cell monolayers and the stability of formation over a 12-month period. The physical characterization studies using differential scanning calorimetry (DSC) were also performed. Formulations of PXCM were prepared by using DMPC in different combinations and a mixture of DMPC and PEG 4600. Dissolution studies showed an increase in dissolution rate and extent of the PXCM from all complexes when compared to be control. DSC studies further confirmed the dissolution behavior of these formulations demonstrating different levels of amorphous to crystalline nature. Results of HPLC analysis from Caco-2cell culture studies showed increase in transport of PXCM from all formulations, when compared to control.

20.Mali Kamalesh *et al* (2014)., [39] Formulated pharmacosomes of ketoprofen by conventional solvent evaporation technique to increase the solubility and bioavailability in different media along with minimizing the GI disturbances. Two different ratio of drug: phospatidylcholine in 1:1 and 1:2 were used to form pharmacosomes. Drug content was found to be 93.28% w/w for ketoprofen phospholipid complex (1:1) and 85.44% w/w for ketoprofen phospholipid complex (1:2). Further studies were carried out by optimizing the

ketoprofen phospholipid complex (1:1) ratio. Scanning electron microscopy and particle size analysis revealed difference between the formulations as to their appearance and size distribution and DSC examination showed the amorphous nature of the drug. Solubility of pure ketoprofen improved which exhibited an increase of 2.09 fold. Dissolution profile of the prepared complex was found to be 93.30% which was much better than pure ketoprofen which was 49.77% in 8 hrs. Formulation of ketoprofen into pharmacosome was found to be a positive approach for improving solubility and bioavailability of the poorly soluble drug.

21.Idha Kusumawati *et al* (2011).,[40] Prepared and evaluated the phospholipid complex of *kaempferia galangal* rhizome extract using phosphatidylcholine to improve the bioavailability of its constituents. Characteristics and analgesic activity of the extract and its marker compound, ethyl *p*-methoxycinnamate(EPMS), were compared to their phospholipid complex (F.Extract and F.EPMS). Characteristics of the free form and their complexes were analysed by DTA and SEM. Their analgesic activity was determined using writhing test. The complex showed better analgesic activity compared to the free form of the both extract and EPMS at an equivalent dosage.

22.Ajay Semalty *et al* (2010).,[41] Developed and characterized aspirin-phospholipid complex for improved oral drug delivery. Aspirin is poorly soluble in water and causes GI irritation. To improve the solubility (and hence the bioavailability) and minimize the GI irritation, its complexes with soya-phospholipid-80% (in 1:1 molar ratio) were prepared in an organic solvent and evaluated for solubility, drug content, scanning electron microscopy (SEM), FT-IR spectra, X-ray diffraction, differential scanning calorimetry and *in-vitro* dissolution study. Aspirin-phospholipid complex were found to be disc shaped with rough surface in SEM. Drug content in a complex was found to be 95.60%. DSC thermograms, XRD and FTIR confirmed the formation of phospholipid. Solubility of the prepared complex was found to be improved. Aspirin complex and pure aspirin showed 90.93% and 69.42% of drug release at the end of 10 hrs dissolution study in pH 1.2 acid buffer. It was concluded that the phospholipid complex of aspirin is of potential use for improving the solubility of aspirin and hence its bioavailability.

23.Jessy Shaji *et al* (2014).,[42] To enhance the transdermal penetration of the poorly water-soluble NSAID, Pirovicam, it was encapsulated it into a nanocarrier namely transferosomes. In order to increase the drug encapsulation into the transferosomes, water soluble cyclodextrin complex solutions of drug were entrapped into aqueous phase of stable unilamellar transferosomes in addition to incorporating into the liposomal bilayer by the thin firm hydration method and sonication. TEM measurement suggested that, the drug cyclodextrin complexes were successfully loaded into the transferosomes without affecting their morphology. At optimal conditions, the mean particle size of double loaded transferosomes was ~158.7 nm and entrapment efficiency of ~85.7% was achieved. The entrapment efficiency was increased when compared with batches not containing the cyclodextrin complexes. The optimized formulation shows no interaction with skin components which was confirmed by skin-vesicles interaction and *ex-vivo* corrosion studies. Transferosomes containing cyclodextrin inclusion complexes released more drug than transferosomes encapsulating non-complexed drug, the drug release being related to entrapment efficiency. The formulation also demonstrated superior anti-inflammatory activity in rodents in *in-vivo* carrageenan induced rat paw edema model.

24.Chandra A *et al* (2008).,[43] Prepared the pharmacosomes of piroxicam by conventional technique, employing maltodextrin and sorbital as base. The morphology of the proniosomes was studied by scanning electron microscopy. The lipid vesicles were evaluated for entrapment efficiency and vesicles size. It was observed that span 60 based formulation produced vesicles of smallest size and higher entrapment efficiency while those of span 80 produced vesicles of least entrapment efficiency. Incorporation of lecithin further enhanced entrapment efficiency. Permeation of losartran from proniosomes based reservoir type transdermal gel formation across excised rat abdominal skin was investigated using keshery chain diffusion cell. There was significant reduction in carrageenan induced rat paw inflammation compared to control. Anti-inflammatory studies revealed that proniosome based transdermal drug delivery system of losartan were promising carriers for delivery of losartan.

25.Sujitha B *et al* (2014).,[44] Formulation and evaluated ethosomes containing losartan by using phospholipid, ethanol, propylene glycol and distilled water by cold method. Prepared ethosomal vesicles were evaluated for vesicular size, shape, entrapment efficiency, *in-vivo* skin diffusion, skin irritation and stability studies. Scanning electron microscopy and size analysis results showed that ethosomes were in spherical, unilamellar, nanometric size. The optimized formulation showed highest entrapment efficiency of 73.59%. This optimized formulation of ethosomes vesicles was further formulates to gel by using carbopol. This kinetic study was found to fit in first order model and observed no remarkable symptoms on skin from skin irritation study.

26.Rajesh N *et al* (2010).,[45] The study was aimed to minimize the local gastrointestinal irritation which is one of the major size efforts to piroxicam after oral ingestion by kinetic control of drug release. Piroxicam was incorporated into into the biocompatible blends of micro crystalline cellulose (MCC) and hydroxyl methyl cellulose (HPMC) matrix pellets using pelletization technique using PVP as binder. The prepared pellets were subjected to micromeritic properties, SEM, DSC, FTIR and stability studies. Solid, free flowing matrix pellets were obtained. More than 98% of the isolated pellets were of particle size range 1.35 to 1.44 mm. The obtained matrix pellets had smooth surfaces, with free flowing and good packing properties. Scanning electron microscopy (SEM) confirmed their spherical structures. Drug loaded MCC/HPMC pellets was stable and compatible as confirmed by DSC and FTIR studies. The released of drug from the blends was controlled up to 20 hrs.

27.Muhammad D. Hussian *et al* (2010).,[14] Evaluated the modulation effects of phospholipids on enhancing the dissolution and oral bioavailability of piroxicam formulations. On the basis of *in-vitro* dissolution studies, dimyristoylphosphatidylglycerol (DMPG) was ranked as the first potent dissolution rate enhancer for the model drug. Thus, the solid dispersion of varying piroxicam/DMPG ratios were prepared and further investigated. Within the concentration range studied (6.4-16.7 wt %), the dissolution rate of piroxicam from the solid dispersion appeared to increase as a function of the carrier weight fraction. The oral bioavailability of piroxicom from the DMPG-based formulations in rats was found to superior to that of the control. Hence, DMPG was regarded as the

most promising carrier-phospholipid for enhancing oral bioavailability of piroxicom and potentially other Class II drugs.

28.Sayed H. Auda *et al* (2010)., [46] Formulated and characterized piroxicam containing polymer films for dermal use. The used polymers were eudragit containing polymer films for dermal use. The used polymers were Eudragit types namely eudragit RL100, RS100,L100 and Eudragit S100. The medicated films consisting of drug and carrier were prepared. The carrier consisted of one or two polymers. The physicochemical characterization was done by IR spectroscopy, DSC and X-ray diffractometry for piroxicam polymeric films and their corresponding physical mixtures as well as the untreated drug and polymer powders to investigate the drug polymer powders to investigate the drug polymer interaction. The results indicated the presence of molecular interactions between piroxicam and both Eudragit L100 and Eudragit S100 and no interactions were found between piroxicam and Eudragit RL100 or Eudragit RS100.*in-vitro* drug release from Eudragit films was also carried out which revealed that the drug release from hydrophilic polymers is faster than that from hydrophobic ones.

AIM AND OBJECTIVES

The aim of the study is to prepare pharmacosomes containing Losartan using different concentrations of soya lecithin by solvent evaporation technique in order to achieve a prolonged release of drug and also to improve the bioavailability of the drug.

The objectives of the study are:

- To formulate pharmacosomes of losartan by solvent evaporation method.
- To characterize the prepared pharmacosomes by different methods including preformulation studies, drug content determination and solubility studies.
- To prepare capsules containing the pharmacosomes.
- To carry out the quality control tests for capsules.
- To perform the vesicle shape determination, X-ray powder diffraction analysis (XRD) and drug release kinetic data analysis of the optimized formulation.
- To carry out the stability studies of the optimized formulation of pharmacosome as per ICH guidelines.

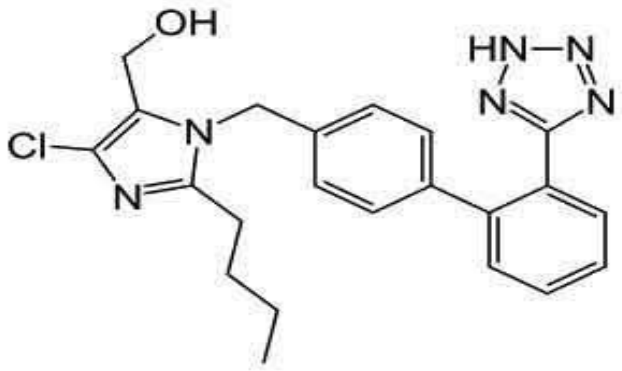
PLAN OF WORK

1. Drug selection.
2. Formulation of pharmacosomes of Losartan by solvent evaporation technique.
3. Preformulation studies of pharmacosomes
    - FT-IR
    - Angle of repose
    - Bulk density
    - Tapped density
    - Drug content determination
    - Solubility studies
4. Filling of the capsules with pharmacosomes.
5. Post formulation studies of capsules.
    - Weight variation
    - Disintegration test
    - *In-vitro* dissolution study
6. Perform the vesicle shape determination and X-ray powder diffraction analysis (XRD) of the optimized formulation.
7. Carry out drug release kinetic data analysis and stability studies of the optimized formulation of pharmacosome as per ICH guidelines.

DRUG PROFILE[52, 53, 54]

LOSARTAN

- **CHEMICAL STRUCTURE**



- **CHEMICAL NAME**

[2-butyl-5-chloro-3[[4-[2-(2H-tetrazol-5-yl)phenyl]phenyl]methyl]imidazol-4-yl]methanol

- **MOLECULAR WEIGHT**

422.917g/mol

- **MOLECULAR FORMULA**

$C_{22}H_{23}ClN_6O$

- **CATEGORY**

Agents acting on the renin- Angiotensin system

Antihypertensive Agents

Anti-Arrhythmia Agents

Cardiovascular Agents

- **DESCRIPTION**

  Physical Description - Solid

  Color - Light yellow solid

  Solubility - It is water soluble, sparingly soluble in ethyl acetate, butyl acetate, and cyclohexane, and the solubility in these three solvent varys little with the temperature.

- **DOSE**

  Diabetic Nephropathy

  Initial dose: 50 mg orally once a day

  Maximum dose: 100mg orally once a day

  Hypertension

  Initial dose: 50 mg orally once a day

  Maximum dose: 100mg orally once a day

- **MELTING POINT**

  184°C

- **PROTEIN BINDING**

  99.7%

- **ORAL BIOAVAILABILITY**

  25-30%

- **STORAGE**

  Store it in well-closed, light resistant container.

- **ROUTES OF ADMINISTRATION**

  Oral

- **HALF LIFE**

  6-9 hours

- **METABOLISM**

  Hepatic

- **EXCRETION**

  Renal and fecal

- **MECHANISM OF ACTION**

  Losartan is a selective, competitive angiotensin II receptor type 1 (AT_1) antagonist, reducing the end organ responses to angiotensin II. Losartan administration results in a decrease in total peripheral resistance (afterload) and cardic venous return (preload). All of the physiological effects of angiotensin II, including release of aldosterone, are antagonized in the presence of Losartan. Reduction in blood pressure occurs independently of the status of the rennin-angiotensin system. As a result of Losartan dosing, plasma renin activity increases due to removal of the angiotensin II.

- **CONTRAINDICATION**

  The drug is contraindication in patients with:

  High amount of potassium in the blood, Renal artery stenosis, abnormally low blood pressure, liver problems, mild to moderate kidney impairment, pregnancy, decreased blood volume.

- **SIDE EFFECTS**

  Abdominal or stomach pain, anxiety, bladder pain, bloody or cloudy urine, chills, cold sweats, coma, cool, pale skin, shortness of breath, irregular heartbeat, difficult breathing, increase hunger, depression.

- **TOXICITY**Hypotension and tachycardia; Bradycardia could occur from parasympathetic (vagal) stimulation.

- **PRECAUTIONS**

Pregnancy:

It can harm unborn baby. Use an effective form of birth control to keep from getting pregnant.

Nursing mothers:

Safety and effectiveness in nursing mothers have not been established

EXCIPIENT PROFILE[58, 59]

SOYA LECITHIN

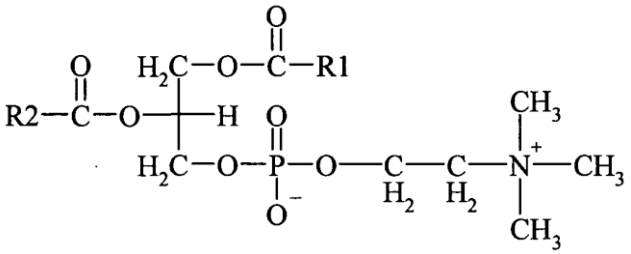
- **SYNONYM**

  Mixed soybean phosphatides, ovolecithin, phospholipon, soybean phospholipids and vegetable lecithin

- **CHEMICAL NAME**

  1, 2-diacyl-sn-glycero-3-phosphocholine

- **CHEMICAL STRUCTURE**



- **CHEMICAL COMPOSITION**

  Contains 21% phosphatidylcholine, 22% phosphatidylethanolamine and 19% phosphatidylinositol, along with other components

- **DESCRIPTION**

  Lecithins vary greatly in their physical form, from viscous semi liquids to powders, depending upon the free fatty acid content. They may also vary in colour from brown to light yellow, depending upon whether they are bleached or unbleached or on the degree of purity.

- **FUNCTIONAL CATEGORY**

  Emollient, emulsifying agent and solubilising agent

- **SOLUBILITY**

  Soluble in aliphatic and aromatic hydrocarbons, halogenated hydrocarbons, mineral oil, and fatty acids. Sparingly soluble in ethanol (95%). They are practically insoluble in cold vegetable and animal oils, polar solvents, and water. When mixed with water, however, lecithins hydrate of form emulsions.

- **DENSITY**

  0.5g/cm^3

- **ISOELECTRIC POINT**

  3.5

- **COMPATIBILITY**

  Incompatible with esterases owing to hydrolysis

- **STABILITY**

  Lecithins decompose at extreme pH. They are also hygroscopic and subject to microbial degradation. When heated, lecithins oxidize, darken, and decompose. Temperatures of 160-180°C will cause degradation within 24 hours.

- **FLAMMABILITY**

  Low

- **MOISTURE CONTENT**

  Are hygroscopic

- **SPECIFIC GRAVITY**

  0.97g/cm^3

- **STORAGE**

  Should be stored in well-closed containers protected from light, moisture and oxidation. Purified solid lecithins should be stored in tightly closed containers at subfreezing temperatures.

- **APPLICATIONS**
    - Lecithins are used in wide variety of pharmaceutical applications like aerosol inhalations, IM injections and oral suspension and are also used in cosmetics and food products.
    - Lecithins are mainly used in pharmaceutical products as dispersing, emulsifying, and stabilizing agents, and are included in intramuscular and intravenous injections, parenteral nutrition formulations, and topical products such as cream and ointments.
    - Lecithins are also used in suppository bases to reduce the brittleness of suppositories, and have been investigated for their absorption-enhancing properties in an intranasal insulin formulation.
    - Lecithins are also commonly used as a component of enteral and parenteral nutrition formulations. Lecithin is a required component of FDA-approved infant formulas.
    - Therapeutically, lecithin and derivatives have been used as a pulmonary surfactant in the treatment of neonatal respiratory distress syndrome.

MATERIALS AND METHODS

Table 1: LIST OF MATERIALS USED AND THEIR SOURCES

MATERIALS	SOURCES
Losartan	Microlabs,Chennai
Soya lecithin	HiMedia Laboratories, Nashik
Dichloromethane	Loba Chemie, Mumbai
Hydrochloric acid	SD Fine chem. Ltd, Mumbai
Chloroform	HiMedia Laboratories, Mumbai

Table 2: LIST OF EQUIPMENTS USED

EQUIPMENTS	SUPPLIERS / MANUFACTURES
FT/IR Spectroscopy/4100	Jasco,Johannesburg, South Africa

Rotary vaccum evaporator	Superfit,India
UV-visible double beam spectrophotometer	Shimadzu,Shimadzu corporation, Philippines
Bulk and tapped density apparatus	Thermonik,Campbell electronics,Mumbai,India
Weighing balance	Shimadzu,Shimadzu corporation, Philippines
Heating mantle	Sunbim, India
Disintegration apparatus	Tab machines, Mumbai, India
Dissolution apparatus	Tab machines, Mumbai, India
Stability chamber	Technico, Chennai, India
pH meter	EUTCH Instruments, India
Scanning electron microscope	JEOL,Japan
XRD-6000 diffractometer	Shimadzu, Japan

DETERMINATION OF λ_{max} [1]

The stock solution of 100µg/ml was prepared by dissolving 100mg of pure Losartan in 100ml of pH 7.4 phosphate buffer. From the stock solution, 10ml was taken and futher diluted to 100ml with the buffer solution. The prepared solution was then scanned in a wavelength range of 200-400nm, to find the maximum absorbance. The maximum wavelength was found to be 234nm and was used for further studies.

DETERMINATION OF STANDARD CURVE[14]

- The serially diluted stock solution was obtained in the range of 2-10µg/ml by taking 0.2, 0.4, 0.6, 0.8 and 1 ml from the stock solution, into 100ml volumetric flask.
- The final solution is made by using phosphate buffer of pH 7.4.
- The serially diluted solutions were measured in a UV spectrometer at 331nm of the drug.
- The calibration curve was plotted by taking absorbance on y-axis and concentration in µg/ml on x-axis, to find the slope.

PREPARATION OF PHARMACOSOMES OF LOSARTAN BY SOLVENT EVAPORATION TECHNIQUE[20]

To prepare the pharmacosomes of losartan, it was first acidified so that the active hydrogen might be available for complexation. Losartan was prepared by acidification of an aqueous solution of losartan using 0.1N hydrochloric acid. It was then extracted into chloroform and subsequently recrystallized. Phosphatidycholine (PC) complex was prepared by associating losartan with PC in various molar ratios. The accurately weighed PC and losartan 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 dessicator for three days and then subjected to characterization.

Table 3: Formulation table of losartan pharmacosomes

Ingredients	F_1	F_2	F_3	F_4	F_5	F_6	F_7
Losartan: 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

PREFORMULATION STUDIES

The discovery and development of new chemical entities (NCEs) into stable, bioavailable, marketable drug products is a long, but rewarding process. Once a NCE is selected for development, choosing the molecular form that will be the active pharmaceutical ingredient (API) is a critical milestone because all subsequent development will be affected by the decision. A well- designed preformulation study is necessary to fully characterize molecules during the discovery and development process so that NCEs have the appropriate properties, and there is an understanding of the deficiencies that must be overcome by the formulation process.[63] The procedure of each preformulation test suitable for capsule is given below.

COMPATIBILITY STUDIES

IR spectra matching approach was done for detecting any possible chemical interaction between drug and excipient. A physical mixture of drug and excipient was prepared and mixture with the suitable quantity of potassium bromide. About 100mg of mixture was compressed to from a transparent pellet using a hydraulic press at 6 tons pressure. It was

scanned from 4000 to 400 cm^{-1} in FTIR spectrometer. The IR spectrum of pure drug and matching was done to detect any appearance or disappearance of peaks.

ANGLE OF REPOSE

It is the maximum angle that can be obtained between the free standing surface of a powder heap and the horizontal plane. It was determined by the funnel was kept vertically at a specified height and the funnel bottom was closed. Weighed accurately 10mg 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.[63] Then the powder cone diameter was measured and angle of repose was calculated by using the following formula.

$$\mathbf{Tan\ \theta = h/r} \qquad (1)$$

Therefore,

$$\Theta = Tan^{-1}\ (h/r)$$

Where, θ = angle of repose

h = height of the cone

r = radius of the cone

Table 4: Standard values for Angle of repose

Angle of repose in degrees	Type of flow
<25	Excellent
25-30	Good
30-40	Satisfactory

>40	Poor

BULK DENSITY

The bulk density was determined by pouring presieved (#40 mesh) powder into a graduated cylinder via a large funnel and measured the volume and weight.[63]

It was calculated in gm/cm^3 by the formula,

$$\textbf{Bulk Density } (\delta_0) = M/V_0 \qquad (2)$$

M= Mass of the sample/ weight of sample

V=Apparent unstirred volume/ Bulk volume.

TAPPED DENSITY

Tapped density was determined by placing a know 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.

The tapped density was calculated in gm/cm^3 by the formula,

$$\textbf{Tapped density } (\delta_t) = M/V_f \qquad (3)$$

M=Weight of the sample

V_f= Tapped volume

COMPRESSIBILITY INDEX/CARR'S INDEX

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

$$\textbf{Compressibility index (\%)} = [(TBD-LBD) \times 100]/TBD \qquad (4)$$

LBD=Loose bulk density

TBD=Tapped bulk density

HAUSNER' S RATIO:

Hausner ratio was calculated by using the following formula[63].

$$\textbf{Hausner's ratio} = (\delta_t/\delta_0) \quad (5)$$

δ_t = Tapped density

δ_0 = Bulk density

Table 5: Scale of flow ability for compressibility index and Hausner's Ratio

CARR'S INDEX	HAUSNER'S RATIO	TYPE OF FLOW
5-15	1.05-1.18	Excellent
12-16	1.14-1.20	Good
18-21	1.22-1.26	Fair-passable
23-35	1.30-1.54	Poor
33-38	1.50-1.61	Very poor
>40	>1.67	Very very poor

DRUG CONTENT DETERMINATION

For the determination of the drug content in losartan pharmosome, the complex equivalent to 50 mg losartan was weighed and added into a volumetric flask with 100 ml of pH 7.4 phosphate buffer. Then the volumetric flask was stirred continuously for 24 hours on a magnetic stirrer. At the end of 24 hr, the dilutions were made suitably and it was measured for the drug content at 234nm UV spectrophotometrically.[24]

SOLUBILITY DETERMINATION

To determine the change in solubility due to complexation, the apparent solubility of losartan and losartan pharmacosomes was determined by adding an excess amount of drug and pharmacosomes to 6 ml 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 solution were then analyzed spectrophotometrically at 234nm.[20]

POST FORMULATION STUDIES

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 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 deviation show in the table and none deviates by more than twice that percentage.[63,64]

Average weight of formulation	Percentage Deviation
Less than 300mg	±10
300mg or more	±7.5

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 a disc 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 lowered between 28-32 cycles per

minute. The time taken for complete disintegration of the complete disintegration of the capsule with no palpable mass remaining in the apparatus was measured and recorded.[63,64]

If one or two capsule fail to disintegrate, repeat the test on 12 additional capsules; NLT 16 of the total 18 capsules tested should disintegrate.

DISSOLUTION:

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 capsule was carried out by keeping the capsule was carried out by keeping the capsules for 10hours in the dissolution medium of pH 7.4 phosphate buffer solution (900ml). At predetermined time intervals, 10ml of sample was withdrawn and was replaced with 10ml fresh buffer solution. The absorbance of the sample was measured by using double beam spectrophotometer at 331nm. The cumulative release of the sample was calculated by using suitable equations with the help of the standard curve.[63,64]

X-RAY POWDER DIFFRACTION (XRD) ANALYSIS:

The crystalline state of Losartan in the different samples was measured using X-ray powder diffractometer (Shimaszu, Japan) at CRL, Karunya University, Coimbatore. The powder sample was placed in an aluminium sample holder. The X-ray generator was operated at 40kV tube voltages and 30mA of tube current, using the Ka lines of cooper 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 diffraction .[21]

SCANNING ELECTRON MICROSCOPY (SEM) ANALYSIS:

To detect the surface morphology of the pharmacosome, SEM of complex was performed by Scanning Electron Microscope JSM 6390 (JEOL, Japan) at CRL, Karunya University, Coimbatore. Sample was kept on an SEM stub using double-sided adhesive tape at 50mA for 6min through a sputter (KYKY SBC-12, Beijing, china). A scanning electron microscope with a secondary electron detector was used to obtain digital images of the pharmacosomes.[39]

DRUG RELEASE KINETIC ANALYSIS[65]

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.

$$C = K_0 t \quad (7)$$

Where

K_0 is the zero-order rate constant expressed in units of concentration /time

T is the time in hours.

A graph of concentration vs. time would yield a straight line with a slope equal to K_0 and intercept the origin of the axis.

$$\text{Log } C = \text{Log } C_0 - kt/2{:}303 \quad (8)$$

Where**,**

C_0 is the initial concentration of drug,

K is the first order constant , and t is the time.

$$Q = Kt^{1/2} \quad (9)$$

Where,

K: is the constant reflecting the design variables of the system

t: is the time in hours.

MECHANISM OF DRUG RELEASE[66]

To evaluate the mechanism of drug release form the capsule , data of drug release were plotted in Korsmeyer peppas equation (Equation 10) as log cumulative percentage of drug released Vs. log time , and the exponent n and was calculated through the slope of the straight line.

$$\mathbf{Mt-M\infty= Kt^n} \qquad (10)$$

Where

Mt/M is the fractional solute release,

T is the release time,

K is a kinetic constant characterizes the mechanism of release of tracers.

If the exponent n=0.45, then the drug release mechanism is Fickian diffusion, and if 0.45≥ n ≥ 0.89, then it is non-Fickian or anomalous diffusion. An exponent value of 0.89 is indicative of Case-II Transport or typical zero-order release.

STABILITY STUDIES

Stability of a drug in a dosage form at different environmental conditions is important, because it determines the expiry date of that formulation. Hence, the stability of the drug in the pharmacosome was studied. Stability studies were conducted according by storing the capsules at 40°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.

RESULTS AND DISCUSSION

CALIBRATION CURVE OF LOSARTAN

The λ_{max} of Losartan pure drug was determined by scanning the prepared solution in the wavelength range of 200-400nm. The maximum wavelength was found to be 234nm. The calibration curve of losartan was constructed by dissolving the drug in pH 7.4 phosphate buffer. The linearity of the curve was found in the concentration range of 2-10µg/ml. A regression coefficient (R^2) value of 0.9989

Table: 6 Calibration curve data of Losartan

Concentration (µg/ml)	Absorbance
2	0.172
4	0.314
6	0.491
8	0.657
10	0.793

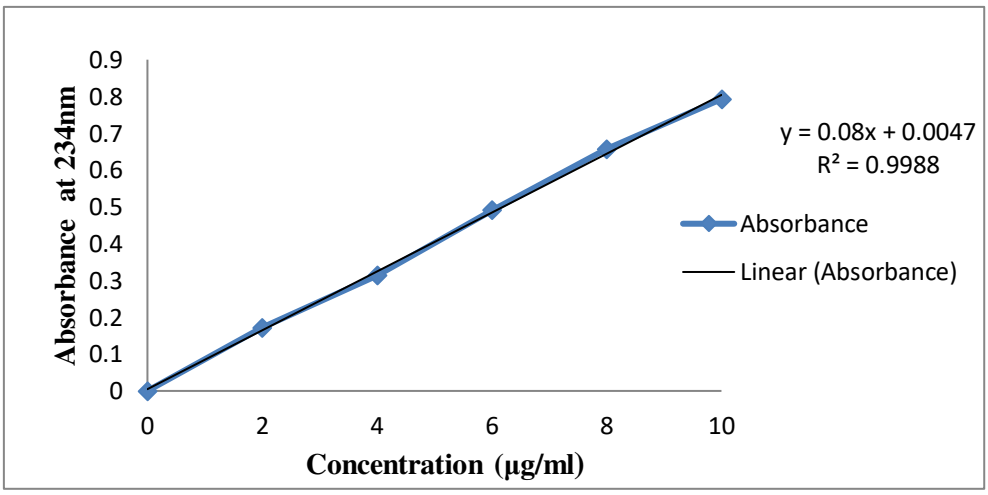


Fig 1: Calibration curve of Losartan

COMPATABILITY STUDIES

The IR spectra of pure drug, losartan and the excipients, soya lecithin was analyzed and composed with IR spectra obtained for the mixture. It was found that the spectra of the drug with excipient showed all the characteristic peaks of Losartan suggesting that there was no compatability problem between the drug and the excipient.

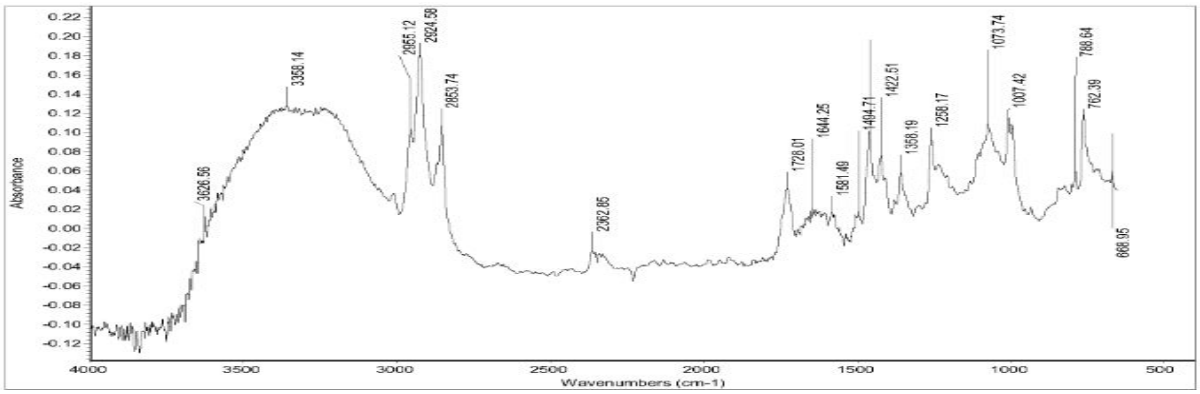


Fig 2: IR spectrum of Losartan pure drug

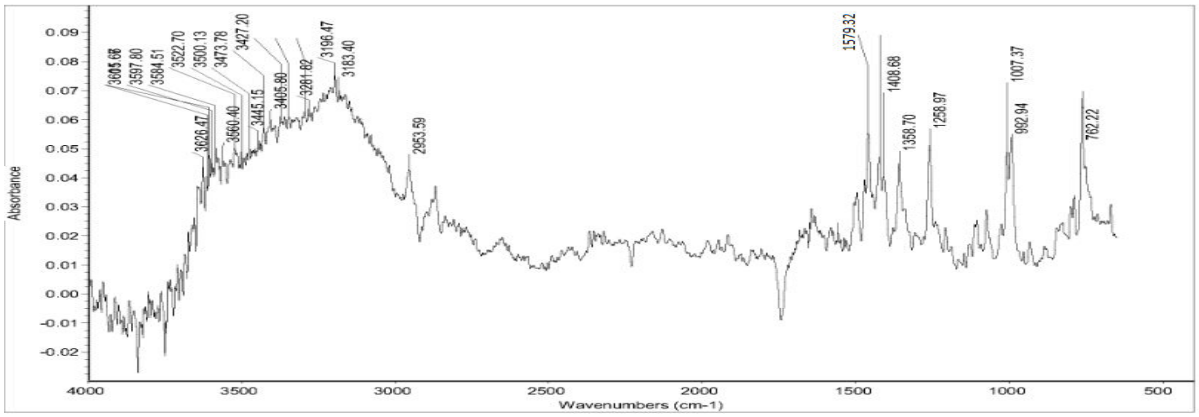


Fig 3: IR Spectrum of Losartan + Soya lecithin

Table 7: Characteristic peak of Losartan and soya lecithin

SPECIFICATION	WAVE NUMBER (CM^{-1})	
	Losartan	PX+ Soya lecithin
C-Cl Stretching	762.39	762.22
C-N Stretching	1422.5	1408.60
C-H Stretching	2955.12	2953.59
N-H Stretching	3358.14	3281.82
-OH Stretching	1358.19	1358.70
C=C Stretching	1581.49	1579.32

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 flowablity and compressibility of the powder formulation.

Table: 8 Results of preformulation studies

FORMULATION	ANGLE OF REPOSE	BULK DENSITY (gm/cm^3)	TAPPED DENSITY (gm/cm^3)
F_1	24º15'	0.554	0.624
F_2	26º53'	0.401	0.453
F_3	24º82'	0.500	0.570
F_4	27º08'	0.433	0.500
F_5	28º30'	0.454	0.525
F_6	27º56'	0.415	0.500

F_7	27°63'	0.500	0.624

The preformulation study of the prepared losartan pharmacosomes powder showed followings:

Angle of repose at a range between = 24°15′ to 27°30′

Bulk density at a range between = 0.41gm/cm^3 to 0.50gm/cm^3

Tapped density at a range between = 0.453gm/cm^3 to 0.624gm/cm^3

The above values indicates that the sample have good flow character. All the results were within the prescribed limits. F_1 formulation showed the best flow property.

DRUG CONTENT STUDIES

The drug content of losartan in the pharmacosomes was estimated by UV spectrophotometery at 234nm using pH 7.4 phosphate buffer.

Table 9: Results of drug content studies

FORMULATION	DRUG CONTENT (%w/w)
F_1	96.83
F_2	96.12
F_3	93.38
F_4	93.56
F_5	90.81
F_6	90.04
F_7	88.60

The drug content of losartan in the complex was found to be in the range of 88.60% - 96.83% 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 96.83%.

SOLUBILITY STUDIES

The change in solubility of losartan due to complexation was determined by evaluating its solubility in water, pH 7.4 phosphate buffer and n-octanol solutions and was estimated by UV spectrophotometry at 234nm

Table 10: Solubility profile in different media

Formulation	Solubility in Water (mg/ml)	Solubility in pH 7.4 phosphate Buffer (mg/ml)	Solubility in n-Octanol (mg/ml)
Pure Drug	0.143	0.196	0.230
F_1	0.787	5.272	5.975
F_2	0.780	5.150	5.641
F_3	0.651	4.836	5.283
F_4	0.693	3.950	4.568
F_5	0.527	3.751	4.190
F_6	0.572	3.863	4.236
F_7	0.616	4.355	4.586

The solubility of the losartan pharmacosomes was found to be much higher than the pure drug. The increase in solubility of Losartan in the complex can be explained by the solublilization theory resulted from the formulation 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 F_1 exhibited the highest degree of solubility.

POST FORMULATION

Table 11: Results of post formulation studies

FORMULATION X	WEIGHT VARIATION (mg)	DISINTEGRATION TIME (Sec)
F_1	41±3.1	224
F_2	49±2.7	246
F_3	62±2.4	234
F_4	70±3.0	245
F_5	79±2.6	242
F_6	91±4.2	233
F_7	102±3.1	255

From the values obtained it was observed that the weight variation was within the specified limits and the disintegration time was in the range of 224-255 sec.

IN-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 time vs. percentage cumulative release.

Table 12: *In-vitro* drug release of Losartan pharmacosomes

Time (hrs)	Pure Drug	% Cumulative Release						
		F_1	F_2	F_3	F_4	F_5	F_6	F_7
0.25	2.51	4.60	3.29	2.83	2.85	3.07	3.95	3.07
0.5	8.66	11.58	10.37	9.88	8.64	9.54	7.85	6.19
1	12.33	21.29	18.07	16.94	14.21	15.73	14.26	13.42
2	19.27	33.16	27.68	25.65	20.14	23.46	23.02	18.85
3	28.21	40.64	38.42	34.49	33.24	41.51	29.51	21.52
4	37.10	53.21	46.63	42.92	40.23	47.43	41.46	32.94
5	43.54	58.55	53.17	48.19	45.75	50.85	49.00	45.18
6	50.98	65.77	59.40	52.08	46.98	52.30	50.76	53.62
7	55.88	73.50	64.81	57.30	51.27	56.74	53.95	54.05
8	57.62	84.16	71.54	62.69	60.20	62.25	63.16	59.54
9	58.27	90.19	82.79	71.20	74.48	74.25	72.60	73.60
10	60.42	94.69	90.05	85.07	83.05	84.44	83.34	79.49

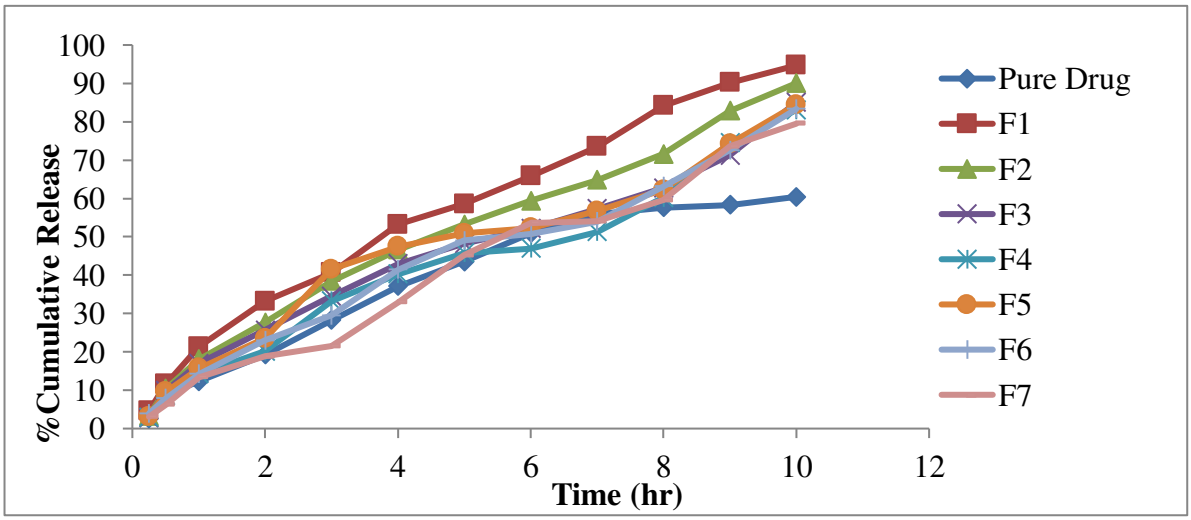


Fig. 4 *In-vitro* comparative diffusion profile of pharmacosomes containing losartan

The pharmacosomes of Losartan showed better dissolution profile than the pure drug. Unlike the free Losartan (which showed a total of only 60.42% drug release at the end of the 10 hour), all the formulation 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 the10th hour. The solid dispersion 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.

X-RAY POWDER DIFFRACTION (XRD) ANALYSIS

The XRD pattern of the pure drug (Losartan), soya lecithin and the selected formulation (F_1) are shown in Fig: 5. Fig: 6 and Fig: 7. Characteristic diffraction peaks were observed for Losartan. 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 Losartan in pharmacosomes.

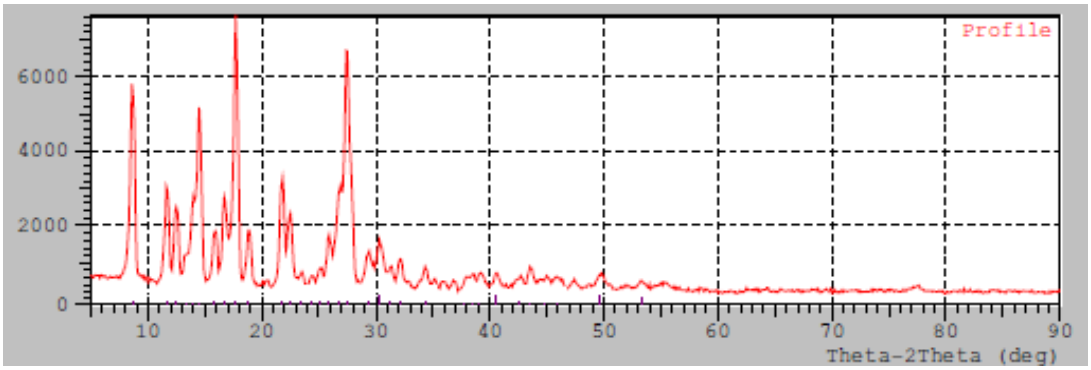


Fig 5: XRD pattern of pure drug (Losartan)

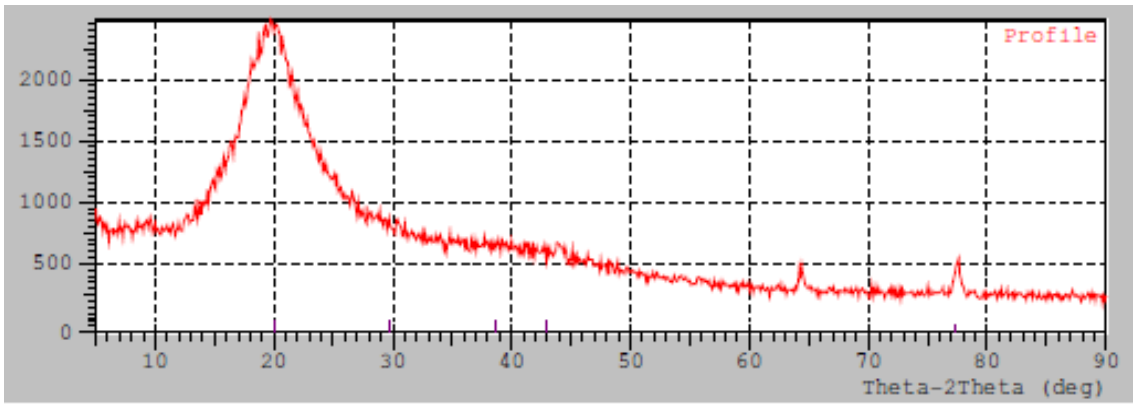


Fig 6: XRD pattern of soya lecithin

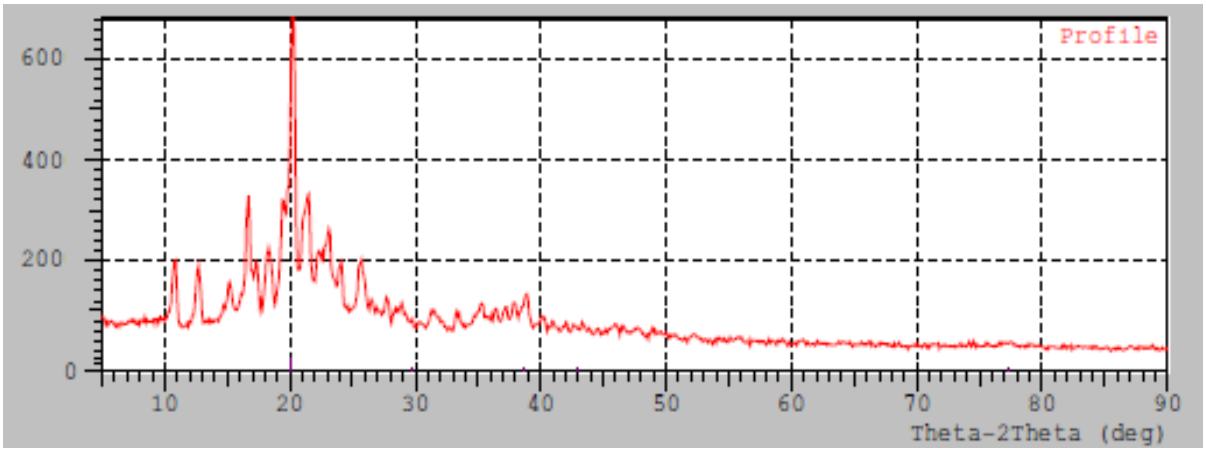


Fig 7: XRD pattern of Losartan pharmacosomes (F_1)

SCANNING ELECTRON MICROSCOPY (SEM) ANALYSIS

Particle morphology was determined by scanning electron microscopy. The SEM image showed that the pharmacosomes were disc shaped.

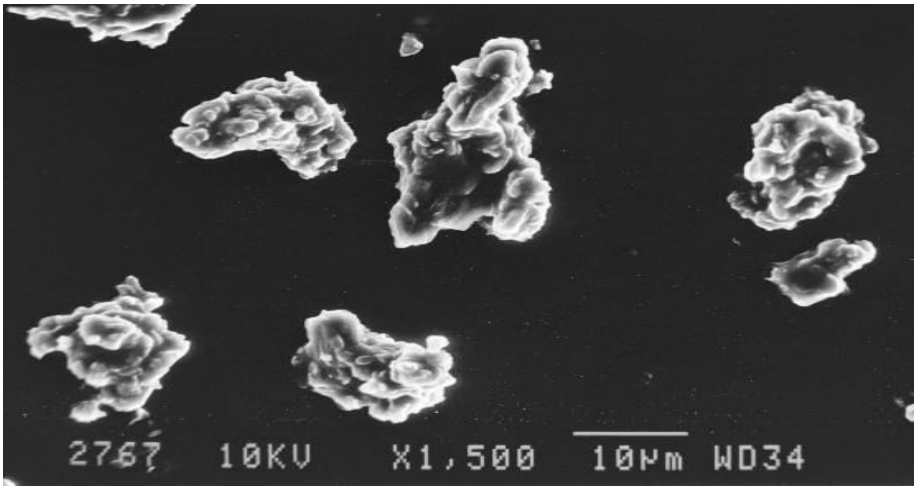


Fig 8: SME image of Losartan pharmacosomes (F_1)

RELEASE KINETIC ANALYSIS

Based on the data obtained from the *in-vitro* drug release studies the best formulation F_1 was analyzed 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 - pappas model in order to find out the mechanism of release from the prepared pharmacosomes. The model that best fits the release data is selected based on the regression coefficient value of various models.

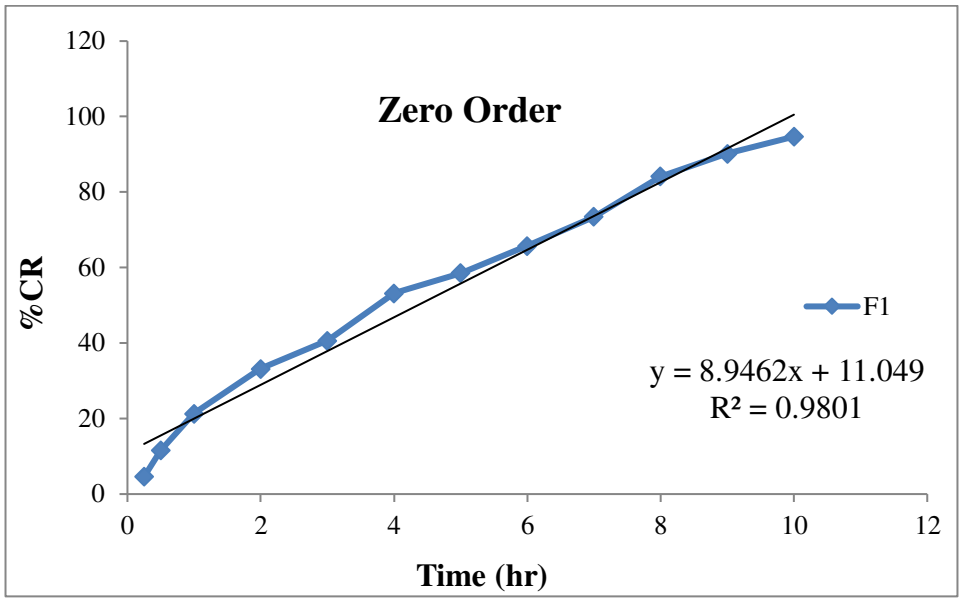


Fig 9: Zero order plot of F_1

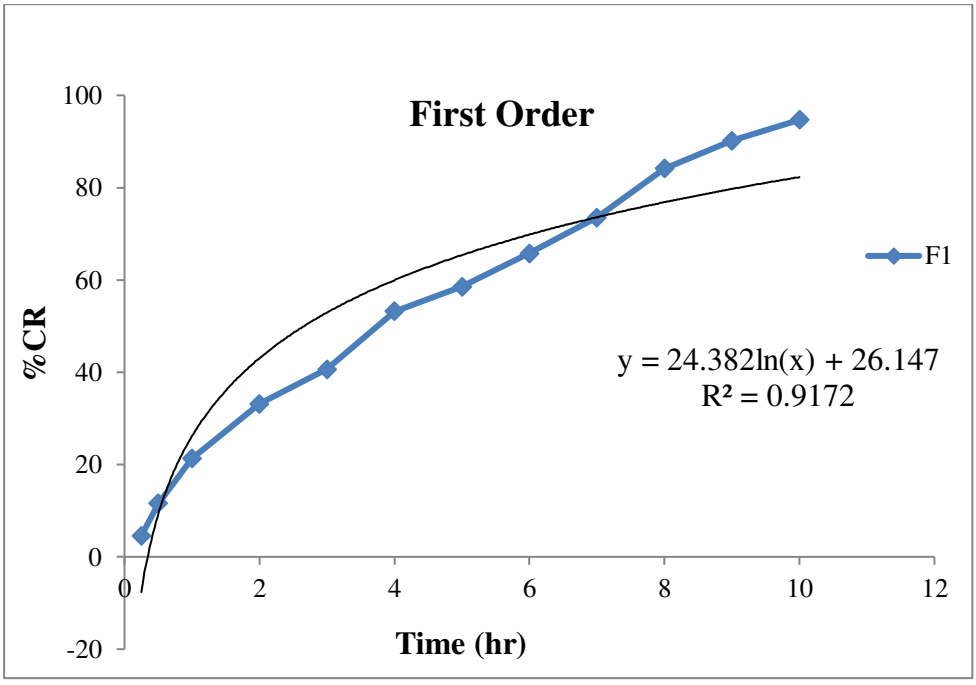


Fig 10: First order plot of F_1

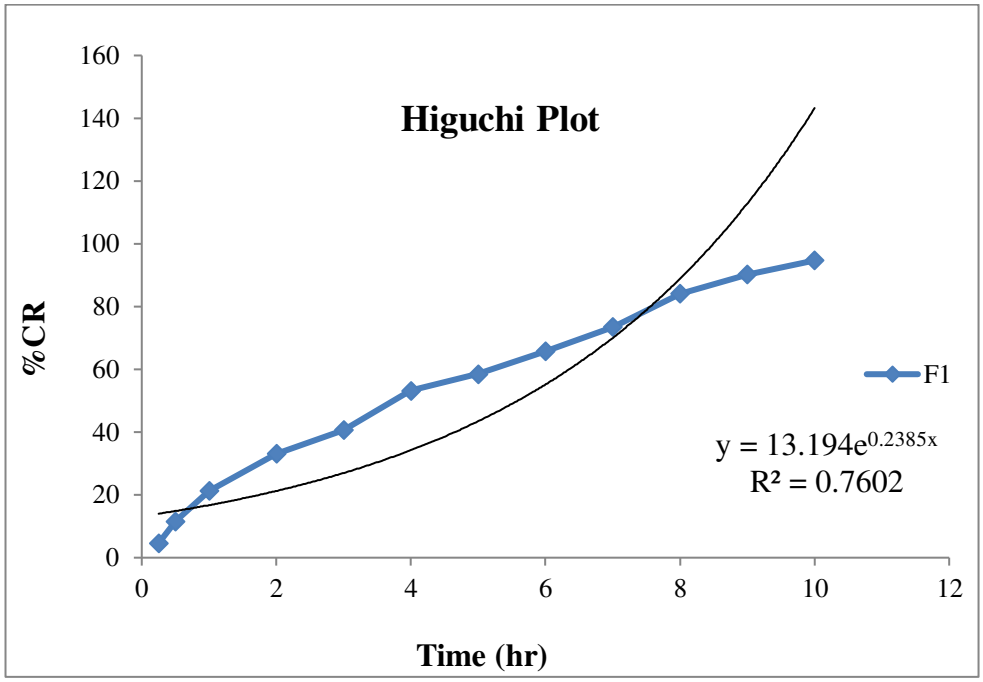


Fig 11: Higuchi plot of F_1

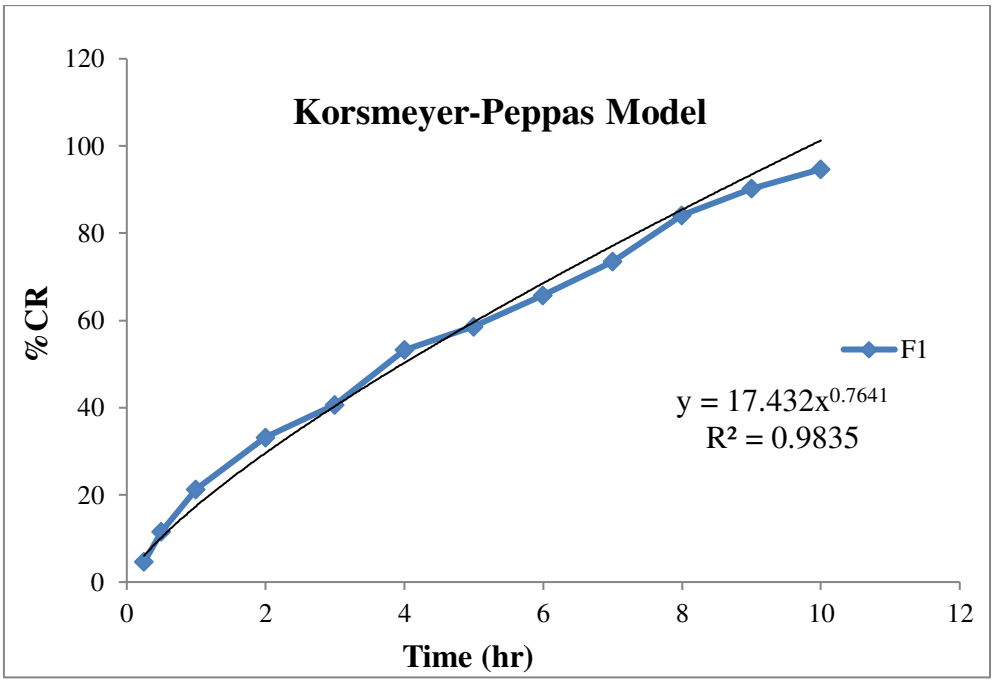


Fig 12: Korsmeyer-Peppas model of F_1

Table 13: Result 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 non- Fickian diffusion mechanism of drug release.

STABILITY STUDIES

Stability studies 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 humidity control oven for 45 days. After 45 days the sample was evaluated for the physical appearance, drug content, and *in-vitro* drug release studies. The values are as shown in the table.

Table 14: Stability studies of F_1 formulation

Sl. no	Accelerated temperature of 40± 2°C/RH 70 ± 5%			
	Parameters	Initial	30th day	45th day
1	Physical appearance	Light Yellow	Light Yellow	Light Yellow
2	Drug content	96.83	95.90	94.97
3	% Cumulative release at 10th hr	94.69	93.78	93.54

After the study for 45 days it was concluded that there was no major changes in the various parameters evaluated like physical appearance, percentage drug content and *in-vitro* drug dissolution study of F_1 at 40± 2°C. Thus, it can be conducted that, F_1 is stable at a temperature of 40± 2°C and at a relative humidity of 70± 5% for a period of 45 days.

SUMMARY

Losartan is an angiotension II receptor antagonist drug used mainly to treat high blood pressure. It is well absorbed oral administration and undergoes significant first-pass metabolism. It may also delay progression of diabetic nephropathy and is associated with a positive clinical outcome in that regard. Lowering high blood pressure helps prevent strokes, heart attacks, and kidney problems. It works by relaxing blood vessels so the blood can flow more easily. It is freely soluble in water and sparingly soluble in ethyl acetate, butyl acetate and cyclohexane, and the solubility in these three solvents varys little with the temperature, which affect it's dissolution in GI fluid and leads to poor bioavailability.

Hence the present study was aimed to develop a newer dosage form, the pharmacosomes, in order to avoid drug loss and to improve the bioavailability of the drug.

Formulation

Losartan pharmacosomes was prepared by the solvent evaporation technique using different ratios of drug and soya lecithin. The prepared pharmacosomes were filled into capsules, a total of 7 formulations were prepared.

Evaluation

Compatibility studies showed that the drug and the excipient are compatible with each other. The pharmacosomes were subjected to various preformulation and post formulation studies. All the parameters obtained were within the limits.

The angle of repose for all the formulations showed good flow character and all the results were within the prescribed limits. The drug content of Losartan in the complexes was found to be in the range 88.60% - 96.83% w/w indicating the presences of an acceptable amount of drug in the formulations. The formulation F_1 (drug: lecithin ratio of 1:1) showed the maximum drug content of 96.84% w/w

The solubility studies revealed that the solubility of the Losartan pharmacosomes was much higher than the pure drug. The formulation F_1 exhibited the highest degree of solubility.

The drug release profile suggested that at the end of the 10 hour study, all formulation showed the percentage cumulative drug release in the range of 79.49% - 94.69%. The formulation F_1 showed the maximum release of 94.69% at the 10^{th} hour. Based on all the above evaluation studies, it was observed that the best formulation was F_1 with a drug: lecithin ratio of 1:1.

The X-ray powder diffraction analysis, scanning electron microscopy, release kinetics and stability studies were conducted for the optimized formulation F_1. The XRD studies confirmed the formulation of the complex. The pharmacosomes were found to be disc shaped in scanning electron microscopy. The release kinetic analysis indicated that the F_1 formulation follows the near Zero order release kinetics and non-Fickian diffusion mechanism of drug release. The formulation was stored in the stability chamber to ascertain the effect of extreme temperature variations on physical consistency and the drug content of the pharmacosome. The results of the stability study suggested that there was no significant alteration in the drug content of the pharmacosome.

On the basis of all the evaluation studies it was observed that the best formulation was F_1 with a drug: lecithin ratio of 1:1.

CONCLUSION

In the present study the Losartan- phospholipid complexes (pharmacosomes) were prepared by a simple and reproducible method. The physicochemical investigations confirmed that Losartan formed a complex with phospholipids with better solubility and dissolution profile. The phospholipid complex of Losartan may be of potential use for improving bioavailability. As the phospholipid complex have also been reported to reduce the GI toxicity of the drugs, the phospholipid complex of Losartan may also be useful or minimizing the GI toxicity of Losartan. The pharmacosomes may be developed for other drugs with poor bioavailability and GI side effects. Thus, the formulated pharmacosomes seem 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 and from better dosage regimen

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