CHAPTER-2

LITERATURE SURVEY

Garces A et al., (2018) investigated the application of NLC and SLN for cutaneous use. It is reported that due to the low viscosity aqueous dispersions of SLN and NLC, it can be applied to the skin by semisolid preparation which shows promising absorption and penetration [1].

Gajanand Sharma et al., (2017) revealed that the NLC for dermal and transdermal applications are unique to make possible interactions at interfaces with the barrier of skin membranes, so that penetration will be more for NLC. NLC has a biodegradable composition, so it is said to be a "nanosafe" carrier [7].

Buparvaquone NLC for the Treatment of Leishmaniases was developed by Lis Marie Monteiro et al., (2017). In this research work, NLC was prepared by homogenization method using Softisan and Megliyol as lipid in a ratio of 3:2. Response surface methodology (RSM) optimization method was used to determine the optimized variables in NLC formulation [60].

Nobiletin-Loaded NLC was prepared and characterized by Wei Huang et al., (2017) by high-pressure homogenization method. Response surface methods with a three-level Box–Behnken design were designed by Wei Huang to validate the effect of formulation variable in characterization of NLC through analysis of variance method. Formulated NLC investigated for the Z-average, Polydispersity, Entrapment efficiency, Zeta potential, morphology and crystallinity [68].

Elisabetta Esposito et al., (2016) performed the encapsulation of Cannabinoid drugs in NLC. It was prepared by the ultrasonication method and optimized by the Nanoparticle recovery and drug encapsulation efficiency. Cryo-TEM studies were performed to determine the morphology of NLC [61].

NLC containing Indomethacin was optimized by Pattravee Niamprem et al., (2016). In this NLC was prepared by high pressure homogenization technique by using different types of lipids and surfactants. Mean particle size, polydisperesity index and zeta potential were measured. The entrapment efficacy of drug in NLC was determined by the HPLC method [62].
The effect of types of solid lipids like stearic acid, palmitic acid and myristic acid on the physicochemical properties and self-aggregation of amphotericin B with NLCs was investigated by Pataranapa Nimtrakul et al., (2016). In this research, NLC was prepared by using high pressure homogenization technique. The mean particle size was affected by the types of solid lipids [132].

Yung-Pin Lin et al., (2016) performed antihyperlipidemic activity of Allium chinense bulbs in Albino Wistar rats using high-fat-diet lipid inducing method [104].

Antihyperlipidemic and hepatoprotective activities of residue polysaccharide from Cordyceps militaris SU-12 was performed by Liqin Wang et al., (2015) and they measured the Total Cholesterol (TC), Triglycerides (TG), Low-Density Lipoprotein Cholesterol (LDL-C), High-Density Lipoprotein Cholesterol (HDL-C) and Very Low-Density Lipoprotein Cholesterol (VLDL-C) of mice serum by using automatic biochemical analyzer. Atherogenic Index (AI) was calculated as (TC − HDL-C) / HDL-C. Triacylglycerides (TG) and Total cholesterol (TC) in livers were analyzed using commercial kits [110].

Yang Yang et al., (2015) performed the evaluation of Transdermal Drug Delivery Systems (TDDS) like In-vitro drug permeation studies across human skin. The In-Vitro and In-Vivo correlation (IVIVC) between the in-vitro percent of drug permeation (X) and in-vivo percent of drug absorption (Y) for these three estradiol TDDS was constructed. There was a high correlation ($R^2$=1.0) with a polynomial regression of $Y=−0.227X^2+0.331X−0.001$ between in-vivo – in-vitro datas [133].

The application and limitations of lipid Nanoparticle in dermal and transdermal drug delivery via the follicular route was briefed by Andreas Lauterbach et al., (2015) [134].

Nanoparticle containing Curcuminoids (Curcuma longa) for topical drug delivery was developed by Cristina M. Zamarioli et al., (2015). In which, Lipid Nanoparticle was produced by the hot melt emulsion method. Percentage of curcuminoids, homogenization time and surfactant ratio are fixed as a 3$^3$ i.e., 3 factor with 3 level, Box–Behnken factorial design to study about the effect of factors in average nanoparticle sizes, zeta potential and polydispersity index in lipid nanoparticle formulation. The optimized nanoparticle is incorporated into hydrogels and performs
the drug release and the skin permeation studies were done. The topical formulation containing SLN-Curcuminoids showed good spreadability, stability and slow release. The skin permeation studies are carried out about 18 hrs [63].

The novel nanostructured supramolecular hydrogels for the topical delivery of anionic drugs was investigated by David Limon et al., (2015). Gel preparation was optimized for the influence of temperature, drug concentration, and solvent proportions and characterized for rheological studies, IR, XRD, AFM, SEM studies, drug content, in-vitro release studies, skin permeation studies in mouse skin etc [70].

Umit Gonullu et al., (2015) formulated and characterized SLN, NLC and nanoemulsion of lornoxicam for transdermal delivery. NLCs are prepared by high pressure homogenization technique at 90°C using Compriitol®888 ATO, Lanette®O and oleic acid as Solid lipid and Liquid lipids. Stability studies for all the formulation at various temperatures were carried out for about 6 months. The drug release studies follows Case I diffusion drug release i.e., Fickian drug diffusion mechanism. The highest rate of drug penetration through rat skin was obtained with NLC [50].

Antihyperlipidemic activity of ethanolic extract of Glycosmis pentaphylla in hyperlipidemic Wistar rats was performed by Syed Safiullah Ghorı et al., (2015) [107].

Phospholipids and their main applications in drug delivery systems was investigated by Jing Li et al., (2015) [135].

NLC system for topical delivery of Terbinafine Hydrochloride (TH) was formulated and characterized by Bharti Gaba et al., (2015). TH-NLC were prepared using high pressure homogenization technique with Glyceryl monostearate as solid lipid, labrasol as liquid lipid and pluronic F-127 (Poloxamer 407) as surfactant and also binary lipid phase was selected in the ratio 6:4 w/w (solid:liquid lipid ratio). Formulated NLCs were characterized by Scanning Electron Microscopy (SEM), Transmission Electron Microscopy (TEM) analyses and Ex-vivo skin permeation study. The in-vitro release study was carried out for 24 hrs as compared to the marketed formulation [73].

Elisabetta Esposito et al., (2014) execute the effect of NLC on percutaneous absorption of Curcumin. NLC morphology and dimensional distribution have been
investigated using Cryogenic Transmission Electron Microscopy (Cryo-TEM), X-ray scattering techniques [74].

Montelukast loaded NLCs by melt emulsification and ultrasonication method was carried out by Arpana Patil-Gadhe et al., (2014). Optimized formulation was lyophilized by adding mannitol as cryoprotectant to get a dry NLC powder. In-vitro release and In-vivo pharmacokinetic studies were carried out for the dry NLC powder formulation [79].

Lijiang Chen et al., (2014) performed in-vivo pharmacokinetic studies of bexarotene nanocrystals in rats by gavage and intravenous administration [112].

Lipid Nanoparticle for oral delivery of Raloxifen was investigated by Punna Rao Ravi et al., (2014). Punna Rao Ravi et al., designed Box–Behnken design to optimize the manufacturing conditions of formulation of lipid nanoparticle. Lipid nanoparticle was prepared by micro-emulsion technique. The following variables are used for optimization like type of surfactant (polysorbate 80), concentration of surfactant (1% and 5% w/v), temperature of surfactant solution (25 and 75 ºC), volume of external phase (10 and 30 ml), speed of homogenization (7500 rpm and 12500 rpm), time of homogenization (2 and 16 min), amount of lipid (0.5 and 1.5 g), time of ultrasonication (5 and 15 min), ultra-sonication amplitude (70% and 100%), ultra-sonication pulse (continuous and pulse mode) and temperature during homogenization (60 and 75 ºC) [53].

The impact of lipid dynamic behavior on physical stability, in-vitro release and skin permeation of Genistein (GEN) loaded Lipid Nanoparticle was discussed by Ligia Marquez Andrade et al., (2014). NLC were prepared by Microemulsion technique using the following lipids and excipients like Glyceryl behenate (Compritol ATO 888), Capric and Caprylic triglycerides (Miglyol 812 N) and surfactant like Polysorbate 80 (Tween 80), Sorbitan trioleate (Span 85), Cetylpyridinium Chloride (CPC) and it was characterized to determine the following parameters like stability studies, Differential Scanning Calorimetry (DSC) analysis, In-vitro drug release, Skin permeation studies, Mean diameter, PI, Entrapment Efficiency (EE) and Drug recovery (REC) etc. Despite of the fact that NLC demonstrated more fluidity, GEN released more slowly from NLC than from SLN. Skin permeation studies
demonstrated that lipid Nanoparticle increased GEN skin retention. More flexible particles (NLC) also favored drug penetration into deeper skin layers. In this study it was concluded that NLC would seem to be a promising formulation for topical delivery [54].

**Arpana Patil Gadhe and Varsha Pokharkar (2014)** prepared and evaluated the Pharmacokinetic parameters in Montelukast-loaded NLC to enhance the bioavailability. *In-vivo* single dose oral pharmacokinetic study has demonstrated and calculated the following parameters like $C_{\text{max}}$, $T_{\text{max}}$, AUC$_{0-t}$, AUC$_{0-\infty}$, AUMC$_{0-t}$, AUMC$_{0-\infty}$, $K_{el}$, $t_{1/2}$, MRT, $V_d$, Clearance, Fr and from the results it is shown that 143-fold improvement in bioavailability as compared to Montelukast- aqueous solution. It also implies that NLC formulation is suitable to improve the bioavailability by sustaining the release of drug in systemic circulation [113].

The advances in lipid-based colloid systems as drug carrier for topical delivery were discussed by Yingjie Zhai and Guangxi Zhai (2014). The authors focus on theories and detailed researches mainly about Liposome, Lipid Nanocapsules, SLN, Microemulsion and NLC, and also they discussed about the application of carriers as transcutaneous delivery system [136].

**Yang Chen** et al., (2014) discussed about novel chemical permeation enhancers for transdermal drug delivery [24].

*In-vitro* and *In-vivo* comparison of solid and liquid oil cores in transdermal Aconitine nanocarriers was revealed by Yong-tai Zhang et al., (2014). This study has compared the transdermal Aconitine delivery using SLN and Microemulsion (ME) vehicles. *In-vivo* studies found that these formulations can loosen the stratum corneum layers and increase skin surface gaps, which enhance the transdermal drug delivery. SLN produced Aconitine release when compared with ME; this transdermal delivery vehicle may reduce the toxicity of the drug [92].

Novel transdermal patch containing diclofenac and teriflunomide for rheumatoid arthritis therapy was designed and evaluated by Yuxiu Zhang et al., (2014). The percutaneous permeation of organic amines salt of drug was investigated by *in-vitro* using a two-chamber diffusion cell with excised rabbit skin as transdermal barrier.
The formulation of the patch was optimized in terms of the concentration of percutaneous permeation enhancer and by the loading dose of drugs [20].

Melike Uner et al., (2014) researched on SLN and NLC of Lorantadine for topical Application. The formulations were evaluated for physicochemical stability and drug penetration through rat skin. SLN and NLC were prepared by high pressure homogenization method. Their Entrapment Efficiency (EE) and Loading Capacity (LC) were examined. The physical stability of Nanoparticle was investigated during 6 months of storage at room temperature (RT), 4 °C and 40°C. Fourier Transform Infrared Spectroscopy (FTIR), Differential Scanning Calorimetry (DSC) and Laser Diffraction (LD) methods were used for the investigation of drug: excipient compatibility studies, thermal behavior and for the particle size of the nanoparticle. In-vitro release and ex-vivo skin penetration of LRT were also studied [45].

NLC containing tacrolimus was prepared by hot melt emulsification employing high pressure homogenization technique and evaluated for In-vivo skin hydration, Transepidermal water loss (TEWL), in-vivo skin deposition analysis by quantification of drug in different skin strata was carried out by Pallavi V. Pople et al., (2013) developed [137].

A. Beloqui et al., (2013) performed the biodistribution studies for NLCs after the intravenous administration of rats and measured the pharmacokinetic parameters like $C_{\text{max}}$, $AUC_{0-24}$, and $\text{MRT}_{0-24}$[12].

SLN based on the controlled release system for topical delivery of Terbinafine Hydrochloride (TH) was formulated by Harshad Vaghasiya et al., (2013). TH loaded SLNs were prepared by solvent injection technique and optimized using $3^3$ full-factorial designs. Effect of drug: lipid ratio, surfactant concentration and volume of organic solvent were studied by the % Entrapment Efficiency (%EE) and Particle Size (PS). Optimized SLNs were incorporated with the Carbopol gel and evaluated the drug content, pH and in-vitro release, ex-vivo retention, in-vivo Pharmacodynamic and stability studies. Drug release from SLNs followed the Korsmeyer–Peppas model indicating Fickian drug release, while the gel followed the Higuchi model. The ex-vivo studies through rat abdominal skin indicated skin retention ability of SLNs as compared to commercial product. The SLNs dispersion and gel exhibited
physicochemical stability under refrigeration upto 3 months. It was concluded that
SLNs incorporated Carbopol gel has the skin targeting ability [64].

Tacrolimus loaded Transfersomes (TFs) for deeper skin penetration enhancement and
also for therapeutic effect improvement was developed by Wei Lei et al., (2013). In
this research different kinds of surfactants, sodium cholate, tween 80 and span 80
were investigated to prepare TFs respectively. Tween 80 was selected as the optimal
surfactant to produce a carrier. Entrapment Efficiency and diameter were also
evaluated. The optimized TFs were further made into gel and in-vitro drug release of
TFs-gel was carried out upto 24 hr till it shows higher drug release pattern than the
commercial ointment [91].

Methoxalen NLC loaded gel for psoriasis through hot homogenization followed by
high speed homogenization technique, using glyceryl distearate, compritol ATO 888
and stearic acid as solid lipid, ethyl oleate as liquid lipid and pluronic F-68
(poloxamer) as surfactant and characterized for the determination of particle size,
polydispersity index (PI), zeta potential, entrapment efficiency and in-vitro release.
This research was performed by Gajanan Shinde et al., (2013). Formulated NLC was
undergone DSC analysis to characterize the state of drug and lipid modification.
Shape and surface morphology were determined by Scanning Electron Microscopy
(SEM). NLC based gel was characterized for drug content, skin permeation, drug
deposition and skin irritation study. NLC based gel Formulations were subjected to
the stability study over a period of 30 days. NLC based gel has not shown any skin
irritation but shown a prolonged release up to 24 hr [25].

Atul Anand Phatak et al., (2013) developed the NLC by using 3 factors, 3 levels
Box Behenken design. NLC was prepared by the modified hot sonication method. The
lipids used in this study were compritol 888 ATO, miglyol and polysorbate 80 acts as
an emulsifier or stabilizer. The independent variables were the combination of lipids
(% w/w), concentration of emulsifier (% w/v), lipid drug ratio and also the response
variables were particle size, percentage entrapment and drug release after 12 hr. The
formulations were also characterized for Particle Size, Entrapment Efficiency, Drug
Loading and depression in melting point [77].
Rania M. Hathout et al., (2012) characterized colloidal soft nano-carriers for transdermal delivery and proved the enhancement of bioavailability of an angiotensin II receptor blocker. They were also evaluated for *ex-vivo* permeation study and comparative pharmacokinetic study that is to be done on healthy human subjects between the selected microemulsions and the commercial oral tablets [21].

NLC containing cyclodextrin for Ketoprofen topical delivery was formulated by M. Cirri et al., (2012). In this research, Compritol 888 ATO (Glyceryl behenate) and Labrafac lipophile were selected for the preparation of NLC by ultrasonication method. Both empty and loaded NLC were suitably characterized for particle size, pH, entrapment efficiency and drug release behavior. The best NLC system was incorporated into a xanthium hydrogel and characterized for drug permeation [138].

Jaleh Varshosaz et al., (2012) studied about the freeze-drying of NLC using cryoprotectants. NLCs were prepared by the solvent emulsification method followed by ultra-sonication method. Different carbohydrate and polymeric cryoprotectants including microcelac® (mixture of lactose and avicel), avicel PH102 (microcrystalline cellulose), mannitol, sucrose, avicel RC591 (mixture of microcrystalline cellulose and sodium carboxymethyl cellulose), maltodextrine, aerosil and PEG4000 were tested initially and then used to lyophilize NLCs [80].

The enhancement effect of surfactants by the penetration of Nitrendipine through rat skin was studied by K. Bhaskar Reddy et al., (2012). The percutaneous permeation of Nitrendipine was investigated in rat skin after the application of water–propylene glycol (50:50% v/v) using the diffusion cell technique. The effect of various surfactants such as Sodium Lauryl Sulphate (SLS), benzalkonium chloride and Tween 80 were evaluated with different concentrations on skin permeability. Flux, lag time and enhancement ratios (ERs) of nitrendipine were measured over 12 hr and compared with the control sample [93].

Abdul Ahad et al., (2012) formulated and optimized nanotransfersomes using experimental design technique for transdermal delivery of Valsartan. Nanotransfersomes bearing Valsartan were characterized for entrapment efficiency, vesicles shape and size, size distribution and skin permeation. *In-vivo* antihypertensive activity was performed on the Wistar rats. Nanotransfersomes
proves significantly that the amount of drug permeated through the skin is found to be more. Nanotransfersomes showed better antihypertensive activity in comparison with liposomes by the better permeation of drug through Wistar rat skin [65].

Transferosomal gel for transdermal insulin delivery was formulated and characterized by Jadupati Malakar et al., (2012). The effect of independent process variables like ratio of lipids (soya lecithin: cholesterol) and ratio of surfactants ( tween 80: sodium deoxycholate) on the in-vitro permeation flux (l g/cm²/h) of the formulated transferosomal gels containing insulin through porcine ear skin was optimized using $2^3$ factorial design. The in-vitro insulin permeation through porcine ear skin from these transferosomal gel followed zero-order kinetics over a period of 24 hr performing case-II drug transport mechanism [66].

Fan Yang et al., (2012) researched on transdermal delivery of the anti-rheumatic agent methotrexate using solid-in-oil nanocarriers. A transdermal delivery experiment was done using the S/O nanocarrier, and the permeation efficiency of drug through Yvalence stucatan micropig skin was evaluated using Franz diffusion cell [94].

Nanoemulsion gel formulation for transdermal delivery of Carvedilol was developed and characterized by Singh Bhuwanesh Pratap et al., (2012) [86].

Bioequivalence study on Simvastatin using human plasma was developed by Selvadurai Muralidharan et al., (2012). Chromatographic separation was carried out on a reversed phase C18 column using the mixture of methanol: 2 mM ammonium acetate and 500 µl of 0.5% formic acid (80:20, v/v) at a flow rate of 1.0 ml/min with UV-VIS detection at 418.35 nm. Various pharmacokinetic parameters including $\text{AUC}_0-t$, $\text{AUC}_0-\infty$, $C_{\text{max}}$, $t_{\text{max}}$, $t_{1/2}$ and elimination rate constant ($K_{el}$) were determined from plasma concentration by applying this above method [99].

In-vitro and in-vivo efficacy of edelfosine-loaded lipid nanoparticle against glioma was researched by Ander Estella-Hermoso de Mendoza et al., (2011). In this study, compritol® and precirol® are used as lipid and tween® 80 as surfactant for the formulation of lipid nanoparticle [56].

Ruiwei Guo et al., (2011) researched on bioadhesive film formed created by a novel organic and inorganic hybrid gel for transdermal drug delivery system. PVA used as a
gel forming agent, Poly (N-vinyl pyrolidone) (PVP) as a tackifier and glycerol as a plasticizer are used for preparation of transdermal drug delivery system [83].

The statistical optimization of Dithranol loaded SLN using $3^2$ full factorial experimental design by the influence of variables like drug: lipid ratio and sonication time of the response variables particle size and % entrapment efficiency (% EE) in order to optimize the formulation of Dithranol (DTH) loaded SLN by the pre-emulsion ultrasonication method. Which was discussed by Makarand Suresh Gambhire et al., (2011). From the statistical analysis of data the polynomial equations were generated. Ex-vivo drug penetration studies using rat skin showed a 2-fold increase in localization of drug in skin as compared to the marketed preparation of drug [57].

Vivek Kumar Gupta, P.K. Karar (2011) optimized the process variables like chemical properties, drug concentration, polymer concentration, cross linking agent and stirring speed for the preparation of chitosan alginate Nanoparticle [58].

Subramaniam Ramachandran et al., (2011) investigated about the antidiabetic, antihyperlipidemic and antioxidant potential from the methanol extract of Tectona grandis flowers in streptozotocin induced diabetic rats [111].

Nimesulide microemulsion based hydrogels for the topical delivery using isopropyl myristate as oil phase, tween 80 and propylene glycol as surfactant and co-surfactant was formulated by Reddy KB et al., (2011). And also they performed in-vitro and ex-vivo studies by using excised rat skins. Carbopol 934 was used to prepare the microemulsions based hydrogel for improving the viscosity of microemulsion under topical administration [95].

L.B. Jensen et al., (2011) performed in-vitro skin penetration properties of SLN in intact and barrier-impaired skin. It was revealed that there is a possibility to obtain a constant high level of drug in the skin when administered with lipid nanoparticle in comparison with an ointment [23].

Topotecan loaded lipid nanoparticle was prepared by microemulsion technique for chemical stabilization and prolonged release by L.G. Souza et al., (2011). Stearic acid
and oleic acid were used as solid and liquid lipids for the preparation of SLNs and NLCs respectively [52].

**Sandy Vrignaud** et al., (2011) prepared the novel drug delivery system for the sustained release of Doxorubicin hydrochloride by a reverse micelle-loaded lipid nanocarriers by using low-energy nano emulsification method and evaluated the parameters like size distribution, surface charge potential, TEM, freeze drying of nanoparticle, assay and encapsulation efficiency, *in-vitro* release studies [75].

**Pallavi V Pople, Kamalinder K Singh** (2011) developed a colloidal modified nanolipid carrier enriched gel and evaluated the parameters like spreadability, *in-vitro* drug release studies, *in-vivo* skin penetration studies using dermatopharmacokinetic (DPK) parameters. Compatibility and mixing behavior of lipid carrier constituents were examined by using DSC, FT-IR. NLC enriched gels showed significantly higher *in-vitro* drug release, skin permeation, and *in-vivo* bioavailability with dermatopharmacokinetic approach in guinea pigs compared to commercial ointment [46].

**Rania A Sanad** et al., (2010) formulated an Oxybenzone loaded NLCs by solvent diffusion method through $2^3$ factorial design and used for the evaluation of the prepared oxybenzone NLCs. They investigated about the effect of three independent variables namely liquid lipid type (miglyol 812 and oleic acid), liquid lipid concentration (15% and 30%), and oxybenzone concentration (5% and 10% with respect to total lipids) on the parameters like particle size, entrapment efficiency and the *in-vitro* drug release in franz diffusion cell after 8 hrs. The candidate Oxybenzone-loaded NLC dispersion was then formulated into gel by adding 1% (w/w) carbopol 934 under magnetic stirring at 800 rpm [8].

**Gregor Cevc, Ulrich Vierl** (2010) reviewed on nanotechnology and the transdermal route. They also discussed about the application of nanotechnology in transdermal drug delivery system and the role of surfactant in micelle formation [84].

The preservation of NLC and its storage condition was discussed by **Wasfy M. Obeidat** et al., (2010) [139].
Losartan Potassium transdermal Patches was formulated and evaluated for its moisture content, moisture uptake, thickness, film folding endurance, tensile strength, skin irritation, surface morphology and \textit{In-vitro} drug release performed by \textbf{Arnab Bagchi (2010)}. Skin permeation of the loaded drug through albino mice skin was studied using Kesary-Chien diffusion cell [85].

\textbf{Chih-Chieh Chen} et al., (2010) evaluated the effects of lipophilic emulsifiers on the oral administration of Lovastatin NLC and also investigated the physicochemical characterization like particle size, zeta potential, drug loading capacity, release properties and pharmacokinetics studies [13].

\textbf{Alaa Eldeen B. Yassin} et al., (2010) performed the optimization of 5-Fluorouracil SLN by double emulsion-solvent evaporation technique (w/o/w) using triglyceride esters, dynasan 118 along with soya lecithin as their lipid parts. Different formulation parameters; including types of dynasan, soyalicithin: dynasan ratio, drug: total lipid ratio and polyvinyl alcohol (PVA) concentration were studied with respect to particle size and drug entrapment efficiency [59].

SLN and NLC by hot homogenization technique followed by ultrasonication and fabricated them into transdermal hydrogels using hydrogels forming polymer like carbopol 934 (1%), xanthan gum (1%), HPC (2%) and chitosan (1%) developed by \textbf{Kesavan Bhaskar} et al., (2009). They evaluated for various parameters like particle size, zeta potential, assay, entrapment efficiency, occlusion test, high-resolution transmission electron microscopy, scanning electron microscopy, \textit{in-vitro} drug release for 24 hrs, skin membrane preparation, \textit{ex-vivo} permeation studies, \textit{in-vivo} studies, pharmacokinetic evaluation of SLN and NLC enriched hydrogels on animals, efficacy of transdermal gels against hypertension in rats, skin irritation test [48].

Flurbiprofen loaded lipid Nanoparticle by hot homogenization followed by sonication technique and then incorporated into the freshly prepared hydrogels for transdermal delivery formulated by \textbf{Kesavan Bhaskar (2009)}. The stability studies are performed for all the formulations and examined for its particle size after 90 days of storage at RT. DSC analysis were performed to characterize the state of the drug and lipid modification. Further they also evaluated for the \textit{in-vitro} drug release characteristics, rheological behaviour, pharmacokinetic and pharmacodynamic studies [49].
Antihyperlipidemic activity of *Hibiscus sabdariffa* Linn. leaves and calyces extracts in rats discussed by Pooja C Ochani and Priscilla D Mello (2009) [108].

Sarah Kuchler et al., (2009) enhanced the penetration of the drug through skin by using lipid nanoparticle. Compritol 888 ATO and poloxamer 188 are used as lipid and surfactant respectively for this study [22].

Subhashis Chakraborty et al., (2009) explained about the different approaches in the design of lipid-based formulations and also about the *in-vitro* dissolution testing methodology for lipid based drug delivery system [6].

Ander Estella-Hermoso de Mendoza et al., (2008) formulated a lipid nanoparticle by emulsification solvent evaporation method and evaluated the parameters like encapsulation efficiency, particle size, size distribution and zeta potential. Thermal analysis, differential scanning calorimetry and X-ray diffraction measurements were also performed for the freeze-dried lipid nanoparticle clearly in order to elucidate the solid state of both lipids and drug in lipid Nanoparticle [76].

The effects of cryoprotectants on the freeze-drying of Ibuprofen loaded Solid Lipid Microparticles (SLM) revealed by Lijuan Zhang et al., (2008). Glucose, Mannitol and Sucrose were chosen as the cryoprotectants. Glucose (5-15%) is proved to be the most effective one in preventing particles aggregation and in inhibiting leakage from drug-loaded particles during the SLM freeze-drying process [81].

The molecular interactions, internal structure and drug release kinetics of rationally developed polymer–lipid hybrid nanoparticle was studies by Yongqiang Li et al., (2008)[96].

Psoralen Lipid Nanoparticle (NLC and SLN) for topical delivery researched on Jia-You Fang et al., (2008). NLC showed respective mean particle sizes of about 200 – 300 nm. DSC thermograms are used to suggest the defects in the crystalline lattice of the lipid cores and smaller particle sizes [47].

Kopparam Manjunath et al., (2005) studied about the pharmacokinetics, tissue distribution and bioavailability of Clozapine SLN after intravenous and intraduodenal administration. SLN have been developed using various triglycerides (Trimyristin, Tripalmitin and Tristearin), soyalecithin 95%, poloxamer 188 and stearylamine as a
positive charge inducer by hot homogenization followed by ultrasonication method. Particle size and surface charge were measured using Malvern Zetasizer. Pharmacokinetic studies of clozapine incorporated in SLNs, after intravenous (i.v.) were done using conscious male Wistar rats [55].

Physical stability of NLC before and after incorporation into hydrogel formulations was performed by E.B. Souto et al., (2004). For the present investigation four different gel-forming agents (xanthan gum, hydroxyethylcellulose 4000, carbopol 943 and chitosan) were selected for hydrogel preparation. NLCs made from Tripalmitin were prepared by hot high pressure homogenization and then incorporated it into the freshly prepared hydrogels [17].

P. Rama Rao et al., (2003) performed a comparative study on in-vivo evaluation of Propranolol hydrochloride after oral and transdermal administration in rabbits. Transdermal patches of Propranolol hydrochloride were formulated by employing ethyl cellulose and polyvinylpyrrolidone as film formers. The pharmacodynamic (PD) and pharmacokinetic (PK) performance of propranolol following transdermal administration was compared with that of oral administration. This study was carried out in a randomized cross-over design in male New Zealand albino rabbits. The PK parameters such as maximum plasma concentration (C max), time for peak plasma concentration (t max), mean residence time (MRT) and area under the curve (AUC 0-α) were significantly (P<0.01) different following transdermal administration compared to oral administration. In contrast with the oral delivery, a sustained therapeutic activity was observed over a period of 24 h after transdermal administration in comparison with the oral administration. The relative bioavailability of Propranolol was increased about fivefold to six fold after transdermal administration as compared to oral delivery [82].

The pharmacokinetics and pharmacodynamics of Captopril from transdermal hydrophilic gels in normotensive rabbits and spontaneously hypertensive rats was evaluated by Pao-Chu Wu et al., (2000) [118].
The literature survey leads the research to the following impressions:

- It was concluded that NLC loaded transdermal patches was a novel technique to enhance the solubility and permeability of BCS class II drugs like Simvastatin and Carvedilol, which having less bioavailability.

- It shows that there was no any reproducible formulation technique for the formulation of nanostructured lipid carrier.

- It also confirms that there is no any specific reason for the selection of formulation and process variables which responsible for the formulation of stable and optimized NLC.

- Existing literatures dose not performed the in-vivo pharmacokinetic and pharmacodynamic activity of selected drugs through NLC transdermal patch dosage form.

- Hence, the objective of the present research work is to develop and characterize a Nanostructured lipid carrier (NLC) enriched Transdermal Dosage form to enhance the bioavailability of Simvastatin and Carvedilol.