REVIEW OF LITERATURE:

Ankarao et al., (2011) Mucoadhesive bilayered buccal tablets of carvedilol was prepared using HPMC, SCMC and carbpol-934 as bioadhesive polymers and EC as backing layer and was evaluated for different parameters. It was concluded that drug release was by non-fickian mechanism and mucoadhesive tablets of carvedilol can be a good approach in improving bioavailability of carvedilol by bypassing first pass metabolism\textsuperscript{10}.

Choudary S Praveen et al., (2011) conducted a study to prepared single unit bilayered floating tablet of carvedilol phosphate using compression technique and secondly use of Ocimum basilicum as a gelling agent along with HPMC and to compare the drug release with marketed formulation. The drug release was found to be 93.80\% in 24 Hrs and floating lag time around 5 min. So now floating tablets is found to be a good approach for sustained release formulation of carvedilol phosphate\textsuperscript{11}.

Bhutani S et al., (2007) conducted study which evaluated carvedilol controlled release formulation in HTn patients who are off treatment and who are taking two or more drugs. Patients were randomized as placebo, CR20mg, CR40mg, 80mg once daily. After 6 weeks BP was monitored and found that Carvedilol has a dose dependent anti-hypertensive effect which persists for 24 hrs and adverse effect profile was same for placebo and drug treated groups\textsuperscript{12}.

Weber M. et al (2007) conducted study in which carvedilol, a fast dissolving tablets were formulated by direct compression method using natural super disintegrants like plantago ovata, Lepidium sativum, fenugreek and guar gum. Formulations prepared were evaluated for pre and post compression parameters and the results showed that formulation with mucilage of plantago
ovata showed better disintegrating property and release profile was better than other formulations.\textsuperscript{13}

\textbf{Madhu Sudhan G. et al., (2009)} conducted study to evaluated better UV spectroscopic method for evaluation of carvedilol drug. Drug solubility and assay sensitivity was checked in methanol and absorbance of drug was measured at 241nm and wavelength range was 200-350nm. Linear calibration range was 50-150\%. This method was checked for carvedilol tablets and was found that it was accurate and precise and can be used for estimating drug content in carvedilol formulations.\textsuperscript{14}

\textbf{Sharma V et al., (2012)} studied calcium alginate beads of carvedilol phosphate for treatment of cardiovascular diseases was prepared and evaluated. Different calcium alginate formulations with varying polyethyleneimine concentrations was prepared and evaluated by 32 factorial design and RSM as statistical methods and it was concluded that the drug release profile was a pulsed one and that it was suitable for the treatment of chronotherpy of cardiovascular diseases.\textsuperscript{15}

\textbf{Theivarasu C. et al., (2010)} conducted study where osmotic pump capsule of carvedilol was designed. The capsule has a pore forming water soluble additives which on coming in contact with water dissolve and form porous structure. It was evaluated for different parameters and cellulose acetate was used as semipermeable membrane. It was concluded that the release of drug increased with increase in osmogent and it was proportional to level of pore former and glycerin.\textsuperscript{16}

\textbf{Agarwal V et al.,(2013)} conducted study where carvedilol compressed tablets with sustained release core and immediate release core were formulated and evaluated. Sustained release effect was achieved with HPMC and PEO WSR 205.
The powder blends were evaluated for pre compression parameters and post compression parameter were also evaluated and was found that carvedilol content in immediate release coat was released within 3 min and sustained release was seen at different times in 24 hrs\textsuperscript{17}.

Kumar G et al., (2009) stated that Oral dosage forms are more popular than any dosage forms but has many disadvantages So fast dissolving tablet dosage form was coined. In this dissolution rate is increased which increases the absorption of the drug. As carvedilol is class II drug according to BCS classification its dissolution is the rate limiting step in absorption. So effort was made in formulating the FDT of carvedilol\textsuperscript{18}.

Shah R et al., (2011) conducted study where novel liquisolid technique was made using a non volatile solvent, Carrier, coating materials and a disintegrant to enhance the dissolution of a poorly water soluble drug(Carvedilol). Liquisolid tablets of carvedilol were formulated using PEG, PG glycerin as non volatile solvent, Avicel PH 101 and 102, Aerosil as carrier and other coating materials. It was evaluated for various parameters and found that formulation containing 20% drug in PEG400 with Avicel as carrier and Aerosil as coating showed 98.4%drug release within 20min when compared to marketed formulation\textsuperscript{19}.

VESICULAR CARRIERS FOR TOPICAL DELIVERY:

In the early 1990s, a greater knowledge was gained on vesicle and many types of vesicles and vesicular derivatives have been tested for their abilities for transdermal drug delivery. Most experiments however have centered on liposomes, since derivatives only add to their basic properties. Vesicles are closed, spherical membrane that separates a solvent core from the surrounding solvent. They are typically composed of phospholipids, mainly phosphotidyl choline (PC) as in
liposome while it has been suggested that the external envelop of a liposome would allow it to pass through lipophilic, skin most researches showed that liposome vesicle become trapped within the top layer of the stratum corneum cells.

**Lboutounne et al., (2004)**: The study was conducted where liposomes were investigated in 3 formulations. The study state of TMP incorporated in each formulation was at 6hr 173+-1.06 (ethonolic solution) 120.4+-1.06(liposome) 93.82+-0.88(PLG nanospheres). The controlled values of TMP incorporate in PLG nanospheres increase the drug content in the skin. These work showed for controlling TMP release in topical activity

**Chetoni et al., (2004)**: conducted study to investigate liposomal formulation of acyclovir (ACV) in comparison with a commercial ACV ointment for topical administration. These drugs to determine the pharmacokinetic profile in the aqueous humor of rabbits after topical administration. The ACV liposome were produced a high drug concentration in aqueous humor with respect to 3 formulations containing the same ACV concentration and showed a 90 mints. In spite of much high dose (1.5vs0.18mg) AUC were produced by the strength of 3% ointment was 1.6 times greater than that of liposomal vesicle

**Bhatia et al., (2004)**: conducted study where Liposomes of tamoxifen were prepared and characterized by using Malvern mastersize, optical microscope and micromeretic the stability was tested for a period of 5 week for their drug holding capacity and were also evaluated for in-vitro skin permeation by using mice skin these result were compared with a formulation of aqueous solution and Carbopol gel contains tamoxifen in equal proportions. These result revealed that the liposome stored at 2-8°C were most stable (5% drug loss) over 5 weeks storage the solution and Carbopol gel. It was concluded that the phospholipids improve the
amphiphilic nature of the vesicle and hence modified the properties of the keratinized layer. The findings supported to be a better alternative to deal with skin problems\textsuperscript{22}.

**Khandare et al., (2001):** This study involves preparation and evaluation nimesulide niosome for topical application. Niosomes using 5 different surfactants (tween 80 and 60, span 80, 60 and 20) in different proportional by ether injection technique were prepared and studied for encapsulation efficiency after incorporating them in to gel base\textsuperscript{23}.

**Satturwiar et al., (2001):** conducted study where Ketoconazole an antifungal drugs was encapsulated has niosomes for topical application. They were made by thin film hydration technique using surfactant tween 40,80, cholesterol and ketoconazole in 5 different ratio by weight and were characterize for size shape entrapment efficiency and in-vitro drug release another set of niosomes were prepared in FAPG base and tested for in-vitro antifungal activity using cup and plate method\textsuperscript{24}.

**Arnardottir et al., (1996):** Various types of liposomes of clindamycin phosphate were made and the drug release was investigated through semi permeable synthetic membrane. A suspension of multi lamellar liposome’s (1%clindamycin phosphate) exhibited highest retention\textsuperscript{25}.

**Vora B et al., (1996):** conducted study where niosomes based transdermal system was prepared for contraceptive delivery. These compact niosomes were made by coacervation phase separation method by using spans, cholesterol with or without phospholipids and the drug levonorgestral\textsuperscript{26}.
**NOVAL VESICULAR CARRIER – ETHOSOMES:**

Classical liposomes are of little or no values as carriers for transdermal delivery because they do not deeply penetrate the skin, but rather remain confined to the upper layer of stratum corneum. Only specially designed vesicle were shown to be able to allow transdermal delivery. Ethanol is known as an efficient permeation enhancer. Discovered lipid vesicular system emboding ethanol in relatively high concentrations, which was named as ethosomes.

**Godin et al., (2004):** conducted study where Bacitracin a model polypeptide antibiotic was formulated as ethosomes in order to study the dermal and intracellular delivery for bacitracin by employing for various techniques namely scanning electron microscopy, transmission electron microscopy, differential scanning calorimetric and ultracentrifugation. Bacitracin and fluorescently labeled bacitracin ethosomes were characterized for shape, lamellarity, fluidity, size distribution and entrapment efficiency. It was informed that efficient delivery of antibiotics of deep skin from ethosomal application is highly beneficial in reducing possible side effects and other drawbacks associated with systemic treatment.

**Jain et al., (2004):** The research work involved the encapsulation ziduvudine an antiviral drug as a novel vesicle carrier ethosomes for enhance transdermal drug delivery and was evaluated by comparison with liposome. The ethosomes of ziduvudine were characterized in vitro and in vivo locally designed keshry-chien type of diffusion cell was used to study the penetration of ziduvudine on skin. Fluorescence microscopy using rhodamine123 as fluorescence probe was used to conform better skin permeability of ethosomes transdermal flux study were performed on the optimize ethosomal formulation which showed 78.5+-
2.5mg/cm²/hr. across the rat skin as compared to 5.2+-0.5 for control hydroethonolic solution drug and 7.2+-0.6ug/cm²/hr. for ethonolic drug solution from these studies it was concluded that the ethosomal formulation disrupted the skin bilayered organization this lead to enhance skin permeability which was further conformed by fluorescence microscopy\textsuperscript{28}.

\textbf{Lodzki et al., (2003):} conducted study where Cannabidiol (CBD) a new drug for treatment of rheumatic disease was designed as a transdermal delivery system as a ethosomal carrier. These CBD ethosomes were characterized by transmission electron microscopy, confocal laser scanning microscopy and differential scanning calorimetry. The result revealed that CBD phosphotidyl choline from an eutectic mixture. In vivo administration of ethosomal CBD to nude mice produced significant accumulation of drug in the skin and under laying muscle. After transdermal application to the obtain mice for 72hr steady state levels were attained in the above 24hr and lasted up to the end of the experimental at 72hr\textsuperscript{29}.

\textbf{Touitou et al.,(2001):} This investigation involved trans cellular delivery of ethosomes phospholipids vesicle carrier containing ethanol in to Swiss albino mice. It was proved by confocal laser scanning micrographs that ethosomes facilitated the penetration of all probes in to the cells as observed by the high intensity fluorescence. When incorporated with hydro ethanolic solution or classic liposome almost no fluorescence was detected\textsuperscript{30}.

\textbf{Touitou et al., (2000):} This investigation explains a novel carrier for enhance transdermal delivery ethosomal system containing phospholipids, ethanol and water. The skin permeation was demonstrated by diffusion cell experiment. Ethosomal system composing of soya phosphotidyl choline 2\% ethanol 30\% and
water were containing multi lamellar vesicle by electron microscope. NMR studies conformed the bilayered configuration of the lipids. The average vesicle size was measured by dynamic light scattering and was modulated by ultra- centrifugation proved that the ethosomes had high entrapment capacities for molecule of various lyophilicity\textsuperscript{31}.

**Dyan et al., (2000):** A novel ethosomal carrier containing trihexyphenidyl HCL (THP) was investigating for the delivery of THP from ethosomes vs classic liposomes. The THP concentration was increased from 0-3% and the size of the vesicle were measured which were found to decrease from 154 to 90 nm. This can be attributed to the surface activity of THP it was observed that ethosomes had higher entrapment efficiency fluorescent probe to the deeper layer of the skin when compared to the standard liposome\textsuperscript{32}.

**Horwitz et al., (1999):** conducted study where 5% acyclovir was formulated as ethosomes and was compared commercial 5% ACV cream zovirax and that of drug free vehicle in the treatment of recurring herpes labialis with double blind randomized clinical study. The investigation revealed the crusting with ethosomal ACV as 1.6 days significantly shorter than the time with acyclovir cream 4.3 days and that of the free vehicle 4.8 days in this arm, the loss of crust for ethosomes was shorter 3.5 days in comparison with the commercial cream 6.4 days and the drug free vehicle 6.1 days was found to not to reach statistical significant. The finding revealed to improved efficiency of the new liposome preparation when compared to zovirax cream in the treatment of recurrent herpes labials\textsuperscript{33}.

**ENHANCEMENT OF PERCUTANEOUS ABSORPTION:**

Drug penetration can, in some cases, be increased with enhancers which efficiently decrease the barrier assistance of the stratum corneum. Phospholipids
are a potential group of penetration enhancers. Being composed of natural body constituents and being biodegradable, topically administered phospholipids can be generally considered as safe. Although the behavior of phospholipids has been investigated in numerous studies, the exact mechanism is not fully understood.

**Sang-chul shine et al., (2005):** This study involved the preparation of bioadhesive Carbopol gels containing retinoic acid has sustained release formulations. Three parameters namely temperature, receptor medium, drug concentration were measured in order to study the drug release characteristics from the Carbopol gel. Direct proportionality was observed between the concentration of the drug and the drug release from the gel. Similarly direct proportionality also observed between them and drug release among the enhancer glycols and non-ion surfactants polyoxyethylene to oleylether showed the best enhance effect

**Gondaliya et al., (2002):** This research work involved the investigation and examination of the preparation as well as evaluation of nimesulide clear aqueous gels and emulsion using Acrypol940 P.A.32 factorial design for optimization of aqueous gel formulation. It was found to elicit better permeation through the rat skin. Various formulations namely clear aqueous gel formulation containing 15%w/w ethanol 20%w/w propylene glycol and 30%w/w PEG400 showed maximum drug penetrate in the range of 18-68% which was proved in vivo diffusion study. Chromophore EL, a lipophilic penetration enhancer increase the drug diffusion further percutaneous absorption was significantly improved when nimesulide was incorporated in to emulgel

**Koshela et al., (1998):** This investigation studied the enhancement of percutaneous absorption of naproxen by phospholipid; the findings revealed that the phospholipid of skin permeation of naproxen from aqueous gel further it was
found that 32% m/m of ethanol or propylene glycol in the aqueous gel formulation in the presence of phospholipid increase the percutaneous absorption of naproxen. The penetration enhancement effect of phospholipid with ethanol was however more significant that of the phospholipid with propylene glycol\textsuperscript{36}.

**RELEASE STUDY THROUGH RAT SKIN:**

Release study of drug in any topical formulation can be done by cellophane membrane, animal skin or human cadaver skin. Cellophane membrane is not good and true barrier for drug molecule as stratum corneum present in the skin. It is also reported that there is no animal skin that completely mimics the penetration characteristics of human skin. The conditions of skin can also affect the drug absorption.

**Patel et al., (1995):** conducted study where a transdermal gel employing 2% w/w Metoprolol tartrate as drug, 0.75 w/w carbopol as gelling agent Dimethyl formamide, ethanol and poly ethylene glycol absorbance enhancers were used was prepared and evaluated by using Franz diffusion cell and rat skin for all the gel formulation cumulative % release and correlated cumulative % release were calculated it was informed that all the gel showed zero order release kinetics\textsuperscript{37}. 