REVIEW OF LITERATURE

Review of past work that has been done on repaglinide and transdermal patches:

Sara Nicoli et al., [17] investigated the in vitro kinetics of release and permeation of caffeine from bioadhesive transdermal films made of polyethylene membrane impregnated with isopropyl myristate. These films are not self-adhesive but become adhesive when applied to wet skin. The data obtained in the present work suggest that caffeine release from transdermal bioadhesive films was controlled either by the permeability characteristics of the skin or by the film itself, depending on drug loading.

Amir Mehdizadeh et al., [18] evaluated different matrix, drug-in-adhesive (DIA) and reservoir transdermal formulations of fentanyl with a target of designing a suitable DIA formulation of fentanyl. Different types & amounts of liquid, Pressure sensitive adhesives (PSAs) were used and evaluated with respect to drug release and adhesive properties. It was concluded that acrylic PSAs showed the best adhesion and release properties.

Hock S. Tan et al., [19] reviewed the use of PSAs for TDDS. Adhesives are a critical component in TDDS. This review discusses the three most commonly used adhesives (polyisobutylenes, polyacrylates and silicones) in TDDS and provides an update on recently introduced TDD products and recent developments of new adhesives.

Anna M Wokovich et al., [20] provided an overview on types of transdermal delivery system, their anatomy, the role of adhesion failure modes and how adhesion can be measured to improve transdermal adhesive performance.

Adrian C. Williams et al., [21] have discussed a detailed review on Penetration enhancers which penetrate into skin to reversibly decrease the barrier resistance and improve transdermal delivery of drugs. Many potential sites and modes of action have been identified for skin penetration enhancers that are considered in this review.
Naseem Ahmad Charoo et al., [22] investigated the penetration enhancing potential of tulsi and turpentine oil on transdermal delivery of flurbiprofen. In the present work, the authors have optimized a flurbiprofen loaded binary solvent mixture composition of propylene glycol: isopropyl alcohol (30:70 v/v) which is then fabricated into a reservoir type of transdermal formulation by encapsulating the drug reservoir solution within a shallow compartment, moulded from polyester backing film & microporous ethyl vinyl acetate membrane. The prepared patches were subjected to in vitro drug permeation through rat abdominal skin & various in vivo pharmacodynamic studies. In conclusion, the turpentine oil showed superior absorption enhancing properties on rat skin as compared to the tulsi oil treated, solvent treated and normal control groups due to increased disruption of stratum corneum with negligible skin irritation.

M. Gandhimathi et al., [23] developed a simple, precise and rapid RP-HPLC method for the determination of repaglinide in pharmaceutical dosage forms. The method was carried out on a Shim-pack, RP-C18 column using a mixture of methanol: 0.1% v/v triethylamine (50:50 v/v) as mobile phase and detection was done at 235 nm using nimesulide as internal standard. The retention time (t_R) of repaglinide and internal standard nimesulide were found to be 3.40 and 2.04 min, respectively. The linearity range was 0.1 to 0.5 µg/ml.

G. D. Gupta et al., [24] prepared matrix type transdermal polymeric membrane systems of repaglinide by using eudragit NE 30D as polymer. Various formulations were prepared using oleic acid, tween-60, span-80 & isopropyl myristate as permeation enhancers at a concentration of 15% w/w based on polymer weight & subsequently evaluated for in vitro permeation enhancing effect by using 30% v/v methanolic isotonic phosphate buffer pH 7.4 as receiver phase & human cadaver skin as barrier. Different models were applied to evaluate release mechanism and kinetics. It was found that span-80 showed the best enhancement effect. Prepared patches were also evaluated for various physico-chemical characteristics.

Sunil K. Jain et al., [25] designed a controlled release system to increase its residence time in the stomach without contact with the mucosa through the preparation of floating microspheres by the emulsion solvent diffusion technique consisting of (i) calcium silicate (FLR) as porous carrier; (ii) repaglinide, an oral hypoglycemic agent;
and (iii) Eudragit S as polymer. The effect of various formulation and process variables on the internal and external particle morphology, micromeritic properties, *in vitro* floating behavior, physical state of the incorporated drug, drug loading and *in vitro* drug release was studied. Incorporation of FLR in the microspheres proved to be an effective method to achieve the desired release behavior and buoyancy. The designed system, combining excellent buoyant ability and suitable drug release pattern, could possibly be advantageous in terms of increased bioavailability of repaglinide.

Srinivas Mutalik *et al.*, [26] prepared reservoir type transdermal systems of glipizide using drug-containing carbopol gel as drug reservoir and ethyl cellulose as well as ERS100, ERL 100 and ethylene vinyl acetate (EVA) as rate-controlling membranes. The prepared patches were subsequently evaluated for *in vitro*: drug content and drug permeation studies and *in vivo* for: acute and long-term hypoglycemic activity, effect on glucose tolerance, biochemical and histopathological studies, skin irritation test and pharmacokinetic studies in mice. Based on the *in vivo* study the authors have concluded that a 1 cm² glipizide transdermal system prepared with EVA19% membrane showed a cumulative amount of 269.05µg drug permeation at the end of 24 h. Hence, a transdermal system of glipizide with an area of approximately 18 cm² would be sufficient to provide an optimum effect in humans.

Srinivas Mutalik *et al.*, [27] have prepared glipizide matrix transdermal systems for diabetes mellitus using the combinations of EC/ PVP K30 and ERL 100/ ERS 100. The systems were evaluated for various *in vitro* and *in vivo* parameters as mentioned in the above article. The *in vitro* drug release study through albino mice skin revealed that glipizide release was influenced by PVP K30 and ERL 100 content of the patches. The *in vivo* results revealed that the patches successfully prevented the severe hypoglycemia in the initial hours and they were also effective on chronic application. The present study showed that matrix transdermal patches of glipizide exhibited better *in vivo* performance than oral glipizide administration in mice as well reversing the diabetic complications.

Zoran Mandic *et al.*, [28] used potentiometric and spectrophotometric titration methods for the determination of ionization behavior, lipophilicity and solubility
profile of repaglinide. Lipophilicity profiles were evaluated by determination of partition coefficients of neutral & ionized forms of repaglinide in biphasic octanol/water system. The intrinsic solubilities of repaglinide were determined from the solubility data & temperature dependence of intrinsic solubilities were evaluated using Van’t Hoff equation. The author concludes that the log P value of 3.97 indicates high lipophilicity of repaglinide which together with the intrinsic solubility of 34 µg/ml at 37°C enables its rapid absorption from the gastrointestinal tract.

Bijaya Ghosh et al., [29] carried out in vitro iontophoretic delivery of glipizide across the pig skin. The target flux of glipizide was calculated to be 0.4147 µmol h⁻¹. As the highest flux obtained was 0.2727 µmol cm⁻² h⁻¹, the author says that glipizide is a promising candidate for iontophoretic delivery.

Ekapol Limponsa et al., [30] prepared a diltiazem hydrochloride transdermal drug delivery system by using hydroxypropyl methylcellulose (HPMC) and EC as hydrophilic & hydrophobic film formers respectively. DBP & TEC were used as hydrophobic and hydrophilic plasticizers. Effects of HPMC/EC ratios and plasticizers on mechanical & physical properties of free films were studied. Influence of various enhancers on in vitro release and permeation through pig ear skin of diltiazem HCl films were evaluated. It was found that, the film composed of 8:2 HPMC/EC, 30% DBP and 10% isopropyl myristate, isopropyl palmitate or Tween 80 loaded with 25% diltiazem HCl should be selected for manufacturing transdermal patch by using a suitable adhesive layer and backing membrane.

M.V.S. Reddy et al., [31] developed matrix-type TDDS of carvedilol using polymeric combinations of ERL/RS 100 & EC/PVP by the solvent evaporation technique. The prepared patches were evaluated for weight variation, drug content, folding endurance, % moisture content, % moisture uptake, drug-polymer interaction by FTIR/DSC studies and in vitro skin permeation studies by using rat abdominal skin. The in vivo studies in rats indicated that carvedilol patches provided steady-state plasma concentrations with minimal fluctuations & improved bioavailability of 62% (for ERL:RS 100, 8:2) and 71% (for EC:PVP, 7.5:2.5) in comparison with oral administration.
Srinivas Mutalik et al. [32] prepared matrix type transdermal patches containing glibenclamide using different ratios of EC/ PVP and ERL/ ERS by solvent evaporation technique. All the prepared patches were subjected to physicochemical studies, in vitro release and in vitro permeation studies through mouse skin. The microphotographs obtained by SEM showed the formation of pores on the surface of the patches after in vitro skin permeation studies. Based on physicochemical & in vitro skin permeation studies, the formulations with EC: PVP (3:2) and ERL: ERS (4:1) were selected for in vivo experiments. The hypoglycemic activity of the patches in comparison with oral glibenclamide administration was studied for acute (24h) and long-term (6weeks) effect in both normal and streptozocin-induced diabetic mice. Various biochemical parameters and histopathological studies were carried out in diabetic mice after treating for 6 weeks. The patches were subjected to skin irritation test, oral glucose tolerance test and pharmacokinetic evaluation in mice. The results revealed that the patches successfully prevented the severe hypoglycemia in initial hours which is the major side effect associated with oral route and maintained similar effect during long-term treatment also. The patches produced better improvement with all the tested biochemical parameters compared to oral administration. The pharmacokinetic evaluation showed that the patches could maintain almost steady state concentration of drug within the pharmacologically effective range for prolonged period of time.

Prakash V. Diwan et al., [33] developed acrylate based TDDS for glibenclamide by mercury substrate method. Patches were evaluated for its hypoglycemic activity in normal and streptozotocin induced diabetic rats in comparison with its oral therapy. In vivo results concluded that, the developed transdermal system is effective in preventing the frequent hypoglycemic episodes encountered after oral glibenclamide administration in diabetic rats.

Troy Purvis et al., [34] had produced rapidly dissolving formulations of the poorly water-soluble drug repaglinide using an innovative new technology, ultra-rapid freezing (URF), and investigated the influence of different types and levels of excipients on repaglinide stability. It was found that URF process yielded fast-dissolving formulations that were physically & chemically stable, resistant to alkali.
Michele Trotta et al., [35] prepared deformable liposomes to investigate the effectiveness of dermal administration of methotrexate (MTX). The phospholipids used to prepare the liposomes were soybean lecithin (PC) or hydrogenated lecithin (HPC) and dipotassium glycyrrhizinate (KG) as surfactant. Liposomes size, entrapment efficiency and MTX release through dialysis membrane were determined and the interaction between MTX and liposomes was investigated using DSC. The MTX amount permeated through pig skin were three to four fold higher using liposomes containing KG compared to those from water solution or normal liposomes. These results suggest that liposomes containing KG may be of value for the topical administration of MTX in the treatment of psoriasis.

Shashikant D Bharhate et al., [36] Transdermal patches of carvedilol were prepared by using combination of polyvinyl alcohol (PVP) and polyvinyl pyrrolidone (PVP K30) along with glycerin, polyethylene glycol 400 and propylene glycol as plasticizers. The prepared formulations were evaluated for thickness, drug content uniformity, folding endurance, percent elongation at break, tensile strength, in-vitro permeation studies. It was observed that the system with PVA:PVP in the ratio 8:6 along with used plasticizers was a promising controlled release transdermal drug delivery system for carvedilol. Formulated transdermal patches of carvedilol, exhibits zero-order release kinetics.

Amir Mehdizadeh et al., [37] evaluated different matrix, drug-in-adhesive (DIA) and reservoir transdermal formulations of fentanyl with a target of designing a suitable DIA formulation of fentanyl. Different types & amounts of liquid, pressure-sensitive adhesives (PSAs) were used and evaluated with respect to drug release and adhesive properties. It was concluded that acrylic PSAs showed the best adhesion and release properties.

Anna M Wokovich et al., [38] provided an overview on types of transdermal delivery system, their anatomy, the role of adhesion failure modes and how adhesion can be measured to improve transdermal adhesive performance.

Umesh D Shivhare et al., [39] Transdermal films of carvedilol were prepared by using Eudragit RL100 (ERL100) either alone or in combination with Eudragit RS100 (ERS100), hydroxypropyl methylcellulose K15LV (HPMC), and ethyl cellulose (EC).
The drug release was extended over a period of 24 h from all formulations. The formulation A5 showed 98.33 cumulative % drug releases in 24 h and followed zero order kinetics. The drug transport mechanism was observed to be Fickian. The cumulative % drug diffused through artificial permeation membrane (cellophane A 393) from same formulation was 100.52 % over a 12 h. The mechanism of drug release was governed by Peppas model and the drug diffusion rate followed zero order kinetics. The formulation A5 comprising of polymers ERL 100, ERS 100, EC and HPMC in 7:1:1:1 ratio fulfills the requirement of good TDDS.

Bijaya Ghosh et al., [40] carried out in vitro iontophoretic delivery of glipizide across the pig skin. The target flux of glipizide was calculated to be 0.4147 µmol h$^{-1}$. As the highest flux obtained was 0.2727 µmol cm$^{-2}$ h$^{-1}$, the author says that glipizide is a promising candidate for iontophoretic delivery.

Ubaidulla U. et al., [41] has studied the effect of iontophoresis and permeation enhancer on Carvedilol from Transdermal films. And concluded that the combination of permeation enhancers and iontophoresis could be useful for increasing the skin permeability of Carvedilol through the matrix TDDS.

Tashiro Y. et al., [42] has studied effect of lipophilicity on in-vivo iontophoretic delivery of β blockers. In many β -blockers, the relationships between plasma drug concentrations and pharmacological effects (decreasing heart rate and blood pressure, etc.) has been estimated and the effect of drug properties on the absorption processes in the iontophoretic transdermal delivery of beta blocker.