CHAPTER 2

2.1. M. Bharkatiya, et al [38].

Prepared and evaluated TDDS patches without drug, to studied effect of plasticizers on physical charactarics of TDD Patches to investigate their possibility. DBP, PEG 400, PG used as plasticizers. Drug free TDD patches are prepared and evaluated for average weight, average thickness, and percentage of flatness, surface pH, swellability, and skin irritation.

The maximum formulations were shown 100% of flatness. Higher Swellability, WVTR was observed in patches with PVP: HPMC K4M with PEG 400. The patches were observed to free from irritation of skin.

Reasonably concluded that plasticizers have a greater influence on the physical characteristics of TDD patches.

2.2. Pravin et al [39].

The investigation reported that TDD patches of Enalapril using hydrophilic polymers. The mixture of acetone and distilled water (9:1) used as solvent for formation of films and Glycerin as a plasticizer.

The matrix types of patches prepared on 5x5 cm fabricated glass. Thickness, weight to be increased with increasing polymeric grade and ratio in formulation. FTIR, DSC results confirm that there is no any considerable reaction in drug - excipients. The Enalapril maleate release characterized by performing ex vivo drug release across rat and cadaver skin by Franz diffusion cell, in this 1cm$^2$ diameter of patch was used. Diffusion medium is buffer pH 7.2, temperature 37±1°C, agitation speed is 50 rpm maintained.

In vitro dissolution conducted by USP type of dissolution test instrument it was equipped with fractional collector; the test patch assembly was very carefully positioned in vessel. The periodically collected samples and analyzed at 207 nm. In vitro reports observed to follow Higuchi kinetics. Ex vivo results were obtained on rat skin, human skin the diffusion studies which were showed significant difference.

2.3. Mario Grassi et al [40].

This reported literature deal with physical and mathematical modeling description of drug release. The structure of matrix and topology are matched and
analyzed three-dimensional network, in this framework, the release mechanisms are calculated with import key factors, e.g. Matrix swelling, erosion, dissolution (recrystallization), drug–polymer interaction, drug diffusion, early drug distribution and particle size distribution of powdered matrix systems.

The attention is mainly focused on theoretical approaches concerning matrix swelling equilibrium and kinetics, drug dissolution, drug permeation, drug polymer reaction, initial drug distribution, matrix erosion.

This review notes the acquaintance of the phenomenon ruling drug release matrix systems is appropriate from both the physical and modeling point of view, although further developments are forever possible and desirable.

2.4. K. Basavaraj et al [41].

This paper described TDD patches of Ondansetron. The TDD patches made by different polymers on mercury substrate. The study also extended for investigation of influence of plasticizer (DBP and PG) and penetration enhancer by using kesharychein diffusion cell.

In vitro experiments conducted on rat skin. The study results indicated that hydrophilic polymer better drug release than the liphophilic polymers and both polymers combinations used. The drug release found to be following first order kinetics. And also permeation enhancer formulations found to better permeation enhancement.

2.5. Amir Mehdizadeh et al [42].

The research is to formulate and evaluate new drug-in-adhesive (DIAPs) fentanyl Patches. Reservoir Patch (RPs) consists of a backing layer, drug reservoir, and rate controlling membrane and covered with protective release liner. The drug may exist as either in liquid form or a gel form or dispersed in a polymeric material, for this used full factorial design.

This is simple and accurate method, they have easy peel test at 180°, designed to measure, evaluate adhesive properties of TDD patches. In vitro study by dissolution apparatus. The released drug estimated by HPLC. Results showed that kinetics obeyed the Higuchi model, which indicating the diffusion CDD mechanism.
This investigation to found that amount of fentanyl needed for each 10 cm² (3.3 mg) per three-days (DIAP).

2.6. Jitendra Banweer et al [43].

They reported that topical delivery of Lisinopril dihydrate by incorporation of penetration enhancer. Lisinopril dihydrate is low bioavailability. This can overcome by route of administration change, suggested that TDD of drugs. TDD patches prepared by HPMC, PVA (50:50), glycerol as plasticizer and water-methanol (70:30) used as solvent to solubilized incorporated components. DMSO and PG were added in combinations but ratios are different as penetration enhancers.

In vitro diffusion studies performed through goat skin. Methanol: distilled water (30:70) used as diffusion medium; temperature maintained at 37°C, the collected samples were evaluated at 560 nm by spectrophotometer. The patch contain DMSO: PG (70:30), in 10% showed desired % of drug release per 24 hr, all patches were showed excellent physical and chemical properties. This investigation to conclude that TD release of Lisinopril dihydrate offer best control release of drug, formulation containing DMSO: PG in 10 % was showed high flux rate.

2.7. IS Iman et al [44].

Reported that TDD patches of chlorpheniramine maleate followed by $2^4$ factorial design, in which CA and EC used as polymers, PEG 400, PG used as plasticizer.

The TDD patches prepared and tested for thickness, weight, tensile strength, Stability study. Dissolution test was conducted in 900 ml of phosphate buffers at temperature 32°C, at100 rpm by USP II dissolution apparatus. The obtained samples were measure at 261 nm spectrophotometrically. They conducted ex vivo studies through rabbit ear skin.

They conducted in vivo and B.A studies using New Zealand white rabbit’s average weights in range of 2-2.25 kgs. Cross over design six rabbits divided in to two groups one group administered with TDD patch and another group treated with oral tablet. The collected samples used for isolation of plasma and then drug content estimated by using HPLC.
Finally compared bioavailability of CPM Transdermal system with CPM oral tablets. They found that patch has better bioavailability than oral dose.

2.8. Rakesh P. et al [45].

Developed matrix-type of TDD system of aceclofenac by mixing of different parts of HPMC and EC polymers, in this 15% DBP is added as plasticizer and the oleic acid, isopropyl myristate are used for enhancing penetration of active moiety. The formulation by HPMC and permeation enhancer was shown good in vitro (Wistar albino rat). This investigation conclude that (15 %) oleic acid and (10 %) Isopropyl myristate containing formulas were showed desirable amnt of drug release through rat skin.

2.9. Jeevana Jyothi B. et al [46].

Propranolol hydrochloride was developed successfully as prolonged release transdermal gel by using different polymers, Maltodextrin, span 40, span 60 and cholesterol by slurry, slow stirring method. These are prepared as proniosomal gels by using carbopol 940 by simple stirring.

The gels were evaluated for entrapment efficiency, In vitro skin permeation studies, scanning electron microscopy (SEM) analysis, vesicle size analysis, drug excipients interaction studies and Pharmacokinetic studies by using male wistar rats.

All formulations exhibited similar diffusion characteristics, but F5 was considered as promising formulation because 20% amount of drug released in 2 hrs which is deemed to be required for providing initial loading dose with in 2 hrs for controlled drug delivery system and also. Formulation F5 evidenced 81.26% of drug release and it is considered as promising formulation with ideal prolonged release for 12 hrs. The in vitro kinetic data found to be non fickian diffusion.

The pharmacokinetic parameters were calculated from the plasma concentrations of the drug and Peak plasma concentration, Cmax was found to be 526.24 ng/ml and tmax was 12 hrs, AUC0-α 24 was found to be 9403.58 ng. h/ml and AUC0-α was 14581.86 ng.hr/ml. Elimination rate constant (Ke) calculated from semi logarithmic plot was found to be 0.053 hrs⁻¹. Elimination half life (t1/2) was found to be 13.08 hrs.
2.10. D. Prabhakar. et al [47].

In this investigation developed Tizanidine hydrochloride ethosomes in suspension using different ratios of soya lecithin, ethanol and cholesterol by following cold method. The best ethosomes formulated in transdermal patches form by addition of suitable quantity of HPMC E15 as film forming agent and triethyl citrate as plasticizer. All these formulations are characterized by performing different evaluation tests e.g. Drug-excipients compatibility, entrapment efficiency, vesicle size and shape, zeta potential, in vitro drug release and stability.

Ethosomal suspension: Ethosomal suspension was prepared by dissolving Tizanidine hydrochloride, phospholipids (soybean lecithin) and cholesterol in ethanol. Propylene glycol was added during mixing, this ethanolic mixture was heated at 30°C in a water bath. Where as in another beaker, distilled water also heated at 30°C. This heated water was slowly added to ethanolic mixture of Tizanidine hydrochloride with continuously stirring at 700 rpm. The solution was allowing the formation of vesicles.

Preparation of Ethosomal Patch: Ethosomal patches were prepared by dissolving the weighed amount of HPMC E15 in solvent mixture of dichloromethane (DCM) and methanol (M) (1:1) on magnetic stirrer, then to added 3.75 ml of ethosomal suspension during stirring to get uniform mixing of suspension with polymer solution, after formation of homogenous mixture incorporated triethyl citrate as plasticizer then again continuously mixed to obtained uniform mixture, this solution was poured into moulds and allow for drying for 24 hrs at room temperature and the obtained patches were stored in desiccators. FTIR studies were showed no incompatibility between drug and excipients. The size of the ethosomes was found in the range of 217.0 nm to 472.7 nm and the entrapment efficient was found in the range of 33.98 ±0.68 to 65.69 ±0.39%. Zeta potential of optimized formulation ET5 and ET10 was found to be -39.7 and -42.1 respectively; high zeta potential prevents the aggregation between vesicles and enhances its physical stability. The stability studies of optimized formulations ET5 and ET10 were shown no significant change in entrapment efficiency. In vitro drug release of ethosomal suspensions were shown in the range of 60.12±0.23 to 95.61±2.59% per 24 hrs. The in vitro drug release of ethosomes patches were found in the range of 5.23±0.59 to 89.17±0.45% per 24 hrs. Thus ethosomes creating a new opportunities for topical application of Tizanidine hydrochloride.