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DESIGN AND INVITRO CHARACTERIZATION OF REPAGLINIDE TRANSDERMAL PATCHES

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ABSTRACT

TDDS are noninvasive and controlled release methods of delivering drugs to patients, improving compliance and therapeutic effectiveness. Repaglinide, a short-acting insulin secretagogue used to treat type 2 diabetes mellitus, was used in this study to formulate and evaluate a transdermal gel. A preformulation study was conducted to confirm that Repaglinide was compatible with the selected polymers and excipients. Physical properties of the gel formulations, including pH, viscosity, spreadability, and uniformity of drug content, all met acceptable standards for topical applications. Compared to other formulations, the gel formulation containing HPMC exhibited the highest drug release and permeation rates. Differential Scanning Calorimetry (DSC) and Fourier Transform Infrared Spectroscopy (FTIR) analyses confirmed that Repaglinide is stable within the gel matrix and does not interact with the polymer. Transdermal gel containing Repaglinide developed in this study provides sustained drug release and improved therapeutic outcomes for patients with type 2 diabetes.

Key words: Repaglinide, Transdermal Drug Delivery System, Sustained Release, Gel Formulation.

INTRODUCTION

The development of transdermal drug delivery systems (TDDS) has proved to be an attractive alternative to conventional oral and parenteral drug delivery methods due to their ability to deliver medications controlled and sustained, improve bioavailability, and improve patient compliance by reducing the frequency of dosage (Karl, D. M. *et al.*, 2002 & Davies, M. J. *et al.*, 2009). A TDDS bypasses the first-pass metabolism, resulting in more consistent plasma levels and fewer gastrointestinal side effects. (Prausnitz, M. R., *et al.*, 2008) As an oral insulin secretagogue, repaglinide faces challenges such as low bioavailability and frequent dosing when used to treat type 2 diabetes.

This problem could be addressed by developing a transdermal gel formulation of repaglinide (Aulton, M. E., *et al.* 2013).

Repaglinide has a short plasma half-life and requires multiple daily doses to control blood glucose. Due to extensive first-pass metabolism in the liver, it has a limited oral bioavailability (Finnin, B. C., *et al.*, 1999). Repaglinide can be delivered transdermally to overcome these limitations by ensuring sustained release, enhancing its bioavailability, and reducing dose frequency (Kalia, Y. N., *et al.*, 2001).

To ensure effective drug penetration through the skin, repaglinide is formulated into a transdermal gel using suitable polymers and penetration enhancers.

As part of this study, a transdermal gel containing repaglinide will be formulated and evaluated, with a focus on optimizing the formulation for optimal drug release and

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permeation. In vitro drug release and permeation profiles will be determined for the prepared gels based on their physical properties, pharmaceutical content, viscosity, and physical properties. In order to improve patient compliance and therapeutic effectiveness in the treatment of type 2 diabetes, we intend to develop a robust transdermal delivery system for repaglinide (Williams, A. C., *et al.*, 2004 & Kydonieus, A. F., *et al.*, 1987).

MATERIALS AND METHODS

Materials Used

Repaglinide, Eudragit RL 100, Eudragit RS100, Eudragit RLPO, Acetone, Ethyl acetate, Dichloromethane, Chloroform, Dibutyl phthalate, Aloe juice, Sodium CMC (200-300 cps), Carbopol 934, Hydroxy propyl methyl cellulose (50 cps), Methyl cellulose (28-32%), Tween 20, DMSO, Olive oil, Sodium hydroxide, Potassium dihydrogen phosphate, Potassium chloride, Calcium chloride.

Equipments Used

U.V. spectrophotometer, Analytical balance, Ultra sonicator, Magnetic stirrer, Hot air oven, pH meter, Brook field viscometer.

Estimation of Repaglinide:

The following official methods are available for the estimation of Repaglinide.

HPLC method, Capillary zone electrophoresis, Gas chromatography, U.V. method, Colorimetry.

A spectrophotometric method based on the measurement of extinction at 247 nm in 7.4 phosphate buffer was used in the present study for the estimation of Repaglinide from the diffusion fluids (Raghuraman S, *et al.* 2002).

Standard solution:

100 mg of Repaglinide was dissolved in 7.4 phosphate buffer in a 100 ml volumetric flask and the solution was made up to the volume with 7.4 phosphate buffer.

Construction of calibration curve:

The standard solution of Repaglinide was subsequently diluted with 7.4 phosphate buffer to obtain a series of dilutions containing 2, 4, 6, 8 and 10 µg of Repaglinide per ml of solution. The absorbance of the above dilutions was measured in Shimadzu double beam UV spectrophotometer at 247 nm using in 7.4 phosphate buffer as blank.

Preparation of drug free films of

Eudragit RL 100, eudragit Rs 100 and eudragit RLPO

Casting on mercury surface technique was employed for the preparation of drug free films. The films were prepared by dissolving the polymer (Eudragit RL100, Eudragit RS 100 and Eudragit RLPO) in various solvents

namely acetone, chloroform, dichloromethane and ethyl acetate. Dibutyl phthalate at a concentration of 15%w/w of polymer was used as a plasticizer in the preparation of films. 8ml of the casting solution was poured in a glass bangle (6.2cm diameter) containing mercury placed on a horizontal flat surface. The rate of evaporation was controlled by inverting a funnel over the petri plate. After 24hrs the dried films were taken out and stored in a desiccator.

EVALUATION OF RATE CONTROLLING MEMBRANE

All the rate controlling membranes were evaluated for the following parameters

Physical appearance and Thickness uniformity:

The films were visually inspected for colour, clarity, flexibility and smoothness. The free films prepared were evaluated for physical appearance by visual observation. The thickness of the films was measured by a 'Screw gauge'. The mean of the five observations were calculated. .

Folding Endurance:

The folding endurance was measured manually for the prepared films. (Utsumi, I, *et al.* 1961) A strip of film (2x2 cm) was cut evenly and repeatedly folded at the same place till it broke. The number of times the film could be folded at the same place without breaking gave the exact value of folding endurance.

Water Vapour Transmission (W.V.T) Rate:

For this study, vials of equal diameter were used as transmission cells. These cells were washed thoroughly and dried in an oven. About 1.0 g of calcium chloride was taken in the cell and the polymeric films measuring 3.14 Cm² area were fixed over the brim with the help of an adhesive (Fites A.L. *et al.*, 1970).

Drug Diffusion Study:

Drug diffusion study was conducted using Franz diffusion cell⁴. The receptor compartment was filled with 15 ml of phosphate buffer having pH 7.4 as diffusion media. Polymeric film was mounted on the donor compartment with the help of an adhesive.

Permeability Coefficient:

From the drug diffusion data the permeability coefficient for various films was calculated (Chakkapan S, *et al.*, 1994).

Formulation Of Drug Reservoir Gels From Aloe Juice:

Different drug reservoir gels were formulated. The central parenchymatous pulp was scooped out with a spatula from the aloe leaves and the pulp was washed repeatedly with water and finally washed with 0.1N

sodium hydroxide (NaOH) solution to elevate the p^H of aloe pulp, which is highly acidic due to presence of acemannan. The treated pulp was placed in a blender to obtain the juice. The obtained juice was prefiltered using a cotton bed to remove left over rind particles. Then the juice was subjected to repeated vacuum filtration until a clear liquid was obtained. To the clear liquid obtained, required quantities of polymer were weighed and dispersed uniformly ensuring that no lumps of polymer were left. Specified amount of Repaglinide, sodium benzoate were weighed accurately and added into the polymer dispersion slowly with continuous trituration to obtain a gel. In case of carbopol gel, specified amount of carbopol 940 was soaked in 20 ml of aloe juice overnight to form lump free mixture, which is allowed to stand to free entrapped air. Carbopol gellifies under alkaline conditions, a solution of 0.5N NaOH was added drop wise until a gel was formed. The resulting gels were filled in collapsible tubes in a dark room to prevent photo oxidation.

EVALUATION OF DRUG RESERVOIR GELS:

The drug reservoir gels were evaluated for the following parameters

Drug content (Sankar V, et al., 2005):

The Repaglinide gel (1gm containing 50 mg) was dissolved in 50 ml of phosphate buffer (pH 7.4) solutions. The absorbance was measured after suitable dilution at 247 nm against the corresponding blank solution. The blank solutions were prepared with gels free from drug.

p^H and viscosity (Sakarkar D M, et al., 2004):

The pH of the dispersion was measured using pH meter (Systronics Digital –DI-707). The pH of the gels were measured before and after the incorporation of the drug. Viscosity of the gels was determined using a Brook field viscometer. In the present study, gels were subjected to a shear rate ranging from 10 and 90% .The rheogram and viscosity were obtained with the software rheocal.

Extrudability (WankhadeVikranth P, et al., 2010):

Closed collapsible tubes containing gel was pressed firmly at the crimped end. When the cap was removed gel extrudes until pressure is dissipated. The weight in grams that was required for extruding 0.5 cm of ribbon of gel in 10 seconds was determined. The results for all the formulations were recorded as extrusion pressure in grams.

Spreadability (Panigrahi L, et al., 1997):

Spreadability of formulation was determined with the apparatus proposed &fabricated by Multimeret al. It consists of wooden block provided with two glass slides. Lower slide was fixed on wooden block and upper slide with one end was tied to glass slide and other end tied to weight pan. A gel equivalent to 2.5 g was placed between two slides and 1000 g weight was placed over it for 5 minutes to press the sample to a uniform thickness. 100g of weight was added to pan. The time (in seconds) required to separate the two slides was taken as a measure of Spreadability. Shorter time interval to cover the distance of 7.5 cm indicates better Spreadability.

Drug diffusion study:

Drug diffusion study was conducted using Franz diffusion cell. The receptor compartment was filled with 15 ml of phosphate buffer having pH 7.4 as diffusion media. Eudragit RLPO film was mounted on the donor compartment with the help of an adhesive. 0.5 g of the gel (25 mg of Repaglinide) was taken into the donor compartment. Dialysis membrane was kept between the receptor compartment and the donor compartment. Magnetic stirrer was set at 50 rpm and whole assembly was maintained at 32 ± 0.5 °C. The amount of drug released was determined by withdrawing 1 ml of sample at regular time intervals for 3 hours. The volume withdrawn was replaced with equal volume of fresh buffer solution. Samples were analyzed for drug content using a UV spectrophotometer at 241 nm for Repaglinide.

Preparation and Characterization Of Gels Containing Permeation Enhancers:

Three different permeation enhancers namely olive oil, dimethyl sulfoxide and tween 20 were incorporated into the gels. These gels were also evaluated for drug content, pH and viscosity, Extrudability, Spreadability and diffusion studies.

Drug polymer Interaction studies:

The IR spectra for the Repaglinide, Eudragit RLPO sodiumcarboxy methyl cellulose and developed transdermal formulations were recorded on JASCO FT-Infra red spectrophotometer using KBr pellet technique (1:100) at the resolution rate of 4cm^{-1} . Spectrum was integrated in transmittance mode at the wave number range 400 to 4000cm^{-1} .

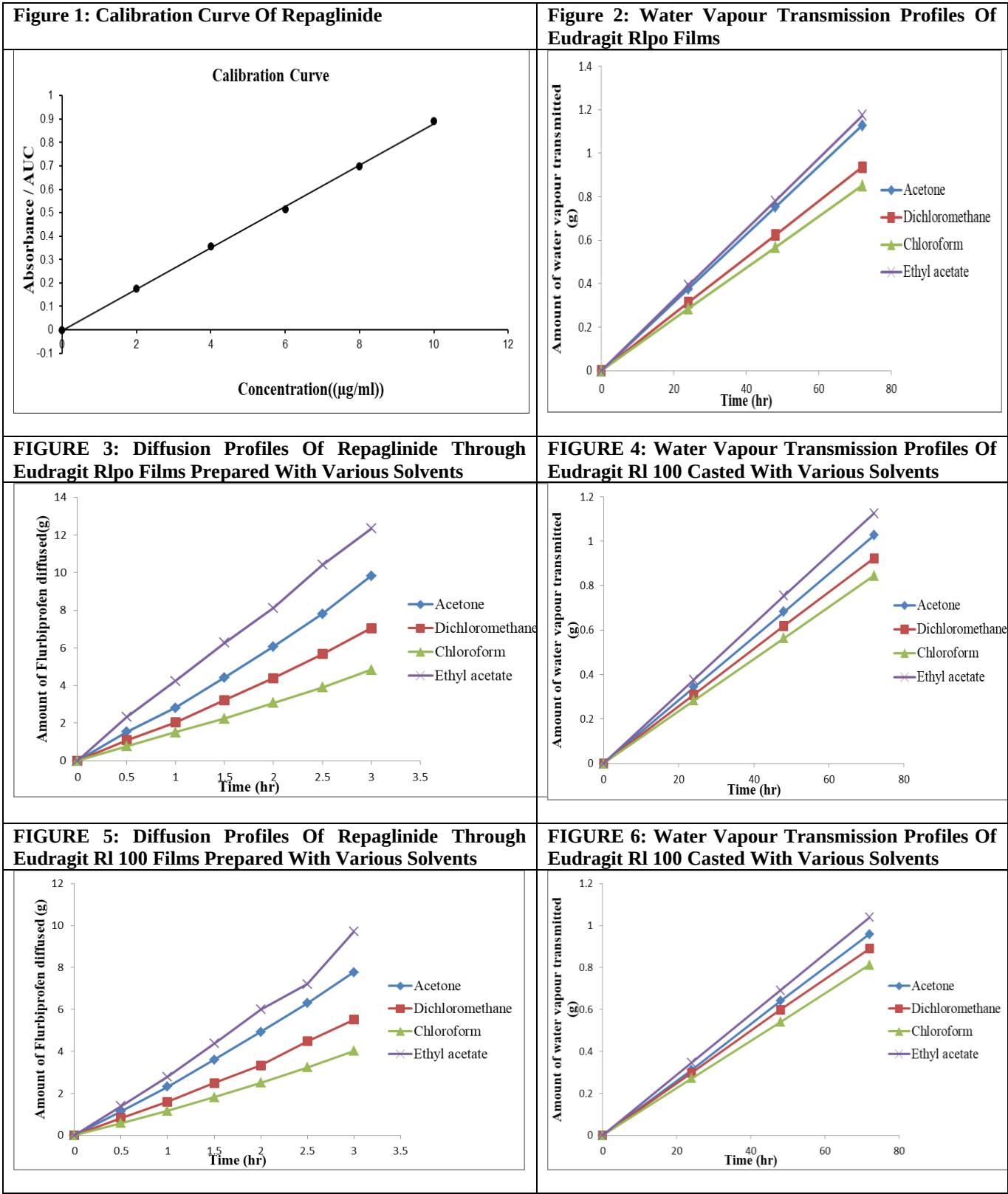
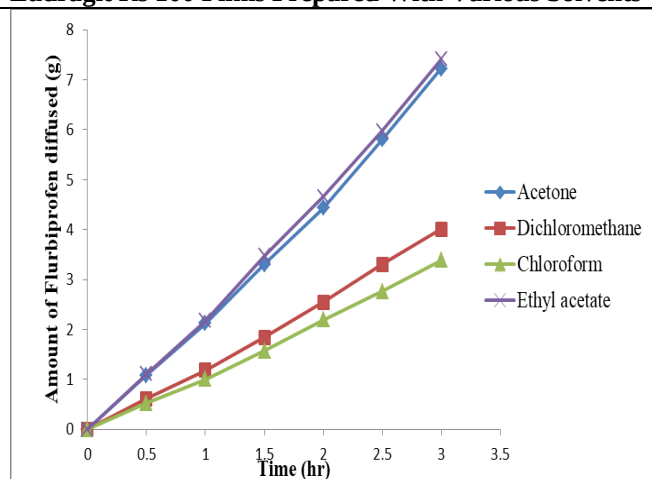
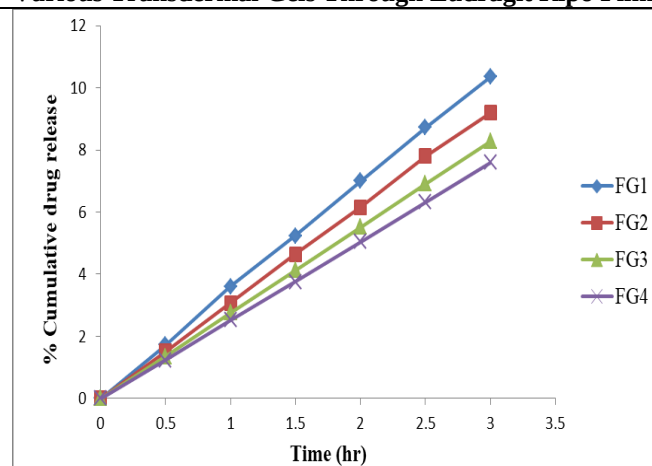
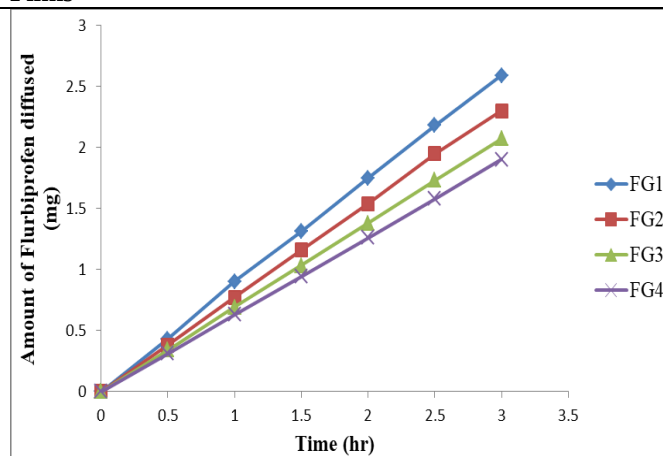
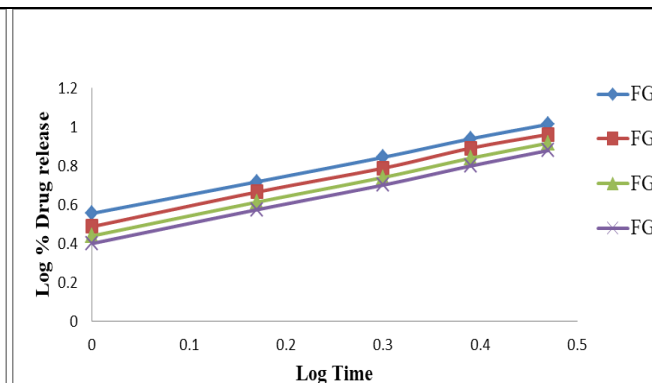


FIGURE 7: Diffusion Profiles Of Repaglinide Through Eudragit Rs 100 Films Prepared With Various Solvents**FIGURE 8: Diffusion Profiles Of Repaglinide From Various Transdermal Gels Through Eudragit Rlpo Films****FIGURE 9: Zero Order Plot Of Repaglinide From Various Transdermal Gels Through Eudragit Rlpo Films****FIGURE 10: Peppas Plot Of Repaglinide From Various Transdermal Gels Through Eudragit Rlpo Films****FIGURE 11: Diffusion Profiles of Repaglinide From Transdermal Gels Containing Different Permeation Enhancers Through Eudragit Rlpo Films****FIGURE 12: Zero Order Plot Of Repaglinide From Transdermal Gels Containing Different Permeation Enhancers Through Eudragit Rlpo Films**

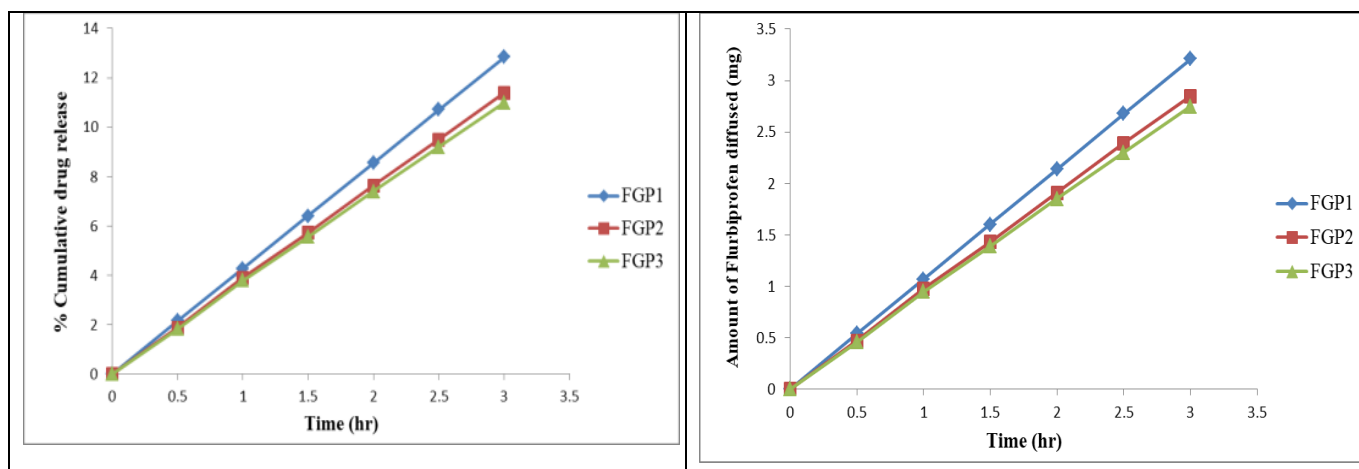


FIGURE 13: Peppas Plot Of Repaglinide From Various Transdermal Gels Containing Different Enhancers Through Eudragit Films

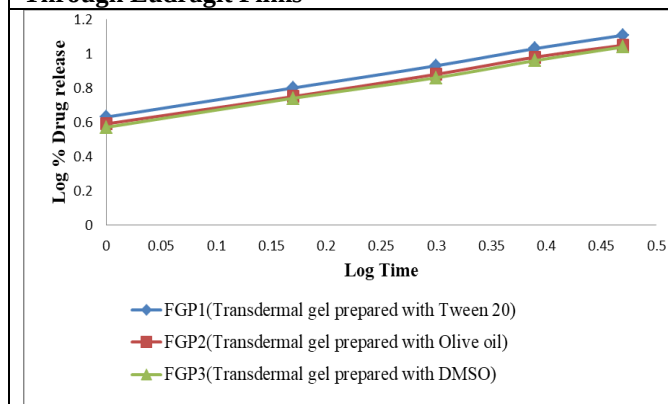


FIGURE 15: ZERO ORDER PLOT OF OPTIMIZED FORMULATION (PGP1)

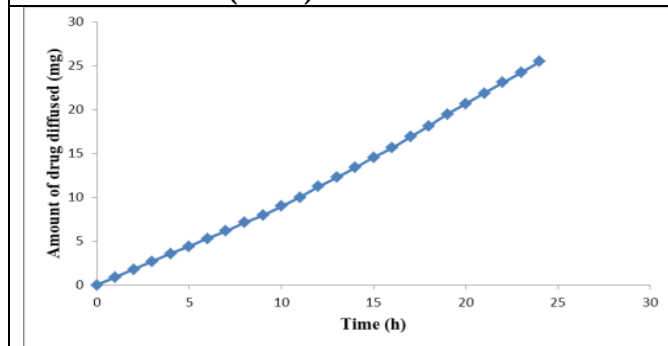


FIGURE 14: DIFFUSION PROFILE OF OPTIMIZED FORMULATION (PGP1)

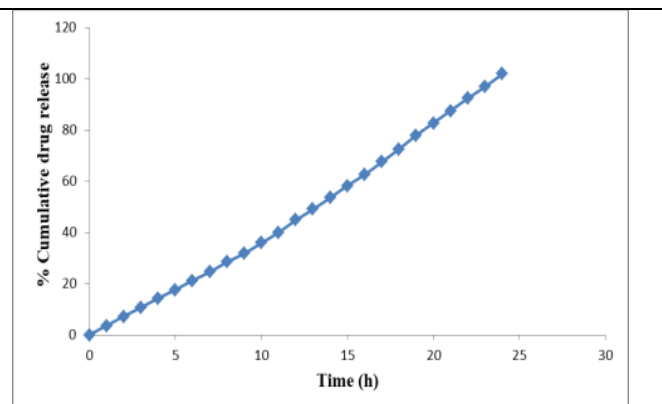
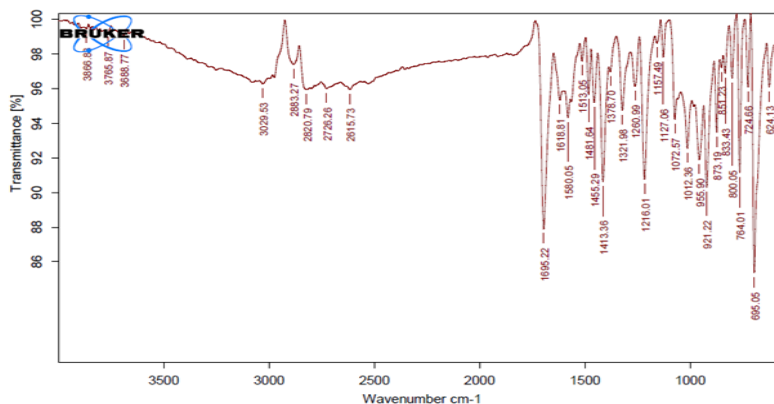


FIGURE 16: IR SPECTRA OF PURE DRUG (REPAGLINIDE)

FIGURE 17: IR SPECTRA OF OPTIMIZED FORMULATION



CONCLUSION

The present investigation has been directed at the development of transdermal formulations for Repaglinide and its controlled release characterization evaluation. The in vitro drug diffusion studies were employed to determine the drug release characteristics of the above formulation and it was found to be provided slow and controlled release over 24 hrs. The drug release

characteristics from the formulation were found to be dependent upon polymer, casting solvent, plasticizer and permeation enhancer incorporated in the formulation. Upon the fulfillment of major objective of the present investigation, the transdermal formulations of Repaglinide are directed for controlled drug delivery and to improve the bioavailability.

REFERENCES

1. Karl, D. M. The efficacy and safety of repaglinide in type 2 diabetes mellitus. *Clinical Therapeutics*, 24(3); (2002): 473-490.
2. Davies, M. J., Jarvis, J., & Piya, M. K. Newer agents for blood glucose control in type 2 diabetes: focus on the early phase. *Expert Opinion on Pharmacotherapy*, 10(15); (2009): 2433-2450.
3. Prausnitz, M. R., & Langer, R. Transdermal drug delivery. *Nature Biotechnology*, 26(11); (2008): 1261-1268.
4. Aulton, M. E., & Taylor, K. M. G. Aulton's Pharmaceutics: The Design and Manufacture of Medicines. *Elsevier Health Sciences*. (2013).
5. Finnin, B. C., & Morgan, T. M. Transdermal penetration enhancers: applications, limitations, and potential. *Journal of Pharmaceutical Sciences*, 88(10); (1999): 955-958.
6. Kalia, Y. N., & Guy, R. H. Modeling transdermal drug release. *Advanced Drug Delivery Reviews*, 48(2-3); (2001): 159-172.
7. Williams, A. C., & Barry, B. W. Penetration enhancers. *Advanced Drug Delivery Reviews*, 56(5); (2004): 603-618.
8. Kydonieus, A. F., & Berner, B. Transdermal Delivery of Drugs. *CRC Press*. (1987)
9. Raghuraman S, velrajan R, Ravi B, Jeyabalan D, Benito J, Shankar V. Design and evaluation of propranolol hydrochloride buccal films. *Ind. J. Pharm. Sci.* 64(1); 2002: 32-6.
10. Utsumi, I, Ida, T, Takahashi, S and Sugimoto, Water vapour transmission properties of polymeric materials N, *J. Pharm. Sci.* 50;1961; 592-597.
11. Fites A.L. Banker G.S. and Smolen V.F Controlled Drug release through Polymeric films, *J. Pharm. Sci.* 1970; 59(5): 610-613.
12. Chakkapan S,Gandhi K, Thomas S,Katkam RR, Shrivastava R. Studies in transdermal drug delivery systems for estradiol. *Indian J Pharm Sci.* 1994; 56(4): 122-55.
13. Sankar V, Chandrasekharan A K, Durga S. Formulation and stability evaluation of diclofenac sodium ophthalmic gels. *Indian J. Pharm. Sci.* 2005; 67(4): 473-76.
14. Sakarkar D M, Shrikhande V N. Studies on formulation development, characterization and transdermal permeation of nimesulide from emulgel. *Int. J. Pharm. Excip* 2004; 3(3): 57-61.
15. WankhadeVikranth P, BobadeNishan N, AtramSandip C, Pande S.D, Trapar K.K. Development and evaluation of cosmeceutical hairstyling gel. *Journal of Pharmacy Research.* 3(12): 2010; 3045-3050.
16. Panigrahi L, John T, Hiremanth SRR. Formulation and evaluation of lincomycinHCl gels. *J. Pharm. Sci.* 59: 1997; 330-34.