INTERNATIONAL JOURNAL OF PHARMACEUTICAL RESEARCH AND DEVELOPMENT (IJPRD)
Platform for Pharmaceutical Researches & Innovative Ideas
www.ijprd.com

TRANSDERMAL APPROACH OF ANTIDIABETIC DRUG GLIBENCLAMIDE:A REVIEW

ANKIT SHARMA[*1]

[1]Indore institute of pharmacy, indore

ABSTRACT

Transdermal drug delivery system (TDDS) provides a means to sustain drug release as well as reduce the intensity of action and thus reduce the side effects associated with its oral therapy. Transdermal drugs are self-contained, discrete dosage form .

Diabetes Mellitus is a chronic metabolic disorder characterised by high blood glucose concentration hyperglycemia caused by insulin deficiency. often combine with insulin resistance.

WHO report- WHO projects 346 million people worldwide have diabetes. In 2004, an estimated 3.4 million people died from consequences of high blood sugar. Glibenclamide is a potent oral sulfonylurea hypoglycemic agent. It has to passess some physiochemical properties which cause capable of facilitating the sorption of drug by the Stratum corneum. Glibenclamide (M.W. 494.004 g/mol) and negligible skin degradation. Therefore controlled released Transdermal prepration of Glibenclamide was prepare to give sustain effect as compared to conventional multiple oral dosing. It is currently available for treating hyperglycemia in Non insulin dependent Diabetes Mellitus (NIDDM-type 2)

Keywords: Transdermal drug delivery system, Diabetes Mellitus, Glibenclamide**,** Antidiabetic agent.

Correspondence to Author

ANKIT SHARMA

ADD. 333 SMRITI NAGAR, AIRPORT ROAD,INDORE ,452005

Email: ankttsharma2030@gmail.com

INTRODUCTION

Throughout the past two decades, the transdermal patch has become a proven technology that offers a variety of significant clinical benefits over other dosage forms. Transdermal drug delivery offers controlled release of the drug into the patient, it enables a steady blood-level profile resulting in reduced systemic side effects and sometimes, painless and offer multi-day dosing. It is generally accepted that they offer improved patient compliance. Transdermal patch or adhesive patch or skin patch used to deliver a controlled dose of a drug through the skin over a period of time. A skin patch uses a special membrane to control the rate at which the liquid drug contained in the reservoir within the patch can pass through the skin and into the bloodstream. Some drugs must be combined with substances, such as alcohol, that increase

their ability to penetrate the skin in order to be used in a skin patch. Transdermal delivery provides a leading edge over injectables and oral routes by increasing patient compliance and avoiding first pass metabolism respectively. Transdermal delivery not only provides controlled, constant administration of the drug, but also allows continuous input of drugs with short biological half-lives and eliminates pulsed entry into systemic circulation, which often causes undesirable side effects. Thus various forms of Novel drug delivery system such as Transdermal drug delivery systems, Controlled release systems etc.

Diabetes Mellitus is a chronic metabolic disorder characterised by high blood glucose concentration hyperglycemia caused by insulin deficiency .often combine with insulin resistance.

Glibenclamide is a potant oral sulfonylurea hypoglycemic agent. It is currently available for treating hyperglycemia in Non insulin dependent Diabetes Mellitus (NIDDM-type 2)

The drug inhibiting ATP sensitive K^+ chennels in pancreatic beta cells. This inhibition caused cell membrane depolarisation, opening of voltage dependant Calcium channels thus triggering.

Glibenclamide (M.W. 494.004 g/mol) and negligible skin degradation. Plasma haif life is 4-6hrs.

Which make frequent dosing necessary to maintain thereputic blood level of the drug for a long term treatment. Therefore controlled released Transdermal prepration of Glibenclamide was prepare to give sustain effect as compared to conventional multiple oral dosing.

OBJECTIVE

Today about 74% of drugs are taken orally and are found not to be as effective as desired. To improve such characters transdermal drug delivery system was emerged.

Drug delivery through the skin to achieve a systemic effect of a drug is commonly known as transdermal drug delivery and differs from traditional topical drug delivery.

Topical administration of therapeutic agents offers many advantages over conventional oral and invasive methods of drug delivery.

Providing uniform drug delivery.

Enhancement of therapeutic efficiency and maintenance of steady plasma level of the drug.

EXPERIMENTAL METHODS

Method of Preparing Transdermal patch

The patches were prepared by solvent casting method The polymer (Carbopol/HPMC) was taken in a beaker with a minimum quantity of the solvent Then 2/3rd of the solvent was mixed with the other polymers (Eudragit L 100) and was added with stirring at lower rpm initially and later at a higher speed. The plasticizer was added and uniformly mixed and the drug was incorporated with continuing agitation and the volume was made up. The films were cast onto a suitably designed and fabricated glass mould and then dried in oven at 40^{o}C. The films were removed by using sharp blade by inserting along the edges of the film. The dried films were wrapped in butter paper and stored in a closed container away from light and in cool place.

Permeability coefficient4,5 is the velocity of drug passage through the membrane in cm/hrs. Permeability coefficient (P) was calculated from the slope graph of percentage of drug transported v/s time as,

P = slope * Vd / S

Where,

Vd = Volume of donor solution

S = Surface area of tissue.

Flux is defined as the amount of material flowing through a unit crosssectional barrier in unit time .

It is calculated by,

Flux (J) = P * CD

Where,

CD = concentration of donor solution.

Enhancement ratio was used to evaluate the effect of permeation enhancer on diffusion and permeation of selected drug molecules.

It is calculated by,

Enhancement ratio (ER) = Permeability coefficient of drug with enhancer/Permeability coefficient of drug alone

PRINCIPLES OF TRANSDERMAL PERMEATION[4,28]

Earlier skin was considered as an impermeable

protective barrier, but later investigations were carried out which proved the utility of skin as a route for systemic administration. Skin is the most intensive and readily accessible organ of the body as only a fraction of millimeter of tissue separates its surface from the underlying capillary network. The various steps involved in transport of drug from patch to systemic circulation are as follows:-

. Diffusion of drug from drug reservoir to the rate controlling membrane.

. Diffusion of drug from rate limiting membrane to stratum corneum.

. Sorption by stratum corneum and penetration through viable epidermis.

. Uptake of drug by capillary network in the dermal papillary layer.

. Effect on target organ.

The most important criteria for TDDS is that the drug possesses the right physicochemical and pharmacokinetic properties. Transdermal patches offer much to drugs which undergo extensive first pass metabolism, drugs with narrow therapeutic window, or drugs with short half life which causes non- compliance due to frequent dosing.

Advantages of Transdermal Delivery Systems[11,14]

- Reasonably constant dosage can be maintained (as opposed to peaks and valleys associated with oral dosage)
- First pass metabolism in the liver and GI tract is avoided.
- Reduced need for active administration (some patches can last 7 days).
- The patch is noninvasive and dosage can be stopped by removal.
- Easy to apply and to monitor.

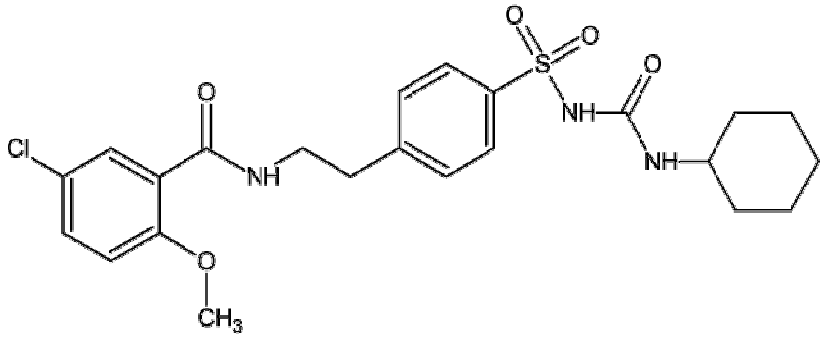
Glebenclamide-The anti-diabetic drug [12]

Glibenclamide, is an anti-diabetic drug in a class of medications known as sulfonylureas. It is also sold in combination with metformin under the trade name Glucovance.

Glibenclamide exerts pancreatic and extrapancreatic actions. It stimulates an increase in insulin release by the pancreatic β-cells. It may also reduce hepatic gluconeogenesis and glycogenolysis. Increased glucose uptake in the liver and utilization in the skeletal muscles.

Matrix-type The drug embedded in a polymeric matrix of polymethyl methacrylate and ethylcellulose was evaluated for its hypoglycemic activity in normal and streptozotocin induced diabetic rats in comparison with its oral therapy.

Structure of Glibenclamide



Duration	24 hours.
Absorption	Readily absorbed from the GI tract (oral); peak plasma concentrations after 2-4hours.
Distribution	Protein-binding: Extensive
Metabolism	Hepatic; converted to very weakly active metabolite
Excretion	Urine (50%); faeces (50%).
Food(before/after)	Should be taken with food.

Glibenclamide Adverse Reactions / Glibenclamide Side Effects: [11,12]

Hypoglycaemia; cholestatic jaundice; agranulocytosis; aplastic anaemia; haemolytic anaemia. Blood dyscrasias (reversible), liver dysfunction, hypoglycaemia, GI symptoms, allergic skin reactions.

Potentially Fatal: Prolonged hypoglycaemia seen in elderly or debilitated patients with hepatic or renal diseases.

Special Precautions: Elderly; malnourished; mild to moderate renal and hepatic disorders. Impaired alertness. Avoid alcohol. Careful monitoring of blood-glucose concentration. Adrenocortical insufficiency. Changes in diet or prolonged exercise may also provoke hypoglycaemia. Increased risk of hypoglcaemia due to its long half-life. Avoid in severe hepatic impairment. Pregnancy, lactation.

Other Drug Interactions:- Increased risk of hypoglycaemia when used with β-blockers. Additive hypoglycaemic effect with insulin and other antidiabetic drugs. Metabolism may be reduced by chloramphenicol and cimetidine. Increased hypoglycemic effect when used with cyclic antidepressants, pegvisomant, corticosteroids, salicylates, sulfonamide derivatives (except sulfacetamide) or fibric acid derivatives. Concurrent use may increase serum levels of ciclosporin. Increased serum levels when used with fluconazole. Metabolism of glibenclamide may be increased when used with rifampin. Concurrent use with coumarin derivatives may cause changes in INR. Concurrent admin with chloestyramine resin may lead to reduced absorption of glibenclamide. Serum levels may be reduced by colesevelam. Therapeutic efficacy may be diminished by luteinizing-hormone releasing hormone analogs. Concurrent use may increase adverse effects of phenytoin. Quinolone antibiotics may affect the efficacy of glibenclamide; monitor blood sugar levels. Hypoglycaemic effect may be reduced by somatropin.

Potentially Fatal: Increased risk of liver toxicity when used with bosentan; avoid concurrent use.

Dosage: Oral Type 2 diabetes mellitus. Adult: Initially, 2.5-5 mg daily, may increase wkly by increments of 2.5 mg daily, up to 15 mg daily. Doses >10 mg daily should be given in 2 divided doses. Max: 20 mg daily. Elderly: Initially, 1.25-2.5 mg daily, may increase by 1.25-2.5 mg daily every 1-3 weeks, if needed.

List of Contraindications

Glibenclamide and Pregnancy:

P - Contraindicated in pregnancy L - Contraindicated in lactation. Category C: Either studies in animals have revealed adverse effects on the foetus (teratogenic or embryocidal or other) and there are no controlled studies in women or studies in women and animals are not available. Drugs should be given only if the potential benefit justifies the potential risk to the foetus.

Glibenclamide and Other Contraindications: Severe or life-threatening hyperglycaemia, severe liver or renal failure, type 1 diabetes, diabetic ketoacidosis with or without coma, patients with severe infection or trauma.

Storage: Oral Store at 15-30°C.

MECHANISM OF ACTION

Permeation enhancers: To increase permeability of stratum corneum so as to attain higher therapeutic levels of the drug penetration enhancers interact with structural components of stratum corneum *i.e.,* proteins or lipids. The enhancement in absorption of oil soluble drugs is apparently due to the partial leaching of the epidermal lipids by the chemical enhancers, resulting in the improvement of the skin conditions for wetting and for transepidermal and transfollicular penetration. The miscibility and solution properties of the enhancers used could be responsible for the enhanced transdermal permeation of watersoluble drugs. Pharmaceutical scientists have made great efforts in transdermal permeation studies using various enhancers for several drug moieties. Example- DMSO.

The common ingredients which are used for the preparation of TDDS are as follows.

 Drug: Drug is in direct contact with release liner. Ex:-Glibenclamide.

 Liners: Protects the patch during storage. Ex:- polyester film.

Adhesive: Serves to adhere the patch to the skin

for systemic delivery of drug.
Ex:- Acrylates, Polyisobutylene, Silicones.

Permeation enhancers: Controls the Release of the drug.
Ex: Terpenes, Terpenoids, Pyrrolidones. Solvents like alcohol, Ethanol, Methanol. Surfactants like Sodium Lauryl sulfate, Pluronic F127, Pluronic F68.

Backing layer: Protect patch from outer environment.
Ex: Cellulose derivatives, poly vinyl alcohol, Polypropylene Silicon rubber.

BIOPHARMACEUTICAL PARAMETERS IN DRUG SELECTION FOR TRANSDERMAL PATCH[6]

- Dose should be low i.e <20mg/day.
- Half life should be 10 hrs or less.
- Molecular weight should be <400.
- Partition coffecient should be Log P(octanol-water) between 1.0 and 4.
- Skin permeability coefficient should be <0.5 X 10-3cm/h.
- Drug should be non irritating and non sensitizing to the skin.
- Oral bioavailability should be low.
- Therapeutic index should be low.

CONCLUSION:

A lot of progress has been done in the field of Transdermal Patches. Due to large advantages of the Transdermal Drug Delivery System, this system interests a lot of researchers.

Many new researches are going on in the present day to incorporate newer drugs via this system. Various devices which help in increasing the rate of absorption and penetration of the drug are also being studied. However, in the present time due to certain disadvantages like large drug molecules cannot be delivered, large dose cannot be given, the rate of absorption of the drug is less, skin irritation, and etc. the use of the Transdermal Drug Delivery System has been limited.

But, with the invention of the new devices and new drugs which can be incorporated via this system, it used is increasing rapidly in the present time.

This review provide an valuable information regarding the transdermal drug delivery systems and its evaluation process details as a ready reference for the research scientist who are involved in TDDS.

The foregoing shows that TDDS have great potentials, being able to use for both hydrophobic and hydrophilic active substance into promising deliverable drugs.

To optimize this drug delivery system, greater understanding of the different mechanisms of biological interactions, and polymer are required. TDDS a realistic practical application as the next generation of drug delivery system.

EXPERIMENTAL WORK:

The experimental work has been performed in the laboratory of Indore Institute Of Pharmacy, Indore (M.P.)

Solubility:

Water:	poor soluble
Ethanol:	poor soluble
Methanol:	Slightly soluble
Chloroform:	Precipitate
Methanolic NaoH:	Freely Soluble
Phosphate buffer:	Freely Soluble
Citrate buffer:	Freely Soluble

Absorbance:

2µg/ml in Methanolic 0.1M –HCL was found to be 215 nm and absorbance was found to be 0.44.

2µg/ml in Phosphate buffer pH 7.3 was found to be 235 nm and absorbance was found to be 0.46.

RESULTS& DISCUSSION

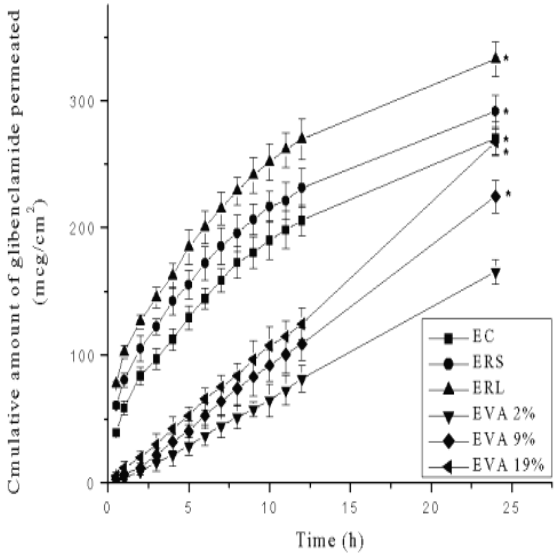
The Glibenclamide is soluble in Phosphate buffer and Methanolic NaoH. The lambda max. was found to be 235 and 215 nm in 0.1M-HCl respectively.

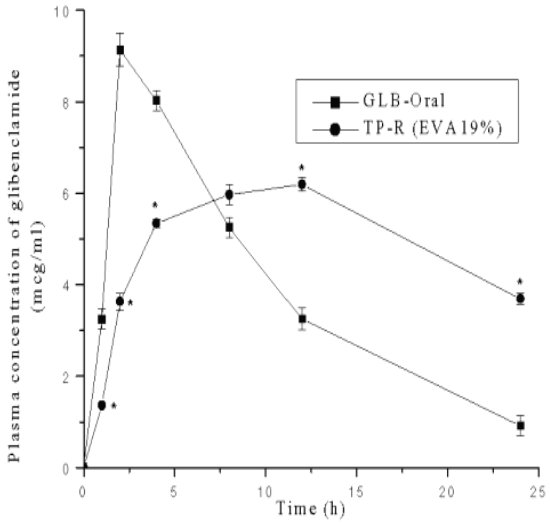
Transdermal drug delivery system is a most suitable system for a long term treatment or for a multi –dose treatment because transdermal patches are prepared for a long period of time in a single dose providing treatment for a day to even up to seven days. Transdermal drug delivery system also increases the bioavailability of drug by avoiding the first pass metabolism and increases the therapeutic efficacy of drug by reaching into the system circulation.

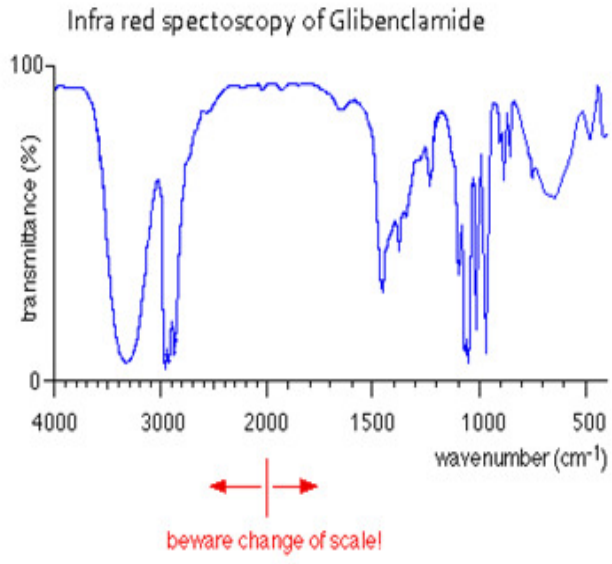
Glibenclamide is a potent oral sulfonylurea class of drug currently available in the market for

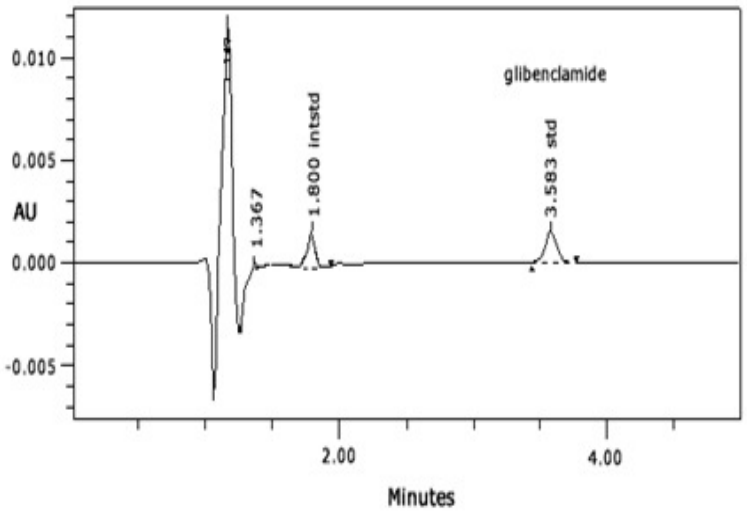
treatment of non-Insulin dependent diabetes mellitus (NIDDM). Polymers HPMC,PVPK-30 and Eudragit RS-100 were selected on the basis of their adhering property and non toxicity. The result of the finding showed excellent adhering property and controlled release. for in vitro skin permeation release containing enhancer DMSO for best formulation HP-1. Glibenclamide transdermal patches were prepared with combination of these polymers.Maximum in vitro drug release, in vitro skin permeation and in vitro skin permeation with DMSO for formulation HP- 1 made suitable for further studies. According to the above observation it was concluded that Glibenclamide was suitable for transdermal drug delivery system.

Result from present study concluded that Glibenclamide in combination with HPMC,PVP – K30 and ERS-100 and with incorporation of PEG-400 (36 %) and (12 %) produced smooth, flexible and transparent film. The release rate of drug through films and permeation across skin increased when the concentration of hydrophilic polymer was increased. In view of the overall result reported in the present study, it is proposed that Glibebclamide can be used in the formulation of matrix type transdermal drug delivery system to prolong the drug release.









ACKNOWLEDGEMENT:

I am thankful to Ingla lab. Pvt. Ltd. Mumbai for providing glibenclamide. Indore institute of pharmacy Indore for practical work.

I am also thankful to our faculty members Mr. Darshan Jamindar, Mr. Dindayal Patidar and Mr. Neeraj Patidar for helping and guidance.

REFERENCES

1. Jain NK. Advances in controlled and novel drug delivery, 1st Ed., CBS Publishers and distributors, New Delhi, 2001 pp.108-110.
2. Bhowmik D,Chiranjib ,Margret C,Jayakar B, Sampath K P. Recent Advances in Transdermal Drug Delivery System. Int.J. PharmTech Res. 2010; 2 (1): 68-77.
3. Shah S. Transdermal Drug Delivery Technology Revisited: Recent Advances. Pharmainfo.net. 2008; 6(5).
4. Aggarwal G. Development, Fabrication and Evaluation of Transdermal Drug Delivery- A Review. Pharmainfo.net. 2009.
5. Jalwal P, Jangra1 A, Dahiya L, Sangwan Y, Saroha R. A Review on Transdermal Patches. The Pharma Research . 2010; 3: 139-149.
6. Chandrashekhar N S, Shobha Rani R H. Physicochemical and Pharmacokinetic Parameters in Drug Selection and Loading of Transdermal Drug Delivery. Indian Journal of Pharmaceutical Sciences. 2008; 70(1): 94-96
7. Parivesh S, Dwivedi Sumeet , Dwivedi Abhishek.. Design, Evaluation, Parameters and Marketed Products of transdermal patches: A Review. Journal of Pharmacy Research. 2010; 3(2): 235-240.
8. Chopda G. Transdermal Drug Delivery Systems : A Review. Pharmainfo.net. 2006; 4(1).
9. Levin G, Kornfeld J, Patel Y R, Damon S. Transdermal Delivery : Success Through A Deep Understanding Of The Skin. *Corium*. [Serial Online]. 2007 [cited 2011 oct 08]. Available online: URL: http:// www.ondrugdelivery.com.
10. Scheindlin S.Transdermal Drug Delivery: Past, Present, Future. interventions. 2004; 4(6): 308-312.
11. Chein Y.W. Transdermal drug delivery and delivery system. In, Novel drug delivery system, Vol. 50, Marcel Dekker, Inc., New york, 1992 pp.301-381.
12. Tripathi K.D. essential of Medical pharmacology,Edn4, Jaypee Brothers medical publishers, 2004, page no.278.
13. Parivesh S, Dwivedi Sumeet , Dwivedi Abhishek.. Design, Evaluation, Parameters and Marketed Products of transdermal patches: A Review. Journal of Pharmacy Research. 2010; 3(2): 235-240.
14. Berner B and John V.A. Pharmacokinetic characterization of Transdermal delivery systems. Jour.Clinical pharmacokinetics 1994; 26 (2): 121-34.
15. Loyd V. Allen Jr, Nicholas G. Popovich, Howard C. Ansel. Pharmaceutical dosage forms and drug delivery systems, 8th Edition., Wolter Kluwer Publishers,New Delhi, 2005 . 298-299.
16. Willams A.C and barry B. W., “Penetration Enhancers,” Adv. Drug Del.Rev.2004;56: 603.
17. Pellet M, Raghavan S.L, Hadgraft J and DavisA.F. “The application of supersaturated systems to percutaneous drug delivery” In: Guy R.H and Hadgraft J. Transdermal drug delivery, Marcel Dekker, Inc., New york 2003. 305-326.
18. Brown M.B and Jones S.A. Hyaluronic acid: a unique topical vehicle for localized drug delivery of drugs to the skin. JEDV 2000;*19:308-31*
19. Tsai J.C, Guy R.H, Thornfeldt C.R, GaoW.N, Feingold K.R and Elias P.M. “Metabolic Approaches to Enchance Transdermal drug delivery”. Jour. pharm. Sci., 1998; 85:643-648.
20. Berner B and John V.A. Pharmacokinetic characterization of Transdermal delivery systems. Jour.Clinical pharmacokinetics 1994; 26 (2): 121-34.
21. Baker W and Heller J. ”Material Selection for Transdermal Delivery Systems”, In Transdermal Drug Delivery: Developmental Issues and Research Initiatives, J.Hadgraft and R.H.Guys,

Eds. Marcel Dekker, Inc.,New york 1989 pp. 293-311.
22. Wiechers J. Use of chemical penetration enhancers in Transdermal drug delivery-possibilities and difficulties. Acta pharm. 1992 : 4: 123.
23. Yamamoto T, Katakabe k, Akiyoshi K, Kan K and Asano T. Topical application of glibenclamide lowers blood glucose levels in rats. Diabetes res. Clin. Pract. 1990; 8: 19-22.
24. Al- Khamis K, Davis S.S and Hadgraft J. Microviscosity and drug release from topical gel formulations. Pharm. Res. 1986; 3: 214-217.
25. Anon. Transdermal delivery systems-general drug release standards. Pharmacopeial Forum, 1980; 14: 3860-3865.
26. Mayorga P, Puisieux F and Couarraze G. Formulation study of a Transdermal delivery system of primaquine. Int. J. pharm. 1996; 132: 71-79.
27. Deo M.R, Sant V.P,Parekh S.R, Khopade A.J and Banakar U.V. Proliposome-based Transdermal delivery of levonorgestrel. Jour. Biomat. Appl. 1997; 12: 77-88.
28. Singh J, Tripathi K.T and SakiaT.R. Effect of penetration enhancers on the *invitro* transport of ephedrine through rate skin and human epidermis from matrix based Transdermal formulations. Drug Dev.Ind. Pharm. 1993; 19: 1623-1628.
29. Wade A, Weller P.J. Handbook of pharmaceutical Excipients. Washington, DC: American Pharmaceutical Publishing Association; 1994: 362- 366.
30. Rhaghuram reddy k, Muttalik S and Reddy S. Once– daily sustained- release matrix tablets of nicorandil: formulation and *invitro* evaluation. AAPS Pharm.Sci.Tech. 2003;4:4.
31. Shaila L, Pandey S and Udupa N. Design and evaluation of matrix type membrane controlled Transdermal drug delivery system of nicotin suitable for use in smoking cessation. Indian Journ. Pharm. Sci. 2006;68: 179-184
32. Aarti N, Louk A.R.M.P, Russsel.O.P and Richard H.G. Mechanism of oleic acid induced skin permeation enhancement *in vivo* in humans. Jour. control. Release 1995; 37: 299-306.
33. Wade A and Weller P.J. Handbook of pharmaceutical Excipients. Washington, DC: American Pharmaceutical Publishing Association 1994; 362-366.

*****