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FORMULATION AND EVALUATION OF GLIBENCLAMIDE TRANSDERMAL PATCHES

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ABSTRACT:
The aim of the present research study was to prepare and evaluate the Glibenclamide transdermal patches in order to enhance the permeation of the drug and to study the effectiveness of the two polymers used and their physiochemical properties to know about the *invitro* drug profile. The main polymers used here are Chitosan, HPMC and Ethyl cellulose. Employing these polymers shows no interaction with the drug. Glibenclamide transdermal patches was prepared by Solvent Casting technique. Thus, the prepared formulation was evaluated under the parameters like thickness, weight uniformity, folding endurance, moisture content, moisture loss, drug content, drug profile, *invitro* drug release performed by using Franz diffusion cells. Drug delivery through the skin gives a systemic effect and does not alter the plasma level concentrations of the drug. Thus, Glibenclamide transdermal patch is used asa control drug delivery system and administrable frequency of the drug is minimized .

KEY WORDS: Transdermal Patches, Glibenlamide, HPMC, ethyl cellulose.

INTRODUCTION:

Introduction to Diabetes Mellitus:

Diabetes Mellitus (DM) is a group of metabolic disorders. It is a chronic metabolic disorder in which the body loses its ability to respond or produce insulin which leads to hyperglycemia in the body. Diabetes Mellitus is also known as Diabetes which is referred as a disorder with “sweet urine” and excessive loss of muscles. The symptoms are frequent urination, thirst, heavy appetite.

In a healthy human, the blood glucose levels are controlled by the Insulin hormone. This hormone is produced by the β-cells of pancreas specifically Islets of Langerhans. Insulin is released by the pancreas to maintain the increased blood glucose levels in the body. The complete loss of insulin production by the β-cells results in the Type-1 Diabetes. Type-2 diabetes is also referred as Insulin resistance in which the elevated levels of blood glucose in the body affects the muscles and tissues of an individual. All forms of DM increase the risk of long-term complications. Inadequate uptake of insulin and the insensitivity of its receptors plays a vital role in all forms of the Diabetes Mellitus[15].

Introduction to Transdermal Drug Delivery System:

A transdermal patch is a painless method of delivering the drugs systematically by applying a drug formulation on the skin to obtain a systematic circulation through the skin at a predetermined rate.

Development of the novel drug delivery systems has been renewed from the last years. This development improves the patient complication to a significant extent.

The main target of TDDS is to deliver the drug into blood circulation through skin at designed rate with minimal patient drug interactions. On administrating via the oral route, the drugs undergo first pass metabolism, to solve this condition TDDS has been implemented to administer the drug and observed that the interactions are minimized even if they are taken once in a week. This is the comfortable dosage form it is non-invasive, avoids the first-pass metabolism, can have multiday therapy, and can be terminated at any point of time. The site of application should be neat and clean, not oily, and hairless. The system consists of several layers:

- A backing layer which protects from external environment and water
- A drug reservoir on a semipermeable membrane and this controls the release of the drug.
- An adhesive to be attached onto the skin
- A liner as it protects the patch and adhesive.

The below figure illustrates the layers in a medicated patch

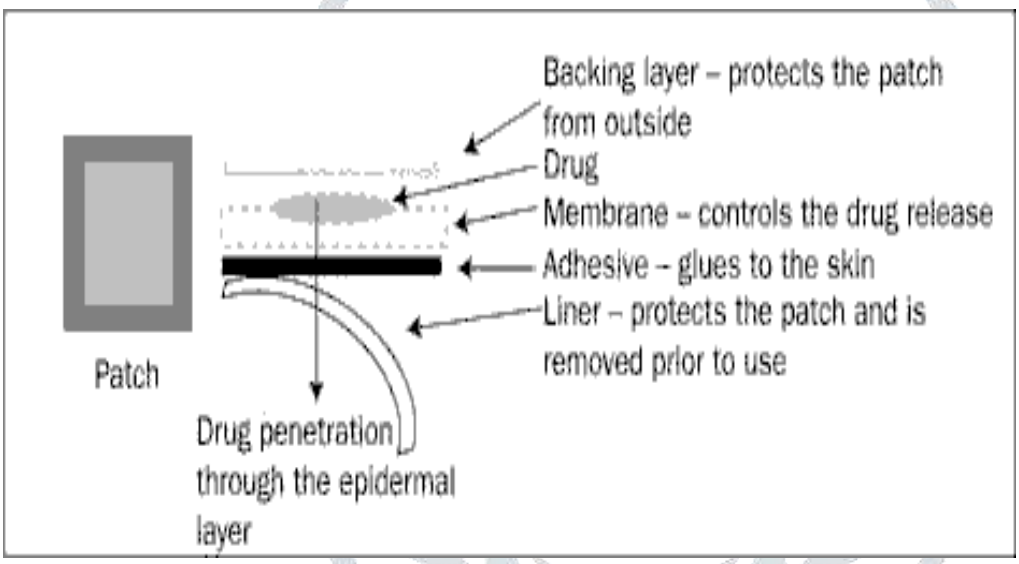


Fig 1. A Diagrammatic representation of the Transdermal Patch

Even patches, consists extracts from the plants, animals, minerals which was had become more popular at the ancient times in the Egyptian regions and in Babylonian medicine.

However, the routine usage of transdermal delivery systems is now commonly practiced in the 20th century when technology was developed to enable the administration through the skin to achieve systemic effects. The plasma half-life of Glibenclamide transdermal patch is about 4 to 6 hrs which makes frequent dosing necessary to maintain and regulate the therapeutic blood levels of the drug for a long-term treatment.

The current target of the NDDS is to formulate the matrix type of transdermal patches of Glibenclamide as a model drug with combination of HPMC, EC to reduce of side effects observed when administrated in the patient. The first transdermal patch approved by FDA in the year was SCOP this delivered scopolamine to treat the motion sickness.

Most of the transdermal patches show zero order kinetics at which the drug is being released from several hours to few days.

Few evidences have reported in observing the Percutaneous absorption in the patients administrated with the transdermal patches in which the blood levels of the detectable excreta of the drug and its metabolites in the urine and through the clinical response of the patient.

Being more passively administrable, a transdermal patch and its delivery into the skin to its target site is a multistep process.

- Diffusion of the drug from the rate controlling membrane.
- Dissolution takes place within and release from the formulation.
- Sorption by the inner layers of the skin and penetration via the epidermis the outermostlayer.
- Effect on the target site.
- Diffusion through the stratum corneum, through the lipidic intercellular pathway[14].

ADVANTAGES:

- It avoids the drug to bypass the first pass metabolism.
- No peaks in the plasma concentration leads to the decreased risk of the side effects.
- It can be administrated as a substitute for the oral route.
- The patch can be terminated at any time.
- No gastro intestinal compatibility is seen.
- Undesirable effects are minimized.
- Transdermal patch even used for a shorter period of time with the drug having shorter biological half-lives gives better curing.
- Fluctuation in the drug levels is minimized.
- Self-administrable

DISADVANTAGES:

- This system cannot deliver the ionic drugs.
- High drug levels in the blood can't be achieved.
- It can't develop the drugs of large molecular size.
- Local irritation at the site of administration.
- Long term adherence is difficult.

LIMITATIONS:

- The drugs with the hydrophilic structures permeate the skin slowly and does not reach therapeutic level.
- The excipients in the drug may cause local edema and local irritation
- Preferable dose is less than 5mg /day.
- Transdermal delivery of the larger dosed drugs i.e., more than 10-25mg/day is difficult.
- Dermatitis is seen in some patients.

- The dosage changes from person to person and with age.

FACTORS THAT INFLUENCE TRANSDERMAL DRUG DELIVERY:

The factors that influence the TDDS are of mainly two kinds. They are:

A. Biological factors include:

- Skin condition
- Skin age
- Blood flow
- Regional skin sites
- Skin metabolism
- Species differences

B. Physiological factors include:

1. Skin hydration
2. Temperature and pH
3. Diffusion coefficient
4. Drug concentration
5. Partition coefficient
6. Molecular size.

FORMULATION OF TRANSDERMAL DRUG DELIVERY SYSTEMS:

1. Polymers:

A polymer is a molecule, prepared from joining together many small molecules known asmonomers.

Ideal properties of the polymers to be used in a transdermal delivery:

- The molecular weight and chemical functionality of the polymer affects the diffusion and release of the drug.
- Stable polymer is chosen.
- Inexpensive polymer must be selected.
- Nontoxic polymer must be employed.
- Larger size drug molecules cannot develop transdermal delivery.
- The polymer must be easily manufacture.

2. Penetration Enhancers:

These are compounds which promote the permeability of the skin. Permeation enhancers can also be defined as substances that are capable of promoting penetration of drugs into skin and transdermal therapeutic systems offers a more reliable pathway of administering drug through the skin of an individual.

Ideal properties of the permeation enhancers:

- A permeation enhancer must possess a controlled and reversible action.
- It should maintain the physical and chemical compatibility with the drug and also the other excipients.
- It should not cause loss of any body fluids or electrolytes.
- It must be nontoxic, non-allergic, non-irritating.
- It should possess the ability to act at particular predictable duration.
- It must be odorless, colorless.
- It should be economically acceptable.

PREPARATIONAL METHODS OF TRANSDERMAL DRUG DELIVERY SYSTEMS:

Various preparational methods are to prepare a transdermal patch. Thy are:

- Solvent casting method
- Asymmetric TPX membrane method
- Circular Teflon Mould method
- Mercury substrate method
- By using free films method
- By using the Pro liposomes

Here we employ the solvent casting method to prepare the Glibenclamide transdermal patch.

Conditions in which patches can be used are as follows:

- In the situations where the patient is unable to take the oral medication.
- When the individual suffers intolerable side effects.
- Administrable to the patients who cannot self-medicate because of their analgesia.
- It is used in combinations to yield synergistic effects.

Conditions in which the patches should not be used are as follows:

- The condition where the treatment for acute pain is necessary.
- The situation where the dose titration is essential.
- Treatment with the lower dose of or equal dose to 30mg/day

AVOIDANCE OF THE DRUG TO FIRST PASS METABOISM:

Many routes of administration, like suppository, IV, IM, inhalational aerosol, transdermal, or sublingual forms of drugs avoid the first-pass effect because they allow drugs to be get directly absorbed into the systemic circulation.

The first pass metabolism is a common phenomenon of the metabolism of a drug and the concentration of a drug when administered orally decreases its potency before reaching to the systemic circulation. A fraction of the drug is lost during the mechanism of absorption of the drug in the liver or in the gut.

The liver degrades many medicines to such a level that only a small quantity of active medicament of the drug reaches to the systemic circulation from the liver. The first pass metabolism can be avoided by 4 systems, these effects the first pass of the drug are the gastrointestinal lumens presents in the enzymes, enzymes present in the gut wall, bacterial andhepatocytes.

The first pass metabolism can also be avoided by administering the drugs with larger bioavailability than the competing drug[13].

LITERATURE REVIEW:

V G Jamakandi, et al (2009)

The present investigation was aimed to evaluating the possibility of using different polymeric grades of hydroxy propyl methyl cellulose for the development of trans dermal drug delivery

systems of Nicorandil, an antianginal drug. Prepared matrix – type patches were evaluated for their physicochemical characterization followed by in vitro evaluation. Selected formulations were subjected for their ex vivo studies on porcine ear skin.

B.K. Sridhar, et al (2008)

Investigated chemically modified Chitosan by treating with two different aldehydes like acetaldehyde and propionaldehyde to form Schiff's bases these bases produces polymer A and B respectively. FTIR data have confirmed the reaction carried out on Chitosan. Etoricoxib polymeric films of Chitosan, modified Chitosan and Chitosan / HPMC blend were prepared and evaluated the bursting strength, swelling index, chitosan / HPMC were having better dissolution studies and longer duration of action.

G.S. Sanap, et al (2008)

Prepared transdermal patches of Indapamide using HPMC and ethyl cellulose polymers by incorporating glycerin and dibutyl phthalate as plasticizers, respectively.

J.R. Patel, et al. (2009)

The aim of the present investigation was to prepared of matrix type transdermal patches of glibenclamide were prepared using different polymers by solvent evaporation technique. Polyethylene glycol (PEG) 400 was used as plasticizer and dimethyl sulfoxide (DMSO) was used as penetration enhancer. Prepared matrix – type patches were evaluated for their physicochemical characterization followed by in vitro evaluation. Selected formulations were subjected for their in vivo studies on skin.

D. Prabhakar, et at (2013)

The present investigated was aimed to evaluating transdermal drug delivery patches. Drug delivery through the skin to achieve a systemic effect without producing any fluctuations in plasma concentration of the drug. Topical administration of therapeutic agents offers many advantages. And also provide controlled release of the drug for extended period to time. Approaches for preparation of trans dermal patches, evaluation of trans dermal system.

Dr. S.J. Shankar, et al (2015)

The aim of the present investigation was to prepared Gilbenclamide transdermal patches and to study the influence of various polymer combination of Polyvinyl alcohol, Hydroxy propyl methyl cellulose, Eudragit RL – 100 in different ratios, di butyl phthalate, dimethyl sulfoxide was added by solvent casting method. And polymer rations on physiochemical parameters includes in vitro drug release studies and ex vivo studies were performed by using Franz diffusion cells.

P.Rama Bharathi, et al (2013)

Trans dermal systems are ideally suited for diseases that demand chronic treatment. Hence an antidiabetic agent of both therapeutic and prophylactic usage has been subjected to transdermal investigation Glibenclamde a first-generation hypoglycemic agent faces problems

like poor solubility with large individual variation and extensive metabolism. In this study, matrix type transdermal drug delivery system of glibenclamide, and antidiabetic drug were prepared by solvent casting method using different polymers like HPMC / PVP / CMC in varied ratios. Dibutyl phthalide was used as plasticizer and dimethysulfoxide (DMSO) and propylene glycol was used a permeation enhancer.

Peeush Singhal et al.(2012)

Have reviewed on the novel technique to enhance the therapeutic efficacy and safety of drugs in transdermal drug delivery system. They suggested that the conventional oral dosage forms have significant drawbacks of low bioavailability due to hepatic first pass metabolism and tendency to produce rapid blood level spikes, leading to a need of frequent dosing, which can be both cost

ineffective and inconvenient and to improve such character's transdermal drug delivery system had been emerged.

Ekapol Limpongsa and et al.(2008)

prepared the suitable polymeric films for the development of diltiazem hydrochloride transdermal drug delivery systems. Hydroxypropyl methyl cellulose (HPMC) and ethyl cellulose (EC) were used as hydrophilic and hydrophobic film formers, respectively. Effect of HPMC/EC ratios and plasticizers on mechanical properties of free films were studied. Effects of HPMC/EC ratios on moisture uptake, in vitro release and permeation through pig ear skinof diltiazem HCL films were evaluated.

The films composed of 8:2 HPMC/EC, 30% DBP and 10% IPM, IPP or tween 80 loaded with 25% diltiazem HCL should be selected for manufacturing transdermal patch by using a suitable adhesive layer and backing membrane. Further in vitro permeation and in vivo performance studies are required

K. M. Yerramsetty et al. (2010)

have studied the effect of different enhancers on the transdermal permeation of insulin analog. They used chemical penetration enhancers to increase the permeability of transdermal drug delivery for insulin administration. Their result indicated that specific functional groups are not directly responsible for enhanced insulin permeation. Rather, permeation enhancement is produced by molecules that exhibit positive log values and possess at least one hydrogen donor or acceptor.

P.R. VERMA et al. (2012)

Designed and formulated controlled transdermal delivery of propranolol using HPMC matrices and in vitro and in vivo evaluation of patches developed by different grades of HPMC: K4M, K15M and K100M drug release follows Higuchi rather than zero order.

Mohammad Aquil et al (2003)

formulated monolithic matrix type transdermal drug delivery system of metoprolol tartrate using polymers like Eudragit RL 100 and poly vinyl pyrrolidone by film casting on a mercury substrate and characterized in vitro by drug release studies, skin permeation studies and drug- excipients interaction analysis.

MATERIALS AND METHODS:

List of materials:

Acetic acid, chitosan, chloroform, ethanol, glycerin, glycerol, HPMC 5 CPS, sodium hydroxide, potassium hydroxide, calcium chloride, potassium dihydrogen phosphate.

List of equipment:

Balance, hot air oven, UV spectrometer, magnetic stirrer, PH meter, screw gauge. Method Before we are studying about Glibenclamide pre formulation studies we have to understand and study the physical and chemical characters of glibenclamide. Reformulation studies give the information about nature of the drug and drug combinations with exceptions and their interactions. In the characterization studies certain common test were performed to the active ingredient.

DRUG CHARACTERIZATION:

Solubility analysis:

Slightly soluble in ethanol and methanol. Insoluble in water and ether. Dissolved in dial diluted water of alkali hydroxide.

Procedure:

The solubility studies were performed in phosphate buffer solution. This procedure was prescribed in USP.

The excess amount of drug was added to phosphate buffer solution was solution at PH 7.4 in each case. the above solution was placed in the water bath shake it for 24 hours at 32 degrees. After 24 hours spectrometric value at 228nm solution was analyzed. At this point we analyze the absorption maxima.

Stock solution:

10 mg of Glibenclamide was accurately weighed and dissolved in a required quantity of methanol and make up to 100 ml by using phosphate buffer.

Procedure:

Equal equivalence of 0.2, 0.4, 0.6, 0.8, 01.0, 1.2, 1.4, 1.6, 1.8, 2 microliters respectively run from the stock solution by using above solution made up 10 mlby using 7.4 phosphate buffer solution. Prepared solution was scanned and absorbance were measured at 228 nm against blank solution by using the values draw the graph concentration versus absorbance.

FORMULATION OF DRUG LOADED FILMS:

In the present experiment we have used solvent casting method to prepare a drug film Chitosan and chitosan /HPMC solutions are prepared by dissolving in polymer 0.1%w/v acetic acid solutions, HPMC solution was prepared by mixture of water and ethanol in the 8: 2 ratios.

To the above solution add 20% and 30% weight by weight of glycerol. Glycerol is used as plasticizer in this experiment. Glibenclamide was added in small portion of chloroform and stirred for 20 minutes. Pour the polymeric solution which contain drug in the Petri dish. Keep it drying for 40 degrees the tried films are removed from the Petri dish and store in desiccator until use.

COMPOSITION OF DRUG LOADED FILMS:

FORMULATION	**GLIBENCLAMIDE** (mg)	**GLYCEROL**	**POLYMERS**	**POLYMER** 100 **(%)**
D1	40	20	Plain chitosan	2
D2	40	30	Plain chitosan	2
D3	40	30	Plain chitosan + HPMC	1+1
D4	40	20	Plain chitosan +HPMC	1.5+0.5
D5	40	30	Plain HPMC	2.5
D6	40	20	Plain HPMC	2.5

EVALUATION TESTS:

Physical characterization:

- **Physical appearance:**

All the prepared transdermal patches were tested for color, clarity, flexibility under smoothness.

• **Tensile strength:**

By using texture analyzer find the tensile strength of the transdermal patches at 500 GM loaded cell. During measurement, film was pulled by top clamp Atta a rate of 10 mm per minute. for each Film repeat the same 4 times.

Tensile strength was calculated using below formula

Tensile strength (kg/mm2) = Breaking force/Cross section area of sample Elongation at break (%) =Increase in length at breaking point/Original length.

• **Swelling index**

Soak the films in distilled water and 0.5, one, 2, 4, 8 and 24 hours remove the films in determined time. after removing the films blotted to remove the excess water and weigh it.

Swelling index was calculated from the weight increase as follow

Swelling index=$(W_2-W_1)/W_1$ Where

W_1 = Weight before immersion in the medium

W_2= Weight after immersion in the medium

. • **Thickness of the films:**

The thickness of the film was measured at 5 different points by using digital micro meter. The average value of five values is calculated.

• **Folding endurance:**

Folding endurance of transdermal patches was calculated by observing the number of times film would be folded at the same place without breakage it gives the exact value of the foldingendurance.

Water vapor transmission:

In a glass vial fix the film which is adhesive containing one gram of fused calcium chloride as desiccant. After that place the glass vial in desiccator containing 200 ml of saturated potassium chloride solution. The vials are taken out after 1,2,3,4,5,6,7,8days and weigh it.storage of water vapor transmission were calculated by taking the total period of 7 days.

• **Percentage of moisture content:**

The prepared films are weighed individually and place them desiccator containing calcium chloride. At normal room temperature. Then take it out and weigh it until constant values shown.

Percentage of moisture content = (Initial weight -Find final weight/final weight) ×100

• **Drug content:**

The prepaid transdermal patches cut at the specified area into small pieces these pieces are taken in a 50 ML volumetric flask in this for 25ml of phosphate buffer PH 7.4heat the content at 45 degrees for 15 minutes and kept it 24 hours with occasionally string.

The volume was made up to 50 ML with buffer solution similarly blank was carried out using drug free patches. The solution was filtered and absorbance was measure at 228 nm.

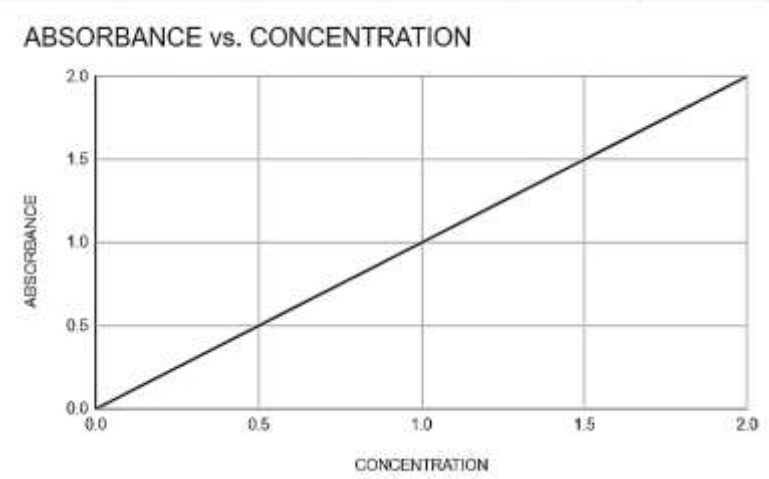
RESULTS:

PREFORMULATION STUDIES:

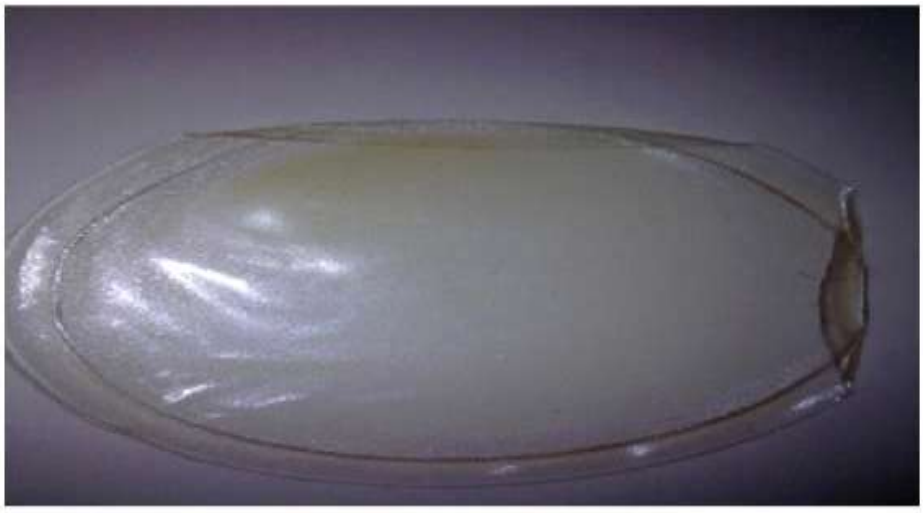
Calibration data of Glibenclamide:

SL.NO.	CONCENTRATION	ABSORBANCE
1	0.2	0.021
2	0.4	0.169
3	0.6	0.287
4	0.8	0.394
5	1.0	0.562
6	1.2	0.593
7	1.4	0.687
8	1.6	0.724
9	1.8	0.932
10	2.0	1.113

Calibration curve for Glibenclamide:



D_4 GLIBENCLAMIDE TRANSDERMAL PATCH



PHYSICOCHEMICAL PROPERTIES OF GLIBENCLAMIDETRANSDERMAL PATCHES

Formulation code	Appearance	Tensile Strength	Folding endurance	Drug Content	Weight Uniformity	Flatness (%)	Average Thickness
D1	Smooth, Flexible	3.8	118	2.3	0.466	96	0.249
D2	Smooth, Flexible	4.0	122	2.55	0.454	97.5	0.271
D3	Smooth, Flexible	4.6	128	2.61	0.436	95.4	0.190
D4	Smooth, Flexible	4.9	130	2.56	0.433	97	0.208
D5	Smooth, Flexible	3.0	78	2.60	0.439	95.5	0.150
D6	Smooth, Flexible	3.7	82	2.59	0.426	97	0.169

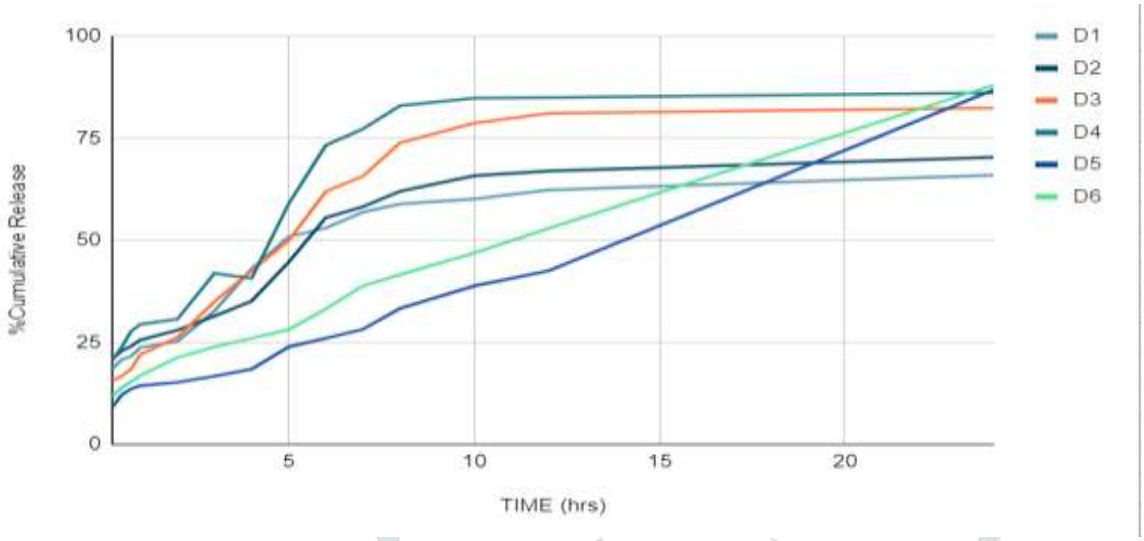
PHYSICOCHEMICAL PROPERTIES OF GLIBENCLAMIDETRANSDERMAL PATCHES

Formulation code	Moisture Content (%)	Moisture Uptake (%)	WaterVapor Transmission (gm/cm. day)	% Swelling index			
				5 mins	10mins	30mins	60 mins
D1	5.7	11.5	0.08555	73.2	75.7	76.8	78.6
D2	6.6	12.8	0.016	75.5	77.1	78.5	79.0
D3	16	17.5	0.182	66.3	67.5	70.1	72.2
D4	15.7	19.2	0.201	67.0	68.2	72.3	78.3
D5	11.2	13.5	0.012	60.4	63.4	64.1	65.6
D6	12.6	14.3	0.138	62.1	64.3	66.0	67.7

IN VITRO DIFFUSION PROFILES OF TRANSDERMAL PATCHES

TIME (hrs)	% CUMULATIVE RELEASE					
	D1	D2	D3	D4	D5	D6
0.25	18.5	21.0	15.6	20.7	9.2	11.8
0.5	20.7	22.9	16.7	23.8	12.12	13.9
0.75	21.5	24	18.4	27.7	13.6	15.4
1.0	23.7	25.6	22.0	29.4	14.4	16.9
2	25.2	28.0	26.2	30.7	15.2	21.3
3	32.7	31.4	35.0	41.9	16.7	23.9
4	43.0	35.1	42.5	40.7	18.4	26.0
5	50.9	44.6	49.9	59.0	23.9	28.1

6	53.0	55.5	62.0	73.3	26.0	33.2
7	56.9	58.2	65.7	77.3	28.2	38.8
8	58.9	62.0	73.9	83.0	33.3	41.6
10	60.1	65.8	78.7	84.8	38.8	46.9
12	62.3	67.0	81.1	85.0	42.5	52.9
24	66.0	70.3	82.4	86.1	86.9	88.0



***In vitro* diffusion profile of Transdermal Patches**

DISCUSSIONS

PREFORMULATIONS STUDIES:

Solubility study:

The solubility study was performed to check the media of phosphate buffer is with pH 7.4 in order to maintain. the sink conditions. The solubility of the drug was found to be 9.8% mg/ml in buffer solution and 11.34 mg/ml in polymeric solution when compared to phosphate buffer solution. Hence, phosphate buffer was chosen as permeation medium.

Calibration curve for the Glibenclamide:

A phosphate buffer of pH 7.4 helps to develop the calibration curve for Glibenclamide. Hence, a plot was obtained with the concentration range between 0.2-2mg/ml and absorbance measured at 228 nm. The absorbance of standard solution was shown in the **table of Calibration data of Glibenclamide** and mechanism is drawn. Then 'k' and 'b' values were 19.3853 and – 0.7277 respectively.

FORMULATION DEVELOPMENT OF TRANSDERMAL FILMS

Formulation of Drug Loaded Films:

By using the solvent casting technique drugs loaded films were formulated with the variable ratios of the plasticizer dot. these films are thin, smooth, flexible end, it transparent. By increasing the plasticizer concentration, flexibility and smoothness also increases. These prepared patches are subject to physical chemical properties, which are shown in the above tables.

Loaded films were found to be similar in thickness and the percentage of flatness of the drug loaded films were same. D4 shows highest tensile strength while D5 shows the lowest tensile strength. All the films are uniform in weight and have the same drug content. Plain chitosan and film show around 5-7 % of the moisture content and HPMC film show around 11-14 % of the moisture content with no change in absorption. Because of the HPMC show highest moisture content.

RELEASE KINETICS:

By using the above parameters, experiments were performed. It is confirmed that Glibenclamide undergoes zero order kinetics. It also releseas the active medicament in to the systemic circulation at a controlled rate. While observing the *invitro* diffusion profiles, D4 is good. It has shown a sustained release of the drug.

CONCLUSION:

The hepatic first pass metabolism of the Transdermal Drug Delivery System was studied along with the short half-life of less than 4 hours. Glibenclamide transdermal patch was prepared with the help of chitosan, HPMC. Among all the patches obtained, D4 shows the control release of drug hereby confirming that the chitosan: HPMC (75:25) with the30% plasticizer including assuming that it might be suitable for the sustainable release of the drug in the Transdermal Drug Delivery Systems.

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