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Formulation and Development of Transdermal Patches of Glibenclamide and Comparative Effect of Various Herbal Extracts on Ex Vivo Release

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Abstract

In the pursuit of crafting and assessing transdermal patches containing Glibenclamide, this investigation was chiefly orchestrated. Diverse polymers were harnessed in this endeavour, and a pivotal exploration into the influence of extracts derived from Capsicum Fruit extract on the bioavailability of Glibenclamide was conducted. The congruence between the physical and chemical attributes of the medication and the foundation of the patches underwent scrupulous scrutiny via Infrared Spectroscopy (FTIR). The findings yielded no discordance in physical and chemical properties between the medication and the patch base. A comprehensive evaluation of the formulated transdermal patches ensued, encompassing assessments of weight variance, plumpness, folding endurance, humidity levels, moisture retention, ex-vivo drug release, and ex-vivo drug absorption. The discerning diffusion analyses were executed through the utilization of the Franz Diffusion cell and Everted gut Sac method. The most optimal formulation, denoted as F15, exhibited the following characteristics: a thickness of 0.247±0.005mm, uniform weight distribution at 0.170±0.102gm, moisture uptake of 7.312±1.12%, moisture content at 5.045±0.214%, and drug content measuring 80.80±0.91%. Furthermore, it demonstrated an impressive folding endurance of 25±3.33. The pinnacle of its performance manifested in a cumulative drug release percentage of 70.74±1.15 within an 8-hour timeframe and an absorption rate of 4.341±0.34% in a span of 120 minutes.

Keywords: *Glibenclamide, Capsicum Fruits, FTIR, Moisture Content, Ex Vivo*

1. Introduction

The pharmacokinetics of Glibenclamide, a compound with the chemical name 5-Chlor- N- (2- {4- [(cyclohexylcarbamoyl) sulfamoyl] phenyl} ethyl)-2-methoxybenzamid, delves into the intricate realm of bioavailability, which elucidates the extent and efficiency of its entry into systemic circulation and subsequent accessibility at the pivotal site of action. Remarkably, intravenous medications achieve the pinnacle of bioavailability, whereas the oral route often incurs a diminished bioavailability owing to the intricacies of drug absorption and the labyrinth of first-pass metabolism [1]. Within this realm, the trifecta of solubility, dissolution, and intestinal permeability stands as the

triad of paramount importance, wielding their influence over the process of oral drug assimilation. These pivotal factors are assessed through the prism of the biopharmaceutics characterization framework, a sophisticated system that classifies pharmaceutical agents into four distinct categories. Type I encompasses compounds with exceptional solubility and superior permeability, while Type II represents those with modest solubility but substantial permeability. Type III houses drugs with impressive solubility but limited permeability, and lastly, Type IV harbors compounds with meager solubility and marginal permeability. It is noteworthy that many frequently employed antibiotics find their place in the Type III and Type IV classifications within this framework [2].

Diabetes, a chronic metabolic malady characterized by persistent hyperglycemia due to a deficiency in insulin production, becomes the focal point of therapeutic intervention. In this context, Glibenclamide emerges as a potent oral remedy, wielding its efficacy to combat this relentless ailment [3]. Transitioning into the domain of drug delivery systems, the transdermal route assumes an exalted position replete with advantages that supersede conventional modalities of drug administration. The paramount advantage lies in its prowess to surmount the complexities of drug absorption, facilitating a consistent and protracted release of therapeutic agents [4]. In the annals of pharmaceutical history, 1982 marked a seminal moment when the United States FDA granted approval for the scopolamine transdermal patch, developed by GlaxoSmithKline, to combat motion sickness. This heralded a new era in transdermal drug delivery [6]. Notably, the United States has sanctioned over 35 transdermal delivery products, catering to a diverse spectrum of pathophysiological conditions [7].

The merits of transdermal drug delivery systems extend beyond the ordinary dosage forms and oral controlled delivery systems. It distinguishes itself by circumventing the perils of hepatic first-pass metabolism, diminishing the frequency of administration, mitigating gastrointestinal side effects, and enhancing patient adherence [8]. The field of transdermal drug delivery has witnessed a remarkable surge in research endeavours in recent years. A pivotal driver for this surge lies in the expanding repertoire of medications that can be efficaciously administered through the skin gateway, achieving clinically relevant concentrations within the systemic circulation.

This noteworthy advancement is attributable to the ingenuity of pharmaceutical technologists who have not only conceptualized the transdermal delivery system as the quintessential non-oral foundational drug delivery modality but have also translated it into a highly efficient commercial venture [9]. In the realm of long-term and recurrent drug utilization, the transdermal route emerges as the preferred avenue for maintaining optimal plasma concentrations [10].In consonance with the dynamic landscape of drug discovery, the assessment of the permeability attributes of prospective drug candidates has assumed an increasingly pivotal role during the phases of lead selection and optimization [11].

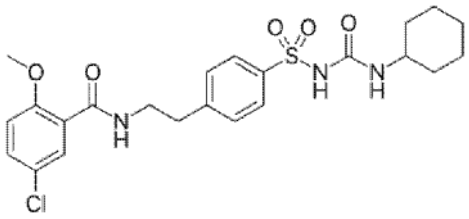

Figure 1: chemical structure of Glibenclamide

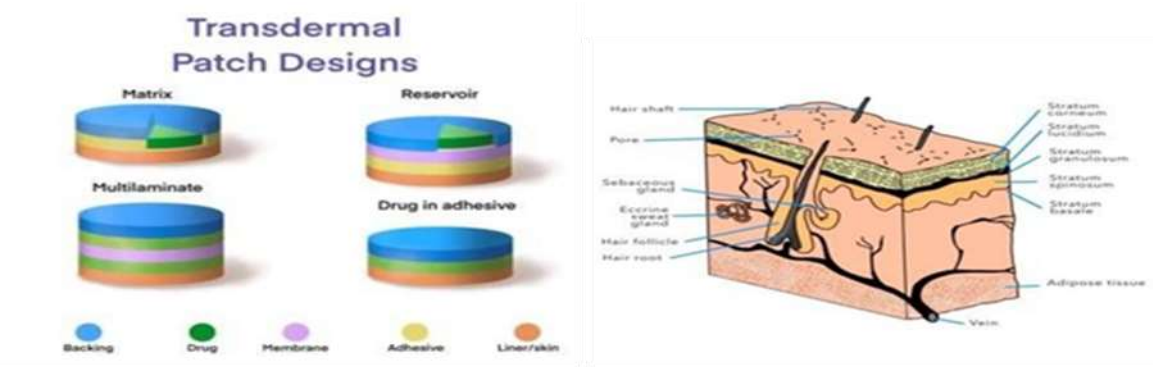

Figure 2: Transdermal Patches Design and Skin Structure

Drug & Chemical

Glibenclamide was obtained as a complimentary sample from Leben Laboratories Pvt. Ltd. in Akola, Maharashtra. Various other components were sourced from a research laboratory based in Mumbai. All the ingredients acquired for the study were of analytical grade.

Plant Material Used

Plant Materials Capsicum Fruits were obtained from local market impurities also foreign material is inspected then removed and authenticated from botanist.

Capsicum fruits [12]

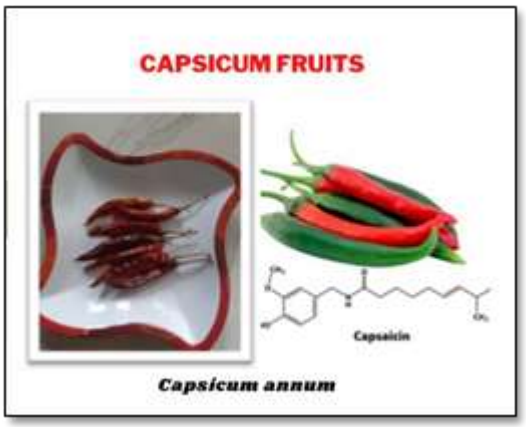

Figure 3: Capsicum Fruits

Synonyms: Capsicum Fruit Synonyms: capsicums, chilli, bell peppers, long pepper, hot pepper.

Biological source: It consists of dried ripened capsules of capsicum annum belonging to family Solanaceae.

Chemical constituent: It contains Capsaicin 0.5 to 0.9%. Capsicum also contains fixed oil 4 to 16% and ascorbic acid is the other content of the drug.

Uses: Externally, it's used as a carminative, an appetizer, and a stomachic; internally, it's used to treat rheumatism, lumbago, and neuralgia. It's also found in a variety of spices.

Ethnomedicinal use

It is used for the stomach upset, tooth pain, for improving circulation, can relieve pain, used to reduce the low-density lipoproteins, osteoarthritis related problems can be solved, used to manage the post herpes neuralgia, used to treat the pain associated with shingles, diabetic neuropathy, fibromyalgia, back pain and trigeminal neuralgia. It acts as a best counter irritant agent.

Successive Solvent Extraction [13,14]
Successive hot extraction of Capsicum fruits was performed using a Soxhlet apparatus to determine the most bio-enhancing extract. The extraction process involved the following solvents: 1) Chloroform, 2) Butanol, 3) Methanol, 4) Ethanol, and 5) Aqueous.

To prepare all the extracts via successive extraction, the raw material was air-dried in the shade until a consistent weight was achieved. Subsequently, the dehydrated samples of all materials were ground into coarse powder. For the extraction process, 50 grams of the crude powder from Capsicum Fruits were placed in the Soxhlet apparatus. Successive extractions were carried out using different solvents (Chloroform, Butanol, Methanol, Ethanol, and Aqueous). The resulting extracts were filtered using a funnel and Whatman No. 1 paper. Each remaining extract was then concentrated to dryness under reduced pressure at 40°C using an evaporator and stored at 4°C for further analysis.

Pre-formulation Studies
Melting Point: Glibenclamide exhibited a melting point of 170°C.

Drug, Extract, and Polymer Interaction
To examine potential interactions between the pure drug amoxicillin and a range of excipients, including HPMC, PG, PEG 400, glycerine, and ascorbic acid, as well as various extracts from Capsicum fruits, Fourier-transform infrared spectroscopy (FTIR) was utilized. This analysis aimed to detect any observable drug-polymer interactions using the KBr pellet technique. All the samples underwent FTIR analysis within the wavelength range of 4000 to 650 cm1.

Standard Curve of Glibenclamide [15]
Stock solution of Glibenclamide was produced in 100ml volumetric flask previously filled with 50ml of Phosphate buffer 7.4 and final volume marked up to 100ml with phosphate buffer 7.4 given concentration of 1000 µg/ml further dilutions were made to obtain concentration range of 5-50 µg/ml. The standard solutions prepared as above were used to obtain calibration curve in order to find the unknown concentration of Glibenclamide, for further study.

Formulation and Development of Transdermal Patches [16,17]
Transdermal patches were prepared using the solvent casting method, incorporating various polymers. Initially, 3ml of distilled water was added to pre-weighed HPMC (Hydroxypropyl Methylcellulose). The polymer was then continuously stirred with a magnetic stirrer for 15 minutes to induce swelling. Subsequently, the polymer solution was blended with propylene glycol. Glibenclamide was weighed and added to 2ml of water. The polymer dispersion and the drug solution were thoroughly mixed, and citric acid was added to the mixture. This solution was allowed to sit for a period to allow the removal of any bubbles. Afterward, the solution was poured into petri dishes and left at room temperature for 24 hours to facilitate proper drying. On the following day, the films were carefully removed by peeling, and square pieces with dimensions of 2x2cm were cut from them. These films were then packaged in aluminium foil and stored for further analysis and studies.

Evaluation of Transdermal Delivery Patches
The Physicochemical evaluation of transdermal patches are based on following parameters

Thickness of patch [18]

For this study screw gauze check was done at 5 different points and average was taken.

Weight uniformity [19]

Random 5 films were selected and weighed properly to find out any weight variation.

Folding endurance [20]

It was calculated by folding the film at same sport until it breaks gives value for folding endurance.

Percentage moisture content [21]

Before and after weight of patches were calculated by using desiccator.

Percentage moisture uptake [22]

The weighed patches were reserved in desiccators at room temperature for 24h comprising saturated solution of potassium chloride in order to maintain 84% RH. After 24h, the patches were reweighed and determined the percentage moisture uptake from the formula.

Drug content [23]
A certain area of film was dissolved in a phosphate buffer solution. The contented was stirred to dissolve the transdermal patch. The content was relocated to a volumetric flask. The absorbance of the solution was measured and content of drug was determined.

Bio enhancing Activity Model
Preparation of phosphate buffered saline pH 7.4 [7]

0.19 g of potassium dihydrogen phosphate, 2. 38 g of disodium hydrogen orthophosphate, and 8 g of NACL changed into weighed appropriately and dissolved in distilled water, subsequently the quantity become made up to 1000 ml with distilled water. The pH of the buffer changed into attuned to 7. 4.

A) Ex-vivo Permeation Study [24,25,26]

Goat skin was prepared and used for ex vivo penetration experiments in Franz diffusion cells. The cells had a surface area of 3.14 cm^2 and a receptor chamber volume of 15 ml. Treated goat skin was placed between the receptor and donor compartments, with the transdermal patch on top. The system was maintained at a constant temperature of 37.5 ºC ± 0.5ºC using a phosphate buffer at pH 7.4. A clamp secured the compartments together. Samples were periodically withdrawn and replaced with phosphate buffer to control drug permeation. Absorbance was measured against a reference phosphate buffer. Drug concentration was determined using a Glibenclamide standard curve in phosphate buffer at pH 7.4. The cumulative drug penetration across the patch area over time was plotted."

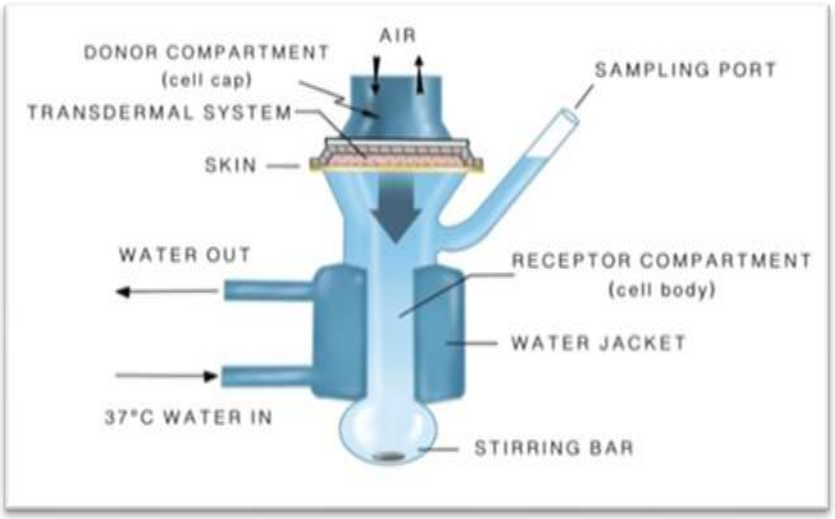

Figure 4: Franz Diffusion Cell

Everted Gut Sac Model [27,28]
Goat small intestine was obtained from a local market after slaughter. It was divided into two segments, each measuring 15 cm, with an estimated diameter of 0.7 cm. One end of the intestine was tied and everted using a glass rod. A cannula was connected to the other end to create a pouch, into which a small volume of drug-free phosphate buffer was added. To keep the tissue alive, continuous oxygen supply was provided using an oxygen pump and phosphate buffer solution. The temperature was maintained at 37± 0.5oC throughout the procedure. After eversion, the mucosal side faced outward, and the serosal side was inside. The stratum corneum side of the skin was kept in close contact with the release surface of the transdermal patches. Absorbance measurements were taken using a spectrophotometer.

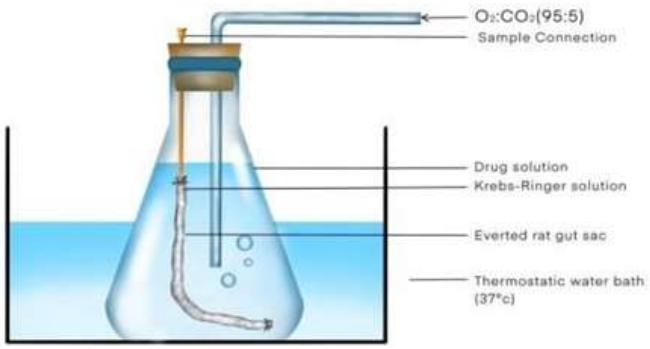

Figure 5: Everted Gut Sac Model

Table 1: Formulation code (Glibenclamide+Extracts)

Formulations	Content
F1	Glibenclamide
F12	Glibenclamide+ Capsicum Fruit Chloroform Extract
F13	Glibenclamide+ Capsicum Fruit Butanolic Extract
F14	Glibenclamide+ Capsicum Fruit Methanolic Extract
F15	Glibenclamide+ Capsicum Fruit Ethanolic Extract
F16	Glibenclamide+ Capsicum Fruit Aqueous Extract

Table 2: Calibration readings of Glibenclamide

S. N	Concentration(µg/ml)	Absorbance
1	5	0.201
2	10	0.403
3	15	0.598
4	20	0.795
5	25	0.989
6	30	1.179

Table 3: Formulation Design for Capsicum fruit Extracts+ Glibenclamide

Ingredients	FORMULATION CODE					
	F1	F12	F13	F14	F15	F16
Glibenclamide	100mg	100mg	100mg	100mg	100mg	100 mg
HPMC	400 mg	400 mg	400 mg	400 mg	400 mg	400 mg
PG	0.4ml	0.4ml	0.4ml	0.4ml	0.4ml	0.4ml
PEG-400	0.4ml	0.4ml	0.4ml	0.4ml	0.4ml	0.4ml
Citric Acid	10mg	10mg	10mg	10mg	10mg	10mg
Water	Up to 5ml	Up to 5ml	Up to 5ml	Up to 5ml	Up to 5ml	Up to 5ml
Chloroform extract	-----	50mg	-----	-----	-----	-----
Butanolic Extract	-----	-----	50mg	-----	-----	-----
Methanolic Extract	-----	-----	-----	50mg	-----	-----
Ethanolic Extract	-----	-----	-----	-----	50mg	-----
Aqueous extract	-----	-----	-----	-----	-----	50mg

3. Results and Discussion

All the formulated patches efficiently worked subjected to diffusion examine which is supported out with the assist of the Franz diffusion cellular technique and Everted gut sac model. Samples have been amassed at predetermined time and absorbance of each sample becomes measured with the help of spectrophotometer which will discover the %of drug content. The result of the diffusion studies has been mentioned in graph by means of plotting time in x axis and cumulative % launch in y axis in addition to % absorbance against time in case of Everted gut sac version. At some point of this have a look at it has been discovered that herbal bioenhancers like cumin seed extract can be used in conjunction with contemporary medication like Glibenclamide with a purpose to increase bioavailability of drug.

1.Compatibility studies of drug and extract as well as drug and polymers were studied with the help of FTIR shows no drug extract and drug polymer interaction, result of which shown in fig.7- 12

2. Physicochemical parameters like % moisture content, thickness, weight variation etc are within limit shown in table 4

3. Ex vivo permeability studies are mention in table 5 and fig. 13

4. Everted Gut Sac studies are mention in table 6 and fig.14

Amongst all the extract Methanolic extract of Capsicum Fruit **(F15)** showed significant increase in % CDR as well as in drug absorbance.

Order of permeation enhancing effect Franz Diffusion cell studies

As an extension to this work In-vivo studies and clinical research on human being can be carried out in future.

Table 4: Evaluation of patches of Capsicum fruit Extracts+ Glibenclamide

Parameters	FORMULATION CODE					
	F1	F12	F13	F14	F15	F16
Thickness (mm)	0.221± 0.008	0.311± 0.005	0.312± 0.102	0.202± 0.010	0.274± 0.101	0.274± 0.145
Weight uniformity(gm)	0.180± 0.009	0.175± 0.009	0.170± 0.007	0.177± 0.009	0.170± 0.102	0.172± 0.140
% Moisture uptake	7.202± 1.62	9.124± 2.145	7.312± 1.747	9.145± 2.11	7.312± 1.12	8.347± 1.45
% Moisture content	4.776± 0.543	5.890± 0.663	4.551± 0.636	4.434± 0.207	5.045± 0.214	6.045± 0.214
% Drug content(mg)	79.2± 0.63	78.89± 0.142	74.89± 0.34	82.74± 0.02	80.80± 0.91	80.92± 0.45

All data are presented in Average ± SD, n=3

Table 5: % CDR of Capsicum fruit Extracts+ Glibenclamide patches

Time in hrs.	Formulation Code					
	F1	F12	F13	F14	F15	F16
0.5	2.32 ±0.35	2.38 ±0.14	4.23 ±0.81	5.14 ±0.62	7.41 ±0.66	3.11 ±0.34
1.0	4.30 ±1.09	4.34 ±0.37	4.89 ±1.12	6.45 ±0.23	8.87 ±0.76	4.60 ±0.76
1.5	6.12 ±1.22	6.14 ±0.45	6.97 ±0.65	7.45 ±0.57	9.19 ±0.45	6.78 ±1.23
2.0	8.04 ±1.01	8.13 ±1.01	10.61 ±0.59	11.23 ±0.41	13.94 ±0.41	9.76 ±0.71
2.5	9.11 ±1.56	9.17 ±0.67	13.34 ±0.50	15.89 ±0.19	18.76 ±0.41	11.24 ±0.57
3.0	10.88 ±1.10	11.03 ±0.15	17.67 ±0.19	20.49 ±0.69	23.88 ±0.71	14.67 ±1.43
4.0	13.44 ±1.67	13.48 ±0.63	24.90 ±1.16	27.15 ±0.87	31.44 ±1.12	18.34 ±1.61
5.0	24.67 ±1.05	24.72 ±1.12	30.71 ±0.60	34.59 ±0.81	36.21 ±0.49	28.74 ±0.14
6.0	35.34 ±1.55	35.39 ±1.34	41.87 ±0.49	47.55 ±0.38	50.03 ±1.13	38.15 ±0.37
8.0	53.21 ±1.27	54.14 ±0.17	60.13 ±0.98	65.67 ±0.89	70.74 ±1.15	58.64 ±1.21

*All information is offered in Average ± SD, n=3

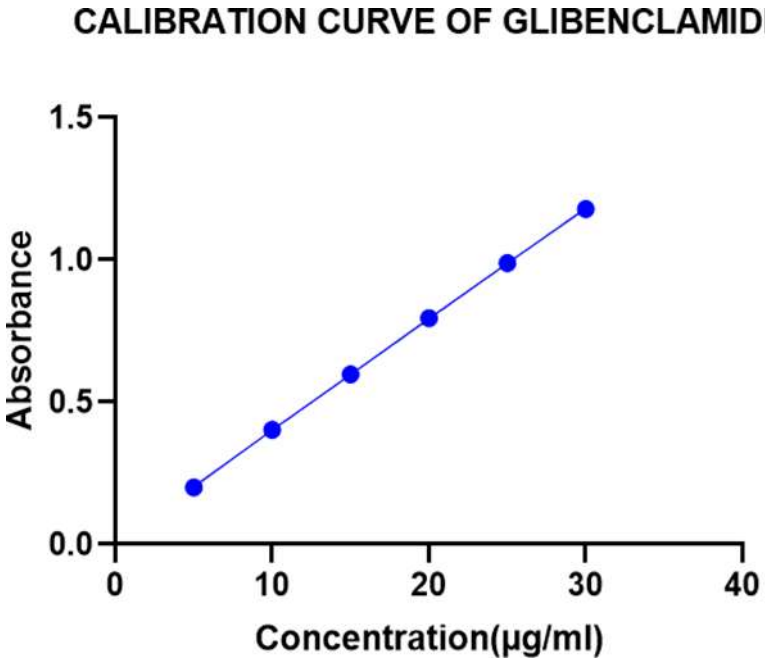

Figure 6: Calibration Curve of Glibenclamide

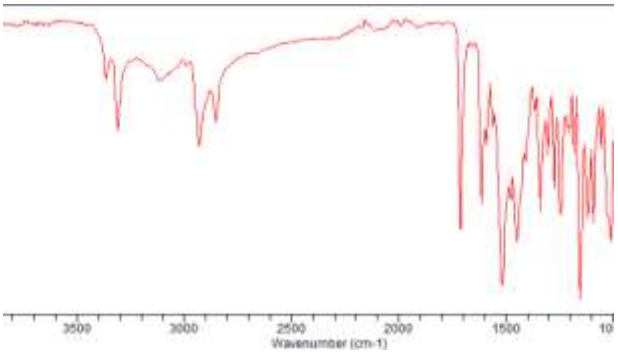

Figure 7: IR Spectra of F1 Formulation

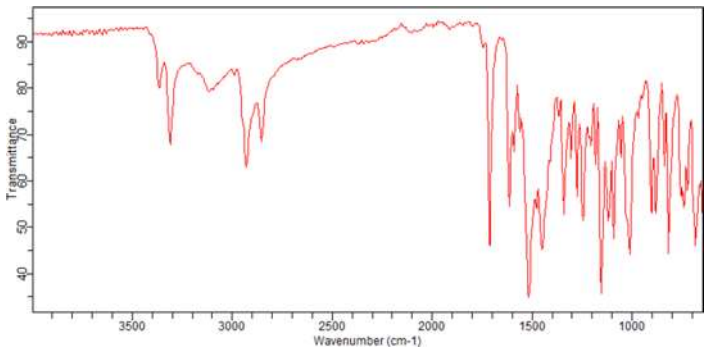

Figure 7: IR Spectra of F1 Formulation

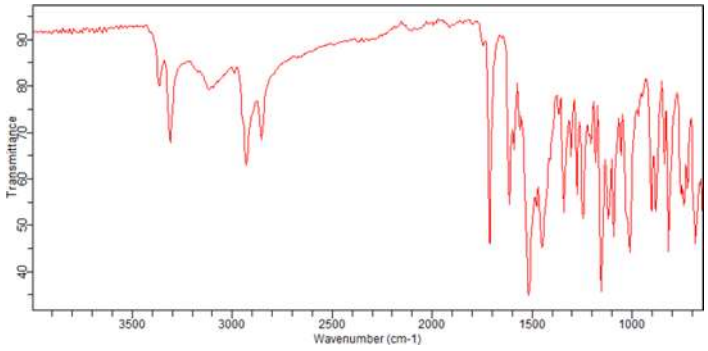

Figure 8: IR Spectra of F12 Formulation

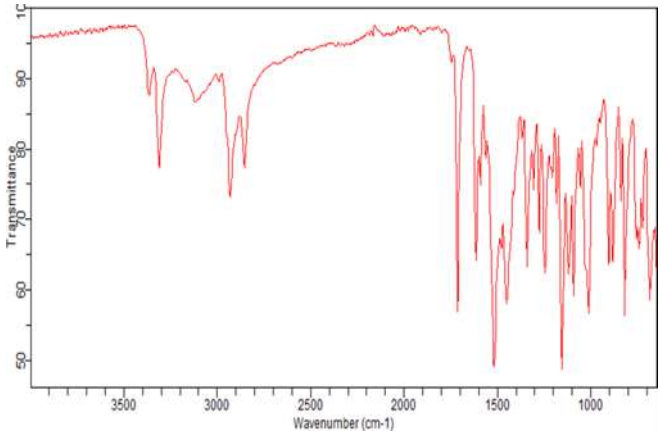

Figure 9: IR Spectra of F13 Formulation

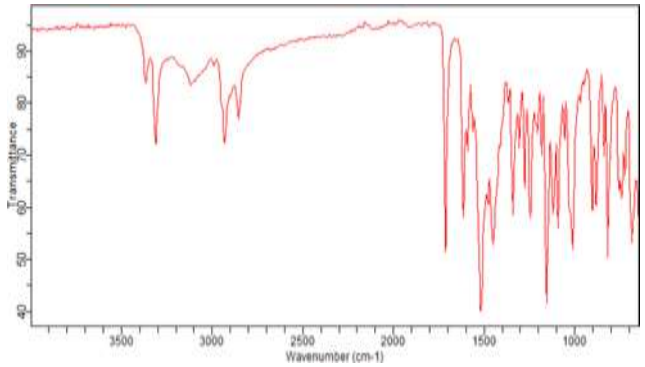

Figure 10: IR Spectra of F14 Formulation

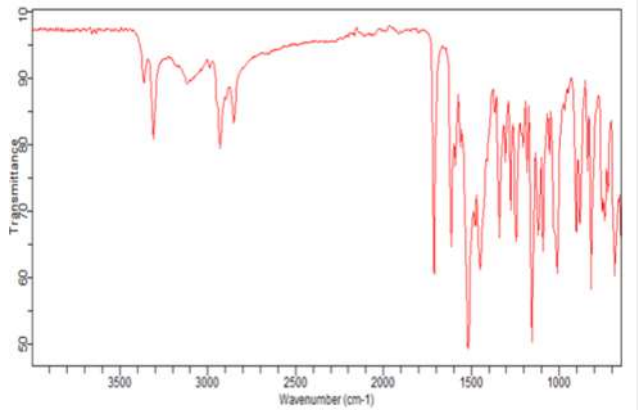

Figure 11: IR Spectra of F15 Formulation

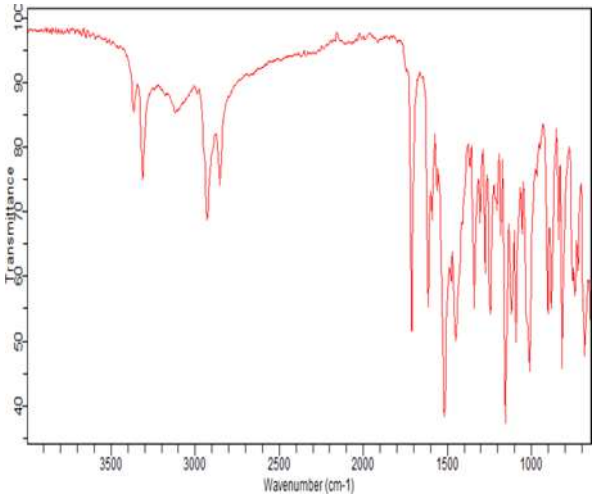

Figure 12: IR Spectra of F16 Formulation

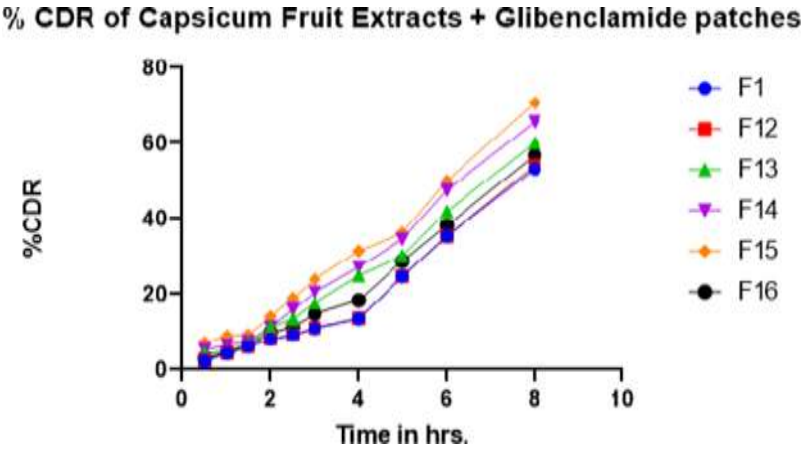

Figure 13: %CDR of Capsicum Fruit Extracts and Glibenclamide

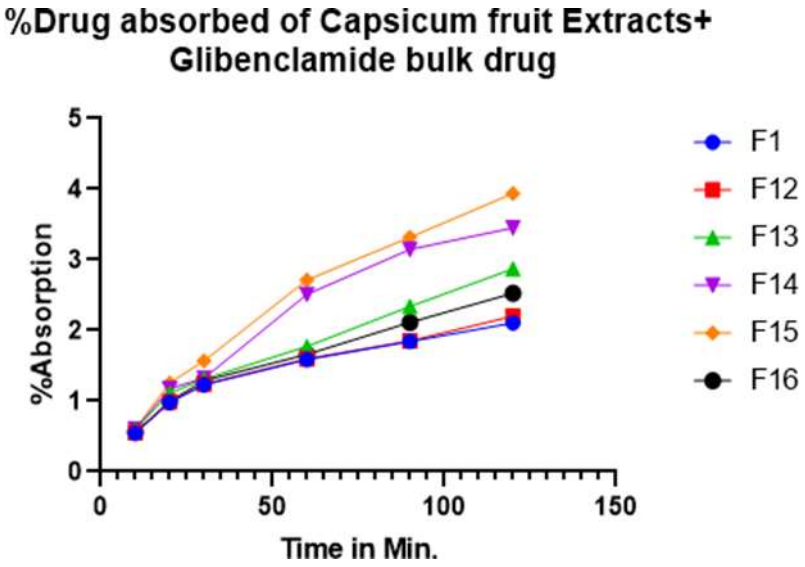

Figure 14: % Drug absorbed of Capsicum fruit Extracts and Glibenclamide

4. Conclusion

In conclusion, herbal drugs in the form of extracts can be a viable option for formulating transdermal patches, offering a novel approach to drug delivery. Transdermal patches containing Glibenclamide were developed using the solvent evaporation method, incorporating various extracts from Capsicum

fruits alongside Glibenclamide. The drug exhibited compatibility with different extracts and polymers, with all extracts demonstrating some degree of bio enhancing effect compared to individual Glibenclamide patches. Among all the formulations, F15 displayed a significant increase in drug release and drug absorption.

Acknowlegement
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Conflict of Interest
Authors have no conflict of interest regarding this research work.

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