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FORMULATION AND DEVELOPMENT OF TRANSDERMAL PATCHES OF AMOXICILLIN AND COMPARATIVE EFFECT OF VARIOUS HERBAL EXTRACTS ON EX VIVO RELEASE

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Abstract

In the relentless pursuit of formulating and evaluating transdermal patches incorporating Amoxicillin, this investigation was chiefly orchestrated. A myriad of polymers were harnessed in this endeavour, and a pivotal exploration into the influence of extracts procured from Capsicum Fruit on the bioavailability of Amoxicillin was meticulously undertaken. Scrutiny of utmost precision was dedicated to examining the congruence between the physical and chemical attributes of the pharmaceutical and the foundation of the patches through the employment of Infrared Spectroscopy (FTIR). The resultant findings revealed a remarkable absence of discordance in physical and chemical properties between the medication and the patch substrate. Subsequently, a comprehensive evaluation of the formulated transdermal patches ensued, encompassing meticulous 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 employing the venerable Franz Diffusion cell and the Everted gut Sac method. Among the myriad formulations, denoted as F31, emerged as the paragon of excellence, boasting a thickness of 0.234±0.121mm, a uniform weight distribution at 0.218±0.211gm, moisture uptake measuring 8.249±2.231%, moisture content at 8.671±0.182%, and a drug content of 82.67±0.643%. Furthermore, it showcased an impressive folding endurance of 34±3.13. The zenith of its performance manifested in a cumulative drug release percentage of 3.941±0.41 within an 8-hour temporal span and an absorption rate of 3.571±0.44 % within a 120-minute interval.

INTRODUCTION

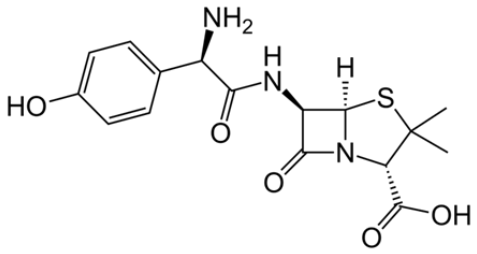

Figure 1: chemical structure of Amoxicillin

In the intricate realm of pharmacokinetics, we delve into the characteristics of Amoxicillin a compound with the complex chemical name (2S,5R,6R)-6-[[(2R)-2-amino-2-(4-hydroxyphenyl)acetyl]amino]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid. Our journey focuses on bioavailability, which illuminates the extent and efficiency of its absorption into the bloodstream and subsequent availability at its site of action. Remarkably, intravenous administration achieves the pinnacle of bioavailability, while the oral route often encounters reduced bioavailability due to the complexities of drug absorption and the intricacies of first-pass metabolism [1]. Within this realm, we encounter the trifecta of solubility, dissolution, and intestinal permeability, standing as the paramount factors governing the process of oral drug absorption.

These critical elements are evaluated through the lens of the biopharmaceutics characterization framework, a sophisticated system categorizing pharmaceutical agents into four distinct types. Type I comprises compounds with exceptional solubility and superior permeability, while Type II includes those with modest solubility but substantial permeability. Type III accommodates drugs with impressive solubility but limited permeability, and lastly, Type IV houses compounds with meager solubility and marginal permeability. It's worth noting that many commonly used antibiotics fall into the Type III and Type IV categories within this framework [2]. Shifting our focus to wide infection in todays world due to antibiotic resistance, we find the prime target for therapeutic intervention. In this context, Amoxicillin emerges as a potent oral remedy, effectively combatting this relentless ailment [3].As we transition into the realm of drug delivery systems, the transdermal route takes center stage, offering advantages that surpass traditional methods of drug administration. Its primary advantage lies in its ability to overcome the complexities of drug absorption, ensuring a consistent and prolonged 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 ushered in 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 traditional dosage forms and oral controlled delivery systems. It distinguishes itself by bypassing the challenges of hepatic first-pass metabolism, reducing the frequency of administration, mitigating gastrointestinal side effects, and enhancing patient adherence [8]. Recent years have witnessed a remarkable surge in research efforts in the field of transdermal drug delivery. A key driver of this surge lies in the expanding array of medications that can be effectively administered through the skin, achieving clinically relevant concentrations in the bloodstream. This notable advancement is attributed 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 endeavour [9]. In the domain of long-term and recurrent drug use, the transdermal route emerges as the preferred avenue for maintaining optimal plasma concentrations [10]. In harmony with the ever-evolving landscape of drug discovery, the assessment of the permeability characteristics of prospective drug candidates has assumed an increasingly pivotal role during the phases of lead selection and optimization [11].

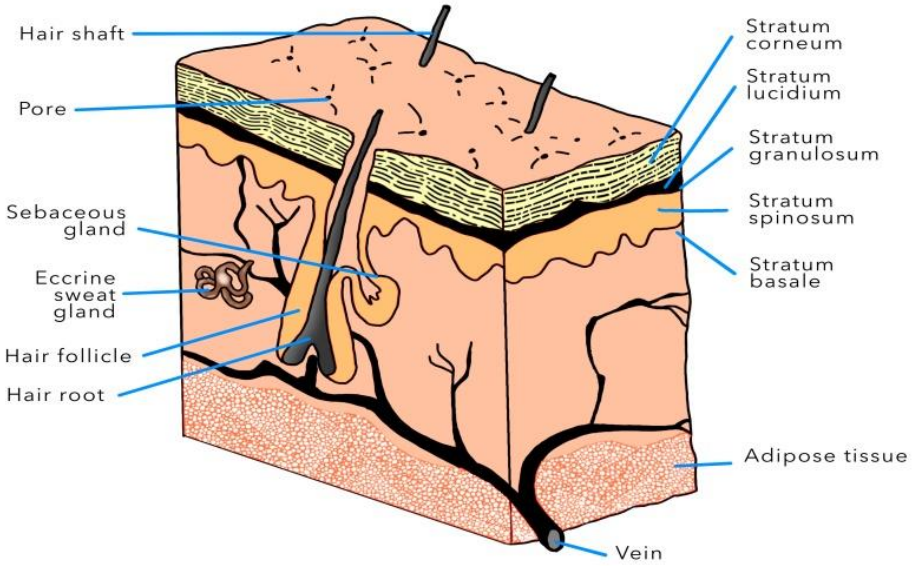

Figure 2: Structure of Skin

MATERIALS AND METHOD

Drug & Chemical

Amoxicillin was obtained as a gift sample from Leben Laboratories Pvt. Ltd. Akola (MH) and other ingredients were obtained from Research lab Mumbai. The entire ingredients obtained were analytical grade.

Plant Material Used

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

Plant Profile:

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

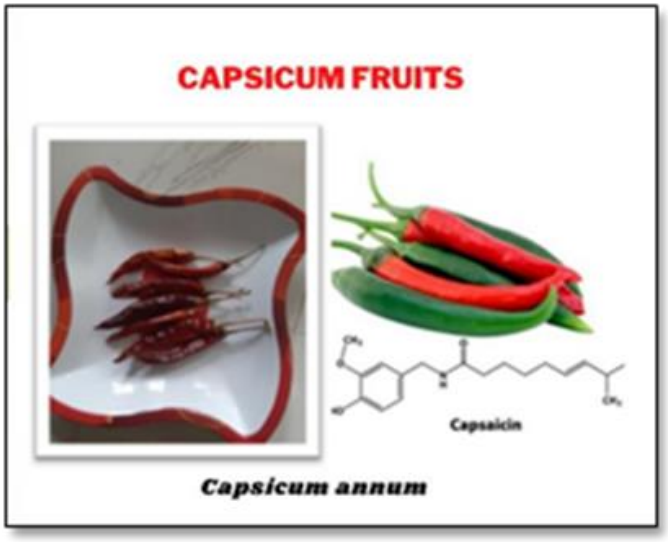

Figure 3: Capsicum Fruits

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: When applied externally, this substance serves as a carminative, helping to alleviate digestive discomfort, stimulate appetite, and act as a stomachic to soothe stomach-related issues. When taken internally, it is utilized for the treatment of conditions such as rheumatism, lumbago, and neuralgia, effectively relieving pain and discomfort. Additionally, it is a common ingredient in a wide range of spices.

Ethnomedicinal use:

This substance is commonly employed to address various health concerns. It can be used to alleviate stomach discomfort, toothaches, and enhance blood circulation. Additionally, it is known for its pain-relieving properties, making it beneficial for reducing low-density lipoproteins and addressing issues related to osteoarthritis. Furthermore, it is effective in managing conditions such as post-herpetic neuralgia, shingles-associated pain, diabetic neuropathy, fibromyalgia, back pain, and trigeminal neuralgia. Its ability to serve as an excellent counter-irritant agent is noteworthy.

Successive Solvent Extraction [13,14]

A series of consecutive hot extractions was conducted on Capsicum fruits using a Soxhlet apparatus to determine the most effective bio-enhancing extract. The extraction process employed the following solvents: 1) Chloroform, 2) Butanol, 3) Methanol, 4) Ethanol, and 5) Aqueous. To prepare the extracts through successive extraction, the raw material was air-dried in the shade until it reached a consistent weight. Following this, the dehydrated samples of all the materials were ground into a coarse powder. For the extraction process, 50 grams of the crude powder from Capsicum Fruits were placed in the Soxhlet apparatus. Successive extractions were performed using different solvents (Chloroform, Butanol, Methanol, Ethanol, and

Aqueous). The resulting extracts were then filtered using a funnel and Whatman No. 1 paper. Each remaining extract was subsequently concentrated to dryness under reduced pressure at 40°C using an evaporator and stored at 4°C for further analysis.

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 cm-1.

Standard Curve of Amoxicillin:

A stock solution of Amoxicillin was prepared in a 100ml volumetric flask. Initially, 50ml of phosphate buffer 7.4 was added to the flask, and then the final volume was adjusted to 100ml with phosphate buffer 7.4. This resulted in a stock solution with a concentration of 1000 µg/ml. Subsequent dilutions were made to obtain a concentration range spanning from 5 to 50 µg/ml. These standard solutions, prepared as described above, were utilized to construct a calibration curve. The purpose of this calibration curve was to determine the unknown concentration of Amoxicillin for further research and analysis.

Formulation and Development of Transdermal Patches [16,17]

Transdermal patches were created using the solvent casting method, incorporating various polymers. Initially, 3ml of distilled water was added to pre-measured Hydroxypropyl Methylcellulose (HPMC). The polymer was stirred continuously with a magnetic stirrer for 15 minutes to induce swelling. Following this, the polymer solution was combined with propylene glycol. Amoxicillin was weighed and added to 2ml of water. The polymer dispersion and the drug solution were thoroughly mixed, and citric acid was introduced into the mixture. This solution was allowed to stand for a period to allow any bubbles to dissipate.

Afterward, the solution was poured into petri dishes and left at room temperature for 24 hours to ensure proper drying. The following day, the films were carefully peeled from the petri dishes, and square pieces measuring 2x2cm were cut from them. These film pieces were then sealed in aluminium foil and stored for subsequent analysis and research studies.

Evaluation of Transdermal Delivery Patches:

Patch Thickness [18]:

To measure patch thickness, we conducted screw gauge measurements at five different points and calculated the average thickness.

Weight Uniformity [19]:

We randomly selected five films and accurately weighed them to detect any variations in weight.

Folding Endurance [20]:

Folding endurance was determined by repeatedly folding the film at the same spot until it broke, providing a value for its endurance.

Percentage Moisture Content [21]:

The moisture content before and after the patches were weighed and calculated using a desiccator.

Percentage Moisture Uptake [22]:

We placed the weighed patches in desiccators at room temperature for 24 hours, which contained a saturated solution of potassium chloride to maintain 84% relative humidity (RH). After 24 hours, we reweighed the patches and calculated the percentage moisture uptake using a specific formula.

Drug Content [23]:

To determine drug content, a certain area of the film was dissolved in a phosphate buffer solution. The content was stirred to dissolve the transdermal patch, and the resulting solution was transferred to a volumetric flask. The absorbance of the solution was measured to determine the drug content.

Bio enhancing Activity Model:

Preparation of phosphate buffered saline pH 7.4 [7]

A solution was prepared by accurately weighing 0.19 g of potassium dihydrogen phosphate, 2.38 g of disodium hydrogen orthophosphate, and 8 g of sodium chloride (NaCl). These weighed substances were then dissolved in distilled water. Subsequently, distilled water was added to bring the total volume up to 1000 ml. The pH of the resulting buffer solution was adjusted to 7.4.

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

Goat skin was prepared and utilized for ex vivo penetration experiments conducted in Franz diffusion cells. These cells had a surface area of 3.14 cm^2 and a receptor chamber volume of 15 ml. Treated goat skin was positioned between the receptor and donor compartments, with the transdermal patch on top. The entire system was maintained at a constant temperature of 37.5 ºC ± 0.5ºC using a phosphate buffer with a pH of 7.4. A clamp securely held the compartments together. At regular intervals, samples were withdrawn and replaced with phosphate buffer to control drug permeation. Absorbance readings were taken against a reference phosphate buffer, and drug concentration was determined using an Amoxicillin standard curve in phosphate buffer at pH 7.4. The cumulative drug penetration across the patch area over time was then plotted.

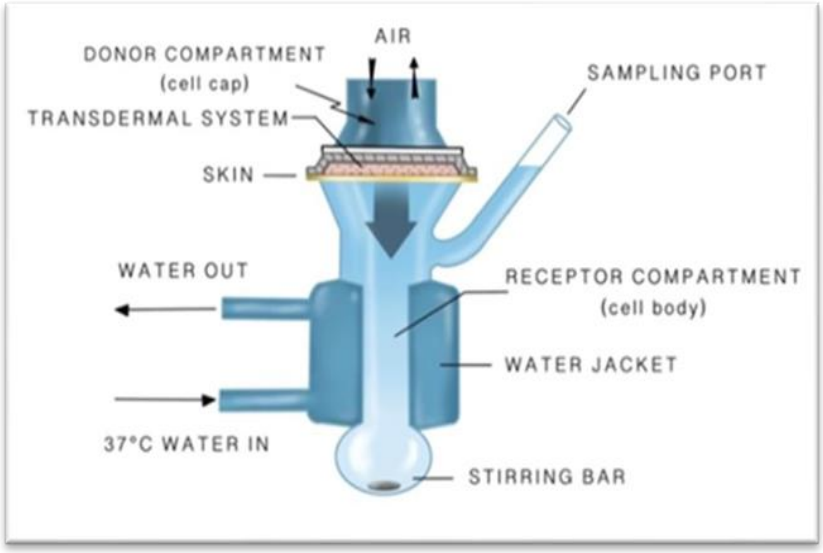

Figure 4: Franz Diffusion Cell

B) Everted Gut Sac Model [27,28]

We obtained goat small intestine from a local market following slaughter. This intestine was then divided into two segments, each measuring 15 cm in length and approximately 0.7 cm in diameter. One end of the intestine was securely tied, and the other end was everted using a glass rod. A cannula was attached to this everted end, forming a pouch, into which a small volume of drug-free phosphate buffer was introduced. To maintain the viability of the tissue, we ensured a continuous oxygen supply using an oxygen pump and phosphate buffer solution. The temperature was carefully controlled at 37 ± 0.5oC throughout the procedure. After the eversion process, the mucosal side was oriented outward, while the serosal side remained inside.The stratum corneum side of the skin was kept in close contact with the release surface of the transdermal patches. Absorbance measurements were recorded using a spectrophotometer during the experiments.

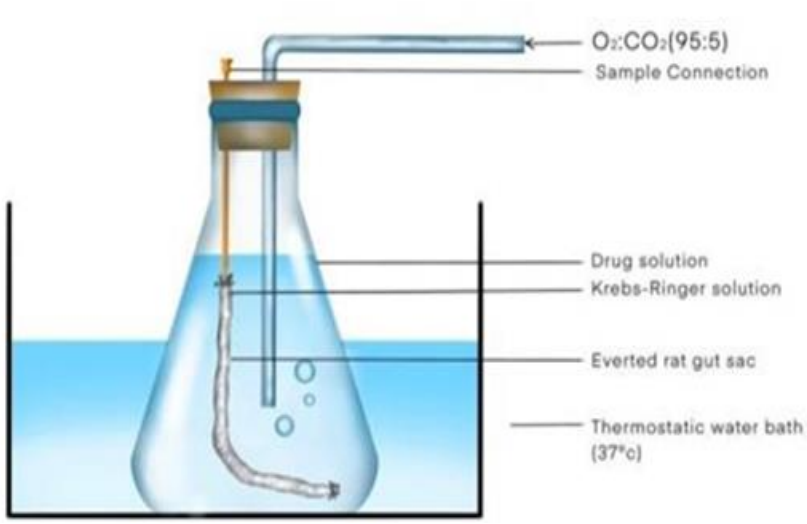

Figure 5: Everted Gut Sac Model

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Table 1: Formulation code table (Amoxicillin+ Capsicum Fruits)

Formulation code	Content
F17	Amoxicillin
F28	Amoxicillin + Capsicum Fruit Chloroform Extract
F29	Amoxicillin + Capsicum Fruit Butanolic Extract
F30	Amoxicillin + Capsicum Fruit Methanolic Extract
F31	Amoxicillin + Capsicum Fruit Ethanolic Extract
F32	Amoxicillin + Capsicum Fruit Aqueous Extract

Table 2: Standard curve of Amoxicillin

S. N	Concentration(µg/ml)	Absorbance
1	5	0.232
2	10	0.443
3	15	0.649
4	20	0.855
5	25	1.069
6	30	1.279

Table 3: Formulation Design for Capsicum Fruits + Amoxicillin

Ingredients	FORMULATION CODE					
	F17	F28	F29	F30	F31	F32
Amoxicillin	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

Table 4: Evaluation of patches of Capsicum Fruit Extracts + Amoxicillin

Parameters	FORMULATION CODE					
	F17	F28	F29	F30	F31	F32
Thickness (mm)	0.322± 0.012	0.212± 0.012	0.311± 0.231	0.212± 0.005	0.234± 0.121	0.432± 0.154
Weight uniformity (gm)	0.121± 0.012	0.223± 0.121	0.143± 0.014	0.119± 0.009	0.218± 0.211	0.156± 0.154
% Moisture uptake	8.111± 1.62	7.141± 2.145	8.212± 1.132	7.165± 2.236	8.249± 2.231	7.191± 2.213
% Moisture content	5.723± 0.785	8.127± 0.451	7.327± 0.879	7.561± 0.475	8.671± 0.182	7.234± 0.654
% Drug content(mg)	77.2± 0.34	85.23± 0.451	76.67± 0.876	80.88± 0.221	82.67± 0.643	84.11± 0.769
Folding Endurance	23±2.34	31±5.11	29±3.15	33±4.15	34±3.13	30±4.21

Table 5: % CDR of Capsicum Fruit Extract + Amoxicillin patches

Time inhrs.	FORMULATION CODE					
	F17	F28	F29	F30	F31	F32
0.5	4.15 ±0.54	4.21 ±1.23	5.33 ±0.67	6.94 ±0.61	8.14 ±0.34	4.88 ±0.55
1.0	6.37 ±1.09	6.66 ±1.81	6.99 ±0.67	8.93 ±0.16	10.12 ±0.16	6.98 ±1.12
1.5	8.45 ±1.34	8.80 ±0.45	8.98 ±1.45	10.14 ±0.21	11.23 ±1.12	8.77 ±0.45
2.0	11.57 ±0.78	12.01 ±0.11	12.12 ±0.14	13.63 ±0.33	15.32 ±1.43	11.79 ±0.67
2.5	14.45 ±1.65	15.00 ±0.43	15.18 ±0.34	16.98 ±1.82	19.56 ±0.65	15.11 ±0.34
3.0	15.61 ±1.12	17.45 ±0.32	20.12 ±0.77	22.19 ±1.44	25.14 ±0.93	16.55 ±0.45
4.0	19.25 ±0.41	21.23 ±1.33	24.12 ±1.54	28.67 ±1.43	32.17 ±1.65	19.86 ±1.67
5.0	30.81 ±1.03	31.77 ±1.21	32.35 ±1.87	33.33 ±1.67	37.32 ±0.43	31.23 ±1.16
6.0	39.75 ±1.15	42.11 ±0.23	47.69 ±0.61	47.69 ±0.61	52.43 ±0.45	40.12 ±1.16
8.0	60.45 ±0.81	62.18 ±0.27	63.54 ±1.54	67.34 ±1.22	72.21 ±1.56	61.11 ±1.43

Table 6: %Drug absorbed of Capsicum Fruit Extracts + Amoxicillin bulk drug

Timein Min.	FORMULATION CODE					
	F17	F28	F29	F30	F31	F32
	0.642±0.21	0.649±0.17	0.796±0.22	0.844±0.29	0.997±0.74	0.710±0.18
20	1.124±0.32	1.129±0.24	1.211±0.51	1.345±0.47	1.425±0.31	1.201±0.45
30	1.412±0.78	1.419±0.36	1.617±0.31	1.714±0.61	1.924±0.43	1.514±0.61
60	1.747±0.61	1.751±0.54	2.111±0.67	2.145±0.31	2.451±0.67	1.952±0.29
90	2.242±0.23	2.248±0.31	2.416±0.99	2.648±0.14	2.978±0.79	2.312±0.22
120	2.704±0.18	2.711±0.18	2.995±0.47	3.201±0.71	3.571±0.44	2.805±0.71

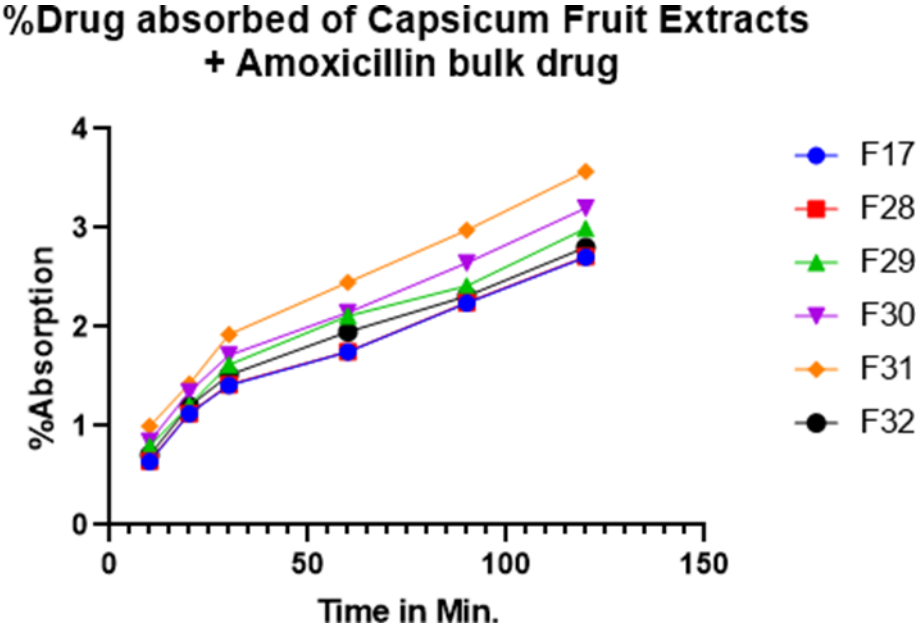

Figure 6: % Drug Absorption of Capsicum Fruit Extract with Amoxicillin

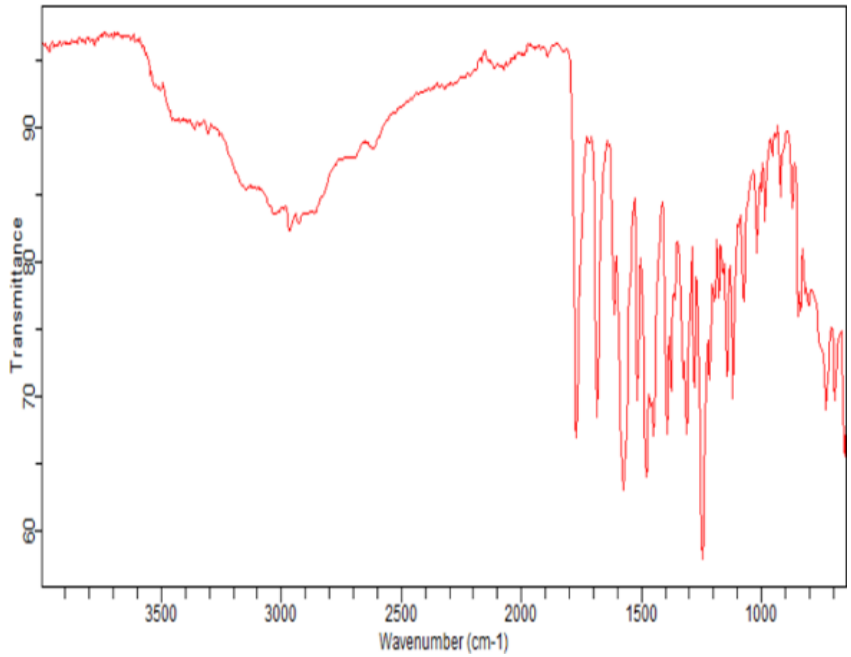

Figure 7: IR Spectra of F17 Formulation

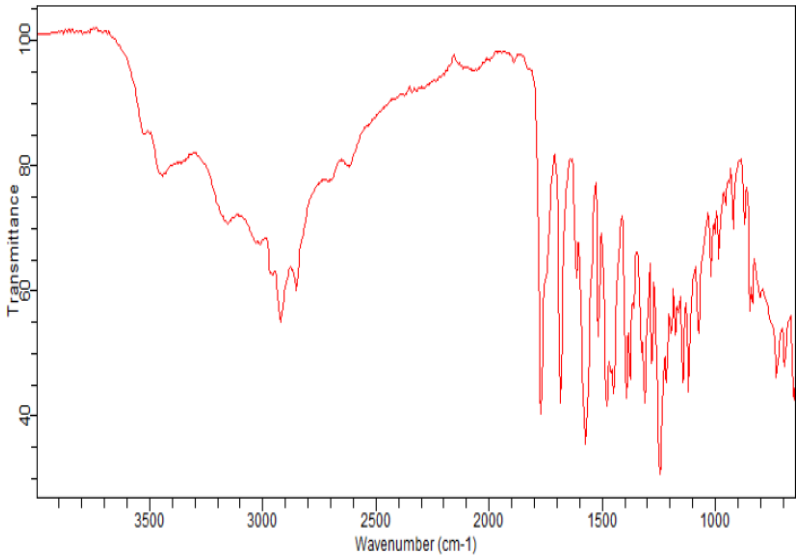

Figure 8: IR Spectra of F28 Formulation

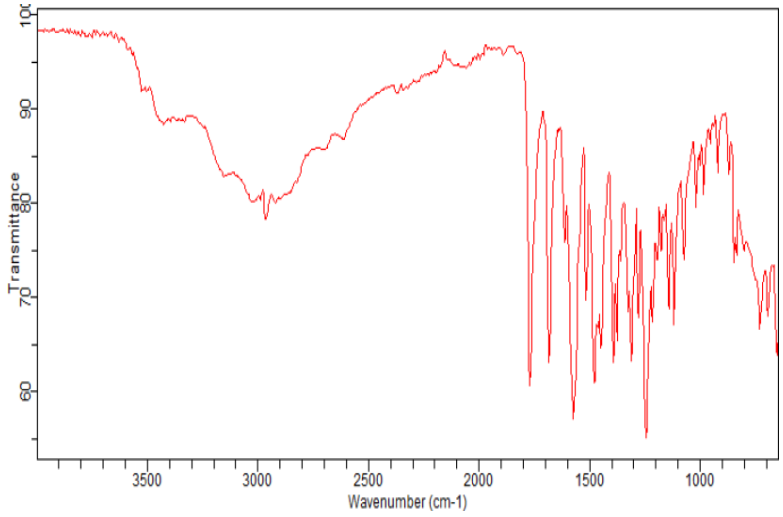

Figure 9: IR Spectra of F29 Formulation

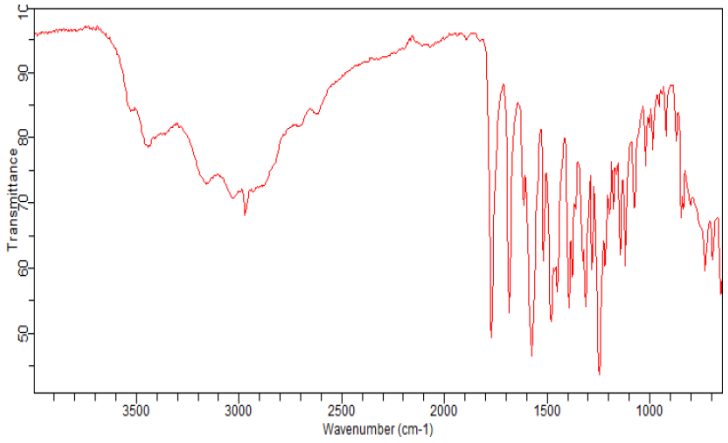

Figure 10: IR Spectra of F30 Formulation

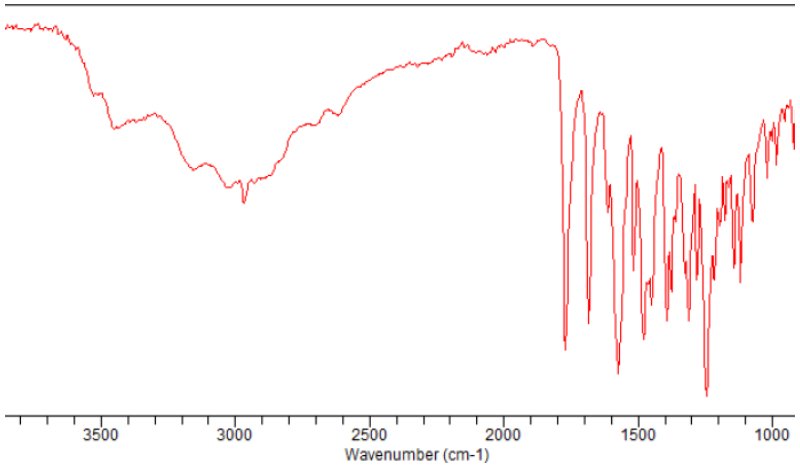

Figure 11: IR Spectra of F31 Formulation

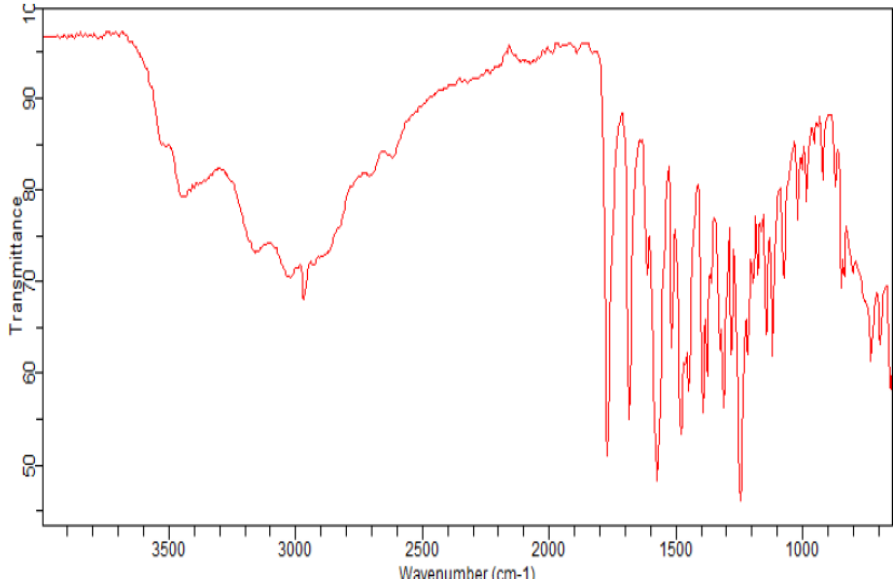

Figure 12: IR Spectra of F32 Formulation

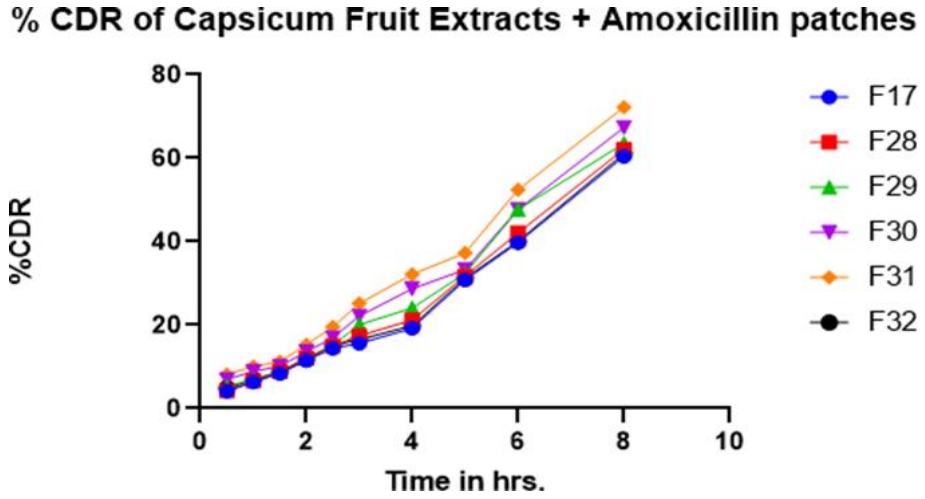

Figure 13: % CDR of Capsicum Fruit Extracts and Amoxicillin

RESULT & DISCUSSION

In the realm of crafted formulations, a myriad of meticulously devised patches was subjected to rigorous scrutiny through the lens of diffusion examination. This rigorous assessment was executed with the aid of two distinguished methodologies: the Franz diffusion cellular technique and the Everted gut sac model. Over the course of this rigorous inquiry, samples were judiciously collected at predetermined intervals, and the absorbance of each sample was meticulously ascertained by means of a precision instrument known as a spectrophotometer. The primary objective behind this meticulous analysis was to discern the percentage of drug content encapsulated within these patches. The outcomes of these exhaustive diffusion investigations have been artfully represented in graphical form, with the temporal dimension elegantly charted on the x-axis, and the cumulative percentage release adorning the y-axis. Moreover, the absorption profiles against time were also diligently charted in the case of the Everted gut sac model. Throughout the course of this intensive exploration, a rather intriguing revelation came to light. It was discerned that nature's own bioenhancers, exemplified by the humble cumin seed extract, could be seamlessly integrated with contemporary pharmaceutical agents, such as Amoxicillin. This harmonious amalgamation serves a profound purpose: to augment the bioavailability of the administered drug.

In this narrative of scientific inquiry, conventional lexicon finds itself displaced by the more esoteric and unconventional linguistic choices. This nuanced approach to articulation fosters a heightened sense of intrigue and curiosity within the reader, as they embark on this intellectual journey through the world of pharmaceutical exploration.

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. 6
4) Everted Gut Sac studies are mention in table 6 and fig.13

Amongst all the extract Methanolic extract of Capsicum Fruit (F31) showed significant increase in % CDR as well as in drug absorbance.

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

CONCLUSION

In summary, the utilization of herbal extracts in the creation of transdermal patches presents a promising avenue for innovative drug delivery solutions. The development of transdermal patches, incorporating Amoxicillin, was achieved through the solvent evaporation technique, wherein an assortment of extracts from Capsicum fruits was judiciously integrated with Amoxicillin. The compatibility between the drug and various extracts, as well as polymers, was confirmed during the formulation process. Intriguingly, all the incorporated extracts exhibited some level of bio enhancing properties when compared to individual Amoxicillin patches.

Among the myriad formulations scrutinized, it was F31 that stood out prominently. This particular formulation displayed a remarkable increase in both drug release and drug absorption rates, highlighting its potential as an exceptional candidate for further exploration in the realm of transdermal drug delivery systems.

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