To Design Development and Evaluate of Transdermal Drug Delivery System Containing Antihypertensive Drug.

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Abstract-

Abstract

Hypertension management often involves long-term medication adherence, which can be challenging due to frequent dosing and side effects. Transdermal drug delivery systems offer a promising solution by providing controlled release and improved patient compliance. This study aimed to design, develop, and evaluate a transdermal patch containing an antihypertensive drug. The patch was formulated using polymers and permeation enhancers, and its physicochemical properties, in vitro drug release, and skin permeation were evaluated. In vivo studies were conducted to assess pharmacokinetics and pharmacodynamics. The results showed that the optimized patch provided sustained drug release, enhanced skin permeation, and significant blood pressure reduction. The transdermal system demonstrated improved therapeutic efficacy and patient compliance compared to conventional oral formulations. This study highlights the potential of transdermal drug delivery systems for effective hypertension management.

Keywords: Hypertension, pharmacodynamics, polymers

INTRODUCTION

TRANSDERMAL DRUG DELIVERY SYSTEM (TDDS)

Traditional drug treatment systems that involve multiple doses have much more troubles [(1)]. The drug delivery at a controlled rate is a novel perspective to administer medication into the blood at a predestined rate. This would not only bypass biotransformation but should also maintain efficacious and long-lasting therapeutic levels [(2)]. To achieve this unimpaired skin acts as a drug reservoir to deliver consistent delivery of a medicament into the blood. Following the penetration of the skin, the medicaments initially reach the blood and then delivered to the receptor or site of the target, which usually relatively far away from the starting point to exert a clinically beneficial effect [(3)].

The principle of transdermal drug delivery system is that they could provide controlled drug delivery (have constant drug concentration in plasma) over a prolonged period of time. It is anticipated that transdermal drug delivery system can be designed to input drugs at appropriate rates to maintain suitable plasma drug levels for therapeutic efficacy, without the periodic sojourns into plasma concentration that would accompany toxicity (or) lack of efficacy [(4)]. Transdermal delivery of antihypertensive is one of the prime focus areas of drug delivery systems. Various antihypertensive such as metoprolol, clonidine, propranalol, bupranolol, isosorbide dinitrite, verapamil, nifedipine, etc., have been studied for their suitability in transdermal therapeutic systems [(5)].

Over the past twenty-five years, as the expense and complication involved in marketing new drug entities have increased with concomitant recognition of the therapeutic advantage of controlled drug delivery system. There are several seasons for the attractiveness of these dosage forms. It is generally recognized that for many disease states, a substantial number of therapeutically effective compounds already exist. Side effects or the necessity to administer the compound in a clinical setting, however, often limits the effectiveness of this drug.The goal in designing controlled drug delivery systems is to reduce the frequency of dosing and increase effectiveness of the drug by localization at the site of action. Reducing the dose required (or) providing uniform drug delivery [(6)].

Controlled release drug administration means not only prolonged release, but also implies predictability and reproducibility of drug release kinetics. Controlled drug delivery system is the one, which delivers the drug at a predetermined rate, systematically, for a specific period of time[(7)].

1. MATERIAL AND METHODS

Table no. 5.1: Material Used

EQUIPMENTS

Sr. No.	Ingredient	Source
1	Amlodipine	Gift sample from ipca laboratories limit.
2	Pectin	Himedia Laboratories, Mumbai.
3	Isopropyl myristate (IPM)	Ozone International, Mumbai.
4	PEG	Qualigens Fine Chemicals, Mumbai

Sr. no.	Equipment	Model/Company
1	Franz Diffusion Cell	Chemdyes Corporation Thane
2	UV Visible Spectrophotometer	JASCO V 530
3	FT/ IR Spectrometer	Perkin Elmer
4	Digital balance	Atcom Products
5	Hot air oven	Bioera Life
6	Magnetic stirrer	PA401208
7	Laboratory stirrer with variable speed control	Skeltek
8	Sonicator	Equiptronic

Procedure for fabrication of transdermal film:

Transdermal films were prepared by the film casting method of specially designed glass molds with plastic transparent sheets.

↓

Different ratios of polymer were used for preparation of films.

↓

Varying ratio of polymer dissolved in water.

↓

Then drug which dissolved in small quantity of methanol was incorporated in polymer solution obtained by stirring with glass rod for 10 min.

↓

The penetration enhancer (Isopropyl Myristate) is added to Drug- polymer solution.

↓

The solution is poured on petridish using rod. The rate of evaporation of solvent was controlled by inverting cup funnel. After 24 hrs.

↓

The dried films were out and stored in desiccator between sheets of paper [75].

Table No.7 Formulation of TDDS

Formulation code	Drug (mg)	Pectin	PEG 400	Isopropyl Myrisate (IPM)	Water: Methanol
F1	10	150	0.5	0.5	8:2
F2	10	150	0.5	1.0	8:2
F3	10	150	0.5	1.5	8:2
F4	10	160	0.5	1.7	8:2
F5	10	160	0.5	1.8	8:2
F6	10	160	0.5	2.0	8:2

PREFORMULATION STUDIES

Before the formulation of a drug substance into a dosage form, it is essential that it should be chemically and physically characterized. Preformulation studies give the information needed to define the nature of the drug substance and provide a framework for the drug combination with pharmaceutical excipients in the fabrication of a dosage form. In the present work, pre-formulation studies on the compatibility between drug and polymer were carried out using thin layer chromatography and Infra- Red spectroscopy.

IR Determination

Fourier Transform Infrared Spectroscopy, also known as FTIR Analysis or FTIR Spectroscopy, is an analytical technique used to identify organic, polymeric, and, in some cases, inorganic materials. The FTIR analysis method uses infrared light to scan test samples and observe chemical properties. A change in the characteristic pattern of absorption bands clearly indicates a change in the composition of the material or the presence of contamination.

If problems with the product are identified by visual inspection, the origin is typically determined by FTIR microanalysis. This technique is useful for analyzing the chemical composition of smaller particles, typically 10 -50 microns, as well as larger areas on the surface [78].

Fig.10: Fourier Transform Infrared Spectroscopy (FTIR)

Drug identification

Method - Spectrophotometer method (UV)

UV spectrophotometry refers to absorption spectroscopy or reflectance spectroscopy in part of the ultraviolet and the full, adjacent visible regions of the electromagnetic spectrum. Being relatively inexpensive and easily implemented, this methodology is widely used in diverse applied and fundamental applications. The only requirement is that the sample absorb in the UV-Vis region, i.e. be a chromophore. Absorption spectroscopy is complementary to fluorescence spectroscopy. Parameters of interest, besides the wavelength of measurement, are absorbance (A) or transmittance (%T) or reflectance (%R), and its change with time [79].

Procedure for the Preparation of Standard Curve:-

Amlodipine 50 mg each, were accurately weighed and dissolved separately in 50ml of methanol.

Five ml of the above solutions diluted separately to standard stock solution of 100 mcg/ml eight dilutions ranging 5-40 mcg/ml made.

The absorbance of each sample was measured using UV-visible spectrophotometer. 0.1 N HCl as blank.

The calibration curve was drain by plotting concentration Vs. and absorbance to obtain standard calibration curve [80].

Fig.11: UV Spectrophotometer

5. Differential Scanning Calorimetry (Dsc) -

Differential Scanning Calorimetry (DSC) is a thermoanalytical technique in which the difference in the amount of heat required to increase the temperature of a sample and

reference is measured as a function of temperature. Both the sample and reference are maintained at nearly the same temperature throughout the experiment.

Generally, the temperature program for a DSC analysis is designed such that the sample holder temperature increases linearly as a function of time. The reference sample should have a well-defined heat capacity over the range of temperatures to be scanned.

Additionally, the reference sample must be stable, of high purity, and must not experience much change across the temperature scan. Typically, reference standards have been metals such as indium, tin, bismuth, and lead, but other standards such as polyethylene and fatty acids have been proposed to study polymers and organic compounds, respectively.

Fig.no 12 Differential Scanning Calorimetry (Dsc) -

2. EVALUATION

Characterization of the transdermal patches

Physical appearance

All the transdermal patches are visually inspected for color, clarity, flexibility and smoothness [(81)].

Weight uniformity

Three patches from each batch are accurately weighed using a digital balance. The average weight and the standard deviation values are calculated from the individual weights [(82)].

Thickness

The thicknesses of the drug loaded polymeric films are measured using a digital vernier caliper. The measurements are made at five different points, four at the corners and one at the centre of the patch. The average and standard deviation of five readings were calculated for each formulation [(83)].

Folding endurance

Folding endurance of patches is determined by repeatedly folding the small strip of film at the same place till it breaks. The number of times, the film could be folded at the same place till it breaks will give the value of folding endurance [(84)].

Percentage moisture content

The prepared films are weighed individually and kept in a desiccator containing silica gel at room temperature for 24 hours. The films were again weighed and the percentage moisture content is calculated using the formula:

Percentage moisture content = [(Initial weight – Final weight)/Final weight] x 100 [(85)]

Estimation of drug content

Transdermal patches of specified area and weight are cut into small pieces and are transferred into 100mL standard flask. About 5mL of methanol is added to dissolve the patch and then mix up to 100mL with phosphate buffer pH 6.8. Similarly, a blank is also prepared using drug free patch. The solutions are filtered and the absorbance is measured at λmax 365 nm using UV visible spectrophotometer [(86)].

1. **Permeation Studies**

   The in vitro permeation studies were carried out using Dialysis membrane. The membrane was prepared using following procedure. The membrane is cut into appropriate size & socked in liquid glycerol for 24 hours for permeable characteristics [(87)].

The permeation study was conducted using open tubular cell in the static mode with an effective diffusion area 2.8cm^2. The capacity of receptor compartment was 200ml and temperature was maintained at 37^{0}C±1 by means of temperature controller of magnetic stirrers. Drug concentration in donor compartment was 7.473mg/ml Receptor solution was phosphate buffer 6.8 which was continuously stirred at 100 rpm with Teflon – coated bar movement placed inside the cell [88].

Dialysis membrane was mounted between donor and receptor compartment of the cells and lower side of membrane is in direct contact with the receptor medium. After fixing of patch on membrane, the 5ml of solution withdrawn at specific time interval and equal volume of phosphate buffer 6.8 added to receptor solution in an attempt to maintain drug concentration constant throughout the experiment (24 hrs). The amount of drug permeated from receptor solution at predetermined times were analyzed by UV-visible spectrophotometer [89].

2. **In vitro diffusion study**

The in vitro release profile of Amlodipine from a transdermal device was determined. An open tubular cell was used for the diffusion studies. The dialysis membrane was mounted between donor and receptor compartment of diffusion. The receptor compartment of the diffusion cell was filled with phosphate buffer 6.8. The prepared matrix patch was placed over the membrane. The temperate of the receptor compartment was maintained at 32±1^{0}C. The receptor solution was stirred with Teflon coated magnet stirrer throughout the experiment. Aliquots of receptor fluid were withdrawn at predetermined time intervals and replaced immediately with same volume of the fresh fluid, the samples were analyzed at 365 nm using spectrophotometrically [90].

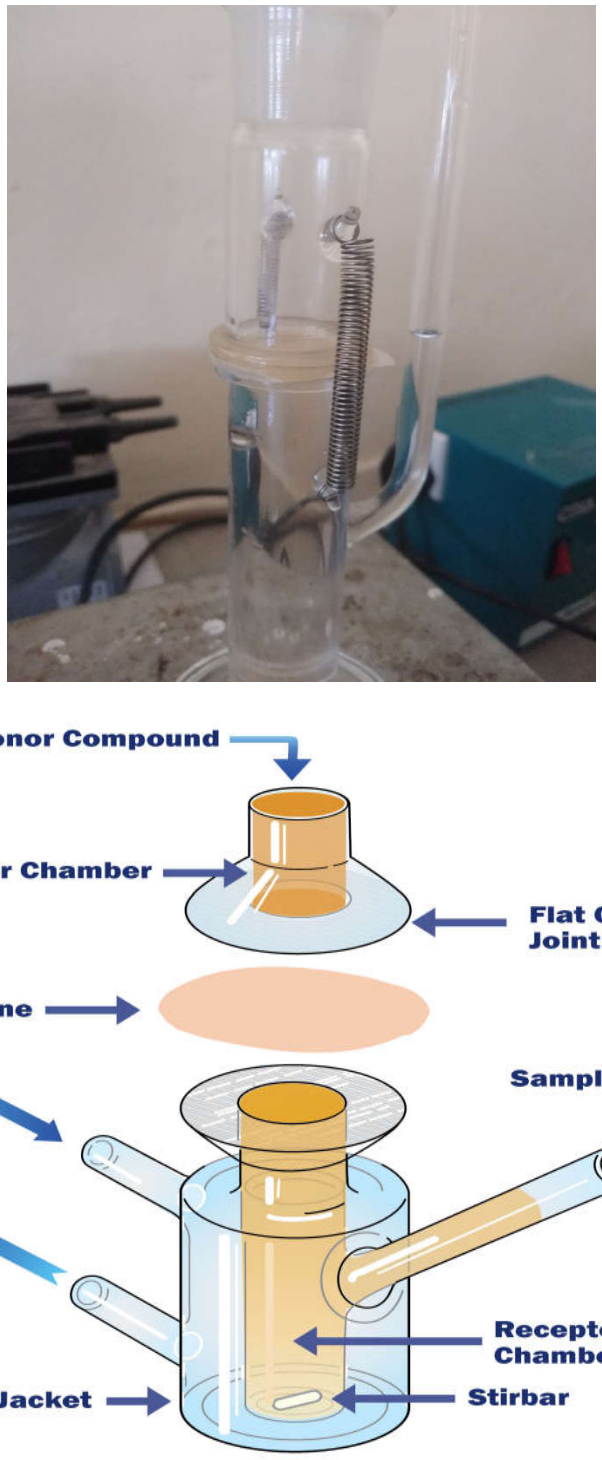


Fig.12: Franz Diffusion Cell Apparatus

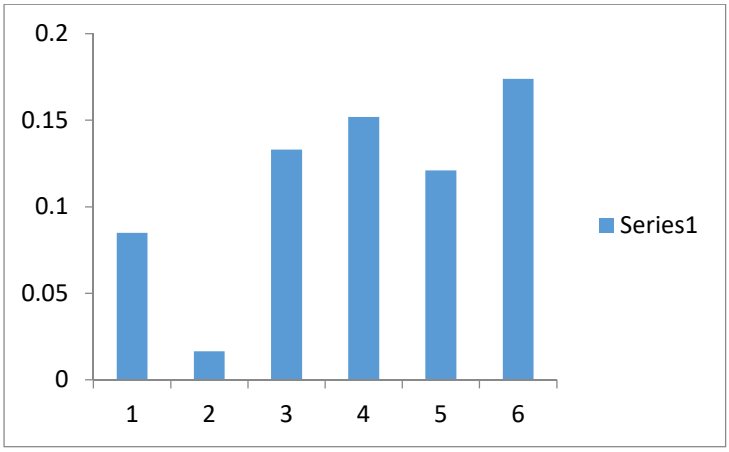
3. RESULT AND DISCUSSION

A. PREFORMULATION STUDIES

1. Melting point determination: 201^0C

2. Solubility studies:

Tableno.8: Solubility of Amlodipine



Graph No.1: solubility of amlodipine in different solvent

Sr. No.	Solvent	Absorbance
1	Distilled Water	0.085
2	Methanol	0.0165
3	Ethyl alcohol	0.133
4	0.1M HCL	0.152
5	Chloroform	0.121
6	DSMO	0.174

3. Drug Identification

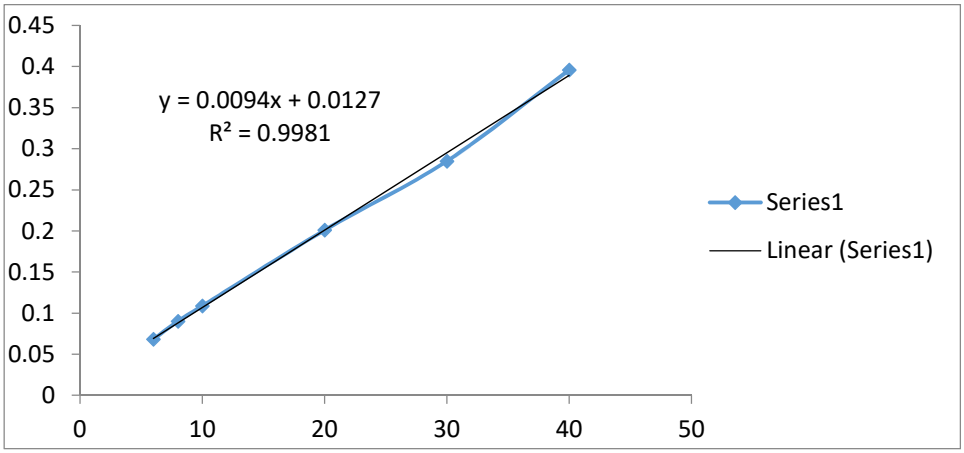
Method - Spectrophotometer method (UV)

Procedure for the Preparation of Standard Curve:-

Amlodipine 50 mg each, were accurately weighed and dissolved separately in 50ml of methanol. Five ml of the above solutions diluted separately to standard stock solution of 100 mcg/ml eight dilutions ranging 5-40 mcg/ml made. The absorbance of each sample was measured using UV-visible spectrophotometer. 0.1 N HCl as blank. The calibration curve was drain by plotting concentration Vs. and absorbance to obtain standard calibration curve. The results were shown in table and figure [95].

Table No.9: Absorbance of Amlodipine

Concentration (mcg/ml)	Absorbance(365nm)
6	0.0682
8	0.0901
10	0.109
20	0.201
30	0.285
40	0.396



Graph No.2: Standard Curve for Amlodipine

Discussion

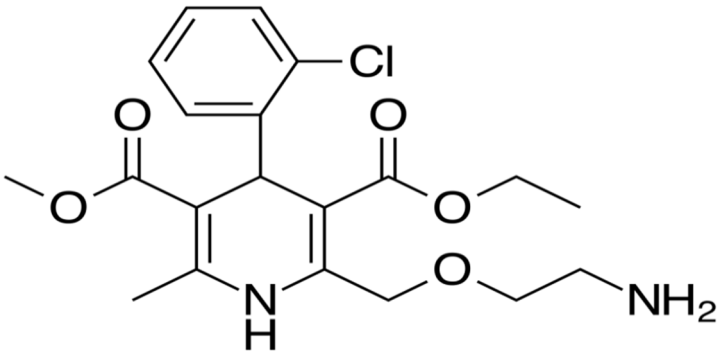
The UV- absorbances of the Amlodipine were performed at 25 mcg/ml concentration in phosphate buffer 6.8 and their wavelength were found and compared with monograph

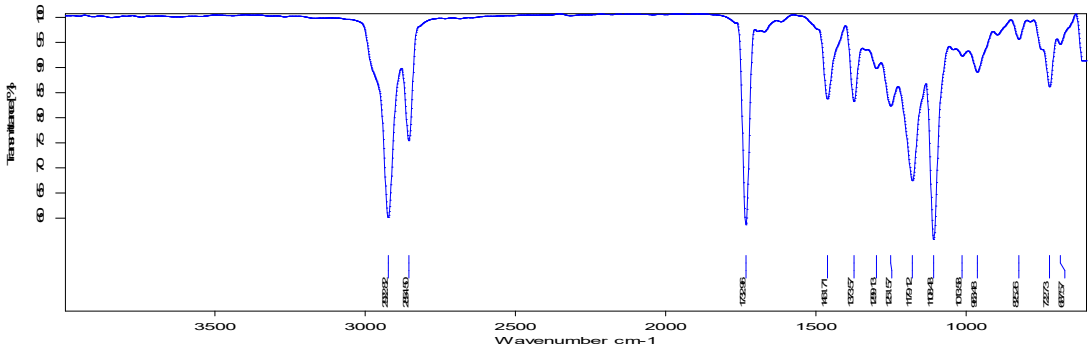
4. Infra-Red Spectrum

Table No.10: IR Spectrum of Amlodipine

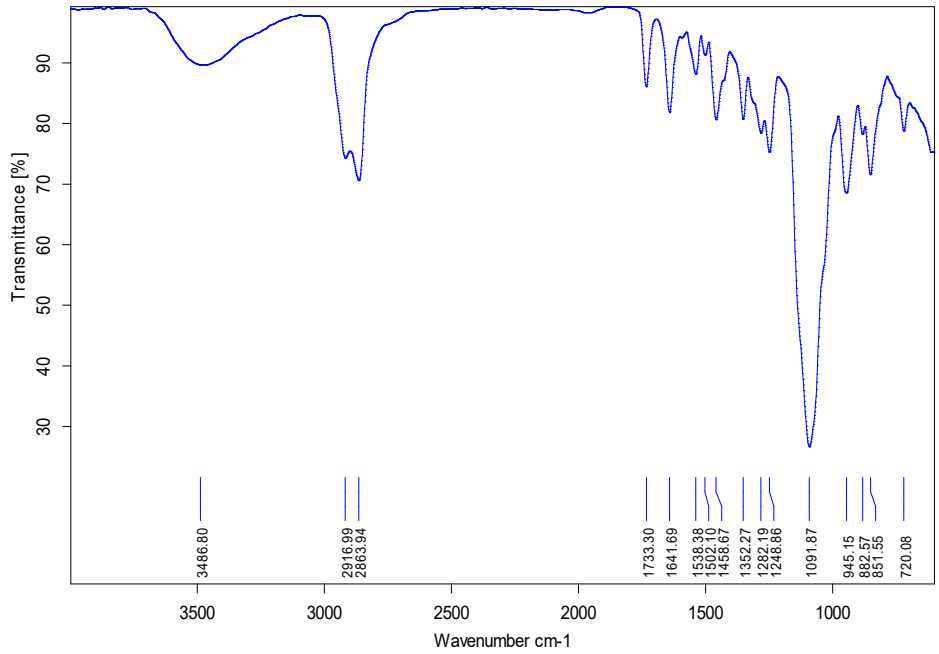
Sr. no	Frequency cm -1	Functional Group
1	2922	NH Stretching
2	2854	CH-aliphatic
3	1732	C=0 ester
4	825	C - C1 (C1 vibration)
5	1299	- C- 0 - ester
6	1373	– C - CH3
7	963	- C = C - aromatic
8	1179	C - 0 Stretching
9	1251	Phenolic Stretching

The structure of Amlodipine was confirmed by IR spectrum (performed by KBr pellet method).



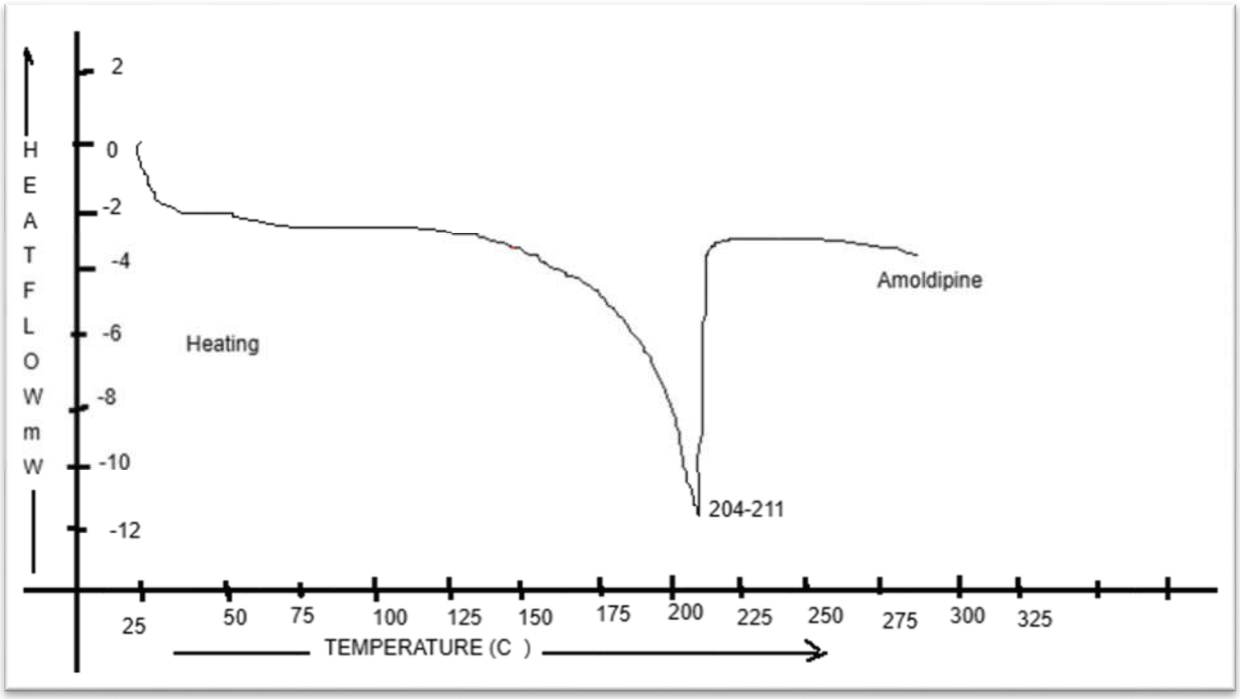


Graph No.3: IR Spectrum of Amlodipine

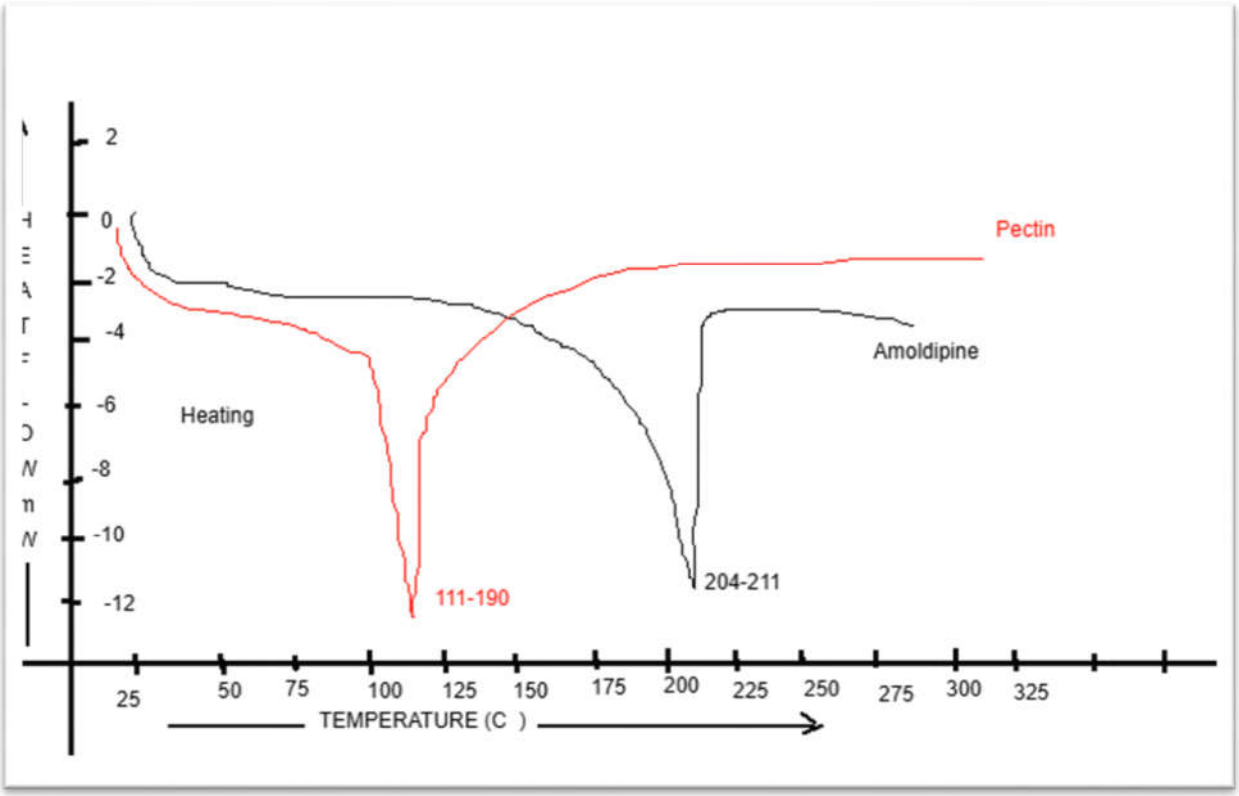


GraphNo.4: IR Spectrum of Amlodipine + pectin

5. Differential Scanning Calorimetry (Dsc) -



Graph No.3: IR Spectrum of Amlodipine



GraphNo.4: IR Spectrum of Amlodipine + pectin

B. PHSICOCHEMICAL EVALUATION:

Table no.11: Physico-chemical parameters of amlodipine patch

Formulation code	Physical Appearance	Weight Variation (grams)	Thickness (mm)
F1	Transparent, Flexible, Smooth	0.346±0.045	0.150±0.121
F2	Transparent, Flexible, Smooth	0.398±0.024	0.187±0.036
F3	Transparent, Flexible, Smooth	0.406±0.051	0.190±0.017
F4	Transparent, Flexible, Smooth	0.401±0.051	0.186±0.017
F5	Transparent, Flexible, Smooth	0.409±0.051	0.192±0.017
F6	Transparent, Flexible, Smooth	0.400±0.051	0.191±0.017

Table no.11: Physico-chemical parameters of amlodipine patch

Formulation code	Moisture Content (%)	Moisture Uptake (%)	Drug Content (mg/cm^2)
F1	6.46±1.26	5.93±1.20	0.6134±0.008
F2	5.83±0.45	4.66±1.28	0.5765±0.006
F3	5.16±1.00	4.7±1.11	0.6213±0.007
F4	5.10±1.00	4.8±1.11	0.6113±0.007
F5	5.80±1.00	423±1.11	0.5711±0.007
F6	6.10±1.00	4.8±1.11	0.6013±0.007

IN VITRO DRUG RELEASE PROFILE:

Diffusion profile of amlodipine in phosphate buffer 6.8

Table No.12: In Vitro Release Profile F1 Formulation

Sr. no.	Time in hours	Absorbance	Concentration in mcg/ml	% drug release
1	0	0	0	0
2	1	0.018	0.09	8.34
3	2	0.021	0.17	19.4
4	3	0.024	0.28	20.3
5	4	0.031	0.46	35.8
6	6	0.045	0.97	49.1
7	8	0.069	1.27	51.4
8	16	0.148	1.86	68.9
9	24	0.297	3.56	80.3

Graph No.5: In vitro Drug Release Profile for F1 Formulation

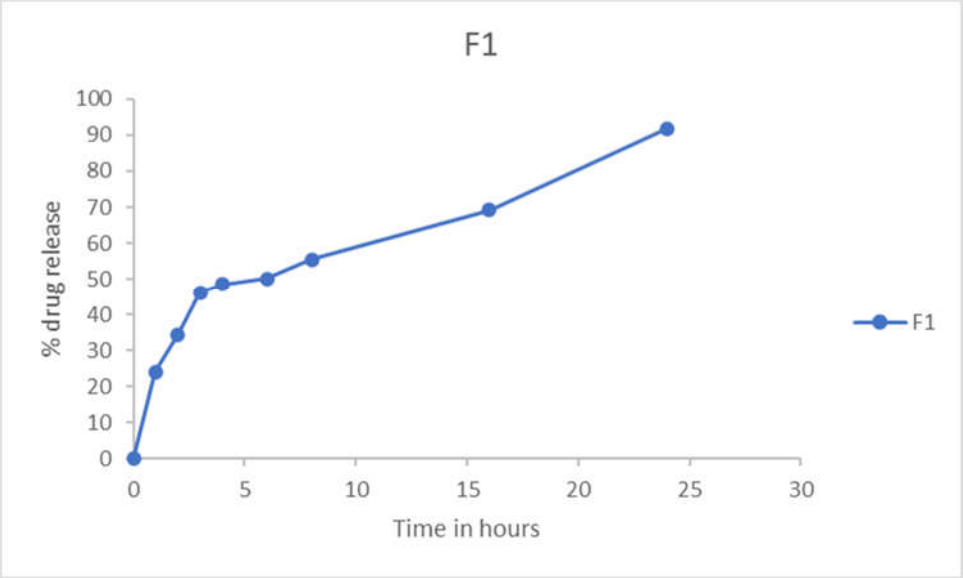


Table No.13: In Vitro Release Profile F2 Formulation

Sr. no.	Time in hours	Absorbance	Concentration in mcg/ml	% drug release
1	0	0	0	0
2	1	0.025	0.12	13.8
3	2	0.034	0.29	21.37
4	3	0.062	0.38	29.05
5	4	0.078	0.46	35.9
6	6	0.095	0.54	40.5
7	8	0.113	0.65	44.7
8	16	0.243	1.98	68.4
9	24	0.328	3.89	85.2

Graph No.6: In vitro Drug Release Profile for F2 Formulation

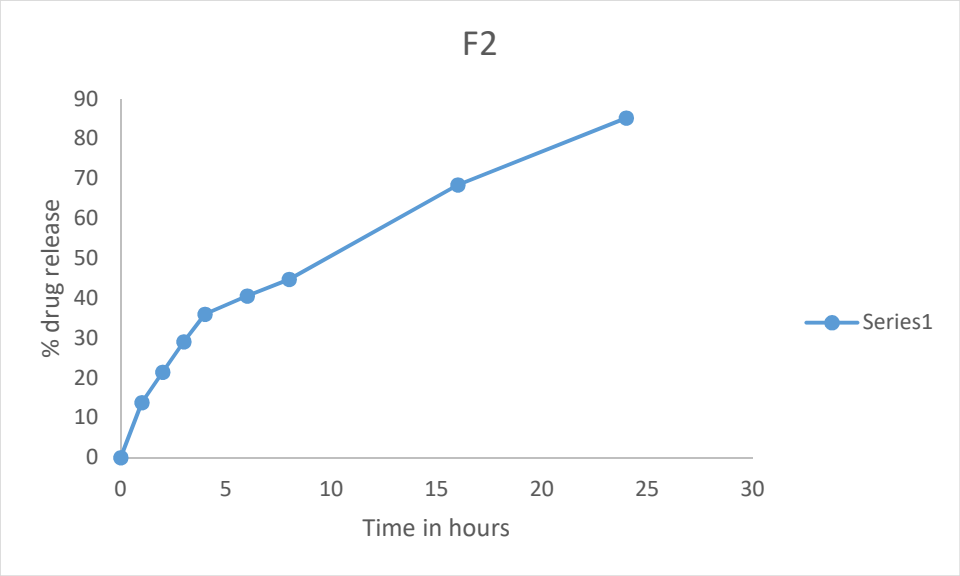


Table No.14: In vitro release profile F3 Formulation

Sr. no	Time in hours	Absorbance	Concentration in mcg/ml	% drug release
1	0	0	0	0
2	1	0.078	0.31	24.1
3	2	0.084	0.44	34.4
4	3	0.088	0.61	46.2
5	4	0.091	0.68	48.5
6	6	0.092	0.77	50.1
7	8	0.093	0.81	55.4
8	16	0.122	2.91	69.2
9	24	0.254	4.31	91.8

Graph No.7: In vitro Drug Release Profile for F3 Formulation

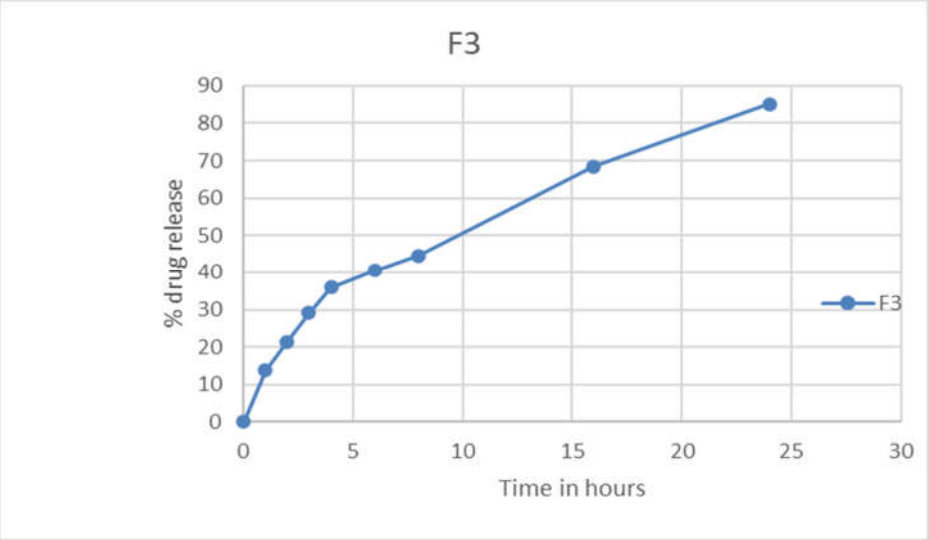


Table No.14: In vitro release profile F4 Formulation

Sr. no	Time in hours	Absorbance	Concentration in mcg/ml	% drug release
1	0	0	0	0
2	1	0.078	0.31	23.1
3	2	0.084	0.44	36.4
4	3	0.088	0.61	43.2
5	4	0.091	0.68	48.5
6	6	0.092	0.77	51.1
7	8	0.093	0.81	55.4
8	16	0.122	2.91	64.2
9	24	0.254	4.31	90.8

Graph no .14: In vitro release profile F4 Formulation

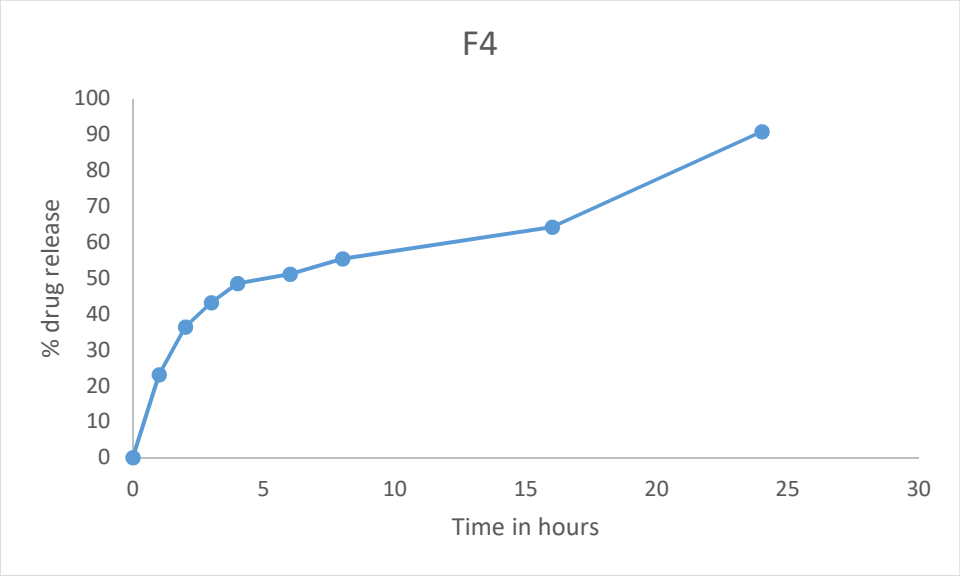


Table No.14: In vitro release profile F5 Formulation

Sr. no	Time in hours	Absorbance	Concentration in mcg/ml	% drug release
1	0	0	0	0
2	1	0.078	0.31	25.1
3	2	0.084	0.44	38.4
4	3	0.088	0.61	40.2
5	4	0.091	0.68	49.5
6	6	0.092	0.77	52.1
7	8	0.093	0.81	59.4
8	16	0.122	2.91	63.2
9	24	0.254	4.31	88.8

Graph no .14: In vitro release profile F5 Formulation

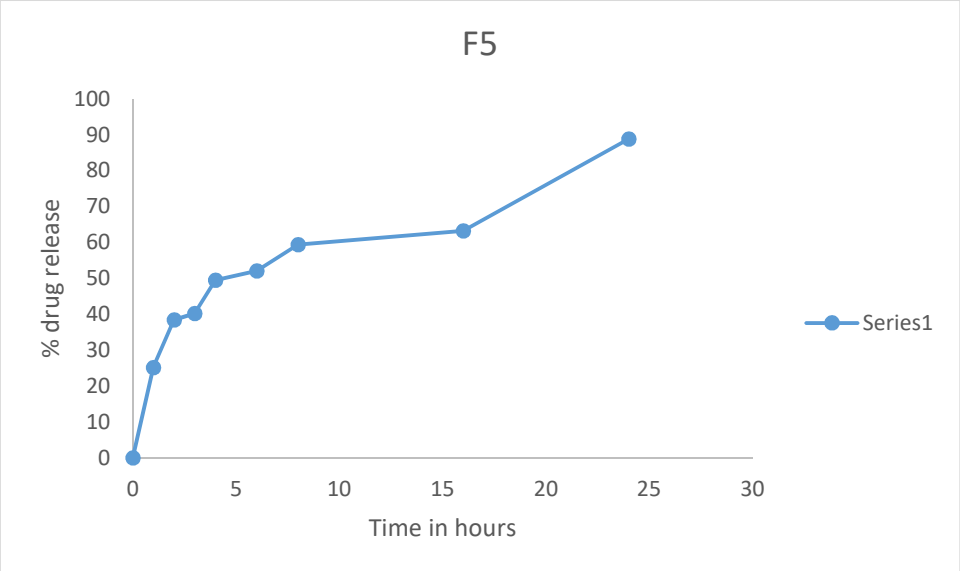
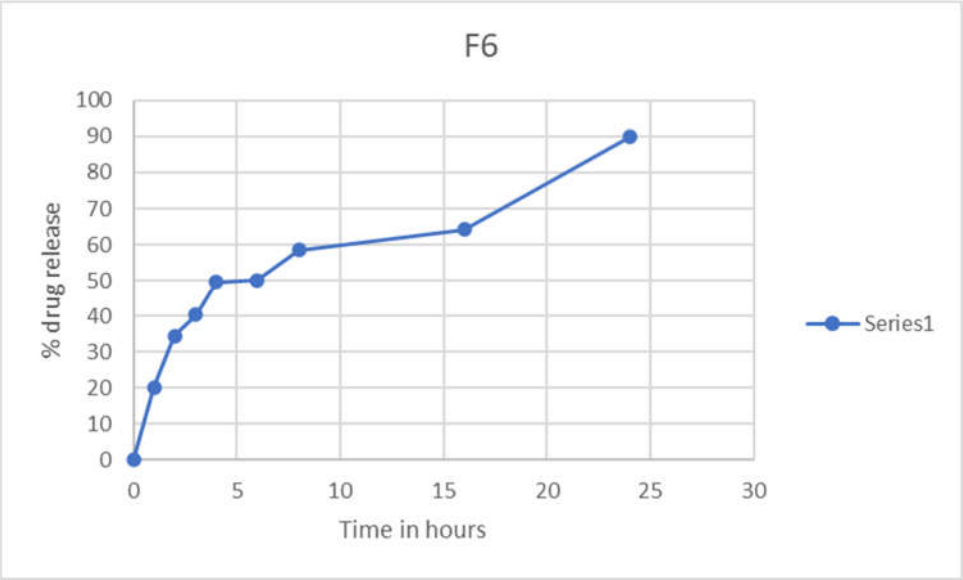


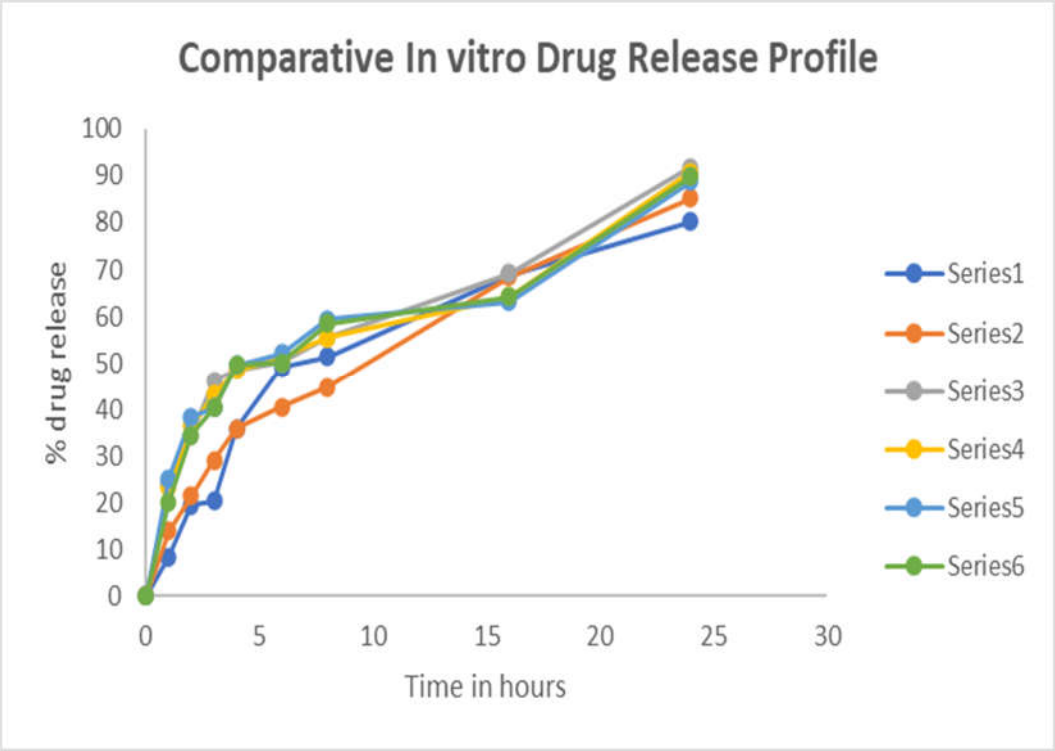
Table No.14: In vitro release profile F6 Formulation

Sr. no	Time in hours	Absorbance	Concentration in mcg/ml	% drug release
1	0	0	0	0
2	1	0.078	0.31	20.1
3	2	0.084	0.44	34.4
4	3	0.088	0.61	40.2
5	4	0.091	0.68	49.5
6	6	0.092	0.77	50.1
7	8	0.093	0.81	58.4
8	16	0.122	2.91	64.2
9	24	0.254	4.31	89.8

Graph no .14: In vitro release profile F6 Formulation



Graph No.8 Comparative In vitro Drug Release Profile



CONCLUSION

The formulation of transdermal films were prepared using different ratio of the same polymers which assigned in increasing order according to permeation rates F1>F2>F3<F4<F5<F6. The results indicate that the films prepared with Pectin as polymer of 1:20 (Drug: pectin) F3 was found to be best during in vitro study. Hence conclude that the increase in the concentration of polymer increases the drug release profile [97].

From the IR interpretation and UV- results the sample confirmed to be of amlodipine.

Melting point, partition coefficient, and solubility determined experimentally and molecular weight taken from literature.

All physicochemical character support that the drug amlodipine may be suitable for transdermal drug delivery system.

In vitro studies carried out using F1, F2,F3,F4,F5, and F6 formulation as F3 formulation shows better release F1, F2,F4,F5, and F6 Hence, finally conclude that the study shows the feasibility of formulating rate controlled transdermal drug delivery system for amlodipine in order to achieve improved bioavailability and nullifying the common adversities of the drug [98].

ACKNOWLEDGE-

The author would like to thank the Samarth Rural Educational Institute's Samarth Institute of Pharmacy, university library, and all other sources for their help and advice in writing this review.

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