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Original Article

FORMULATION AND EVALUATION OF NIFEDIPINE TRANSDERMAL DRUG DELIVERY SYSTEMS

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ABSTRACT

The aim of this present research work is to formulate and evaluate transdermal patches using Nifedipine. At present Nifedipine is available as tablets in the market.

Patients are non-cooperative to these dosage forms. Hence transdermal drug delivery system has started gaining popularity and acceptance as new drug delivery systems, because they are easy to administer and lead to better patient compliance.

The λmax of Nifedipine in 7.4pH phosphate buffer solution was found to be 229nm.

The objective of the study is to design and evaluation of Nifedipine transdermal patches using polymers such as HPMC K 15M, HPMC K 100Mand HPMC K200M.

The preparation of Nifedipine transdermal patches by solvent casting method.

In-vitro skin permeation studies were performed by using a Franz diffusion cell with a receptor compartment capacity of 22.5 mL. The amount of plasticizer tween 80 was critical for patch formation and separation properties. Tween 80 was selected for solubility enhancer and plasticizer during shelf-life period.

It was concluded that formulations F-5 was found to be satisfactory batch and was optimized for the desirable properties.

Keywords: *Nifedipine, transdermal patches, Franz diffusion cell, Tween 80.*

INTRODUCTION

Traditional multi-dose medication systems face issues related to absorption, metabolism, and patient compliance. Transdermal drug delivery systems (TDDS) offer a promising solution by delivering drugs at a controlled, consistent rate through the skin, bypassing first-pass hepatic metabolism, and maintaining a steady therapeutic level in the bloodstream.

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Physiology of Human Skin

The skin, the body's largest organ, comprises two main layers:

• **Epidermis:** The outer layer, consisting of various strata including the basal layer (stratum germinatum), stratum granulosum, stratum lucidum, and the stratum corneum, which provides the primary barrier for drug penetration.

• **Dermis:** Contains connective tissue, blood vessels, lymphatics, nerves, hair follicles, and glands.

Drug Penetration Pathways

Drugs can penetrate the skin through three primary routes:

• Appendageal Route: Through hair follicles and sweat ducts, but these represent a small surface area (0.1% of total skin surface).

• **Transcellular Route:** Directly through corneocytes, which are surrounded by lipid layers.

• **Intercellular Route:** Through the lipid matrix between corneocytes, which is the most common pathway for small, uncharged molecules.

Stratum Corneum: Rate-Limiting Barrier

The stratum corneum is the primary barrier to drug absorption. It has high resistance to diffusion compared to the viable epidermis and dermis. The stratum corneum's structure and composition, including keratin and lipid layers, contribute to its role as a rate-limiting barrier.

Pharmacokinetic Model for Percutaneous Absorption

Pharmacokinetic models describe drug partitioning and diffusion through skin layers, including the stratum corneum and dermal microcirculation. Key parameters include the rate constants for drug transport across these layers and the diffusion coefficients.

Factors Affecting Transdermal Permeation:

• **Physicochemical Properties:** Partition coefficient, solubility, and molecular weight affect drug permeation.

• **pH Variation:** Affects the ionization of drugs and their permeability.

• **Co-solvents and Surface Activity:** Influence drug solubility and permeation.

• **Complexation:** Can alter drug solubility and permeability.

• **Molecular Weight:** Smaller molecules generally permeate more easily, but large molecules may also be considered for TDDS with appropriate formulations.

Drugs Studied for TDDS

Various drugs have been studied for their suitability for TDDS, focusing on factors like their physicochemical properties and clinical efficacy.

Commercially Available TDDS

Several TDDS products are available commercially, targeting various therapeutic needs.

Evaluation of TDDS

In Vitro Testing:

• Skin Preparation: Includes selection and preparation of skin models (human, animal, or artificial membranes).

• Franz Diffusion Cell: Commonly used for testing, involving skin mounted on a diffusion cell with a diffusion medium.

• Drug Release Profile Modeling: Includes various mathematical models to describe the drug release kinetics, such as Zero Order, First Order, Korsmeyer-Peppas, Higuchi, and Hixson-Crowell models.

MATERIALS

Table 1: The following excipients were selected after compatibility studies:

Nifedipine	**Hetero Labs, Hyderabad**
HPMC K15M, K100M, K200M	S.D. Fine Chemicals, Mumbai
PVP K30	S.D. Fine Chemicals, Mumbai
Tween 80	S.D. Fine Chemicals, Mumbai
Sorbitol	S.D. Fine Chemicals, Mumbai

EQUIPMENT

Table 2: The list o equipment's

Electronic Balance	**Shimadzu Corporation, Japan**
pH Meter	Metler Toledo, India
UV-Visible Spectrophotometer	Labindia, India
Dissolution Apparatus TDT-08L	Labindia, India
Vernier Caliper	Mitutoyo, Japan
Disintegration Tester (USP)	Electro Lab, India
Hot Air Oven	Servewell Instruments
Gyratory Shaker	Lab India
Sonicator	Lab India

METHODOLOGY

Calibration curve of Nifedipine in 7.4pH phosphate buffer:

a) Preparation of 7.4pH phosphate buffer

50ml of 0.2M potassium dihydrogen orthophosphate solution was taken in a 200ml of volumetric flask, to which 22.4ml of 0.2M sodium hydroxide solution was added. Then volume was made up to the mark with distilled water and pH was adjusted to 7.4 with dilute sodium hydroxide solution [64].

b) Preparation of Nifedipine standard stock solution (100µg/ml) in 7.4 pH phosphate buffer solution

A standard stock solution of Nifedipine was prepared by dissolving accurately weighed 10mg of Nifedipine in 7.4pH phosphate buffer solution in a 100ml volumetric flask and the volume was made up to 100ml by using 7.4pH phosphate buffer solution to obtain a stock solution of 100µg/ml.

c) Determination of λmax of Nifedipine

From the standard stock solution, 1 ml was taken into 10ml volumetric flask. The volume was made up to 10ml with 7.4pH phosphate buffer solution. The resulting solution containing 10µg/ml was scanned between 200 and 400nm. The λmax was found to be 229nm and was used as analytical wavelength.

d) Calibration curve of Nifedipine in 7.4pH phosphate buffer solution

From stock solution, appropriate aliquots were pipette into different volumetric flasks and volumes were made up to 10 ml with 7.4pH phosphate buffer solution so as to get drug concentrations of 1,2,3,4 and 5µg/ml. The absorbencies of these drug solutions were estimated at λmax 229nm against a blank of 7.4pH phosphate buffer solution. This procedure was performed in triplicate to validate the calibration curve.

Fourier transform infrared radiation

The infrared absorption spectra of pure drug, pure polymer and physical mixture of polymer and drug were performed for polymer drug interaction studies between 4000 cm-1to 400 cm-1by KBr pellet method.

Formulation of Nifedipine transdermal patches

Procedure

Transdermal patches of Nifedipine were prepared by solvent casting method. Take DCM and Ethanol in 1:1 ratio and dissolve the drug first. Then add the ingredients one by one and dissolve it properly in continuous stirring.

The solutions were cast on to glass petri plate of 9 cm diameter and were dried in the oven at 70°C till a peelable film was formed. Then dried films were cut into rectangular shape pieces, with 4.0 cm2 (2.0 cm × 2.0 cm) total surface area. Desired quantity of Nifedipine was 10 mg (dose of drug) per 4.0 cm2 films.

Table 3: Formulation of Nifedipine Transdermal patches

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
Nifedipine	10	10	10	10	10	10	10	10	10
HPMC K15M	10	20	30	-	-	-	-	-	-
HPMCK100M	-	-	-	10	20	30	-	-	-
HPMCK200M	-	-	-	-	-	-	10	20	30
PVP K30	20	40	60	20	40	60	20	40	60
Tween-80	10	10	10	10	10	10	10	10	10
sorbitol	60	40	20	60	40	20	60	40	20

Evaluation of Trans dermal patches

1. Thickness

2. Weight variation

3. Drug content

4. Folding endurance

5. Tensil strength

6. In-vitro drug release

1. **Thickness:** The thickness of patches was measured at three different places using a micrometer and mean values were calculated.

2. **Weight variation:** The patches were subjected to mass variation by individually weighing randomly selected patches. Such determinations were carried out for each formulation.

3. **Drug content:** Patches of specified area (1 cm2) were dissolved in 5 mL of dichloromethane and the volume was made up to 10 mL with phosphate buffer pH 7.4; dichloromethane was evaporated using a rotary vacuum evaporator at 45 °C. A blank was prepared using a drug-free patch treated similarly. The solutions were filtered through a 0.45µm membrane, diluted suitably and absorbance was read at 274 nm in a double beam UV-Vis spectrophotometer.

4. Folding endurance: This was determined by repeatedly folding one film at the same place till it broke. The number of times the film could be folded at the same place without breaking/cracking gave the value of folding endurance

5. Tensile strength: In order to determine the elongation as a tensile strength, the polymeric patch was pulled by means of a pulley system; weights were gradually added to the pan to increase the pulling force till the patch was broken. The elongation i.e. the distance travelled by the pointer before break of the patch was noted with the help of magnifying glass on the graph paper, the tensile strength was calculated as kg cm-2.

6. *In-vitro* skin permeation studies: In-vitro skin permeation studies were performed by using a Franz diffusion cell with a receptor compartment capacity of 22.5 ml. The excised rat abdominal skin (Wistar albino) was mounted between the donor and receptor compartment of the diffusion cell. The formulated patches were placed over the skin and covered with paraffin film. The receptor compartment of the diffusion cell was filled with phosphate buffer pH 7.4. The whole assembly was fixed on a magnetic stirrer, and the solution in the receptor compartment was constantly and continuously stirred using magnetic beads at 50 rpm; the temperature was maintained at 32 ± 0.5 °C. The samples were withdrawn at different time intervals and analysed for drug content spectrophotometrically. The receptor phase was replenished with an equal volume of phosphate buffer pH 7.4 at each sample withdrawal. The cumulative percentages of drug permeated per square centimetre of patches were plotted against time.

STABILITY STUDIES:

In designing a dosage form it is necessary to know the inherent stability of the drug substance, to have an idea of what excipients to use, as well as how best to put them together with the drug and to know that no toxic substance is formed. Limits of acceptability and therefore compromises must be reasonably defined. Because the measurements of these aspects of stability as well as determination of shelf life or expiration date for the

final dosage form require long term stability studies for confirmation, they can be expensive and time consuming. Consequently, it is necessary to define those study designs and conditions that show the greatest probability of success. The objective therefore of a stability study is to identify and help avoid or control situations where the stability of the active ingredient may be compromised.

Rationale for stability studies:

- There may be chemical degradation of active drug leading to a substantial lowering of the quantity of therapeutic agent in the dosage form.
- Although chemical degradation of the active drug may not be expensive, a toxic product may be formed in the decomposition process.
- Instability of drug product can lead to substantial lowering in the therapeutic efficiency of the dosage form.

Table 4: Stability Storage Conditions

Stability Storage Category Testing schedule for Physical and Chemical attributes

Stability Storage Category	Testing schedule for Physical and Chemical attributes
LONG TERM 25°C ± 2°C / 60% ± 5% RH	3, 6, 9, 12, 18, 24 and annually till expiry and 6 Months hence after.
ACCELERATED 40°C ± 2°C / 75% ± 5% RH	1, 2, 3 & 6 Months
INTERMEDIATE 30°C ± 2°C / 60% ± 5% RH	3, 6, 9 & 12 Months
ZONE IV 30°C ± 2°C / 70% ± 5% RH	3, 6, 9, 12, 18, 24 and annually till expiry and 6 Months hence after.

RESULTS AND DISCUSSION

Calibration curve of Nifedipine in 7.4 pH phosphate buffer solution:

Standard calibration curve of Nifedipine was drawn by plotting absorbance versus concentration. The λmax of Nifedipine in 7.4pH phosphate buffer solution was found to be 229nm.

Table 5: Calibration data of Nifedipine in 7.4pH phosphate buffer at 229nm

Concentration (µg/ml)	Absorbance
0	0
1	0.147
2	0.314
3	0.481
4	0.624
5	0.789

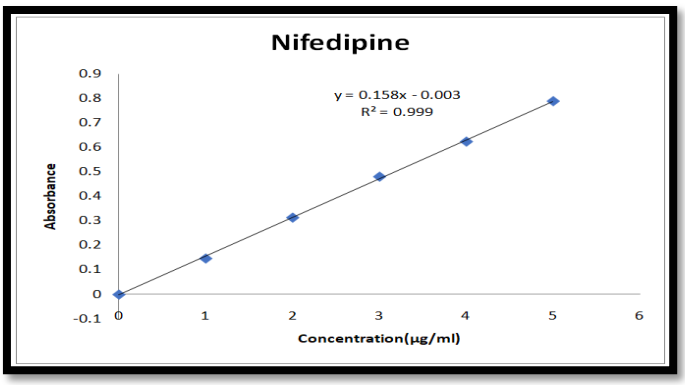

Fig 1: Standard calibration curve of Nifedipine in 7.4pH phosphate buffer solution

Compatibility study by FTIR:

The compatibility of the drug with polymer was evaluated by performing FTIR analysis of standard drug and best formulation.

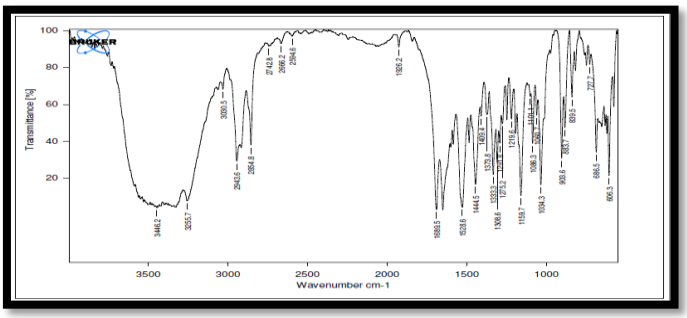

Fig 2: FTIR graph of Nifedipine pure drug

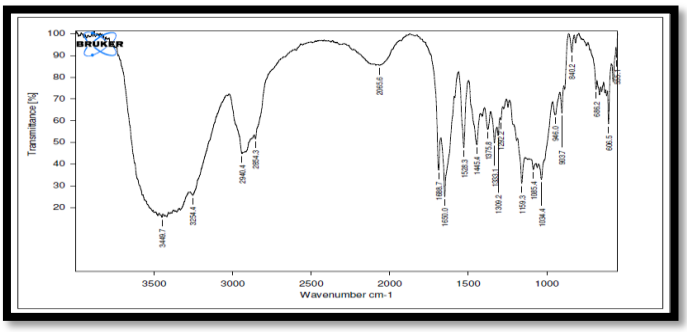

Fig 3: FTIR graph of Nifedipine optimized formulation

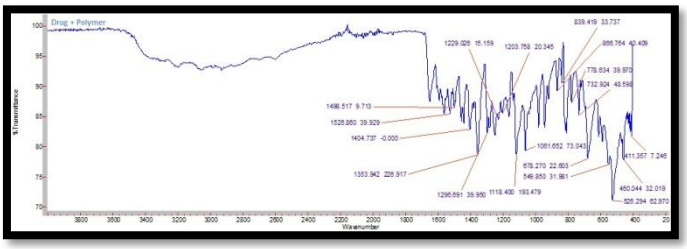

Fig 4: FTIR graph of Nifedipine with polymer

Table 6: Evaluation parameters of Nifedipine Transdermal patches

Formulation code	Thickness (mm)	Weight variation (mg^2/cm^2)	Drug content (mg^2/cm^2)	Folding endurance	Tensil strength (mg/cm^2)
F1	162±0.57	24.90±0.004	98.23±0.18	201±1.52	2.74±0.01
F2	158±1.52	24.50±0.02	99.14±0.27	199±2.51	2.96±0.04
F3	153±1.52	25.60±0.02	99.67±0.33	212±1.52	3.12±1.79
F4	160±0.57	26.80±0.07	98.83±0.28	219±2.08	3.04±0.20
F5	157±0.55	27.30±0.06	99.37±0.27	210±2.52	2.83±0.14
F6	152±0.57	26.30±0.05	99.95±0.48	206±1.52	2.92±0.28
F7	147±2.08	27.80±0.07	99.67±0.17	218±2.64	3.15±0.10
F8	138±1.52	28.60±0.08	99.82±0.31	237±2.08	2.86±0.13
F9	156±0.13	26.20±0.05	99.37±0.26	204±2.64	2.46±0.28

Table 7: In-vitro drug release data for Transdermal patches

Time (Hrs.)	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
1	32±1.52	28±0.57	25±0.57	20±1.154	16±0.13	5±1.73	12±0.50	5±0.13	0±0.13
2	46±2.52	39±1.15	34±1.15	38±0.57	24±0.50	8±0.57	20±1.09	11±0.32	3±0.28
3	58±0.57	52±0.58	50±0.65	59±1.52	36±0.88	15±0.73	28±0.59	19±0.32	9±0.86
4	64±1.15	59±1.15	55±0.52	67±0.66	53±0.94	20±0.57	42±1.52	31±0.57	17±0.87
6	85±1.73	78±0.57	69±0.58	78±0.72	64±1.15	29±0.28	56±0.57	42±0.61	28±0.57
8	96±0.06	89±0.58	81±0.04	84±0.52	78±1.73	48±0.90	62±1.15	55±0.47	43±0.28
10	100±0.59	95±0.58	89±0.13	99±0.32	86±1.74	56±0.26	75±0.60	67±0.65	51±0.36
12	100±0.61	96±0.76	96±1.52	100±0.13	98±0.92	74±0.57	81±1.52	73±0.56	63±0.56

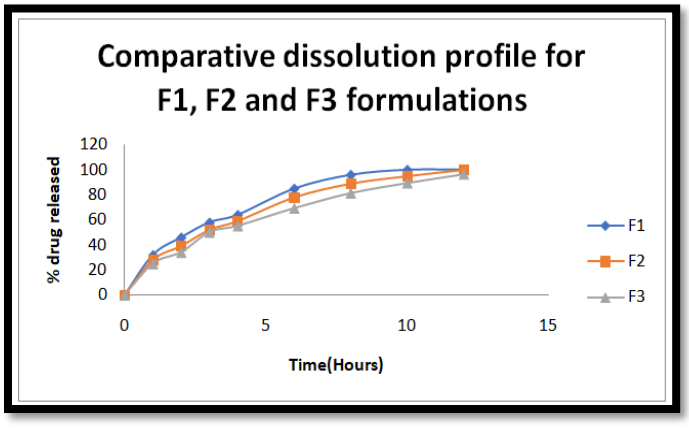

Figure 5: Comparative Dissolution profile for F1, F2 and F3 formulations

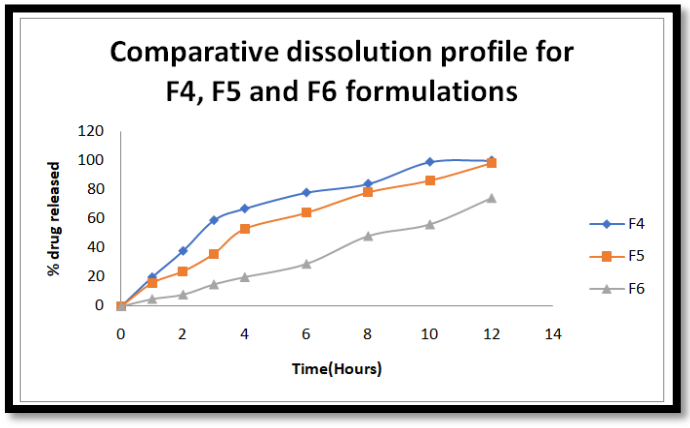

Figure 6: Comparative Dissolution profile for F4, F5 and F6 formulations

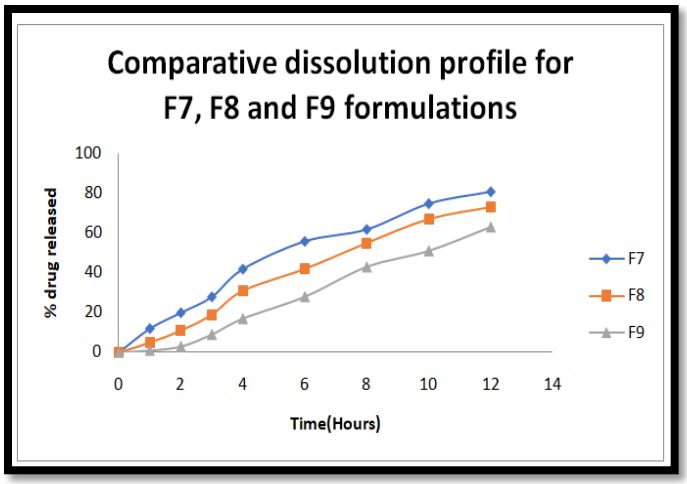

Figure 7: Comparative Dissolution profile for F7, F8 and F9 formulations

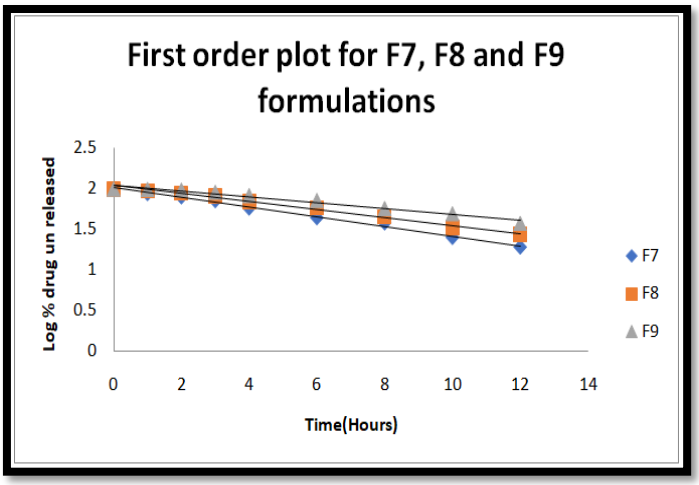

Figure 10: First order plot for F7, F8 and F9 formulations

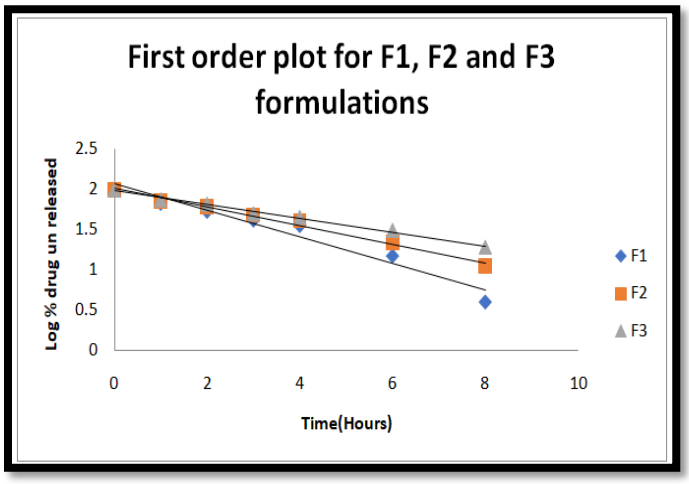

Figure 8: First order plot for F1, F2 and F3 formulations

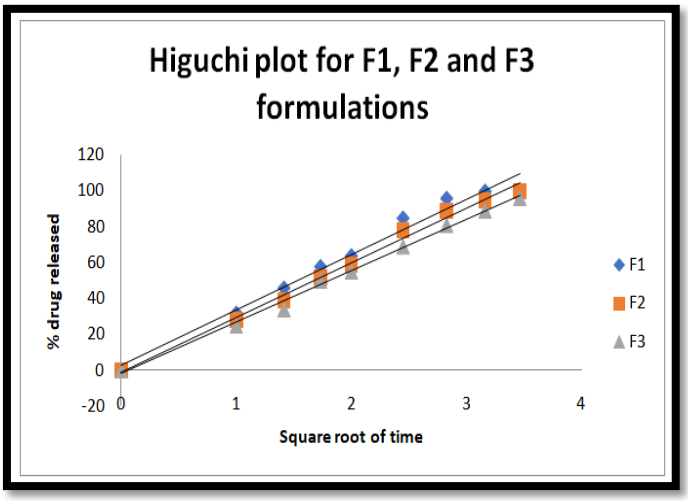

Figure 11: Higuchi plot for F1, F2 and F3 formulations

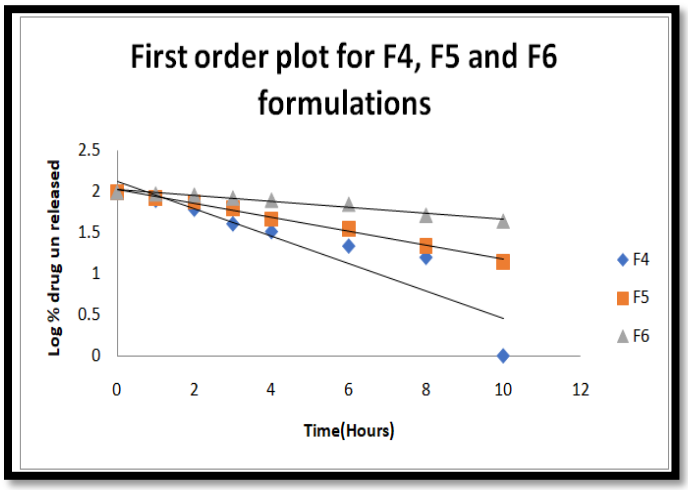

Figure 9: First order plot for F4, F5 and F6 formulations

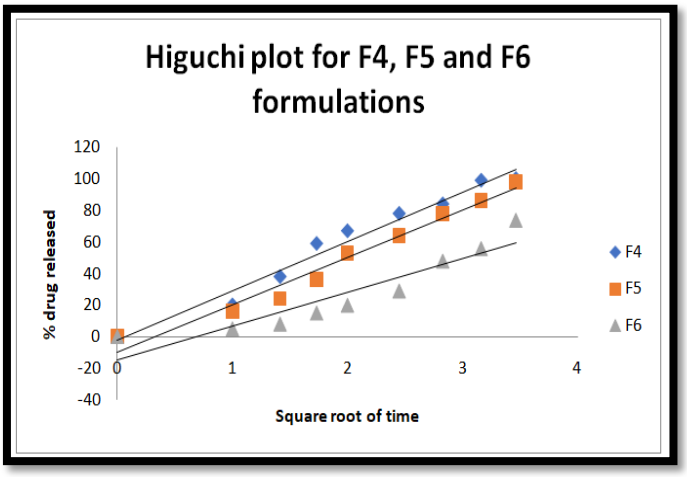

Figure 12: Higuchi plot for F4, F5 and F6 formulations

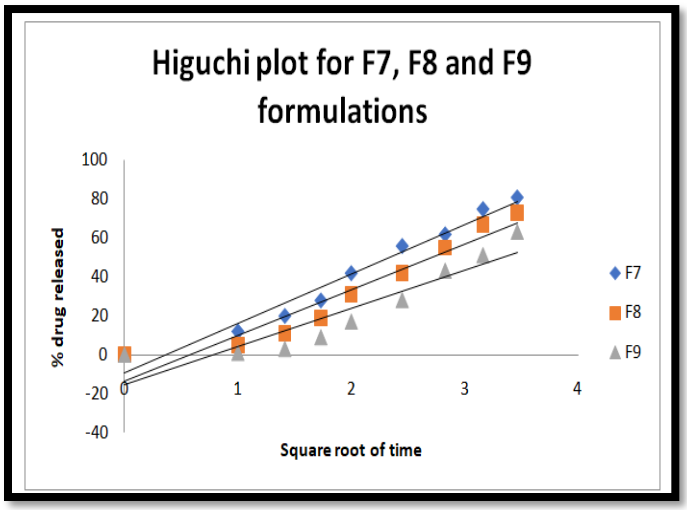

Figure 13: Higuchi plot for F7, F8 and F9 formulations

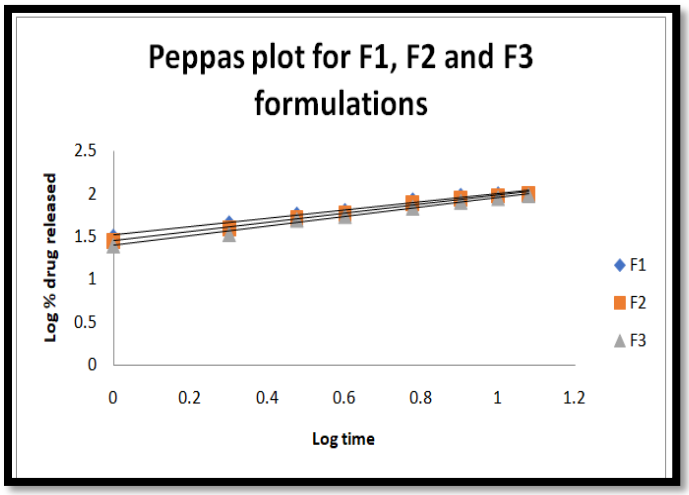

Figure 14: Peppas plot for F1, F2 and F3 formulations

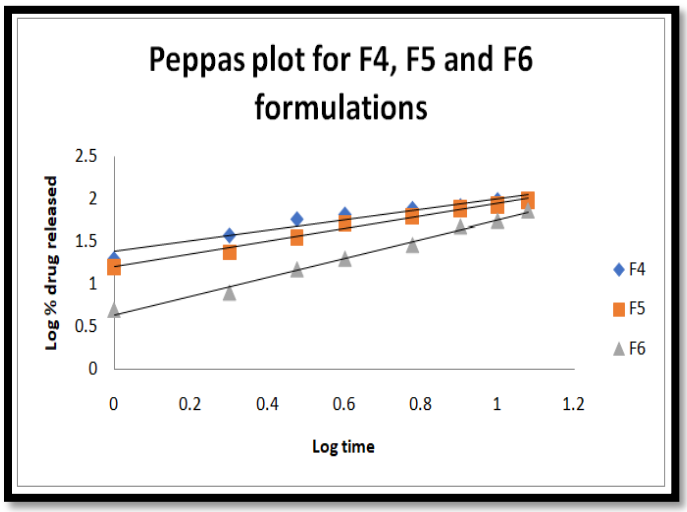

Figure 15: Peppas plot for F4, F5 and F6 formulations

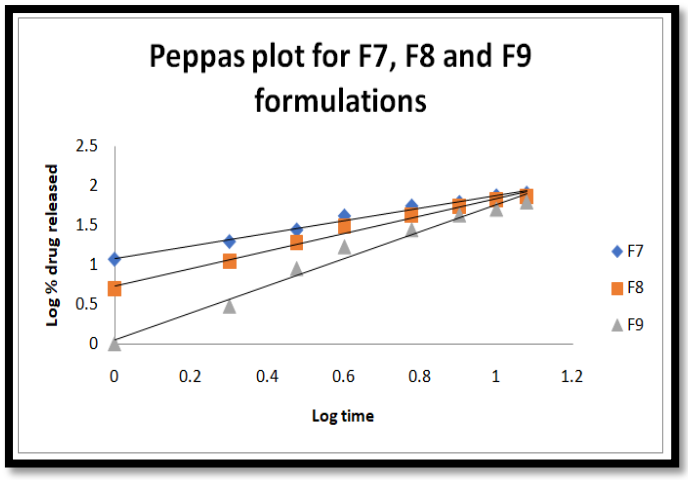

Figure 16: Peppas plot for F7, F8 and F9 formulations

Table 8: R2 and 'n' result table

Formulation code	R2 Values				N Value
	Zero order	First order	Higuchi	Peppas	
F1	0.852	0.951	0.98	0.982	0.483
F2	0.9	0.986	0.992	0.991	0.535
F3	0.918	0.992	0.995	0.99	0.556
F4	0.869	0.84	0.973	0.94	0.624
F5	0.96	0.991	0.971	0.984	0.753
F6	0.988	0.964	0.867	0.989	1.113
F5	0.963	0.992	0.966	0.987	0.793
F6	0.987	0.99	0.926	0.986	1.103
F7	0.987	0.969	0.858	0.979	1.709

STABILITY STUDIES:

Selected formulation F5 was stored at 40°C ± 2°C / 75% ± 5% RH or a period of 3 months.

Table-9: In-vitro release profile of F5 during Stability studies (40°C ± 2°C / 75% ± 5% RH)

Time (Hrs.)	Initial	Month 1	Month 2	Month 3
0	0	0	0	0
1	16	15	16	14
2	24	22	25	24
3	36	35	36	33
4	53	53	51	51
6	64	62	63	62
8	78	77	76	75
10	86	84	85	84
12	98	97	97	98

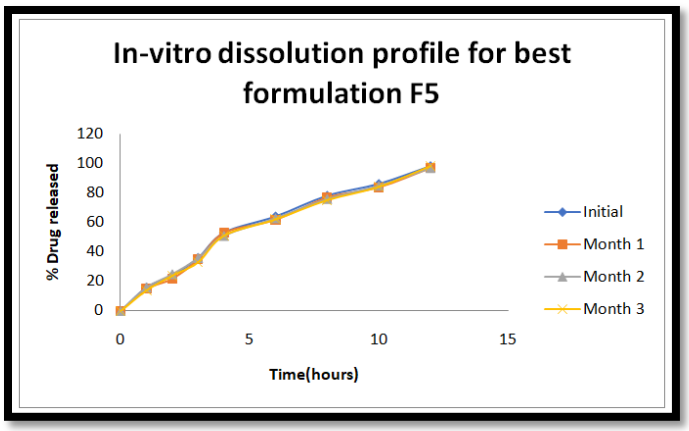

Fig. 17: In-vitro release profile of F9 during Stability studies (40°C ± 2°C / 75% ± 5% RH)

SUMMARY & CONCLUSION

Nifedipine transdermal patches were successfully developed using HPMC K15M, HPMC K100M, and HPMC K200M. Currently, nifedipine is marketed only as tablets, which often face patient resistance. To address this issue, the transdermal drug delivery system has emerged as a preferred alternative due to its ease of use and enhanced patient compliance. The formulation of the patches was notably influenced by the amount of the plasticizer, Tween 80, which played a crucial role in ensuring the patches' formation and separation properties. In-vitro skin permeation studies were conducted using a Franz diffusion cell with a receptor compartment capacity of 22.5 mL. Tween 80 was chosen both as a solubility enhancer and a plasticizer to maintain the patches' effectiveness during their shelf life. The optimized formulation, F5, was stored at 40°C ± 2°C / 75% ± 5% RH for a period of 3 months. It was concluded that formulation F5 demonstrated satisfactory performance and was optimized for its desirable properties.

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