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Formulation and In Vitro Characterization of Clonidine HCl Transdermal Drug Delivery System

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Abstract:
The present study aims to formulate and evaluate matrix-type transdermal patches of Clonidine Hydrochloride (Clonidine HCl) to achieve sustained drug release, enhanced bioavailability, and improved patient compliance in the treatment of hypertension. Transdermal patches were developed using solvent casting technique with polymers such as Carboxy Methyl Chitosan and Hydroxypropyl Methylcellulose (HPMC 5 cps), in combination with plasticizers like PEG 400. Six different formulations (F1–F6) were prepared and evaluated for physicochemical parameters including thickness, weight variation, tensile strength, folding endurance, and drug content uniformity. In vitro drug release was studied using a Franz diffusion cell over 12 hours. Release kinetics were analyzed using Zero-order, First-order, Higuchi, and Korsmeyer-Peppas models. FTIR spectroscopy was used to assess drug-excipient compatibility. All formulations showed satisfactory physical characteristics. Among them, formulation F4 exhibited optimal properties with uniform drug content (97.32 ± 1.64%) and maximum cumulative drug release (99.34% in 12 hours). The drug release followed ***Zero-order kinetics****, indicating a controlled release mechanism. FTIR analysis confirmed no significant interaction between drug and excipients.*

Key words: *Clonidine HCl; Transdermal Patch; Solvent Casting; Carboxy Methyl Chitosan; HPMC; Controlled Drug Release; Zero-order Kinetics; Franz Diffusion Cell; FTIR Compatibility.*

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I. Introduction:

The creation of innovative drug delivery methods has attracted a lot of attention lately, and transdermal drug delivery has emerged as a viable substitute for more conventional methods like parenteral or oral administration. Transdermal patches stand out among these due to their prolonged drug release, higher bioavailability, avoidance of first-pass metabolism, decreased frequency of dose, and improved patient compliance. These systems minimize gastrointestinal side effects and guarantee regulated plasma levels by delivering medications through the skin into the systemic circulation.

Clonidine hydrochloride (Clonidine HCl), a centrally acting alpha-2 adrenergic agonist, is primarily used to treat hypertension, attention-deficit hyperactivity disorder (ADHD), and specific pain disorders. Despite its demonstrated therapeutic efficacy, Clonidine HCl has limitations when administered orally, such as substantial first-pass hepatic metabolism and a short biological half-life, requiring numerous daily doses. These difficulties make Clonidine a strong choice for transdermal medication administration.

By reducing the peaks and troughs that come with oral dosing, transdermal application of clonidine HCl can assist sustain constant plasma concentrations over extended periods of time. By removing the need for regular dosing, it also improves patient convenience. However, creating such patches necessitates optimizing a number of formulation factors in addition to having a thorough grasp of the drug's physicochemical characteristics and skin permeability.

A transdermal patch typically consists of a drug reservoir, polymer matrix, permeability enhancers, plasticizers, and backing membranes. The choice and combination of polymers such as Hydroxypropyl Methylcellulose (HPMC), Ethyl Cellulose (EC), and Polyvinyl Alcohol (PVA) is critical in determining the drug release profile and mechanical strength of the patch. Furthermore, permeation enhancers such as propylene glycol, DMSO, or oleic acid are used to help medication molecules pass the stratum corneum, the skin's primary barrier.

To guarantee transdermal patches' uniformity, safety, and effectiveness, characterisation is a crucial first step. Thickness, weight fluctuation, drug content homogeneity, moisture content, tensile strength, folding durability, in vitro drug release, and skin penetration tests are important evaluation criteria. By assessing the

patch's physical integrity, drug loading effectiveness, and release kinetics, these tests aid in quality control and formulation improvement.

This paper will describe a comprehensive investigation on the formulation and characterisation of a transdermal patch containing Clonidine HCl, with the goal of creating a stable, effective, and patient-friendly dosage form. The study looks at how different polymers and formulation variables affect the drug release behavior and physical features of the patch. Ultimately, the goal is to improve Clonidine HCl's therapeutic potential through an effective transdermal delivery method.

II. Materials and Methods:

i. Analytical method development:

A.UV scan:
A 100mg of Clonidine Hcl was accurately weighed and was first dissolved in 35ml methanol solution. The solution was then diluted using phosphate buffer (pH- 7.4) to 100 ml. (stock solution-I). Take 10ml solution from stock solution 1 and volume make up to 100ml with phosphate buffer to get 100 µg/ml concentrations (stock solution-II). Take 10 ml solution from stock II and volume make up to 100 ml with buffer to get 10 µg/ml. 10 µg/ml solution was scanned from 200-400nm.

B. Construction of calibration curve:
A 100mg of Clonidine Hcl was accurately weighed and was first dissolved in 35ml methanol solution. The solution was then diluted using phosphate buffer (pH- 7.4) to 100 ml. (stock solution-I). Take 10ml solution from stock solution 1 and volume make up to 100ml with phosphate buffer to get 100 µg/ml concentrations (stock solution-II). It was further diluted with phosphate buffer pH – 7.4 to get solutions in concentration range of 2,4,6,8 and 10 µg /ml. The absorbances of these solutions were determined spectrophotometric ally at 271.

ii. Pre formulation study

A. Colour, Odour, Taste and Appearance:
The drug sample was evaluated for its Colour, Odour and Appearance.

B. Melting point determination:
Melting point of the drug sample was determined by capillary method by using melting point apparatus.

C. Determination of solubility:
The solubility of Clonidine Hcl was determined by adding excess amount of drug in the solvent.
The Clonidine Hcl has very low aqueous solubility. Its solubility is not reported in any official book, so determination of solubility is important. The solubility was determined in distilled water and phosphate buffer pH 7.4. The procedure can be detailed as follows.
Saturated solution of Clonidine Hcl prepared using 10 ml. of distilled water/ phosphate buffer pH 7.4 in 25 ml volumetric flasks in triplicate. Precaution was taken so that the drug remains in medium in excess. Then by using mechanical shaker, the flasks were shaken for 48 hours. The sample withdrawn (1 ml after filtration) was diluted with appropriate medium and analyzed by using UV spectrophotometer at 271 nm for phosphate buffer and distilled water respectively.

iii. Formulation of transdermal patches

Preparation of blank patches:
Polymers of single or in combination were accurately weighed and dissolved in respective solvent and then casted in a Petri-dish with mercury as the plain surface. The films were allowed to dry overnight at room temperature.

Formulation of Drug Incorporated Transdermal Patches:
The matrix-type transdermal patches containing Clonidine Hcl were prepared using different concentrations of Carboxy Methyl Chitosan and HPMC 5cps. The polymers in different concentrations were dissolved in the respective solvents. Then the drug was added slowly in the polymeric solution and stirred on the magnetic stirrer to obtain a uniform solution. PEG 400 was used as plasticizers. Then the solution was poured on the Petri dish having surface area of 78 cm2 and dried at the room temperature. Then the patches were cut into 2x2 cm^2 patches. Drug incorporated for each 2x2 cm^2 patch was 240 mg. the formulation table is given in table no. 6.1.

Table: Formulation of Clonidine Hcl Patches

Formulation Code	Drug	Polymer	Drug Polymer Ratio	Plasticizer	Drug Polymer Ratio	Rate Controlling Memrane
	Clonidine Hcl (mg)	Carboxy Methyl Chitosan (mg)	HPMC 5cps (mg)	PEG 400	Glycerin 30% w/w of Polymer (ml)	Ethyl Cellulose (%W/W)
F1	50	230	-	1:1	0.057	2
F2	50	350	-	1:1.5	0.083	2
F3	50	470	-	1:2	0.115	2
F4	50	-	230	1:1	0.057	2
F5	50	-	350	1:1.5	0.083	2
F6	50	-	470	1:2	0.115	2
Casting Solvent		Water (3ml)				Chloroform

iv. Evaluation Parameters of patches

iv. 1. Physical evaluations

a. Thickness

The thickness of films was measured by digital Vernier calipers with least count 0.001mm. The thickness uniformity was measured at five different sites and average of five readings was taken with standard deviation.

b. Folding endurance

The folding endurance was measured manually for the prepared films. A strip of film (4x3 cm) was cut evenly and repeatedly folded at the same place till it broke. The number of times the film could be folded at the same place without breaking gave the exact value of folding endurance.

c. Weight variation[47]

The three disks of 2*1 cm^2 was cut and weighed on electronic balance for weight variation test. The test was done to check the uniformity of weight and thus check the batch- to- batch variation.

d. Drug content Determination

The prepared drug contained patches specified surface area (2 cm^2) were cut and dissolved in (5% of methanol contained) 100ml of pH 7.4 phosphate buffer, and vigorously shaked for 12hrs, and then sonicated for 15 minutes, centrifuged at 5000 rpm for 30 min. Filter the drug contained polymeric solution through 42 number whatmann filter paper, then 1ml of the filtrate was taken in a test tube and dilute it for five times with same solvent by using double beam Uv-Visible spectrophotometer to determined drug content at λmax 271 nm. Respected Placebo patch was taken as a blank solution.

Flatness: A transdermal patch should possess a smooth surface and should not constrict with time. This can be demonstrated with flatness study. For flatness determination, one strip is cut from the centre and two from each side of patches. The length of each strip is measured and variation in length is measured by determining percent constriction. Zero percent constriction is equivalent to 100 percent flatness.

% constriction = I1 – I2 X 100

I2 = Final length of each strip

I1 = Initial length of each strip

iv. 2. *In-vitro* Drug Diffussion Study:

The in vitro study of drug permeation through the semi permeable membrane was performed using a franz type glass diffusion cell. The modified cell having higher capacity (25 ml) is used to maintain sink condition. This membrane was mounted between the donor and receptor compartment of a diffusion cell. The transdermal patch was placed on the membrane and covered with aluminum foil. The receptor compartment of the diffusion cell was filled with isotonic phosphate buffer of pH 7.4. The hydrodynamics in the receptor compartment were maintained by stirring with a magnetic bead at constant rpm and the temperature was maintained at 37±0.5ºC. The diffusion was carried out for 12 h and 1 ml sample was withdrawn at an interval of 1 h. The receptor phase was replenished with an equal volume of phosphate buffer at each sample withdrawal. The samples were analyzed for drug content spectrophotometrically at 271 nm

v. Drug release kinetics:

Diffusion data of above two methods was fitted in Zero order, First order and Higuchi equations. The mechanism of drug release was determined by using Higuchi equation.

Zero-Order Kinetics:

Zero order as cumulative amount of Percentage drug released vs time

$$C=K_0t$$

Where K0 is the zero-order rate constant expressed in units of concentration/time and t is the time in hours. A graph of concentration vs time would yield a straight line with a slope equal to K0 and intercept the origin of the axes.

First order kinetics:

First order as log cumulative percentage of log (%) cumulative drug remaining vs time,

$$L o g C = L o g C o - k t / 2.303$$

Where C0 is the initial concentration of drug, k is the first order constant, and t is the time.

Higuchi Model:

Higuchi's model as cumulative percentage of drug released vs square root of time

$$Q = K t 1/2$$

Where K is the constant reflecting the design variables of the system and t is the time in hours. Hence, drug release rate is proportional to the reciprocal of the square root of time.

Kors meyer Peppas equations:

Korsmeyer peppas equation used to determine the mechanism of drug release form the polymer matrix of the tablet. Log cumulative percentage of drug released VS Log time, and the exponent n was calculated through the slope of the straight line.

$$Mt/M\infty=Ktn$$

Where $Mt/M\infty$ is the fractional solute release, t is the release time, K is a kinetic constant characteristic of the drug/polymer system, and n is an exponent that characterizes the mechanism of release of tracers. For cylindrical matrix tablets, if the exponent $n = 0.45$, then the drug release mechanism is Fickian diffusion, and if $0.45 < n < 0.89$, then it is non-Fickian or anomalous diffusion. An exponent value of 0.89 is indicative of Case-II Transport or typical zero-order release.

vi. Compatibility study

FTIR study:

The infrared spectrum of the pure Clonidine Hcl sample was recorded and the spectral analysis was done. The dry sample of drug was directly placed after mixing and triturating with dry potassium bromide.

III. RESULTS AND DISCUSSION

Initially the drug was tested by UV to know their significant absorption maximum which can be used for the diffusion study of the drug.

Analysis of drug:

A. UV scan: The lambda max of Clonidine Hcl was found to be 271 nm.

B. construction of calibration curve:

Table 8.1: Standard graph of Clonidine Hcl

Concentration(µg/ml)	Absorbance(at 271 nm)
0	0
2	0.119
4	0.225
6	0.334
8	0.442
10	0.559

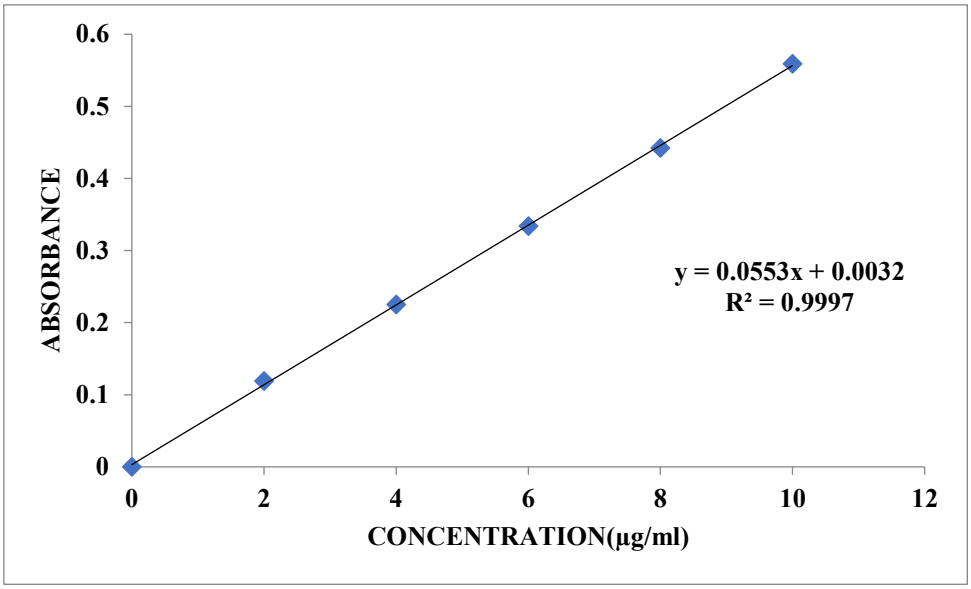

Figure : Standard calibration curve of Clonidine Hcl

C. Melting point determination:

Table : Results of melting point determination tests of drug

Drug	Reported melting point
Clonidine Hcl	207 to 210.0^{0}c

D. Determination of solubility:

Table: Solubility Determination

Solvent	Drug solubility(mg/ml)
Distilled water	0.0403
Ph 7.4 phosphate buffer	78.3

Evaluation of Patch

The thickness of formulations F1 to F6 varied when compared to other formulations, owing to differences in polymer concentrations. For all other formulations, it ranged from 0.031 ± 0.005 to 0.039 ± 0.001 mm. Weight variations range from 62±5.41 to 69±5.36 mg across all formulations (F1-F6). Folding endurance for formulations F1 to F6 ranged from 71 ± 0.12 to 78 ± 2.65, indicating their ability to tolerate skin folding. The percentage of drug content in all formulations ranged from 96.2 ± 3.67 to 99.11 ± 2.41.

Table : Evaluation of patches

Formulation Code	Average weight(mg)	Thickness (mm)	Folding endurance	Flatness (%)	Flatness (%)	% Drug Content
F1	65±1.05	0.031 ± 0.005	73 ± 1.25	98	Transparent	96.2 ± 3.67
F2	69±5.36	0.035±0.006	78 ± 2.65	96	Transparent	99.11 ± 2.41
F3	67±2.84	0.039±0.001	71 ± 0.12	99	Transparent	98.10 ± 3.29
F4	62±5.41	0.033±0.007	78 ± 1.41	97	Transparent	97.32 ± 1.64
F5	66±9.18	0.036±0.002	75 ± 2.32	100	Transparent	98.42 ± 4.35
F6	63±4.69	0.032±0.005	77 ± 1.14	99	Transparent	97.24 ± 2.15

***In vitro* diffusion study:**

All the formulation *in vitro* diffusion study was carried out by using Franz type diffusion cell under specific condition such as temp maintained at 32 ± 0.5 ºC. The diffusion was carried out for 12 h and 5 ml sample was withdrawn at an interval of 1 h.

Table : *In vitro* drug permeation of Clonidine Hcl containing different concentrations of Carboxy Methyl Chitosan

Time (hr)	F1	F2	F3
0	0	0	0
1	18.43	15.25	20.15
2	22.31	20.98	25.37
3	29.55	23.14	32.71
4	32.39	28.34	38.32
5	41.32	35.71	42.29
6	52.64	40.64	49.14
7	59.41	47.71	54.75
8	65.29	53.68	65.62
9	72.37	61.29	72.34
10	79.56	73.42	79.97
11	82.14	88.27	89.28
12	89.35	93.91	96.41

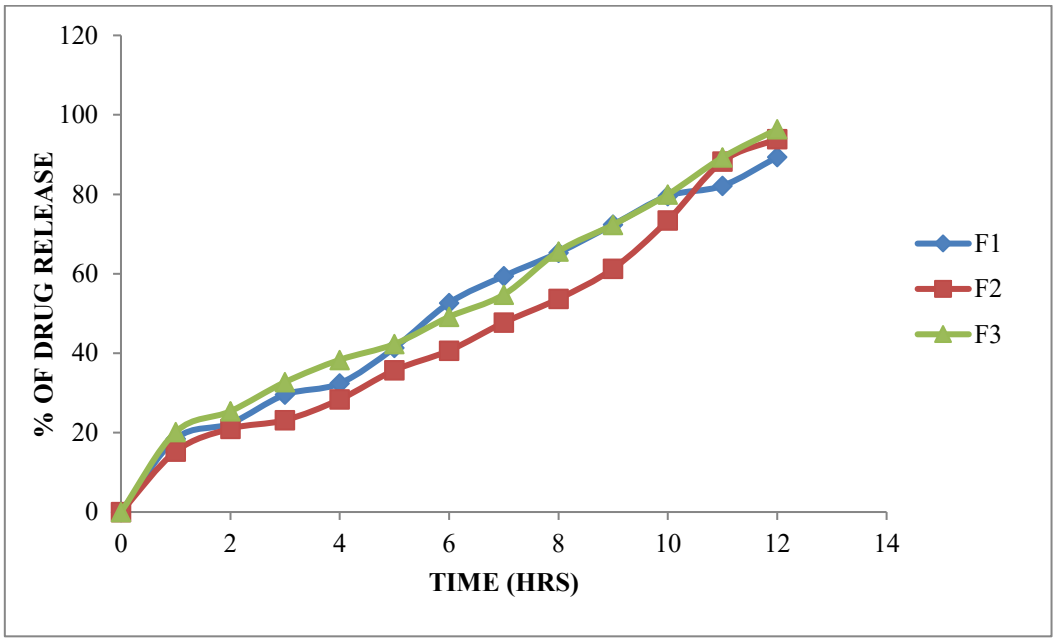

Figure: Cumulative % drug permeation of Clonidine Hcl patch (F1, F2, F3)

Drug release or permeation from the patch depended on the concentration of polymer in the matrix. Formulations F1 through F3 were made using varying amounts of carboxymethyl chitosan (230, 350, and 470 mg). The overall amount of medication that permeated within 12 hours was higher at low polymer concentrations. The largest amount of medication released at 12 hours was 93.91% with a 350 mg polymer concentration. The highest drug release of 96.41 was observed at the desired time period with a polymer concentration of 470 mg. Therefore, the F3 formulation demonstrated complete drug release at the targeted time period out of the three formulations.

Table: *In vitro* drug permeation of Clonidine Hcl containing different concentrations of HPMC 5cps

Time	F4	F5	F6
0	0	0	0
1	13.31	11.14	8.29
2	16.29	16.29	16.34
3	22.47	20.34	21.15
4	26.92	26.52	17.67
5	39.34	30.49	23.24
6	42.16	36.43	31.76
7	48.47	42.73	35.43
8	55.21	46.37	42.51
9	68.32	59.14	59.39
10	76.97	66.25	64.47

11	83.28	72.98	70.21
12	99.34	87.14	78.86

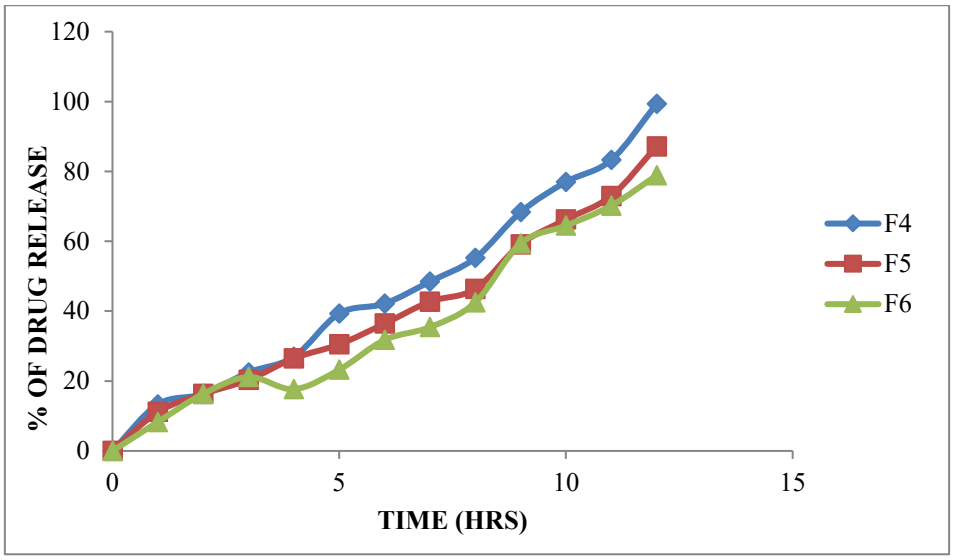

Figure: Cumulative % drug permeation of Clonidine Hcl patch (F4, F5, F6)

The formulations F4 to F6 were created with varying concentrations of HPMC 5cps (230, 350, and 470mg), and the drug release or penetration from the patch was dependent on the polymer concentration in the matrix. The polymer concentration of 230mg (F4) demonstrated maximum drug release of 99.34 within 12 hours. The 350mg (F5) polymer concentration resulted in the highest medication release of 87.14% at 12 hours. The polymer concentration of 470mg (F6) resulted in 78.86% reduced drug release after 12 hours. Among the six formulations, F4 demonstrated good drug penetration from the patch. F4 formulation met all in vitro evaluation requirements.

Kinetic models for Clonidine Hcl

The kinetics of drug release were explained by a variety of models. The acquired data were fitted into zero-order, first-order, Higuchi, and Korsmeyer-Peppas release models in order to examine the mechanism of the drug release rate kinetics of the dosage form.

Table: Kinetics data of F4 Clonidine Hcl patch

CUMULATIVE (%) RELEASE Q	TIME (T)	ROOT (T)	LOG(%) RELEASE	LOG (T)	LOG (%) REMAIN	RELEASE RATE (CUMULATIVE % RELEASE / t)	1/CUM % RELEASE	PEPPAS log Q/100	% Drug Remaining	Q01 /3	Qt1 /3	Q01/3-Qt1/3
0	0	0			2.000				100	4.642	4.642	0.000
13.31	1	1.000	1.124	0.000	1.938	13.310	0.0751	-0.876	86.69	4.642	4.426	0.216
16.29	2	1.414	1.212	0.301	1.923	8.145	0.0614	-0.788	83.71	4.642	4.374	0.267
22.47	3	1.732	1.352	0.477	1.889	7.490	0.0445	-0.648	77.53	4.642	4.264	0.378
26.92	4	2.000	1.430	0.602	1.864	6.730	0.0371	-0.570	73.08	4.642	4.181	0.461
39.34	5	2.236	1.595	0.699	1.783	7.868	0.0271	-0.405	60.66	4.642	3.929	0.712
42.16	6	2.449	1.625	0.778	1.762	7.027	0.0237	-0.375	57.84	4.642	3.867	0.774
48.47	7	2.646	1.685	0.845	1.712	6.924	0.0206	-0.315	51.53	4.642	3.721	0.920
55.21	8	2.828	1.742	0.903	1.651	6.901	0.0181	-0.258	44.79	4.642	3.551	1.090
68.32	9	3.000	1.835	0.954	1.501	7.591	0.0146	-0.165	31.68	4.642	3.164	1.477

76.97	10	3.162	1.886	1.000	1.362	7.697	0.0130	-0.114	23.03	4.642	2.845	1.796
83.28	11	3.317	1.921	1.041	1.223	7.571	0.0120	-0.079	16.72	4.642	2.557	2.085
99.34	12	3.464	1.997	1.079	-0.180	8.278	0.0101	-0.003	0.66	4.642	0.871	3.771

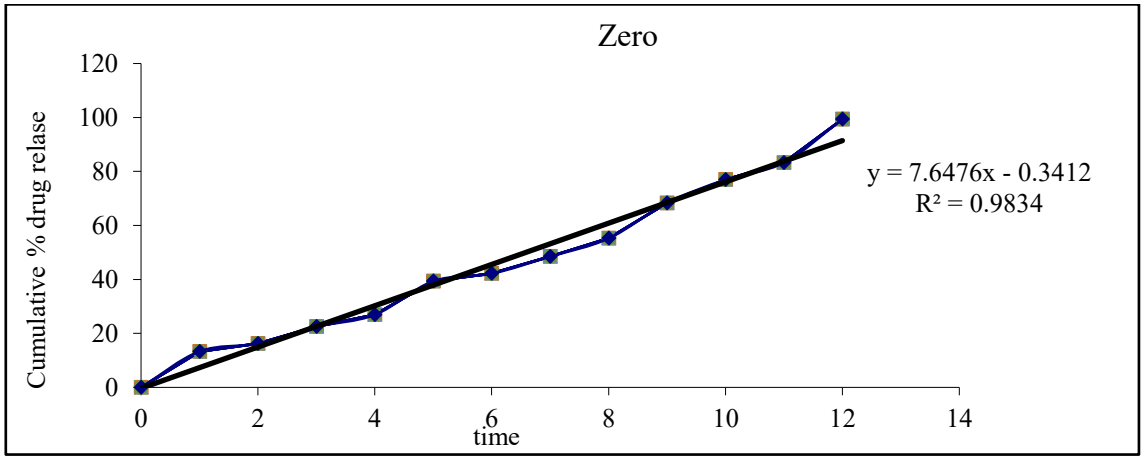

Figure: Graph of Zero order kinetics

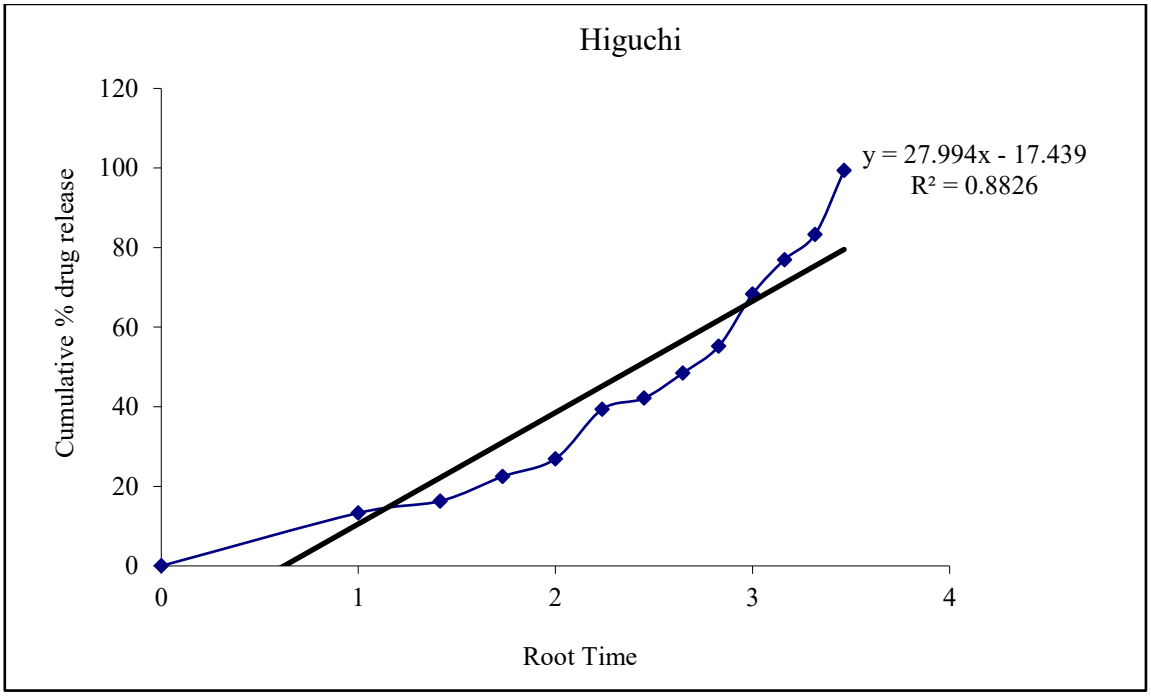

Figure: Graph of Higuchi release kinetics

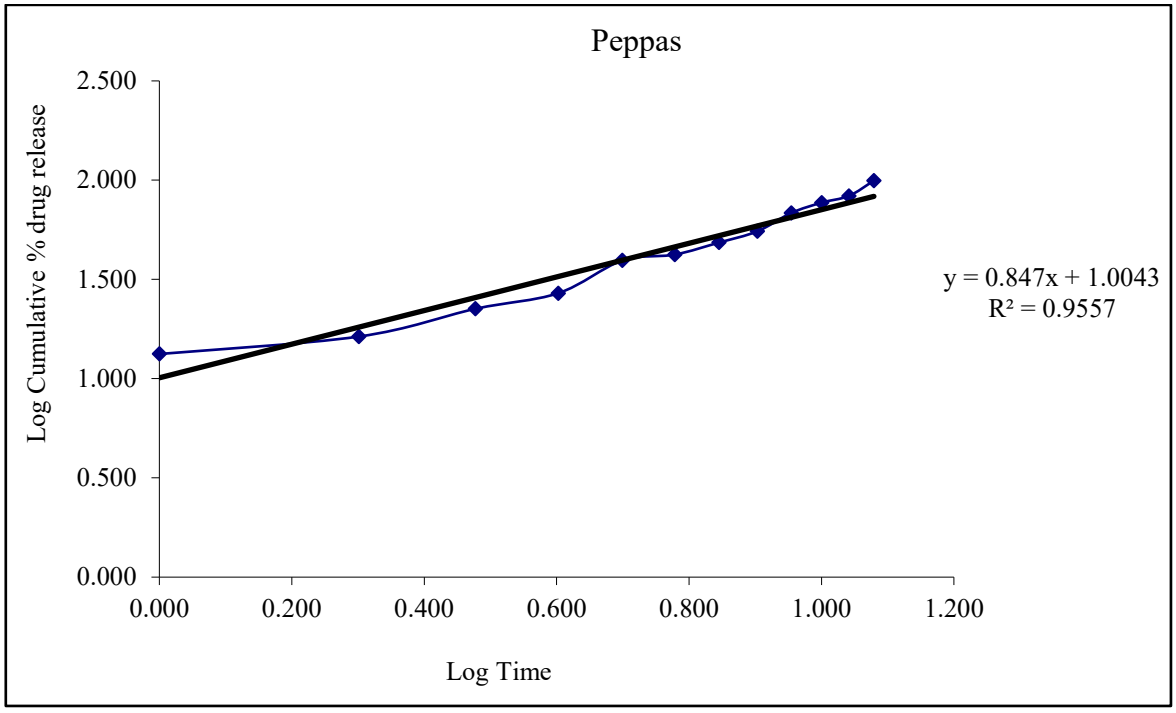

Figure :Graph of peppas release kinetics

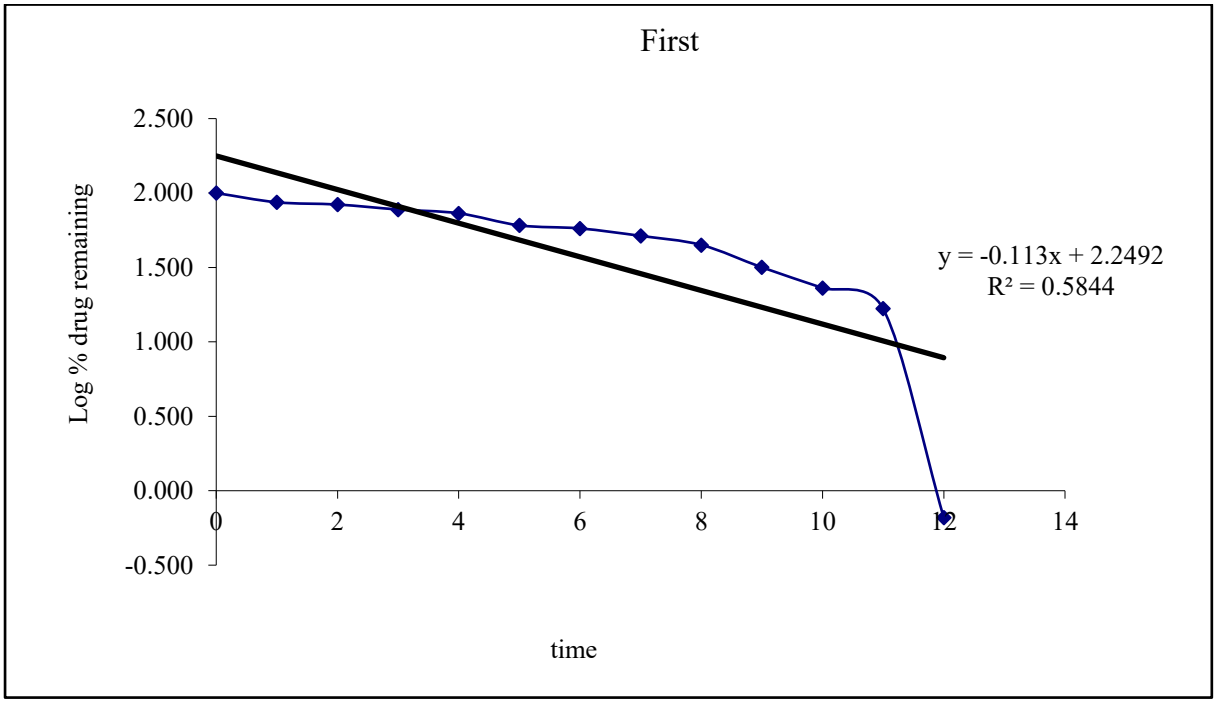

Figure: Graph of First order release kinetics

From the above data the optimized formulation followed Zero order kinetics model rule.

Compatibility studies:

IR SPECTROSCOPY:

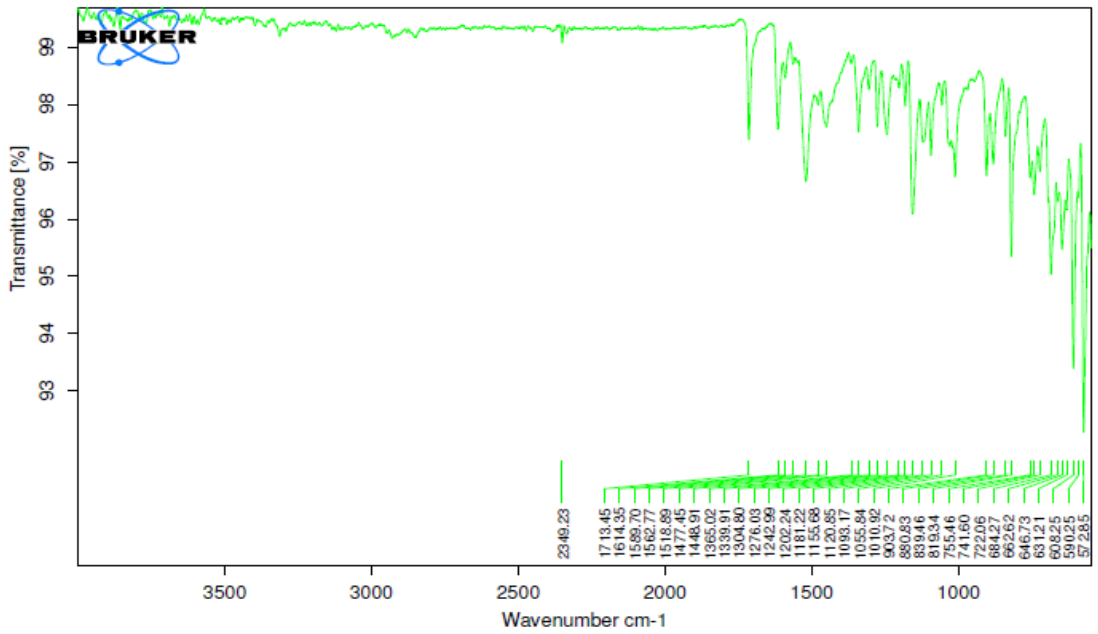

Figure : FTIR Spectrum of pure Clonidine Hcl drug

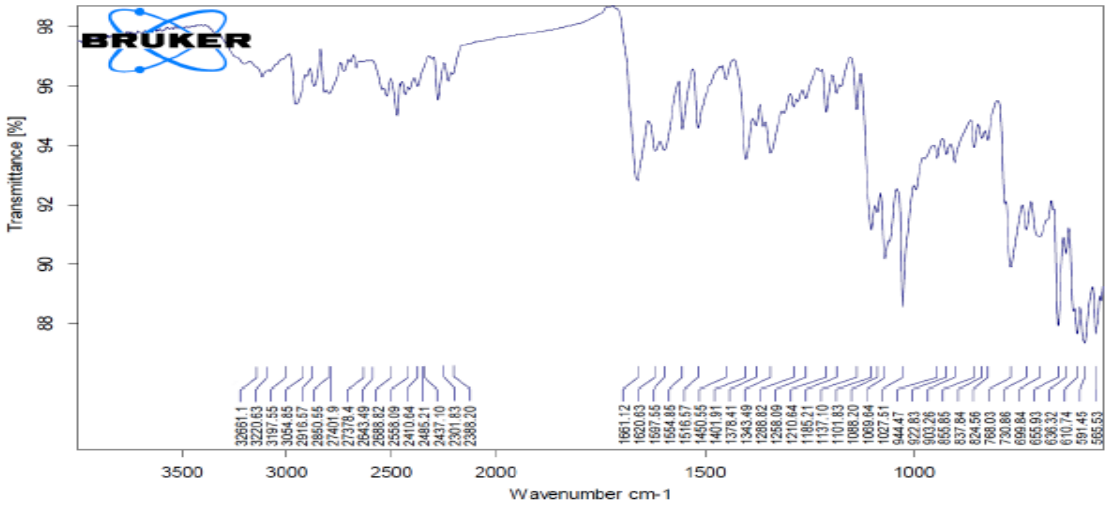

Figure: FTIR of Optimized formulation

The compatibility studies of the drug with excipients indicate no characteristic visual changes and no additional peaks were observed during FT-IR studies.

IV. CONCLUSION

The current study attempted to design and construct Clonidine Hcl patches employing several types of polymers, Carboxy Methyl Chitosan and HPMC 5cps, using a solvent evaporation approach. The medicine used has been extensively examined for its efficacy in treating relapse types of multiple sclerosis. Clonidine Hcl was successfully formulated as controlled release transdermal patches, reducing the frequency of administration and improving patient compliance. Based on the experimental results, the F-4 formulation was chosen as the best among all of the formulations. The formulation's in-vitro drug diffusion investigation demonstrated regulated release.The optimal formulation yielded evaluation parameters that were all deemed satisfactory. Numerous kinetic models, including zero order, first order, Higuchi model, and Peppas model, were fitted to the data gathered from the in-vitro release investigations. Drug release by diffusion technique from the polymer follows zero order release, according to the kinetic data. The creation and evaluation of the Clonidine HCL patches was successful in releasing the medication for a prolonged duration of 12 hours, based on the observations.

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