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Formulation of transdermal approach for the treatment of angina using Nifedipine as a model drug

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ABSTRACT

The purpose of this research was to develop a matrix-type transdermal therapeutic system containing drug Nifedipine with different ratios of polymeric systems by the Solvent evaporation technique by using Dibutyl phthalate to the polymer weight, incorporated as plasticizer. Glycerol was used to enhance the transdermal permeation of Nifedipine.The physicochemical compatibility of the drug and the polymers studied by infrared spectroscopy suggested absence of any incompatibility. Formulated transdermal patches were physically evaluated with regard to thickness, weight variation, drug content, flatness, tensile strength and folding endurance. *In-vitro* drug studies of formulations were performed by using Franz diffusion cells. The results followed the release profile of Nifedipine followed mixed peppas release kinetics. However, the release profile of the optimized formulation F6 (98.87% at 12hr) indicated that the permeation of the drug from the patches was governed by a diffusion mechanism.

Keywords*:* Nifedipine,a CMC, Eudragit RL 100, HPMC E 15LV, Transdermal drug delivery and solvent evaporation technique.

INTRODUCTION

Transdermal patch (Skin patch) uses a special membrane to control the rate at which the liquid drug contained in the reservoir within the patch can pass through the skin and into the Bloodstream. Some drugs must be combined with substances, such as alcohol, that increase their ability to penetrate the skin in order to be used in a skin patch. Drugs administered through skin patches include scopolamine (for motion sickness), nicotine (for quitting smoking), estrogen (for menopause and to prevent osteoporosis after meno pause), nitroglycerin (for angina), and lidocaine to relieve the pain of shingles (herpes zoster). Molecules of insulin and many other substances, however, are too large to pass through the skin. Patches applied to the skin eliminate the need for vascular access by syringe or the use of pumps. Transdermal patches were developed in the 1970s and the first was approved by the FDA in 1979 for the treatment of motion sickness.[1-3]It was a three-day patch that delivered scopolamine. In 1981, patches for nitroglycerin were approved, and today there exist a number of patches for drugs such as clonidine, fentanyl, lidocaine, nicotine, nitroglycerin, oestradiol, oxybutinin, scopolamine, and testosterone. There are also combination patches for contraception, as well as hormone replacement.[4,5] Depending on the drug, the patches generally last from one to seven days. The major advantages provided by transdermal drug delivery include the following: improved bioavailability, more uniform plasma levels, longer duration of action resulting in a reduction in dosing frequency, reduced side effects and improved therapy due to maintenance of plasma levels up to the end of the dosing interval compared to a decline in plasma levels with conventional oral dosage forms. Transdermal patches have been useful in developing new applications for existing therapeutics and for reducing first-pass drug-degradation effects. Patches can also reduce side

effects; for example, oestradiol patches are used by more than a million patients. annually and, in contrast to oral formulations, do not cause liver damage. of two major sub-categories - therapeutic and cosmetic), aroma patches, weight loss patches, and Non medicated patch markets include thermal and cold patches, nutrient patches, skin care patches (a category that consists patches that measure sunlight exposure. [6,7]
A transdermal patch or skin patch is a medicated adhesive patch that is placed on the skin to deliver a specific dose of medication through the skin and into the bloodstream.

Advantages

- They can avoid gastrointestinal drug absorption difficulties covered by gastrointestinal pH, enzymatic activity and drug interaction with food, drink and other orally administration drug.
- They can substitute for oral administration of medication when the route is unsuitable as with vomiting and diarrhea.
- To avoid the first pass effect e.g. Transdermal Nitroglycerin. It is rapidly metabolized by the liner when taken orally.
- They are noninvasive, avoiding the inconvenience of parenteral therapy.
- They provided extended therapy with a single application, improving compliance over other dosage forms requiring more frequent dose administration e.g. Tradermal clonidine day.
- The activity of drugs having a start half life is extended through the reservoir of drug in the therapeutic delivery system and its controlled release.
- Drug therapy may be terminated rapidly by removal of the application from the surface of the skin.[8,9]

Disadvantages

- Some patients develop contact dermatitis at the site of application from one or more of the system components, necessitating discontinuation.
- Only potent drugs are suitable candidates for transdermal patch because of the natural limits of drug entry imposed by the skin's imperability.
- Some drugs e.g. scopolamine transdermal patch placed behind the ear, it is uncomfortable.
- Long time adhere is difficult. [10,11]

Physiology of the Skin

Skin of an average adult body covers a surface of approximately 2 m 2 and receives about one-third of the blood circulating through the body. Skin contains an uppermost layer, epidermis which has morphologically distinct regions; basal layer, spiny layer, stratum granulosum and upper most stratum corneum, it consists of highly cornified (dead) cells embedded in a continuous matrix of lipid membranous sheets. These extracellular membranes are unique in their compositions and are composed of ceramides, cholesterol and free fatty acids. The human skin surface is known to contain, on an average, 10-70 hair follicles and 200-250 sweat ducts on every square centimeters of the skin area. It is one of the most readily accessible organs of the human body.[12-14]

MATERIALS

NifedipineProvided by SURA LABS, Dilsukhnagar, Hyderabad. NaCMCYarrow-Chem products, Mumbai, Eudragit RL 100 Yarrow-Chem products, Mumbai.HPMC E 15LV Accord labs, Secunderabad. PEG-400 Accord labs,Secunderabad, ChloroformMerck SpecialitiesPvt Ltd, Glycerol Karnataka Fine Chem Laboratory Chemicals (Bengaluru, India), Dibutyl phthalate, Avantor Performance Materials India Limited (Haryana, India), Methanol Merck SpecialitiesPvt Ltd.

METHODOLOGY

Analytical method development

A. UV scan

A 100mg of Nifedipine 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 100µg/ml concentrations (stock solution-II). Take 10 ml solution from stock II and volume make up to 100 ml with buffer to get 10µg/ml. 10µg/ml solution was scanned from 200-400nm.

B. Construction of calibration curve

A 100mg of Nifedipine 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 5, 10, 15, 20 and 25 µg /ml. The absorbances of these solutions were determined spectrophotometrically at 240 nm.

Reformulations 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 Nifedipine was determined by adding excess amount of drug in the solvent.
The solubility was determined in distilled water and phosphate buffer pH 7.4. The procedure can be detailed as follows.
Saturated solution of Nifedipine 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 240 nm and 243 nm for phosphate buffer and distilled water respectively.

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 Nifedipine were prepared using different concentrations of Na CMC,Eudragit RL 100 and HPMC E 15LV polymers. 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. Glycerol 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. The formulation table is given in Table 1.

.Table 1: Formulation of Nifedipine patches

INGREDIENTS	FORMULATION CHART								
	F1	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
Nifedipine	10	10	10	10	10	10	10	10	10
Na CMC	10	20	30	-	-	-	-	-	-
Eudragit RL 100	-	-	-	10	20	30	-	-	-
HPMC E 15LV	-	-	-	-	-	-	10	20	30
PEG-400 (ml)	20	20	20	20	20	20	20	20	20
Chloroform: Methanol (1:1) (ml)	10:10	10:10	10:10	10:10	10:10	10:10	10:10	10:10	10:10
Glycerol (ml)	5	5	5	5	5	5	5	5	5
Dibutyl phthalate*(ml)	6	6	6	6	6	6	6	6	6

RESULT 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

UV scans

The lambda max of Nifedipine was found to be 240 nm.

Construction of calibration curve

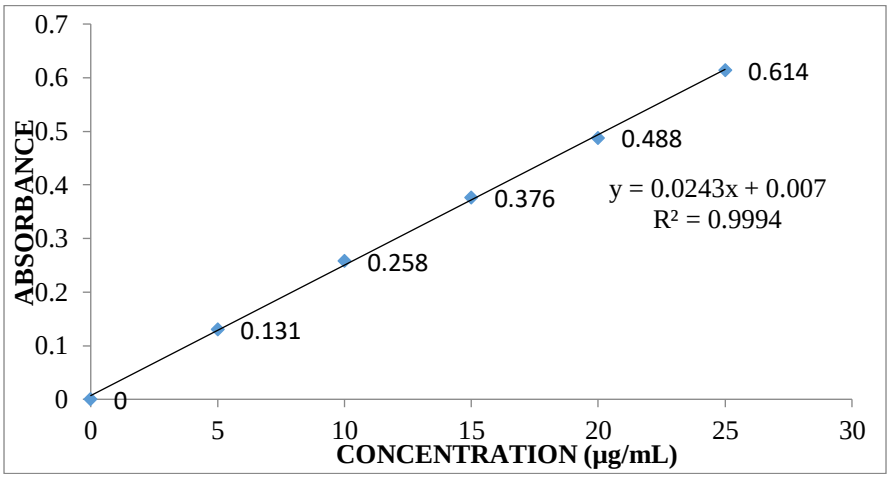

Fig1: Standard calibration curve of Nifedipine

Preformulation study

Totally, nine formulation trials were done with the aim to achieve the successful matrix type Nifedipine transdermal patches. The blend trials prepared for the drug was evaluated for various physical parameters and content uniformity of drug by UV.

Colour, odour, taste and appearance

Table 2: Results of identification tests of drug

Parameter	Nifedipine
Color	White
Odor	Odorless
Taste	Bitter
Appearance	A white powder

Melting point determination

Table 3: Results of melting point determination tests of drug

Drug	Reported melting point
Nifedipine	172-174^{0}C

Determination of solubility:

Table 4: Solubility Determination

Solvent	Drug solubility(mg/ml)
Distilled water	0.0177 mg/mL

Evaluation of Patch

The formulations F1 to F9 were varying in thickness when compared to other formulations which is due to the variation in the polymer concentration. Which shows the increase in polymer concentration increases the thickness of patch. For all other formulations it was found to be in between 0.051±0.006 to 0.059±0.001mm.All formulations from F1 to F9 Shows weight variation in between 116±2.60 to 120±6.14mg.Folding endurance from formulations F1 to F9 was found to be in between 70 ± 5.16 to 79 ± 2.53which can withstand the folding of the skin.All formulations showed % drug content from 95.26 ±2.10 to 99.43 ±9.99.

Table 5: Evaluation of patches

Formulation Code	Average weight (mg)	Thickness (mm)	Folding endurance	Flatness (%)	Flatness	% Drug Content
F1	120±5.93	0.056±0.004	70 ± 5.16	96	Transparent	95.26 ±2.10
F2	119±1.64	0.052±0.002	76 ± 1.52	98	Transparent	98.90 ±0.36
F3	118±0.13	0.059±0.001	72 ± 6.90	98	Transparent	97.83 ±6.29
F4	116±2.60	0.051±0.006	78 ± 0.16	94	Transparent	96.16 ±9.15
F5	119±1.89	0.053±0.004	75 ± 5.72	96	Transparent	98.97 ±4.48
F6	120±6.14	0.055±0.003	79 ± 2.53	96	Transparent	99.43 ±9.99
F7	117±2.79	0.056±0.004	76 ± 7.10	94	Transparent	98.82 ±3.15
F8	119±1.36	0.057±0.001	70 ± 9.98	97	Transparent	98.97 ±2.27
F9	118±0.42	0.054±0.004	71 ± 4.43	97	Transparent	97.34 ±7.60

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 6: *In vitro* drug permeation of Nifedipine containing different concentrations of Na CMC

Time(hr)	F1	F2	F3
0	0	0	0
1	27.42	25.69	21.41
2	34.39	30.09	27.69
3	47.60	42.16	38.34
4	56.51	50.65	44.61

5	67.62	63.19	50.08
6	78.37	70.67	58.39
7	85.26	78.76	64.56
8	96.78	86.54	71.98
9	99.82	92.34	86.18
10		98.54	90.14
11			97.34
12			

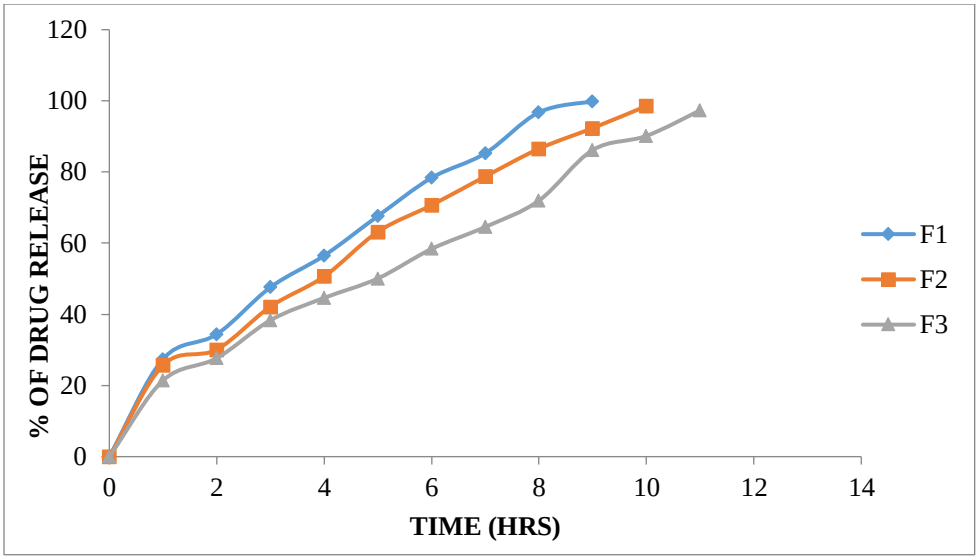

Fig2: Cumulative % drug permeation of Nifedipine patch (F1, F2, F3)

The formulations F1 to F3 were prepared by different concentrations of Na CMC (10, 20, 30mg) the drug release or drug permeation from the patch was dependence on the concentration of polymer in the matrix. At high polymer concentration the drug permeation is more 12 hours it was total amount of drug was permeated.

Table 7: *In vitro* drug permeation of Nifedipine containing different concentrations of Eudragit RL 100

Time(hr)	F4	F5	F6
0	0	0	0
1	32.26	27.92	22.92
2	48.78	32.65	30.36
3	55.36	43.89	37.61
4	67.23	54.32	44.53
5	76.98	62.87	51.88
6	87.46	67.90	64.46
7	95.68	75.36	71.87
8	98.14	82.77	79.29
9		89.53	86.14
10		97.91	92.49
11			96.73
12			98.87

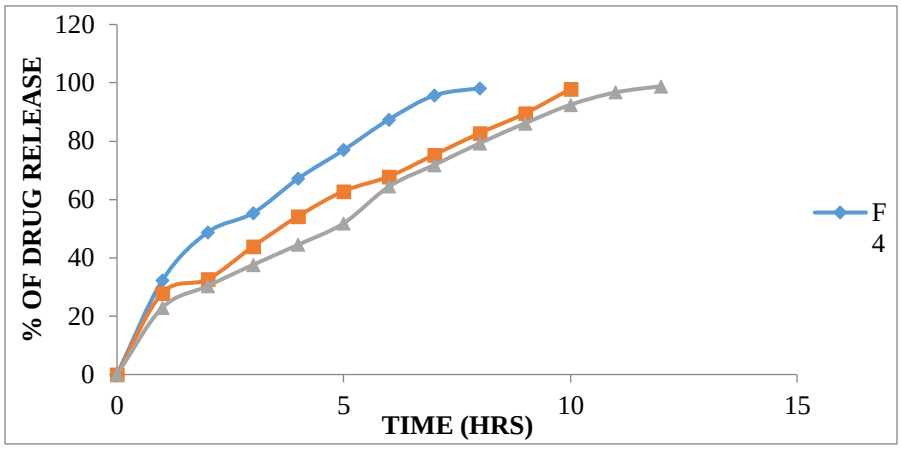

Fig 3:Cumulative % drug permeation of Nifedipine patch (F4, F5, F6)

The 10mg concentration of polymer was showed maximum drug released at 8 hours 98.14 %. The 20mg concentration of polymer was showed maximum drug release 97.91 at 10 hours. Hence in that 3 formulations F6 formulations showed total drug release at desired time period.

Table 8: *In vitro* drug permeation of Nifedipine containing different concentrations of HPMC E 15LV

Time	F7	F8	F9
0	0	0	0
1	36.54	30.14	25.30
2	46.41	38.79	31.26
3	55.05	46.23	36.71
4	61.60	52.90	43.82
5	67.35	57.44	50.19
6	75.12	64.15	56.53
7	89.28	73.20	64.75
8	95.46	77.38	72.89
9	96.65	83.02	79.93
10		92.11	85.42
11		98.97	90.82
12			95.36

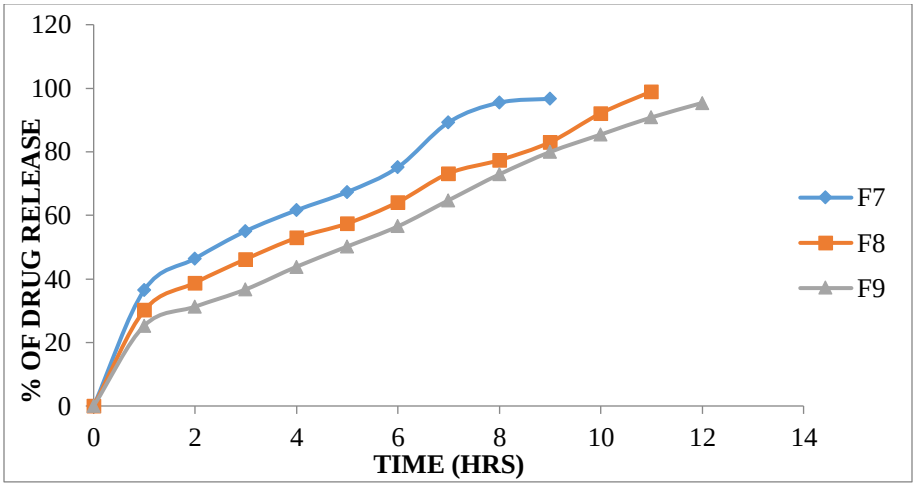

Fig 4: Cumulative % drug permeation of Nifedipine patch (F7, F8, F9)

The formulations F7 to F9 were prepared by different concentrations of HPMC E 15LV (10, 20, 30mg) the drug release or drug permeation from the patch was dependence on the concentration of polymer in the matrix. The 10mg (F7) concentration of polymer was showed maximum drug release 96.65 within 9 hours. The 20mg (F8) concentration of polymer was showed maximum drug released at 11 hours 98.97 %. The 30mg (F9) concentration of polymer was showed less drug release 95.36 at 12 h. Among all 9 formulations F6 formulation showed good drug permeation from the patch. Among all *in vitro* evaluation parameters F6 formulation passed all evaluation parameters.

Kinetic models for Nifedipine

Various models were tested for explaining the kinetics of drug release. To analyze the mechanism of the drug release rate kinetics of the dosage form, the obtained data were fitted into zero-order, first order, Higuchi, and Korsmeyer-Peppas release model.

Table9:Kinetics data of F6 Nifedipine patch

CUMULATIVE (%) RELEASE Q	TIME (T)	ROOT (T)	LOG(%) RELEASE	LOG (T)	LOG (%) REMAIN	RELEASERATE (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
22.92	1	1.000	1.360	0.000	1.887	22.920	0.0436	-0.640	77.08	4.642	4.256	0.386
30.36	2	1.414	1.482	0.301	1.843	15.180	0.0329	-0.518	69.64	4.642	4.114	0.527
37.61	3	1.732	1.575	0.477	1.795	12.537	0.0266	-0.425	62.39	4.642	3.966	0.675
44.53	4	2.000	1.649	0.602	1.744	11.133	0.0225	-0.351	55.47	4.642	3.814	0.828
51.88	5	2.236	1.715	0.699	1.682	10.376	0.0193	-0.285	48.12	4.642	3.637	1.004
64.46	6	2.449	1.809	0.778	1.551	10.743	0.0155	-0.191	35.54	4.642	3.288	1.354
71.87	7	2.646	1.857	0.845	1.449	10.267	0.0139	-0.143	28.13	4.642	3.041	1.600
79.29	8	2.828	1.899	0.903	1.316	9.911	0.0126	-0.101	20.71	4.642	2.746	1.895
86.14	9	3.000	1.935	0.954	1.142	9.571	0.0116	-0.065	13.86	4.642	2.402	2.240
92.49	10	3.162	1.966	1.000	0.876	9.249	0.0108	-0.034	7.51	4.642	1.958	2.683
96.73	11	3.317	1.986	1.041	0.515	8.794	0.0103	-0.014	3.27	4.642	1.484	3.157
98.87	12	3.464	1.995	1.079	0.053	8.239	0.0101	-0.005	1.13	4.642	1.042	3.600

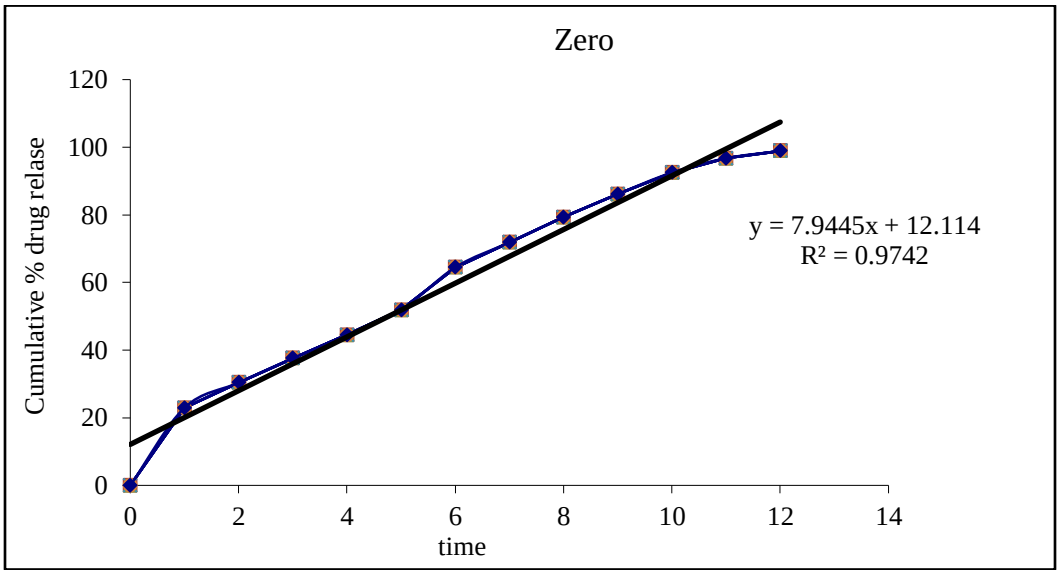

Fig 5: Graph of Zero order kinetics

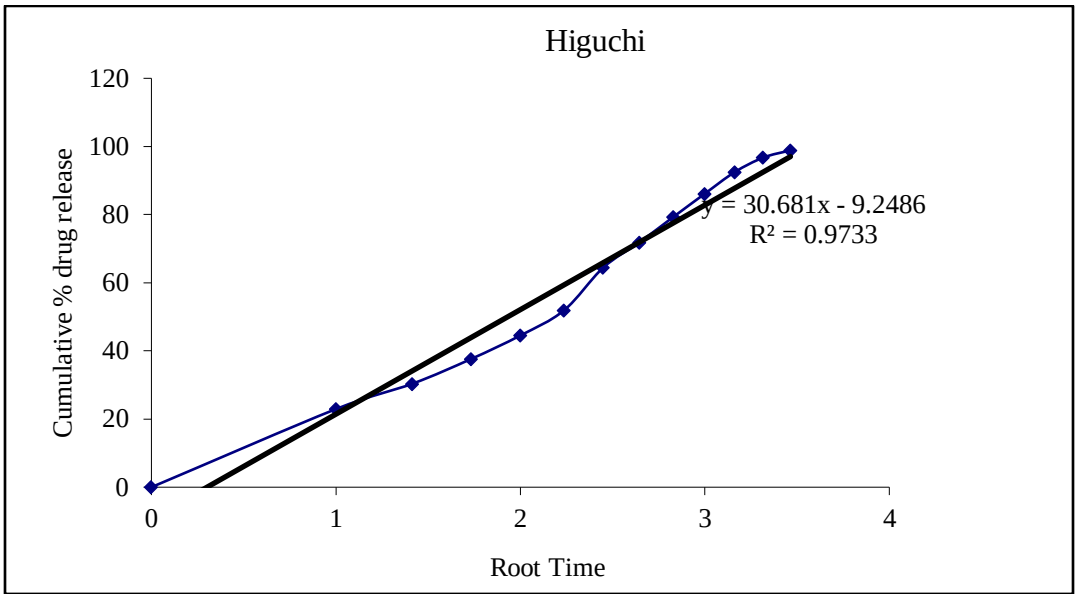

Fig 6: Graph of Higuchi release kinetics

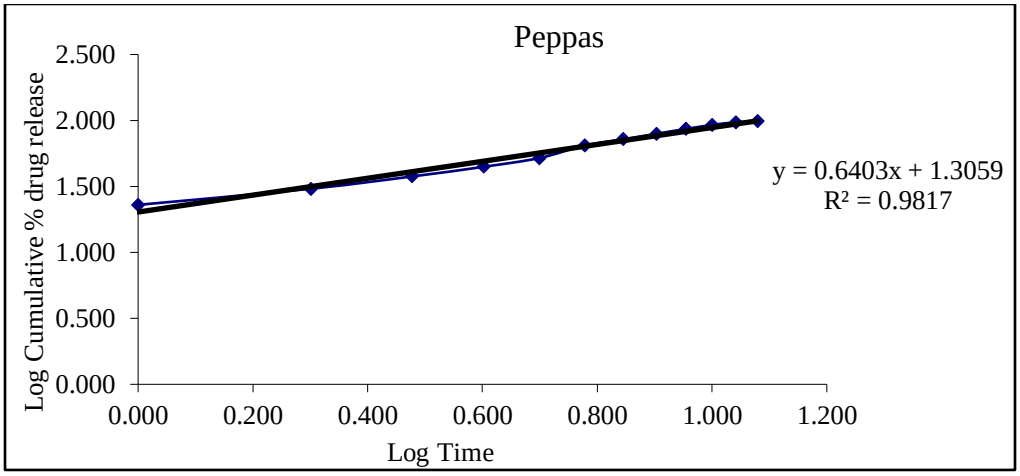

Fig 7: Graph of peppas release kinetics

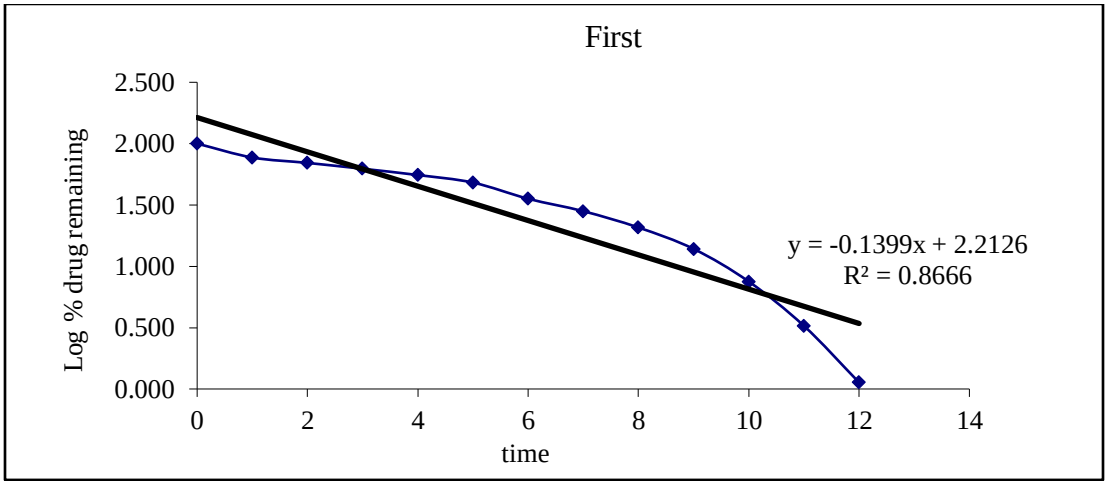

Fig 8: Graph of First order release kinetics

From the above data the optimized formulation followed peppas release kinetics model rule.

Compatibility Studies

Ir Spectroscopy

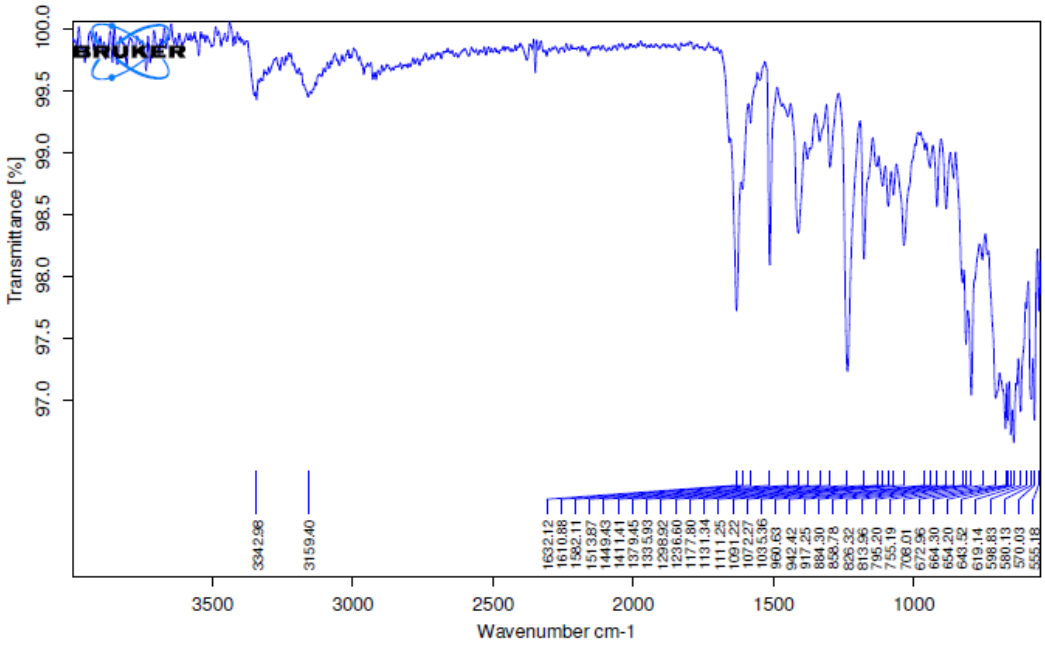

Fig 9: FTIR Spectrum of pure Nifedipine drug

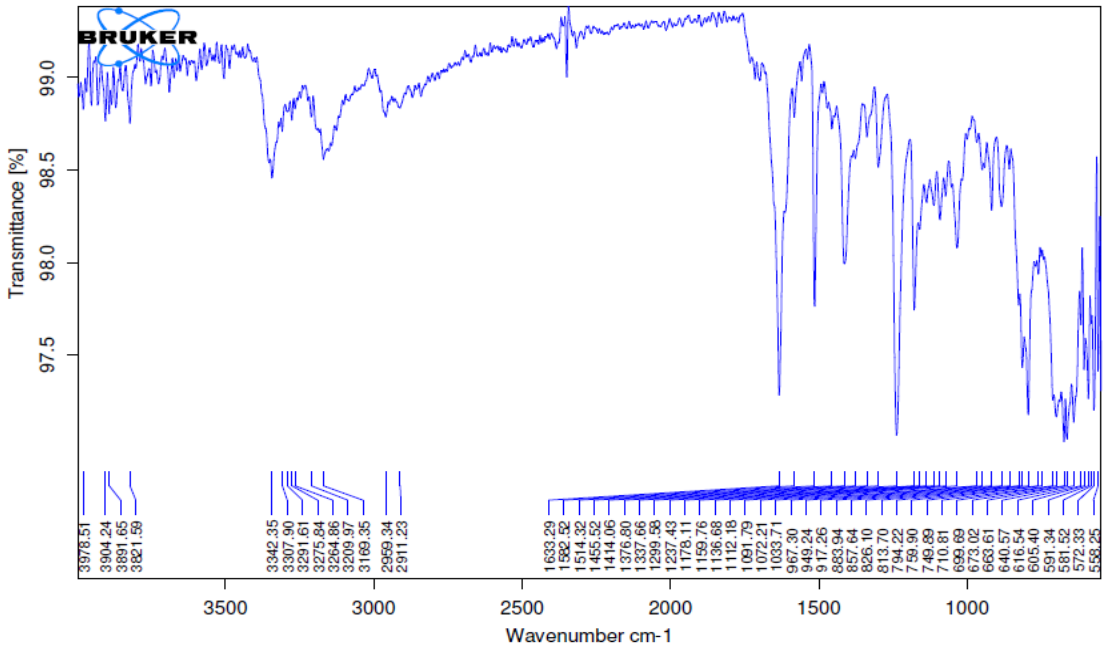

Fig 10: FTIR of Optimized formulation

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

CONCLUSION

The method of preparation of transdermal patches of Nifedipine presented in this research work is simple.Transdermal patches were prepared by using polymers like Na CMC, Eudragit RL 100 and HPMC E 15LV. Consideringsolubility of drug and polymer, the solvent system of Chloroform and Methanol was chosen. Dibutyl phthalate was used as a plasticizer.All formulation also showed good physicochemical properties like thickness, weight variation, drug content, flatness, folding endurance, Flatness, % drug content and *in vitro* drug release and the values were found to be within the acceptable limits.The *in-vitro* release data showed that drug release from the patch formulation have been affected by types of polymer and concentration of polymer.The formulation F6 containing Eudragit RL 100 showed good mechanical and physicochemical properties were selected as a suitable formulation for further studies.The transdermal patches of Nifedipinewere prepared using the different types of polymers in different concentration with permeation enhancer and plasticizer was found to be completely compatible with the drug molecule and the designed formulation release the drug in a sustained fashion over a prolonged period of time. Based on the *in vitro* release studies, formulation F6 were considered as the best formulations.The formulation F6 showed a maximum release and permeation of drug for longer time period up to 12 h. Hence, it can be concluded that Nifedipinecan be successfully formulated as the transdermal patch that can release the drug for an extended period of time up to 12 hours in a sustained manner. Such a drug delivery system can be used to avoid the side effects associated with the therapy and can safely deliver the drug with better patient compliance.Based on the observations, it can be concluded that the attempt of formulation and evaluation of the Nifedipine patches was found to be successful in the release of the drug for an extended period of 12 hrs.

REFERENCES

1. MaliAD, BatheR, PatilM. An updated review on transdermal drug delivery systems.Int J of Adv in Sci Res.2015;1(6):244-54. doi: 10.7439/ijasr.v1i6.2243.
2. Shaila L, Pandey S, Udupa N. Design and evaluation of matrix type membrane controlled transdermal drug delivery system of nicotinesuitable for use in Smoking Cessation. Indian JPharmSci.2006;68:179-84.
3. Aarti N, Louk ARMP, Russsel.O.P and Richard H.G. Mechanism of oleic acid induced skin permeation enhancement in vivo in humans. JControl Release.1995;37:299-306.
4. Brown MB, Jones SA. Hyaluronic acid: A uniquetopicalvehicle for localized drug delivery of drugs to the skin. Jedv.2000;19:308-18.
5. Tsai JC, Guy RH, Thornfeldt CR, Gaow.N, Feingold K. R and Elias P.M. Metabolic Approaches to Enchance Transdermal Drug Delivery.JPharmSci.1998;85:643-8.
6. Berner B, John VA. Pharmacokinetic characterization of transdermal delivery systems. ClinPharmacokinet. 1994;26(2):121-34. doi: 10.2165/00003088-199426020-00005, PMID 8162656.
7. Baker W, Heller J. Material selection for transdermal delivery systems. In: Hadgraft J, Guys RH, editors. Transdermal drug delivery: developmental issues and research initiatives. New York: Marcel Dekker, Inc;1989. p. 293-311.
8. Yamamoto T, Katakabe K, Akiyoshi K, Kan K, Asano T. Topical application of glibenclamide lowers blood glucose levels in rats. Diabetes ResClinPract.1990;8:19-22.
9. Reddy KR, Mutalik S, Reddy S. RhaghuramRk, Muttalik S, ReddyS.Once – dailysustained- release matrix tablets of nicorandil: formulation and in-vitroevaluation. AAPSPharmSciTech.2003;4(4):480-8. doi: 10.1208/pt040461.
10. Shaila L, Pandey S, Udupa N. Design and evaluation of matrix type membrane controlled transdermal drug delivery system of nicotinesuitable for use in Smoking Cessation. Indian J PharmSci. 2006;68:179-84.
11. Aarti N, LoukArmpOp R. RichardHg. Mechanism of Oleic Acid Induced Skin Permeation Enhancement in Vivo in Humans. JControl Release.1995;37:299-306.
12. Prabhakar D, Sreekanth J, Jayaveera KN. Transdermal drug delivery patches: areview. J Drug DelivTher.2013;3(4):213-21. doi: 10.22270/jddt.v3i4.590.
13. Yie W,Chien. Novel drugdeliverysystems.2nded, M. Vol. 50. Dekker;2005. p. 301-80.
14. KelebE, SharmaRK.Transdermal drug delivery system-design and evaluation.IntJ Adv PharmSci.2010;1(3):201-11.
15. Ankush I, Shembale.Useful permeation enhancers for transdermal drug delivery A review, IJPRD.2010;5:1-6.
16. Brian W, Barry.Dermatological formulationspercutaneousabsorption;18:95-126.
17. Jain NK.Controlled and novel.Drug Deliv.1997:100-15.
18. SonlS, Vinod K, Dixit.Transdermal penetration enhancers, categorization. Indian Drugs.1992;29(11):465-71.