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Research

Formulation and evaluation of transfersomal transdermal patch of hydrochlorothiazide

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Abstract

The objective of present investigation has been focused on formulation and characterization of Hydrochlorothiazide loaded transfersomal transdermal patch as an alternative delivery method for localized drug action to the targeted site. Hydrochlorothiazide was encapsulated into transfersome vesicle using different edge activators and characterized for particle size, vesicle morphology by scanning electron microscopy, entrapment efficiency and drug release. Later, the optimized F4 transfersome formulations were selected for patch preparation by solvent casting method. Transfersomal vesicles were found to be nanometric range [below 400 nm] with spherical structure. F4 formulation showed maximum drug release of 97.25 % and entrapment efficiency of 96.75 %. Based on the *in vitro* permeation studies, Hydrochlorothiazide loaded transfersomal patch was found to have greater drug permeation of Hydrochlorothiazide. The results obtained revealed that Hydrochlorothiazide in all the formulations was successfully entrapped with good uniformity and followed Peppas release kinetics model. This research work suggested that Hydrochlorothiazide loaded transfersomal transdermal patch can be a novel alternative approach to oral therapy in the treatment of high blood pressure and swelling due to fluid buildup.

Keywords: Transdermal patches, Hydrochlorothiazide and transfersome.

INTRODUCTION

NOVEL DRUG DELIVERY SYSTEM

[1]For many decades treatment of an acute disease or a chronic illness has been mostly accomplished by delivery of drugs to patients using various pharmaceutical dosage forms including tablets, capsules, pills, suppositories, creams, ointments, liquids, aerosols and injectables, as drug delivery systems are the primary pharmaceutical products commonly seen in the market, even though these drug delivery system ensure a prompt

release of drug, it is necessary to take this type of drug several times a day to achieve as well as to maintain the drug concentration with in the therapeutically effective range needed for the treatment. This results in significant fluctuations in drug level.

In the past two and a half decades several advancements have been made. They have resulted in the development of new techniques for drug delivery. These techniques are capable of controlling the rate of drug delivery, sustaining the durationof therapeutic activity and targeting the delivery of drug to a cell or tissue. Recently pulsatile drug delivery system is gaining importance. These advancements have led to the development of several novel drug delivery systems that could revolutionalise the method of medication and provides a number of therapeutic benefits.

[2]Novel drug delivery system can be broadly divided into two classes

Sustained Release Drug Delivery System

Sustained release drug delivery system is described as a pharmaceutical dosage form formulated to retard the release of a therapeutic agent such that its appearance in the systemic circulation is delayed and/or prolonged and its plasma profile is sustained in duration. The onset of its pharmacological action is often delayed and the duration of its therapeutic effect is sustained (e.g. coated granules).

Controlled Release Drug Delivery System

Controlled release drug delivery system has a meaning that goes beyond the scope of sustained drug release. It implies a predictability and reproducibility in the drug release kinetics. The release of drug ingredients from a controlled release drug delivery system proceeds at a rate profile that is not only predictable kinetically but also reproducible from one unit to another.

Controlled release drug delivery system can be classified into four categories

Rate-Preprogrammed Drug Delivery System

In this system, the release of drug molecules from the drug delivery system has been preprogrammed at specific rate profiles. This was achieved by systemdesigning which controls the molecular diffusion of drug molecules in and/or across the barrier medium with in or surrounding the delivery system. (e.g.) implants, transdermal system[3].

Activation – Modulated Drug Delivery System

The release of the drug molecule from this delivery system is activated by some physical, chemical or biochemical process and/or facilitated by the energy supplied externally. The rate of drug release is then controlled by regulating the process applied or energy input. Based on the nature of the process applied or the type of energy used, these activation modulated drug delivery system can be classified in to three categories:

1. Physical–e.g.:Osmotic pressure activated drug delivery system- osmotic pump[4], iontophoresis activated drug delivery system
2. Chemical- e.g.:pH activated drug delivery system[6]
3. Biochemical-e.g.: Enzyme activated drug delivery system[7]

Feed Back –Regulated Drug Delivery System

The release of the drug molecule from the delivery system is activated by a triggering agent, such as biochemical substance in the body and regulated by its concentration viz. some feed back mechanisms. The rate of drug release is then controlled by the concentration of triggering agent detected by a sensor in the feed back regulated mechanism. E.g. bio-responsive drug delivery system, glucose triggered insulin delivery system[8].

Site-Targeting Drug Delivery System

In this system the drug molecules are circumventing the other tissues and moving towards the specific diseased site and get released. This will enhance the therapeutic effectiveness and reduces the toxicity to other healthy tissues and improvethe treatment spectrum e.g. Niosomes, Microspheres.

MATERIALS

Soya lecithin-Purchased from Loba Chemie, Mumbai, Tween 80-Purchased from SD Fine Chem Ltd., Mumbai, Span 80-Purchased from Merck Limited, Mumbai (India), Methanol-Purchased from Himedia, Mumbai, Chloroform-Purchased from SD Fine- Chem Limited, Mumbai, Eudragit L 100-Purchased from SD Fine- Chem Limited, Mumbai, Ethylcellulose-Purchased from Loba Chemie Pvt Ltd. (Mumbai, India), Propylene glycol-Purchased from SD Fine- Chem Limited, Mumbai, Dimethyl sulfoxide-Purchased from Merck Limited, Mumbai (India)

METHODOLOGY

Identification and Characterization of Drug

Preparation of reagents

Preparation of 0.2M NaOH Solution

Dissolved 4g of Sodium hydroxide pellets in to 1000mL of Purified water and mixed

Preparation of pH 6.8 Phosphate buffer

Dissolved 6.805 g of Potassium dihydrogen phosphate in to 800mL of purified water and mixed added 112mL of 0.2M NaOH solution and mixed. Diluted to volume 1000mL with purified water and mixed. Than adjusted the pH of this solution to 6.8 with 0.2M NaOH solution.

a) Determination of absorption maxima

A solution containing the concentration 10 µg/ ml drug was prepared in 5.5 phosphate buffer UV spectrum was taken using Lab India Double beam UV/VIS spectrophotometer (Lab India UV 3000+). The solution was scanned in the range of 200 – 400 nm.

b) Construction of standard graph

100 mg of Hydrochlorothiazide was dissolved in 100 mL of pH 6.8 phosphate buffer to give a concentration in 1mg/mL (1000µg/mL) 1 ml was taken and diluted to 100 ml with pH 5.5 phosphate buffer to give a concentration of 0.01 mg/ml (10µg/ml). From this stock solution aliquots of 1 ml, 2 ml, 3 ml, 4 ml, 5 ml, were pipette out in 10 ml volumetric flask and volume was made up to the mark with pH 5.5 phosphate buffer to produce concentration of 10, 20, 30, 40 and 50 µg/ml respectively. The absorbance of each concentration was measured at respective (λ_{max}) i.e., 255 nm.

Organoleptic properties

Take a small quantity of sample and spread it on the white paper and examine it visually for color, odour and texture.

Determination of Hydrochlorothiazide Melting point

The melting point of Hydrochlorothiazide was determined by capillary tube method according to the USP. A sufficient quantity of Hydrochlorothiazide powder was introduced into the capillary tube to give a compact column of 4-6 mm in height. The tube was introduced in electrical melting point apparatus and the temperature was raised. The melting point was recorded, which is the temperature at which the last solid particle of Hydrochlorothiazide in the tube passed into liquid phase**.**

Determination of Hydrochlorothiazide Solubility

Determination of solubility of drug by visual observation. An excess quantity of Hydrochlorothiazide was taken separately and adds in 10 ml of different solutions. These solutions were shaken well for few minutes. Then the solubility was observed and observations are shown in the Table.

FORMULATION OF TRANSFERSOMES

Preparation of Hydrochlorothiazide loaded transfersomes Soya lecithin along with surfactants tween80/span 80 was placed in a round bottomed flask. The solvent system is then added to the mixture and the ingredients were dissolved in the solvent (Chloroform: methanol) by hand shaking. The flask was attached to a rotary evaporator and immersed in water bath maintained at 60^{o}C, rotated with 100rpm for 45min. Formation of thin film at the bottom was observed. The thin film is hydrated using 6.8pH buffer. The resultant solution was sonicated in ultra sonicator for 10mins.

Table 1: Formulation composition of Hydrochlorothiazide Transfersomes

Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8
Hydrochlorothiazide	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5
Soya lecithin : Tween 80	1:1	1:2	1:3	1:4	-	-	-	-
Soya lecithin : Span 80	-	-	-	-	1:1	1:2	1:3	1:4
Methanol : Chloroform	1:2	1:2	1:2	1:2	1:2	1:2	1:2	1:2

RESULTS AND DISCUSSIONS

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 Hydrochlorothiazide was found to be 255 nm.

B. construction of calibration curve

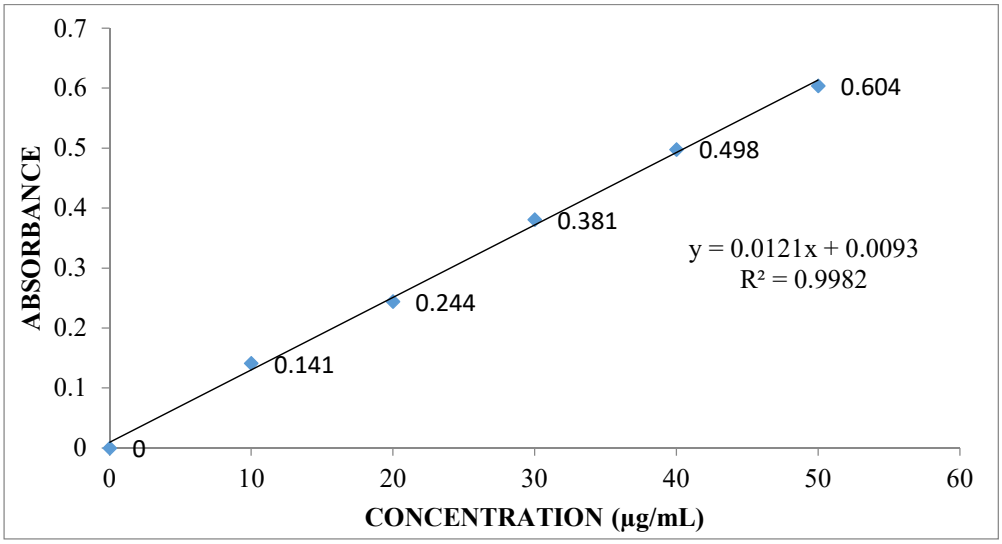

Fig 1: Standard calibration curve of Hydrochlorothiazide

Standard graph of clozapine was plotted as per the procedure in experimental method and its linearity is shown in Table and Fig. The standard graph of Hydrochlorothiazide showed good linearity with R^2 of 0.998, which indicates that it obeys "Beer- Lamberts" law.

Characterization of Transfersomes

Table 2: Percentage yield, Drug Content, Entrapment Efficiency of all Transfersomes formulations

FORMULATION	PDI	Particle Sizes	Zeta Potential	Entrapment Efficiency
F1	0.80	286.12	0.565 ± 0.37	80.14
F2	0.48	301.64	0.660 ± 0.38	92.36
F3	0.35	365.92	0.672 ± 0.37	95.67
F4	1.26	382.76	0.678 ± 0.32	96.75
F5	0.65	295.17	0.563 ± 0.34	75.92
F6	0.87	334.87	0.573 ± 0.35	86.24
F7	0.76	397.34	0.591 ± 0.41	90.47
F8	1.32	400.51	0.605 ± 0.27	92.64

The particle size of transfersome was found to be in the range of 286.12 to 382.76 nm with Soya lecithin: Tween 80 whereas for Soya lecithin: Span 80 it was in the range of 295.17 to 400.51 nm. Entrapment efficiency of Hydrochlorothiazide loaded transfersome formulations was found to be in range of 75.92 % to 96.75 % as shown in Table. The concentration and type of edge activator used has a very crucial effect on entrapment efficiency.

Zeta potential results reveal that Soya lecithin: Tween 80 transfersomes possess negative charge at pH 6.8 indicating that a weak electrostatic repulsive force exists in niosomal bilayer. Also, the inclusion Tween 80 transfersomes found to have increased the zeta potential. Particles with zetapotential close to zero have been found less phagocytable in comparison with charged particles. The nature and density of charge on the surface of

transfersomes influence the extent of biodistribution as well as interaction and uptake of transfersomes by target cells. F4 formulation highest zeta potential and it had good stability. Vesicle morphology Transfersome with Soya lecithin: Tween 80 was selected as optimal carrier owing to smaller particle size, good entrapment efficiency and maximum elasticity and hence used for SEM analysis. Shape and surface morphology of transfersome formulation was studied using scanning electron microscopy at various magnifications as shown in fig. 5. The drug loaded transfersome formulation was found to be smooth, spherical in shape with sharp boundaries having internal aqueous space.

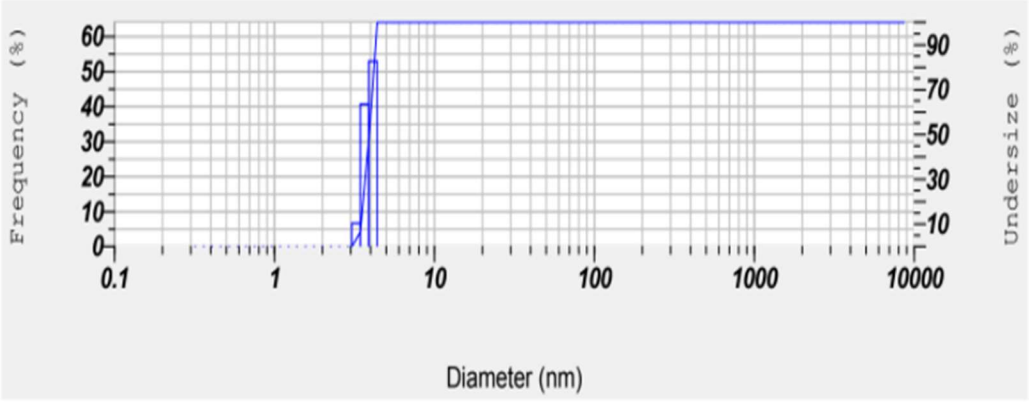

Fig 2: Particle size of F4 Formulation

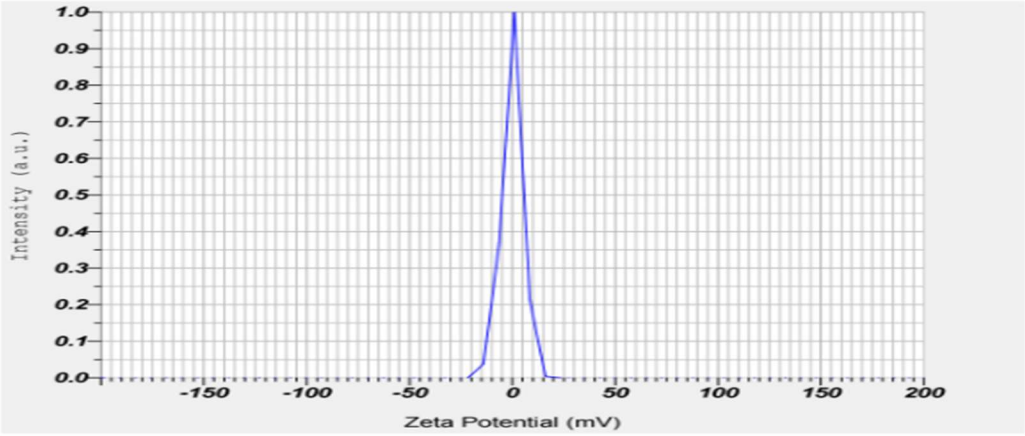

Fig 3: Zeta potential of F4 Formulation

%Drug release

Table 3: *In vitro* dissolution studies of F1-F8 Transfersomes formulations in percentage

Time (hour)	F1	F2	F3	F4	F5	F6	F7	F8
0	0	0	0	0	0	0	0	0
1	15.07	18.04	26.13	31.08	13.61	16.98	18.80	20.61
2	21.14	28.11	36.20	42.14	17.25	21.16	23.35	26.15
3	35.36	42.00	45.33	53.93	25.32	26.05	31.86	39.77
4	41.55	51.95	55.16	60.32	32.64	37.43	45.81	47.53
6	50.09	57.36	61.86	68.26	37.86	40.17	53.82	56.48
8	56.17	62.14	75.36	73.66	43.17	48.35	62.37	67.27
10	60.93	76.23	83.24	87.92	51.05	56.42	69.96	71.79
12	67.49	81.11	90.79	97.25	58.82	73.29	76.87	82.42

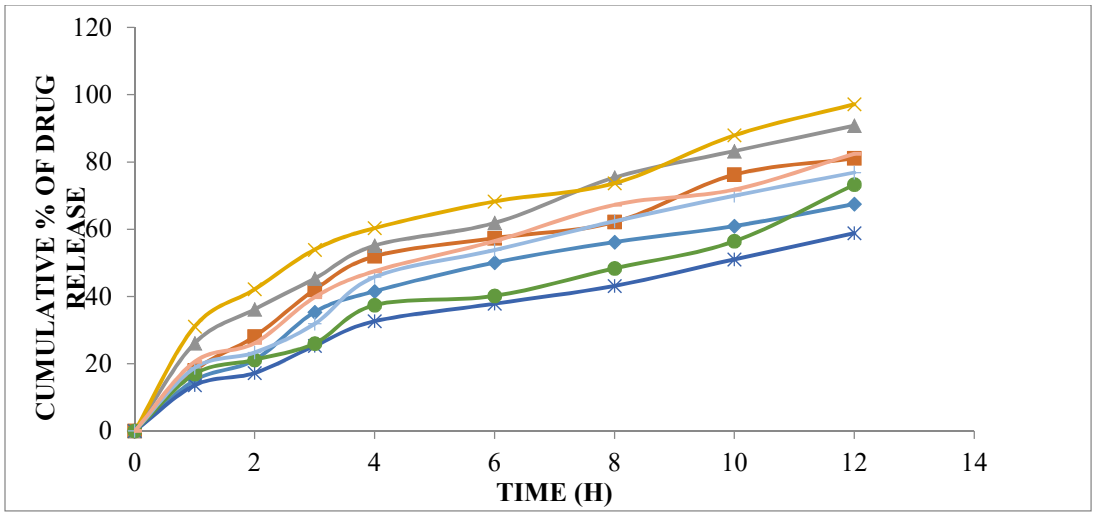

Fig 4: *In vitro* dissolution studies of F1-F8 Transfersomes formulations

In vitro studies of selected formulations were carried out in PBS pH 6.8 and results were shown in Figure. It was clearly observed from the data as shown in Figure that *in vitro* drug release of Transfersomes containing Tween 80 of different quantities was sharply increased up to 12 hr. Maximum drug release that is, 97.25%, was reported in case of Transfersomes containing 1:4 ratio Transfersomes as shown in Figure. F4 formulation considered as optimised formulation (97.25%).

SEM

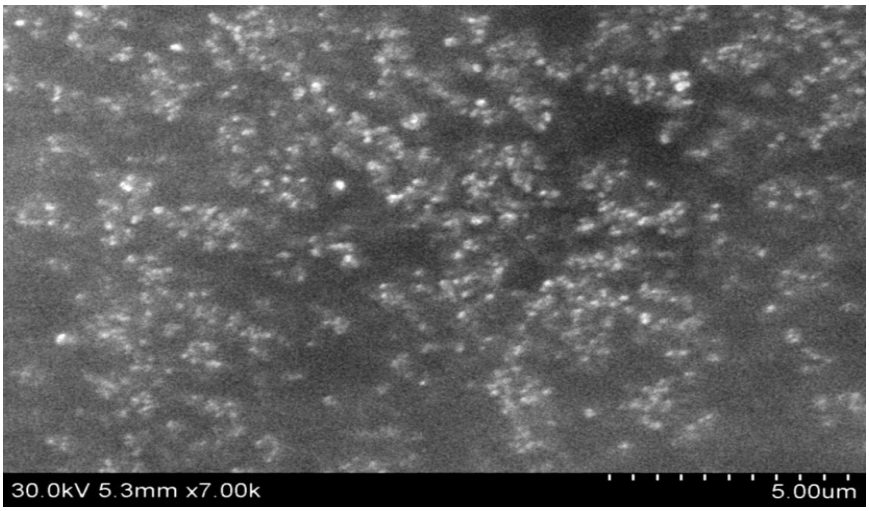

Fig 5: Hydrochlorothiazide Transfersomes optimised formulation (F4)

SEM studies showed that the Hydrochlorothiazide - loaded Transfersomes had a spherical shape with a smooth surface as shown in Figure. The transdermal patch was prepared using solvent casting method from the optimised Transfersomes formulation F4 formulation. The prepared optimised Transfersomes F4 formulation was loaded into the patch formulation. The formulations of Transfersomes transdermal patches are shown in methodology table.

Evaluation of Patch

The formulations F4TP1 to F4TP4 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 0.050 ± 0.003 to 0.061 ± 0.003 mm.

Folding endurance from formulations F4TP1 to F4TP4 was found to be in between 74± 1.57 to 87± 1.69 which can withstand the folding of the skin. All formulations showed % drug content from 96.26 to 98.20.

Table 4: Evaluation of Transfersomal transdermal patches

Formulation Code	Thickness (mm)	Folding endurance	Flatness (%)	Appearance	% Drug Content
F4TP1	0.050 ± 0.003	85± 1.69	98	Transparent	96.14 ± 0.96
F4TP2	0.053 ± 0.005	76± 0.35	100	Transparent	95.89 ± 1.75
F4TP3	0.057 ± 0.001	82± 0.62	98	Transparent	97.11 ± 2.32
F4TP4	0.061 ± 0.003	87± 1.57	99	Transparent	98.01 ± 0.21

***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 37 ± 0.5ºC. The diffusion was carried out for 12 hr and 5 ml sample was withdrawn at an interval of every 1 hr.

Table 5: *In vitro* drug permeation of Hydrochlorothiazide containing different concentrations

Time(hr)	F4TP1	F4TP2	F4TP3	F4TP4
0	0	0	0	0
1	25.86	28.09	32.16	39.42
2	34.34	32.60	45.34	47.71
3	41.99	45.98	51.49	55.86
4	47.20	59.59	62.14	68.90
6	54.39	64.32	69.39	70.61
8	60.26	75.64	78.20	84.55
10	63.15	77.81	89.31	91.74
12	77.01	83.83	94.78	98.17

The *in vitro* release studies of various formulations of Hydrochlorothiazide loaded Transfersomal transdermal patch was also done for 12 h in phosphate buffer pH 6.8. A constant temperature and pressure conditions were maintained throughout the experiment. The *in vitro* drug release studies of Hydrochlorothiazide Transfersomal transdermal patches at different time intervals are shown in fig. The drug release was found to be F4NT4 formulation with the highest release of 98.17% thus regarded as the optimised formulation. The release was initially found to be burst followed by the gradual sustained increase in free drug concentration.

Release Kinetics

To analyze the drug release mechanism the *in vitro* release was fitted into various release equations and kinetic models first order, zero order, Higuchi and Korsmeyer-peppas. The release kinetics of optimized formulation is shown in Table and in following Figures.

Table 6: Release kinetics of optimised formulation

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
39.42	1	1.000	1.596	0.000	1.782	39.420	0.0254	-0.404	60.58	4.642	3.927	0.714
47.71	2	1.414	1.679	0.301	1.718	23.855	0.0210	-0.321	52.29	4.642	3.739	0.902

55.86	3	1.732	1.747	0.477	1.645	18.620	0.0179	-0.253	44.14	4.642	3.534	1.108
68.9	4	2.000	1.838	0.602	1.493	17.225	0.0145	-0.162	31.1	4.642	3.145	1.497
70.61	6	2.449	1.849	0.778	1.468	11.768	0.0142	-0.151	29.39	4.642	3.086	1.556
84.55	8	2.828	1.927	0.903	1.189	10.569	0.0118	-0.073	15.45	4.642	2.491	2.151
91.74	10	3.162	1.963	1.000	0.917	9.174	0.0109	-0.037	8.26	4.642	2.021	2.620
98.17	12	3.464	1.992	1.079	0.262	8.181	0.0102	-0.008	1.83	4.642	1.223	3.418

The prepared optimised Transfersomal transdermal patch was subjected to the drug release kinetics and release mechanism. The formulation were studied by fitting the drug release time profile with the various equations such as Zero order, First order, Higuchi and Korsmeyer pappas. The data revealed a better fit to the Peppas release kinetics.

FT-IR

FTIR spectra of the drugs and the optimised formulation were recorded. The FTIR spectra of pure Hydrochlorothiazide drug, optimised formulation shown in the below figures respectively. Drugs are also present in the physical mixture, which indicates that there is no interaction between drug and the polymers, which confirms the stability of the drug. There was no disappearance of any characteristics peak in the FTIR spectrum of drug and the polymers used. This shows that there is no chemical interaction between the drug and the polymers used. The presence of peaks at the expected range confirms that the materials taken for the study are genuine and there were no possible interactions.

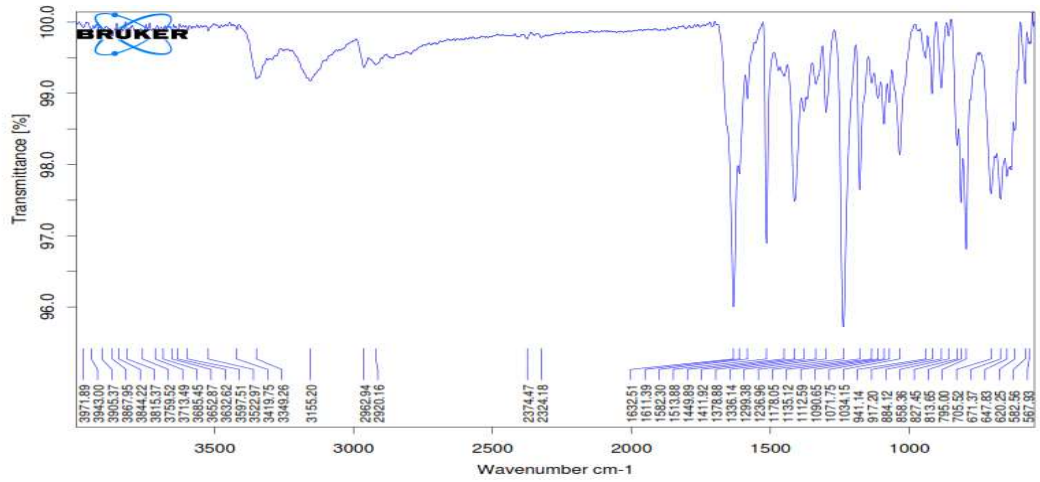

Fig 6: FT-IR graph of Hydrochlorothiazide

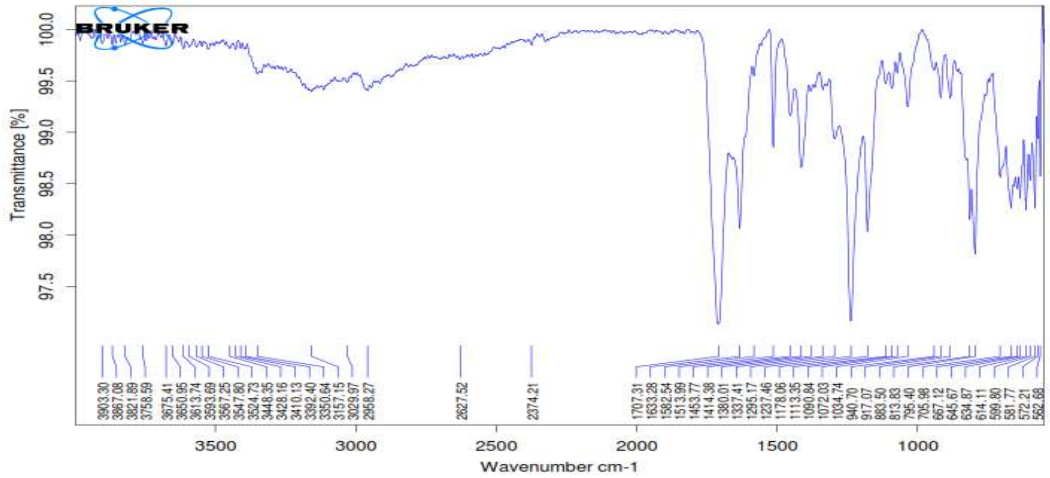

Fig 7: FT-IR graph of optimised formulations

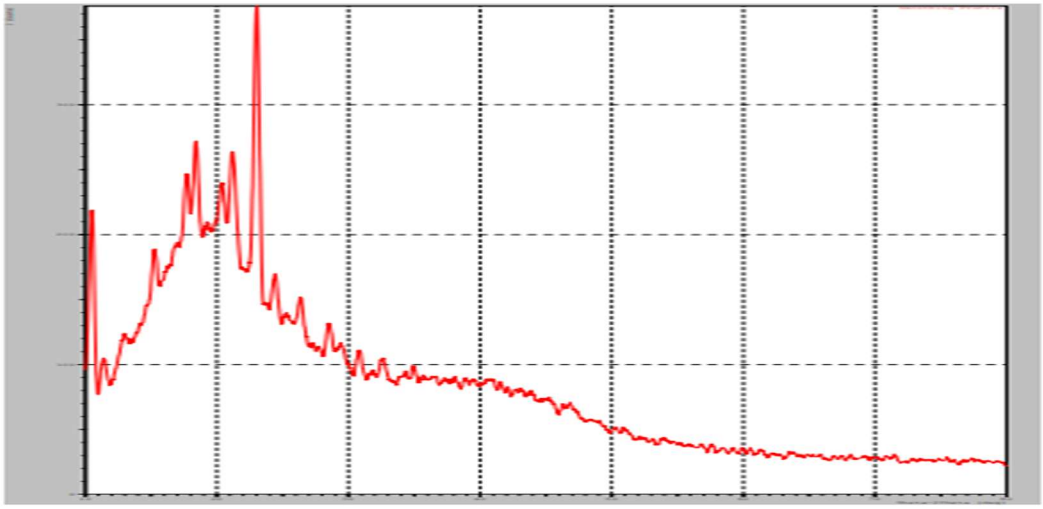

Fig 8: XRD graph of optimised formulations

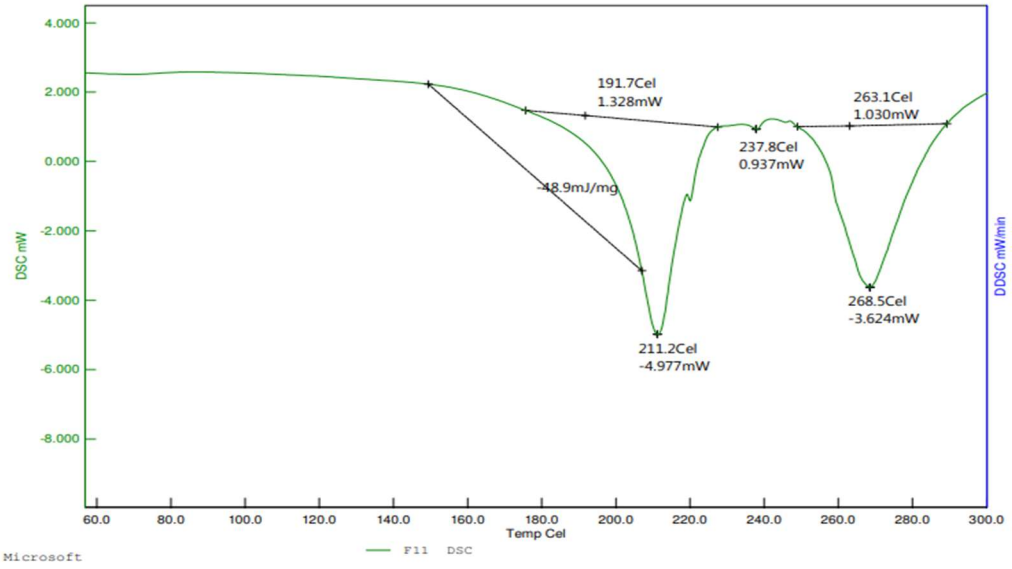

Fig 9: DSC graph of pure drug

CONCLUSION

The objective of the present study was to develop transdermal matrix patch of Hydrochlorothiazide and assess its feasibility for transdermal application. Hydrochlorothiazide is a diuretic medication used in the treatment of high blood pressure and swelling due to fluid buildup. Low dose maintenance therapy of Hydrochlorothiazide has the capability to reduce potential side effects and improved patient compliance which are more common with conventional drug delivery. Hydrochlorothiazide loaded Transfersomes were prepared using a surfactant (Tween 80 and span 80. showed the best entrapment efficiency and percent drug released within 12 h. F4 showed better entrapment efficiency as of 96.75%, minimal mean vesicular diameter as of 382.76 µm, and zeta potential as of 0.678 ± 0.32mV. Maximum drug release, that is, 97.25%, was reported in the F3 formulation. F4 formulation considered as optimised formulation. Among the formulations prepared, Hydrochlorothiazide loaded Transfersomes (F4) and Hydrochlorothiazide loaded Transfersomal transdermal patch (F4TP4) was fixed to be optimised formulations, which had maximum drug release of 97.17%. The optimised Transfersomal transdermal patch

(F4NT4) revealed a better fitted to first order release kinetics. Thus formulated Hydrochlorothiazide loaded Transfersomal transdermal patch represents to be an efficient and stable vesicular carrier for the transdermal delivery of an diuretic drug like Hydrochlorothiazide.

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