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TRANSDERMAL PATCH OF RAMIPRIL LOADED CHITOSAN NANOPARTICLES DISPERSED IN CARBOPOL GEL

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ABSTRACT

The main aim to improve the systemic bioavailability of Ramipril by the design of transdermal drug delivery based on chitosan nanoparticles dispersed into gels. When chitosan nanoparticles dispersed into gels consisting of poloxamer and carbopol the resulting formulation exhibited thixotropic behavior with a prolonged drug release properties. Our study demonstrated that the designed nanoparticles gel transdermal delivery system has a potential to improve the systemic bioavailability and the therapeutic efficacy of Ramipril loaded chitosan nanoparticles dispersed in carbopol gels. There is no incompatibility between drug and polymers by performing FTIR and DSC. To characterize the rate controlling membrane of transdermal patches. The thickness ranged between TNPGF1 to F9 0.11 ± 0.05 mm to 0.19 ± 0.07 mm, which indicates that they are uniform in thickness. The different batches of formulations weights variations were relatively good uniformity of weight variations among the various batches was observed, with all formulations and ranged from 1.40 ± 1.2% to 1.78 ± 2.0%. The flatness study showed that all the formulations had the same strip length before and after their cuts, indicating 99% flatness. The tensile strength of the TNPGF1 to TNPGF9 shows the 10.14 ± 1.19 to 12.78 ± 2.45 shows the excellent viscosity. The total amount of drug is present in the transdermal patches of TNPGF1 to TNPGF9 was found to be 90.5 ± 0.3 % to 98.5 ± 0.1 %. *In-vitro* Franz's diffusion drug Release Studies of among all formulations best formulation TNPGF6. The drug release through the transdermal patches of Ramipril, follows first order kinetics with diffusion controlled mechanism.

Keywords: Ramipril, Nanoparticles, Gels, Folding endurance, Tensile strength.

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INTRODUCTION

Transdermal drug delivery system: At present, the most common form of delivery of drugs is the oral route. While this has the notable advantage of easy administration, it also has significant drawbacks namely poor ability due to hepatic metabolism (first pass) and the tendency to produce rapid blood level spikes (both high and low), leading to a need for high and/or frequent dosing, which can be both cost prohibitive and inconvenient [1].

Advantages

1. Transdermal drug delivery can be used as an alternative delivery system for patients who cannot tolerate oral dosage forms.
2. Avoid the first pass effect e.g. transdermal nitroglycerin. It is rapidly metabolized by the liver when taken orally [2].
3. Drug therapy may be terminated rapidly by removal of the application from the surface of the skin.
4. It is of great advantage in patients who are nauseated or unconscious.
5. Allows continued drug administration permitting the use of a drug with short biological half-life.

Disadvantages

1. The drug, the adhesive or other excipients in the patch formulation can cause erythema, itching, and local edema.

2. The barrier function of the skin changes from one site to another on the same person, from person to person and also with age [3].
3. Some drugs e.g. scopolamine transdermal patch placed behind the ear, it is uncomfortable.
4. Adhesion may vary with patch type and environmental conditions.
5. Drugs that require high blood levels cannot be administered.

MATERIALS AND METHODS

The pure drug of Ramipril was obtained from Hetero drug Limited, Hyderabad and excipiens like Chitosan, Poloxamer, HPMC, Pentasodium tripolyphosphate, Dimethyl sulfoxide, Carbopol, Acetic acid, dimethyl sulfoxide obtained from Pharmaceutical Pvt Ltd, Navi Mumbai.

Formulation of Ramipril Loaded chitosan nanoparticles dispersed in carbopol gel:

Preparation of Nanoparticles:

Nanoparticles were Prepared by the ionic gelation technique at room temperature with combinations of different ratio of chitosan as shown in table and Pentasoidum tripoly phosphate. Chitosan was dissolved in acetic acid solution adjusted to pH 4.5 and TPP was dissolved in Milli-Q water (The system monitors the ion concentration by measuring the electrical resistivity of the water). TPP solution was added drop wise to an equal volume of chitosan solution under magnetic stirring at 650 rpm over 60 min. Ramipril loaded chitosan nanoparticles were prepared by the same method mentioned above, but that the appropriate amount of Ramipril was dissolved in chitosan solution before the dropwise addition of TPP solution [4].

Formulation of gels:

Poloxamer gels were prepared by using the cold technique. Poloxamer was slowly added into certain volume of cold Milli Q water (5-10 ^{o}C) with constant stirring for 60 min at 650 rpm. Additional amount Of Cold Milli-Q water was added to the solution at 30 min to make up to the volume [5]. Poloxamer solutions were kept in the refrigerator (4-5 ^{o}C) over night then kept at room temperature for a further 24 h Carbopol 940 (1% and 2 % w/v) gels were prepared by dispersing appropriate amount of carbopol into certain volume of Milli-Q water At room temperature with constant stirring for 60 min at 650 rpm. Milli-Q water was added to the solution at 30 min to Make up the volume to the total amount. Carbopol gels were kept at room temperature for 24 h. Poloxamer and carbopol combination gels were prepared with similar methods as above. Both were stirred at 650 rpm for 60 min [6]. At 30 min, the two were mixed and Milli Q Water was added to the mixture with stirring to make up the volumes to the total amount. These gels were kept at room temperature for 24h.

Formulation of nanoparticles / gels transdermal delivery Systems:

The prepared Ramipil loaded chitosan naoparticles dispersed in carbopol gels incorporated in transdermal molds and the characteristics of resultant transdermal delivery systems was evaluated [7].

Table 1: Formulation design of Transdermal Patches of Ramipril Loaded chitosan nanoparticles dispersed in carbopol gels TNPGF1 to TNPGF5

Ingredients	TNPGF1	TNPGF2	TNPGF3	TNPGF4	TNPGF5
Ramipril (gms)	1	1	1	1	1
Chitosan (gms)	2	2	2	2.5	2
Polaxamer (gms)	5	5	5	4	4
HPMC (gms)	2	1	0.5	1	1
Pentasodium tripolyphosphate (gms)	0.5	0.5	0.5	0.5	0.5
Dimethyl sulfoxide (ml)	1	1	1	1	1
Carbopol (gms)	2	2	2	2	2
Acetic acid (ml)	15	15	15	15	15

Table 2: Formulation design of Transdermal Patches of Ramipril loaded chitosan nanoparticles dispersed in carbopol gels TNPGF6 to TNPGF9

Chemical name	TNPGF6	TNPGF7	TNPGF8	TNPGF9
Ramipril (gms)	1	1	1	1
Chitosan (gms)	3	1	1	1
Polaxamer (gms)	4	3	3	3
HPMC (gms)	1	1.5	1.5	1.5
Pentasodium tripolyphosphate (gms)	0.5	0.5	0.5	0.5
Dimethyl sulfoxide (ml)	1	1	1	1
Carbopol (gms)	2	2	2	2
Acetic acid (ml)	15	15	15	15

Evaluation studies:

Drug-Polymer Compatibility studies

FT-IR Spectra: Prior to the development of the dosage forms, infrared spectra of the physical mixture of the Ramipril, polymers individually and the mixture of drug and polymer were taken. The drug-Polymer Interaction were studied by FTIR spectrometer, shimadzu 8400S 2% w/w of the sample with respect to a potassium Bromide mixed with drug KBr [8].

Differential scanning calorimetry: The output of a DSC is a plot of heat flux (rate) versus temperature at a specified temperature rate [9]. DSC provides information about the physical properties of the sample as crystalline or amorphous nature and demonstrates a possible interaction between drug and polymers in formulations.

Physicochemical evaluation of films:

Thickness of the Patch: The thickness of patches was measured at three different places using a micrometer (Mitutoyo Co., Japan) and mean values were calculated [10].

Weight Variation: The patches were subjected to mass variation by individually weighing randomly selected patches [11]. Such determination was carried out for each formulation.

Moisture Content: The patches (n =3) were weighed individually and kept in a desiccator containing calcium chloride at 37 °C for 24 hrs. The final weight was noted when there was no change in the weight of individual patch [12]. The percentage of moisture content was calculated as a difference between initial and final weight with respect to final weight.

Moisture Uptake: A weighed film kept in desiccators at 40 °C for 24h was taken out and exposed to two different relative humidity of 75% RH (saturated solution of sodium chloride) and 93% RH (saturated solution of ammonium hydrogen phosphate) in two different desiccators respectively at room temperature then the weights were measured periodically to constant weights [13].

Flatness: Longitudinal strips were cut out from the prepared medicated film the lengths of each strip were measured. Then variation in the length due to the non-uniformity in flatness was measured [14]. Flatness was calculated by measuring constriction of strips and a zero percent constriction was considered to be equal to a hundred percent flatness.

$$\text{Constriction (\%)} = \frac{L1-L2}{L2} \times 100$$

Where,

L1- initial length of strip

L2 - final length of strip.

Determination of 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 [15]. The elongation i.e. the distance traveled 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.

Folding Endurance: This was determined by repeatedly folding one film at the same place till it broke. The Timber of times the film could be folded at the same place without breaking gave the value of folding endurance [16].

Water Vapour Transmission (WVT) Rate: WVTR is defined as the quantity of moisture transmitted through unit area of film in unit time. The film was fixed over the brim of a glass vial, containing 3 g of fused calcium chloride as desiccant, with an adhesive tape [76]. The vial was weighed and kept in desiccators containing saturated solution of potassium chloride to provide relative humidity of 84%. The vial was taken out and weighed at every 24 hrs interval for a period of 72 hrs [17]. The water vapour transmission rate was calculated from the plots of amount of water vapour transmitted versus time.

Drug Content Determination: The patches at 1cm2 were cut and added to a beaker containing 100ml of Phosphate buffered solution of pH 7.4. The medium was stirred with a Teflon coated magnetic bead for 5hrs [18]. The solution was later filtered and analyzed for drug content with proper dilution at 219 nm spectrophotometrically.

***In vitro* Franz's diffusion studies of Transdermal patches of Ramipril though chitosan nanoparticles dispersed in carbopol gels:** *In vitro* release studies can be performed in a modified Franz diffusion cell over a period of time 12 hours. At specific time intervals, aliquots of samples containing the released drug are taken from the acceptor compartment and are quantified using a suitable method [19]. The fabricated film was placed on the rat skin and attached to the diffusion cell such that the cell's drug releasing surface towards the receptor compartment which was filled with phosphate buffer solution of pH 7.4 at 37±1 °C. The elution medium was stirred magnetically. The aliquots (5ml) were withdrawn at predetermined time intervals and replaced with same volume of phosphate buffer of pH 7.4. The samples were analyzed for drug content using UV spectrophotometer at 219 nm.

Mathematical modeling of release kinetics [20]: The in vitro drug release data were fitted to various release kinetic models namely first order (Ln Qo- k1 t), zeroorder Q= (Qo_ko t), Higuchi equations (Q=kh 2)1/2, Korsemeyer-Peppas (logQtvs log t),

Where

Qt, is the cumulative amount of drug released at time t and

Q_0 is the initial amount of drug present in Microspheres.

Ko is the zero order release rate constant, k1 is the first order release rate constant, and kh is the diffusion rate constant.

RESULTS AND DISCUSSION

Compatability Studies:

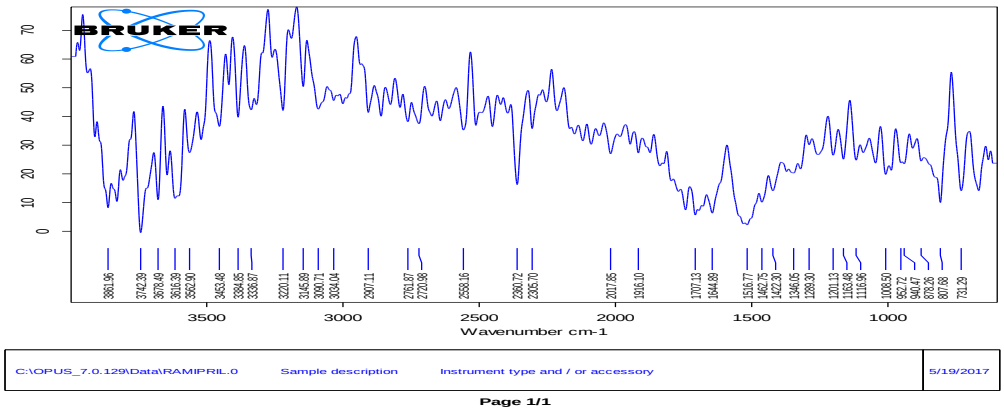

Figure 1: FTIR Spectra of Ramipril (pure drug)

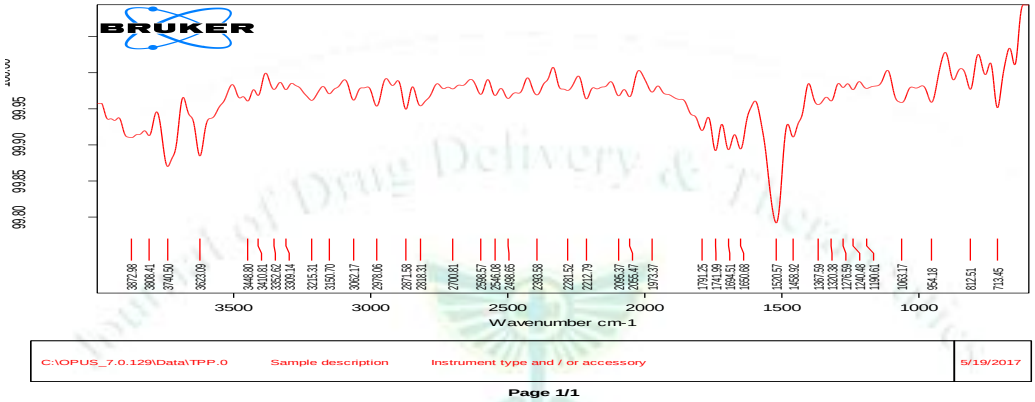

Figure 2: FTIR Spectra of TPP

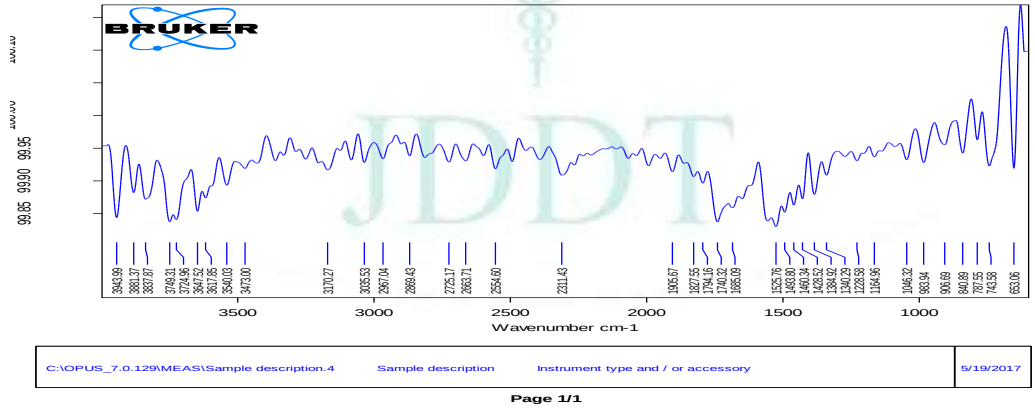

Figure 3: FTIR Spectra of Carbopol

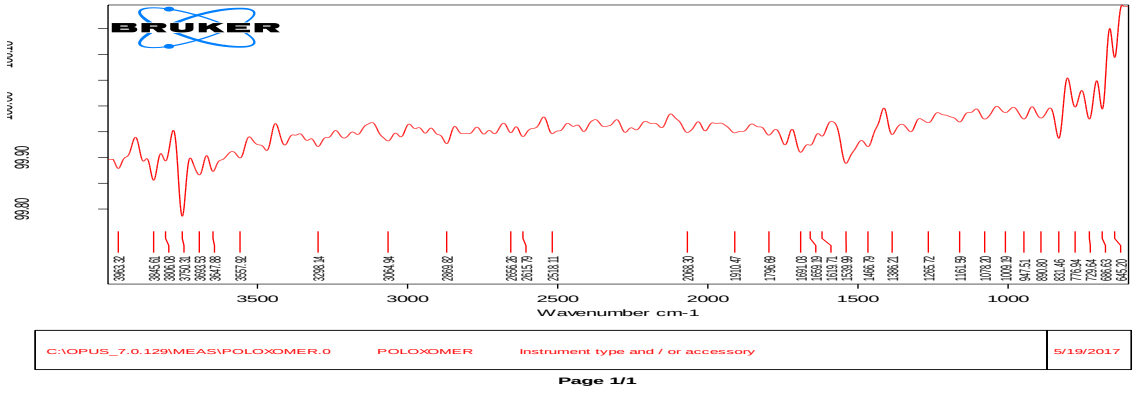

Figure 4: FTIR Spectra of Poloxamer

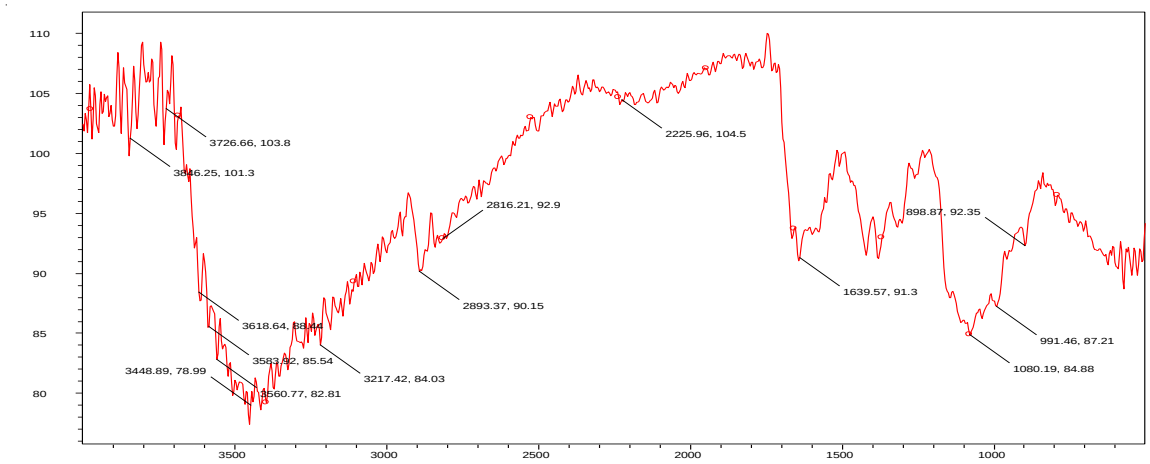

Figure 5: FTIR Spectra of chitosan

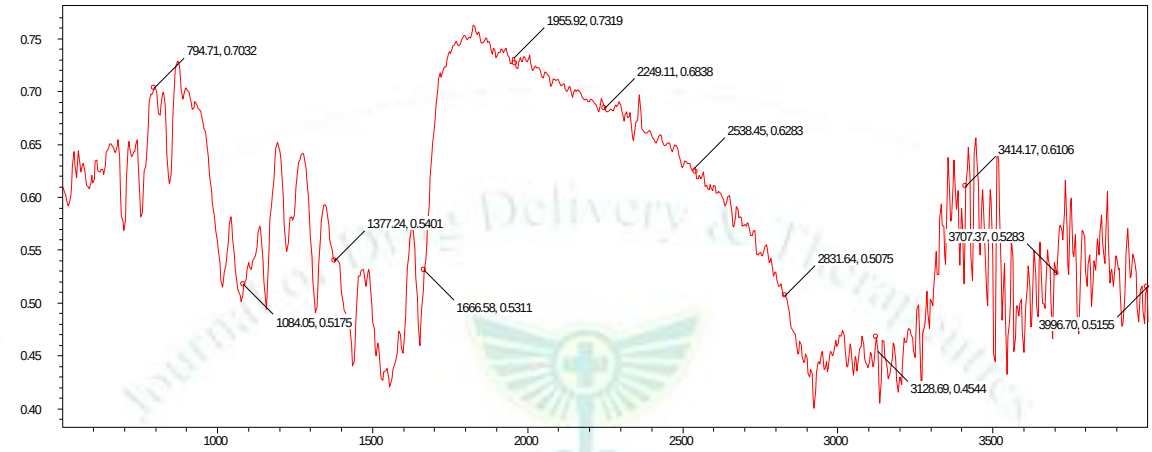

Figure 6: FTIR Spectra of HPMC

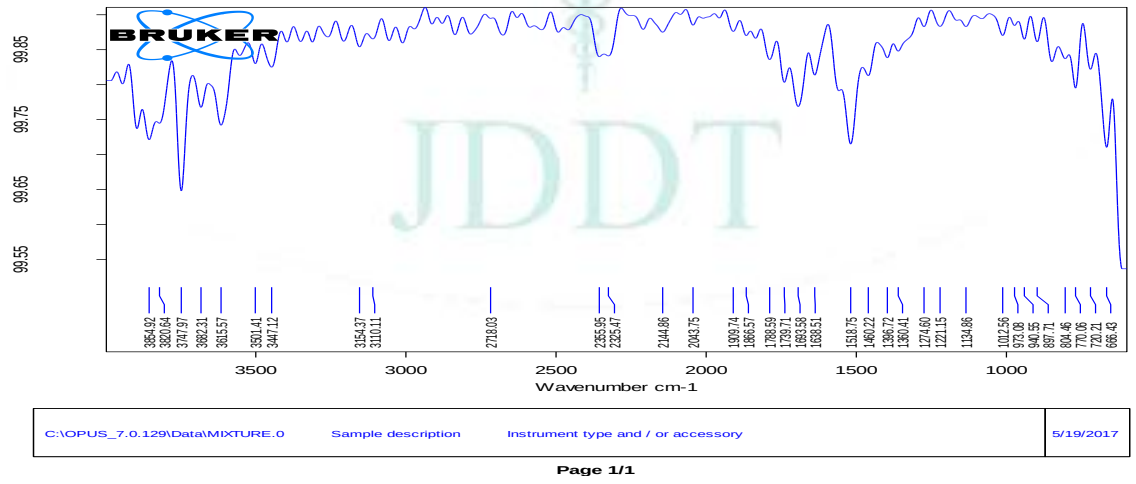

Figure 7: FTIR Spectra of Mixtures

Table 3: FTIR spectrum of observed and characteristic peak of Drug, Excipients & Mixture of compounds

FTIR Spectrum	IR absorption bands (cm-1)		Bond	Functional group
	Observed peak	Characteristic peak		
Ramipril	3678.49,3616.39,3562.90,3453.48,3384.85.	3000-3700	O-H stretch	Alkenes, aromatic
	2907.11,2761.87,2720.98.	2500-3000	C-H stretch	Alkenes, aromatic ring
	2558.16,2360.72,2303.70.	2100-2660	C=C stretch	Alkynes
	1707.13,1644.98,1462.75, 1422.30,1346.05.	600-1500	C-Cl stretch	Alkenes
TPP	3623.09,3448.80,3410.81,3352.62,3309.14,	3000-3700	O-H stretch	Alkenes, aromatic

	3215.31,3150.70	3100-3330	N-H strceh	Aromatic ring
	2978.58,2871.58,2818.31,2700.81,2598.57,2546.08	2500-3000	C-H stretch	Alkenes ,aromatic ring
	2498.65,2393.58,2281.52,2212.79	2100-2660	C=C stretch	alkynes
Carbopol	3647.52,3617.85,3540.03,3473.00,3170.27,3035.53	3000-3700	O-H strech	Alkenes,aromaric
	2967.04,2869.43,2725.17,2663.71,2554.60	2500-3000	C-H strech	Alkenes,aromaric ring
	1493.80,1046.32,983.94,906.69,840.89,789.55,743.58,653.06	600-1500	C-Cal strech	Alkanes
Poloxamer	3693.53,3647.88,3557.92,3298.14,3064.94	3000-3700	O-H stretch	Alkenes,aromaric
	2869.82,2656.26,2615.79,2518.11,	2500-3000	C-H stretch	Alkenes, aromaric ring
	1466.79,1386.21,1265.72,1161.59,1078.20,1009.19,947.51,890.80,831.46,776.94,729.64,686.63,645.20	600-1500	C-Cl stretch	Alkenes
Chitosan	3618.64,3583.92,3448.89,3560.77	3000-3700	O-H stretch	Alkenes, aromatic
	3217.42	3010-3300	N-H stretch	aromatic
	2893.37,2225.96,	2850-2960	C-H stretch	alkanes
	1639.57	1600-1900	C=O stretch	Aldehydes, ketones,
HPMC	794.71	600-1500	C-Cl stretch	Alkenes
	1084.05	1000-1300	C-O stretch	Alcohols, ethers
	1666.58	1660-1580	C=O stretch	Alkenes
	2249.11,2538.45	2100-2660	C=C stretch	Alkynes
Mixture of compounds	3682.31,3615.57,3501.41, 3447.12,3154.37,3110.11	3000-3700	O-H stretch	Alkenes, aromatic.
	2718.03		C-H stretch	Alkenes, aromatic ring
	2355.95,2325.47,2144.86, 2043.75	2100-2660	C=C stretch	Alkynes
	1739.71,1693.58	1680-1760	>C=O	Aldehydes, ketones.

DSC spectra:

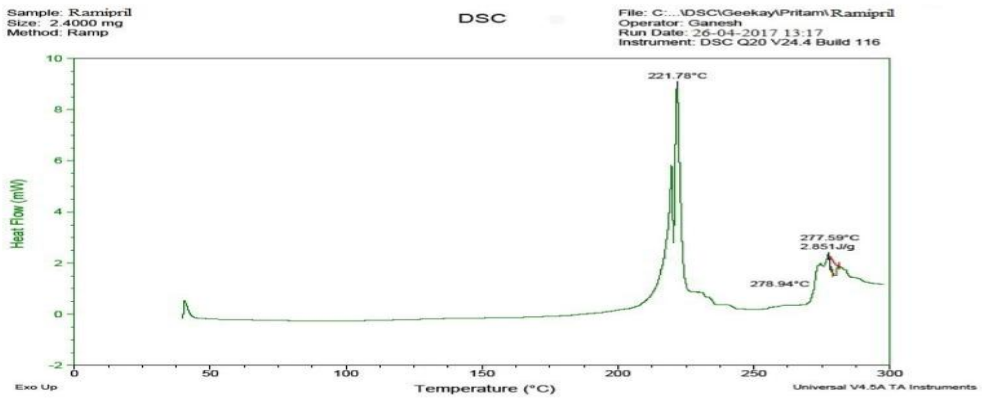

Figure 8: DSC Spectrum of Ramipril

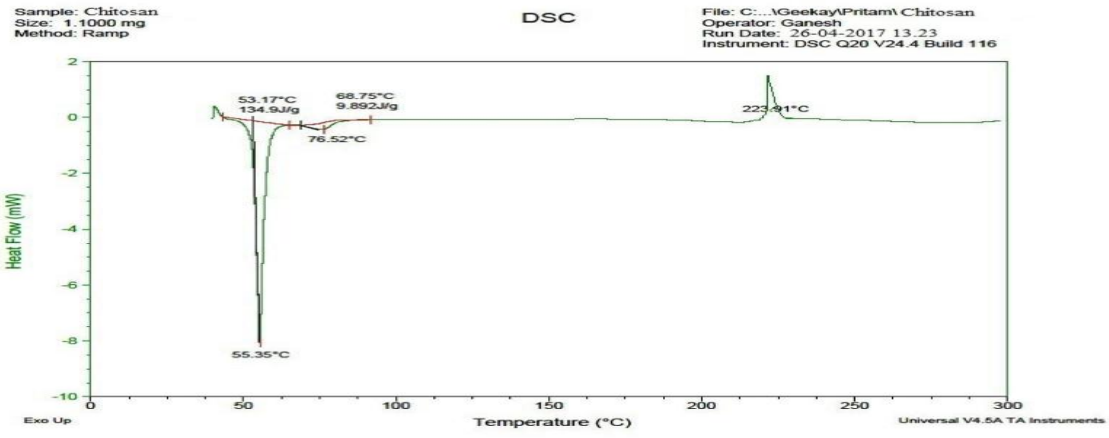

Figure 9: DSC Spectrum of Chitosan

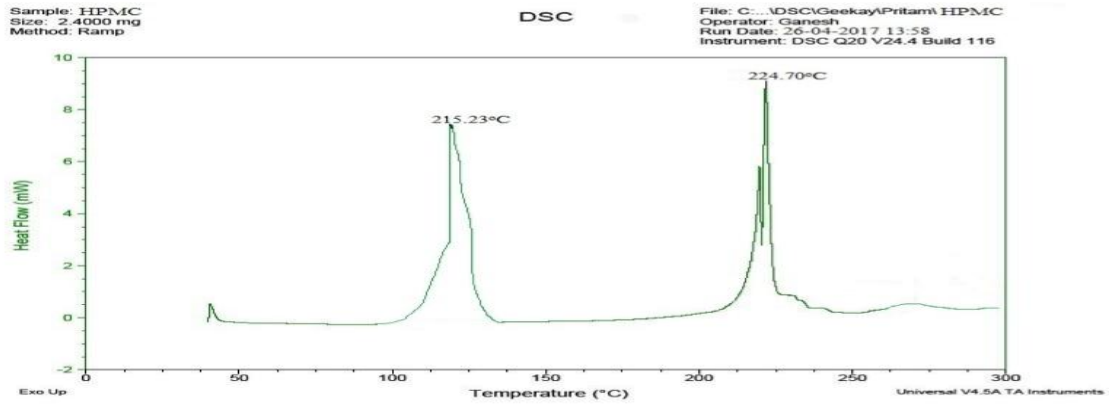

Figure 10: DSC Spectrum of HPMC

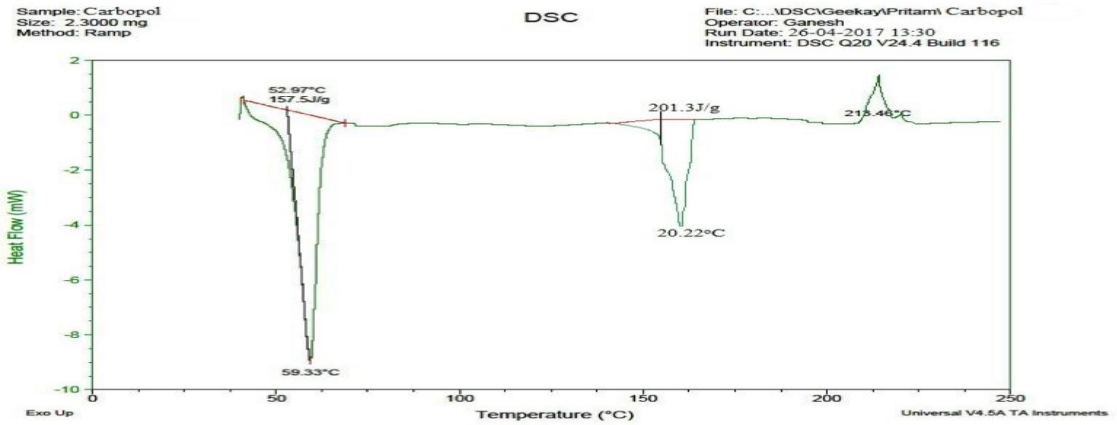

Figure 11: DSC Spectrum of Carbopol

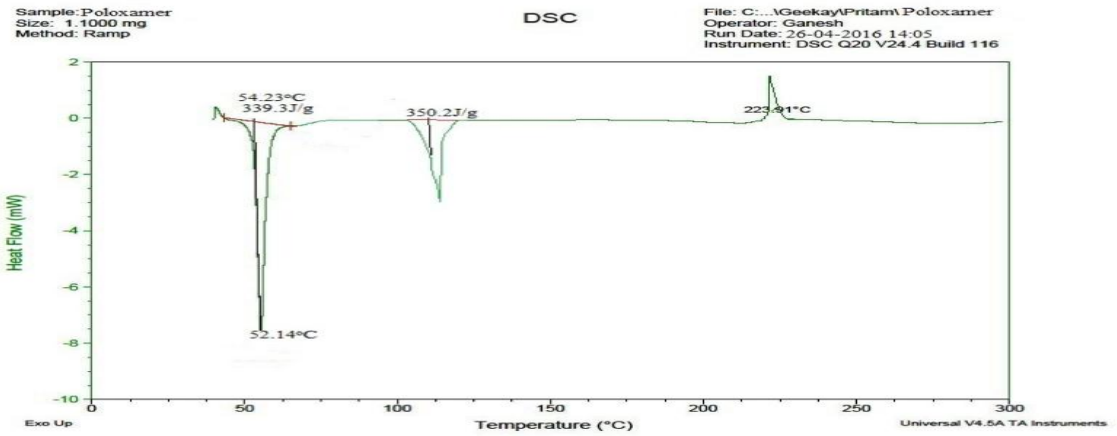

Figure 12: DSC Spectrum of Poloxamer

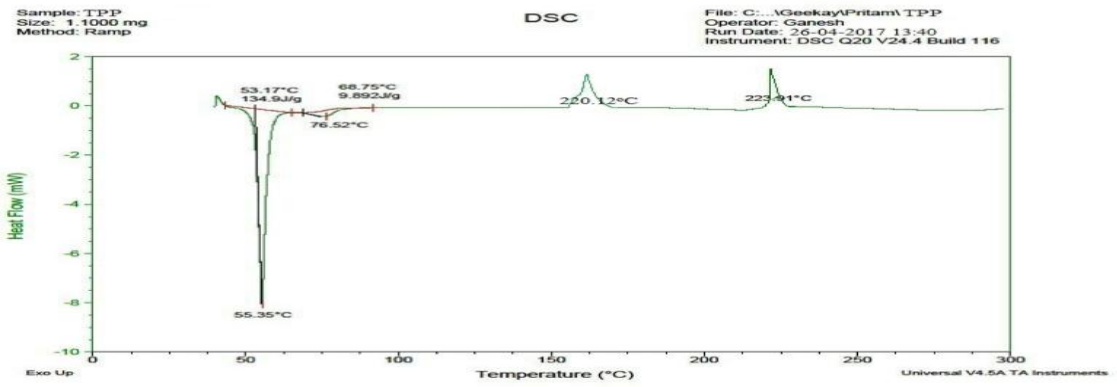

Figure 13: DSC Spectrum of TPP

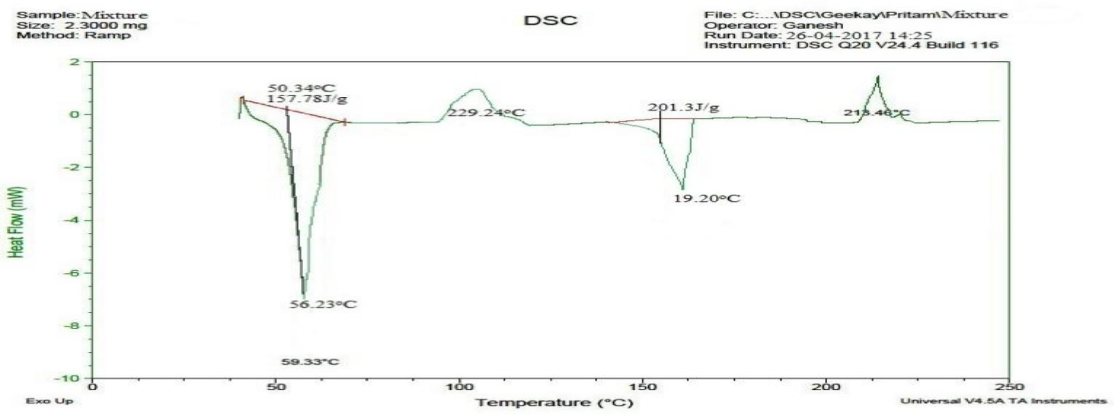

Figure 14: DSC Spectrum of Mixtures

Table 4: DSC Spectrum of ramipril, Excipients & Mixtures

SI.No	Ingredients	Endothermic peak	Exothermic peak
1	Ramipril	2.8515 J/g & 277.59°C	--
2	Chitosan	223.91 °C	55.35 °C
3	Hydroxyl propyl methyl cellulose	224.70 °C &215.23 °C	--
4	Carbopol	52.96 °C/157.5 J/g	20.22 °C/201.3 J/g
5	Poloxamer	54.23 °C/339.3 J/g	223.91 °C/350.2 J/g
6	TPP(Pentasodium tripolyphosphate)	53.17 °C/134.9 J/g	220.1 °C
7	Mixtures	229.24 °C/201.3 J/g	50.34 °C/157.78J/g

Evaluation of ramipril transdermal patchs

Physicochemical Evaluation of Films

Thickness of the Patch: The thickness ranged between 0.11 ± 0.05 mm to 0.19 ± 0.07 mm, which indicates that they are uniform in thickness as shown in the Table 5.

Weight Variation: The different batches of formulations weights variations were relatively good uniformity of weight variations among the various batches was observed, with all formulations and ranged from 1.40 ± 1.2% to 1.78 ± 2.0%. The results indicate that the process employed to prepare patches in this study was capable of producing patches with uniform drug content and minimal patch variability. As shown in the Table 5.

Moisture Uptake: Moisture content and moisture uptake studies indicated that the increase in the concentration of hydrophilic polymer was directly proportional to the increase in moisture content and moisture uptake of the patches. The moisture content of the prepared formulations was low, which could help the formulations remain stable and reduce brittleness during long term storage. The moisture uptake of the formulations was also low, which could protect the formulations from microbial contamination and reduces bulkiness. As shown in the Table 5.

Flatness: The flatness study showed that all the formulations had the same strip length before and after their cuts, indicating 99% flatness. Thus, no amount of constriction was observed; all patches had a smooth, flat surface; and that smooth surface could be maintained when the patch was applied to the skin. As shown in the Table 5.

Determination of Tensile Strength: The Tensile strength of the TNPGF1 to TNPGF9 shows the 10.14 ± 1.19 to 12.78 ± 2.45 shows the excellent viscosity. As shown in the Table 5.

Folding Endurance: Folding endurance test results indicated that the patches would not break and would maintain their integrity with general skin folding when applied. As shown in the Table 5.

Water Vapour Transmission (WVT) Rate: The WVTR was found to be TNPGF1 to TNPGF9 4.87 ± 0.45 to 1.23 ± 0.21. As shown in the table 5.

Drug Content Determination: The total amount of drug is present in the transdermal patches of TNPGF1 to TNPGF9 was found to be 90.5 ± 0.3 % to 98.5 ± 0.1 %. As shown in the table 5.

In vitro release drug diffusion studies were performed using modified Franz diffusion cell

In vitro release studies can be performed in a modified Franz diffusion cell over a period of time 5 hours. At specific time intervals, aliquots of samples containing the released drug are taken from the acceptor compartment and are quantified using a suitable method of determination Such as UV VISIB spectroscopy Ramipril = ג max 219. The sink condition is usually maintained by replacing the volume of aliquots taken by similar volumes of the buffer to resemble constant clearance of drugs from their physiological site of action. The drug release parameters as shown in table 6.

Table 5: Physicochemical Evaluations of Films

	TNPG1	TNPG2	TNPG3	TNPG4	TNPG5	TNPG6	TNPG7	TNPG8	TNPG9
thickness	0.11± 0.03	0.12± 0.05	0.13± 0.04	0.15± 0.06	0.14± 0.01	0.18± 0.01	0.11± 0.05	0.13± 0.02	0.19± 0.07
Weight variation	1.65± 1.5	1.78± 2.0	1.61± 1.0	1.65± 1.5	1.22± 2.5	1.40± 1.2	1.55± 0.5	1.65± 1.5	1.65± 1.5
Moisture uptake	3.105± 0.15	2.125± 0.25	3.135± 0.35	2.145± 0.25	3.155± 0.45	4.24± 0.23	2.135± 0.15	3.145± 0.35	1.123± 0.65
Flatness%	95%	94%	96%	95%	98%	99%	98%	96%	95%
Tensile strength(psi)	11.11± 1.11	10.14± 1.19	11.12± 2.12	11.11± 1.18	12.11± 2.01	11.12± 2.00	12.78± 2.45	2.56± 2.67	11.76± 2.12
Folding endurance	130.1±0.22	120.5±3.20	164.2±2.00	240.1±3.10	150.2±2.10	199± 1.00	210.2±2.10	310.2±3.20	206± 3.10
Water vapour transmission	3.67± 0.22	2.68± 0.12	4.67± 0.24	1.23± 0.21	2.12± 0.42	3.00± 0.22	2.12± 0.12	3.80± 0.23	4.87± 0.45
Drug content	95.1± 0.2	93.7± 0.4	90.5± 0.3	91.5± 0.2	92.2± 0.4	98.5± 0.1	93.1± 0.2	94.2± 0.3	88.2±0.2

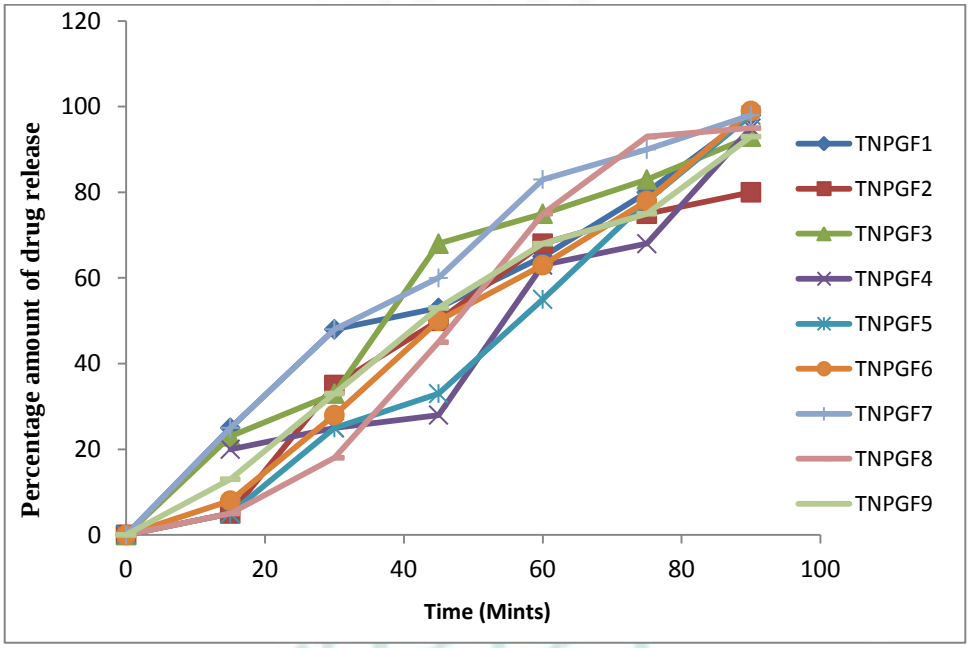

Figure 15: Cumulative % amount of drug release of Transdermal patch of Ramipril loaded chitosan nanoparticles dispersed in carobopol gels TNPGF1 to TNPGF9

Table 6: Release order kinetics of Transdermal patch of Ramipril loaded chitosan nanoparticles dispersed in carobopol gels TNPGF1 to TNPGF9

F. Code	Zero order		First order		Higuchi		Korse meyer pappas	
	R^2	M	R^2	M	R^2	M	R^2	M
TNPG1	0.973	10	0.596	0.024	0.958	98.73	0.951	1.526
TNPG2	0.952	9.821	0.692	0.026	0.902	95.12	0.983	1.558
TNPG3	0.949	10.47	0.643	0.025	0.935	103.6	0.964	1.539
TNPG4	0.939	9.940	0.706	0.025	0.814	92.11	0.963	1.490
TNPG5	0.973	11.13	0.771	0.027	0.812	101.1	0.12	0.005
TNPG6	0.986	11.66	0.785	0.029	0.858	108.3	0.995	1.56
TNPG7	0.951	29.10	0.699	0.032	0.920	284.9	0.979	1.789
TNPG8	0.955	12.32	0.790	0.029	0.820	113.6	0.993	1.584
TNPG9	0.988	10.41	0.749	0.028	0.919	99.97	0.985	1.538

CONCLUSION

The present work showed that transdermal delivery system for ramipril based on chitosan nanoparticles dispersed into gel was successfully prepared and characterized. There is no Incompatibility between drug and polymers by performing FTIR and DSC. To characterize the rate controlling membrane of transdermal patches. The thickness ranged between TNPGF1 to F9 0.11 ± 0.05 mm to 0.19 ± 0.07 mm, which indicates that they are uniform in thickness. The different batches of formulations weights variations were relatively good uniformity of weight variations among the various batches was observed, with all formulations and ranged from 1.40 ± 1.2% to 1.78 ± 2.0%. The flatness study showed that all the formulations had the same strip length before and after their cuts, indicating 99% flatness. The Tensile strength of the TNPGF1 to TNPGF9 shows the 10.14 ± 1.19 to 12.78 ± 2.45 shows the excellent viscosity. The total amount of drug is present in the transdermal patches of TNPGF1 to TNPGF9 was found to be 90.5 ± 0.3 % to 98.5 ± 0.1 %. *In-vitro* Franz's diffusion drug Release Studies among all formulations the best formulation was TNPGF6. The drug release through the transdermal patches of Ramipril follows First order kinetics with diffusion controlled mechanism. Effect of penetration enhancer like dimethyl sulfoxide has been checked on *in-vitro* permeation of drug and was found to be effective. Gels may create a drug reservoir to provide the system with ramipril over long period of time to control the blood pressure.

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