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Formulation and Evaluation of Transdermal Patch and Gel of Nateglinide

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ABSTRACT

The objective of the present work was to formulate Transdermal Drug Delivery systems of Nateglinide, an antidiabetic drug belonging to meglitinide class with a half life of 1.5 hrs. Transdermal patches containing nateglinide were prepared by solvent casting method using the combinations of HPMC:EC, PVA:PVP, HPMC:Eudragit RS 100, Eudragit RL100:RS100 in different proportions and by incorporating different permeation enhancers (polyethylene glycol 400, DMSO). The transdermal patches were evaluated for their physicochemical properties like thickness, weight variation, folding endurance, percentage moisture absorption, percentage moisture loss, *in-vitro* diffusion studies & *ex-vivo* permeation studies. Transdermal Gel was formulated using HPMC, carbopol 934, carbopol 940 and methyl cellulose. Gels were evaluated for homogeneity, pH, viscosity, drug content, *in-vitro* diffusion studies & *ex-vivo* permeation studies. By comparing the drug release F5 (HPMC:EC) formulation was selected as optimized formulation as it could sustain the drug release for 12 hrs i.e. 99.2% when compared to gel. Stability studies were carried out according to ICH guidelines and the patches maintained integrity and good physicochemical properties during the study period.

INTRODUCTION

Transdermal drug delivery systems (TDDS) are defined as self-contained discrete dosage forms which when applied to the skin, deliver the drug through the skin at controlled rate to the systemic circulation[1]. A transdermal drug delivery is a formulation or device that maintains the blood concentration of the drug within the therapeutic system window ensuring that drug levels neither fall below the minimum effective concentration nor exceed the minimum toxic dose. Transdermal drug delivery promises many advantages over oral administration, such as decrease in dosing frequency, reduction in gastrointestinal side effects, reduced incidence of systemic toxicity, avoidance of hepatic first-pass metabolism and improved patient compliance[2]. Some of the characteristics features that a drug candidate should possess to be suitable for transdermal delivery include short half-life, small molecular size, low dose[3].

Transdermal gel formulations provide a suitable delivery system for drugs because they are thixotropic, greaseless, easily spreadable, easily removable, emollient, non-staining, compatible with several excipients and water-soluble or miscible. The release of drug from topical preparations depends on the physicochemical properties of the vehicle and the drug employed[4,5].

Nateglinide, 3-phenyl-2-[(4propan-2ylcyclohexane carbonyl) amino] propanoic acid, lowers blood glucose by stimulating the release of insulin from the pancreas by closing ATP-dependent potassium channels in the membrane of the β cells[6,7]. Nateglinide, an anti-diabetic drug belongs to the meglitinide category. It has short half life of 1.5 hr. Nateglinide has rapid onset and short duration of action. It has been used alone or in combination with other medications to treat patients with type 2 diabetes. Nateglinide is available in 60 and 120 mg immediate release tablets which is required to be administered twice or thrice a day[8].

The purpose of the present work was to develop transdermal drug delivery of Nateglinide in order to decrease dosing frequency, minimize side effects, and increase bioavailability by using different grades of polymers.

MATERIALS AND METHODS

Materials

Nateglinide was a kind gift sample from Dr Reddy's laboratories, Hyderabad India; HPMC K100 by Colorcon Asia pvt ltd; dibutylpthalate, dimethylsulfoxide, were procured from S D Fine-Chem Limited, Carbopol 934, 940 by Noveon, propyleneglycol(400) by Nice chemicals Pvt.ltd.

Methods

Preparation of transdermal patch

Drug-loaded matrix-type transdermal patches of nateglinide were prepared by using solvent casting method. Polymers were accurately weighed and dissolved in chloroform: methanol (1:1) solution and kept aside to form clear solution. Drug was dissolved in the above solution. Dibutyl phthalate was added as plasticizer and polyethylene glycol 400 and DMSO were added as permeation enhancers. The resultant mixture was cast on the petridish and dried at room temperature for 24h. After 24h, the dried patches were taken out and stored in a desiccator for further studies.

Formulations of Transdermal Patch

The composition of the formulae used for preparation of the transdermal delivery system are revealed in Tables 1-4.

Table 1: Formulation of Transdermal Patch Containing HPMC & EC

Ingredients	F1	F2	F3	F4	**F5**	F6
Drug (mg)	50	50	50	50	**50**	50
HPMC (mg)	100	150	175	100	**150**	175
EC (mg)	100	50	25	100	**50**	25
PEG (%w/v)	30%	30%	30%	-	**-**	-
DMSO (%w/v)	-	-	-	30%	**30%**	30%
DBP (%w/v)	30%	30%	30%	30%	**30%**	30%
Methanol:chloroform	1:1	1:1	1:1	1:1	**1:1**	1:1

Table 2: Formulation of Transdermal Patch Containing PVA & PVP

Ingredients	F7	F8	F9	F10	F11	F12
Drug (mg)	50	50	50	50	50	50
PVA (mg)	100	150	175	100	150	175
PVP (mg)	100	50	25	100	50	25
PEG (%w/v)	30%	30%	30%	-	-	-
DMSO (%w/v)	-	-	-	30%	30%	30%
DBP (%w/v)	30%	30%	30%	30%	30%	30%
Methanol:chloroform	1:1	1:1	1:1	1:1	1:1	1:1

Table 3: Formulation of Transdermal Patch Containing EUDRAGIT RL & RS 100

Ingredients	F13	F14	F15	F16	F17	F18
Drug (mg)	50	50	50	50	50	50
Eudragit RL (mg)	100	150	175	100	150	175
Eudragit RS (mg)	100	50	25	100	50	25
PEG (%w/v)	30%	30%	30%	-	-	-
DMSO (%w/v)	-	-	-	30%	30%	30%
DBP (%w/v)	30%	30%	30%	30%	30%	30%
Methanol:chloroform	1:1	1:1	1:1	1:1	1:1	1:1

Table 4: Formulation of Transdermal Patch Containing EUDRAGIT RS & HPMC

Ingredients	F19	F20	F21	F22	F23	F24
Drug (mg)	50	50	50	50	50	50
Eudragit RS (mg)	100	150	175	100	150	175
HPMC (mg)	100	50	25	100	50	25
PEG (%w/v)	30%	30%	30%	-	-	-
DMSO (%w/v)	-	-	-	30%	30%	30%
DBP (%w/v)	30%	30%	30%	30%	30%	30%
Methanol:chloroform	1:1	1:1	1:1	1:1	1:1	1:1

Evaluation of patches [9,10]

The patches were evaluated for the following physicochemical properties:

Patches were evaluated for thickness, weight variation.

Folding Endurance

A film was taken and folded at the same place till it breaks. The number of times the film could be folded at the same place without breaking gives the exact value of folding endurance.

Percentage Moisture Absorption

To check the physical stability of the film in high humidity conditions, accurately weighed films were placed in a desiccators containing saturated solution of aluminium chloride (79.5% RH) for three days. The films were re-weighed and the percentage moisture absorption was calculated using the formula.

$$\text{Percentage moisture absorption} = \frac{\text{Final weight} - \text{initial weight} \times 100}{\text{Initial weight}}$$

Percentage Moisture Loss

To check the extent of moisture loss from freshly prepared film, accurately weighed films were placed in a desiccator containing fused anhydrous calcium chloride for 72 hrs. After 72 hrs, the films were reweighed and percentage moisture loss was calculated using the formula:

$$\text{Percentage moisture loss} = \frac{\text{Initial weight} - \text{Final weight} \times 100}{\text{Initial weight}}$$

Drug content

A specified area of patch was dissolved in 100 ml of phosphate buffer pH 6.8. Then the solution is to be filtered through a filter medium and appropriate dilutions were made with same buffer solution. The absorbance was measured UV Spectrophotometrically at 220 nm

***In-vitro* Drug Release Studies**

In-vitro drug release from both patch and gel was studied using Franz diffusion cell with a receptor compartment capacity of 25 ml. The dialysis membrane having a pore size 0.45 µ was mounted between the donor and receptor compartment of the diffusion cell. The prepared transdermal formulation was placed on the dialysis membrane. The receptor compartment of the diffusion cell was filled with phosphate buffer pH 6.8. The whole assembly was fixed on a magnetic stirrer, and the solution in the receptor compartment was continuously stirred magnetically and the temperature was maintained at 32±0.5°C. The samples were withdrawn periodically, and replaced with fresh phosphate buffer solution. The concentration of the drug was determined by UV Spectrophotometry (Lab India) at 220 nm.

***Ex-vivo* studies**

A protocol (IAEC/SVCP/2015/001) for the study was prepared. After approval from Institutional Ethics Committee permission as per ICMR the study was conducted as per the protocol.

Male albino rats (200-250 g) were sacrificed by aspiration of ethyl ether and the abdominal skin was carefully excised from the underlying connecting tissue using scalpel. The skin was carefully removed and washed after removing subcutaneous fat and other visceral tissue. Freshly excised skin was mounted on Franz diffusion cell to assess *in-vitro* permeation of drug from patch and gel. Donor and receptor compartments were separated by freshly excised rat skin. The receptor compartment was filled with phosphate buffer (pH 6.8). The receptor fluid was stirred with a magnetic stirrer at a speed of 50 rpm and the temperature was maintained at 32±0.5°C. Formulation was placed in the donor compartment. Samples were withdrawn periodically. The receptor phase was immediately replaced with equal volume of fresh receptor fluid. The amount

of Nateglinide in the samples was determined by UV Spectrophotometry (Lab India) at 220 nm using freshly prepared pH 6.8 phosphate buffer as blank.

Kinetic Modeling of Drug Release

Data obtained from *in vitro* release study was fitted into various kinetic equations. The kinetic models used were zero order (cumulative percentage of drug release versus time), first order (log cumulative percentage of drug remaining versus time), the Higuchi model (cumulative percentage of drug release versus square root of time), and Korsmeyer-Peppas (log cumulative percent drug release versus log of time). Regression (R^2) values were calculated for the linear curves obtained by regression analysis.

Drug Excipients Compatibility Study

Fourier transform infrared (FTIR) technique was used to study the physical and chemical interaction between drug and excipients. FTIR spectra of nateglinide, and optimized formulation F5, GF5 were recorded using KBr pellet method on FTIR (FTIR-1700, Shimadzu, Kyoto, Japan).

Stability studies

The stability studies were carried out for optimized formulation of nateglinide transdermal patch (F5). The formulation was stored at 40º ± 2ºC/75% ± 5% RH for 3 months (Climatic zone IV condition for accelerated testing) to assess their stability. The protocol of stability studies was in compliance with the ICH guidelines. After intervals of 30, 60, and 90 days, samples were withdrawn and tested for drug content, thickness, weight variation.

Preparation of Transdermal Gel

Transdermal gels were prepared by weighing required quantities of either hydroxyl propyl methyl celluloseK100 or carbopol 934, 940 or methyl cellulose. Gel base was prepared by hydration of gelling agent. Accurately weighed nateglinide was dissolved in methanol and the methanolic solution of drug was added slowly with stirring (400-600 rpm) in the previously prepared gel base. Triethanolamine was added to adjust the pH. Propylene glycol was added with stirring. The final quantity was made up to 20gm with distilled water. The prepared gel was kept for 24h for complete polymer desolvation.

Table: 5 Formulation of transdermal gel containing Carbopol 934 and HPMCK100

S.NO	Ingredients	F1	F2	F3	F4	F5	F6
1	Drug (gms)	0.05	0.05	0.05	0.05	0.05	0.05
2	Carbopol 934(gms)	0.1	0.15	0.2	-	-	-
3	HPMC K100(gms)	-	-	-	0.1	0.15	0.2
4	Triethanolamine (ml)	0.4	0.4	0.4	0.4	0.4	0.4
5	Methanol	q.s	q.s	q.s	q.s	q.s	q.s
6	Methyl paraben (gms)	0.75	0.75	0.75	0.75	0.75	0.75
7	Propylene glycol (%v/w)	30%	30%	30%	30%	30%	30%
8	Distilled water up to	20	20	20	20	20	20

Table: 6 Formulation of transdermal gel containing Carbopol 940 and Methyl Cellulose

S.NO	Ingredients	F7	F8	F9	F10	F11	F12
1	Drug (gms)	0.05	0.05	0.05	0.05	0.05	0.05
2	Carbopol 940 (gms)	0.1	0.15	0.2	-	-	-
3	Methyl cellulose (gms)	-	-	-	0.1	0.15	0.2
4	Triethanolamine (ml)	0.4	0.4	0.4	0.4	0.4	0.4
5	Methanol	q.s	q.s	q.s	q.s	q.s	q.s
6	Methyl paraben (gms)	0.75	0.75	0.75	0.75	0.75	0.75
7	Propylene glycol (%v/w)	30%	30%	30%	30%	30%	30%
8	Distilled water up to	20	20	20	20	20	20

Evaluation of Gel [11,12]

Measurement of pH

The pH of various gel formulations was determined by using digital pH meter (Systronics India).

Homogeneity

It was determined by visual inspection for the appearance of gel and presence of any aggregates/lumps.

Viscosity

The viscosity of the formulations was determined using a Brookfield digital viscometer equipped with spindle S64. The gel formulations were placed in the sample holder of the viscometer and allowed to settle for 5 min and the viscosity measured at a rotating speed of 50 rpm at room temperature (25 - 27^{o}C).

Drug content

An accurately weighed quantity of the gel was dissolved in 100 ml of phosphate buffer of pH 6.8. Then the solution was filtered through a filter medium and appropriate dilutions were made with same buffer solution. The absorbance was measured UV spectrophotometrically at 220 nm using phosphate buffer (pH 6.8) as blank.

RESULTS AND DISCUSSION

Transdermal patch was evaluated for weight variation, folding endurance, thickness, drug content, percentage moisture loss, percentage moisture absorption. The results are summarized in Table 6.

Table 7: Physical characteristics of Nateglinide transdermal patches from F1-F12

Formulation Code	Weight Variation (Mg) ±SD(N=3)	Folding Endurance	Thickness (Mm) ±SD(N=3)	Drug Content (%) ±SD(N=3)	%Moisture Loss ±SD(N=3)	%Moisture Absorption ±SD(N=3)
F1	292±2.01	263	0.15±0.034	94.8±0.81	7.32±0.12	9.31±0.27
F2	330±2.12	291	0.17±0.027	97.8±0.89	8.69±0.54	6.54±0.79
F3	362±2.51	300	0.18±0.025	96.5±0.72	10.36±0.32	6.59±0.58
F4	409±2.19	220	0.15±0.015	93.1±0.31	8.52±0.21	10.1±0.79
F5	420±1.87	209	0.16±0.032	93.8±0.43	7.25±0.72	8.52±0.81
F6	396±2.41	221	0.18±0.012	94.2±0.57	6.48±0.63	7.65±0.22
F7	280±2.01	303	0.19±0.022	90.9±0.23	8.57±0.65	5.26±0.37
F8	313±1.57	310	0.16±0,028	91.2±0.12	8.40±0.97	5.17±0.12
F9	390±2.83	330	0.14±0.022	91.8±0.38	7.90±0.54	6.23±0.42
F10	254±2.56	284	0.15±0.010	90.9±0.23	7.21±0.45	4.21±0.15
F11	270±2.61	299	0.17±0.019	91.0±0.12	6.58±0.82	4.97±0.27
F12	301±2.32	301	0.11±0.029	91.8±0.38	7.92±0.63	5.02±0.38

Table 8: Physical characteristics of Nateglinide transdermal patches from F13-F24

Formulation Code	Weight Variation (Mg) ±SD(N=3)	Folding Endurance	Thickness (Mm) ±SD(N=3)	Drug Content (%) ±SD(N=3)	%Moisture Loss ±SD(N=3)	%Moisture Absorption ±SD(N=3)
F13	243±1.02	265	0.22±0.011	84.5±0.32	6.21±0.91	5.35±0.32
F14	272±1.51	278	0.25±0.03	84.7±0.44	6.28±0.88	5.38±0.21
F15	297±2.43	290	0.27±0.032	83.1±0.52	6.34±0.06	5.41±0.33
F16	221±1.89	254	0.28±0.021	85.1±0.43	5.52±0.201	4.86±0.06
F17	293±2.26	265	0.29±0.024	85.7±0.32	5.74±0.142	4.92±0.92
F18	302±2.56	278	0.16±0.011	86.1±0.68	5.87±0.98	5.01±0.42

F19	382±2.19	203	0.14±0.036	92.4±0.28	4.78±0.24	8.17±1.31
F20	391±2.63	210	0.18±0.029	93.1±0.13	4.23±0.52	9.11±1.37
F21	398±3.02	236	0.19±0.089	94.4±0.19	6.10±0.63	11.12±1.4
F22	272±2.05	272	0.15±0.047	96.2±0.48	4.77±0.05	5.72±0.13
F23	296±1.57	294	0.21±0.032	95.2±0.11	5.68±0.17	4.19±0.13
F24	313±2.37	298	0.22±0.025	94.5±0.28	6.68±0.06	3.93±0.04

From the results obtained, it is clear that the physical parameters evaluated for different formulations were within the limits.

***In-vitro* drug release studies**

The release characteristics of the formulation were studied through dialysis membrane. *In-vitro* diffusion studies were carried out in phosphate buffer (pH 6.8) for 12 hours.

Table 9: Cumulative percentage drug release of Nateglinide patch F1-F24

Formulation Code	%Cumulative Release	Formulation Code	%Cumulative Release
F1	92.1±0.12	F13	94.3±0.32
F2	94.9±0.09	F14	95.6±0.05
F3	90.6±0.07	F15	92.5±0.29
F4	96.8±0.52	F16	94.2±0.19
F5	**99.2±0.05**	F17	96±0.63
F6	96.1±0.36	F18	95.2±0.12
F7	97.1±0.55	F19	92.2±0.27
F8	86±0.59	F20	96.1±0.64
F9	85±0.29	F21	91±0.38
F10	88.5±0.43	F22	96.8±0.12
F11	88.01±0.42	F23	92.9±0.77
F12	88.9±0.18	F24	95.3±0.32

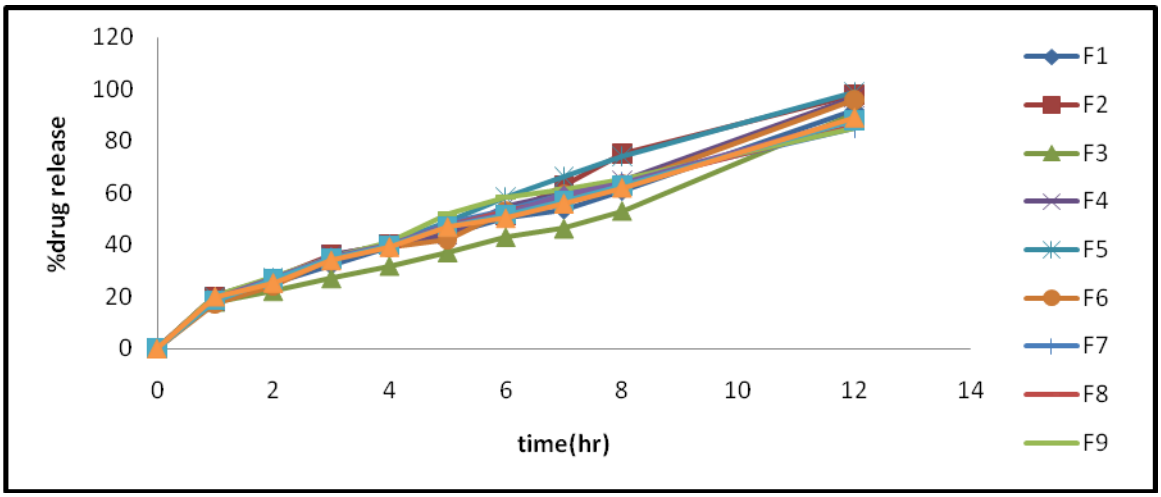

Figure 1: Drug release of F1 to F12

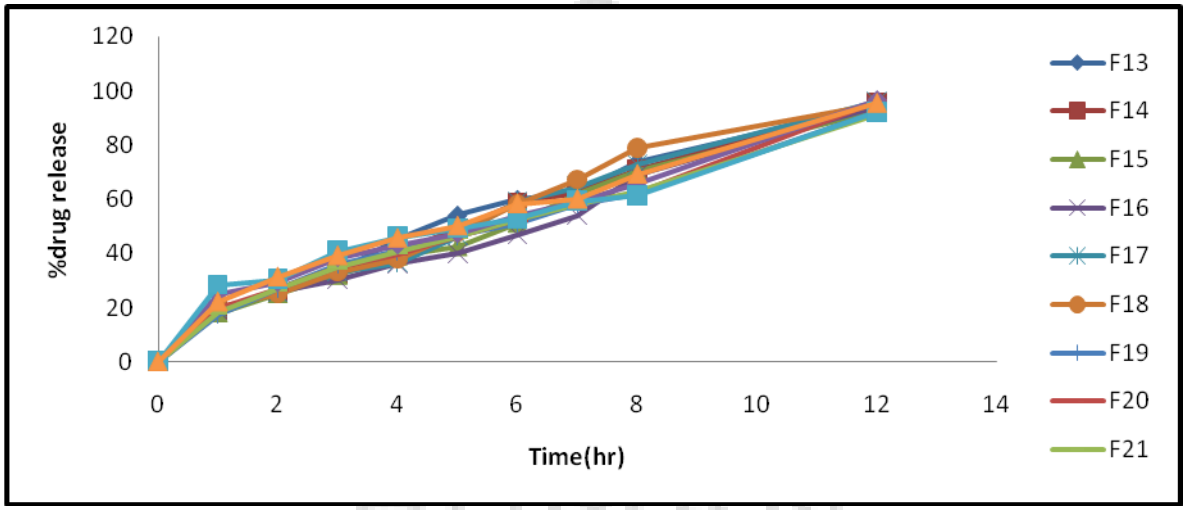

Figure 2: Drug release of F13 to F24

Based on the *in-vitro* drug release F5 formulation was selected as it could sustain the drug release (99.2%) for 12hrs when compared to the other formulations.

Evaluation of Transdermal Gel

Transdermal gel formulations were evaluated for homogeneity, pH, viscosity and drug content.

Table 10: Characterization of transdermal gel

Formulation code	Homogeneity ±SD(n=3)	pH ±SD(n=3)	Viscosity (cps) ±SD(n=3)	Drug content ±SD(n=3)
GF1	++	6.56±0.19	3245.3±1.11	95.32±0.15
GF2	+++	6.62±0.28	3897.1±1.01	97.63±0.13
GF3	+++	6.73±0.21	4280.5±1.3	98.75±0.14
GF4	+++	6.79±0.29	3221.3±1.39	96.24±0.17
GF5	**+++**	**7.05±0.17**	**4687.2±1.2**	**97.39±0.16**
GF6	+++	6.96±0.19	4167.2±1.21	93.54±0.14
GF7	++	6.11±0.06	2193.3±2.15	92.82±0.15
GF8	+++	6.82±0.24	3192.1±3.25	94.44±0.20
GF9	++	6.35±0.18	4388.1±3.08	92.36±0.35
GF10	++	6.81±0.35	2098.9±1.23	97.92±0.31
GF11	++	6.72±0.47	2291.9±1.58	96.98±0.48
GF12	++	6.59±0.91	3180.1±2.61	97.54±0.41

pH was adjusted between 6.11-7.05 & viscosity was found to be 2098-4687 cps, drug content was found to be 92.36-98.75%. It is clear from the above results that the evaluated parameters were within the limits.

***In-vitro* diffusion studies**

The release characteristics of the formulation were studied using Franz diffusion cell through dialysis membrane. *In-vitro* studies were carried out using phosphate buffer (pH 6.8) for 6 hours.

Table 11: Cumulative percentage drug release of Nateglinide gel GF1-GF12

Formulation Code	Cumulative % Drug Release	Formulation Code	Cumulative % Drug Release
GF1	81.2±1.12	GF7	82.1±1.16
GF2	78.1±0.89	GF8	80.5±0.19
GF3	72.3±0.68	GF9	81.1±0.28
GF4	85.1±0.83	GF10	75.1±0.17
GF5	**88.5±0.34**	GF11	73.2±0.15
GF6	80.1±0.11	GF12	74.2±0.18

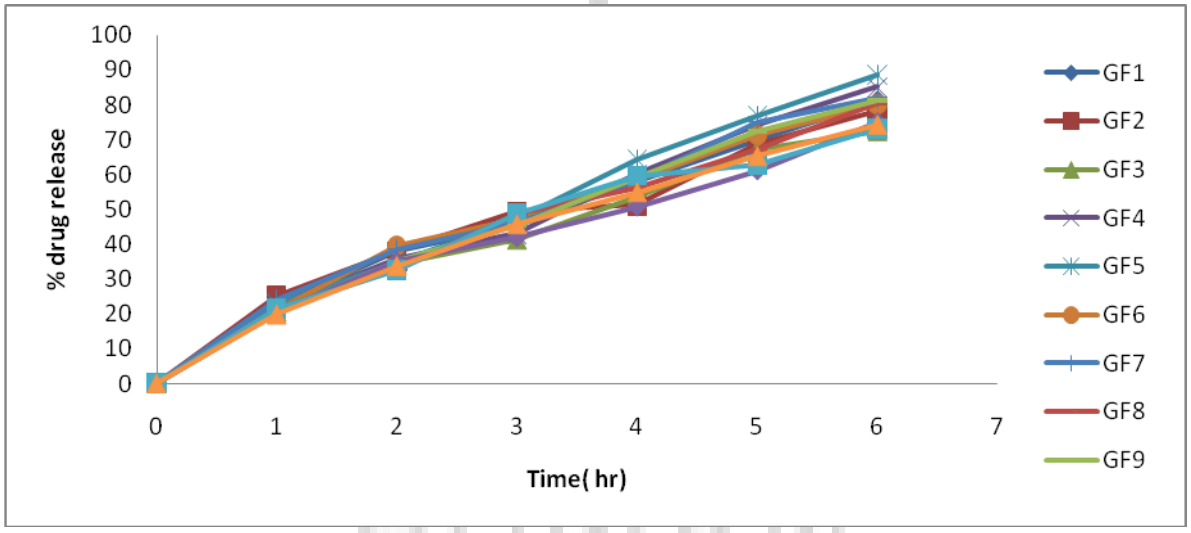

Figure 3: Percentage drug release of Nateglinide gel of F1 to F12

Based on the *in-vitro* drug release formulation F5 was selected and it was reported that 88.5% drug release in 6hrs compared to other formulations.

***Ex-vivo* permeation studies**

Ex-vivo studies were performed on selected formulations of transdermal patch (F5) and transdermal gel (GF5) using excised male albino rat skin.

Table 12: *Ex-vivo* permeation studies

Formulation	%Drug Release±SD (n=3)
Transdermal Patch (F5)	97.9±0.45 in 12hrs
Transdermal Gel (Gf5)	89±1.29 in 6hrs

From the *Ex-vivo* studies it is clear that transdermal patch (F5) could sustain the drug release (97.9%) for 12hrs when compared to the GF5.

Cumulative % Drug Release Vs Time Profile of Optimized Formulation (F5) and Marketed Formulation (Glinate®)

The cumulative percentage drug release of optimized formulation F5 was compared with marketed formulation Glinate® (60 mg).

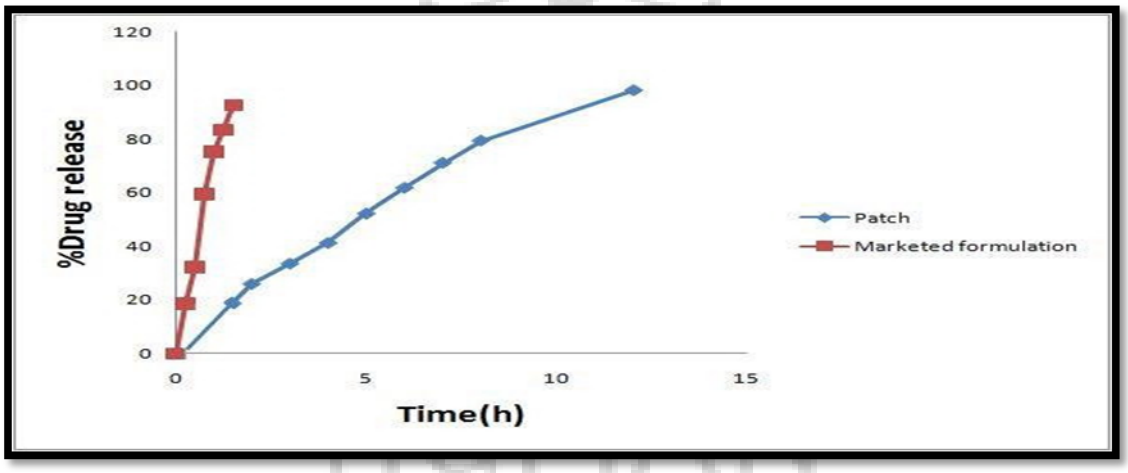

Figure 4: Cumulative % drug release of optimized formulation (F5) and marketed formulation

By comparison of selected formulation (F5) and marketed formulation (Glinate®), it was reported that the release of drug in transdermal patch (F5) reported sustain drug release compared to marketed formulation.

Drug Release Kinetics

In order to determine the release model, the *in-vitro* release data of optimized formulation (F5) were subjected to Zero order, First order, Higuchi, Kors-peppas, Hixson Crowell release models.

Table 13: Regression analysis of optimized formulation (F5)

Type of drug release kinetics	R^2 value
Zero order	0.960
First order	0.979
Higuchi	0.999
Kors-Peppas	0.888
Hixson Crowell equation	0.971

Among the models tested, the drug release profiles of F5 was found to be best fit with Higuchi release model based on the regression coefficient (R^2=0.999) indicated that the permeation of the drug from the patches was governed by a diffusion mechanism as the thickness of the drug depletion zone increases with time.

Drug-excipient compatibility studies

The IR spectrum of the formulation F5 recorded by FTIR spectrometer which are compared with standard functional group frequencies of nateglinide. The characteristic peaks of the optimized formulation followed the same as that of the drug alone with minor differences. Thus there may be no drug-excipient interactions.

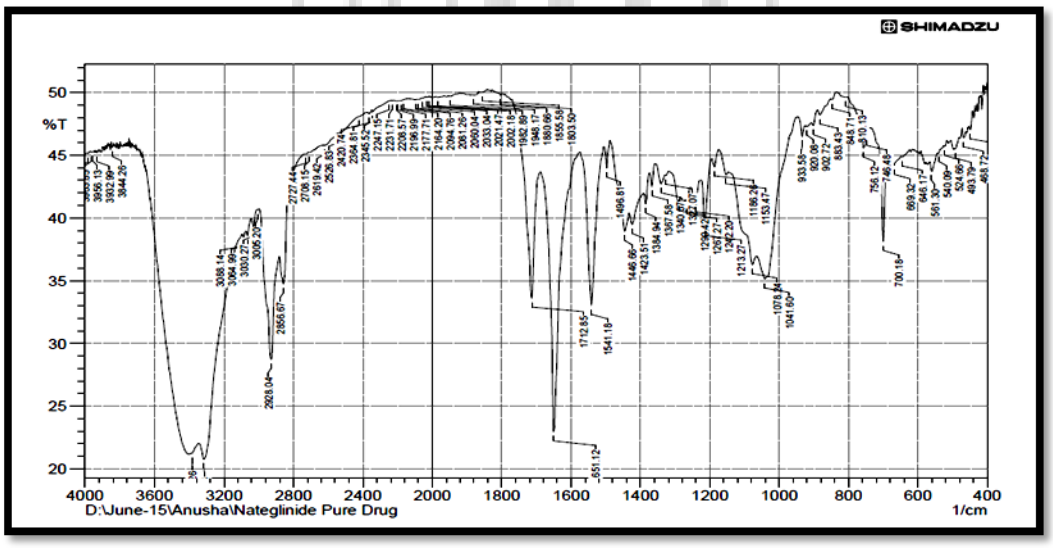

Figure 5: FTIR of Nateglinide pure drug

Table 14: Characteristics Peaks of Pure Drug

Functional Group	Reported Value (cm^{-1})	Observed value (cm^{-1})
CH	2850-2960	2856.67
NH	3300-3500	3383
C=O	1680-1760	1712

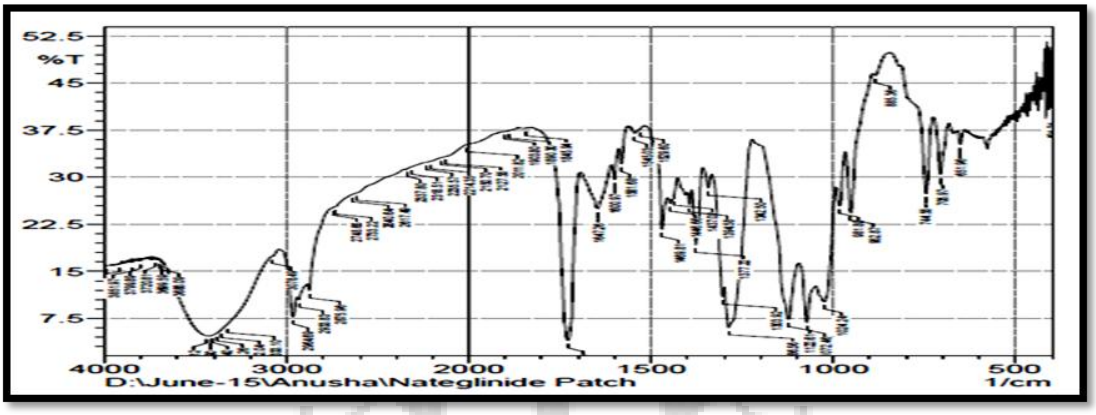

Figure 6: FTIR of Nateglinide transdermal patch

Table 15: Characteristics peaks of Nateglinide patch

Functional Group	Reported Value (cm^{-1})	Observed value (cm^{-1})
CH	2850-2960	2857.96
NH	3300-3500	3383.1
C=O	1680-1760	1728.28

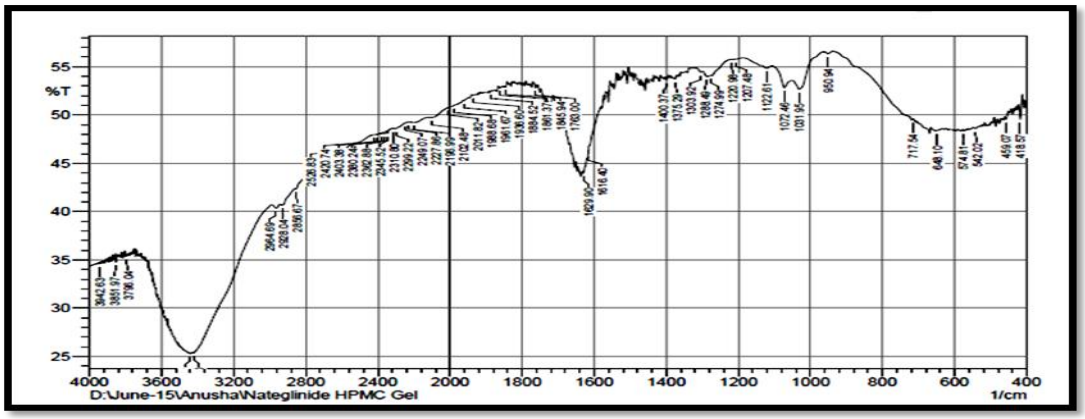

Figure 7: FTIR of Nateglinide transdermal gel

Table 16: Characteristics peaks of Nateglinide gel

Functional Group	Reported Value (cm^{-1})	Observed value (cm^{-1})
CH	2850-2960	2856.67
NH	3300-3500	3419.9
C=O	1680-1760	1763

Stability Studies

Stability studies were performed at 40º ± 2ºC/75% ± 5% RH for 3 months. The physical appearance, thickness, weight variation, drug content was monitored for the optimized formulation F5 for a period of 90 days.

Table 17: Stability data of optimized formulation (F5)

Time (months)	Thickness (mm) ±SD(n=3)	Weight Variation (mg) ±SD(n=3)	Drug Content (%) ±SD(n=3)
0	0.16±0.032	420±1.87	93.8±0.43
1	0.15±0.045	419±1.52	93.2±0.32
2	0.14±0.062	405±1.69	92.8±0.52
3	0.13±0.059	401±1.68	92.2±0.44

As per ICH guidelines stability studies were conducted for optimized formulation F5 and it was observed that there was no change in the physical appearance of the optimized formulation. And thickness, weight variation, drug content was reported within the limits.

CONCLUSION

Transdermal patch of Nateglinide was formulated using different film forming polymers and different permeation enhancers but film formulated using HPMC K100: EC and DMSO as permeation enhancer sustain the drug release (99.2%) for 12hrs when compared to other formulations. Transdermal gel formulated using HPMC K100 showed better drug release than

formulations prepared using Carbopol 934, Carbopol 940 and methyl cellulose. The optimized formulations were also subjected to drug-excipient interaction studies and stability studies. By comparison it was concluded that transdermal patch of Nateglinide showed better sustained release than transdermal gel. Transdermal patch of Nateglinide was also compared with marketed formulation (Glinate®) and the patch showed better sustained drug release than marketed formulation and thus it can be concluded that Transdermal Patch (F5) of Nateglinide has better drug release.

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