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DESIGN AND *IN VITRO* EVALUATION OF TRANSDERMAL PATCHES OF NATEGLINIDE

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ABSTRACT :

The present study was an attempt to develop transdermal patches of nateglinide for treating diabetes. The transdermal patches of nateglinide were prepared by the solvent evaporation method using polymers such as HPMC K15M, PVP K30 and ethyl cellulose (EC). The developed formulations were subjected to various physicochemical evaluations such as weight variation, thickness, folding endurance, drug content, flatness, release studies and kinetics. Based on the release aspects and physicochemical studies of the parameters, formulation NT7 is considered an optimised formulation, which shows a higher percentage of drug release, 98.29%, in 24 hours in a controlled manner with a diffusion-mediated mechanism.

Keywords: Transdermal patches, Nateglinide, Solvent evaporation and Diffusion studies.

1. Introduction

Transdermal drug delivery systems (TDDS) are dosage forms designed to deliver a therapeutically effective dose of drug across a patient's skin [(1)]. The transdermal product's goal of dosage design is to maximise the flux through the skin into the systemic circulation and simultaneously minimise the retention and metabolism of the drug in the skin [(2)].

Transdermal drug delivery offers potential and serves as a surrogate for the oral route of administration in improving the bioavailability of many drugs [(3)]. The main advantages of transdermal delivery include avoiding first-pass metabolism, utilising the skin's enormous surface area, facilitating easy administration and termination of action, and delivering the drug in a controlled manner, making this route more attractive for drug delivery [(4)].

Nateglinide is an anti-diabetic drug with a short half-life (1.4 hours) and low bioavailability (approximately 73%). It undergoes extensive first-pass metabolism, necessitating a transdermal drug delivery system to maintain therapeutic levels. The present study aimed to prepare and evaluate transdermal patches of nateglinide using the solvent evaporation technique with hydrophilic and hydrophobic polymers, such as HPMC K15 M, PVP K30, and ethyl cellulose, to achieve controlled drug release.

2. Materials and Methods

2.1. Materials

Nateglinide was obtained as a gift sample from Hetero Drugs (Hyderabad), HPMC K100M from Litmus Organics Pvt Ltd., Ethyl cellulose from Asha Cellulose India Pvt Ltd, Propylene glycol from Balaji Amines Ltd, and Dimethylsulfoxide from Maha Sai Laboratories. Dibutyl phthalate procured from R Chemine Products Pvt. Ltd. All other chemicals and solvents were analytical reagent grades.

2.2. Methods

2.2.1. Formulation of transdermal patches

Transdermal patches containing nateglinide were prepared by the "solvent evaporation technique". The drug reservoir was prepared by dissolving HPMC, PVP and EC in a solvent (1:1) mixture. Dibutyl phthalate was used as a plasticiser. The DMSO was used as a permeation enhancer. The drug was added to the homogeneous dispersion under slow stirring with a magnetic stirrer. The uniform dispersion was cast on pre-lubricated petri dishes with liquid paraffin and dried at room temperature. The films were stored between sheets of wax paper in desiccators [(6)]. The formulations are listed in Table 1.

Table 1: Formulations of nateglinide transdermal patches

Formulations	NT1	NT2	NT3	NT4	NT5	NT6	NT7	NT8	NT9
Nateglinide (mg)	120	120	120	120	120	120	120	120	120
HPMC K15M (mg)	300	200	100	300	200	100	300	200	100
PVP K30 (mg)	150	100	50	-	-	-	75	100	50
Ethyl cellulose (mg)	-	-	-	150	100	50	75	100	50
n-dibutyl phthalate (ml)	10	10	10	10	10	10	10	10	10
DMSO (ml)	5	5	5	5	5	5	5	5	5
Methanol:chloroform (1:1) ml	15	15	15	15	15	15	15	15	15

2.2.2. Evaluation of transdermal patches

i) Folding endurance:

The endurance power of the drug was determined by repeatedly folding a small strip of patches at the same place till it broke. The number of times the films could be folded at the same place without breaking gave the value of folding endurance [(7)].

ii) Weight variation:

For the weight variation test, each patch was weighed individually, and the average weight and standard deviation were calculated.

iii) Thickness:

The thickness of patches was measured at three different places using a micrometre, and mean values were calculated [(8)].

iv) Drug content:

The uniformity of drug content of the transdermal patch was determined, based on the dry weight of drug and polymer used, employing a UV/VIS spectrophotometer method. The Patches of specified area (1 cm^2) were dissolved in 10 ml of methanol and kept on a magnetic stirrer to provide continuous stirring. The resulting solution was transferred to a volumetric flask, appropriate dilutions were made with phosphate buffer pH 7.4, filtered through a 0.22 µm filter, and analysed for nateglinide content at 225 nm by a UV-visible spectrophotometer [(9)].

v) Flatness:

Three longitudinal strips were cut out from each patch: one from the centre, one from the left side, and one from the right side. The length of each strip was measured, and the variation in length because of non-uniformity in flatness was measured by determining per cent constriction, with 0% constriction equivalent to 100% flatness [(10)].

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

Where L1- initial length of strip, L2 - final length of strip.

vi) *In-vitro* drug release studies:

The fabricated patch was placed on the diffusion membrane and attached to the diffusion cell such that the cell's drug-releasing surface faced the receptor compartment, which was filled with phosphate buffer solution of pH 7.4 at 37±1ºC. The elution medium was stirred magnetically. The aliquots (5ml) were withdrawn at predetermined time intervals and replaced with the same volume of phosphate buffer of pH 7.4. The samples were analysed for drug content using a UV spectrophotometer at 225nm [(11)].

2.2.3. Release kinetics

The dissolution data were fitted to release models such as zero-order, first-order, diffusion and exponential equations, which have been described in the literature. The order of drug release from matrix systems was defined by using zero-order and first-order kinetics. The mechanism of drug release from matrix systems was studied by using the Higuchi equation, the erosion equation and the Peppas-Korsemeyer equation [(12)].

3. Results and Discussion

3.1. Physicochemical evaluation studies

The physicochemical parameters, including weight variation, thickness, drug content, folding endurance, and flatness, were measured, and all the

parameter results are satisfactory [13]. The results of the patches are shown in Table 2.

Table 2: Physicochemical evaluation tests for transdermal patches

Formulations	Weight variation (mg)	Thickness (mm)	Drug content (%)	Folding endurance	Flatness (%)
NT1	132.97±2.79	0.37±0.06	98.31±1.92	233±3.27	96.52±2.41
NT2	129.84±3.15	0.33±0.04	96.24±2.25	221±4.01	96.10±2.85
NT3	127.32±2.34	0.31±0.07	95.02±2.01	214± 3.12	95.81±3.05
NT4	129.02±3.10	0.43±0.08	99.10±2.86	252±3.86	97.16±5.19
NT5	124.52±2.65	0.38±0.03	98.71±3.19	245±3.59	97.11±3.74
NT6	121.76±2.81	0.34±0.05	99.05±2.74	238±6.14	97.02±4.82
NT7	130.71±3.12	0.39±0.02	99.87±3.14	251±5.25	98.57±5.10
NT8	128.14±3.26	0.35±0.06	98.29±2.62	246±4.72	97.63±3.91
NT9	125.35±2.41	0.32±0.02	98.61±2.48	240±3.91	97.11±3.45

The thickness ranged between 0.31±0.07 to 0.43±0.08 mm, indicating uniform thickness. The weight patches ranged between 121.76±2.81 to 132.97±2.79 mg, indicating that the patch weights of different batches were relatively similar. Good uniformity of drug content among the various batches was observed, with all formulations ranging from 95.02±2.01 to 99.87±3.14 %. 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 [14].

The flatness study showed that all the formulations in the range between 95.81±3.05 to 98.57±5.10 % had the same strip length before and after their cuts, indicating the results are very near 100% flatness. Thus, no amount of constriction was observed; all patches had a smooth, flat surface, and that soft surface could be maintained when the patch was applied to the skin. Folding endurance test results range from 214±3.12 to 251±5.25, indicating good strength and elasticity of the patches, which would not break and maintain their integrity when applied to general skin folding [15].

3.2. In vitro release studies:

The drug release from transdermal patches varied depending on the polymer composition and nature. The release pattern of nateglinide from formulated transdermal patches is shown in Fig 1.

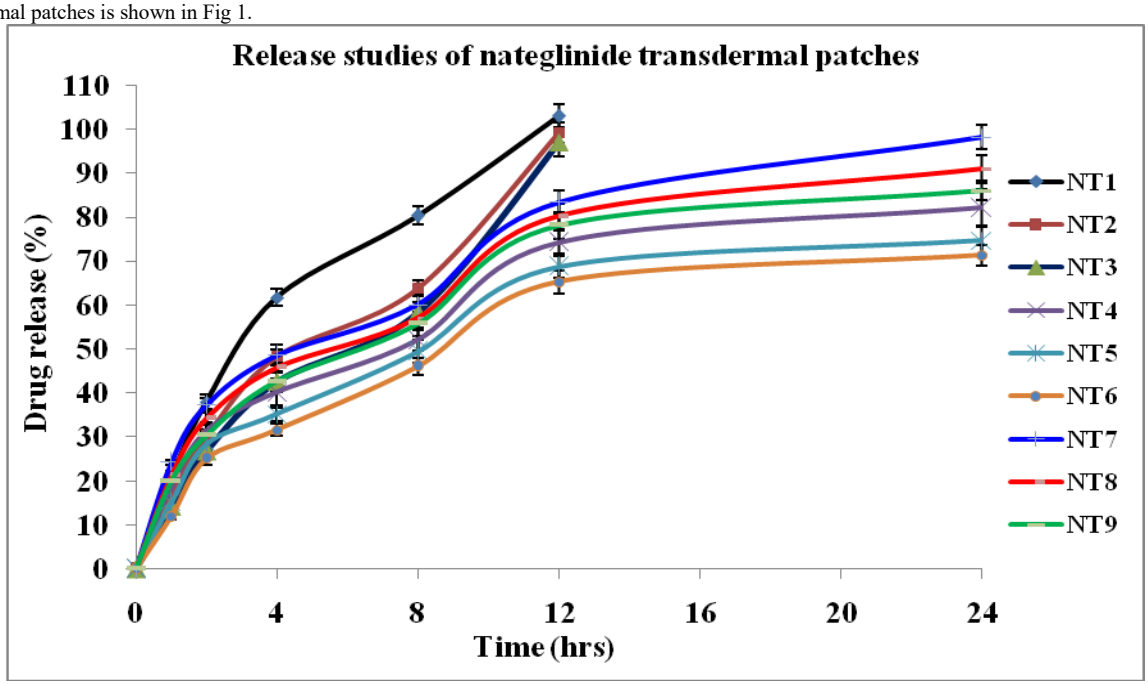

Fig 1: Release studies of transdermal patches of nateglinide

Among all the developed formulations, the highest in vitro release was achieved with NT7, 98.29% in 24 hrs, and it is considered the optimised formulation. The NT 7 contains a higher amount of HPMC and an equal ratio (1:1) of PVP and EC. As the HPMC concentration increases, the percentage of drug release increases due to its high hydrophilicity, which absorbs water, resulting in more drug release from the pores of the patches because of adequate porosity and diffusivity [13].

Whereas, PVP contained formulations (NT1 to NT3) showed drug release was found to be 97.18 to 103.12 in 12 hrs due to the low viscosity of the polymer, and it does not control the release of the drug up to 24 hrs. In the case of EC containing formulations (NT4 to NT6), they showed 71.45% to

82.17% in 24 hrs. The EC is a hydrophobic polymer with reduced affinity for water, resulting in decreased drug release and permeation. EC is used as a "better release retardant" as compared to PVP-containing formulations. So, the combination of EC and PVP with HPMC achieved controlled drug release for a more extended period [15].

3.3. Release kinetics

The kinetic studies of the release profile gave us helpful insight into the mechanism of drug release from the transdermal patches. The release indicated homogeneous drug diffusion. The diffusion data were subjected to regression analysis and fitted to kinetic models, and the results are shown in Fig 2. It was found that the optimised Formulation (NT7) followed zero-order kinetics (0.988) and the Higuchi model (0.981). The zero-order release describes the systems where the drug release rate is independent of the concentration of the dissolved substance. The Higuchi model suggests that drug release occurs by diffusion [16].

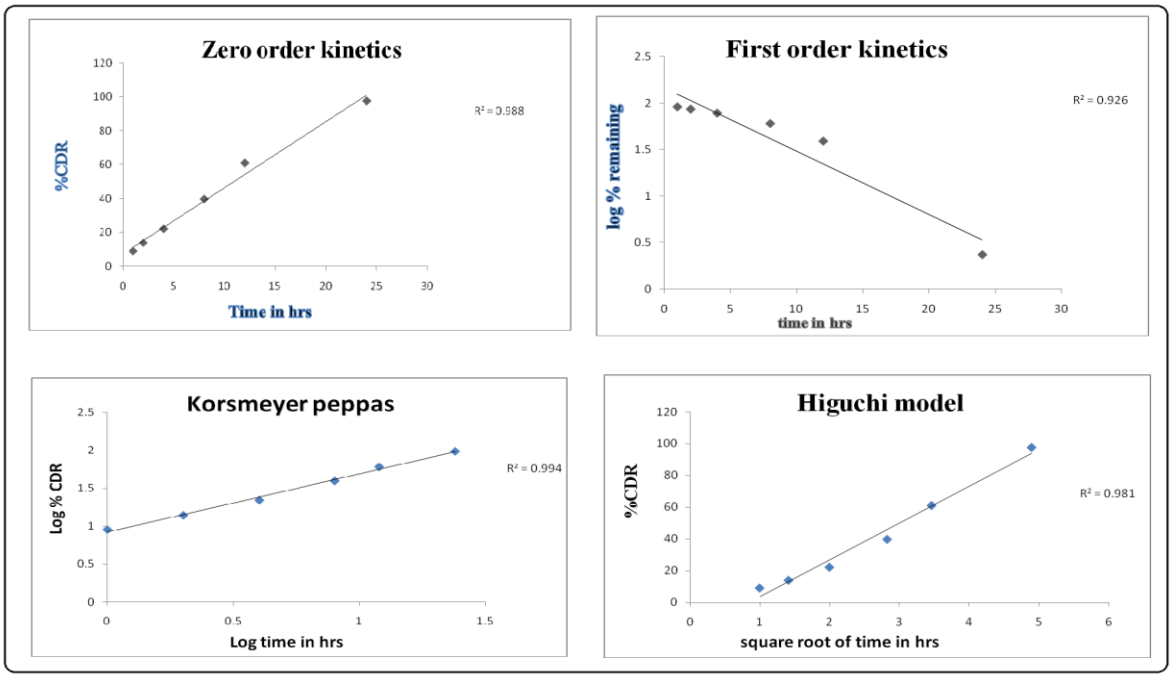

Fig 2: Release kinetics of optimised Formulation (NT7) of transdermal patch

4. Conclusion

The developed transdermal patches of nateglinide using different polymers, HPMC, PVP K30, and EC, had shown satisfactory results for all the formulations. Based on the results of various evaluation parameters such as thickness, weight variation, drug content and higher folding endurance, flatness and in vitro release of the drug for a period of 24 h, it was concluded that HPMC K15M, PVP K30 and EC in an equal ratio may result in controlled release formulations. The optimised Formulation NT7 showed a higher percentage of drug release, 98.29% and it followed zero-order kinetics and the Higuchi model.

Conflicts of interest

The authors have no known conflict of interest concerning the present article.

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