CODEN [USA]: IAJPBB ISSN : 2349-7750

NDO AMERICAN JOURNAL OF
PHARMACEUTICAL SCIENCES

SJIF Impact Factor: 7.187

https://doi.org/10.5281/zenodo.5508667

Available online at: http://www.iajps.com Research Article

DEVELOPMENT AND CHARACTERIZATION OF GLICLAZIDETRANSDERMAL PATCHES

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Article Received: July 2021 **Accepted:** August 2021 **Published:** September 2021

Abstract:

Gliclazide is used in the treatment of type-II diabetes. The main aim and objective is the development and characterization of GLICLAZIDE patch using various polymers such as HPMC k15m, Eudragit S100 by solvent evaporation method. Here Di-butyl phthalate is used as plasticizer and Dimethyl sulfoxide (DMSO) is used as permeation enhancer where as water and ethanol are used as solvents. The formulated patches are evaluated for thickness, weight variation, folding endurance, moisture absorption, and moisture loss along with In-vitro drug dissolution parameters. The drug release studies are carried out by Franze diffusion cell by using pH buffer solution. The drug release is carried out for 8 hrs. Before formulating, the pre formulation studies are evaluated such as FTIR, organoleptic characters such as colour, odour, and appearance. The kinetic profile data is also recorded for optimised formulation and they follow zero order reaction. The stability studies are performed for 90days for optimised formulation under accelerated conditions.

Keywords: Gliclazide, transdermal patch, 7.4 pH buffer.

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Please cite this article in press Nagarjuna Narala et al, ***Development And Characterization Of Gliclazide Transdermal Patches.,*** *Indo Am. J. P. Sci, 2021; 08(9).*

INTRODUCTION:

Transdermal patch (Skin patch) is defined as the appropriate membrane that restricts the rate at which the liquid active ingredient within the patch can pass over the skin and into the blood tissue. Some active ingredients are combined along with the substances such as alcohol, to enhance their ability to permeate into the skin in order to be applied in a skin patch. Most drugs such as scopolamine nicotine, estrogen, nitroglycerin, and lidocaine are transformed through the skin patches to diminish the pain of shingles (herpes zoster). Molecules such as insulin, which are too big to pass over the skin. Their retrieval using syringes and pumps inserting in to skin can be overcome by these patches as they eliminate the use for vascular access. These transdermal patches are also designed for the skin treatments. These were developed in 1970s and the first was accepted in 1979 for diagnosis of motion sickness. Scopolamine is the first drug is used in the design of transdermal patch. In 1981 the patch of Nitroglycerine was accepted. Now-a-days numerous patches are available for different drugs like clonidine, fentanyl, lidocaine, nicotine, nitroglycerine, oxybutynine, testosterone. [1]

Transdermal patch is needed when: [2]

1. The transdermal patch is needed to the patient when the patient is in coma and/or has intolerable side effects and unable to take drugs in through oral means.
2. To enhance the reliable transformation of drug when the body or the part of the body is under pain condition. This might be useful in patients with cognitive impairment or those who for other reasons through which they are not able to self-medicate with their analgesia. So that the pain control is enhanced by predictable drug delivery.
3. To promote harmonious effects, when formulated in combination with other increasing strategies.

Mechanism of Action of Transdermal Patch:

The application of the transdermal patch and the flow of the active drug constituent fromthe patch to the circulatory system via skin occur through various methods.

Iontophoresis: [3] Iontophoresis is a physical process in which ions flow diffusively in amedium driven by the use of an electric current. Here a few milliamperes of current is transferred to an electrode placed in the medium, along with the preparation with square centimetres which promote drug transfer beyond the barrier. Eg. For cystic fibrosis the pilocarpine drug is transformed. For new advancement of treating of anaesthesia the lidocaine is used.

Electroporation: [4] Electroporation is a process of delivering short and high voltage electrical pulses to the skin. After electroporation, the absorption of the skin for dispersal of drugs is enhanced by 4 orders of magnitude. During the transformation of electrical pulses to the stratum corneum, the electrical pulses are believed to form transient aqueous pores in the stratum corneum, through which active ingredient delivery produces. The electrical pulses transfer painlessly by applying closely spaced electrodes using closely spaced electrodes to inhibit the electric field within the nerve- free stratum corneum.

Application by ultrasound: [5] By applying the ultrasound especially slow density ultrasound, it has been shown to increase the delivery of different active ingredient along with the macroparticles. It is also known as sonophoresis.

Use of microscopic projection: [6] Transdermal patches with microscopic projections called micro needles were used to promote transdermal drug delivery. The micro needles ranging generally from 10-100 µm in length are arranged in arrays. When micro needles are pushed into the skin, these arrays produce microscopic breaks that are large adequate to transfer the macromolecules, but small enough that the patient does not feel the penetration or pain. The active ingredient is superficially coated on the micro needles to aid in accelerated penetration. Advancement in formulating cutaneous vaccines for tetanus and influenza forms the basis of this process. This principle is also used in development of different techniques for producing transdermal patches using thermal poration, magnetophoresis, and photomechanical waves.

Types of Transdermal Patch:

Single-layer Drug-in-Adhesive: [7] Single layer drug in the adhesive is one type of design in which the adhesive layer is one of the system consisting of the active ingredient. It also serves to maintain the different layers that are combined together, including entire system of the skin. It is also responsible for the discharge of the active ingredient. It is surrounded by a temporary liner and a backing.

Multi-layer Drug-in-Adhesive: [8] The multi-layer drug-in adhesive patch is similar to the single-layer system. In this, both adhesive layers are responsible for discharging active ingredient. Also, one layer of drug-in-adhesive system however is added to the another layer of drug-in-adhesive, commonly abstracted by a membrane (but not in all cases). This patch also has a temporary liner-layer and a

permanent backing.

Reservoir: [9] The reservoir system is different from the single and multi layer drug-in- adhesive system. The reservoir system consists of an active ingredient solution separated by active ingredient layer. The drug layer is a liquid compartment containing a drug solution or suspension detached by the adhesive layer. This patch is also backed by the backing layer. In this type of system the rate of release is zero order.

Matrix: [10] The matrix system consists of active ingredient layer in the form of semisolid matrix suspension or suspension. The adhesive layer in this patch surrounds the drug layer moderately overlaying it.

Organoleptic characters: Preformulation studies like organoleptic characters such as taste, odour, colour can be observed by visually.
Solubility studies: The drug solubility parameter carried out by water , ethanol, methanol, DMSO, acetone,
FTIR studies: The pure drug, GLICLAZIDE and the physical mixtures of drug and polymers were mixed separately with IR grade KBr and corresponding pellets were prepared and scanned in wavelength region between 4000 to 400 cm^{-1}. The spectra of the drug were compared with polymers.

Calibration of GLICLAZIDE in pH 7.4 buffer:
Preparation of standard stock solution: 10mg of GLICLAZIDE drug was taken and dissolved in pH 7.4 buffer solution. The volume is adjusted up to 10ml in volumetric flask. It is 1000ppm.

Preparation of 2nd stock solution: Take 1ml of sample from 1st stock solution and dilutewith medium make up to mark in 10 ml of volumetric flask it is 100ppm.

Vapour Patch: [11] The vapour patch not only consist of adhesive layer, but also has different layers combined together which discharges the vapour. The vapour patches are novel patches in the market and they discharge fundamental oils for up to 6 hours. By discharging these essential oils they are intended for applying in cases of decongestion mainly. Other vapour patches on the market are controller vapour patches that enhance the quality of sleep. Vapour patches that eliminate the quantity of cigarettes that one smokes in a month are also available on the market.

MATERIALS AND METHODS:

Pre-formulation studies:
Methodology:

Then take 1ml from 2nd stock solution and make up to 10 ml of volumetric flask with medium. It is 10ppm. This is kept under absorbance in U.V visible spectroscopy at 228nm. λ_{max} is noted. Serial dilutions are prepared like 2,4,6,8,10 and check absorbance in U.V visible spectroscopy.

Calibration of GLICLAZIDE in methanol:
Preparation of Standard stock solution: 10mg of GLICLAZIDE drug was taken dissolved in methanol and volume is adjusted to 10 ml in volumetric flask. It is 1000ppm.

Preparation of 2nd stock solution: Take 1ml of sample from 1st stock solution and dilutewith medium make up to mark in 10 ml of volumetric flask it is 100ppm.

Then take 1ml from 2nd stock solution and make up to 10 ml of volumetric flask with medium. It is 10ppm. This is kept under absorbance in U.V visible spectroscopy at 228nm. λ_{max} is noted. Serial dilutions are prepared like 2,4,6,8,10 and check absorbance in U.V visible spectroscopy.[12-19]

Table-1: Formulation table of GLICLAZIDE transdermal patch

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
GLICLAZIDE	50mg	50mg	50mg	50mg	50mg	50mg	50mg	50mg	50mg
HPMC k15m	50mg	-	50mg	80mg	100mg	-	100mg	150mg	-
Eudragit S100mg	-	50mg	50mg	80mg	-	100mg	100mg	-	150mg
DBP(plasticizer)	2ml	2ml	2ml	2ml	2ml	2ml	2ml	2ml	2ml
DMSO(permeation enhancer)	3ml	3ml	3ml	3ml	3ml	3ml	3ml	3ml	ml
Water	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
Methanol	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s

Formulation table of GLICLAZIDE transdermal patch:

Procedure: The GLICLAZIDE transdermal patch prepared by solvent casting method

Polymer solution: The polymers which are selected for GLICLAZIDE patch are dissolved in respective solvents such as water and ethanol by stirring at 500rpm for 1hr.

Drug solution: The drug solution was added to polymer solution by homogeneousmixing. Then add plasticizer DBP (dibutyl phthalate) and permeation enhancer such as DMSO. The resultant mixture is then poured into the petri plate and dry it 24 hrs for at 45^0C.After drying, by using sharp blades the patch was removed.

Evaluation parameters:

Physical appearance: All the prepared GLICLAZIDE films were observed for colour, clarity, flexibility, and smoothness.

Folding endurance: The folding endurance is one of the evaluation parameter. Folding endurance of the patches was resolved by repeatedly folding at the same place till it broke. This was repeated for all formulated GLICLAZIDE patches for 3 times and the mean values plus standard deviation was calculated.

Thickness of the film: The thickness of each film was measured by using screw gauze. The thickness was measured at three different places on each film and the average thickness of the film was taken as the thickness of the film.

Weight uniformity: The prepared patches are dried at 60^0C for 4hrs before testing. A specified area of 4.52 $cm^2$of patch is cut in different parts of the patch and weigh in digital balance. The average weight and standard deviation values are calculated from the individual weights.

Flatness: Flatness was estimated randomly by selecting five longitudinal strips that were cut out from medicated patch of each formulation; the length of each strip was calculated before and after putting them at room temperature for 30 minutes. Variation in length due to non uniformity of flatness was calculated by percent constriction, with 0% constriction as 100% flatness.

$$\text{Percent constriction} = \frac{\text{Final length} - \text{Initial length}}{\text{Initial length}} \times 100$$

Drug content: The buccal films (2 cm^2) were added to conical flask containing 100 ml ofphosphate buffer pH 7.4 with 0.5% SLS. This was then stirred with magnetic bead at 400 rpm for2 hrs. The contents were filtered and the filtrate was analysed spectrophotometrically for drug content at 228 nm. Similarly blank buccal films were prepared. Where, Dt = Total amount of the drug in the patchDa = Amount of drug released

$$\text{Drug content (Da)} = \frac{\text{Weight of drug in patch (Dt)}}{\text{Total weight of patch}}$$

Conditions:

a. **Medium:** Phosphate buffer pH 7.4 containing 0.5% SLS
b. **RPM:** 200
c. **Temperature:** 37 ± 0.5^0C
d. **Time intervals:** 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12hours

Moisture absorption studies: The films were dispensed accurately and kept in a desiccators containing aluminium chloride to maintain 79.50% RH. After 3 days, the films were taken out and weighed. The percentage of moisture uptake was calculated using the following formula.

% Moisture uptake content = (Final wt - Initial wt/Initial wt) X 100

Moisture loss studies: Three films were weighed individually and kept in a desiccator containing calcium chloride at 37^0C for 24 hrs. Then the final weight was noted when there was no further change in the weight of the patch. The percentage of moisture loss was calculated using the following formula.

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

In-vitro Drug Release Studies: In-vitro dissolution studies carried out by using a modified Franz diffusion cell. The dissolution medium here is 7.4 pH phosphate buffer. In Franz diffusion cell the medium was poured about 10ml and the semi-permeable membrane is kept around the Franz diffusion cell. The dissolution studies are done for 12 hours. The time intervals maintained for 1hr. 1ml of aliquot was withdrawn and same amount of sample was replaced in diffusion cell. The withdrawn aliquot was diluted with 7.4 ph phosphate buffer .The absorbance is analysed under U.V visible spectroscopy at the 228nm.

Kinetic profile: Kinetics and mechanism of drug release from all formulation was evaluated on the basis of zero order, Higuchi equation and Pappas model. Correlation coefficient (r2) and slope value for each equation were calculated. Zero order plots for all formulations were found to be linear in both dissolution media. That indicates it may follow zero order mechanism. Higuchi plot was found to be linear, which indicates diffusion may be the mechanism of drug release for each formulation. Peppas plot was found good linear, n > 0.5 for all formulations, indicated that drug release may follow anomalous diffusion. Zero order plot for F4 formulation was found to be linear in both dissolution medium, it considered as a best fit for drug release.

Stability Studies: Stability of a drug has been defined by placing particular formulation, in a specific container, to remain within its physical, chemical, therapeutic and toxicological specifications throughout its shelf life. The purpose of the stability testing is to provide information on the quality of a drug substance or its product, which varies with time under the effect of environmental factors such as temperature, humidity and light. Recommended storage conditions, re-test periods and shelf lives are to be established.

RESULTS:

Pre- formulation studies:

Oraganoleptic characters:

Table-2: Oraganoleptic characters

Properties	Results
Description	Crystals
Taste	Tasteless
Odour	Bitter
Colour	White colour.

Discussion:

The organoleptic properties of GLICLAZIDE were found to be white to off white in colour, odourless and slightly unpleasant in taste and were as per the specifications.

Solubility:

Table-3: Solubility

Solvent	Solubility properties of drug (1gm)
Water	Insoluble in Water
Chloroform	Sparingly soluble
Methanol	Freely Soluble

DISCUSSION:

GLICLAZIDE was found to be slightly soluble in water, sparingly soluble in chloroform and freely soluble in methanol.

Calibration curve in 7.4 buffer solution:

Table-4: Calibration curve in 7.4 buffer solution

S.NO	Concentration (µg/ml)	Absorbance(nm)
1	0	0
2	10	0.18
3	20	0.35
4	30	0.51
5	40	0.69
6	50	0.89

FT-IR STUDIES:

Fig-1: FTIR study of pure drug of GLICLAZIDE

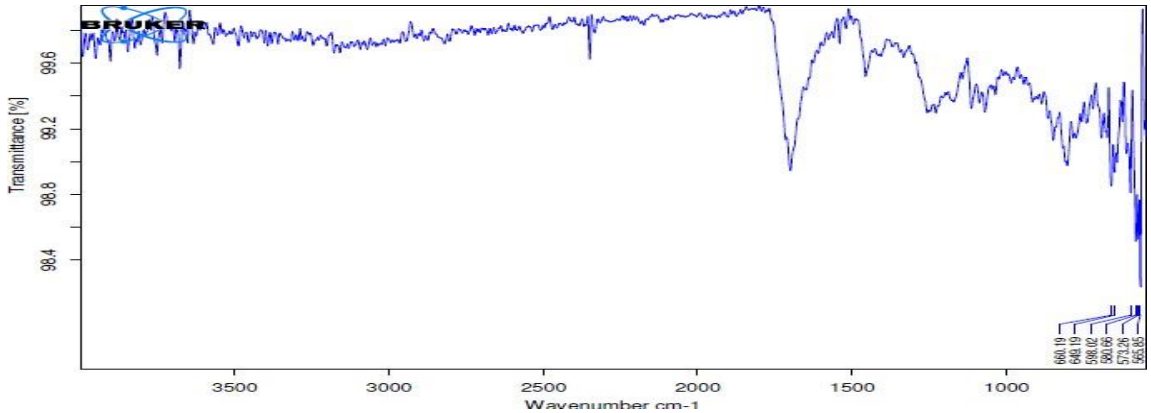
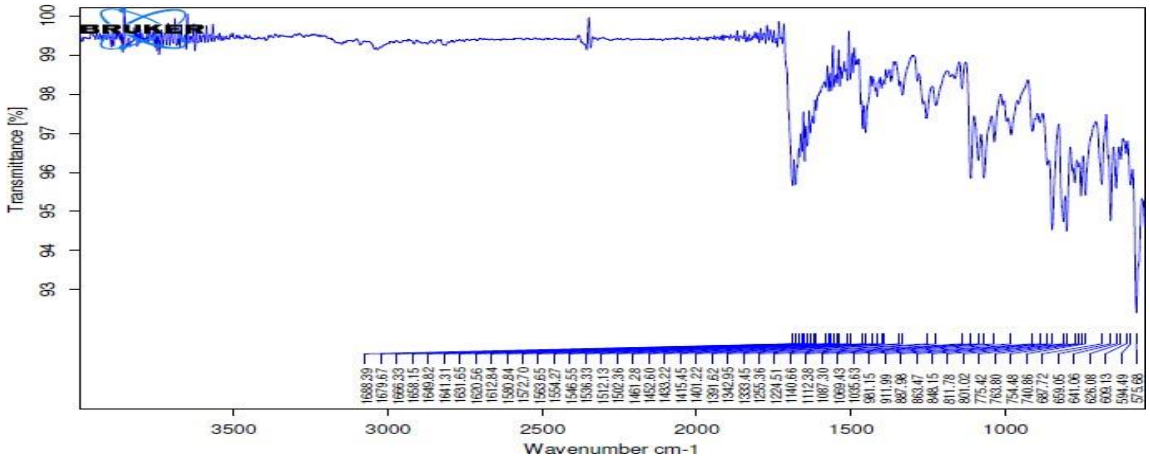


Fig-2: The FTIR spectra of the GLICLAZIDE drug + Eudargit S100 + HPMC k15m



DISCUSSION:

Compatibility studies were performed using FTIR spectrophotometer. The FTIR spectrum of pure drug and physical mixture of drug and polymers were studied. The characteristic absorption peaks were observed at 1146.57cm^{-1},1087.98cm^{-1}, 687cm^{-1},2934cm^{-1}for the pure GLICLAZIDE and absorption peaks were observed at 1148.650 cm^{-1},1085cm^{-1},680 cm^{-1} ,1716 cm^{-1},2850 cm^{-1} for drug and polymer mixture show that how they were in official limits (±100 cm^{-1}) the drug is compatible with excipients.

Evaluation studies for GLICLAZIDE transdermal patch F1-F9:

Table-6: Evaluation studies for GLICLAZIDE transdermal patch F1-F9

Formulation code	F1	F2	F3	F4	F5	F6	F7	F8	F9
Thickness (mm)	0.28± 1.4	0.25± 1.1	0.25±1.7	0.24±1.6	0.27± 1.2	0.31± 1.3	0.28±1.7	0.32±1.6	0.30±1.8
Weight variation (mg)	181 ± 1.2	182 ± 1.2	191±1.4	198±1.2	194 ± 1.2	196 ± 1.2	200±1.4	200±1.2	200±1.8
Drug content Uniformity	98.41±0.3	98.26 ±0.4	98.84±0.6	98.82±0.5	98.41±0.3	98.26 ±0.4	99.24±0.6	98.82±0.5	98.25±0.8
Folding endurance	304 ± 2	301±1	302±8	301±8	300 ± 2	299 ±1	302±9	301±8	30`1±9
Swelling index	26.22	30.53	31.62	33.6	21.22	30.53	31.61	30.6	32
% of moisture loss	6.62	7.51	7.86	7.58	8.8	7.98	6.68	6.2	6.65
% of moisture absorption	10.24	11.23	12.59	11.45	10.6	10.23	11.76	11.56	11.24

Discussion: All the above formulations are kept for the evaluation studies such as the weight variation, folding endurance, drug content, swelling index. All F1-F9 formulations come under within range of limits.

In vitro drug release studies of all formulations F1-F9:

Table-7: In vitro drug release studies of all formulations F1-F9

Time (Hrs)	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
1	20.51	22.21	10.44	15.61	14.64	15.31	18.20	18.21	19.84
2	32.52	30.52	21.64	25.34	28.64	28.64	28.61	25.53	36.64
3	45.5	49.3	31.24	35.64	38.64	40.64	41.55	42.35	46.64
4	58.4	68.51	42.4	48.34	49.51	58.64	59.61	52.31	68.51
5	78	82.74	55.31	58.64	59.84	69.64	75.64	65.64	79.64
6	95.55	98.51	67.64	68.55	71.96	78.22	89.54	76.85	86.52
7	-	100.84	78.55	76.64	78.41	88.64	95.64	87.34	90.54
8	-	-	80.95	87.64	89.5	95.64	99.64	94.31	95.73

Kinetic study for the optimized formulation(F7):

Table-8: Kinetic study for the optimized formulation(F7)

Time (Hrs)	%cdr	Log T	√T	Log%cdr	ARA	Log%ARA
0	0	1	0	1	100	2
1	18.20	0	1	1.26	81.78	1.911
2	28.61	0.30102	1.413	1.44	71.39	1.854
3	41.55	0.47711	1.731	1.62	58.43	1.765
4	59.61	0.60203	2	1.78	40.39	1.605
5	75.64	0.69896	2.235	1.86	24.34	1.385
6	89.52	0.778152	2.448	1.94	10.46	1.018
7	95.64	0.845096	2.644	1.95	4.33	0.632
8	99.64	0.90308	2.826	1.98	0.34	-0.454

Stability dissolution profile of F-7 for 1st, 2nd & 3rd months:

Table-9: Stability dissolution profile of F-7 for 1st, 2nd & 3rd months

S.No	Time (Hrs)	Initial	F-7 (1st Month)	F-7 (2st Month)	F7 (3st Month)
1	0	0	0	0	0
2	1	18.3	18.4	18.25	18.4
3	2	28.4	28.4	28.1	28.5
4	3	41.5	42.46	41.44	41.64
5	4	59.5	60.4	59.64	59.4
6	5	75.5	75.26	75.25	75.53
7	6	89.4	89.35	89.51	89.51
8	7	95.5	95.56	95.54	95.55
9	8	99.6	99.63	99.54	99.65

CONCLUSION:

The development and characterization of GLICLAZIDE transdermal patch is done by using synthetic polymers such as HPMC, Eudragit S100. Di butyl phthalate is used as plasticizer and Dimethyl sulfoxide is used as permeation enhancer. The patch is formulated by applying by Solvent Casting method. After formulation development the evaluation parameters validated and all came under the range of limits .The drug release the optimized formulation F7 was found to be 99.65%. The kinetic profile validated for optimized formulation shows the product follow zero order and Higuchi equation. The stability studies carried out for 90 days there is no degradation in optimized formulation in drug release and drug content studies.

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