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Original Research Article

An Assessment of the Formulated Medicated Transdermal Patches Containing an Antidiabetic Drug: an in-Vitro Study

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Abstract

Aim: The current research aims to formulate and evaluated medicated transdermal patches containing an antidiabetic drug.

Material & Methods: In the present study was conducted by the Department of Pharmacology, DMCH, Laheriasarai, Darbhanga, Bihar, India. An attempt has been made to develop a matrix-type transdermal therapeutic system comprising of various PVP K30, MC ratios and solvent evaporation techniques. A good penetration enhancer would improve drug delivery from various polymer-based transdermal patches. Transdermal patches of the matrix type are made. All prepared formulations were tested for weight variation, thickness, drug content, moisture content, moisture uptake, flatness, and in vitro drug release. Bath F3 was optimised formula from all formulation baths shows linear zero order release for 24 hours, with a cumulative percentage of drug diffusion of 87.35% from 4cm2 patches. It has been determined that polymer concentration.

Results: The formulated films were examined for colour, clearness, softness and elasticity. It was précised by digital Vernier calipers. Three reading were taken for standard deviation after thickness measured at five various site of patch. The thickness of Glimepiride patches were between112.48-124.26µm. The folding endurance of patches was found to be satisfactory between 121.49±2.36 to 128.42±0.46. This shows that patches would maintain their integrity and not break easily. The moisture content in the patches was ranged from 1.38 ± 0.26 to 2.80 ± 0.20% (for formulation F series and formulation respectively). The weight variation of Glimepiride patches were in between 250 to 280 mg. This showed uniformity in weight of patches while the % drug content of Glimepiride in patches were between 96.00 to 95.15±0.85% this shows passable drug content in patches.

Conclusion: When the concentration of PVP K30 increases in the primary layer, the in – vitro diffusion rate increases, and when the concentration of PVP K30 decreases, the drug diffusion decreases. It allows for more controlled drug release from the patch.

Keywords: Glimepiride, Matrix Type Transdermal Patch, PVP K30, Methyl Cellulose.

Introduction

Transdermal drug delivery is one of the most capable techniques for drug application. During the past few years, interest in the development of transdermal drug delivery systems for existing drug molecules has been renewed. [1] Development of a transdermal delivery system for existing drug molecules not only improves the drug's performance in terms of safety and efficacy but also therapeutic benefit and improves patient compliance. [2] The fundamental goal of a transdermal medication delivery system is to deliver pharmaceuticals into the systemic circulation through the skin at a predefined pace with little fluctuation between and within patients. [3] It is a medicated adhesive patch which is placed directly above the skin to deliver a exact dose of medication through the skin with a predetermined rate of release to reach into the bloodstream. [4] Skin patch (Transdermal patch) uses a special membrane to control the rate at which the liquid drug contained in the reservoir within the patch can pass through the skin and into the Bloodstream.

The most significant advantages provided by the following are some examples of transdermal medication delivery: increased bioavailability and effect duration, resulting in a reduced dosing frequency, plasma levels are more uniform, and adverse effects are reduced. [1] Delivery of drug not only in controlled manner but also permits continuous input of drugs with short biological half-lives and removes pulsed entry into systemic circulation. controlled release offers by using transdermal drug delivery into the patient & enables a steady blood-level profile in order to reduced systemic side effects and sometimes effortless and offer multi-day dosing. It's proved helpful in minimising the effects of first-pass medication degradation. [3] The majority of transdermal patches are made to release the active ingredient. For several hours to days following application to the skin, the chemical has a zero-order rate. Drugs penetrate multiple layers of skin and permeate the epidermis into systemic circulation in transdermal patches. [2]

Glimepiride is a sulphonylurea-class oral antidiabetic medication with a medium to long half-life. [5] It is a sulfonylurea of the second generation that is used to treat type 2 diabetes. It causes a rapid release of insulin from pancreatic beta cells by inhibiting ATP sensitive k+ channels, which causes depolarization and Ca2+ influx sensitivity which can improve medication penetration through the skin. In general, once medication molecules break the stratum corneal barrier, they move swiftly and easily into deeper dermal layers, allowing for systemic uptake. Hence the current research aims to formulate and evaluated medicated transdermal patches containing an antidiabetic drug.

Material & Methods

In the present study was conducted by the Department of Pharmacology, DMCH, Laheriasarai, Darbhanga, Bihar, India for 10 months

Glimepride and Methyl cellulose was obtained from spectrum reagents and chemicals Pvt. Ltd., Edayar, Cochin. PVP K30 was obtained from oxford lab fine—Chem. Ltd, Maharashtra. Polyethylene glycol 400 was obtained from Indian Research Product, Chennai. Tween-20 was obtained from Isochem Lab Angamaly, Kochi. [6] Chloroform and methanol was obtained from Isochem Lab Kanjikoda, Palakkad. All other materials and chemicals used were of either pharmaceutical or analytical grade.

Methodology

Matrix type transdermal patches containing Glimepiride were prepared by solvent evaporation technique. Overall, three batches were formulated using

different ratios of MC and PVPK30. Casting solution was prepared by dissolving weighed quantities of polymer PVPK30 and MC (total weight of polymers were kept 500 mg), and plasticizer (36% w/w of polymers) and penetration enhancer (12% w/w of polymers) in an appropriate solvent system. The base of the ring was wrapped with aluminum foil. [7] A glass bangle as a mould was placed in the petridish above the aluminum foil. A fixed volume (5ml) of polymeric solution with drug and plasticizer was poured on to the petridish and inverted funnel was placed on the petridish to facilitate the evaporation of solvent at a controlled rate over the drying period of 24 h at room temperature. The dried film were removed and cut into 2 cm area and kept in a desiccator further used. 6 Total polymeric weight: 500 mg

Density of PEG400 =1.13 therefore, Amount used 0.180 ml

Plasticizer = (36% w/w total polymeric weight)

Density of tween 20 is 1.095 g/mL therefore amount used

0.06 ml penetration enhancer = (12% w/w of total polymeric weight)

Preliminary studies:

I**. Determination of λ-max**:

A 10mg of Glimepiride was accurately weighed and was first dissolved in 35ml methanol solutions. These solutions then diluted using phosphate-buffer pH-7.4 to 100 ml. UV spectrum was recorded in the wavelength range 200-400nm.

II. **Preparation of calibration curve for Glimepiride:**

Concentration was made using the phosphate buffer pH 7.4 media. It was analysed spectrophotometrically by measuring the absorbance at 228 nm wavelength. The absorbance value are shown in table no. The figure no shows standard calibration curves with slope 0.0717 and regression value 0.9999. The curve was found to be linear in the range 2-12 µg/ml at the drug solution of with concentration of 100µg/ml was prepared. Serial dilution 2, 4, 6, 8, 10,12µg/ml

III**. Fourier Transform Infrared (FT-IR) Spectral Studies of Glimepiride:**

The spectrum of Glimepiride was obtained by means of a FTIR spectrophotometer. FT-IR spectra of Glimepiride drug were recorded on Agilent carry 630 ATR FTIR Spectrophotometer. Sample was placed in sample holder; the scanning was performed between 4000 cm-1 to 400 cm-1 range.

IV. **Drug excipients interaction studies:**

The compatibility of drug and polymers under experimental conditions is important prerequisite before formulation. It is essential to verify that the drug does not react with the polymer and excipients in process condition and does not affect the shelf-life of product or any other unwanted effects on the formulation. The physical mixture of drug & polymers were used for determination of Infrared spectrums.

Evaluations of transdermal patches:

1. **Physical Appearance:**

The formulated films were examined for colour, clearness, softness and elasticity.

2**. Thickness:**

It was précised by digital Vernier calipers. Three reading were taken for standard deviation after thickness measured at five various sites of patch. The thickness of Glimepiride patches was between110.46-122.23µm.

3. **Weight Variation Test:**

Firstly, the three patches were chosen randomly from all batches then three films were chosen and weighed separately from individual formulation and calculated the mean for weight variation test and standard weight was estimated. The weight

variation of Glimepiride patches were in between 250 to 280 mg. This showed uniformity in weight of patches while the % drug content of Glimepiride in patches were between 95.00 to 95.25±0.84% this shows passable drug content in patches.

4. **Folding Endurance**

The folding endurance of patches were found to be satisfactory between 120.66±2.42 to 128.66±0.48. This shows that patches would maintain their integrity and not break easily during handling. The tensile strength was found to be in the range of 0.31 to 1.31 kg⁄mm2. As the concentration of hydrophilic polymer HPMC E15 was increased the tensile strength was found to be increased. All film showed 100% flatness. It was calculated physically for formulated patches. The patches were cut and constantly folded over at similar position till it was broken. Number of times the patch could be folded over at similar position without breaking or cracking given the value of folding Endurance.

5. **Flatness**

The films were cut from formulated patches longitudinally and lengths of individual films were calculated. The difference in length due to the non-uniformity in flatness was measured. It was estimated through measured constraint of films and zero percent constraint was considers to be equals to a hundred percent flatness.

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

Where,

L1: Initial lengths of film

L2: Final lengths of film

Determination of Glimepiride content:

A sample of 1 cm x 1 cm of the patch was cut and weighed accurately. Each sample was

dissolved in 100 mL of phosphate buffer solution and stirred for 24 hour using magnetic

stirrer. The solution was analyzed by UV-VIS spectrophotometer at 220 nm. The total

content of Glimepiride was calculated. The value was mean + SD of the three

determination

Weight variation and drug content

The weight variation of Glimepiride patches was in between 250 to 280 mg. This showed uniformity in weight of patches while the % drug content of Glimepiride in patches were between 95.00 to 95.25±0.84% this shows passable drug content in patches.

Results

Table 1: Physical appearance of batch F1 to F3

Formulation	Flexibility	Smoothness	Transparency	Stickiness
F1	Flexible	Smooth	Opaque	Non-Sticky
F2	Flexible	Smooth	Opaque	Non-Sticky
F3	Flexible	Smooth	Opaque	Non-Sticky

The formulated films were examined for colour, clearness, softness and elasticity.

Table 2: Thickness of batch F 1 to F3

Formulation	Thickness (µm)
F1	**112.48 ±1.25**
F2	**116.12± 1.20**
F3	**124.26±1.65**

It was précised by digital Vernier calipers. Three reading were taken for standard deviation after thickness measured at five various site of patch. The thickness of Glimepiride patches were between112.48-124.26µm.

Table 3: Folding endurance, flatness and tensile strength

Formulation Code	Parameters		
	Folding Endurance	Flatness	TensileStrength kg⁄mm²
F1	121.49 ±2.36	100%	0.32±0.038
F2	126.40±0.44	100%	0.64±0.206
F3	128.42±0.46	100%	1.34±0.316

The folding endurance of patches was found to be satisfactory between 121.49±2.36 to 128.42±0.46. This shows that patches would maintain their integrity and not break easily.

Table 4: Moisture Content and Moisture Absorption Studies and E. Weight variation and drug content

Formulation	Moisture content	Moisture absorption
F1	1.38 ± 0.26%	1.48±0.42%
F2	1.58 ± 0.52%	3.56±0.54%
F3	2.80 ± 0.20%	5.50±0.52%
	Average weight (Mg)	% Drug content
F1	252.48±2.44	96.00±0.32
F2	254.46±2.824	94.36±0.32
F3	262.38±3.14	95.15±0.85

The moisture content in the patches was ranged from 1.38 ± 0.26 to 2.80 ± 0.20% (for formulation F series and formulation respectively). The weight variation of Glimepiride patches were in between 250 to 280 mg. This showed uniformity in weight of patches while the % drug content of Glimepiride in patches were between 96.00 to 95.15±0.85% this shows passable drug content in patches.

Table 5: In vitro skin permeation study

Time	Cumulative % drug diffuse	Cumulative % drug Diffuse	Cumulative % drug Diffuse
0	0	0	0
1	1.05	1.42	4.16
2	2.24	2.48	9.21
3	3.40	3.64	17.3
4	4.64	4.86	25.5
5	6.74	8.32	37.22
6	11.9	12.40	49.55
7	15.25	16.4	57.54
8	19.01	21.29	66.89
9	25.55	27.33	68.40
10	32.76	34.66	69.68
11	36.64	40.22	71.84
12	41.49	45.43	73.43
13	44.7	49.81	77.33
14	47.33	53.47	79.31
15	49.51	56.44	81.19
24	62.38	70.20	88.12

The volume of the receptor compartment was maintained at 60ml. The receptor compartment was provided with the sampling port from one side to withdraw samples at the predetermined time intervals for estimation of drug content by UV spectrophotometer. The receptor medium was phosphate buffer saline (PBS) pH 7.4 containing 30%v/v PEG-400 as solubilizer.

Discussion

Transdermal drug delivery system (TDDS) is a widely accepted means of drug delivery, and transdermal patches are devised to treat various diseases. [8] TDDS are extended-release dosage forms that can offer a stable systemic drug concentration and avoid first pass metabolism. They can even avoid gastrointestinal problems associated with drugs and low absorption. [9] These therapeutic advantages reflect the higher marketing potential of TDDS. [10] Most of the drug molecules penetrate through the skin through intercellular micro route and therefore the role of permeation or penetration enhancers in TDDS is vital as they reversibly reduce the barrier resistance of the stratum corneum without damaging viable cells. [11]

Overdosing becomes a concern due to fluctuation in peak plasma concentration following oral and parenteral administration, making it a challenge in monitoring effective plasma concentration. Transdermal drug delivery systems offer several benefits be- cause drugs administered are able to bypass hepatic first-pass metabolism and factors that alter pharmacokinetics in the gastrointestinal tract. This significantly improves systemic bioavailability with reduced risk of side effects associated with concentration. This generally improves patient compliance as it is easy and convenient to apply with a lesser dosing frequency, as the drug is released at a predetermined rate over a prolonged period. [12] Seong et al [13] reported double-layered, bullet-shaped microneedles with swellable tips which are capable of loading insulin for interlocking-mediated adhesion to skin tissue and prolonged insulin delivery. The mechanical interlocking adhesion was achievable through increasing volume of swellable tips. Insulin loaded onto the tips diffuses through the swollen hydrogel into skin. Chen et al [14] proposed a microneedle patch system consisting of poly- γ-glutamic acid (γ-PGA). A supporting structure composed of polyvinyl alcohol (PVA)/polyvinyl pyrrolidone (PVP) was added to provide mechanical strength for full insertion into the skin and counteract skin deformation during skin insertion which often occurs with the microneedle system.

The formulated films were examined for colour, clearness, softness and elasticity. It was précised by digital Vernier callipers. Three reading were taken for standard deviation after thickness measured at five various sites of patch. The thickness of Glimepiride patches were between112.48-124.26μm. The folding endurance of patches was found to be satisfactory between 121.49±2.36 to 128.42±0.46. This shows that patches would maintain their integrity and not break easily. The moisture content in the patches was ranged from 1.38 ± 0.26 to 2.80 ± 0.20% (for formulation F series and formulation respectively). The weight variation of Glimepiride patches were in between 250 to 280 mg. This showed uniformity in weight of patches while the % drug content of Glimepiride in patches were between 96.00 to 95.15±0.85% this shows passable drug content in patches. Alam et al [15] fabricated a nanostructured lipid carrier (NLC) using high-pressure homogenization and ultrasonication to load pioglitazone (PZ) in diabetes management. An in vivo pharmacokinetic study elucidated that bioavailability of PZ using NLC was 2.17 times better than PZ

(Piosys) tablets. Shinde et al [16] studied microemulsion gel transdermal de- livery of Repaglinide (RPG) in drug permeation and antidiabetic effect. Microemulsion systems were prepared by mix- ing oil (kept under 8%), surfactant, co-surfactant and wa- ter. 0.6% (w/w) of xanthan gum was added to the formulation to prepare a microemulsion gel with mean globule size of 36.15 ±9.89 nm while RPG was loaded into it un- der ultrasonication.

Conclusion

The concentration of Methyl cellulose when increased into primary layer In Vitro diffusion rates were also increased and also as concentration of PVP when increased, the drug diffusion rate was decreased and vice versa. Batch F3 was the optimized formulation showing uniform thickness, good tensile strength, drug content uniformity and good folding endurance. The formulation F3 showed linear zero order release for 24 hours with cumulative % drug diffused of 87.35% from 4 cm2patch of batch F3.

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