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Development and characterization of Glibenclamide containing Transdermal Patches

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ABSTRACT

Transdermal drug delivery has had a rich past and is now emerging as a major alternative to other delivery systems. As this technique has matured and new fundamentals have been integrated into its development, new products and applications have shown new ways in which skin can play a larger part in healthcare and quality of life. Improved delivery has been shown for drugs of differing. The cumulative percentage of drug released in 12 h was found to be minimum and maximum for the formulations F4 and F10 *i.e.* 81.023 ± 3.013 % and 98.564 ±3.005%.The results of the drug content in all the formulations were found to be in the range of 96 to 98 %. The maximum moisture loss was 4.3300 ± 0.0360 %. The prepared film had tendency to absorb moisture effectively. Glibenclamide is a third generation oral anti-diabetic sulphonylurea drug frequently prescribed to patients of type 2 diabetes. Glibenclamide therapy improves postprandial insulin/C-peptide response, and overall glycaemia control. The development of Glibenclamide transdermal patch for anti-diabetic will be an excellent dosage form for market strategy due to its very fast action and better patient compliance.

Keywords: Transdermal, cyclodextrin, formulation, release

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INTRODUCTION

Glibenclamide is a third generation oral anti-diabetic sulphonylurea drug frequently prescribed to patients of type 2 diabetes. Glibenclamide therapy improves postprandial insulin/C-peptide response, and overall glycaemia control. The problem arrived by the oral Glibenclamide therapy upon the bioavailability due to its poor solubility leading to irreproducible clinical response, in addition to adverse effects like dizziness and gastric disturbances [1]. As a potential for convenient, safe and effective anti-diabetic therapy, the transdermal delivery system for Glibenclamide was being developed. Glibenclamide is an anti-diabetic drug in a class of medications known as sulfonylureas. It is also sold in combination with metformin under the trade name Glucovance. Glibenclamide exerts pancreatic and extrapancreatic actions. It stimulates an increase in insulin release by the pancreatic β-cells. It may also reduce hepatic gluconeogenesis and glycogenolysis. Increased glucose uptake in the liver and utilization in the skeletal muscles[2].

Many drugs from natural[3–5] and synthetic sources have been formulated in transdermal drug delivery systems e.g., nicotine, anti-histamines, beta-blockers, NSAIDS, calcium channel blockers, contraceptives, anti-arrhythmic drugs, insulin, anti-viral drugs, hormones, interferon's and anti-cancer agents etc. In 1969 first US Patent (US 3426754) on transdermal drug delivery device was issued to Bierenbaum et al., 1969 for the invention of breathable medical dressing. Stability and skin permeation of salbutamol base from adhesive matrix transdermal patches containing antioxidants and skin permeation enhancers were studied. Optimal therapy of a disease requires an efficient delivery of active drug to the tissues, organs that need treatments. Very often dosed far in excess to those required in the cells have to be administered in order to achieve necessary therapeutically effective concentration. This unfortunately may lead to toxicological, undesirable and immunological effects in non-target tissue and takes a lot of time. A transdermal patch is lead to better management of the disease condition with very fast action.Development of a transdermal patch's demands considerable understanding of the amount of drug. TDDS is limited by the amount of drug that can be incorporated into each unit dose, and another factor is mechanical strength. In

order to allow tdds they are made of either very porous & soft-molded matrices of compressed into patch's with very low compression force, which makes the easy handle on the transdermal route [6].The development of Glibenclamide transdermal patch for anti-diabetic will be an excellent dosage form for market strategy due to its very fast action and better patient compliance.

MATERIALS AND METHODS

Chemicals

Glibenclamide was kindly provided by Delta Pharma. Co. (Mumbai, India). Chitosan (MW 150,000, deacetylation degree 75–85%), β-cyclodextrin, cineole, menthol, limonene and streptozotocin were purchased from Sigma Chemical Company (St. Louis, USA). Oleic acid was purchased from Fluka (Germany). Sodium dihydrogen phosphate was supplied from S. D. fine-chem. Ltd. (Mumbai, India) and disodium hydrogen phosphate was purchased from BDH Laboratory Supplies (Poole England). Lactic acid, acetic acid and ethanol were supplied from Adwic, Banglore. All other ingredients are of analytical grade.

Preparation of Glibenclamide-cyclodextrin complex

The continuous variation method 29 was utilized to determine the stoichiometric ratio of Glibenclamide-β-CyD complex by spectrophotometric measurements. The absorbance values of fixed total concentration (0.072 mmol/l) of Glibenclamide and β-CyD were measured at 226 nm. If it was found that the absorbance values of these solutions were different from the sum of the corresponding values of their components.

Preparation of Chitosan Films

Chitosan (1.5% w/v) was dissolved in water containing 2 % w/v of a 1:1 mixture of lactic acid and acetic acid solution and stirred overnight using a magnetic stirrer. The resulting solution was filtered through a sintered glass filter to remove the extraneous matter. The resulting solution was medicated with the drug or its equivalent amount of the Glibenclamide complex followed by sonication for 2 hours. Two concentrations of Glibenclamide were used in preparing the films[7].

Characterization

- **Physical Appearance**

All the prepared patches were visually inspected for color, clarity, flexibility and smoothness[8].

- **Thickness Uniformity**

The thickness of the formulated film was measured at 3 different points using a mitutoya thickness guage 7301 made in Japan thickness of three reading was calculated. Average thickness was determined[8].

- **Folding Endurance**

The folding endurance was determined to determine flexibility of film. The flexibility of the film is needed to handle the film easily and for comfortable, secured application of film on the wound. It was determined by repeatedly folding one film at same place till it breaks or folded up to 300 times manually. The number of times of film could be folded at the same place withoutbreaking give the value of folding endurance[8].

- **Water Absorption Capacity**

It is of utmost importance, if they are used for biological applications and wound healing. It is used to measure the capacity of film to absorb wound exudates. The initial weight of 1inch of dry film was noted. Then this film was placed in 15ml. of distilled water taken in Petri plate. The weight of the film was noted periodically at first hour, second hour, third hour and 24th hour. Every time after noting the weight, the film was placed in fresh water[9]. Water absorption capacity of the film was calculated using a formula:

$$\%\ Moisture\ Absorption = \frac{Final\ weight - Initial\ weight}{Initial\ weight} \times 100$$

- **Percentage Moisture Loss**

The films were weighed accurately and kept in a desiccators containing anhydrous calcium chloride. After 3 days, the films were taken out and weighed[9]. The moisture loss was calculated using the formula:

$$\%\ Moisture\ Loss = \frac{Final\ weight - Initial\ weight}{Initial\ weight} \times 100$$

- **Water Vapor Transmission Rate**

Glass vials of 5 ml capacity were washed thoroughly and dried to a constant weight in an oven. About 1 g of fused calcium chloride was taken in the vials and the polymer films of 2.25 cm^2 were fixed over the brim with the help of an adhesive tape. Then the vials were weighed and stored in a humidity chamber of 80-90 % RH condition for a period of 24 h[10]. The vials were removed and weighed at 24 h time intervals to note down the weight gain.

$$Transmission\ rate = \frac{Final\ weight - Initial\ weight}{Initial\ weight} \times 100$$

- **Tensile strength**

Tensile strength of the film was determined with Universal strength testing machine (JUSTY, Tensile Testing Machine, JTM 50 digital). The sensitivity of the machine was 1 g. It consisted of two load cell grips. The lower one was fixed and upper one was movable. The test film of size (10 × 10 mm^2) was fixed between these cell grips and force was gradually applied till the film broke[10]. The tensile strength of the film was taken directly from the dial reading in kg. Tensile strength is expressed as follows:

$$Tensile\ strength = \frac{Tensile\ lload\ at\ break}{Cross\ sectional\ area}$$

- **Drug content**

An accurately cut patch of 1cm^2 area was taken and added to a beaker containing 1 ml phosphate buffer solution of pH 7.4 The beaker was kept 24 hours with occasion shaking[10]. The sample was analyzed drug content using UV spectrophotometer 248nm.This study was performed for 3 times for a single patch.

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

The *in vitro* evaluation was carried out in the modified Franz diffusion cell. This consists of an upper donor compartment and the lower receptor compartment, surrounded by water jacket for circulation of water to maintain the temperature inside at 32±1.0C.The uniformity of solution in the receptor phase was maintained by stirring at high speed of 100 rpm (approximately) using a tiny magnetic bead the volume of receptor compartment was maintained at 60 ml and the diffusion surface are of 0.785 cm^2. The receptor compartment was provided with the sampling port on one side, to withdraw sample at the predetermined time intervals[10] for estimation of drug content by UV spectrophotometer.

RESULTS

- **Physical Appearance**

All the prepared transdermal patches were uniform without any deformity. The patches were opaque.

- **Thickness Uniformity**

The average thickness of prepared film was found in the range of 0.02266 ± 0.0015 mm to 0.03533 ± 0.0025

- **Folding Endurance**

This test was performed to evaluate the flexibility of the films, the films were analysed by folding endurance studies. The values were in the range of 138 to 176 as seen in the formulation. This study uncovered the fact that the films were capable to bear the mechanical pressure along with good flexibility.

- **Water Absorption Capacity**

IT is an important parameter which is very necessary in case if the patches are meant to be applied over the surface of the wound. This phenomenon is utilized to assess the capability of film to absorb wound exudates. The prepared film had tendency to absorb moisture effectively.

- **Percentage Moisture Loss**

The films are weighed accurately and kept in a desiccators containing anhydrous calcium chloride. After 3 days, the films were taken out and weighed. The maximum moisture loss was 4.3300 ± 0.0360 %

- **Tensile strength**

The maximum tensile strength was found to be 0.6130 ± 0.0010 kg/cm^2.

- **Drug content**

The drug content uniformity of all the formulations was determined. The results of the drug content in all the formulations were found to be in the range of 96 to 98 %.

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

The cumulative percentage of drug released in 12 h was found to be minimum and maximum for the formulations F4 and F10 *i.e.* 81.023 ± 3.013 % and 98.564 ±3.005%. The *in-vitro* release data obtained from different formulations of Glibenclamide was plotted for cumulative percent drug release versus time.

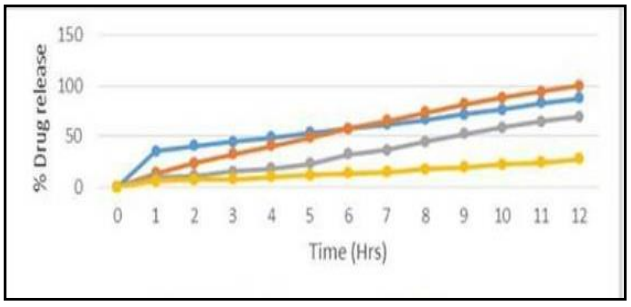

Fig 1: *In vitro* drug dissolution studies of prepared patches

DISCUSSION

Transdermal drug delivery has had a rich past and is now emerging as a major alternative to other delivery systems. As this technique has matured and new fundamentals have been integrated into its development, new products and applications have shown new ways in which skin can play a larger part in healthcare and quality of life. Improved delivery has been shown for drugs of differing[11]. However, subjective and objective analysis of these devices is required to make sure scientific, regulatory and consumer needs are met. The devices in development are more costly and complicated compared with conventional transdermal patch therapies[12]. As such they could contain electrical and mechanical components that could increase the potential safety risks to patients owing to poor operator technique or device malfunction. In addition, effects of the device on the skin must be reversible, because any permanent damage to the stratum corneum will result in the loss of its barrier properties and hence its function as a protective organ[11]. Transdermal drug delivery provides some desirable performances over conventional pharmaceutical dosage formulations, such as avoiding gut and hepatic first-pass metabolism, improving drug bioavailability, reducing dose frequency, lessening the side effects and, thus, improved patient compliance[13]. From the above work it can be concluded that glibenclamide transdermal patches could be promising carrier in management of type 2 diabetes mellitus.

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