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Effects of Chemical Enhancers on the Release of Glipizide through matrix Patch

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Abstract: The aim of the present investigation was to investigate the effect of chemical enhancers on the release of glipizide through transdermal matrix patch using different ratio of different chemical enhancers. L-menthol, oleic acid and n-octanol were tried over the glipizide matrix patch. The used concentrations of L-menthol and oleic acid were 1%, 1.5% and 2.0% and concentration of n-octanol was 1%. To prepare the transdermal matrix-patch, ethyl cellulose (EC) and poly vinyl pyrrolidone (PVP) were used as polymers. Di-Butyl phthalate (DBP) was used as plasticizer at 30 % concentration of the total polymer weight. Then these transdermal patches were evaluated for drug release. Drug release rates were different for different formulation. Here, addition of chemical enhancers has decreased the percentage release.
Key words: matrix patch, glipizide, ethyl cellulose, polyvinyl pyrrolidone, Di butyl phthalate, n-octanol, L-menthol, oleic acid.

Introduction

Diabetes mellitus is a major and growing health problem worldwide and an important cause of prolonged ill health and early death.[1] It is a chronic metabolic disorder characterized by a high blood glucose concentration (hyperglycemia) caused by insulin deficiency and it is often combined with insulin resistance.[2-4] Glipizide is an oral blood-glucose-lowering drug of the sulfonylurea class. Glipizide has been in extensive use to treat NIDDM and acts by increasing the release of endogenous insulin as well as its peripheral effectiveness. It has been associated with severe and sometimes fatal hypoglycemia and gastric disturbances like nausea, vomiting, heartburn, anorexia and increased appetite after oral therapy.[5] Since these drugs are usually intended to be taken for a long period, patient compliance is also very important. Transdermal delivery has many advantages over oral route of drug administration; it avoids hepatic first pass metabolism, termination of further administration, long term duration, potentially decreases side effects and improves patient compliance. So different attempts were made to formulate transdermal glipizide patches[6-11] which will reduce frequency of dosing and some of the complications of higher dose oral therapy. Patches were prepared using EC as a main polymer, PVP as a co-polymer. Ethyl cellulose and PVP combinations were used earlier by the researchers to formulate the transdermal patches. There is also the feasibility of transdermal delivery of glipizide. Glipizide (molecular weight 445.5 Da) showed favorable partition coefficient (log octanol/buffer: 0.28 ± 0.12) and negligible skin degradation. The present work was done to study the effect of different enhancers in different concentrations in the transdermal delivery of glipizide.

Experimental

Preparation of Patches:

Glipizide (B. P) was kindly donated from Sun Pharma, Span Industrial Complex, Dadra. Ethyl cellulose (N 22) was gifted from Pharma- Signet Chemical Corporation, Mumbai, India. Polyvinyl pyrrolidone (K-30) was obtained from SRL Pvt. Ltd., Mumbai, India. DBP was purchased from Qualigens Fine Chemicals, India. Oleic acid was purchased from Loba Chemical Pvt. Ltd., Mumbai, India and n-octanol was purchased from Burgoyne Burbidges, Bombay. L-menthol was kindly gifted by Hindusthan Aromatics Limited, Lucknow. All other chemicals used in the study were of analytical grade.

For preparation of the patches, 300 mg of EC was dissolved in 5 ml Chloroform followed by the addition of 100-200 mg PVP by stirring the total mass with a magnetic stirrer. Later 15 mg of the drug and the plasticizer DBP (30% of the total polymer weight) were added to the solution and stirred for 15 – 20 m. Then for different formulation, these three different chemical enhancers at different concentration were added and again stirred for 15 min. The total mass was slowly

poured into the center of SS rings having a backing layer of aluminum foil. The total mass was dried at room temperature for 48 h. The dried patches were taken in a plastic seal bag and stored in desiccators. The patch characteristics are presented in Table 1.

Evaluation Study and Results

The *in vitro* release studies were carried out in a modified Keshary-chien diffusion cell. A piece of matrix patch (circular, 2.5 cm diameter) was mounted carefully on the donor compartment. The donor compartment was empty and the backing membrane side of the matrix patch was open to the atmosphere while the receptor compartment was filled with freshly phosphate buffer saline pH 7.4. Outside the receptor compartment, water from a constant temperature bath flowed continuously through the jacket at 37±0.5°. The receptor liquid was slowly stirred by magnetic stirrer at 40-50 rpm. The temperature in the release/permeation area was maintained below 37°(at least a 3-4 ° temperature drop). The volume of the receptor liquid (53 ml) was such that the piece of the matrix patch (drug side) just touches the receptor liquid surface horizontally for molecular diffusion. Samples (2 ml) were withdrawn at different intervals and replaced immediately with the same volume of saline solution. Samples were analyzed spectrophotometrically at 276 nm after suitable dilution and average of 3 readings were recorded (Table 2).

The percent release from F1 patch was 49.87% after 8 h. The result was satisfactory. After addition of chemical enhancers the percentage release of drug has become less. The percentage of release from F2, F3, F4 formulations are 37.30%, 44.22% and 41.70% respectively. This happens probably due to the formation of bigger diameter conjugate with the drug, which results the slow movement of the conjugate through the capillary paths.

The percent release of the drug from F5 patch was 63.20%. After addition of these chemical enhancers, percentage release of the drug from patches has become less after 8 h. The percentage of release from F6, F7, F8 formulations are 38.16%, 46.1% and 42.17% respectively after 8 h.

Again the effect of enhancers over the release of glipizide through matrix patches was evaluated by addition of these enhancers. The percentage release of glipizide from F9 patch was 47.97% after 8 h.

The effects of L-menthol and oleic acid were slightly better at lowest concentrations. The percentage release from F10, F11 and F12 are 39.75%, 48.81% and 49.97% respectively. This is probably due to the higher amount of PVP (200 mg in place of 150 mg), which is hydrophilic in nature and so increases the diffusion velocity. At higher concentration of L-menthol and oleic acid, it is interesting to note that percentage release decreases to the values of 30.1%, 40.86%, 30.09% and 37.6% from F13, F14, F15, and F16 respectively. The data confirms the earlier assumption of the formation of molecular conjugates.

TABLE 1: PATCH CHARACTERISTICS

Patch composition EC: PVP: drug (mg): enhancer (%)	Formulation code	Drug content (mg/cm^2)
300 : 100 : 15 : 0	F1	0.548
300 : 100 : 15 : 1	F2	0.550
300 : 100 : 15 : 1	F3	0.549
300 : 100 : 15 : 1	F4	0.550
300 : 150 : 15 : 0	F5	0.551
300 : 150 : 15 : 1	F6	0.550
300 : 150 : 15 : 1	F7	0.549
300 : 150 : 15 : 1	F8	0.548
300 : 200 : 15 : 0	F9	0.550
300 : 200 : 15 : 1	F10	0.548
300 : 200 : 15 : 1	F11	0.548
300 : 200 : 15 : 1	F12	0.549
300 : 200 : 15 : 1.5	F13	0.550
300 : 200 : 15 : 1.5	F14	0.551
300 : 200 : 15 : 2	F15	0.550
300 : 200 : 15 : 2	F16	0.551

TABLE 2: PERCENTAGE RELEASE

Formulation code	Cumulative release (%)
F1	49.87% ± 0.010
F2	37.30% ± 0.009
F3	44.22% ± 0.011
F4	41.70% ± 0.008
F5	63.20% ± 0.012
F6	38.16% ± 0.009
F7	46.10% ± 0.007
F8	42.17% ± 0.011
F9	47.97% ± 0.009
F10	39.75% ± 0.009
F11	48.81% ± 0.008
F12	49.97% ± 0.099
F13	30.10% ± 0.058
F14	40.86% ± 0.024
F15	30.09% ± 0.035
F16	37.60% ± 0.015

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