

RESEARCH ARTICLE

FORMULATION AND EVALUATION OF MATRIX DIFFUSION CONTROLLED TRANSDERMAL DRUG DELIVERY SYSTEM OF GLIPIZIDE

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ABSTRACT:

There has been a tremendous increase in interest for transdermal drug delivery system for sustain release dosage form in chronic manageable diseased conditions like diabetes, hypertension etc to reduce the frequency of dosing. It reduces the risk of exposing the body to drug above maximum safe concentration in case of dosage form failure in comparison to oral sustained release drug delivery system. It also reduces the frequency of dosing and improves patient compliance. Transdermal patches of Glipizide were formulated to achieve sustain release pattern within the therapeutic range. HPMC 5cps, HPMC 15cps, HPMC K-100M, Ethyl cellulose (EC), Eudragit RS 100 (ERS-100) and Polyvinylpyrrolidone (PVP) K30 were used as matrix forming polymer. Propylene glycol was used as penetration enhancer. Polyethylene glycol (PEG) 400 and n-dibutyl phthalate (n-DB) were used as plasticizer. Methanol and chloroform were used as solvents. Patches were prepared by solvent casting method. Prepared patches were evaluated for physicochemical parameters like weight variation, thickness, folding endurance, drug content, % moisture absorption and % elongation break test. Patches prepared, from each batch, gave release profile for over 10 hours. Cumulative amount of drug release in 12 hours from all the prepared formulations were found to be in following order: F1 > F3 > F4 > F10 > F9 > F6 > F8 > F7 > F2 > F5 > F11 > F12. Prepared patch from HPMC 5 cps and ethyl cellulose (F1) exhibited good characteristics for sustained release action and other parameters evaluated.

Key-words: sustained release patches, Glipizide, transdermal patches, diabetes.

INTRODUCTION:

Diabetes mellitus is a chronic metabolic disorder characterised by high blood glucose level due to insulin deficiency. It is a major and still growing health problem worldwide. Glipizide is a second generation sulfonylurea used as oral hypoglycaemic agent. Glipizide (sulfonylureas) provoke release of insulin from pancreas by acting on sulfonylurea receptors on the pancreatic β cell membrane. Transdermal patches of glipizide offer an advantage of reduced dosing frequency, thus enhancing patient compliance. Drug delivery through skin bypasses hepatic first pass metabolism which cannot be bypassed in oral route. Glipizide is used in NIDDM and acts by increasing the release of endogeneous insulin and its peripheral effectiveness.¹² The present study was aimed at development of matrix diffusion controlled transdermal patches using different polymers and different penetration enhancers. Literature survey revealed that use of HPMC 5cps^{17, 18}, EC¹⁷ and PVP K 30¹⁸ as polymers forms matrix patches and gives release for more than 10 hours. Literature survey also revealed that use of PEG 400 as plasticizer produced films with high folding ndurance.¹⁸

MATERIALS AND METHODS:**Materials:**

Glipizide was received as a gift sample from Ronak Pharmaceuticals pvt Ltd., Patan. Eudragit RS 100 was received as a gift sample form Roehm Pharma polymers. HPMC 5 cps, HPMC 15 cps, PVP K 30, HPMC K 100M, Ethyl cellulose, Propylene glycol, PEG 400, n-dibutyl

phthalate, Methanol and Chloroform were purchased from Central Drug House (P) Ltd., New Delhi.

Method:^{7,11}

Preparation of patches: Matrix type transdermal patches loaded with Glipizide were prepared by solvent casting method. Required quantities of polymers were weighed and dissolved in 10 ml mixture of methanol and chloroform in the ratio 1:1. Sonicate for 30 min. Stir for 1 hour on a magnetic stirrer at 400rpm. 73.88 mg of drug was weighed and added to the above solution. Required quantity of PEG 400, n-DB (as plasticizers) and propylene glycol (as penetration enhancer) were measured and added to the above solution. Stir on a magnetic stirrer at 400 rpm for 2 hours. The resulted uniform solution was cast on a Petri dish of area 66.50 cm², previously containing a layer of mercury. An inverted funnel was placed over the Petri dish to prevent the fast evaporation of the solvent. After 24 hours, the dried patches were taken out, cut into pieces of 3cm * 3cm (area = 9 cm² and containing 10mg of the Glipizide) and stored in a desiccator.

EVALUATION:^{1,2,7,11}**1. Weight uniformity:**

The prepared patches are to be dried at 60°C for 4 hours before testing. Weight uniformity was done by weighing 5 different patches of each batch. All the patches, selected at random, should be uniform in size (3cm * 3cm). Calculate the average weight of three.

Table 1: Formulation for Glipizide transdermal patches

BATCH CODE	INGREDIENTS								
	HPMC 5 cps (mg)	HPMC 15 cps (mg)	HPMC K 100M (mg)	EC (mg)	PVP K30 (mg)	ERS 100 (mg)	PG (mg)	PEG 400 (ml)	n-DB (ml)
F1	460	-	-	840	-	-	208	0.3	0.3
F2	1070	-	-	-	230	-	208	0.3	0.3
F3	650	-	-	650	-	-	208	0.3	0.3
F4	500	-	-	800	-	-	208	0.6	-
F5	980	-	-	-	320	-	208	-	0.6
F6	-	460	-	840	-	-	208	0.2	0.4
F7	-	650	-	650	-	-	208	0.4	0.2
F8	-	500	-	800	-	-	208	0.1	0.5
F9	460	-	-	-	-	840	208	0.26	0.26
F10	650	-	-	-	-	650	208	0.26	0.26
F11	-	-	650	650	-	-	208	0.3	0.3
F12	-	-	450	850	-	-	208	0.2	0.4

2. Thickness of the patch:

The thickness of the patch is measured by digital micrometer at different points. For each formulation, three patches were used. The average value for the thickness of single patch was determined.

3. Folding endurance:

A strip of specific area (3cm * 3cm) is to be cut evenly and repeatedly folded at the same place till it broke. The number of times the film could be folded without breaking gave the value of folding endurance.

4. Percentage moisture content:

Three patches of the same composition were weighed and kept on desiccators containing fused calcium chloride at 37°C until no change in weight of the individual patches was observed. This weight was noted as the final weight. The percentage moisture content was calculated as a difference between individual and final weight. An average is shown in table-2.

5. Moisture uptake:

To determine the moisture uptake of the patches, three weighed patches of the same batch (kept in desiccator at 37°C until constant weight) were exposed to two different relative humidity conditions: 75% RH (saturated solution of sodium chloride) and 93% RH (saturated solution of ammonium hydrogen phosphate) respectively at room temperature. After 24 hours, the films were re-weighed and percentage moisture uptake was determined from the below mentioned formula:

$$\% \text{ moisture content} = \frac{\text{initial weight} - \text{final weight}}{\text{final weight}} * 100$$

6. Percentage elongation break test:

Percentage elongation is determined by measuring the length just before the breaking point. The percentage elongation can be determined from the below mentioned formula:

$$\% \text{ elongation} = \frac{L1 - L2}{L2} * 100$$

Where;

L1 = final length of each strip.

L2 = initial length of each strip.

7. Drug content:

The film of 2 cm² was cut into small pieces and taken into 100ml volumetric flask containing 20ml methanol. This methanolic solution was diluted with phosphate buffer pH 7.4 up to 100ml. the solution was filtered through whatmann filter paper and the drug content was determined on UV spectrophotometer at λ_{max} 275nm after suitable dilutions.

8. In-vitro drug release studies:

The in-vitro drug release studies were carried out in a Franz diffusion cell. The cellulose acetate membrane (pore size = 0.45 μ m) was mounted between donor and the receptor compartment of the diffusion cell. The transdermal film was placed on the cellulose acetate membrane and covered with aluminum foil. The receptor compartment was filled with freshly prepared phosphate buffer pH 7.4 (55ml). The whole assembly was fixed on a magnetic stirrer with hot plate apparatus. The solution in receptor compartment was stirred at 35-45 rpm and temperature was maintained at 32 \pm 0.5°C. Sample (3ml) was withdrawn at different interval and replaced with the same volume of the phosphate buffer pH7.4. Samples were analyzed spectrophotometrically at 275nm.

9. Skin irritation study for F1:

Skin irritation testing can be performed on the healthy Albino rabbits weighing between 1.2-2.5 kg. Remove the hair from the dorsal surface and clean the dorsal surface using rectified spirit. Aqueous solution of formalin 0.8% was used as a standard irritant. Prepared transdermal patches of area 15 cm² were used as test patches. 0.8% of formalin solution was applied in the right dorsal surface of each rabbits whereas test patches were applied on the left dorsal surface. The patches were removed after 24 hours and skin was examined.

Table 2: Physicochemical evaluation parameters

Batch Code	PARAMETERS				
	Weight Variation (Mean (mg) ± SD)	Thickness (Mean (mm)± SD)	Moisture CONTENT (Weight %)	Water Absorption (Weight %)	
				75% RH	93% RH
F1	365 ± 2.06	0.15 ± 0.021	1.12	1.79	2.09
F2	364 ± 4.02	0.14 ± 0.029	1.13	1.81	2.32
F3	358 ± 3012	0.20 ± 0.031	1.18	2.02	2.82
F4	354 ± 3.41	0.17 ± 0.020	1.14	2.55	2.73
F5	357 ± 5.11	0.15 ± 0.015	1.18	3.01	3.45
F6	359 ± 3.91	0.19 ± 0.018	1.23	3.52	3.79
F7	351 ± 2.98	0.16 ± 0.040	1.14	1.92	2.18
F8	361 ± 5.03	0.18 ± 0.025	1.18	3.30	3.64
F9	367 ± 4.08	0.15 ± 0.013	1.19	3.39	3.65
F10	362 ± 5.09	0.19 ± 0.025	1.20	3.42	3.71
F11	342 ± 3.58	0.20 ± 0.023	1.23	3.68	3.89
F12	341 ± 3.59	0.18 ± 0.019	1.25	3.78	3.97

Table 3: Evaluation parameters

BATCH CODES	PARAMETERS			
	FOLDING ENDURANCE	% Elongation break test	% drug content	% cumulative drug release
F1	210 ± 5.2	40.2 ± 0.012	99.38 ± 4.02	55.87 ± 0.009
F2	212 ± 3.2	41.8 ± 0.014	97.02 ± 3.32	40.37 ± 0.010
F3	200 ± 7.3	39.7 ± 0.012	99.02 ± 5.22	51.14 ± 0.044
F4	198 ± 3.9	35.8 ± 0.016	96.91 ± 4.13	49.38 ± 0.097
F5	215 ± 5.5	41.9 ± 0.011	98.83 ± 5.91	38.31 ± 0.021
F6	210 ± 7.6	36.2 ± 0.017	96.79 ± 3.51	45.16 ± 0.014
F7	204 ± 7.1	32.1 ± 0.13	97.18 ± 2.99	42.58 ± 0.029
F8	211 ± 3.8	31.3 ± 0.15	98.23 ± 3.12	43.31 ± 0.032
F9	217 ± 4.1	42.1 ± 0.11	99.17 ± 4.72	45.31 ± 0.029
F10	214 ± 7.7	40.3 ± 0.19	99.03 ± 4.18	46.43 ± 0.078
F11	208 ± 4.3	33.2 ± 0.13	98.02 ± 5.02	31.46 ± 0.096
F12	212 ± 5.3	34.09 ± 0.14	98.09 ± 6.01	30.59 ± 0.057

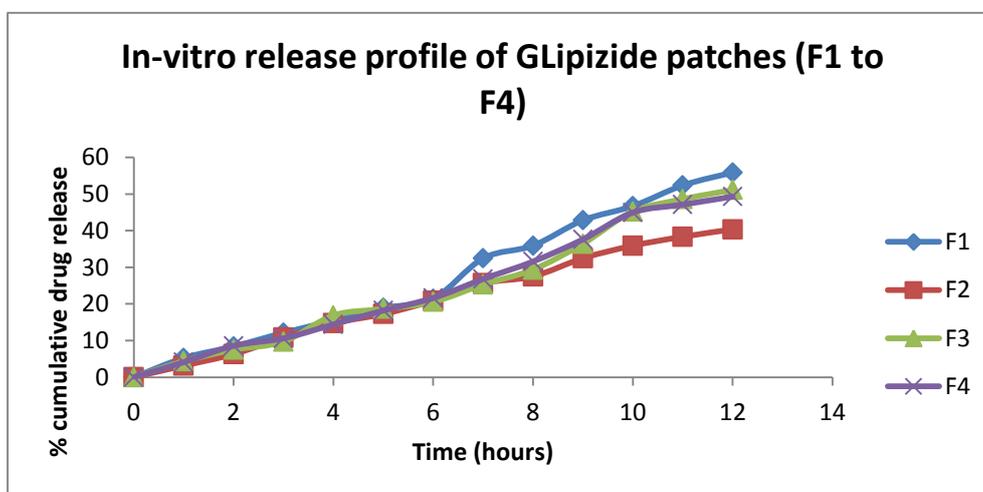


Figure 1: In vitro release profile of Glipizide patches (F1 to F4):

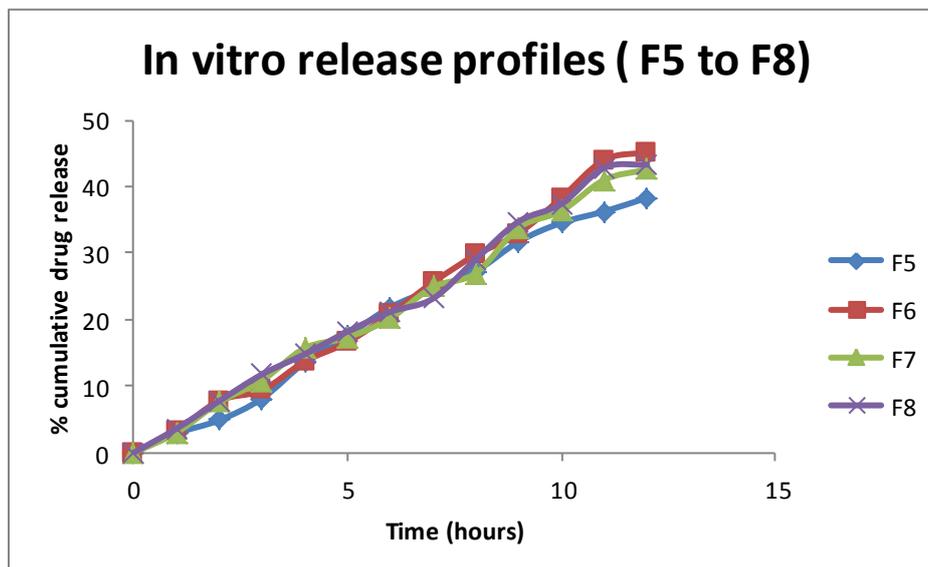


Figure 2: in vitro release profiles (F5 to F8)

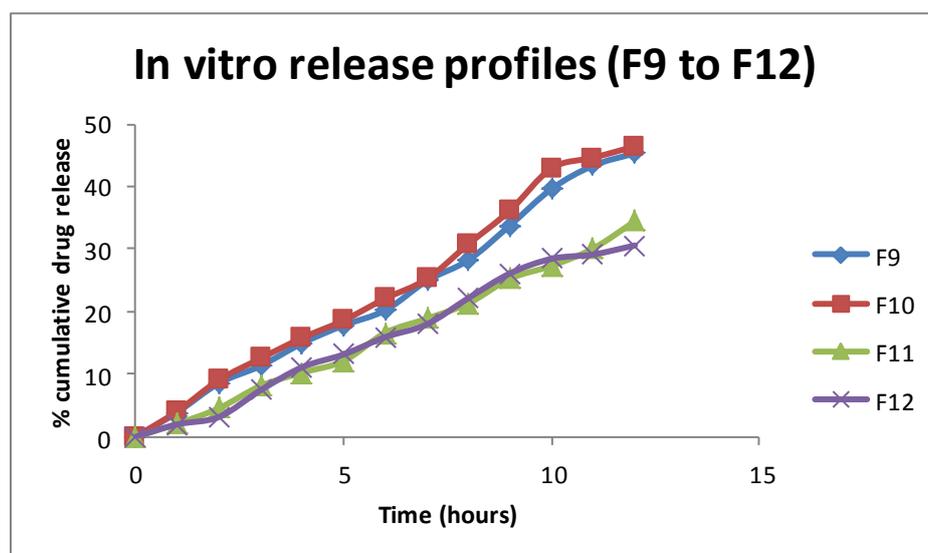


Figure 3: In vitro release profiles (F9 to F12)

RESULTS AND DISCUSSION:

Transdermal patches of Glipizide were prepared by solvent evaporation method in a Petri-dish on a mercury platform with an inverted funnel to control the rate of evaporation of the solvent. Different formulation (as shown in table 1) containing Glipizide were prepared to achieve the sustain release pattern within the therapeutic range.

3.1 Investigation of drug-polymer compatibility:

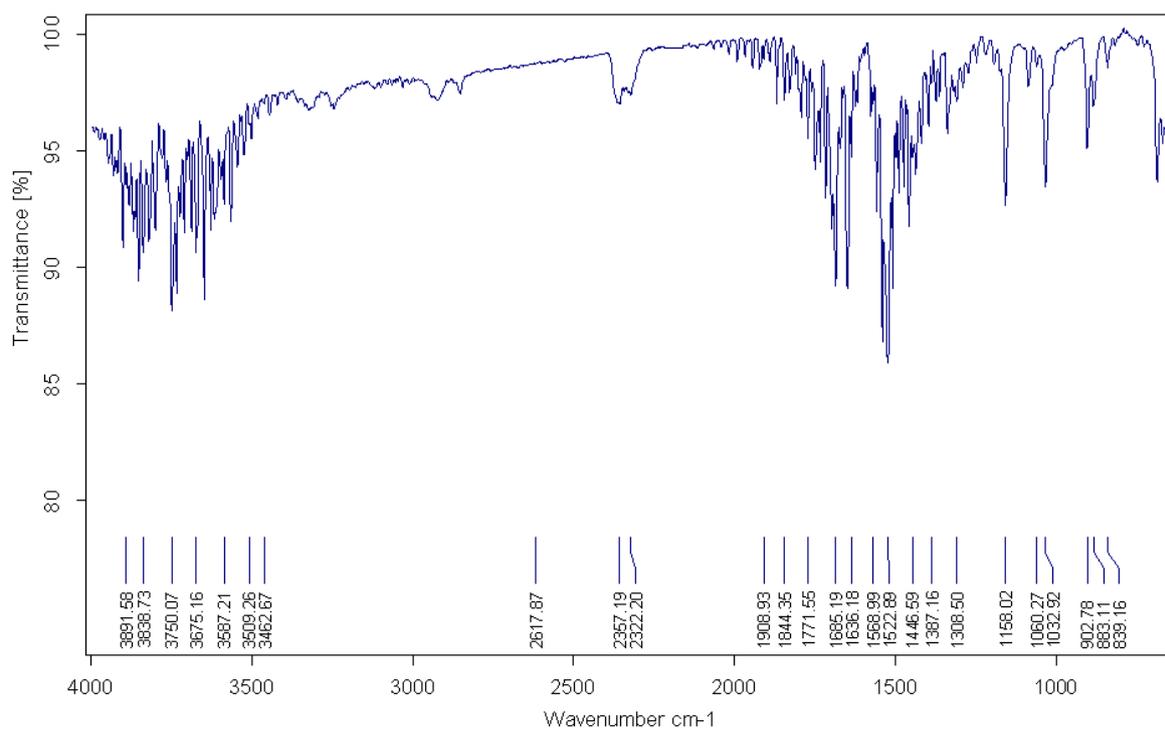
Drug - polymer compatibility was checked by comparing the IR spectra of formulations with that of the pure drug. No significant changes in the functional groups between the two spectra were observed. This ensured the compatibility of polymer with that of the drug.

3.2 Transparency:

Patches prepared from HPMC-PVP had maximum transparency, followed by HPMC-EC and HPMC -ERS.

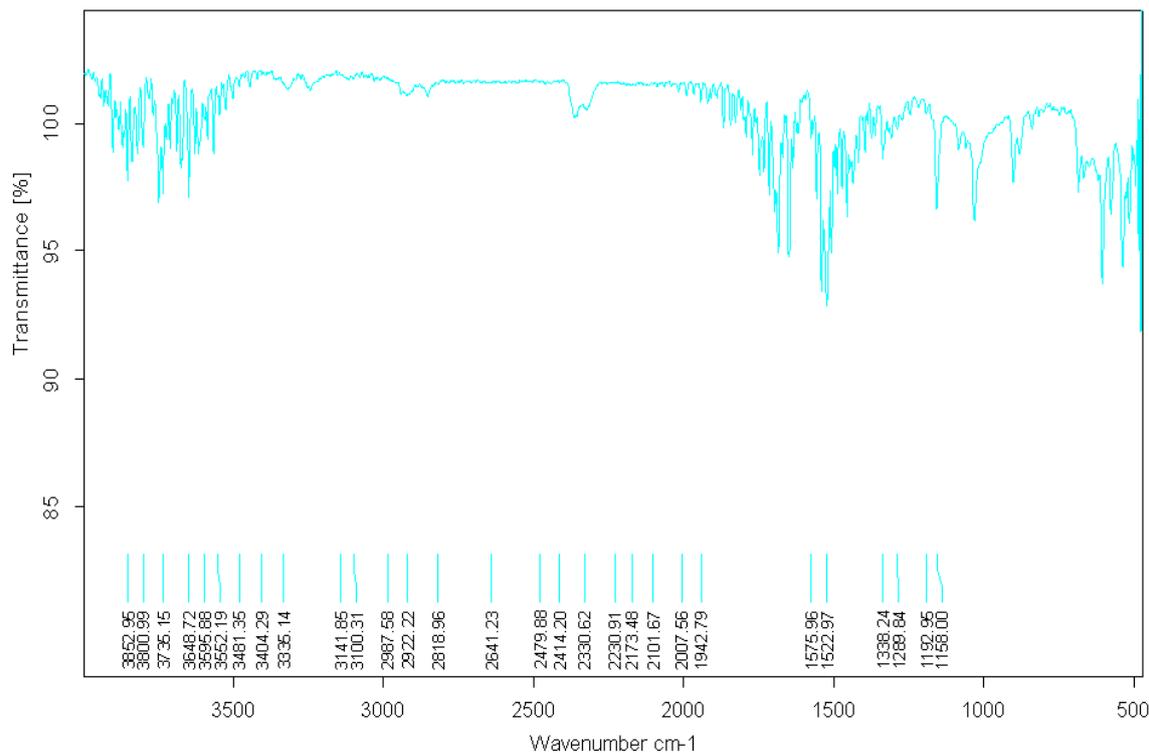
3.3 Physicochemical evaluation of transdermal patches:

The results of the physicochemical evaluation of the transdermal patches are described in table 2 and table 3. The weight variation of all the formulations varied in between 351 ± 2.98 and 365 ± 2.06 . The variation in the thickness of all the formulation was in the range 0.14 ± 0.029 to 0.20 ± 0.031 . Moisture content of these patches was found to vary from 1.12 to 1.25. Water absorption at 75%RH and 93%RH was observed from 1.79 to 3.78 and 2.09 to 3.97 respectively. This difference in the moisture content and water absorption was may be due to the difference in hydrophilicity of the polymers and extent of solvent evaporation during formulation. Folding endurance was found to be in between 180 ± 7.7 and 217 ± 4.1 . The % elongation break test was found to be from 31.3 ± 0.15 to 42.1 ± 0.11 . Folding endurance and % elongation break test was found maximum in formulation containing Eudragit RS 100 and PVP K 30 as polymers. The % drug content and % cumulative drug release was found maximum in formulation F1 (batch code).



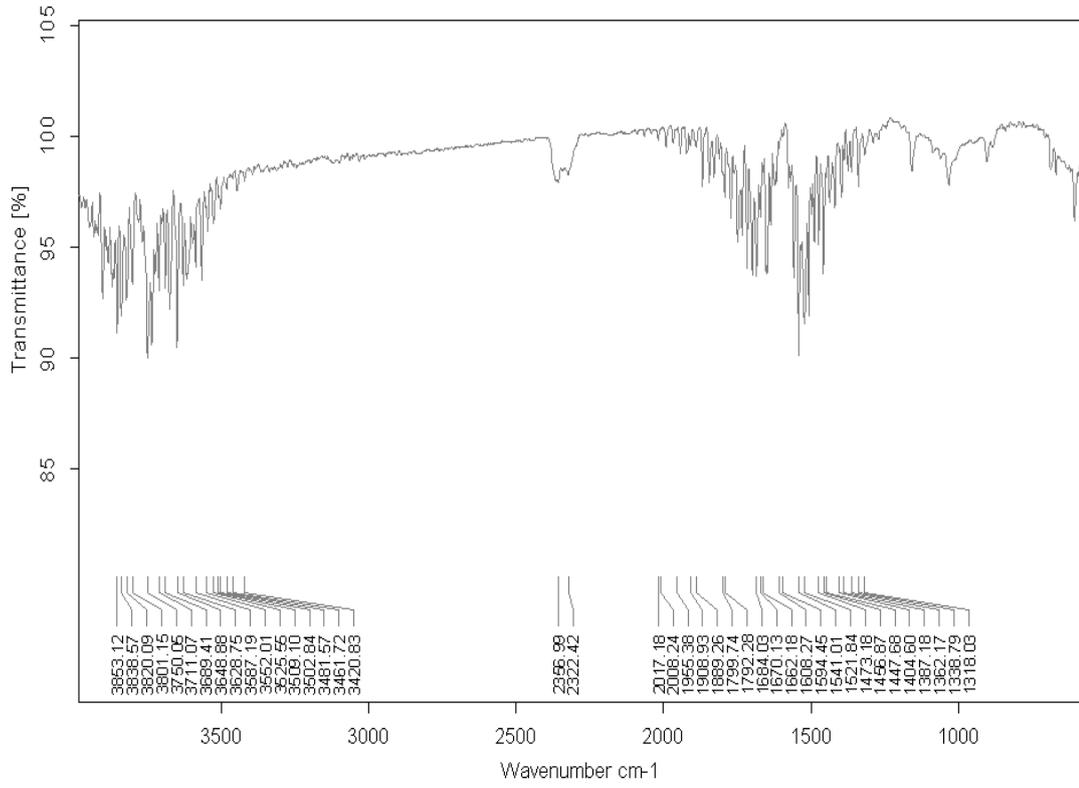
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Figure 4: IR spectra of Glipizide



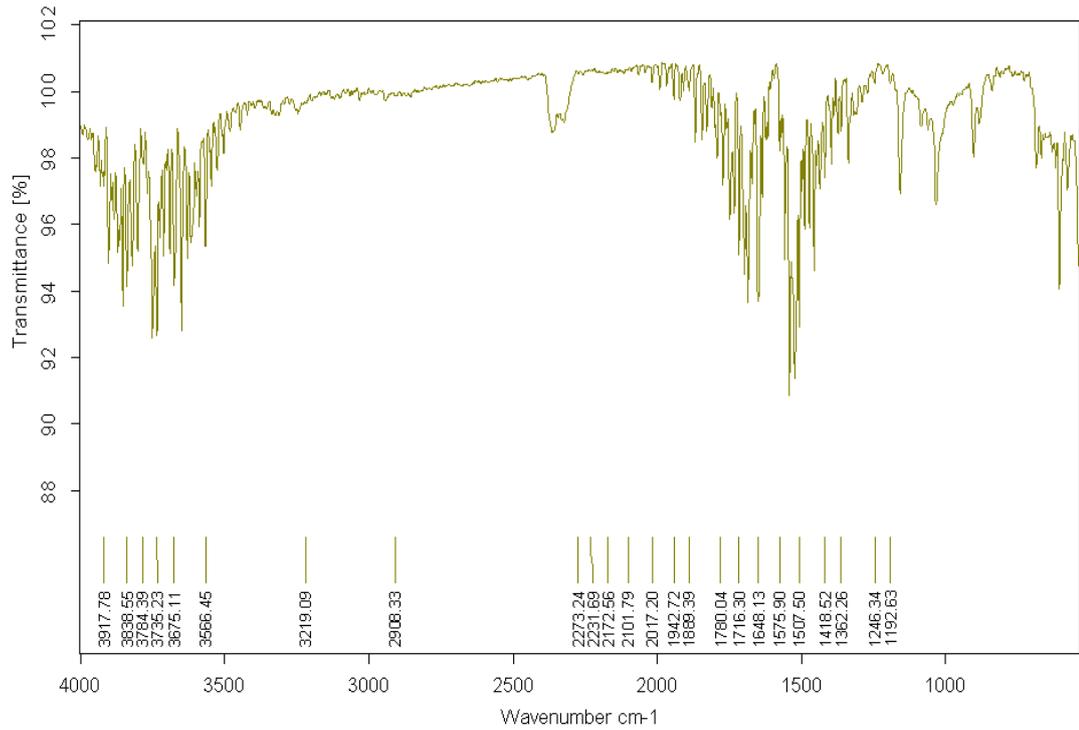
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Figure 5: IR spectra of mixture of Glipizide, HPMC 5 cps and Ethyl cellulose



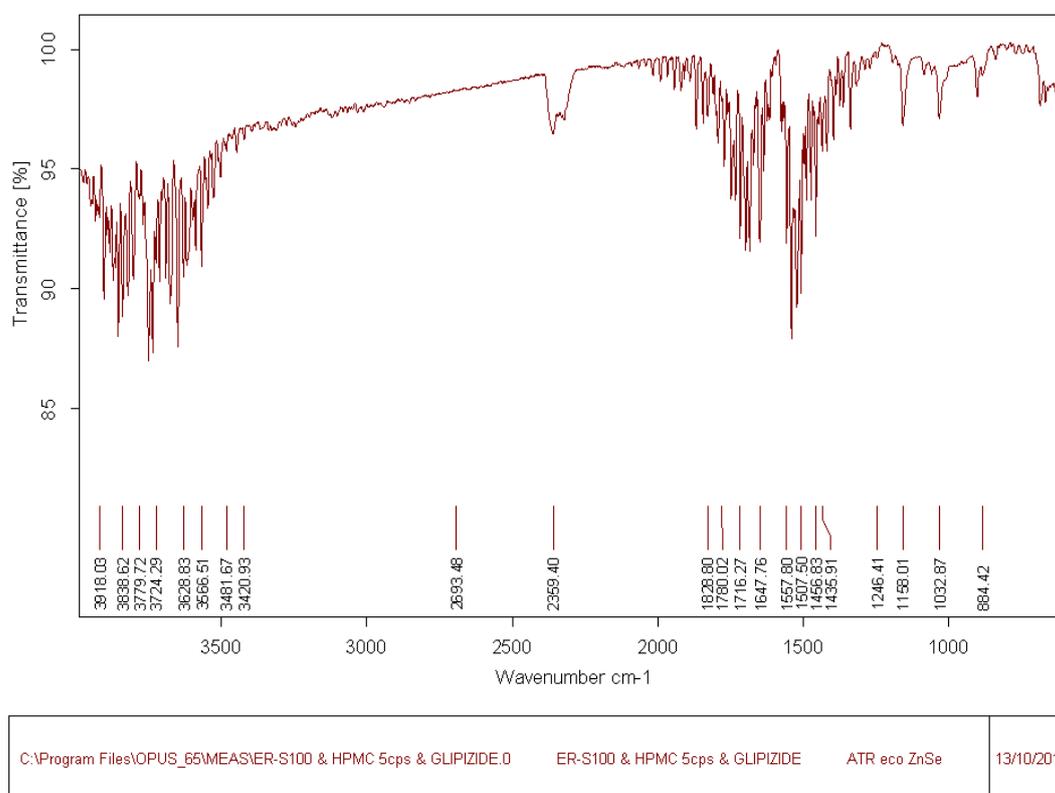
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Figure 6: IR spectra of mixture of Glipizide, HPMC 5 cps and PVP K 30



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Figure 7: IR spectra of mixture of Glipizide, HPMC K 100 and Ethyl cellulose



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Figure 8: IR spectra of mixture of Glipizide, HPMC 5 cps and Eudragit RS 100

3.4 *In-vitro* release studies:

In-vitro release studies for all the prepared patches were carried out for 12 hours. % cumulative drug release after 12 hours was taken and compared for all the patches. F1 exhibited maximum drug release at the end of 12th hour. Results are as shown in the table.

3.5 Skin irritation study:

Based on physicochemical evaluation and *in-vitro* release rate studies, F1 was selected for skin irritation test. Skin irritation test was performed on albino rabbits. No signs of erythema or redness were observed for 24 hours after the application of the patch.

DISCUSSION:

IR studies revealed that the drug and polymer were compatible with each other. Of all the batches prepared and evaluated, F1 showed promising results. It was concluded

that HPMC 5 cps and ethyl cellulose are useful in formulating sustained release patches. Moreover, patches prepared from HPMC 5cps and EC (batch code = F1) exhibited better *in-vitro* drug release-time profile. Also, amongst the two plasticizers used alone and in various combinations, batch F9, F5 and F1 produced patches that exhibited high folding endurance and good manageable characteristics. Detailed investigations on *in-vivo* studies needs to be carried out and an *in vivo- in vitro* correlation need to be established to ensure the efficiency and bioavailability of the formulation.

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