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FORMULATION AND EVALUATION OF GLIBENCLAMIDE TRANSDERMAL PATCHES BY USING NATURAL POLYMERS

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ABSTRACT

The objective of present study was to develop matrix type transdermal therapeutic systems of Glibenclamide using natural polymers. Results revealed that prepared patches showed good physical characteristics, no drug-polymer interaction. The in vitro release study revealed that F1 formulation showed maximum release in 8hrs. Formulation F1 was subjected for accelerated stability studies. The F1 formulation was found to be stable as there was no drastic change in the Physico-chemical properties of the patches, which was also confirmed by FTIR. Thus conclusion can be made that stable transdermal patches of Glibenclamide has been developed. The release of Glibenclamide appears to be dependent on lipophilicity of the matrix. Moderately lipophillic matrices showed best release. The predominant release mechanism of drug through the fabricated matrices was believed to be by diffusion mechanism. Based upon the in vitro dissolution data the F1 formulation was concluded as optimized formulation.

KEY WORDS: Glibenclamide, sodium alginate, chitosan, tragacanth, solvent casting technique, drug release studies.

1. INTRODUCTION

Transdermal delivery represents an attractive alternative to oral delivery of drugs these therapeutic systems are defined as ‘self-contained, discrete dosage forms which, when applied to the intact skin, deliver the drug(s), through the skin, at a controlled rate to the systemic circulation. Thus it is anticipated that transdermal drug delivery system can be designed to deliver drug at appropriate rates to maintain suitable plasma drug levels for the

therapeutic efficacy by using skin as the port of entry of drugs.[1,2] The transdermal drug delivery system has potential advantages of avoiding hepatic first pass metabolism, maintaining constant blood level for longer period of time resulting in a reduction of dosing frequency, improved bioavailability, decreased gastrointestinal irritation that occur due to local contact with gastric mucosa and improved patient compliance.[3,4,5] Glibenclamide is a potent oral sulfonylurea hypoglycemic agent. It is currently available for treating hyperglycemia in Non insulin dependent Diabetes Mellitus(NIDDM-type-2). The drug inhibiting ATP sensitive K+ chennels in pancreatic beta cells. This inhibition caused cell membrane depolarisation, opening of voltage dependant Calcium channels thus triggering. It is highly accepted that membrane controlled transdermal systems have the distinct advantage that the drug release rate, which is regulated by permeation through the rate controlling membrane, remain relatively constant as long as drug loading in the reservior is maintained at high level. Hence, the proposed work involves the development and evaluation of transdermal drug delivery systems containing Glibenclamide.[6,7,8]

2. MATERIAL AND METHODS

MATERIAL

Glibenclamide was collected as a gift sample from Reddy's laboratories, Hyderabad and Tragacanth, sodium alginate and chitosan were purchased from AR chemicals, Hyderabed.

METHODODOLOGY[9,10]

Drug excipient compatibility studies

Drug excipients compatibility studies were performed to know the compatibility of excipient with drug at accelerated conditions. The study was conducted by preparing homogenous mixture of excipients with drug and filled in HDPE bags and LDPE bags. Glass vials were exposed to 600 C and 400C/75 %RH for 4 weeks and LDPE bags were exposed to 400C±75 %RH for 4 weeks. Samples were observed periodically for any physical change.

Formulation design

Preparation of transdermal patches

Transdermal patches containing Glibenclamide were prepared by the solvent evaporation technique. The drug Glibenclamide was dissolved insuitable solvent. Polymers chitosan, tragacanth and sodium alginate were taken. These polymeric solution kept under magnetic stirrer after 1 hr get viscous solution. After that drug add into the polymeric solution. Sufficient care was taken to prevent the formation of lumps. Polyethylene glycol was taken as

a plasticizer and permeation enhancer like DMSO, and added to the mixture and mixed well. It was set aside for 2 hours to exclude any entrapped air and was then transferred into a previously cleaned petriplate (40cm^2), drying of patches was carried out in vacuum oven at room temperature. Dried patches were packed in aluminium foil and stored in a desiccator for further evaluation.

Table-1: Formulation Design of Glibenclamide Transdermal Patches.

S. No	Formulation code	Ingredients			
		Drug (mg)	Chitosan	Tragacanth	Sodium alginate
1	F1	100	1000	-	-
2	F2	100	-	1000	-
3	F3	100	-	-	1000
4	F4	100	500	-	500

Fig-1: Glibenclamide transdermal patch.

Evaluation of transdermal formulation[11,12,13]

Physical appearance

All the prepared transdermal films were observed for color, clarity, flexibility, and smoothness.

Folding endurance

Folding endurance of the patches was determined by repeatedly folding at the same place till it broke. The number of times the patch could be folded at the same place without breaking is the folding endurance. This was repeated on all the patches for three 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 to be dried at 60^0C for 4hrs before testing. A specified area of 4.52 cm^2 of patch is to be cut in different parts of the patch and weigh in digital balance. The average weight and standard deviation values are to be calculated from the individual weights.

Drug content

The formulated transdermal films were assayed for drug content in each case. Three patches from each formulation were assayed for content of drug. Each formulation was casted in triplicate and one film from each was taken and assayed for content of drug. The transdermal films (4.52 cm^2) were added to conical flask containing 100 ml of phosphate buffer pH 7.4. This was then stirred with magnetic bead at 400 rpm for 2 hrs. The contents were filtered and the filtrate was analyzed spectrophotometrically for drug content at nm. Similarly a blank was prepared from trans dermal films without drug.

Moisture absorption studies

The films were weighed accurately and placed 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.

$$\text{Perentage moisture uptake} = \frac{\text{Final weight} - \text{Initial weight}}{\text{Initial weight}} \times 100$$

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* release study**

The *in-vitro* study of drug permeation through the Dialysis membrane was performed using a modified Franz type glass diffusion cell. The modified cell having higher capacity is (10 ml) is used to maintain sink condition. The samples were analyzed for drug content spectrophotometrically at 256 nm. The receptor phase was replenished with an equal volume of phosphate buffer at each sample withdrawal.

Percentage of drug release was determined using the following formula.

$$\text{Perentage drug release} = \frac{\text{Da}}{\text{Dt}} \times 100$$

Where, Dt = Total amount of the drug in the patch

Da = The amount of drug released

Stability studies

Optimized medicated films were subjected to short term stability testing. The transdermal films were sealed in aluminium foils and kept in a humidity chamber maintained at 40 ± 2 ^{0}C and 75 ± 5% RH for 30 days as per ICH guidelines. Changes in the appearance and drug content of the stored films were investigated after storage at the end of every week.

3. RESULTS

Drug –excipient compatibility studies

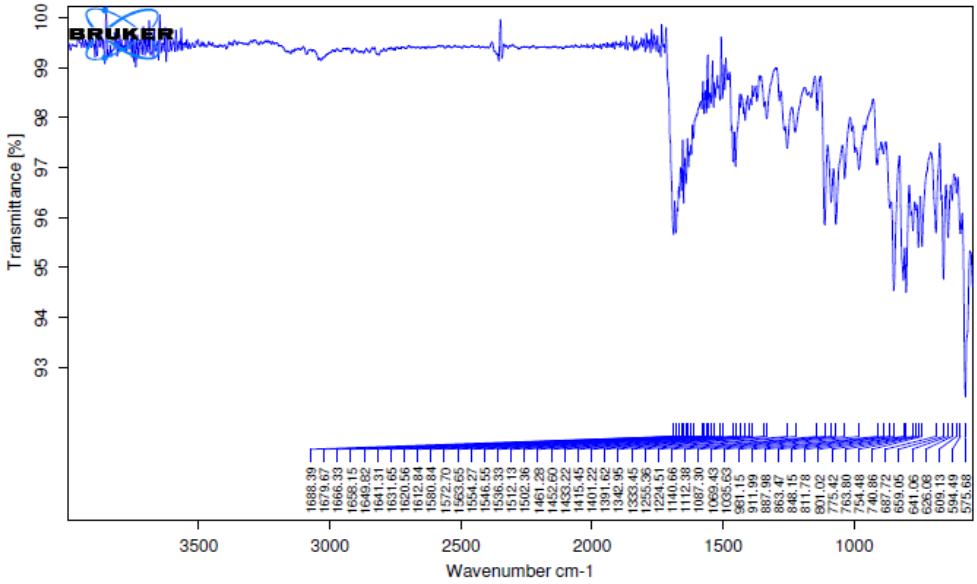

Fig-2: FTIR Studies of Pure drug (Glibenclamide).

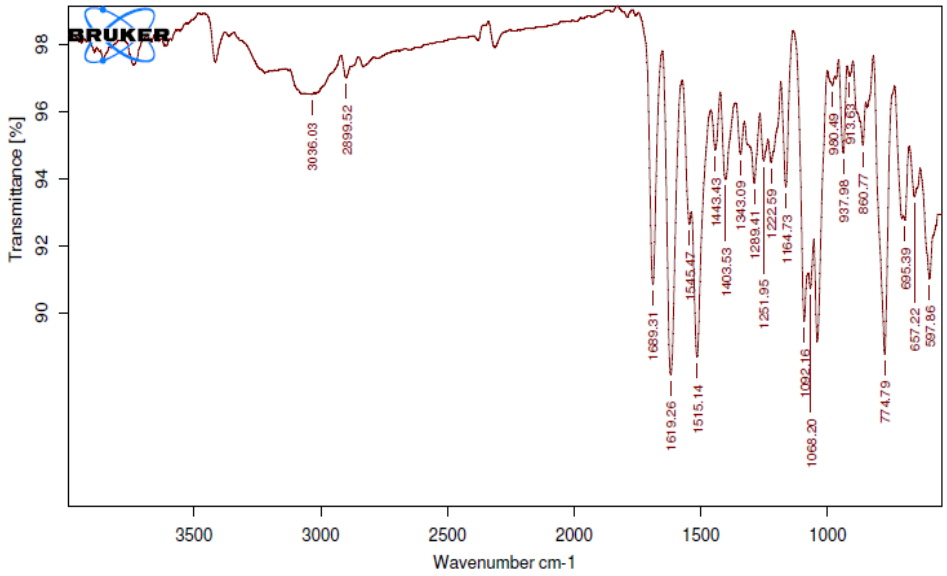

Fig-3: FTIR spectra Optimised formula.

Evaluation of Transdermal formulation[11]

Physical appearance

The prepared patches were found to be uniform, smooth, flexible and homogenous.

Folding endurance

The folding endurance numbers of all the Glibenclamide patches are 226 – 290. The folding endurance number gives the mechanical property of the patches, high folding endurance number indicate that has high mechanical property. The folding endurance number was increased with increasing the HPMC content. These results indicated that the patches would not break and maintain their integrity with general skin folding when applied.

Thickness of the film

Thickness was changed from batch to batch in individual strips of medicated patch carry uniform thickness, which indicates that total medicated patch carry uniform thickness.

Weight uniformity

The mean weights of all the prepared patches. The weights are in the range of 232– 541. The F3 formulation patches showed maximum weight.

Drug content

The drug content analysis of the prepared formulations have shown that the process employed to prepare the patches was capable of giving uniform drug content with minimum

batch variability. All the patches were found to have drug content in the range of 94.54 – 98.96%. So the method employed i.e. solvent evaporation method is satisfactory for the preparation of Glibenclamide transdermal patches.

Table-2: Physicochemical evaluation of Glibenclamide patches.

Formulation code	Weight (mg)	Thickness (µm)	Folding endurance	Drug content (%)
F1	233	200	226	98.96
F2	237	213	290	96.35
F3	232	214	288	95.26
F4	241	219	231	94.54

Table-3: Physicochemical evaluation of Glibenclamide patches.

Formulation code	Moisture loss	Moisture Absorption
F1	5.554	7.865
F2	5.344	7.956
F3	5.264	8.264
F4	5.745	8.315

***In vitro* release study**

Phosphate buffer pH 7.4 was used as medium for the release studies. The drug release profiles of Glibenclamide patches containing different ratios of polymers tragacanth, chitosan and sodium alginate. It was cleared from the release profiles of formulations, that the drug release was governed by polymer nature and content. The formulations F1, F2, F3 and F4 showed the maximum release when comparing with other formulations due to the high concentration of chitosan polymer. The release was decreased as the concentration of hydrophobic polymer increase.

Table-4: *In vitro* drug release profiles of Glibenclamide transdermal patch (F1-F6).

Time (hrs)	% Cumulative drug released			
	F1	F2	F3	F4
0	0	0	0	0
1	23.45	21.24	20.89	24.24
2	35.29	34.52	31.28	30.19
3	43.26	40.29	41.22	42.17
4	52.98	51.26	50.27	53.16
5	63.59	62.29	61.20	60.28
6	72.54	71.22	70.19	73.45
7	81.49	79.32	78.45	80.46
8	96.35	92.44	93.18	94.15

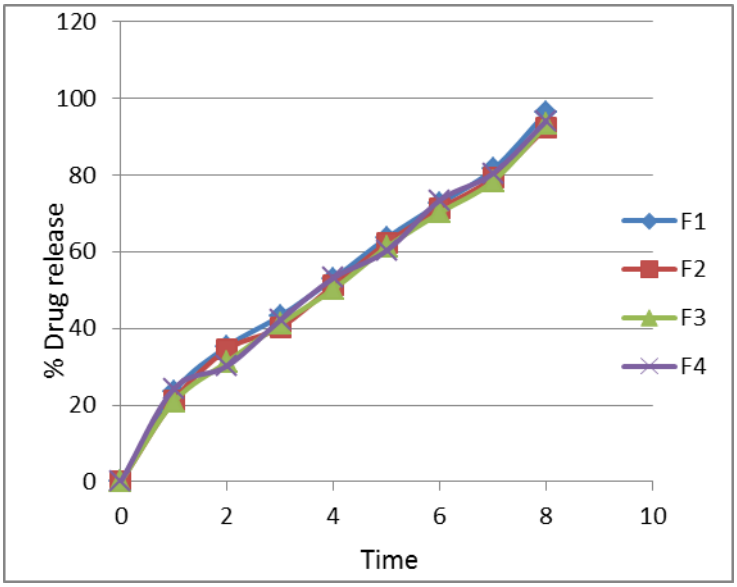

Fig-4: Drug release formulations.

Stability studies

Optimized formulations F1 was selected for accelerated stability studies as per ICH guidelines. The patches were observed for color, appearance and flexibility for a period of three months. The folding endurance, weight, drug content, % cumulative drug release of the formulation was found to be decreasing. This decrease may be attributed to the harsh environment (40^0C) maintained during the studies.

Table-5: Stability studies of optimized formulations at 40 ± 2 ^{0}C and 75 ± 5% RH for 30 days.

Time in days	Drug content (%)	Physical appearance	% Cumulative drug release
0	98.96	No change in color	96.35
30	98.82	Slight yellowish color	96.32

4. CONCLUSION

Results revealed that prepared patches showed good physical characteristics, no drug-polymer interaction and no skin irritation was observed. The F3 formulation was found to be stable as there was no drastic change in the Physico-chemical properties of the patches, which was also confirmed by FTIR. Thus conclusion can be made that stable transdermal patches of Glibenclamide has been developed. F1, F2, F3, F4 formulations showed highest cumulative percentage drug release of 96.35 %, 92.44%, 93.18% and 94.15% were obtained during *in vitro* drug release studies after 8 hrs. The release of Glibenclamide appears to be dependent

on lipophilicity of the matrix. Moderately lipophillic matrices showed best release. The predominant release mechanism of drug through the fabricated matrices was believed to be by diffusion mechanism. Based upon the *in vitro* dissolution data the F1 formulation was concluded as optimized formulation.

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