Original Article

Formulation Development and Evaluation of Transdermal Patches of Miglitol

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Abstract

Transdermal patches are placed on the surface of the skin, which is a polymeric preparation; it delivers the medication at a controlled rate through the dermal layer to produce an active systemic effect. Miglitol transdermal patches were designed with the following primary objectives: better absorption, more consistent plasma drug concentration, enhanced bioavailability, minimal side effects, quick and ease of application, and the advantage to prevent drug release into the body by simply peeling the patch from the skin. Polyethylene glycol 400 serves as a plasticizer with dimethyl sulfoxide (DMSO) which improves the permeation rate. Six formulations (F1-F6) of miglitol transdermal patches were formulated with three different polymers: HPMC, PVP K30 and Eudragit L100 with three different ratios of drug and polymer. The solvent casting method was performed to formulate the patch, which was evaluated for its drug concentration, folding endurance, flatness, moisture absorption, tensile strength and SEM evaluation. The in-vitro drug release profile studies were conducted in pH 5.5 buffer using a Franz Diffusion cell under sink conditions, after which the drug was analyzed spectrophotometrically at 232 nm. The preparation F1 possessed maximum drug release, which showed that miglitol can be formulated as a transdermal formulation in providing effective treatment for diabetes with enhanced patient compliance.

Keywords: Miglitol, HPMC, PEG-400, Eudragit L100, PVP K30, Transdermal patches.

INTRODUCTION

Transdermal drug delivery formulations have made a clear impression in the new era of pharmaceutical dosage forms. It has proven as one of the successful drug delivery systems in the category of novel drug delivery systems. Understanding these innovative new drug delivery methods requires a solid understanding of physiology and the fundamentals of new technology [1]. Since the 1800s, there has been extensive use in the transdermal route.

Transdermal medication delivery has become one of the pharmaceutical industry's fast-growing areas as a result of the quick rise in its market value [2]. There is a lot of potential in using the dermal layer as a drug administration site for both systemic and local effects. The skin is a very effective barrier to medication penetration; hence enhanced techniques are frequently required.

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Additionally, topical use minimizes drug systemic inactivation, reduces gastrointestinal incompatibility and severe toxicological risk. When transdermal patches are applied to the skin, polymeric preparations distribute the medication across the dermis by a predefined amount to produce a generalized systemic effect [3]. They gained popularity as a result of their distinctive advantages. Transdermal drug delivery systems provide the superiority of prevention of drug administration by easily detaching the patch from the skin, as well as the potential benefits of superior absorption, higher controlled plasma levels, enhanced bioavailability, decreased adverse effects and easy application [4].

MATERIALS

Miglitol was obtained from Sigma Aldrich Chemicals Pvt. Ltd, Bangalore. Chloroform, Di-Sodium hydrogen phosphate and Potassium dihydro-orthophosphate were procured from the Sisco research lab, India. DMSO, PVP, PEG400, PEG400, and HPMC were procured from Sisco research laboratories, India. EudragitL100 was purchased from Sigma Aldrich, India. All other reagents employed in this study were of analytical grade.

METHODS

Calibration Curve of Miglitol

The pure drug form of Miglitol (100 mg) was taken and initially dissolved in a required quantity of methanol, and then the volume was adjusted to 100 ml with phosphate buffer pH 5.5 solutions. A 100g/ml stock solution was made and subsequent dilutions were made to get 10, 20, 30, 40, and 50µg/ml. The solution's absorbance was found at 232 nm by using pH 5.5 phosphate buffer as a blank [5].

Differential Scanning Calorimetry (DSC technique)

Differential Scanning Calorimetry studies for miglitol, excipients and combinations of miglitol with excipients were carried out using Shimadzu DSC-60. In this study, miglitol was mixed with the excipient used in the formulation and a thermal analysis of each sample was carried out. Throughout the experiment, the temperature ranged from 25 to 400oC, with the rate of heating at 10oC/min and the flow rate of nitrogen at 30 ml/min was maintained. Then the samples were taken in an aluminum pan, sealed, and then the thermogram was recorded [5].

FORMULATION OF MIGLITOL TDDS

Three different polymers, HPMC, PVP K30 and Eudragit L100 were used to design six distinct transdermal patch formulations in three different drug-to-polymer ratios (F1–F6). The patches were made by solvent casting technique. The casting solution was formulated by dissolving different polymers (HPMC, PVP K30, and Eudragit L100) in suitable solvents (i.e., methanol and chloroform) using a magnetic stirrer (Remi, India) for 15 minutes to get a uniform dispersion. The drug was added at a slow rate to the solution and then the plasticizer (PEG 400) 36% and permeation enhancer (DMSO) 12% were added to the polymeric solution and then dissolved by continuous stirring for a period of 30 minutes, initially at a lower speed and then subsequently at a greater speed. The drug polymeric solution was introduced into a petridish and dried for 12 hours at 40–50°C with air circulation. In order to prevent the solvent from quick evaporation, an inverted funnel was positioned over the mold. By placing a sharp blade along the film's edges, the films were removed. The dried films were sealed in aluminum foil and kept in a dark and cool environment [6].

Table 1. Formula for Miglitol TDDS by Solvent Casting method

S.No.	Ingredients	Formulations of Miglitol TDDS					
		F1	F2	F3	F4	F5	F6
1	Miglitol (mg)	75	75	75	75	75	75
2	HPMC (mg)	300	450	-	-	-	-
3	PVP K30 (mg)	-	-	300	450	-	-
4	Eudragit L100 (mg)	-	-	-	-	300	450
5	PEG 400 (%)	36	36	36	36	36	36
6	DMSO (%)	12	12	12	12	12	12
7	Chloroform: Methanol	1:1	1:1	1:1	1:1	1:1	1:1

EVALUATION OF TRANSDERMAL PATCHES

Drug content determination

A precisely weighed part of the film (21 cm) that has been dissolved in 100 ml of the drug's soluble methanol is used to determine the amount of miglitol present in the sample. The sample solution is then constantly stirred for 24 hours in a shaker incubator. Then the sonication is done for the complete solution. Following sonication and filtering, the amount of miglitol in the solution is found spectrophotometrically at 232 nm using the proper dilution [7].

Folding Endurance

Film folding endurance was done by frequent, excessive levels of folding. The total number of times the films can be folded at a single constant area without rupturing is known as the film's folding endurance [8].

Flatness Determination

A transdermal patch has a uniformly smooth surface texture

and should not shrink over time. With the aid of flatness research, this can be proven. One strip is sliced from the center and sliced into two from each side of the patches to determine flatness. Each strip's length is calculated, and the variance of the length is quantified by calculating the % constriction. 100 % flatness equates to zero % constrictions [9].

$$\% \text{ Constriction} = \frac{I_1 - I_2}{I_1} \text{ X } 100$$

Whereas

I2 = each strip's final length

I1 = each strip's initial length

Percentage moisture loss determination

Each of the prepared films is weighed before being stored in a desiccator for 24 hours at room temperature which contains calcium chloride. Then the films were weighed once more till they display a constant weight after a predetermined interval. The percentage moisture content was found by using the following formula

$$\% \text{ Moisture Loss} = \frac{\text{Initial weight of film - Final weight of film}}{\text{Final weight of film}} \text{ X } 100$$

Percentage moisture absorption determination

The films were precisely weighed before being kept in the desiccator, which was maintained at 84% RH and contains 100ml of saturated KCl solution. The films were taken out of the desiccator after three days and weighed.

$$\% \text{ Moisture Absorption} = \frac{\text{Final weight of film - Initial weight of film}}{\text{Initial weight of film}} \text{ X } 100$$

Tensile strength determination

The tensile strength of polymeric films was calculated by sandwiching them between corked linear iron plates. An iron screen was used to keep one end of the film stationary and the other remaining end was tied to a freely moveable thread using a pulley. The pan is filled with weights gradually, which were fastened to the thread's hanging end. The weight that would just be enough to tear the film was observed. Using the following equation, the tensile strength was determined [10].

$$\text{Tensile strength of film} = F/a.b\ (1+L/I)$$

Whereas

F = force required to break the film

a = film width

b = film thickness

L = film length

I = film elongation at the breaking point.

Scanning Electron Microscopy (SEM)

SEM was carried out to study the film's surface morphology that contained drugs. SEM analysis was used to study the film's shape and surface topography (SEM-JEOL, JSM-840A, Japan). Double-sided adhesive tape was used to mount the test samples on the sample stab. To increase conductivity, the gold coating was made to the samples mounted (200 A°) using ion sputtering equipment at low pressure (0.001 torr) for 5 minutes (JEOL, JFC-1100 E, Japan). The SEM was used to examine the gold-coated samples, and photomicrographs at the proper magnifications were taken [10].

In vitro drug release studies of transdermal patches

Franz Diffusion Cell was used in sink conditions, the in-vitro drug release tests were performed for 24 hours in pH 5.5 buffer. The transdermal system was positioned between the two compartments (Donor-Receptor compartments) of the diffusion cell in this technique. The receptor fluid or buffer is kept in the receptor compartment facing the transdermal system. Temperature and agitation rate are held constant. The receiver compartment solution was constantly stirred using magnetic beads throughout the experiment while the entire assembly was kept on a magnetic stirrer. At regular intervals, a volume of the receptor fluid was taken for spectrophotometric examination at 232 nm and then reintroduced with an equivalent proportion of fresh receptor fluid [11].

RESULTS AND DISCUSSION

Standard curve of Miglitol

Table 2 Standard curve of Miglitol

S. No.	Concentration (µg/ml)	Absorbance
1	0	0
2	10	0.050
3	20	0.101
4	30	0.152
5	40	0.202
6	50	0.253

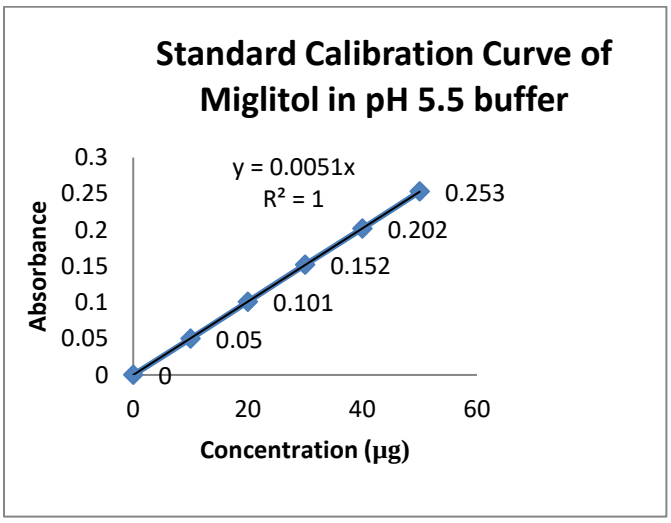

Fig.1. Linearity graph of Miglitol at pH 5.5

Compatibility study using DSC

A prominent endothermic peak was seen in the DSC of Miglitol at 147oC. (melting point). Miglitol and other excipients were physically combined, and this mixture displayed the same thermal behavior (147oC) as an individual. The DSC results also demonstrated that there was a superimposition of the thermograms in the physical mixture of the excipient and miglitol. The physical mixing of miglitol and excipient showed no apparent change in the melting endotherm.

From the DSC studies, it was found that there was no interaction taking place between Miglitol and the other ingredients used in the formulation of Miglitol TDDS.

The DSC images were shown in Fig. 2 to Fig. 3.

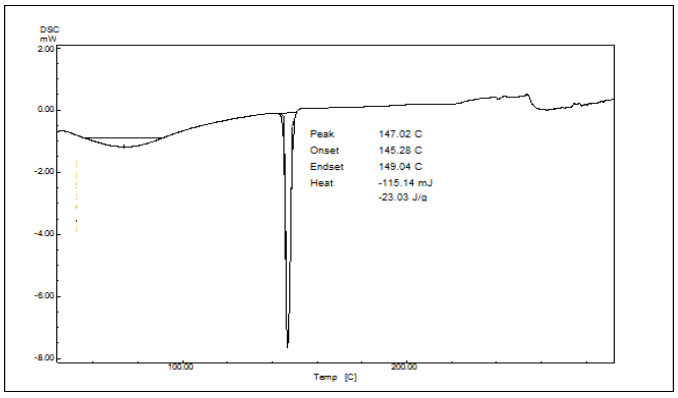

Fig. 2. DSC of Miglitol

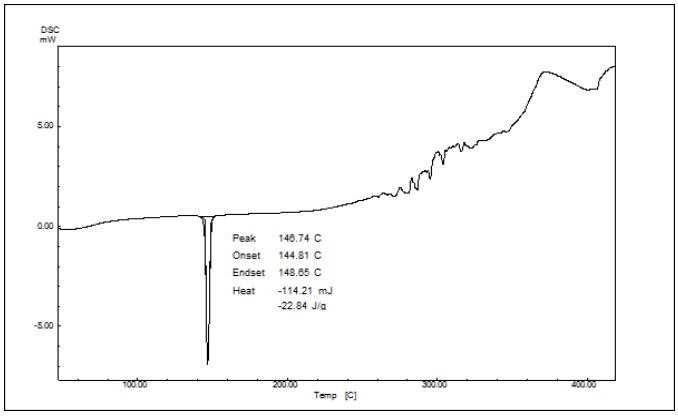

Fig. 3. DSC of Miglitol-Excipient mixture

Weight variation

The weight uniformity was found by weighing five matrices of each preparation. Each film unit was weighed separately on a digital balance, then the film's average weight was taken as the weight of the film [12].

Thickness

The transdermal patches thickness was calculated at three various points by using a micrometer and the mean values were recorded [13].

Percentage moisture loss

The accurately weighed films were kept in a desiccator having anhydrous calcium chloride. The films were weighed after 3 days [14].

Percentage moisture absorption

Accurately weighed films were kept in the desiccator having 100 ml of saturated aluminum chloride solution, which has 84% RH. The films were weighed after 3 days [15]. The results were given below.

Table 3 Weight variation, thickness, %moisture loss, %moisture absorption

Formulations	Weight variation (mg)	Thickness (mm)	Moisture loss (%)	Moisture absorption (%)
F1	48.78 ± 0.76	0.472 ± 0.008	11.59 ± 0.78	14.67 ± 0.55

F2	45.92 ± 0.66	0.454 ± 0.011	11.46 ± 0.51	11.97 ± 0.50
F3	45.20 ± 1.90	0.432 ± 0.008	9.062 ± 0.99	10.88 ± 0.64
F4	46.04 ± 1.38	0.462 ± 0.008	11.41 ± 0.56	8.39 ± 0.67
F5	45.68 ± 0.92	0.448 ± 0.013	10.01 ± 0.55	7.958 ± 0.60
F6	45.50 ± 0.82	0.450 ± 0.012	8.39 ± 0.55	6.692 ± 0.46

Mean ± Standard Deviation (n = 3)

Folding endurance, Flatness and Drug content

The folding endurance, flatness and drug content were performed and the analyzed results were tabulated in table 4. The tensile strength was carried out with the aid of a tensile strength apparatus and the results were given below,

Table 4 Folding endurance, % Flatness and % Drug content

Formulations	Folding endurance	Flatness (%)	Drug content (%)
F1	205.3 ± 0.57	100	98.58 ± 0.03
F2	202.3 ± 2.08	100	97.63 ± 0.03
F3	200.6 ± 1.52	100	97.31 ± 0.01
F4	204.6 ± 0.57	99	98.10 ± 0.03
F5	201 ± 1.73	100	97.47 ± 0.02
F6	202 ± 1.73	100	97.79 ± 0.04

Mean ± Standard Deviation (n = 3)

SCANNING ELECTRON MICROSCOPY (SEM)

Fig. 4. SEM Photograph of Optimized Formulation of Miglitol TDDS (F1)

Scanning Electron Microscope photographs of the Transdermal film formulation F1 were given in fig.4. The SEM photo confirmed that the films were discrete with a uniform distribution of polymers [16].

In Vitro Release Studies of Miglitol TDDS (F1-F6)

Diffusion studies of six formulations (F1-F6) were carried out using pH 5.5 phosphate buffer for 24 hours. The results were tabulated in tables 5 and 6 and fig.5. The cumulative percent release data showed that the F1 formulation was selected as the optimal formulation for the controlled drug release of miglitol since it was found to be better than other formulations. The cumulative percentage released was 95.5 ± 0.41. The optimized concentration of HPMC was found to be 300 mg [17,18].

The increase in HPMC and PVP K30 concentration resulted in a decrease of drug release from F2 and F4, whereas F1 showed ideal drug release at the end of 24 hours and F3 was not ideal. The drug release from Miglitol TDDS prepared with Eudragit L 100 was found to be less due to its hydrophobic nature.

Table 5. Cumulative percentage release of Miglitol TDDS (F1-F3)

S. No.	Time (hrs)	% Cumulative Release		
		F1	**F2**	**F3**
1	0	0.00	0.00	0.00
2	1	4.76 ± 0.40	2.6 ± 0.05	1.58 ± 0.36
3	2	11.58 ± 0.51	7.4 ± 0.55	6.19 ± 0.26
4	3	18.8 ± 0.30	14.6 ± 0.45	12.3 ± 0.37
5	6	23 ± 0.65	20.6 ± 0.25	19.6 ±0.36
6	8	32.5 ± 0.30	28.7 ± 0.75	25.2 ± 0.36
7	10	39.2 ± 0.70	35.1 ± 0.72	31.2 ± 0.06
8	12	47.4 ± 0.45	43.5 ± 0.30	38.1 ± 0.76
9	24	95.5 ± 0.41	90.7 ± 0.26	86.03 ± 0.03

Mean ± Standard Deviation (n = 3)

Table 6 Cumulative percentage release of Miglitol TDDS (F4-F6)

S. No.	Time (hrs)	CUMULATIVE % RELEASE		
		F4	F5	F6
1	0	0.00	0.00	0.00
2	1	2.6 ± 0.72	1.9 ± 0.36	1.26 ± 0.36
3	2	7.4 ± 0.08	6.6 ± 0.25	5.55 ± 0.55
4	3	15.2 ± 0.05	12.6 ± 0.35	11.1 ± 0.41
5	6	21.4 ± 0.41	20.4 ± 0.70	17.4 ± 0.50
6	8	29.3 ± 0.75	25.7 ± 0.45	23.6 ± 0.55
7	10	36.5 ± 0.05	32.3 ± 0.72	29.6 ± 0.05
8	12	44.4 ± 0.50	38.8 ± 0.65	36.5 ± 0.85
9	24	91.42 ± 0.76	87.6 ± 0.41	83.3 ± 0.37

Mean ± Standard Deviation (n = 3)

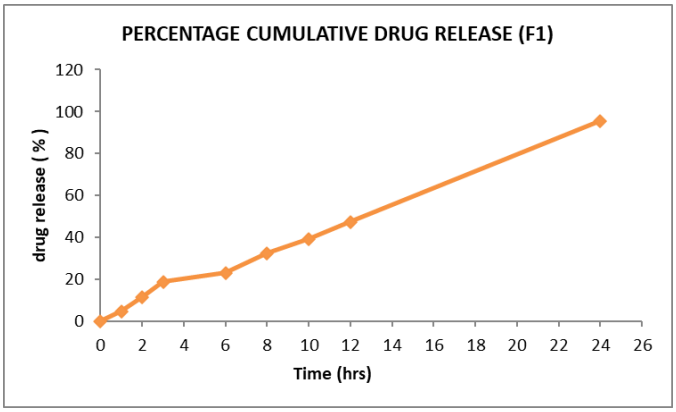

Fig. 5 Graphical representation of Cumulative% drug release of Miglitol TDDS (F1)

Conclusion

Conventional administration of drugs may sometimes prove to be insecure because of erratic responses, overdosing, and constant monitoring. Many fatal diseases necessitate a dosage form capable of releasing drugs for an extended period at a predefined controlled delivery rate at a reasonable cost. Transdermal drug delivery offers a variety of opportunities, such as increased bioavailability, avoiding pre-systemic metabolism and increased drug therapeutic effectiveness by reaching into the systemic circulation.

In the present study, three different polymers, HPMC, PVP K30 and Eudragit L100 were used in various concentrations (300 and 450mg) in the TDDS formulation for Miglitol. Based on the physical appearance of the polymers, such as Eudragit L100, Polyvinyl pyrrolidone K30, and Hydroxypropyl methylcellulose, which are used to fabricate transdermal systems, they have excellent film-forming capabilities. These systems were thin, smooth and highly flexible.

The physicochemical evaluation data indicates that the thickness of the formulations varied between 0.432 ± 0.008 to 0.472 ± 0.008 mm. The result showed that the thickness was uniform. The patch weighed ranged between 45.20 ± 1.90 mg to 48.78 ± 0.76 mg. Nearly 100% flatness has been shown in the patch, which suggests that constriction is negligible in the formulated transdermal patches. The formulation F1 which contains 300mg of HPMC has shown the highest maximum absorption (14.67 ± 0.55) compared to other formulations. This may be caused by the presence of the high hydrophilic nature of HPMC. Because of the hydrophobic nature of the polymer, the formulations F5 and F6 (containing 300 and 450 mg of Eudragit L100, respectively) had the lowest percent moisture absorption. F1 has the highest % moisture loss (11.59 ± 0.78) and F6 has the lowest (8.39 ± 0.55).

The folding endurance studies were carried out in order to evaluate their flexibility. The values ranged between 200.6 ± 1.52 to 205.3 ± 0.57 were observed. This proved that the formulated films had enough strength and excellent flexibility to withstand mechanical pressure. The content of the drug in all formulations was evaluated which showed that the drug was ranging from 97.31% to 98.58% of Miglitol.

The drug release cumulative percentage in 24 hours was seen to be maximum for F1 (95.5 ± 0.41) which was the highest because of the presence of the hydrophilic nature of HPMC which was more permeable than Eudragit L-100 and high hydrophilic polymer (HPMC), which improves the drug's thermodynamic activity in the patches because the polymer absorbs water, swells, and forms pores, increasing the release of the medication.

In conclusion, formulation F1 (300mg of HPMC) has fulfilled the goals of the current study, such as prolonged release and reduced frequency of administration, and this may have improved patient compliance. From the overall results reported in the present study, it is proposed that Miglitol can be formulated as a transdermal drug delivery system for providing effective treatment for diabetes with enhanced patient compliance. Maximum in vitro drug release for formulation F1 is suitable for further in vivo studies.

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