

INVESTIGATION OF KONDAGOGU GUM TO DEVELOP TRANSDERMAL FILM OF REPAGLINIDE

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ABSTRACT

Objective: In the present study, an attempt was made to develop polymeric blend transdermal patch of repaglinide using hydroxypropyl methyl cellulose (HPMC) K4M and kondagogu gum.

Methods: A series of repaglinide drug-incorporated HPMC K4M-kondagogu gum matrix films were prepared by solvent casting method. The prepared transdermal films were evaluated for various parameters such as thickness, tensile strength, folding endurance, % elongation, % moisture content, % moisture uptake, % drug content, *in vitro* drug release, and drug excipient compatibility.

Results: The Fourier-transform infrared spectra of the pure drug as well as drug-incorporated formulation indicated that no chemical interaction occurred between the drug and the polymers used. Differential scanning calorimetry thermograms of the pure drug and prepared formulation indicated that the drug has dispersed in micron level in the prepared films. *In vitro* release study data of prepared formulations were fitted into various mathematical models, and the best-fit model was found to be Higuchi model.

Conclusion: Among all the formulations studied, the formulation F4 was found to be an optimized composition for efficient transdermal delivery of repaglinide for 24 h study period. Stability studies of the drug formulations concluded that the drug was stable in the optimized formulation for the study period.

Keywords: Hydroxypropyl methyl cellulose K4M, Kondagogu gum, Transdermal film, Repaglinide.

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INTRODUCTION

Natural polymers and their derivatives are used extensively to prepare various pharmaceutical dosage forms and novel drug delivery systems and thus can compete with synthetic polymeric materials which are widely utilized in the present market [1]. Natural polysaccharides hold several distinct advantages compared to synthetic polymeric materials as they are non-toxic, biodegradable, less expensive, and easily available.

Over the past few decades, natural biodegradable polysaccharides such as guar gum, chitosan, carrageenans, sodium alginate (Na-alginate), pectin, xanthan gum, gellan gum, and agar have been widely used [2,3]. These polymers can be used in various ways in the formulation of targeted and controlled drug delivery systems as they have different derivatizable groups, a wide range of molecular weight, and varying chemical composition. Transdermal drug delivery system has been showing an increased interest in the drug administration through the skin for both local therapeutic effects as well as for systemic delivery of drugs. Development of transdermal delivery system started in 1970s, and in 1979, the first transdermal patch of scopolamine was approved by the United States FDA for the treatment of motion sickness, and later, a nitroglycerine patch was marketed for the treatment of angina pectoris [4,5].

Fundamentally, thin films are good candidates for targeting sensitive site which may not be possible using tablets or liquid formulations. Transdermal films have shown the capabilities to improve the onset of drug action, reduce the dose frequency, and enhance the drug efficacy [6-9]. Similarly, transdermal films are useful for eliminating side effects of a particular drug and reducing extensive metabolism which is caused by proteolytic enzymes. Ideal films exhibit desirable features such as sufficient drug loading capacity, fast dissolution rate or long residence time at the site of administration, and acceptable

formulation stability. They should also be non-toxic, biocompatible, and biodegradable [10,11].

Kondagogu gum (KG) is the dried exudate obtained from the tree *Cochlospermum gossypium* belonging to the family Bixaceae [12]. It is a high molecular weight complex acetylated polysaccharide consisting mainly of D-galacturonic acid, D-galactose, and L-rhamnose [13]. KG has demonstrated a lot of interest in the preparation of hydrophilic matrix tablets because of its properties such as high water swellability, nontoxicity, and low cost. Unlike other water-soluble gums, it does not dissolve in water but absorbs to form a viscous colloidal solution [14]. Powdered KG swells in cold water to an extent that a 3-4% sol will produce a gel of uniform smoothness and texture.

Kondagogu gum has also been used for biosorption of toxic heavy metals such as nickel and total chromium from aqueous solutions [15]. Gum kondagogu modified magnetic nano adsorbent has also been prepared for removing toxic metal ions from industrial effluents [16]. It was used as a carrier in preparing floating drug delivery system [17] and as a polyelectrolyte complex in combination with chitosan [18]. Even though KG is an important forest product, its commercial exploitation has been limited. Hydroxypropyl methyl cellulose (HPMC) K4M is a water-soluble cellulose derivative designed to perform many functions in pharmacy. It has a viscosity range of 2,700-5,040 cps and widely used in the formulation of films.

Diabetes mellitus is a major and growing health problem worldwide which is an important cause of prolonged ill-health and early death. 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 [19]. Repaglinide is an oral blood glucose-lowering drug of the meglitinide class and used to treat non-insulin-dependent diabetes mellitus. It lowers blood glucose level by stimulating the release

of insulin from the pancreas. It has an extremely short half-life of 1 h. In addition, the oral bioavailability of repaglinide is low (56%) due to extensive hepatic first-pass metabolism. Dosage frequency of repaglinide is 0.5–4 mg and for 3–4 times in a day. It has melting point of 130–131°C and molecular weight 452.58. Topical preparation of repaglinide may be beneficial to the patient since it reduces adverse effects and avoids the hepatic first-pass metabolism [20-22].

In the present study, an attempt was made to develop polymeric blend transdermal patch of repaglinide using HPMC K4M and kondagogu gum. Different formulations were prepared by varying the concentration of gums, and the prepared films were evaluated.

MATERIALS AND METHODS

Materials

Repaglinide was received as gift sample from Lupin Limited, Goa, India. Kondagogu gum was purchased from Girijan Cooperative Society, Government of Andhra Pradesh, Hyderabad, India. HPMCK4M, polyethylene glycol 400, and propylene glycol were purchased from Sigma Aldrich, Mumbai, India. All other chemicals used were of analytical grade and purchased from Loba Chemie, Mumbai, India.

Purification of gum [14]

First, the foreign extraneous matter such as bark was physically separated from kondagogu gum, then powdered using mixer grinder, and passed through sieve #80. The powdered gum was dispersed in distilled water using a magnetic stirrer to get a 1% solution, which is kept in sonicator for 10 min until it was clear and then added to equimolar mixture of acetone and ethanol (2:1 v/v) to get precipitation of gum. Precipitated polymer was kept in an oven at 40°C for drying, powdered, and then used for further studies.

Preparation of transdermal patch [23]

Matrix-type transdermal patches of repaglinide were prepared using solvent casting method (Table 1). Required quantity of polymers, HPMC K4M, and kondagogu gum was accurately weighed and dispersed in water using a magnetic stirrer. The required quantity of drug was dissolved in 5 mL of methanol and added to the polymer solution. To the above mixture, polyethylene glycol 400 (20% w/w of total polymer) as plasticizer and propylene glycol (15% w/w of total polymer) as permeation enhancer were added. The resulted uniform solution was cast on the Petri dish and dried at room temperature for 24 h. The dried films were cut into required size, wrapped in aluminum foil, and kept in a desiccator containing a saturated solution of CaCl₂ as a desiccant (29% RH) at room temperature (32°C) until use.

Mechanical properties [24]

Mechanical properties such as tensile strength and percentage elongation at break of the prepared transdermal films were measured as per ASTM D 685 using Universal Testing Machine (Instron 4309). A minimum of three samples were tested for each composition, and the average value was recorded. The thickness of the dry films was measured using microprocessor coating thickness gauge (Quint sonic, Mumbai, India). Thickness of the patch was measured at three different places, and the mean value was calculated. Six films (2.5 cm²) from each batch were randomly selected for weight variation. Films

were weighed individually, and then the average weight was measured. The difference between individual and average weight indicated the weight variation.

Folding endurance [25]

A strip of film of specific surface area (3 cm × 2 cm) was cut and folded repeatedly at one place till it broke. The number of times the film was folded before breaking at the same place represented folding endurance for the formulation.

Drug content analysis [26]

For drug content analysis, films of known area (2.5 cm × 2.5 cm) were taken in 10 mL of volumetric flask and casting solvent mixture was added to it. The flasks were shaken in a water bath at 37°C for 2 h, filtered through Whatman filter paper No. 1, and suitably diluted before drug content measurement using ultraviolet (UV)-visible spectrophotometer (UV-1800, SHIMADZU, Japan) at 241 nm.

Moisture content [27]

The films of repaglinide were weighed individually and kept in a desiccator containing a saturated solution of CaCl₂ (29% of relative humidity) at room temperature (32°C) for 24 h. Subsequently, the films were weighed intermittently until a constant weight was achieved. The percentage of moisture uptake was calculated based on the difference between final and initial weight divided by initial weight.

Moisture uptake [27]

The weighed films kept in a desiccator for 24 h at room temperature (32°C) were taken out and exposed to 75% relative humidity (saturated solution of NaCl) until a constant weight was obtained. The percentage of moisture uptake was calculated as the difference between final and initial weight divided by initial weight.

Water vapor permeability (WVP) [28]

For WVP measurement, glass test tubes of 25 mL capacity were taken and filled with 20 mL of distilled water. The weight of each filled test tube was measured 1 h before closing the openings of glass test tubes by films. The area available for vapor permeation was 2.54 cm², and all the containers were maintained at constant room temperature (32°C) for 24 h. The final weight was calculated after 1 h, and the WVP was calculated using the following equation:

$$WVP = W/A$$

Where W is the mean loss in weight (g) of the containers and A (m²) is the area of the exposed surface.

Fourier-transform infrared (FTIR) spectrophotometry [20,22]

To evaluate the integrity and compatibility of repaglinide with the carrier polymers and the excipients used in the polymer-drug matrix formulations, IR spectra of the drug and its optimized formulation were obtained by FTIR spectrophotometer (Perkin-Elmer-1000, Japan), using a potassium bromide pellet method.

Differential scanning calorimetry (DSC) [27]

All dynamic DSC studies were carried out using DuPont thermal analyzer with 2010 DSC Q 200, module. The instrument was calibrated

Table 1: Formulation chart for preparing transdermal films

Formulation code	Repaglinide (mg)	HPMCK4M (mg)	Kondagogu gum (mg)	Polyethylene glycol 400 (% w/w)	Propylene glycol (% w/w)
F1	200	1000	-	20	15
F2	200	900	100	20	15
F3	200	800	200	20	15
F4	200	700	300	20	15
F5	200	600	400	20	15
F6	200	500	500	20	15

HPMC: Hydroxypropyl methyl cellulose

before testing using high purity indium metal as standard and the scans of the samples were recorded in the temperature range 0–300°C under nitrogen gas purge at a heating rate of 10°C/min.

In vitro release studies [24,27]

The *in vitro* release of drug from the prepared transdermal films was carried out using vertical type of Franz diffusion cell with a receptor compartment capacity of 22 mL. The jacketed diffusion cell with inlet and exit port for the circulation of water was used to maintain medium temperature at 32±0.5°C. A film specimen of surface area 2.5 cm² equivalent to 15 mg of the drug was placed on 0.22- μ m cellulose acetate membrane which was previously equilibrated by soaking in phosphate buffer pH 7.4 for 24 h. The above medium was used to ensure the sink condition and stability of the drug. The membrane having film on it was immediately placed between the donor and receptor compartment and subsequently secured firmly by a stainless steel clip. The receptor compartment was stirred at 200 rpm with a teflon-coated magnetic bead. Aliquots of 0.5 mL were withdrawn from the receptor compartment at specified time intervals (0, 2, 4, 8, 12, 16, 20, and 24 h) and replaced with equal volumes of fresh buffer maintained at the same temperature. The samples were filtered and analyzed using a UV- Spectrophotometer (Shimadzu 1602, Japan) at 241 nm.

Stability of the transdermal films [22,28]

Stability studies of the optimized formulation of prepared repaglinide transdermal film were carried out to determine the effect of formulation additives on the stability of the drug and also to determine the physical stability of the formulation. The optimized formulation was subjected to stability studies according to the ICH guidelines by storing at 25±2°C/60±5% RH and 30±2°C/65±5% RH for 12 months and 40±2°C/75±5% RH for 6 months (Thermolab, Mumbai, India). The samples were analyzed and checked for changes in physical appearance and drug content at regular intervals.

RESULTS AND DISCUSSION

All formulations were prepared by solvent casting method using water and methanol as solvent system. The repaglinide-loaded films were slightly opaque, having smooth surface and elegant appearance. The physicochemical properties of the films are given in Table 2. The thickness of the films found between 273 and 239 μ m. As the concentration of KG was increased in the formulation, the thickness of the film decreased. This can be attributed to the high density of KG compared to HPMC K4M. The weight of the films varied from 71.8 to 77.4 mg, indicating that different proportion of KG has shown little or no significant impact on weight variation.

The main aim of the folding endurance study on transdermal films is to test the ability of the film to endure stress-based rupture during the application and use. The folding endurance values for the repaglinide films ranged from 240.9±8.7 to 218.3±9.9. This result clearly indicates that the repaglinide films are having optimum flexibility and are not brittle. However, it is clear that as the concentration of KG increased, the folding endurance decreased. This can be attributed to the complex structure and friable nature of KG. The higher values obtained demonstrated that films would maintain the integrity and shape with the natural folding of the skin when applied on it.

The drug content data were indicated good content uniformity with low standard deviation. This indicates that the films of repaglinide with HPMC K4M and KG can be prepared with a higher degree of reproducibility.

The mechanical properties such as tensile strength and % elongation at break of all the repaglinide films were measured, and the data are shown in Table 2. A hard and tough polymeric film, generated from high values of both the studies, is always desired as it has qualities suited best as a drug delivery system for application on the skin. This implies that higher tensile strength values prevent abrasion of the film caused by contact with patient clothing, whereas higher % elongation at break values allows the free movement of film on skin contact without breaking. The % elongation at break values ranged from 43±3.7 to 31±4.1 indicating good flexibility. It is clear that as the concentration of HPMC K4M increased, the value also increased. The tensile strength of the repaglinide films varied from 0.38±0.017 to 0.53±0.016 kg/cm². The tensile strength values increased with increase in the concentration of KG in the film. This increase in value indicates that more force is required to deform the formulations having a high concentration of KG compared to HPMC K4M alone.

The moisture absorption is a tool to indicate how the film would behave during the initial stage of drug release. The lower moisture content in the formulations helps them to remain stable and become a completely dried and brittle film. Again, low moisture uptake protects the material from microbial contamination and bulkiness. The results of moisture content and moisture absorption studies are shown in Fig. 1a. The moisture content and % moisture uptake in the repaglinide films ranged from 6.5 to 11.2 and 11.4% to 33.4%, respectively, indicating that the values increased slightly due to increase of KG concentration in the films. This can be attributed to the hydrophilic nature of KG. The WVP values of the repaglinide films are shown in Fig. 1b. All the WVP values were found to be ranging between 632.17 and 573.74 g/m²/day. The average transepidermal water loss by diffusion through the skin is 300–400 mL/day which corresponds to 157.894–210.526 g/m²/day (normal body surface area is 1.9 m²). The obtained values indicate that the repaglinide films were not occlusive in nature and thereby do not disturb natural process of water loss from body surface.

The FTIR spectra of pure drug repaglinide and formulation F4 are shown in Fig. 2. The FTIR spectra of repaglinide and its formulation were found to be identical. The characteristic IR absorption peaks of repaglinide at 3320 cm⁻¹ (N-H stretching), 2947 cm⁻¹ (C-H stretching), 1728 cm⁻¹ (C=O stretching), and 1460 cm⁻¹ (C-H deformation) were obtained. The FTIR spectra of the pure drug, as well as drug incorporated formulation (F4), indicated that no chemical interaction occurred between the repaglinide and the polymers used. However, a slight change in absorption peaks position was noticed. This result clearly indicates that the drug and polymers used are compatible.

DSC thermograms of the pure drug and prepared formulation were recorded and shown in Fig. 3. From Fig. 3, it is clear that a sharp endothermic peak at 131°C was obtained for pure repaglinide. The melting point of repaglinide has not been seen in the prepared transdermal film, indicating that the drug has dispersed in micron level in the prepared films.

Table 2: Physicochemical properties of repaglinide transdermal films

Formulation code	Thickness (μ m)	Weight variation (mg)	Folding endurance	Drug content (mg)	% Elongation at break	Tensile strength (kg/cm ²)
F1	273±4.3	71.82±2.16	240.9±8.78	15.3±0.65	43±3.7	0.38±0.017
F2	269±3.6	72.29±1.92	236.4±7.39	15.9±0.46	41±3.6	0.39±0.014
F3	262±3.9	73.25±1.57	229.8±7.27	14.5±0.61	38±3.2	0.42±0.018
F4	257±4.1	74.04±1.24	225.2±9.75	15.4±0.53	37±3.9	0.46±0.012
F5	246±2.8	76.92±1.64	221.7±8.82	15.2±0.52	33±3.4	0.49±0.015
F6	239±3.5	77.41±1.53	218.3±9.94	14.6±0.68	31±4.1	0.53±0.016

Mean±SD, n=6

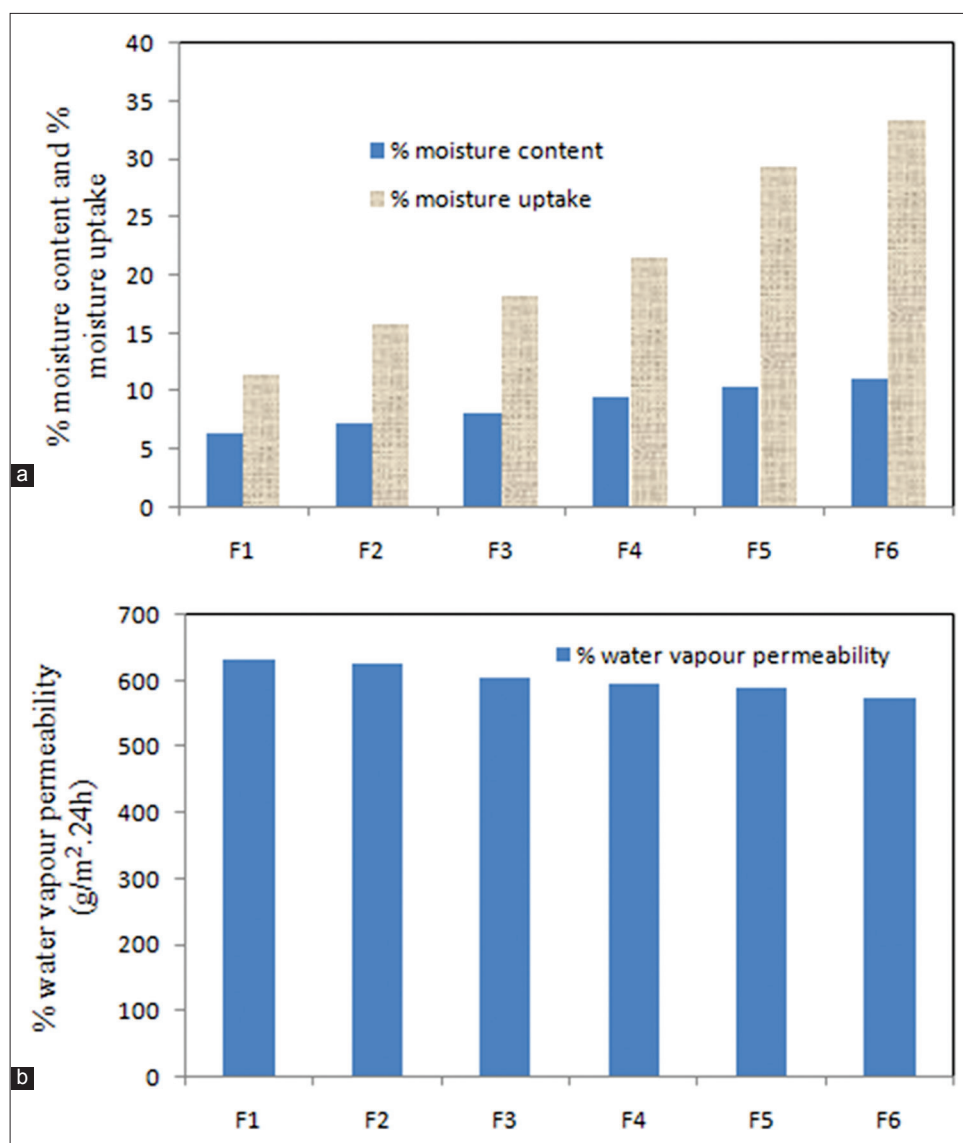


Fig. 1: (a) Percentage of moisture content and moisture absorption, and (b) percentage of water vapor permeation from prepared formulations

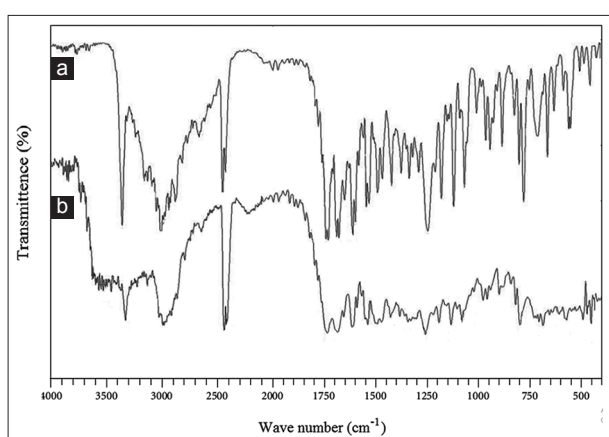


Fig. 2: Fourier-transform infrared spectra of repaglinide (a) and formulation F4 (b)

The drug release characteristics of the formulation were studied in *in vitro* conditions by using artificial semi-permeable membrane. The drug release profiles of the repaglinide films are shown graphically in Fig. 4. From Fig. 4, it is clear that as the concentration of KG in the

formulation increased, the drug release from the transdermal film decreased. From Fig. 4, it is observed that the formulations F1-F3 have released 88.6, 81.3, and 74.1% of the drug within 12 h of the study period. Formulations F1 and F2 have released entire 100% drug by 20 h, whereas formulation F6 has released only 89.5% of drug in 20 h study period, indicating that they are not suitable for the present study. Formulations F3, F4, and F5 have released 99.1, 94.7, and 91.3% of loaded drug indicating their suitability for 24 h drug release.

In vitro release study data of formulations F3, F4, and F5 were fitted into various mathematical models to determine the best-fit model. The best-fit model with the highest regression coefficients (R^2) for all the formulations is given in Table 3, and the best-fit model was found to be Higuchi model. To know the type of diffusion, all data were fitted to Korsmeyer-Peppas equation. The release exponent values ($n=0.558-0.623$) demonstrated anomalous diffusion (non-Fickian model), i.e., the release mechanism followed the combination of diffusion and swelling. This is attributed to the presence of swelling polymers HPMC K4M and KG in the matrix. From Table 3, it was concluded that formulation F4 with R^2 value of 0.9987 is the optimized formulation for 24 h study period.

Stability studies of the optimized repaglinide film were performed to ascertain if the drug undergoes any degradation during its shelf life.



Fig. 3: Differential scanning calorimetry spectra of repaglinide (a) and formulation F4 (b)

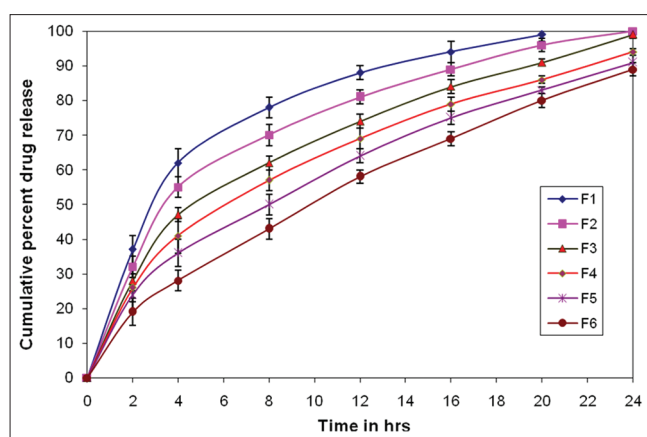


Fig. 4: *In vitro* drug release profiles from the prepared films

In the present study, the optimized formulation F4 was selected for stability studies. The obtained results of stability studies are given in Table 4. From Table 4, it can be concluded that the repaglinide is stable in the optimized formulation for the study period.

CONCLUSION

Repaglinide films were prepared by solvent casting method. The FTIR spectra of the pure drug, as well as drug incorporated formulation, indicated that no chemical interaction occurred between repaglinide and the polymers/excipients used. DSC thermograms of the pure drug and prepared formulation inferred that the drug has dispersed in micron level in the films. *In vitro* release study data of prepared formulations were fitted into various mathematical models and the best-fit model

Table 3: Model fitting data for the prepared formulations

Release model	Formulation code		
	F3	F4	F5
Zero order			
R ²	0.8467	0.8969	0.8292
First order			
R ²	0.9156	0.9342	0.9134
Hixson Crowell			
R ²	0.8421	0.8394	0.8396
Peppas			
R ²	0.8397	0.8746	0.8947
Higuchi			
R ²	0.9915	0.9987	0.9862
n	0.623	0.558	0.617
Best-fit model	Higuchi	Higuchi	Higuchi

Table 4: Stability study data of optimized formulation F4

Stability condition	Sampling interval (months)	Formulation F4	
		Physical appearance	% Drug content
25±2°C/60±5% RH	0	No change	99.7±1.1
	3	No change	98.6±1.3
	6	No change	98.4±1.2
	12	No change	97.4±1.3
30±2°C/65±5% RH	0	No change	99.7±1.1
	3	No change	99.2±1.3
	6	No change	98.7±1.2
	12	No change	98.4±1.4
40±2°C/75±5% RH	0	No change	99.7±1.1
	3	No change	98.6±1.2
	6	No change	97.1±1.3

was found to be Higuchi model. It was concluded that formulation F4 with R² value of 0.9987 is the optimized formulation for 24 hr study period. Stability studies of the drug formulations proved that the drug was stable in the optimized transdermal film formulation for the study period. Therefore, it can be concluded that the prepared film has the potential for transdermal drug delivery of repaglinide with improved permeation profile for longer period of time, thereby increasing the patient compliance.

AUTHORS CONTRIBUTION

All of the authors mentioned in the article have contributed equal efforts in this research work.

CONFLICT OF INTEREST

The authors would like to state that “we have no conflict of interest to declare.”

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