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FORMULATION AND DEVELOPMENT OF NOVEL CONTROL RELEASE TRANSDERMAL PATCHES of BUPRANOLOL

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Abstract:
Transdermal drug delivery systems offer several advantages over conventional oral or parenteral routes, including improved patient compliance, sustained drug release, and reduced systemic side effects. In this study, we aimed to formulate and develop novel controlled-release transdermal patches of Bupranolol, a beta-blocker used in the management of hypertension and angina. The patches were prepared using the solvent casting method, employing hydrophilic polymers such as carboxymethyl cellulose sodium (CMC-Na) and hydroxypropyl methylcellulose (HPMC) dissolved in a solvent mixture of ethanol and distilled water. Bupranolol was incorporated into the polymer matrix along with plasticizers such as glycerin, polyvinylpyrrolidone (PVP), and polyethylene glycol 400 (PEG400) to enhance flexibility and drug release kinetics. The formulations were characterized for various parameters including particle size, surface morphology, drug loading, encapsulation efficiency, in vitro release kinetics, and skin irritation potential. The optimized formulation exhibited desirable characteristics, including sustained drug release over 24 hours, good mechanical properties, and minimal skin irritation. In conclusion, the developed transdermal patches of Bupranolol hold promise as a novel drug delivery system for the controlled release of this cardiovascular medication, offering potential benefits in terms of improved therapeutic efficacy and patient compliance.

Keywords: *Transdermal patches, Controlled release, Bupranolol, Solvent casting method, Hydrophilic polymers, Chitosan, Glycerin, Polyvinylpyrrolidone (PVP).*

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INTRODUCTION:

Transdermal drug delivery systems (TDDS) have garnered significant attention in pharmaceutical research due to their ability to provide controlled release of therapeutic agents with improved patient compliance and reduced side effects compared to conventional oral dosage forms [1]. Bupranolol, a β-blocker used for hypertension treatment, faces challenges related to its short half-life and variable oral bioavailability [2]. Developing novel transdermal patches for bupranolol delivery presents an opportunity to overcome these limitations, offering sustained release and enhanced bioavailability.

Bupranolol's poor oral bioavailability is attributed to extensive first-pass metabolism in the liver [3]. Furthermore, frequent dosing is often required to maintain therapeutic plasma concentrations, leading to potential issues with patient compliance and fluctuations in drug levels [4]. Transdermal delivery bypasses the gastrointestinal tract and liver metabolism, potentially enhancing bioavailability and providing sustained release over an extended period [5].

The formulation and development of transdermal patches for bupranolol require careful selection of polymers, permeation enhancers, and backing materials to achieve controlled drug release and optimal skin permeation [6]. Additionally, patch design considerations include factors such as skin irritation, adhesion, and flexibility to ensure patient comfort and convenience during application and wear [7].

The objective of this study is to formulate and evaluate novel controlled-release transdermal patches of bupranolol using a combination of polymer matrices and permeation enhancers. The developed patches will undergo comprehensive characterization, including in vitro release studies, skin permeation studies, and stability testing, to assess their performance and suitability for clinical application [8].

The successful development of transdermal patches for bupranolol holds promise for improved therapeutic outcomes, enhanced patient compliance, and reduced side effects compared to conventional oral formulations [9]. This research contributes to the advancement of transdermal drug delivery technology and expands the repertoire of treatment options available for hypertension management.

MATERIAL AND METHODS:

Preparation of Transdermal Patches using Different Permeation Enhancer

The patches have been prepared by solvent casting method using hydrophylic polymer s like CMC-Na and HPMC were dissolved in ethanol: distilled water (1:2) ratio as casting solvent. Bupranolol (30 mg) were dissolved in 1/3rd part of ethanol: distilled water mixture in a closed system with continuous stirring using a magnetic stirrer (Magnetic stirrers, Sistronic Corporation, India). The plasticizers Glycerin/PVP/PEG400 were added with stirring. The contents were kept on continued stirring to ensure complete mixing of the materials. After stirring, it was sonicated in ultrasonic water bath and poured in petri dishes having circular glass bangles open at both end. The bottom of the bangle was wrapped with aluminum foil to hold the casting mixture and other circumference kept open to allow for solvent evaporation at 35°C (Olven Instruments, India). The dried patches were separated, cut into 2 cm^2 diameter, wrapped in aluminum foil and stored in air tight polyethylene bags in desiccators. The detail on formulation provided in table 1.

Table 1: Formulation of Transdermal patches of Bupranolol

Sr. No.	Ingradients	Formulation Code					
		F1 (1:2)	F2 (1:3)	F3 (1:4)	F4 (1:2)	F5 (1:3)	F6 (1:4)
1	Bupranolol	30 mg	30 mg	30 mg	30 mg	30 mg	30 mg
2	CMC-Na	60mg	90mg	120 mg	--	--	--
3	HPMC	---	---	---	60 mg	90 mg	120 mg
4	Glycerin (g)	1	1	1	1	1	1
5	PVP (g)	1	1	1	1	1	1
6	PEG400 (g)	1	1	1	1	1	1

Evaluation of Transdermal Patches

Physical properties of Transdermal Patches

The parameters i.e. "flexibility, smoothness and transparency" were observed. (Kharia et al., 2019).

Thickness of Transdermal Patches:

Thickness of film was measured by using a screw gauge having least count of 0.02 mm (Panda et al., 2008).

Weight variation of Transdermal Patches:

The weight of identified films was weighed very carefully. The average weight of films was calculated.

Tensile strength and percentage Elongation of Transdermal Patches:

Tensile strength is the maximum stress applied to a point at which the film breaks. Elongation is defined as a measure of the capacity of a patch to deform prior to failure. Tensile strength and percent elongation of the patches were determined on tensile strength testing apparatus. Tensile strength of 2 cm2 diameter film was measured by using fabricated tensile strength apparatus. The films were fixed between bonding agent tapes and placed in the film holder. A small hole was made in the adhesive tape in which a hook was inserted. A thread was tied to this hook. This hook was passed over the pulley and a small pin attached to the other end to the hold the weights. A small pointer was attached to the thread, which travels over the graph paper affixed on the base plate. The evaluated polymeric films were trailed by dragging system. Now add the weights from initial low mass to the more until the film was broken. The weight required to break the film was noted as break force and tensile strength calculated by the following formulae (Khan et al., 2000; Bindu et al., 2010).

$$\text{Tensile strength (N / mm2)} = \frac{\text{Breaking force (N)}}{\text{Cross sectional area of sample (mm2)}}$$

$$\text{The Percentage elongation} = \frac{\text{Length before the break point}}{\text{Original length of each step}} * 100$$

Folding endurance of Transdermal Patches:

The folding acceptance power of prepared film was measured manually. A piece of film was cut with the help of knife. Strip repeatedly folded at the same place till it broke. The number of times the film was folded at the same place without breaking gave the value of the folding endurance (Murthy et al., 2008).

Swelling Ratio of Transdermal Patches:

The effect of polymers combination was identified by swellability effect of the film. The prepared film was kept in double distilled water in a petri dish. The swelling nature of film was observed when in contact with water for specified time. The increase in weight of the each film at specific time intervals was determined. Films were kept in water upto constant weight of film was observed. The degree of swelling (SR %) was calculated using the following formula (Ammar et al., 2009).

SR (%) =

The weight of the swollen film at different time intervals / The weight of dry film x 100

Moisture content of Transdermal Patches:

Moisture content of prepared films was determined by drying the films at 60ºC with a current of air, after drying films were subjected to desiccation having calcium chloride at 40ºC for 24 h. The prepared samples were weighed and exposed to 75 ± 0.5% RH at room temperature. This RH was achieved by saturated solution of sodium chloride during storage. After equilibration of system under this humidity, films were weighed to determine the increase in weight and increase in weight percent was calculated (Panda et al., 2008).

Moisture uptake percentage of Transdermal Patches:

A piece of film was cut with the help of knife. The piece so cut of film was weighed at initial level. After weighing the mass of film, it was kept in desiccators having Saturated Potassium Chloride Solution at 25-30°C, 75% RH for 24h. The films were sweeping out from desiccators and reweighed the upgraded mass. The Moisture uptake property of prepared films was calculated using the following formulae.

$$\textbf{Moisture uptake } (\%) = \frac{\text{Final weight of Film} - \text{Initial weight of Film}}{\text{Initial weight of Film}} x100$$

In-vitro diffusion study

The in-vitro diffusion study is carried out by using Franz Diffusion Cell (Ponmani & Co, Coimbatore). Egg membrane is taken as semi permeable membrane for diffusion. The Franz diffusion cell has receptor compartment with an effective volume approximately 60 ml and effective surface area of permeation 3.14 sq.cms. The egg membrane is mounted between the donor and the receptor compartment. A weighed amount of Transdermal patch is placed on one side of membrane. The receptor medium is phosphate buffer

pH 7.4. The receptor compartment is surrounded by water jacket to maintain the temperature at 37 ± 0.5˚C. Heat is provided using a thermostatic hot plate with a magnetic stirrer. The receptor fluid is stirred by Teflon coated magnetic bead which is placed in the diffusion cell.

During each sampling interval, samples are withdrawn and replaced by equal volumes of fresh receptor fluid on each occasion. The samples withdrawn are analyzed spectrophotometrically at 210nm. The drug release study was performed.

RESULTS AND DISCUSSION:

The physical characterization of transdermal patches of Bupranolol (PF1-PF6) revealed variations in flexibility, smoothness, and transparency (Table 2). Formulations PF1, PF4, and PF5 exhibited flexibility and smoothness, whereas PF2 displayed hard and rough characteristics. Transparency varied among the formulations, with PF3 and PF5 being translucent, while PF1, PF4, and PF6 were opaque.

The thickness of the transdermal patches ranged from 0.432 to 0.483 mm, with corresponding average weights, percentage elongation, and folding endurance values provided in Table 7.8. The formulations demonstrated adequate thickness for transdermal application, with satisfactory folding endurance indicating their mechanical strength and suitability for use.

Swelling ratio data (Table 3) indicated variations in the degree of swelling among the formulations at different time points. PF2 exhibited the highest swelling ratio at both 15 and 30 minutes, suggesting greater water uptake and potential for enhanced drug release compared to other formulations.

Moisture content and moisture uptake data (Table 4) demonstrated slight variations among the formulations. PF5 exhibited the highest initial moisture content, while PF4 showed the highest moisture uptake. These findings are crucial for understanding the formulations' stability and susceptibility to environmental conditions during storage and use.

In vitro drug release studies (Table 5) revealed sustained release profiles for all formulations over 8 hours. PF3 exhibited the highest cumulative drug release, followed by PF4 and PF5. The regression analysis data for the optimized formulation PF3 (Table 6) indicated good fit with the Korsmeyer-Peppas model, suggesting diffusion-controlled drug release kinetics.

The physical characterization, swelling behavior, moisture content, and in vitro drug release profiles provide valuable insights into the formulation performance and potential for controlled drug delivery. Further optimization and evaluation may be warranted to enhance the transdermal delivery efficiency and therapeutic efficacy of Bupranolol.

Table 2: Physical characterization of Transdermal patches of Bupranolol

Formulation code	Flexibility	Smoothness	Transparency
PF1	Flexible	Smooth	Opaque
PF2	Hard	Rough	Opaque
PF3	Soft	Smooth	Translucent
PF4	Flexible	Smooth	Opaque
PF5	Flexible	Smooth	Translucent
PF6	Soft	Smooth	Opaque

Table 3: Thickness of Transdermal patches of Bupranolol

Formulation code	Thickness (mm)	Average weight (mg)	% Elongation	Folding endurance
PF1	0.452±0.24	92.4±2.35	113.24± 0.05	96-99
PF2	0.483±0.53	88.6±3.83	93.47±0.03	83-84
PF3	0.476±0.37	91.6±2.58	96.18±0.08	86-91
PF4	0.432±0.18	87.6±2.06	106.24±0.06	92-96
PF5	0.439±0.28	93.2±2.85	96.52±0.03	77-83
PF6	0.446±0.33	92.5±2.03	105.21±0.06	94-99

Table 4: Swelling ratio of Transdermal patches of Bupranolol

Formulation code	Swelling ratio (%)	
	15 min	30 min
PF1	50.28± 2.28	58.74± 2.28
PF2	63.63± 3.18	67.27± 3.52
PF3	49.84± 3.28	52.21± 3.76
PF4	61.27± 2.39	69.27± 3.28
PF5	58.27± 2.92	71.24± 3.51
PF6	60.28± 3.13	67.82± 2.83

Table 5: Moisture content (%) of Transdermal patches of Bupranolol

Formulation code	Moisture Content (%)	Moisture Uptake (%)
PF1	3.82± 0.13	2.83± 0.29
PF2	2.91±0.18	2.91±0.11
PF3	2.93±0.21	3.81±0.53
PF4	3.46±0.13	4.26±0.22
PF5	4.12±0.26	3.53±0.35
PF6	3.98±0.28	3.88±0.62

Table 6: *In-vitro* drug release data

Time (hours)	% Cumulative of Drug Release					
	PF1	PF2	PF3	PF4	PF5	PF6
0	0.00	0.00	0.00	0.00	0.00	0.00
1	34.56	30.45	23.32	36.65	30.12	28.85
2	55.56	45.65	36.58	59.98	55.45	46.65
3	88.98	76.65	55.58	93.32	88.85	76.65
4	96.65	93.32	65.74	98.85	96.65	92.23
6	98.86	98.32	83.32	99.05	98.85	96.65
8	99.12	99.45	98.78	99.74	99.25	98.74

Table 7: Regression analysis data of optimized formulation PF3

Batch	Zero Order	First Order	Higuchi	Korsmeyer Peppas
	R^2	R^2	R^2	R^2
PF3	0.971	0.870	0.780	0.991

CONCLUSION:

In conclusion, the formulation and development of novel controlled-release transdermal patches of Bupranolol offer significant advancements in drug delivery technology. Through meticulous optimization and thorough characterization, the study has elucidated crucial insights into the performance and potential applications of these patches. The observed variations in physical properties among different formulations underscore the importance of formulation design in achieving desired patch characteristics. Moreover, the mechanical strength and suitability of the patches for transdermal application have been demonstrated through thickness measurements and folding endurance assessments. The differential water uptake capacities, as indicated by swelling ratio data, suggest the potential of certain formulations to enhance drug release kinetics. However, the susceptibility to environmental moisture, as evidenced by moisture content and uptake analyses, underscores the need for careful consideration during storage and handling. Importantly, the sustained release profiles observed in in vitro studies offer promising prospects for controlled drug delivery, with the optimized formulation (PF3) exhibiting particularly favorable release kinetics. These findings collectively highlight the potential of the developed transdermal patches to provide improved therapeutic outcomes for Bupranolol therapy, offering advantages such as

enhanced patient compliance and minimized side effects**.**

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