DESIGN, DEVELOPMENT AND EVALUATION OF TRANSDERMAL PATCHES CONTAINING GALANTAMINE HYDROBROMIDE

Bariki Rajasekhar[1*], Haranath Chinthaginjala[2]

Abstract

This study aimed to develop an effective transdermal drug delivery system of Galantamine Hydrobromide, an anti-Alzheimer's drug, to improve patient compliance and optimize drug therapy in patients with dementia who often have difficulties adhering to oral medication schedules. Various transdermal patches of GH were prepared using the box-Behnken design of experiments with different polymer combinations. The fabricated patches were evaluated for properties like thickness, folding endurance, drug content uniformity, in vitro drug release, and diffusion studies. The results were compared to conventional tablets containing the same polymer combination. Formulation A2 containing Hydroxy Propyl Methyl Cellulose (HPMC) 137.5 mg, Ethyl Cellulose (EC) 400 mg, and xanthan gum 300 mg had a flux of 212.24 µg/cm2/h, the permeability of 2.32 cm/h, and 27.95% release at 8h, with first-order and non-Fickian drug release kinetics. The optimized transdermal patch formulation had the potential to provide a prolonged release of GH for over 2 d and reduce the frequency of dosing. However, further studies are warranted to confirm the efficacy, safety, and pharmacokinetics of the patches in animal and human models before clinical use.

Key words: Alzheimer's disease, Galantamine Hydrobromide, Transdermal patches

[1]*Research Schloar, Department of Pharmaceutical Sciences, Jawaharlal Nehru Technological University-Anantapur, Ananthapuramu (Andhra Pradesh), India
[2]Department of Industrial Pharmacy, Raghavendra Institute of Pharmaceutical Education and Research (RIPER)- Autonomous, K.R Palli Cross, Ananthapuramu-515721, affiliated to Jawaharlal Nehru Technological University- Anantapur, Ananthapuramu (Andhra Pradesh), India

***Corresponding Author**: Bariki Rajasekhar
*Research Schloar, Department of Pharmaceutical Sciences, Jawaharlal Nehru Technological University-Anantapur, Ananthapuramu (Andhra Pradesh), India

DOI: 10.53555/ecb/2023.12.9.252

Introduction

Alzheimer's disease is a neurological condition characterized by a decline in acetylcholine, a neurotransmitter essential for brain function. It most commonly affects individuals over 60 y of age and is the most prevalent type of dementia. Alzheimer's progressively impairs cognition and physical abilities, eventually resulting in death. The degeneration of acetylcholine in the brain leads to the characteristic symptoms of Alzheimer's Disease, which worsens over time but disproportionately impacts older members of the population. Though incurable currently, treatments aim to slow the progression of this debilitating and terminal illness. Transdermal delivery systems, like medicated skin patches, offer an alternative that can be beneficial for these patients. With transdermal delivery, caretakers can visually confirm that the patch is in place and the proper dose is being delivered. This helps avoid confusion or errors that could occur with oral medication. For dementia patients, the reduced reliance on patient compliance and the ability to easily verify delivery makes transdermal systems an attractive option for drug delivery. Transdermal drug delivery has several advantages over other delivery methods. Its non-invasive application and removal process increases patient compliance. The patch provides a predetermined, consistent rate of drug absorption, increasing bioavailability and decreasing the metabolism of the drug in the liver. These characteristics make transdermal delivery well-suited for sustained, long-term delivery of a drug over 24 h or more. Due to the ease of use for patients and caretakers and the stable dosage and pharmacokinetics, transdermal systems are an attractive delivery method for many drugs, especially those requiring prolonged or frequent doses. The advantages can improve patient experience and outcomes relative to other delivery approaches. Galantamine Hydrobromide belongs to Biopharmaceutics Classification System (BCS) class I drug and is approved to treat Alzheimer's disease. It works as a reversible acetylcholinesterase inhibitor in the central nervous system, with a long half-life of 70 h. GH's low dose requirement, extended half-life, balance of hydrophilic and lipophilic properties, and minimal toxicity make it a good candidate for transdermal drug delivery. The sustained and consistent delivery of GH through a transdermal patch could maintain effective levels of the drug in the body for a prolonged period, which would be beneficial for Alzheimer's patients, given the degenerative nature of the disease and the challenges of oral administration and patient compliance. So GH appears well-suited for administration via a long-acting transdermal delivery system [1,2]. Due to the advantages of transdermal delivery, the market for medicated patches has grown significantly in recent years. The primary objective of this work is to develop a transdermal patch formulation for GH that meets pharmaceutical standards, remains stable and effective, is affordable to produce, and maintains a high level of quality.

Materials and Methods

Materials

The active ingredient, Galantamine hydrobromide, was obtained as a gift from Gallium Pharma Pvt. Ltd. All of the polymers and excipients like Ethyl cellulose (EC), Hydroxypropyl methylcellulose (HPMC) 50 cps, xanthan gum, Polyethylene glycol (PEG), Propylene glycol (PG), Dibutyl phthalate (DBP), Dimethyl Sulfoxide (DMSO), and Methanol were laboratory-grade chemicals procured from SD Fine Chemicals Ltd. in Chennai, India.

Methods

Preparation of patches by solvent casting method

For this study, Galantamine hydrobromide transdermal patches containing Galantamine hydrobromide were produced using the solvent-casting method [3]. The patches were cast onto flat, specially fabricated rectangular glass slides. The solvent casting method involves dissolving the polymers and other components in a solvent, pouring the resulting solution onto a casting surface, and then allowing the solvent to evaporate, leaving behind the patch material containing the active drug. The glass slides provided a smooth, stable surface for casting the patches and facilitating the solvent evaporation process [4].

Trial runs

Trial formulations of the GH transdermal patch were developed using a one factor at a time (OFAT) approach where HPMC was used between concentrations of 100 to 150 mg, EC was used between 300 to 400 mg while xanthan gum was used in the range of 200 to 300 mg. These concentrations are chosen based on the literature review. The goal of these initial trials was to determine the ideal concentrations of individual polymers (HPMC, EC, and xanthan gum) needed to produce patches with acceptable quality and properties. The results from the OFAT trials were then used to further fine-tune the formulations using Box-Behnken design, a quality by design (QbD) approach used for optimization. By first

identifying the concentration ranges of each polymer that could produce adequate patches, these ranges could be refined and the interactions between polymers could be explored using the Box-Behnken design to generate an optimized formulation [5,6]. To prepare the polymeric solution, HPMC 50 cps or ethyl cellulose was dissolved in 50 ml methanol. For xanthan gum, a 50:50 water and methanol mixture (50 ml containing 25 ml water and 25 ml methanol) was used to avoid precipitation and improve solubility. The quantities of each excipient used are shown in table 2. Polyethylene glycol and propylene glycol were added as co-solvents and the mixture was homogenized to achieve uniformity. Dibutyl phthalate was included as a plasticizer. 20 mg of galantamine hydrobromide was added to the polymeric solution and allowed to stand for 1-2 h to remove air bubbles. Sonication was also used to help remove air bubbles. The solution was poured onto glass slides (which are cut into a size of 4 cm x 2 cm) and dried at room temperature. After drying, the patches are peeled from the slides and cut into two halves (each one with a dimension of 2x2 cm), each containing 10 mg of GH. Aluminum foil functions as a backing membrane upon which a medical adhesive tape is used that helps in adhering the patch to the skin. The active side of the patch was covered with wax paper until use. The layers of the patch are shown in fig. 1. All trial formulations were prepared using the solvent casting technique [7].

Box-behnken design

The trial formulations of transdermal patches containing GH were evaluated for various quality control parameters, including physical appearance, folding endurance, swelling index, and percentage of drug released. It is observed from the trial runs that 125 mg of HPMC; 350 mg of ethyl cellulose, and 300 mg of xanthan gum produced optimal results and these ideal concentrations are used as the low, middle, and high values to develop formulations using the Box- Behnken design [8]. As the polymer system significantly impacts the performance of the drug in a transdermal patch, the concentrations of HPMC (50 cps), ethyl cellulose, and xanthan gum were used as the independent variables.

Table 1: Formulation of GH transdermal patches

Formulation	HPMC (mg)	Xanthan Gum (mg)	GH (mg)	Dibutyl Pthalate (ml)	PG (ml)	PEG (mg)	DSMO %	Methanol (ml)
A1	350	275	20	6	2	100	10	qs
A2	400	300	20	6	2	100	10	qs
A3	350	300	20	6	2	100	10	qs
A4	400	275	20	6	2	100	10	qs
A5	375	300	20	6	2	100	10	qs
A6	375	275	20	6	2	100	10	qs
A7	375	250	20	6	2	100	10	qs
A8	375	250	20	6	2	100	10	qs
A9	350	275	20	6	2	100	10	qs
A10	400	250	20	6	2	100	10	qs
A11	375	275	20	6	2	100	10	qs
A12	400	275	20	6	2	100	10	qs
A13	375	300	20	6	2	100	10	qs
A14	350	250	20	6	2	100	10	qs
A15	375	275	20	6	2	100	10	qs

Fig. 1: GH transdermal patches

Results

Weight variation

The weight variation of the transdermal patch formulations ranged from 0.81+0.33 g to 1.64+0.46 g. The formulations containing higher proportions of ethyl cellulose (EC) showed lower weight variation (table 2), while those containing more hydroxypropyl methylcellulose (HPMC) showed higher weight variation. Weight variation can impact dosage uniformity, so lower variation is desirable [9]. Based on these results, EC may be more suitable than HPMC for achieving consistent weight in the patches.

Thickness

The thickness of the developed transdermal patch formulations ranged from 1.01+0.07 mm to 1.68+0.10 mm (table 2). The formulations containing higher amounts of ethyl cellulose (EC) and xanthan gum showed lower thickness, while those containing hydroxypropyl methylcellulose (HPMC) showed higher thickness. Patch thickness can impact properties such as flexibility and wear comfort, so an ideal thickness range may exist [0]. Based on these results, EC and xanthan gum may be more suitable than HPMC for achieving a desirable patch thickness.

Folding endurance

The folding endurance of the prepared transdermal patch formulations, which indicates mechanical strength, ranged from 139+1.99 to 212+4.33 (table 2). Formulations with higher amounts of ethyl cellulose (EC) showed higher folding endurance, followed by those with more xanthan gum and then hydroxypropyl methylcellulose (HPMC). The higher folding endurance of EC could be due to its greater elasticity, which could improve the mechanical strength of the patches beyond the yield point under stress. Higher folding endurance is desirable to ensure a patch can withstand the physical stresses of application, wear, and removal [11]. Therefore, EC may be the most suitable of the polymers for achieving adequate mechanical strength.

Tensile strength

The tensile strength of the prepared formulations ranged from 0.7 kg/cm2 to 4.2 kg/cm2 (table 3). These values indicate the elasticity and ruggedness of the patches and serve as a measure of their durability against wear and tear during usage.

Surface pH

The surface pH of transdermal patch formulations was measured to determine if the pH was suitable for skin contact. The pH values ranged from 7.39+0.13 to 7.84+0.12, indicating a neutral pH (table 2). A neutral pH is desirable for a transdermal patch to avoid irritation to the skin or interference with skin functions. The skin surface pH is typically slightly acidic, so a neutral patch pH will not cause irritation or other issues due to a pH difference. By evaluating the surface pH, formulations with a suitable pH for skin contact could be identified [12-14]. This is important for the comfort, tolerability, and safety of a transdermal patch.

Swelling index

The swelling index of the prepared patches was measured to assess their ability to absorb skin secretions. The swelling index ranged from 1.46 to 3.15 (table 2). Formulations containing xanthan gum showed the highest swelling index, followed by those with ethyl cellulose (EC) and then hydroxypropyl methylcellulose (HPMC). A higher swelling index indicates a greater ability to absorb moisture, which is desirable for transdermal patch comfort and tolerability. By evaluating the swelling index, the polymer concentrations that achieved adequate moisture absorption could be identified [15-16]. This is important for preventing skin irritation from a transdermal patch.

Moisture vapor transmission rate

The moisture vapor transmission rate (MVT) of the transdermal patch formulations ranged from 0.011 to 0.054 mg/cm2/hr (table 2). Formulations containing xanthan gum showed the highest MVT, followed by those with ethyl cellulose (EC) and then hydroxypropyl methylcellulose (HPMC). Higher MVT can enhance comfort by allowing for adequate moisture transmission to and from the skin. By evaluating the MVTR, the polymer concentrations that achieved a suitable rate of moisture transfer could be identified [17]. This ensures that the transdermal patch does not interfere with the natural moisture dynamics of the skin.

Drug content

The drug content of the prepared patches ranged from 95.7%+0.76% to 99.55%+0.28% (table 4). Formulations containing ethyl cellulose (EC) showed the highest drug content, followed by those with xanthan gum and then hydroxypropyl methylcellulose (HPMC). Higher drug content is desirable to ensure the target dose is delivered.

% Moisture uptake

The moisture uptake of the optimized transdermal patch formulations from the Box-Behnken design ranged from 4.48% to 10.94% (table 2). Formulations with higher amounts of ethyl cellulose (EC) showed higher moisture uptake, followed by those with more xanthan gum and then hydroxypropyl methylcellulose (HPMC). Higher moisture uptake can indicate greater hydration of the patch, which may be important for adhesion, flexibility, and wear comfort [18].

% Moisture loss

The moisture loss of the optimized transdermal patch formulations from the Box-Behnken design ranged from 4.14% to 7.56% (table 2). Formulations with higher amounts of ethyl cellulose (EC) showed lower moisture loss, followed by those with more xanthan gum and then hydroxypropyl methylcellulose (HPMC). Lower moisture loss can indicate greater retention of hydration by the patch, which may be important for adhesion, flexibility, and wear comfort [19-21].

Table-2: Results of evaluation parameters of formulations A1 to A15

Formulation code	Wt. Variation (gm)*	Thickness (mm)*	Folding endurance (No of folds)*	Tensile strength (Kg/cm^2)	Surface pH*	Swelling index
A1	1.29±0.81	1.18±0.07	157±2.85	1.3	7.41±0.12	2.27
A2	0.95±0.69	1.25±0.12	218±4.37	4.4	7.4±0.17	3.55
A3	1.29±0.53	1.27±0.11	163±3.24	1.6	7.52±0.23	2.41
A4	1.07±0.64	1.22±0.11	204±3.64	3.7	7.37±0.12	3.35
A5	1.26±0.27	1.43±0.11	191±2.84	3.1	7.54±0.14	3.14
A6	1.24±0.61	1.72±0.14	185±4.23	2.8	7.09±0.15	3.08
A7	0.78±0.37	1.52±0.08	167±3.35	1.8	7.28±0.07	2.68
A8	1.02±0.96	1.57±0.11	175±1.89	2.1	7.31±0.19	2.71
A9	1.26±0.65	1.71±0.11	145±2.03	0.9	7.39±0.16	1.86
A10	1.19±1	1.3±0.12	195±1.85	3.4	7.46±0.19	3.21
A11	1.49±0.59	1.05±0.11	185±1.75	2.8	7.41±0.11	3.08
A12	1.36±0.95	1.41±0.16	210±2.03	4.1	7.49±0.08	3.42
A13	1.41±0.73	1.57±0.09	180±2.12	2.4	7.52±0.14	2.99
A14	1.61±0.5	1.52±0.12	148±2.02	1.1	7.46±0.21	2.04
A15	1.32±0.63	1.72±0.07	185±4.55	2.8	7.49±0.15	3.08

Formulation code	Moisture vapour transmission rate (gm/cm^2)	Drug content (%)*	%Moisture uptake	%Moisture loss	Steady state flux mcg. cm-2. h^{-1}	Permeability coefficient cm. h^{-1}
A1	0.018	96.1±0.82	6.01	7.49	128.51	6.72
A2	0.057	99.9±0.34	10.54	4.44	213.28	3.36
A3	0.022	98±0.81	6.79	7.19	137.89	6.33
A4	0.044	98.2±0.28	9.31	5.12	199.77	3.78
A5	0.034	98.5±0.34	8.82	5.63	188.93	4.3
A6	0.031	99.6±0.49	8.71	6.17	180.07	5.18
A7	0.024	99.2±0.39	7.12	7.03	145.29	5.8
A8	0.027	99.5±0.59	7.64	6.86	160	4.65
A9	0.014	96.3±0.46	4.08	7.86	102.28	7.93
A10	0.037	97.9±0.61	9.16	5.42	196.71	3.95
A11	0.031	97.9±0.64	8.71	6.17	180.07	5.18
A12	0.051	97.2±0.83	9.35	4.87	209.21	3.7
A13	0.029	96.6±0.39	8.02	6.44	165.25	4.86
A14	0.015	96.5±0.39	5.56	7.54	119.73	7.16
A15	0.031	98.5±0.56	8.71	6.17	180.07	5.18

Table 3: In vitro drug release from the transdermal patches A1 to A15

Time(h)	A1	A2	A3	aA4	A5	A6	A7	A8	A9	A10	A11	A12	A13	A14	A15
0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
0.5	20.8	3.7	20.6	6.2	12.3	16.7	18.7	17.8	24.9	8.2	16.7	4.7	16.4	24.8	16.7
1	25.6	5.7	24.7	11.8	16.9	18.5	22.1	21.8	28.7	12.5	18.5	8	20	26.5	18.5
2	27.7	8.4	26.7	13.8	17.6	19.6	23.9	23.4	32.1	15.1	19.6	9.3	21.8	31.1	19.6
3	32.7	9.7	31.4	15.2	20.3	21.1	28.1	27.1	36.4	17.4	21.1	10.3	24	33.5	21.1
4	41	15	37.8	20.2	25.3	25.8	33.8	31.3	43.2	23.7	25.8	17.9	28.4	42.2	25.8
5	41.3	17.8	40.3	22.1	30	32.5	39.4	37.1	46.6	26.8	32.5	19.3	35.2	43.2	32.5
6	45.5	24	44.4	29.9	32.5	34.1	42.3	39.4	48.8	31.6	34.1	27.9	36.7	47.4	34.1
8	48.1	27.1	47.5	34.4	40.6	42.9	46.7	45.5	50.7	37.5	42.9	32.2	44.6	49.3	42.9
10	55.6	31.5	53.6	39.5	44.1	44.8	52.4	50.5	58.4	40.2	44.8	37	48.9	57.3	44.8
12	65.1	37.4	63.2	43.3	49.9	53.9	62.6	60.8	68.6	44.1	53.9	40.4	57.6	68.2	53.9
16	75.8	43.8	73.4	50.7	55.9	59.3	68.6	66.2	81.9	51.9	59.3	45.3	63.1	78.8	59.3
20	77.2	50.3	75.8	58.8	63.9	68.5	75.2	72.8	80.6	61.1	68.5	53.7	72.7	80.2	68.5
24	83.8	59.8	82.1	64.4	71	73.6	79.6	79.4	87.8	68.3	73.6	61.5	77	87.5	73.6
28	95	67	91.7	72.5	75.8	80.5	86.9	84.2	99.6	74.3	80.5	69.2	83.6	98.8	80.5
32	99.5	72.6	98.7	76.4	83.1	84.9	89.6	87.4		80.2	84.9	73.9	86.7		84.9
36		79.1		87.2	90.7	98.7	100.04	98.76		89.8	99.3	82.3	99.9		98.8
40		86.7		91.8	99.5					98.4		89.3			
44		92.3		98.3								98.4			
48		98.3													

Table 4: Summary of the responses for the models generated using Box Behnken design

Response	R^2	Adjusted R^2	Standard deviation	Probability>F
Folding endurance	0.957	0.945	5.08	<0.0001
Tensile strength	0.945	0.929	0.29	<0.0001
Swelling index	0.984	0.955	0.11	<0.0001
% Drug release at 8^{th} hour	0.983	0.953	1.46	<0.0001

Stability studies

The results of the stability studies indicate that the optimized formulation A2 is intact throughout the study period of 30 d with acceptable drug content and physical appearance at different temperatures (4, 45, and 60 °C).

Discussion

The study demonstrated the feasibility of developing an effective galantamine hydrobromide transdermal patch. Several characterization techniques were employed to evaluate the drug-polymer compatibility, physicochemical properties, drug release profiles, and skin irritation potential of the formulated patches [22]. Among the polymers evaluated, ethyl cellulose-based formulations showed the lowest weight variation (0.81+0.33 g), thickness (1.01+0.07 mm), and drug release (27.95% in 8 h), with the highest drug content (99.55%+0.28%), folding endurance (212+4.33), tensile strength (4.2 kg/cm2) and moisture uptake (10.94%). Formulation A2 containing the highest amount of ethyl cellulose (400 mg) demonstrated the most desirable overall properties as evident from the Box-Behnken models and practical values [23]. EC and HPMC can form hydrogen bonds and hydrophobic interactions with each other, leading to a more uniform and stable polymer matrix. Xanthan gum can also form hydrogen bonds and electrostatic interactions with HPMC and EC, further strengthening the matrix. These molecular interactions help form a coherent and cohesive polymer network that can better control drug release. EC acts as the primary release modifier and forms a hydrophobic barrier that retards drug diffusion. HPMC helps swell upon contact with the aqueous medium, which allows water to penetrate the matrix and dissolve the drug. Xanthan gum forms a gel-like layer upon hydration that further slows down the water ingress and drug efflux. The combination of EC, HPMC, and xanthan gum provides a polymer matrix with suitable viscosity and gel strength to sustain the drug release over an extended period of time [24-26]. Each polymer contributes to the overall viscosity and gel properties in a synergistic way. The combined effects of these physicochemical interactions likely optimally modulated the drug release rate from formulation A2. As water penetrates the matrix and the polymers hydrate and swell, they form a porous network structure with interconnected channels [27-30]. The precise combination of polymers in formulation A2 likely created an optimal porous

network microstructure that allowed controlled diffusion of the drug. Among all the formulations, the A2 formulation is found to be a promising once-daily transdermal patch candidate, and ethyl cellulose was found to impart the most desirable performance characteristics.

Conclusion

The present work demonstrates that galantamine hydrochloride can be delivered via a transdermal drug delivery system using a matrix polymeric system of EC, xanthan Gum, and HPMC. The transdermal patch provides a controlled release of the drug, which may allow for reduced dosing frequency in patients with Alzheimer's disease. The non-invasive transdermal patch also increases patient compliance due to its ease of application and removal. Continued testing could also help optimize the patch design and drug delivery rate. Overall, this study shows the potential for transdermal delivery of galantamine hydrochloride, but more research is warranted.

References

1. Saxena M, Mutalik S, Reddy MS. Formulation and evaluation of transdermal patches of metoclopramide hydrochloride. Indian Drugs. 2006;43(9):740-5.
2. Tanwar YS, Chauhan CS, Sharma A. Development and evaluation of carvedilol transdermal patches. Acta Pharm. 2007;57(2): 151-9. doi: 10.2478/v10007-007-0012-x, PMID 17507312.
3. Patel RP, Patel G, Baria A. Formulation and evaluation of transdermal patch of aceclofenac. Int J Drug Del;1(1):41-51. doi: 10.5138/ijdd.2009.0975.0215.01005.
4. Bhatia C, Sachdeva M, Bajpai M. Formulation and evaluation of transdermal patch of pregabalin. Int J Pharm Sci Res. 2012;3(2): 569.
5. Atılay Takmaz EA, Yener G. Effective factors on iontophoretic transdermal delivery of memantine and donepezil as model drugs. J Drug Deliv Sci Technol. 2021;63:102438. doi: 10.1016/j.jddst.2021.102438.
6. Kumar SS, Behury B, Sachinkumar P. Formulation and evaluation of transdermal patch of stavudine. Dhaka Univ J Pharm Sci. 2013;12(1):63-9. doi: 10.3329/dujps.v12i1.16302.
7. Mohabe V, Akhand R, Pathak AK. Preparation and evaluation of captopril transdermal patches. Boll Pharm Res. 2011; 1(2):47-52.
8. Ganti SS, Bhattaccharjee SA, Murnane KS, Blough BE, Banga AK. Formulation and evaluation of 4-benzylpiperidine drug-in-adhesive matrix type transdermal patch. Int J Pharm. 2018;550(1- 2):71-8. doi: 10.1016/j.ijpharm.2018.08.033, PMID 30125654.
9. Kusum Devi V, Saisivam S, Maria GR, Deepti PU. Design and evaluation of matrix diffusion controlled transdermal patches of verapamil hydrochloride. Drug Dev Ind Pharm. 2003;29(5):495- 503. doi: 10.1081/ddc-120018638, PMID 12779279.
10. Kriplani P. Formulation and evaluation of transdermal patch of diclofenac sodium. GJPPS 2018;4(5). doi: 10.19080/GJPPS.2018.04.555647.
11. Jayaprakash S, Halith SM, Firthouse PM, Yasmin YM, Nagarajan M. Preparation and evaluation of celecoxib transdermal patches. Pak J Pharm Sci. 2010;23(3):279-83. PMID 20566440.
12. Shivalingam MR, Balasubramanian A, Ramalingam K. Formulation and evaluation of transdermal patches of pantoprazole sodium. Int J App Pharm. 2021 Sep 7:287-91. doi: 10.22159/ijap.2021v13i5.42175.
13. Singh A, Bali A. Formulation and characterization of transdermal patches for controlled delivery of duloxetine hydrochloride. J Anal Sci Technol. 2016 Nov 28;7(1):25. doi: 10.1186/s40543-016-0105-6.
14. Nair AB, Jacob S. A simple practice guide for dose conversion between animals and human. J Basic Clin Pharm. 2016;7(2):27- 31. doi: 10.4103/0976-0105.177703, PMID 27057123.
15. Sheth NS, Mistry RB. Formulation and evaluation of transdermal patches and to study permeation enhancement effect of eugenol. J Appl Pharm Sci. 2011;(Issue):96-101.
16. Banker GS. The theory and practice of industrial pharmacy. J Pharm Sci. 1970 Oct;59(10):1531.
17. Bala R, Sharma S. Formulation optimization and evaluation of fast dissolving film of aprepitant by using design of experiment. Bull Fac Pharm Cairo Univ. 2018;56(2):159-68. doi: 10.1016/j.bfopcu.2018.04.002.
18. Roy H. Box-Behnken design for optimization of formulation variables for fast dissolving tablet of urapidil. Asian J Pharm AJP. 2018;12(03).
19. Elballa W, Salih M. Influence of partially and fully pregelatinized starch on the physical and sustained-release properties of hpmc- based

ketoprofen oral matrices. Int J Pharm Pharm Sci. 2022 Aug 1:29-34.
doi: 10.22159/ijpps.2022v14i8.45031.

20. Farooqui P, Gude R. Formulation development and optimisation of fast dissolving buccal films loaded glimepiride solid dispersion with enhanced dissolution profile using central composite design. Int J Pharm Pharm Sci. 2023 Jun 1;15(6):35-54. doi: 10.22159/ijpps.2023v15i6.47992.
21. Shinde R, Velraj M. Formulation, optimization, and characterization of transdermal drug delivery systems containing eplerenone. Int J App Pharm. 2022 Jan 7;14(1):198- 207.
doi: 10.22159/ijap.2022v14i1.42827.
22. Alam MI, Alam N, Singh V, Alam MS, Ali MS, Anwer T. Type, preparation and evaluation of transdermal patch: a review. World J Pharm Pharm Sci. 2013;2(4):2199-233.
23. Kanasty R, Low S, Bhise N, Yang J, Peeke E, Schwarz M. A pharmaceutical answer to nonadherence: once weekly oral memantine for Alzheimer's disease. J Control Release. 2019;303:34-41.
doi: 10.1016/j.jconrel.2019.03.022, PMID 30928488.
24. Calhoun A, King C, Khoury R, Grossberg GT. An evaluation of memantine ER+ donepezil for the treatment of Alzheimer's disease. Expert Opin Pharmacother. 2018;19(15): 1711-7.
doi: 10.1080/14656566.2018.1519022, PMID 30244611.
25. Hardainiyan S, Kumar K, Nandy BC, Saxena R. Design, formulation and in vitro drug release from transdermal patches containing imipramine hydrochloride as model drug. Int J Pharm Pharm Sci. 2017 Jun 1;9(6):220. doi: 10.22159/ijpps.2017v9i6.16851.
26. Bashyal S, Shin CY, Hyun SM, Jang SW, Lee S. Preparation, characterization, and in vivo pharmacokinetic evaluation of polyvinyl alcohol and polyvinyl pyrrolidone blended hydrogels for transdermal delivery of donepezil HCl. Pharmaceutics. 2020;12(3): 270. doi: 10.3390/pharmaceutics12030270, PMID 32188083.
27. Kearney MC, Caffarel Salvador E, Fallows SJ, McCarthy HO, Donnelly RF. Microneedle-mediated delivery of donepezil: potential for improved treatment options in Alzheimer's disease. Eur J Pharm Biopharm. 2016;103:43-50. doi: 10.1016/j.ejpb.2016.03.026, PMID 27018330.
28. MNJ, Chandrakala V, Srinivasan S. An overview: recent development in transdermal drug delivery. Int J Pharm Pharm Sci. 2022 Oct 1:1-9.
29. Choudhory N, Kaur T, Singh AP, Singh AP. Formulation and evaluation of maslinic acid-loaded transdermal patches. Int J Curr Pharm Sci. 2021 Nov 15:89-98.
doi: 10.22159/ijcpr.2021v13i6.1933.
30. Walbi IA, Ahmad MZ, Ahmad J, Algahtani MS, Alali AS, Alsudir SA. Development of a curcumin-loaded lecithin/chitosan nanoparticle utilizing a box-behnken design of experiment: formulation design and influence of process parameters. Polymers. 2022;14 (18):3758. doi: 10.3390/polym14183758, PMID 36145903.