Formulation and Characterization of Eudragit-Based Transdermal Patches of Risperidone

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Abstract*—Atypical antipsychotics such as risperidone and olanzapine are effective in the treatment of psychosis, yet oral administration is limited by side effects, poor compliance, and fluctuating plasma concentrations. This study aimed to develop and evaluate Eudragit-based transdermal drug delivery systems (TDDS) of risperidone and olanzapine to overcome these challenges. Transdermal patches were prepared using the solvent casting method with Eudragit RL100/RS100 polymers and various permeation enhancers, including Span 20, sodium lauryl sulphate, benzalkonium chloride, olive oil, jojoba oil, and groundnut oil. The films were evaluated for physicochemical properties, drug content, moisture uptake, folding endurance, and tensile strength. FTIR confirmed drug–excipient compatibility, while SEM revealed uniform surface morphology and penetration of drug into the skin. In vitro drug release and ex vivo permeation studies demonstrated that patches containing enhancers provided markedly higher drug release and flux values compared to patches without enhancers. The best permeation was obtained with Span 20 for olanzapine (26.74 µg/cm²/h) and olive oil for risperidone (23.14 µg/cm²/h). In vivo pharmacological testing in animals confirmed sedative and tranquilizing activity comparable to marketed oral formulations, while pharmacokinetic studies revealed lower Cmax, prolonged Tmax, slower elimination, and enhanced bioavailability for transdermal patches. Skin irritation studies indicated no signs of erythema or edema, and stability testing confirmed formulation robustness. These findings suggest that transdermal patches of risperidone and olanzapine provide sustained release, improved safety, and better patient compliance, representing a promising alternative to conventional oral dosage forms in long-term psychosis management.

***Index Terms*—Risperidone; Olanzapine; Atypical antipsychotics; Transdermal drug delivery system (TDDS); Eudragit RL100/RS100; Permeation enhancers; In vitro and in vivo evaluation; Pharmacokinetics.**

I. INTRODUCTION

Novel drug delivery systems, especially transdermal drug delivery systems (TDDS), improve therapeutic outcomes by enhancing patient adherence, reducing side effects, and maintaining consistent drug levels. TDDS deliver drugs non-invasively through the skin, bypassing gastrointestinal issues and first-pass metabolism. Benefits include suitability for patient's intolerant to oral drugs and steady drug absorption. Examples include fentanyl (pain), nitroglycerine (angina), and scopolamine (motion sickness). Since the first TDDS patch in 1981, over 35 products have driven market growth, though research on psychotropic TDDS is limited.

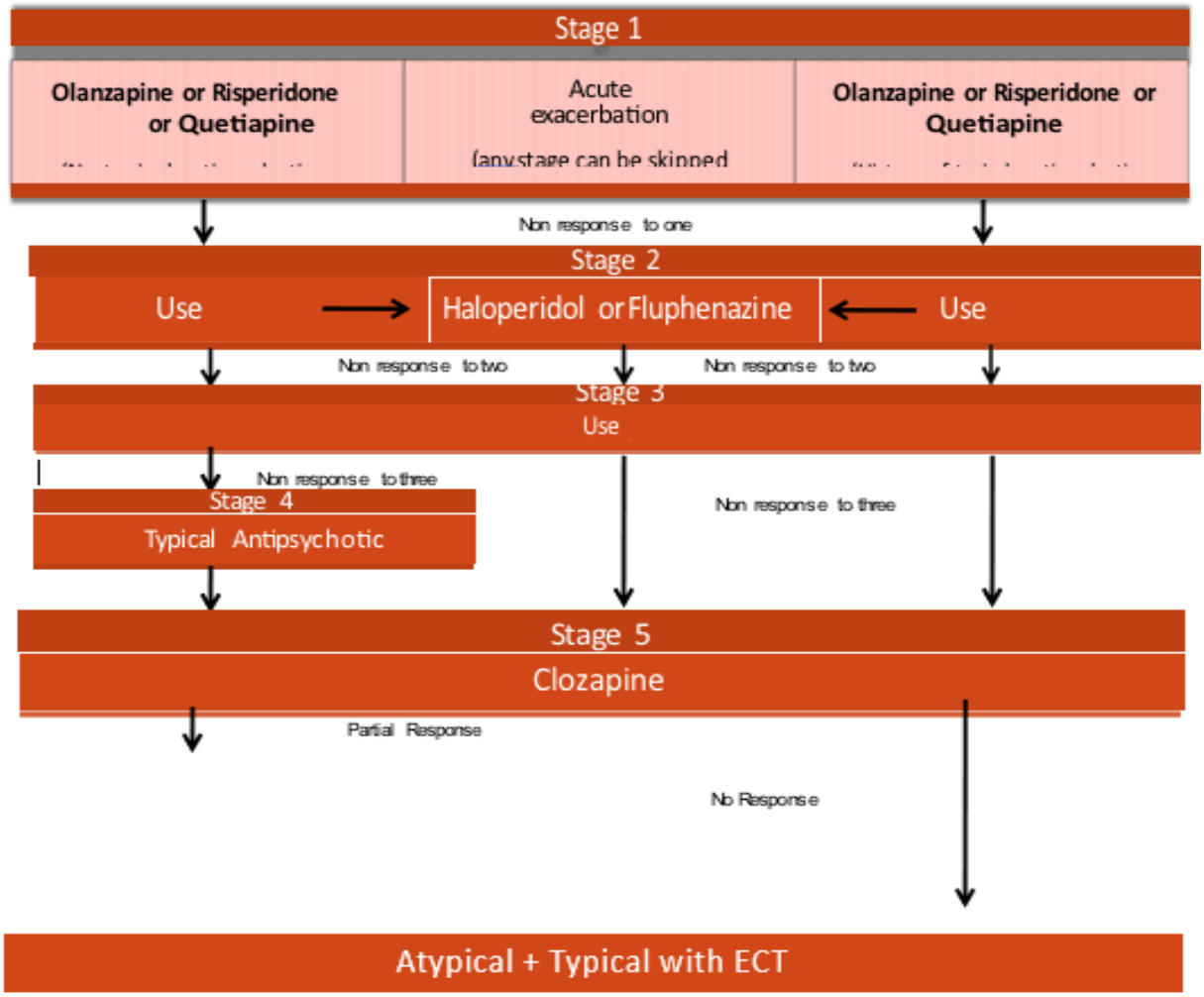


Figure 1: Treatment algorithm for Psychosis (Branford, 2003)

Schizophrenia, a chronic brain disorder affecting ~1% of people, typically emerges in late teens to early thirties, causing hallucinations, delusions, disorganized thinking, and negative symptoms like flat affect or poor attention. Its exact cause, possibly linked to dopamine or monoamine imbalances, remains unclear. Diagnosis involves medical/mental health history and exams to exclude other conditions. Antipsychotics, like chlorpromazine (typical) or risperidone (atypical), manage symptoms but are not curative; atypical ones are safer, targeting both positive and negative symptoms with fewer side effects. Non-adherence and side effects like orthostatic hypotension pose challenges, but long-acting formulations and novel delivery methods (e.g., transdermal, implants) enhance compliance and efficacy.

Transdermal drug delivery systems (TDDS) offer significant benefits for schizophrenia treatment, including improved patient adherence, reduced dosing frequency, and lower relapse rates by maintaining constant drug levels. They bypass first-pass metabolism, minimize over/underdosing, and allow easy termination. Suitable drugs, like olanzapine and risperidone, must be non-ionic, low molecular weight (<500 Da), soluble in oil/water (log P:1-3), low melting point (<200°C), potent (<100 mg daily dose), and non-irritating. The stratum corneum's lipoidal barrier is overcome using hydration, chemical enhancers, or vesicles/liposomes. Advanced technologies like iontophoresis and sonophoresis enhance delivery of drugs like haloperidol and methylphenidate, unrestricted by molecular size or solubility. Transdermal gels provide flexibility and

aesthetics over patches. These innovations expand TDDS applications, improving safety, efficacy, and compliance, with a growing market for psychotropic drug delivery.

Recent advancements in schizophrenia treatment highlight atypical antipsychotics like risperidone and olanzapine, which manage both positive and negative symptoms with fewer side effects than traditional neuroleptics. Risperidone (2–8 mg/day) treats schizophrenia, bipolar disorder, and autism-related behavioral issues, while olanzapine (5–20 mg/day) addresses schizophrenia, mania, and anxiety. Both are typically administered orally or via injection, but noncompliance, causing ~33% of short-stay hospital costs, is a challenge. Transdermal drug delivery systems (TDDS) could improve compliance by providing sustained drug levels, reducing side effects like orthostatic hypotension, and offering easy application/removal. The stratum corneum's barrier requires penetration enhancers (e.g., surfactants, vegetable oils) to facilitate drug absorption. This research proposes developing a TDDS for risperidone and olanzapine using enhancers like surfactants (BC, SLS, span 20) and vegetable oils (olive, jojoba, groundnut) to optimize low-dose, cost-effective therapy with minimal side effects.

II. LITERATURE REVIEW

Recent studies highlight advancements in transdermal drug delivery systems (TDDS) for schizophrenia treatment. Patel et al. (2021, 2020) developed clozapine and quetiapine transdermal patches using Box–Behnken design, achieving enhanced bioavailability (2.18–4.59-fold) compared to oral formulations, with stable flux, tensile strength, and no skin irritation. Heo et al. (2021) demonstrated that asenapine TDDS (3.8–7.6 mg/24 h) reduced psychotic symptoms in a 6-week phase 3 study, offering better adherence and tolerability than sublingual administration. Joshi et al. (2021) optimized a flurbiprofen matrix TDDS with natural enhancers like d-limonene, improving drug permeation without irritation. Mishra et al. (2021) emphasized Quality by Design (QbD) for TDDS, ensuring optimal drug delivery with minimal residual drug. Nalluri et al. (2021) showed microneedle-assisted TDDS enhanced zolmitriptan and rizatriptan permeation, overcoming stratum corneum barriers. Earlier studies (Alam et al., 2009; Karande et al., 2005; Barry et al., 2004) detailed permeation enhancers' role in modifying stratum corneum properties to boost drug permeability. David et al. (2003) noted TDDS bypasses first-pass metabolism, reducing side effects. Patient preference for transdermal over oral delivery was evident in studies by Lake et al. (2000) and Ettinger et al. (1998), citing ease of use and better aesthetics.

III. MATERIALS AND METHODS

Materials

Chemicals: Analytical-grade chemicals were used, including risperidone (Torrent Pharmaceuticals), olanzapine (Ranbaxy Labs), Eudragit RL100/RS100 (Rohm Pharma), dichloromethane, di-n-butyl phthalate, sodium lauryl sulphate, Tween 80, benzalkonium chloride, Span 20, olive oil, jojoba oil, groundnut oil (S.D. Fine Chemicals/Rajesh Chemicals), and others like chloroform, ethanol, and HPLC-grade acetonitrile/methanol (E Merck Ltd.).

Animals: Swiss white mice (25–30g), Wistar rats (150–250g), and white rabbits (1.5–2.5 kg) from Rayat Institute of Pharmacy's Central Animal House were housed in polyacrylic cages under standard conditions (12/12 hr light/dark cycle, 22±2°C, 50–60% humidity, food/water ad libitum). Experimental protocols were IAEC-approved per CPCSEA guidelines.

Equipment: Included UV spectrophotometer (Shimadzu), electronic balance (Afoset), pH meter (Systronic), centrifuge, magnetic stirrer, shaking incubator (Remi), FTIR spectroscopy, HPLC system (Perkin Elmer), dissolution apparatus (Electrolab), scanning electron microscope (JEOL), and tensile strength tester (fabricated at Rayat Institute).

Methodology

Preformulation studies for risperidone and olanzapine included identification, solubility, partition coefficient, melting point determination, and other tests, compared with literature specifications.

Preformulation Studies

- UV Absorption Maxima: Risperidone and olanzapine (10 µg/ml) scanned at 200–400 nm in dichloromethane, methanol, n-octanol, PBS pH 7.4, and PBS with Tween 80 to determine λmax.

- Partition Coefficient: 10 mg drug in 10 ml n-octanol and PBS pH 7.4 shaken for 24 hours; phases separated, analyzed spectrophotometrically, and Ko/w calculated as Co/Cw (Shahi et al., 2008).
- UV Method Validation: Validated for linearity (2–20 µg/ml, λmax 254 nm for risperidone, 248 nm for olanzapine), accuracy, precision (inter/intra-day at 1–4 mg for risperidone, 5–20 mg for olanzapine), selectivity, and robustness.
- Calibration Curves: Prepared in methanol, dichloromethane, n-octanol, PBS pH 7.4, and PBS with Tween 80 (0.25–1% w/v) at 2–20 µg/ml, following Beer's Lambert law.
- Solubility Studies: Excess drug shaken in PBS pH 7.4 and Tween 80 solutions at 37°C for 48 hours; concentrations determined spectrophotometrically.
- Drug-Polymer Interaction: FTIR spectra of risperidone, olanzapine, Eudragit RL100/RS100, and drug-polymer mixes (1:3 KBr) scanned at 450–4000 cm^{-1}.

IV. FORMULATION OF TRANSDERMAL PATCHES

Transdermal patches of risperidone and olanzapine were prepared via solvent casting in a 3.57 cm diameter glass mould. Eudragit RL100/RS100 (500 mg, various ratios) dissolved in 10 ml isopropanol-dichloromethane (60:40), mixed with drug (20% w/w polymer), di-n-butyl phthalate (30% w/w plasticizer), and permeation enhancers (BC, SLS, Span 20, olive/groundnut/jojoba oil at 1%, 5%, 10% w/w). Solutions dried at 35°C for 24 hours, peeled, and backed with 5 cm USP adhesive tape.

Characterization of Transdermal Patches

- Weight Variation and Thickness: Ten patches weighed; thickness measured at five points (Damodaran et al., 2009).
- Drug Content: 100 mg film dissolved in 100 ml dichloromethane, shaken 24 hours, sonicated, filtered, and analyzed at 325 nm (Costa et al., 1997).
- Flatness: Strips from center/sides measured; % constriction = [(l1-l2)/l1]×100 (Chandak and Verma, 2009).
- Folding Endurance: Folds until breakage counted (Chandak and Verma, 2009).
- Tensile Strength: Film stretched via pulley system; tensile strength = break force/[a.b(1+ΔL/L)] (Gannu et al., 2008).
- Moisture Content: Films weighed pre/post 24-hour desiccation; % moisture = [(initial-final)/final] ×100 (Bagyalakshmi et al., 2007).
- Moisture Uptake: Films at 84% humidity; % uptake = [(final-initial)/initial] ×100 (Gannu et al., 2008).
- Microbial Studies: 1 cm^2 patches incubated in nutrient agar at 37°C for 48 hours, examined microscopically.

In Vitro Drug Release Studies

Used modified USP type II apparatus with 900 ml PBS pH 7.4 and Tween 80 (1% for risperidone, 0.75% for olanzapine) at 100 rpm, 32°C. Samples analyzed at 315 nm (olanzapine) and 322 nm (risperidone). Release kinetics fitted to zero-order, first-order, Higuchi, and Korsmeyer-Peppas models (Alam et al., 2009).

In Vitro Permeation Studies

- Skin Preparation: Wistar rat abdominal skin excised, cleaned, stored at -20°C, thawed for use (Ren et al., 2009).
- Permeation: Conducted in 35 ml Franz diffusion cells with PBS pH 7.4 and Tween 80 at 100 rpm, 32°C. Flux, lag time, and enhancement ratio (Epen = Ptreatment/Control) calculated (Jain et al., 2008; Gullick et al., 2010). Target flux: risperidone (5.83–23.33 µg/cm^2/h), olanzapine (12.5–25 µg/cm^2/h) for 10 cm^2 patch.
- SEM Studies: Skin/film fixed, dehydrated, gold-coated, and analyzed via SEM (JSM 6100 JEOL) (Mukherjee et al., 2005).

In Vivo Studies

- Skin Irritation: Draize method on rabbits (5 groups, n=6) with blank/drug-loaded patches, control tape, or 0.8% formalin; erythema/edema scored over 7 days (Jayaprakash et al., 2010).
- Pharmacodynamic Studies: Swiss mice (3 groups, n=4) tested via rota rod and grip tests post-oral (RISPID®, ONZA®) or transdermal (RE3, OD3) administration (Samanta et al., 2003; Zhang et al., 2007).

- Extraction Procedure for Olanzapine from Plasma: Plasma samples in 15 ml borosilicate tubes were mixed with 500 µl 0.1 M Na2CO3 and 10 ml hexane/dichloromethane (85:15), shaken for 5 minutes, and centrifuged at 1800 × g for 5 minutes. The supernatant was transferred, mixed with 200 µl 45 mM KH3PO4 (pH 2.8), shaken for 30 seconds, and centrifuged again. The organic layer was discarded, and the residue reconstituted in 500 µl mobile phase with sonication; 80 µl was injected into the HPLC system (Dusci et al., 2002).

Stability Studies

Transdermal formulations RE3 and OD3 were tested per ICH guidelines at 45°C and 75% relative humidity for 3 months. Triplicate samples were analyzed at 0, 1, and 3 months for physical texture, drug content, and in vitro permeation.

Statistical Analysis

Data (mean ± SD, n=3) were analyzed using Graph Pad Prism 5 with ANOVA and Student's t-test; $p<0.05$ was considered significant.

V. RESULT & DISCUSSION

Preformulation Studies

- Characterization: Risperidone was characterized with a melting point of 170°C, practically insoluble in water, freely soluble in methylene chloride, sparingly soluble in ethanol, and soluble in diluted HCl. Its partition coefficient (n-octanol: PBS pH 7.4) was 3.01 ± 0.16, suitable for transdermal delivery. UV λmax was 325 nm in dichloromethane.
- UV Method Validation: Calibration curves (2–20 µg/ml) showed absorbance from 0.098 to 0.788, with a regression of 0.999, confirming adherence to Beer-Lambert's law. Precision and recovery tests (Table 1) showed low RSD, indicating high robustness. Calibration in various solvents (Table 2) confirmed method specificity.
- Solubility Studies: Solubility was highest in PBS 7.4 with 1% Tween 80 (94.06 ± 0.05 mg/L, Table 3), 11 times higher than plain PBS, making it the chosen receptor fluid for in vitro studies.
- Drug-Polymer Interaction: FTIR confirmed no interactions between risperidone and Eudragit polymers (ERL 100, ERS 100), ensuring compatibility (Figures 2, 3).

Table 1: Results of recovery and precision of risperidone in dichloromethane

S.No.	Amount of drug (mg)	Amount found	% Recovery	Precision (Intra-day)	Precision (inter day)
1	1	1.03±0.05	103	0.12	0.21
2	2	1.98±0.11	99	0.11	0.25
3	4	3.89±0.04	97.2	0.07	0.15

Table 2: Calibration of risperidone in different solvents

Solvent	λ_{max}	Equation(Y=mX+C)	r^2
Dichloromethane	325	0.0386x+0.007	0.999
Methanol	324	0.0361x+0.081	0.998
PBS 7.4	324	0.023x+0.058	0.996
PBS 7.4 with 0.25% Tween 80	314	0.0296x+0.08	0.998
PBS 7.4 with 0.5% Tween 80	322	0.033x+0.013	0.996
PBS 7.4 with 0.75% Tween 80	322	0.0353x+0.003	0.999
PBS 7.4 with 1% Tween 80	322	0.0359x+0.068	0.994
n-Octanol	324	0.028x+.124	0.995

Table 3: Solubility studies of risperidone in different fluids Shamsher et al., 2010).

S. No.	Type of fluid	Concentration (mg/L)
1	PBS 7.4 pH buffer	9.62 ± 0.24
2	Buffer with 0.25% Tween 80	45.17 ± 0.36
3	Buffer with 0.5% Tween 80	66.43 ± 0.17
4	Buffer with 0.75 % Tween 80	87.21 ± 0.28

5	Buffer with 1% Tween 80	94.06 ± 0.05

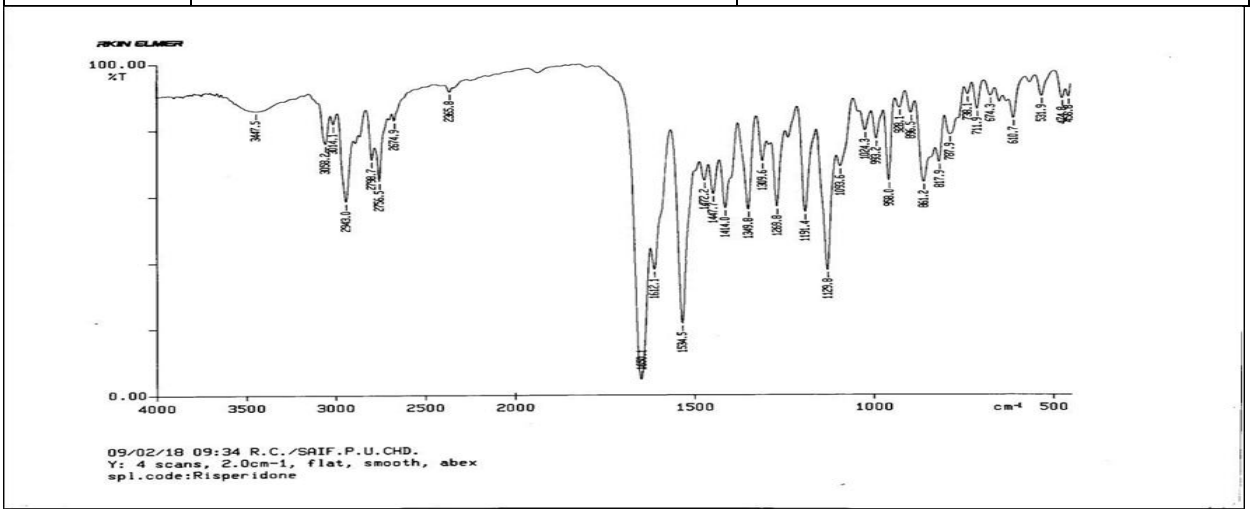
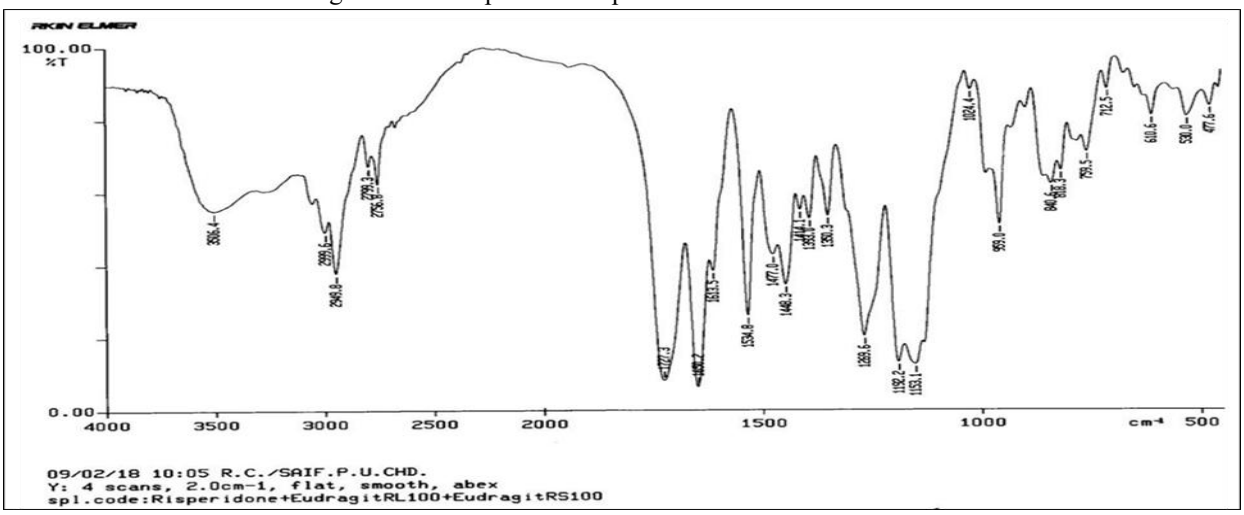


Figure 2. FTIR spectra of risperidone

Figure 3. FTIR spectra of risperidone with ERL & ERS 100



Formulation of Transdermal Patches

- Polymer and Plasticizer: Eudragit RS 100 and RL 100 formed transparent films, brittle without plasticizer. Dibutyl phthalate (30% for RA–RD, 20% for oil-based formulations) improved elasticity. Fixed oils (groundnut, jojoba, olive) acted as additional plasticizers, reducing required dibutyl phthalate to 20% (Table 4).

Table 4: Composition and physicochemical characteristics of prepared formulations of risperidone

Code	ERL 100: ERS 100(500mg)	Permeation enhancer (% w/w of polymer weight)	Average Weight variation (mg)**	Thickness (mm)	Drug content (%)	Folding enduran ce	Flatness %)	Tensile strength (kg/mm^2)
RA1	5:0	-	169.91±1.02	0.56±0.02	94.32±2.14	12±0.51	100±0.00	0.365±0.02
RA2	3:2	-	170.67±1.06	0.61±0.05	95.46±1.62	11±1.00	100±0.00	0.412±0.01
RA3	2:3	-	168.82±2.61	0.58±0.01	95.64±0.57	13±1.00	100±0.00	0.461±0.02
RA4	0:5	-	169.15±1.9	0.61±0.01	97.82±0.62	12±0.50	100±0.00	0.401±0.02
RB1	3:2	BC (1%)	173.23±1.92	0.63±0.02	94.07±1.72	13±2.00	100±0.00	0.444±0.02
RB2	3:2	BC (5%)	172.48±2.63	0.62±0.02	96.38±2.08	12±0.50	100±0.00	0.361±0.01

RB3	3:2	BC (10%)	177.29±1.27	0.67±0.02	95.55±0.49	13± 1.50	100±0.00	0.435±0.03
RC1	3:2	SLS (1%)	172.56±2.48	0.59±0.03	97.46±1.92	13±0.50	100±0.00	0.425±0.04
RC2	3:2	SLS (5%)	172.82±4.31	0.62±0.01	94.39±0.83	11±0.50	100±0.00	0.480±0.01
RC3	3:2	SLS (10%)	178.36±1.21	0.67±0.02	95.78±1.37	12± 1.50	100±0.00	0.361±0.01
RD1	3:2	Span 20 (1%)	170.19±1.81	0.62±0.02	94.53±0.72	12±2.00	100±0.00	0.381±0.02
RD2	3:2	Span 20 (5%)	173.92±1.42	0.64±0.03	96.61±0.19	11±0.50	100±0.00	0.435±0.07
RD3	3:2	Span 20 (10%)	177.89±1.21	0.66±0.02	97.23±0.28	13±0.50	100±0.00	0.478±0.01
RE1	3:2	Olive oil (1%)	170.66±2.44	0.51±0.06	94.50±1.20	13±2.00	100±0.00	0.439±0.02
RE2*	3:2	Olive oil (5%)	173.52±0.91	0.63±0.02	95.16±0.27	12±2.00	100±0.00	0.402±0.05
RE3*	3:2	Olive oil (10%)	176.99±0.82	0.65±0.03	99.25±0.06	11±1.50	100±0.00	0.470±0.01
RF1	3:2	Jojoba oil (1%)	172.27±1.96	0.61±0.02	97.07±1.52	12± 1.50	100±0.00	0.459±0.03
RF2*	3:2	Jojoba oil (5%)	175.43±1.72	0.64±0.03	97.14±0.83	13±1.50	100±0.00	0.363±0.01
RF3*	3:2	Jojoba oil (10%)	176.82±1.16	0.65±0.02	92.92±0.18	13±3.00	100±0.00	0.405±0.04
RG1	3:2	Groundnut oil (1%)	170.61±1.22	0.63±0.04	93.47±0.06	14±1.00	100±0.00	0.422±0.02
RG2*	3:2	Groundnut oil (5%)	173.95±1.52	0.65±0.07	93.50±1.90	14±1.50	100±0.00	0.461±0.02
RG3*	3:2	Groundnut oil (10%)	177.41±1.53	0.66±0.02	95.28±1.59	13±1.00	100±0.00	0.428±0.04

- Concentration of drug (20% w/w of polymer weight) was kept constant in all formulations; BC is benzalkonium chloride, and SLS is sodium lauryl sulphate
- *Formulations, in which 20% w/w of polymer weight of dibutyl phthalate was added, while in other formulations, 30% w/w of dibutyl phthalate was added
- **n = 10 for weight; n=6 for other parameters

Characterization of Patches

- Physicochemical Properties: Patch weights ranged from 168–177 mg, thickness 0.56–0.66 mm, drug content 94–99%, folding endurance 11–14, flatness 100%, and tensile strength 0.36–0.47 kg/mm² (Table 4). Low moisture content (1.99–4.84%) and uptake (3.07–6.97%) ensured stability, with no microbial growth (Figure 4).

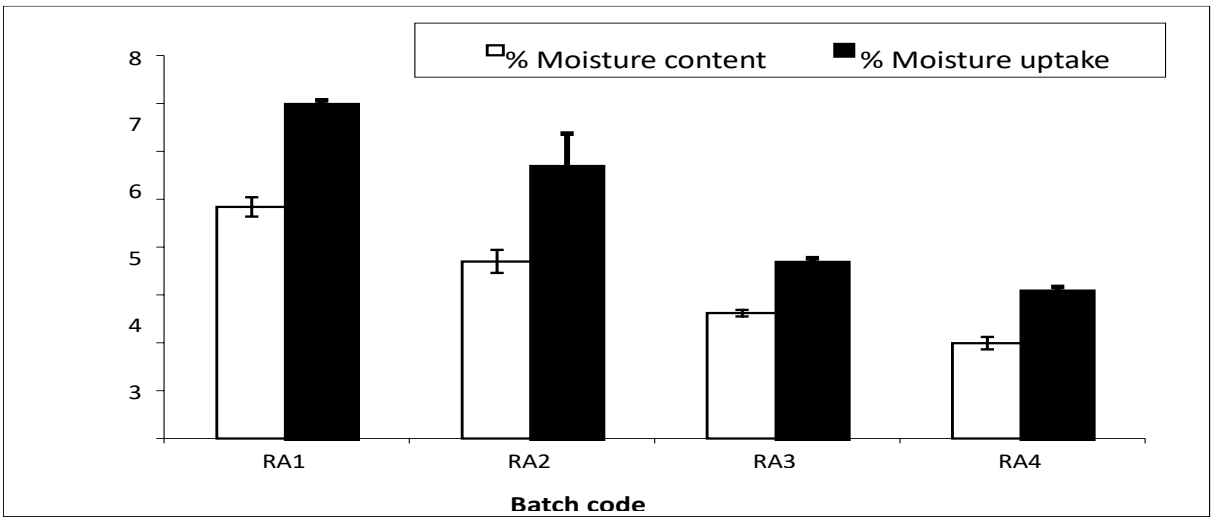


Figure 4: Moisture content and moisture uptake of batch RA containing different proportions of polymer

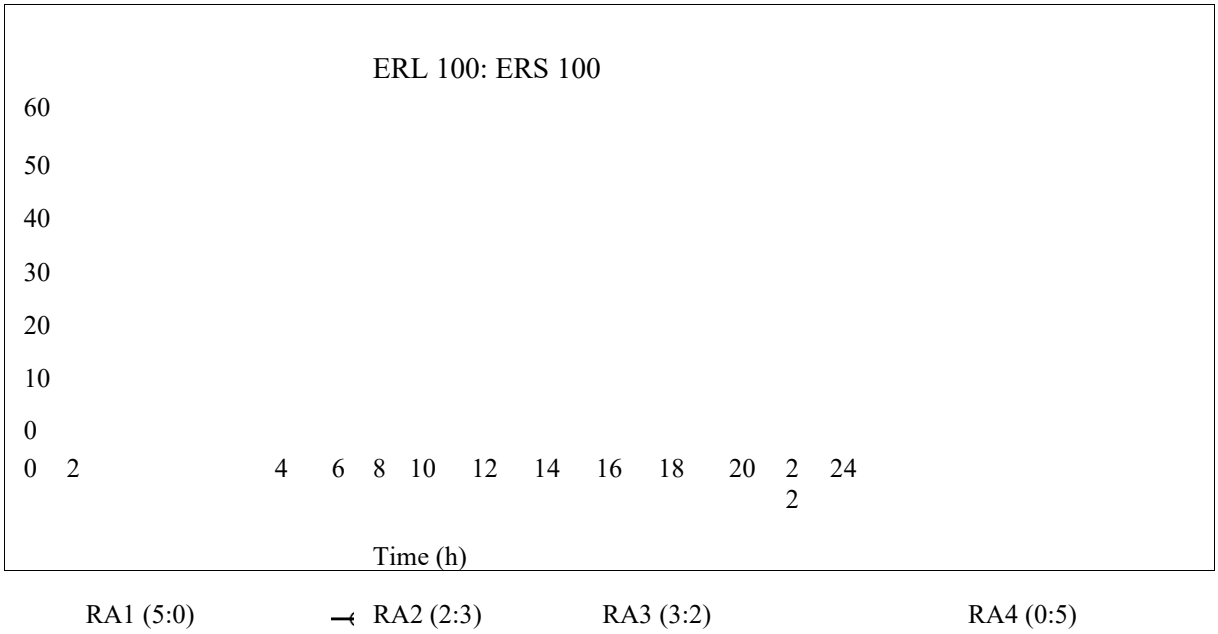
In Vitro Release Studies

- Polymer Effect: ERL 100: ERS 100 (3:2, RA2) showed the highest release (54.49 ± 3.39% at 24 h, Table 5, Figure 5), due to balanced hydrophilicity/lipophilicity. Without enhancers, release was low (41–54%).

Table 5: In vitro release of risperidone TDDS without permeation enhancer

Time (h)	RA1	RA2	RA3	RA4

	% Drug release			
1	12.97±2.71	1.99±0.72	0.24±0.11	1.62±0.79
2	18.79±7.30	2.3±0.32	3.21±1.12	2.40±0.51
4	26.40±6.99	10.74±1.73	5.40±0.48	5.30±0.10
6	29.85±6.55	18.01±4.05	10.74±1.41	7.70±1.58
8	32.36±7.01	20.85±2.15	20.54±1.37	15.57±2.47
12	37.96±3.34	38.21±0.71	38.55±0.43	21.05±2.99
16	42.44±0.39	47.83±3.03	38.58±0.64	28.56±2.57
24	4.15±0.16	54.49±3.39	41.78±0.15	42±2



- Permeation Enhancers: Span 20 (10%, RD3) achieved the highest release (90.51 ± 0.46%), followed by olive oil (87.64 ± 0.79%, RE3). Ionic surfactants (BC, SLS) showed reduced release at higher concentrations due to micelle formation (Tables 6–11, Figures 6–11).

Table 6: In vitro release of risperidone TDDS with BC as enhancer

Time (h)	RB1	RB2	RB3
	% Drug release		
1	1.07±0.22	1.37±0.08	1.66±0.45
2	6.99±1.03	6.57±1.30	3.81±1.05
4	14.26±2.91	23.15±3.94	6.52±0.79
6	42.33±4.08	48.17±3.03	23.95±4.94
8	52.54±3.93	56.94±4.03	35.85±0.868
12	59.05±2.45	69.07±2.88	43.38±3.71
16	68.78±3.13	71.64±3.24	60.21±2.95
24	69.69±0.39	86.32±0.50	83.93±0.70

Figure 6.6: In vitro release profile of risperidone TDDS with BC as enhancer Table 7: In vitro release of risperidone TDDS with SLS as enhancer

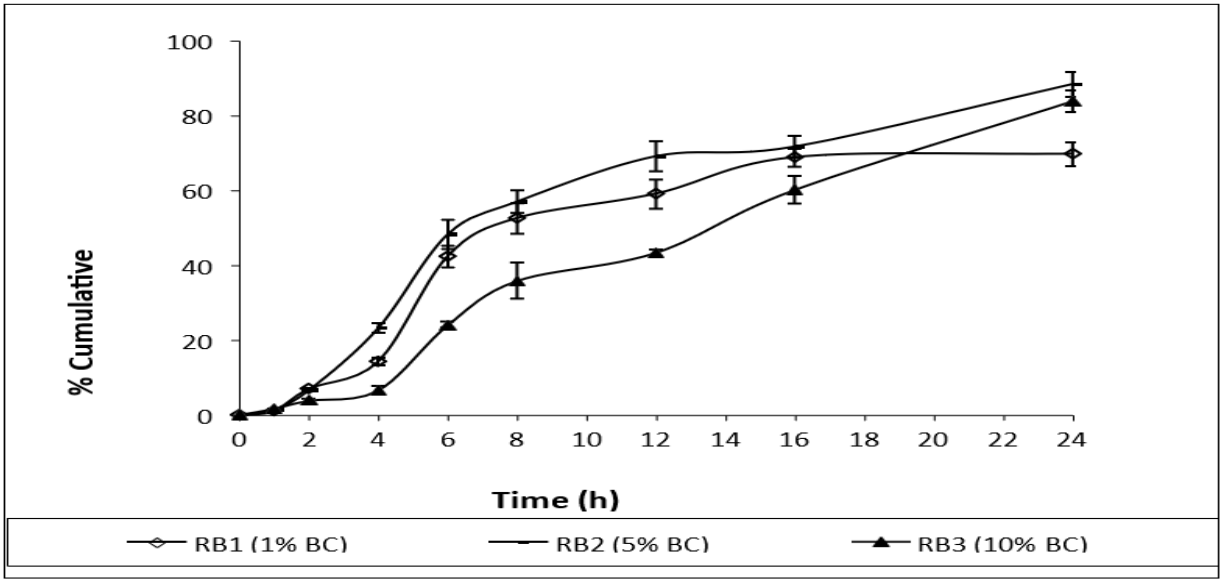


Figure 6.6: In vitro release profile of risperidone TDDS with BC as enhancer

Table 7: In vitro release of risperidone TDDS with SLS as enhancer

Time (h)	RC1	RC2	RC3
	% Drug release		
1	0.19±0.05	0.62±0.27	0.33±0.19
2	0.79±0.44	5.22±1.08	5.16±1.36
4	3.61±1.29	12.38±3.06	9.05±1.62
6	32.51±2.99	23.58±0.84	16.44±1.95
8	36.93±1.27	33.24±6.79	27.81±5.11
12	55.57±6.44	46.15±3.30	39.67±3.28
16	65.64±2.86	63±1.90	57.23±2.78
24	80.31±0.96	81.98±0.75	73.27±0.24

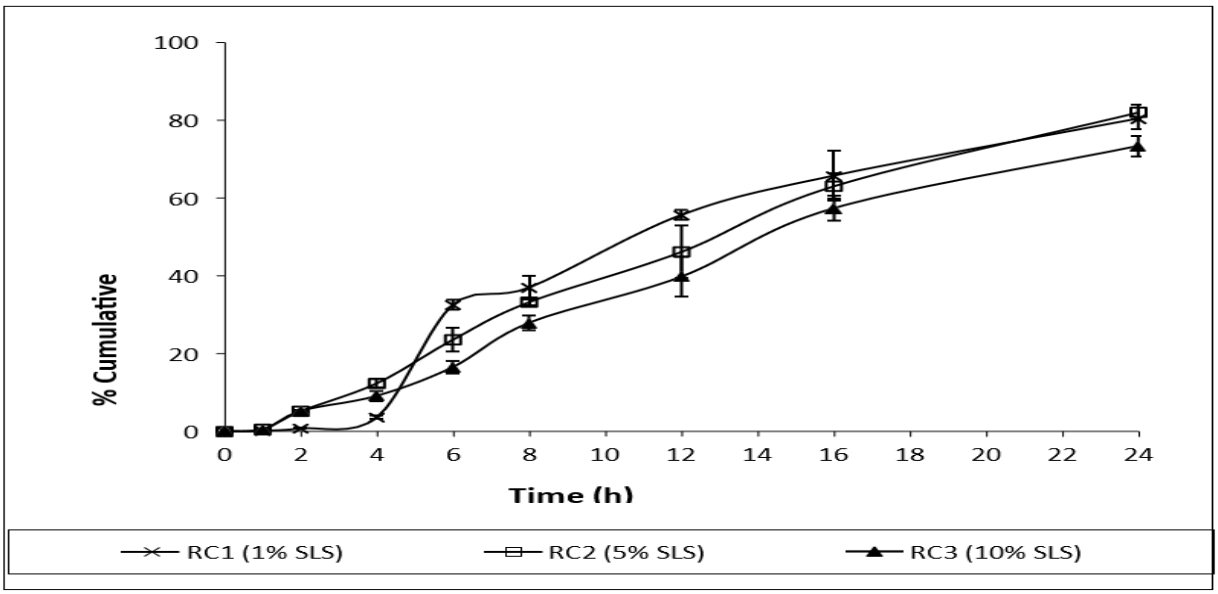


Figure 7: In vitro release profile of risperidone TDDS with SLS as enhancer

Table 8: In vitro release of risperidone TDDS with span 20 as enhancer

Time(h)	RD1	RD2	RD3
	% Drug release		
1	1.62±0.34	2.25±0.82	3.76±0.63
2	5.22±0.95	9.79±1.26	9.43±0.86
4	13.27±2.01	16.64±1.49	23.33±1.48
6	20.95±3.01	25.01±4.17	27.62±2.58
8	27.75±1.23	29.87±3.39	45.77±3.67
12	35.24±4.34	56.17±3.13	54.37±4.48
16	50.63±1.02	66.69±5.96	69.51±2.82
24	69.29±1.84	82.81±0.44	90.51±0.46

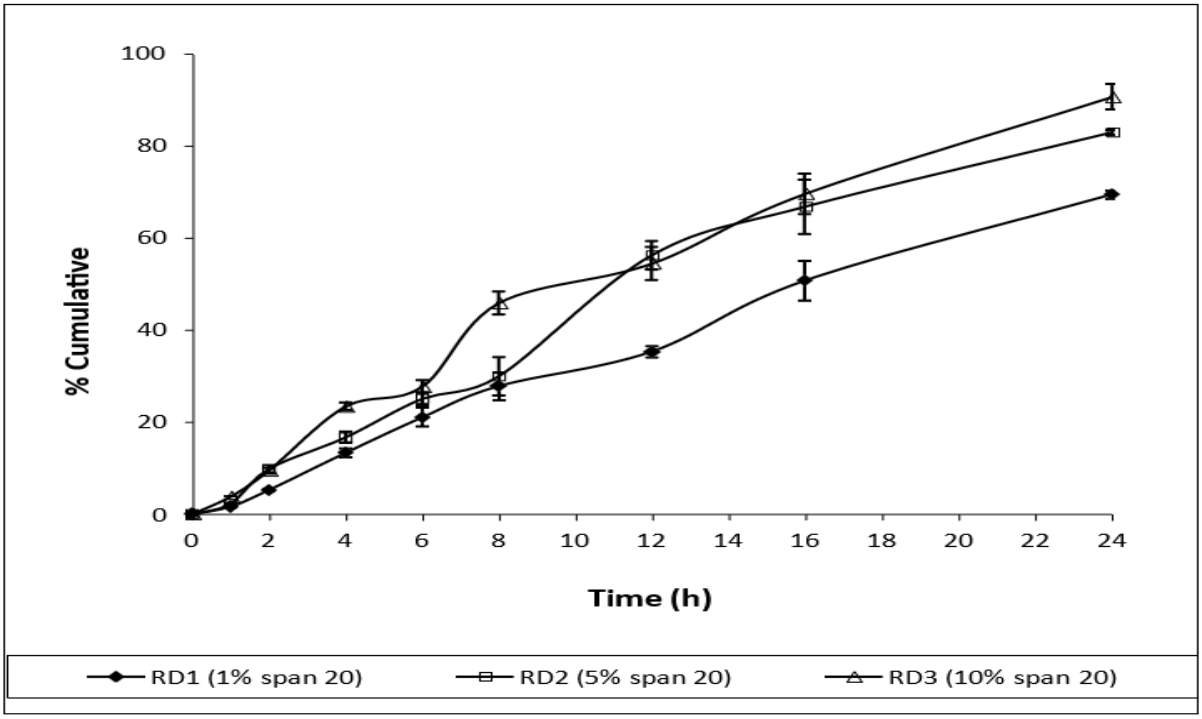


Figure 8: In vitro release profile of risperidone TDDS with span as enhancer

Table 9: In vitro release of risperidone TDDS with olive oil as enhancer

Time(h)	RE1	RE2	RE3
	% Drug release		
1	2.55±0.11	1.89±0.89	3.12±1.64
2	4.70±0.75	7.41±2.24	9.22±1.53
4	11.16±0.25	19.19±2.74	22.18±2.88
6	25.42±2.53	27.69±2.01	34.26±4.24
8	30.07±1.34	39.69±2.88	45.58±3.20
12	42.16±2.46	54.06±1.64	57.37±3.22
16	55.42±1.01	71.8±3.16	66.65±2.64
24	70.98±0.10	83.68±0.30	87.64±0.79

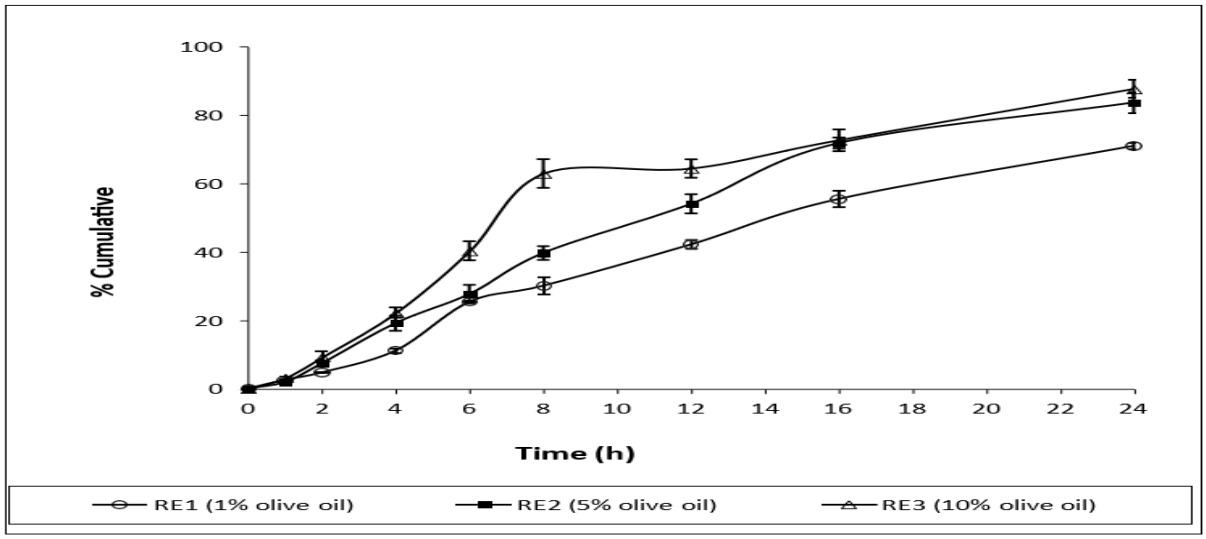


Figure 9: In vitro release profile of risperidone TDDS with olive oil as enhancer

Table 10. In vitro release of risperidone TDDS with jojoba oil as enhancer

Time(h)	RF1	RF2	RF3
	% Drug release		
1	1.98±0.66	1.01±0.20	2.37±0.50
2	5.18±2.14	2.25±1.09	5.12±1.24
4	11.61±3.55	3.69±1.03	17.63±2.64
6	26.21±3.52	14.26±2.92	22.93±4.96
8	34.20±4.94	25.80±2.93	33.08±2.09
12	45.37±2.99	44.44±4.65	37.72±0.85
16	49.98±1.54	52.37±3.89	48.15±3.08
24	67.45±0.58	72.01±1.78	74.62±0.69

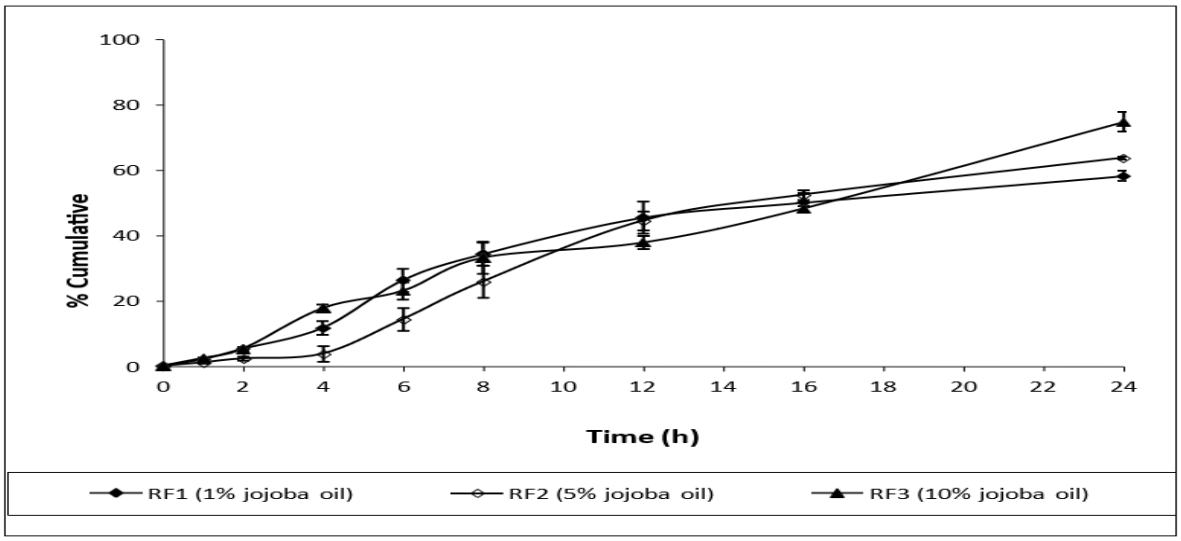


Figure 10: In vitro release profile of risperidone TDDS with jojoba oil as enhancer

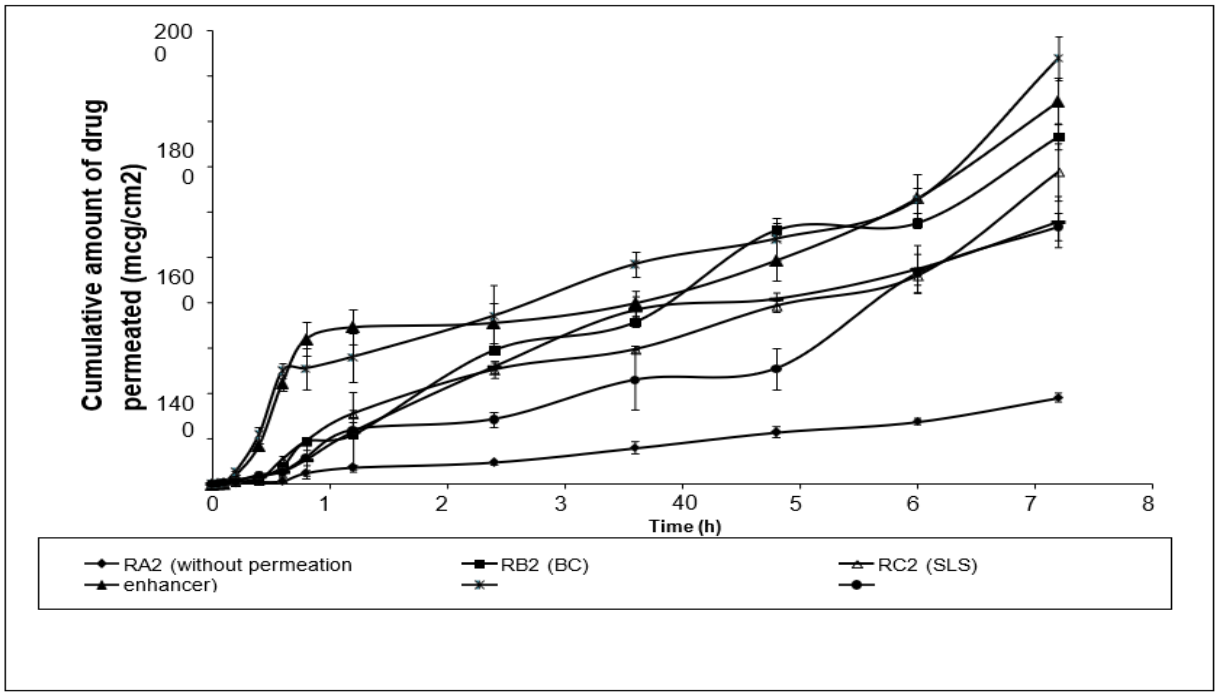


Figure 12: In vitro permeation profile of risperidone transdermal patches

- Drug Loading Effect: Permeation increased with drug loading up to 20%, but not at 25% due to supersaturation (Figure 14).

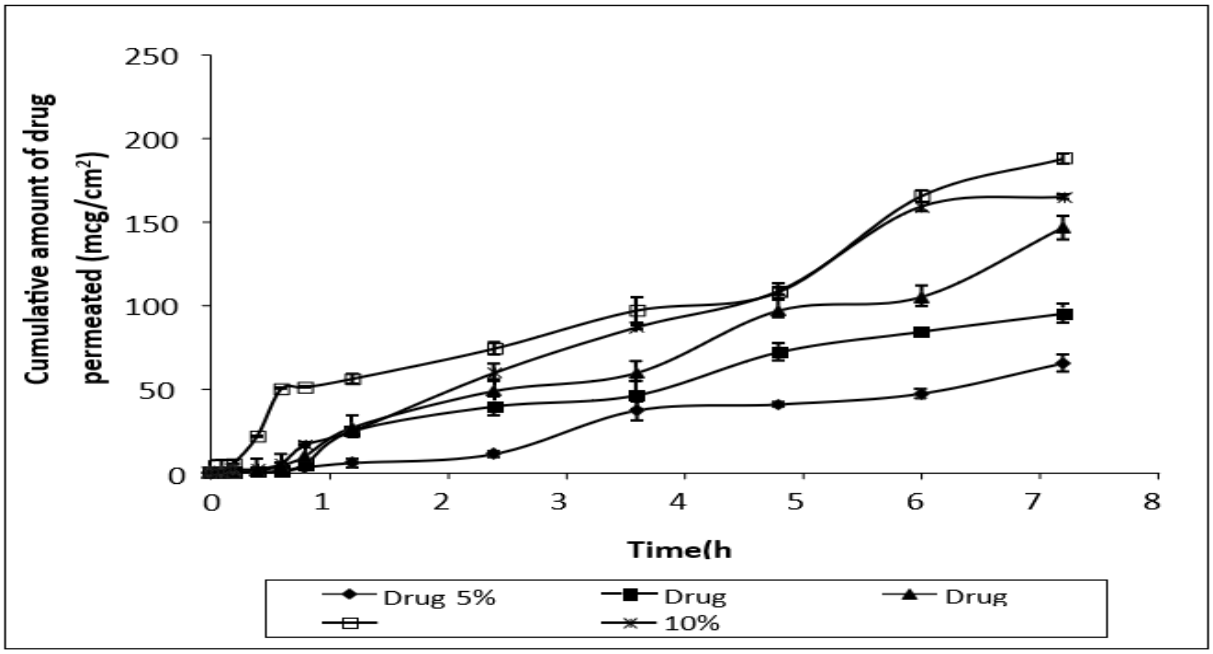


Figure 14: *In vitro* permeation profile of transdermal formulations with different drug loading of risperidone

- SEM Analysis: Uniform drug distribution in patches and skin penetration via appendages were confirmed (Figure 15).

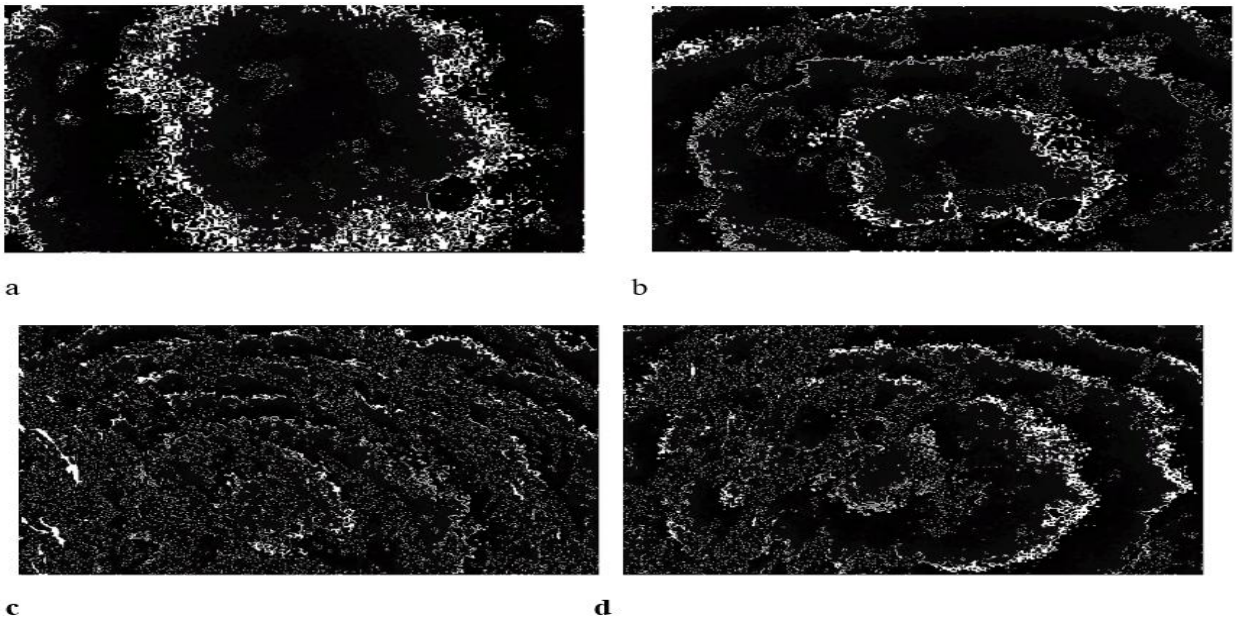


Figure 6.15: SEM scans of a) Distribution of risperidone drug in matrix transdermal patch, b) transdermal patch after release of drug, c) dorsal side of skin before permeation studies d) SEM scan shows drug cluster as such reached at dorsal side from transdermal patch after release

- Patch Size Calculation: A 10 cm² patch with 2.5 mg/cm² risperidone and 10% olive oil achieved a flux of 23.14 µg/cm²/h, meeting the required input rate (58.3–233.3 µg/h) for 72 h.

In Vivo Studies

- Skin Irritation: RE3 showed minimal erythema/edema, comparable to controls, with slight histopathological changes, confirming skin compatibility (Tables 15, 16).

Table 15: Visual Evaluation after skin irritation studies of risperidone TDDS

Rabbit No.	Control		Adhesive tape		Blank Patch		Test formulation RE3		Formalin	
	Erythe ma	Edem a	Erythe ma	Edem a	Erythe ma	Edem a	Erythe ma	Edem a	Erythe ma	Edema
1	0	0	0	0	1	0	1	1	3	3
2	0	0	0	0	1	0	1	0	2	3
3	0	0	1	0	1	1	1	1	3	3
4	0	0	0	0	0	0	0	0	3	3
5	0	0	0	0	0	0	0	0	2	2
6	0	0	1	0	1	0	0	0	3	2

Scores for skin irritation studies: 0 for none, 1 for slight, 2 for well defined, 3 for moderate and 4 for scar formation and severe erythema and edema

Table 16: Histopathological evaluation after skin irritation studies of risperidone TDDS

Rabbit No.	Control		Adhesive tape		Blank Patch		Formulation RE3		Formalin	
	Infarction	Edema	Infarction	Edema	Infarction	Edema	Infarction	Edema	Infarction	Edema
1	-	-	+	-	+	+	+	+	++	+++
2	-	-	+	-	-	-	+	+	++	+++
3	-	-	+	+	+	+	+	+	++	++
4	-	-	-	-	-	-	-	-	++	+++
5	-	-	+	+	+	-	+	+	+++	++
6	-	-	+	+	+	+	-	-	+++	+++
	No ulceration								Hyperplasia,	

Scores for histopathological studies: - for none, + for slight, ++ for well defined, +++ for moderate and ++++ for scar formation and severe infarction and edema

- Pharmacodynamic Studies: Rotarod and grip tests showed RE3's tranquilizing effect (falling time 12–23 s) was comparable to oral risperidone (12–27 s), with longer duration (Table 17).

Table 17: Tranquillizing activity of risperidone TDDS with rotarod apparatus

Dosage forms	Falling time (s)				
	1st hr	6th hr	12th hr	18th hr	24th hr
Control	260	260	250	260	262
Oral risperidone	20	12	20	22	27
RE3 (TDDS)	23	13	14	12	12

Stability Studies

- RE3 remaine
- d stable for 3 months (drug content 96.32–97.03%, $p > 0.05$), with no significant changes in permeation (Figure 16).

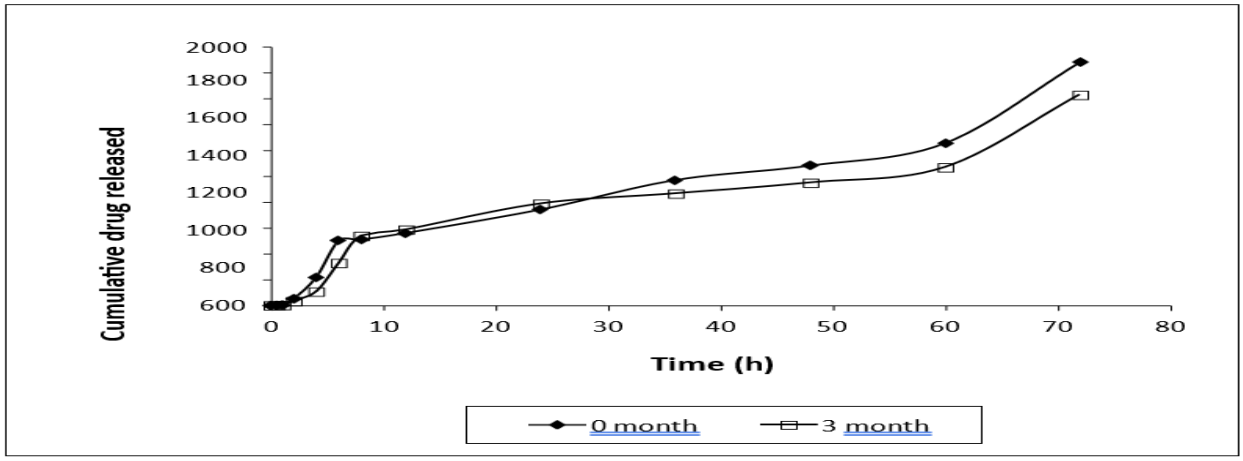


Figure 16: Permeation profile of risperidone TDDS (RE3) after stability studies

Summary

- Risperidone TDDS with ERL 100: ERS 100 (3:2) and 10% olive oil (RE3) provided optimal sustained release, high permeation (due to oleic acid), and therapeutic efficacy comparable to oral administration, with minimal skin irritation and good stability.

VI. CONCLUSIONS

Transdermal drug delivery systems (TDDS) using Eudragit polymers were developed for risperidone (RE3: ERL 100:ERS 100 3:2, 20% risperidone, 20% dibutyl phthalate, 10% olive oil). These formulations achieved sustained release over 72 hours, with risperidone (flux 23.14 µg/cm²/h) and olanzapine (flux 26.74 µg/cm²/h) matching high-dose oral products. Olive oil and Span 20 were the most effective permeation enhancers for risperidone and olanzapine, respectively. Pharmacodynamic studies in rodents confirmed comparable tranquilizing effects to oral formulations, with longer duration. Pharmacokinetic data in rabbits showed olanzapine TDDS had higher bioavailability (116.09%) than oral delivery. Both formulations were stable, safe, and skin-compatible, offering reduced side effects, improved patient compliance, and better dosing regimens. These results support industrial scale-up and provide clinicians with effective alternatives for psychosis management.

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