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Formulation and Evaluation of Transdermal Patches Loaded With Lenalidomide

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ABSTRACT:
The developments of controlled drug delivery systems which are able to manage the rate of distribution, sustain and/or target drug delivery to the tissue have been achieved. The purpose of the present study was to produce appropriate lenalidomide transdermal drug delivery systems with two distinct polymer combinations E RL100 with HPMC E 15; E RS 100 with HPMC E 15. E RL100 and E RS 100 are acrylic acid matrices used to manufacture patches in medicinal polymer matrices for transdermal supply systems reportedly suitable with numerous medicinesIt was contemplated that the TDDS patches with ERL 100 AND HPMC E15 showed better release than patches with ERS 100 and HPMC E15. The formulations comprising d-LIMONENE (12%) was found to meet the required flux. The transdermal patches of Lenalidomide with required flux could be prepared with suitable mechanical properties; further studies are recommended to find their therapeutic utility in humans by pharmacokinetic and pharmacodynamic studies

KEY WORDS- Lenalidomide, Transdermal Patches, HPMC, ERS, d-Limonene

I. INTRODUCTION

The development of controlled drug delivery systems which are able to manage the rate of distribution, sustain and/or target drug delivery to the tissue have been achieved.[(1)]Blood levels are maintained and the system continues to provide drugs over a safe and efficient duration. The potential of pharmacies to recognize successful medicinal products through the use of concepts and technologies for controlled drug-delivery systems, along with higher marketing cost for new pharmaceutical businesses, also provides benefits[(2)]. One of the most common strategies for transdermal skin administration was systemic effects medicinal substances [(3)].This study is designed with two polymer combinations, E RS100 and E HPMC E 15, ERL 100 and HPMC E 15 to build an appropriate matrix-type transdermal delivery system called Ketorolac. The acrylic acid matrices ERL100 and E RS 100 are stated to be useful for several transdermal medicinal products in drug polar matrix films. Penetration improvements that can boost the penetration ofdrugs[(4)]. The study used oleic acid amplifiers in varied concentrates to investigate its influence on medicinal penetration in D-Limonene. Various D-Limonene[(5)].The purpose of the present study was to produce appropriate lenalidomide transdermal drug delivery systems with two distinct polymer combinations E RL100 with HPMC E 15; E RS 100 with HPMC E 15. E RL100 and E RS 100 are acrylic acid matrices used to manufacture patches in medicinal polymer matrices for transdermal supply systems reportedly suitable with numerous medicines.[(6)]The present work was planned as follows to satisfy the aims and objectives. To produce HPMC E15, E RS100, and E RL100 in varied proportions, patches for medication lenalidomide. And to assess the dose forms. [(7)]

➢ **WEIGHT VARIATION**

- Thickness variation
- Folding endurance

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- Estimation of drug content
- Moisture content
- In vitro release study

➢ **POLYMER PROFILE**

1. HYDROXYPROPYLMETHYLCELL ULOSE[8]

Hydroxy propyl methylcellulose is an alkyl cellulose alkyl mixed ether which may be viewed as the methyl cellulose propylene glycol ether. E- Grades are generally suitable as film formers, K-grades are used as thickeners as well as matrix forming agents. It is an odorless, tasteless, white or creamy- white fibrous or granular powder. It is Soluble in cold water, forming a viscous colloidal solution, insoluble in alcohol, ether and chloroform, soluble in CH_3OH:CH_2Cl_2 (1:1) mixture, soluble in mixture of CH_2Cl_2 and isopropyl alcohol and other organic solvents. Its density is about 0.25 to o.70 gm/cm^3 , PH of about 6.0 to 8.0 (1% aqueous solution HPMC E5cps, 15cps (2% aq.solution),HPMC E4M, 4000cps (2% aq.solution),HPMC F4M, 4000cps (2% aq.solution)

2. EUDRAGIT RL 100

Eudragit RL 100 is ammoniomethacrylate copolymers consisting of fully polymerized copolymers of acrylic acid esters with 10% of functional quaternary ammonium group.These Creamy-white granules are Insoluble in water and petroleum ether, soluble in acetone, methanol, Ethanol, dichloromethane, and ethyl acetate.Having density of about0.816 to 0.836 gm/cm3 and viscosity Eudragit RL 100 -15mpa,Eudragit RL 30D- 200mpa respectively.Dry polymer films are stable at temperatures below 30°C, powder tends to form clumps.[9] Dry powders are stable in a closed container for at least 3 years if they exceed 30°C.[10]

3. EUDRAGIT RS 100

Eudragit RL100 is a copolymer made up of polymerized acrylic acid copolymers with 10% functional quaternary ammonium groups. [11]These Creamy-white granules are Insoluble in water and petroleum ether, soluble in acetone, methanol, Ethanol, dichloromethane, and ethyl acetate.Having density of about 0.816 to 0.836 gm/cm3 and viscosity 15mpa.[12]

II. METHODOLOGY

CONSTRUCTION OF STANDARD GRAPH OF LENALIDOMIDE

1. CONSTRUCTION OF STANDARD GRAPH OF LENALIDOMIDE IN PHOSPHATE BUFFER PH 6.8. [13]

The calibration curve resulted in the disintegration of 50 mg lenalidomide into flask volumetry and the machining with a pH 6.8 phosphate buffers. From this stock I solution the 1 ml solution was obtained and up to 10 ml PH 6.8 phosphate buffer and stock II was generated. Subject II pH 6.8-phosphate buffer at 2, 4, 6, 8 and 10 µg/ml was established at concentrations of 0.2, 0.4, 0.6, 0.8 and 1.0 ml. The absorption was measuring spectrophotometrically at 250 nm, with pH 6.8 phosphate buffers as blank.[14]

- **DRUG-EXCIPIENT COMPATIBILITY STUDY**

An examination of Pure Medicine (Lenalidomide), Pure Polymers (HPMC E 15, ERL 100 and ERS 100) and their physical mixtures was performed as used for formulae in which the possible drug-polymer interactions were investigated. [15]

- **PREPARATION OF LENALIDOMIDE TRANSDERMAL PATCHES**

Lenalidomide transdermal patches of matrix type were developed utilizing varied ratios HPMC E 15, ERL100 (KT1-KT5) and HPMC E 15 and ERS100 by means of solvent evaporation technology (KT6 to KT10).[16] The polymers are weighed in the required ratios and can be floated in a solvent mixture for around 6 hours (1:1 ratio of dichloromethane, methanol).[17] The plasticizer included 15% v/w of propylene glycol. The pharmaceutical solution was then added to the polymeric solution, casted on an umbra of Petri, covering a surface area of 69.42 sq.cm.[18]The whole sheet was cut into small parts covering a surface area of 6.9cm2 (2.9cm) approximately seven patches have been obtained. As plasticizing agents, 15% v/w polyethylene glycol and 12% oleic acid as penetration enhancer were used in every formulation.[19]

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TABLE 1."COMPOSITION OF TRANSDERMAL PATCHES WITH PENETRATION ENHANCERS

FORMULATION CODE	D-LIMONENE (%)	OLEIC ACID (%)
C1	4	-
C2	8	-
C3	12	-
D1	-	4
D2	-	8
D3	-	12"

TABLE 2. COMPOSITION "OF LENALIDOMIDE TRANSDERMAL PATCHES

FORMULATION CODE	DRUG (MG)	HPMC E15 (MG)	ERL 100 (MG)	ERS 100 (MG)"
T1	100	50	250	-
T 2	100	100	200	-
T 3	100	150	150	-
T 4	100	200	100	-
T 5	100	250	50	-
T 6	100	50	-	250
T 7	100	100	-	200
T 8	100	150	-	150
T 9	100	200	-	100

- 15% v/w propylene glycol was used as a plasticizer, 12%v/w Oleic acid was used as a penetration enhancer.[20]
- Each patch (6.9 cm2) contains 10mg of Lenalidomide

➢ **CHARACTERIZATION OF LENALIDOMIDE TRANSDERMAL PATCHES**[24]

1. PHYSICOCHEMICAL PROPERTIES

The Patches prepared by the general procedure were evaluated for the following properties
Thickness, Weight Variation, Folding Endurance, Estimation of drug content in polymer patches.[21]

PROCEDURE

Patches were taken from the formulation and cut into little pieces, and a 100 ml solution of 50 mL of methanol and 50 mL of dichloromethane was allowed to dissolve. The solution has been appropriately diluted and solution absorption has been assessed using a UV-Vis spectrophotometer at 250 nm wavelength against the blank methanol dichloromethane (1:1) mix.[22]

- **Moisture Content Determination**

The plots have been carefully weighed and placed in a calcium chloride desiccator for 24 hours at 40°C. The final weight was then reported when the weight of the specific patch was not changed further. In terms of the difference between initial and final weight for the final weight, the humidity % was computed.[23]

Initial weight – Final weight
% Moisture Content = X 100

➢ **IN-VITRO RELEASE STUDIES**

Medication release tests were conducted with the Franz diffusion cell for lenalidomide transdermal patches.[24] Between the donor and receptor boxes the medication-containing patches were maintained, separated by gelatin barrier from these boxes. In order to avoid a concentrated layer of medicinal solution underneath the dialysis membrane, the compartment containing the diffusion medium was agitated with a magnetic bead operated by a magnet stirrer.[25] At suitable times the 3 ml sample was collected from the receptor cabinet and substituted for a pH 6.8 phosphate buffer. Analysis of the phosphate buffer pH 6.8 was performed using a 250nm UV-visible spectrophotometer. [26]

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III. RESULTS AND DISCUSSION

1. CONSTRUCTION OF STANDARD GRAPH OF LENALIDOMIDE

TABLE 3. STANDARD GRAPH OF LENALIDOMIDE IN PH 6.8PHOSPHATE BUFFER

S.NO	CONC (µG/ML)	ABSORBANCE
1	0	0
2	2	0.090
3	4	0.185
4	6	0.249
5	8	0.332
6	10	0.406
7	12	0.482

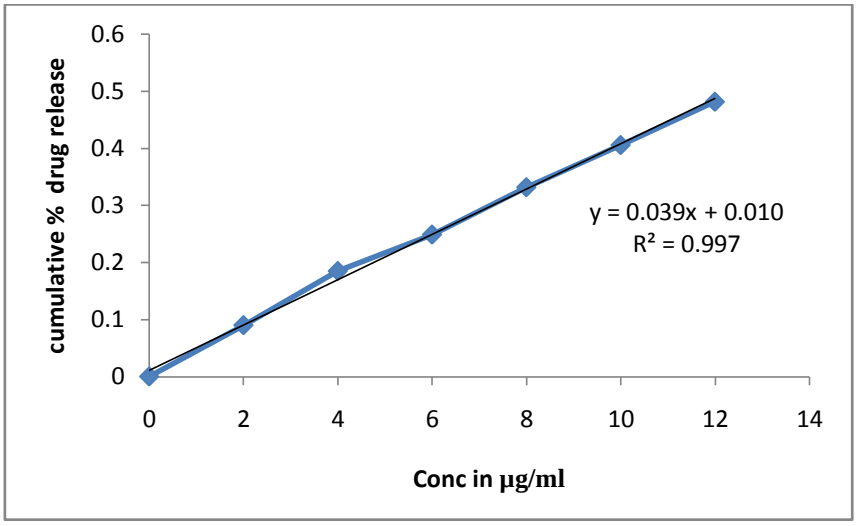

FIG 1. STANDARD GRAPH OF LENALIDOMIDE IN PH 6.8PHOSPHATE BUFFER

DRUG-EXCIPIENTCOMPATIBILITYSTUDY

- TheIR Lenalidomide investigation showed certain additional peaks were observed with physical mixtures, which could be caused by the presence of polymers, for the principal peaks and for the mixture of lenalidomide, ERS 100, and HPMC E15 in addition to the main peaks.[28] All characteristic bands in polymer blends show that there is no interaction with the drug and the polymers employed in this investigation because of functional groups. [29]

2. Development Of Lenalidomide Transdermal Patches

E RS 100, E RL 100 and HPMC E15 patches were developed (Table 1). Many tests were conducted with different polymer concentrations.[30] The study began with 400 mg of polymer and increased polymer levels, which enables the patch to contain more lenalidomide. The medication was precipitated by 400 mg polymer and precipitation reduced when the polymer concentration was increased to 690 mg. With 800 mg of polymers and patches, no precipitation was detected. The amount of polymer used was therefore 800 mg.[31]

Further trials to know the ideal plasticizer concentration for all types of patches were undertaken.[32] The plasticizer was insufficient to produce patches at the level of 5% v/w of the film former. At 5-10% v/w plasticizer concentration, hard and inflexible patches were produced. Additionally, increased plasticizer content above 20% v/w led to a considerable increase in drying time. Patches were therefore produced with a soft, flexible, but not slippery 15 percent v/w of plasticizer.[33]

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Patches with penetration enhancers d-limonene and oleic acid at various doses were also formulated (Table 2).

➢ **Characterization Of Lenalidomide Transdermal Patches**

1. PHYSICOCHEMICAL PROPERTIES

For the following qualities, the patches created using general technique were assessed[34]

2. WEIGHT VARIATION TEST

The Weight variation test results for different transdermal showed patches. As proven by SD values which were less than two.0 for all formulations, results of the test for weight variation were consistent with the weight of patches.[35] The weight of the patches was decreasing with HPMC E15 and vice versa in formulations F1 to F10.

3. THICKNESS VARIATION TEST:

The thickness test results for several transdermal patches. The thickness has been confirmed to be uniform in the thickness variation test. The thickness has grown as the HPMC E15 levels are increased in formulations in A and B series (thickness order in A series (f5>F4>F3>F2>F1and B series F10>F9>F8>F7>F6). For all formulations the SD values were less than 2 indicating more even patches.[36]

4. FOLDING ENDURANCE NUMBER:

Even after folding over 80 times, patches showed no cracks. ERS 100 has patches ranging from 40 to 90; ERL 100 has a patch range from 18 to 85, and has penetration enhancers created formulations ranging from 70 to 105. The number of components with the pending strength indicates the mechanical qualities. Strong folding resistance has strong mechanical characteristics.[37] With the increasing HPMC E15 concentration, the flexible endurance number was increased. These studies indicate that when placed with normal skin manipulation the patch does not break and retain integrity.[38]

5. ESTIMATION OF DRUG CONTENT IN POLYMERIC PATCHES:

For various transdermal patches, drug content values were provided in Tables 9 & 10. The conclusions of the homogeneity of the content showed that the low SD values have been consistently diffused throughout all transdermal patches. In the 6 cm2 region, drug content varies between 9.72 and 10.3 mg. The study of drug content in produced formulations indicated that patches can give a constant medication content and minimum batch variability throughout the investigation. [39]

6. MOISTURE ABSORPTION AND MOISTURE CONTENT STUDY

The results of the humidity content and humidity absorption studies have been shown in table 9 & 10 and figures 10 & 11. The moisture content of the pieces varied between 3.21 and 5.3%, and between 3.3 and 5.63%. (A-series and B-series accordingly for formulation). The humidity absorption ranges from 3.18 to 9.63% in formulations, and from 5.85 to 10.1%. (A-series and B-series accordingly for formulation). The results showed that humidity and moisture absorption were increased by increasing the concentration of hydrophilic polymers (HPMC E15). The small moisture content of the formulations makes it stable and completely dry and brittle. [40]

TABLE 4."WEIGHTS, THICKNESS AND FOLDING ENDURANCE OF LENALIDOMIDE TRANSDERMAL PATCHES"

"FORMULATION	WEIGHT (MG)	THICKNESS (MM)	FOLDING ENDURANCE
F1	100.4±0.17	0.28±0.25	48±7.64
F2	104.6±0.61	0.29±2.05	62.5±1.05
F3	97.8±1.23	0.32±0.45	66.31±3.83
F4	103.2±0.27	0.33±0.42	76.16±5.04
F5	**103.2±0.84**	**0.32±0.29**	**85.33±2.58**
F6	102.1±0.82	0.32±0.14	40±8.91
F7	105.3±0.96	0.35±2.17	50.83±2.15
F8	106.3±0.54	0.39±0.19	73.5±5.95
F9	100.2±1.67	0.40±1.63	84.5±3.90

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F10	98.3±0.28	0.42±1.23	90.67±3.46"

TABLE 5."WEIGHT, THICKNESS AND FOLDING ENDURANCE OF LENALIDOMIDE TRANSDERMAL PATCHES WITH PENETRATION ENHANCERS"

"FORMULATION CODE	WEIGHT (MG)	THICKNESS (MM)	FOLDING ENDURANCE
C1	102±0.15	0.34±0.71	105.1±1.20
C2	103±1.53	0.36±0.42	88.21±0.78
C3	**100±0.84**	**0.33±0.41**	**75.25±2.92**
D1	98±0.94	0.36±0.70	85.25±0.56
D2	95±0.69	0.34±1.35	92.05±1.38
D3	**99±0.44**	**0.37±0.24**	**78.75±1.6"**

TABLE 6."DRUG CONTENT, % MOISTURE ABSORBED AND % MOISTURE CONTENT OF LENALIDOMIDE TRANSDERMAL PATCHES, MEAN ± S.D (N=3)"

"FORMULATION	DRUG CONTENT (MG)	% MOISTURE CONTENT
F1	9.85±0.64	3.3±0.24
F2	10.08±0.56	4.0±0.46
F3	9.72±0.55	4.08±0.88
F4	10.15±0.95	4.21±0.80
F5	**9.82±0.07**	**5.3±0.60**
F6	10.30±0.86	4.3±0.52
F7	9.85±0.29	4.58±0.57
F8	9.82±0.03	4.63±0.45
F9	9.84±0.06	4.93±0.66
F10	9.73±0.64	3.95±0.05"

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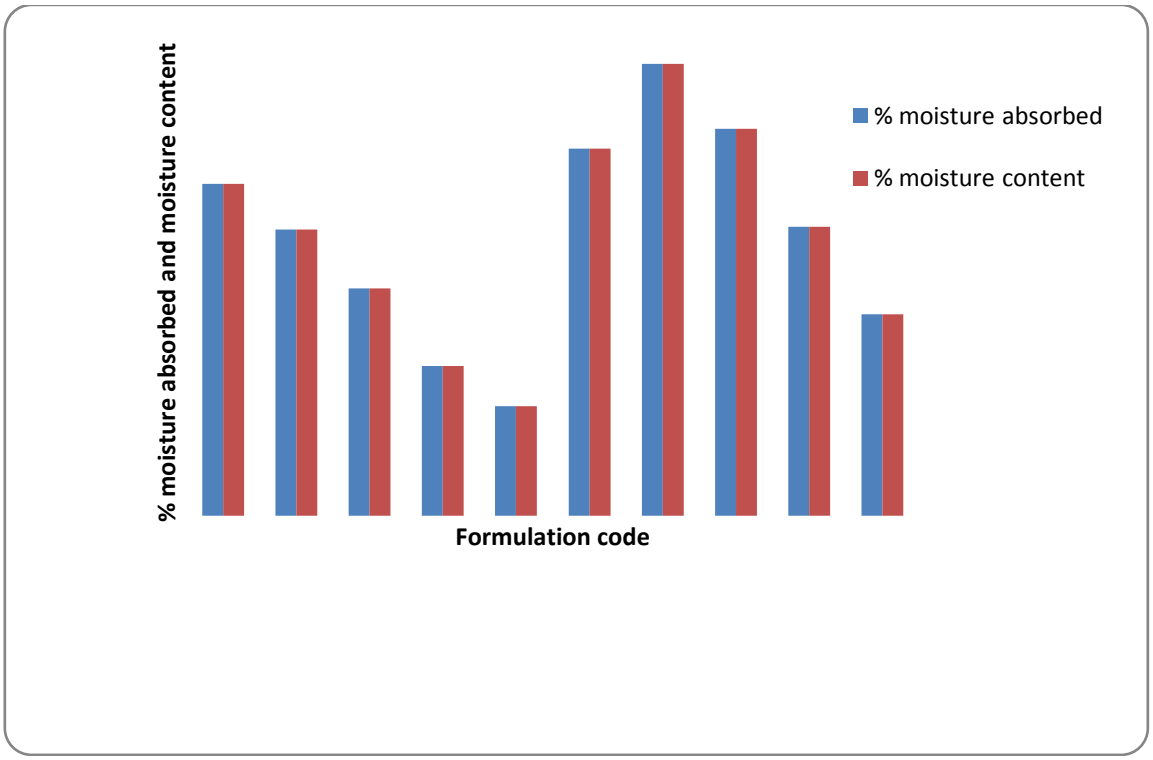

FIG 2. % "MOISTURE ABSORBED AND MOISTURE CONTENT OF LENALIDOMIDE TRANSDERMAL PATCHES, MEAN ± S.D (N=3)"

TABLE 7."DRUG CONTENT, % MOISTURE ABSORBED AND % MOISTURE CONTENT OF LENALIDOMIDE TRANSDERMAL PATCHES WITH PENETRATION ENHANCERS, MEAN ± S.D (N=3)

"FORMULATION CODE	DRUG CONTENT (MG)	% MOISTURE ABSORBED	% MOISTURE CONTENT
C1	14.28±0.82	8.5±0.16	5.6±0.75
C2	14.05±1.05	13.5±1.95	7.55±0.22
C3	**14.52±0.84**	**8.25±1.47**	**4.22±1.22**
D1	14.25±0.68	6.6±2.85	5.45±1.08
D2	14.57±1.07	6.75±3.36	5.82±0.68
D3	**14.25±0.88**	**8.25±1.25**	**3.85±1.22"**

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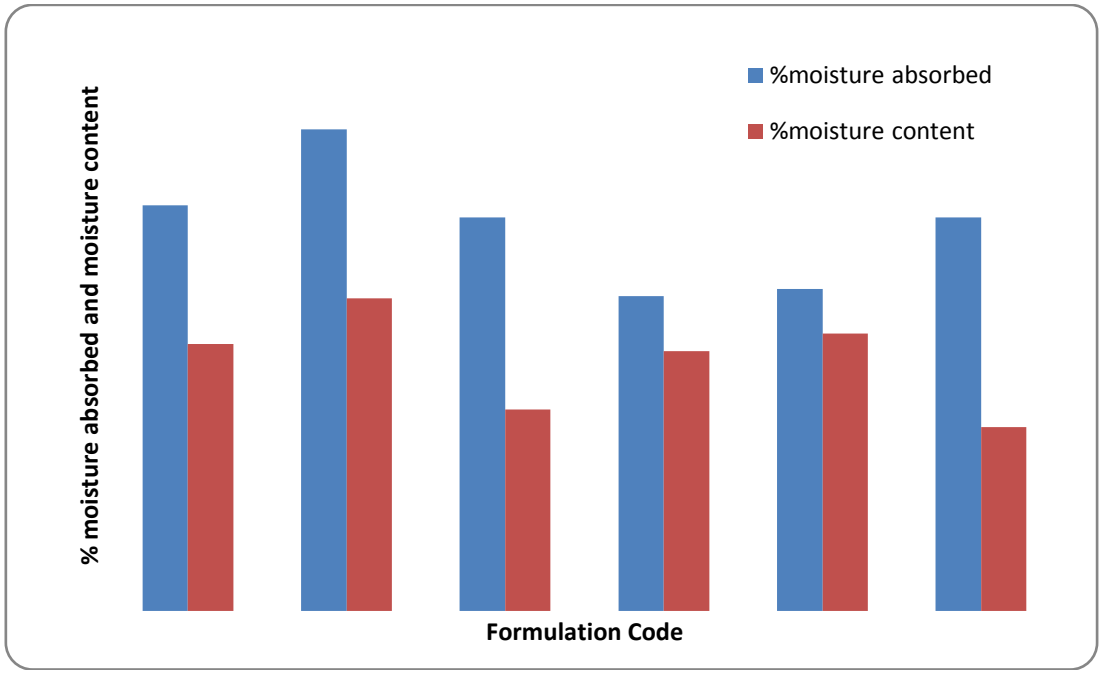

FIG 3. % "MOISTURE ABSORBED AND MOISTURE CONTENT OF LENALIDOMIDE +- TRANSDERMAL PATCHES WITH PENETRATION ENHANCERS, MEAN ± S.D (N=3)"

TABLE 8. MECHANICAL PROPERTIES OF OPTIMIZED FORMULATIONS

"FORMULATION CODE	TENSILE STRENGTH(KG/M^2)	ELONGATION AT BREAK (%MM^{-2})	ELASTIC MODULUS (KG/MM^2)	STRAIN
F5	1.02±0.26	65.92±2.02	2.68±0.38	0.46±0.023
C3	1.09±0.31	69.7±1.06	2.09±0.41	0.52±0.018
D3	1.06±0.11	72.16±1.89	2.84±0.50	0.49±0.037"

IN VITRO DRUG RELEASE STUDIES FROM TRANSDERMAL PATCHES

The Patch made alone with HPMC indicated that in eight hours 87 percent of the drug was presented and kinetics were first ordered. This signifies that the patch was not adequate for 24 hours to release a medicine; a copolymer that reduces the release rate of the drug must be added. The ERL 100 and ERS100 polymers controlled the rates for the controlled release of a medicine.(41)

The results show that the quantity of drug releases has increased as HPMCE 15 has been increased. The release of F1 to F5 (F5>F4>F3>F2>F1) and F6 to F10 (F9>F10>F8>F6>F7) is increasing on the medicinal market.

Formulations The highest percentage of drug releases were found (71.08±0,41 and 68.06±0,41, respectively), with the lowest values of ERL-100 and ERS-100 formulations (36,07±1,98 percent and 35,25±0,62% respectively) being substantially different. During this investigation, the drug release rate increased dramatically due to the increasing concenttrations of hydrophilic polymer (HPMC) in formulations.

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TABLE 8."CUMULATIVE PERCENT RELEASE OF LENALIDOMIDE FROM TRANSDERMAL PATCHES"

"TIME (HRS)	CUMULATIVE % OF DRUG RELEASED, MEAN ± S.D (N=3)				
	F1	F2	F3	F4	F5
0	0	0	0	0	0
1	6±0.06	4.5±2.67	6±1.30	5.7±1.88	6.4±0.62
2	9±1.09	5.9±0.02	10±1.03	8.13±1.09	7.2±1.08
3	9.9±1.78	9.01±0.17	13±1.70	12.42±0.56	9.52±0.37
4	14.9±0.43	13.13±1.19	18±2.50	14.06±1.09	13.7±1.21
5	19±0.10	17±1.08	22.1±1.3	19.05±1.99	16.05±1.05
6	21±0.80	19±1.60	28±0.62	24.38±1.80	20.12±1.96
8	29±0.56	23±0.85	33±1.38	28.3±1.16	34.93±1.39
10	36±1.08	32±1.31	38±1.05	38.5±0.30	43.53±1.38
12	41±0.43	36±1.90	41±3.52	44.8±1.39	56.03±0.30
24	75±1.98	73±1.07	53±0.80	59.1±1.03	**73.08±0.41"**

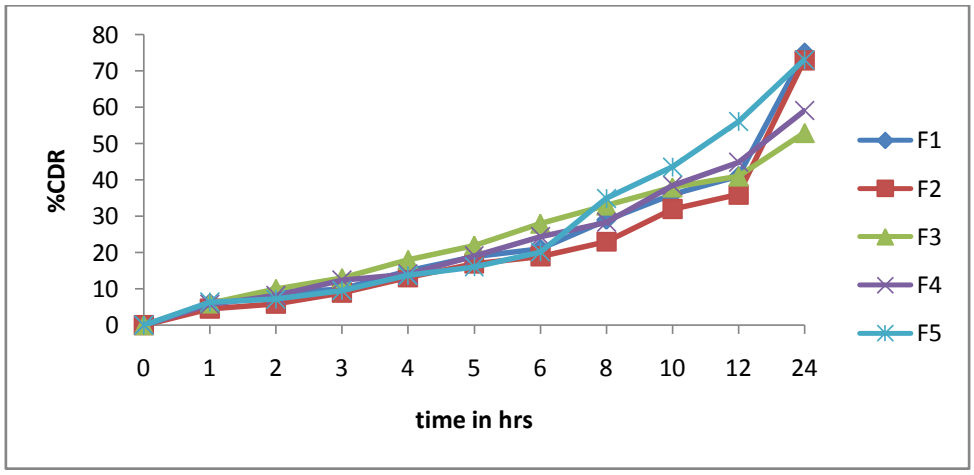

FIG 4."CUMULATIVE PERCENT RELEASE OF LENALIDOMIDE FROM TRANSDERMAL PATCHES F1-F5

TABLE 9. CUMULATIVE PERCENT RELEASE OF LENALIDOMIDE FROM TRANSDERMAL PATCHES F6-F10"

"TIME (HRS)	CUMULATIVE % OF DRUG RELEASED, MEAN ± S.D (N=3)				
	F6	F7	F8	F9	F10
0	0	0	0	0	0
1	4.9±1.43	3.9±0.61	5.75±1.61	5.34±0.68	5.13±1.80
2	6.72±1.74	5.25±1.08	8.1±1.30	9.5±1.18	10.12±1.42
3	9.63±1.50	6.6±1.14	11.5±2.61	15.5±1.07	18.43±0.63
4	11.92±2.49	7.1`3±0.45	12.5±1.41	18.01±0.21	23.21±0.32
5	13.8±2.54	10.43±1.67	16.36±2.67	20.05±1.65	24.53±3.70
6	18.5±1.36	13.22±1.40	19.08±1.43	23.2±1.56	27.41±0.46
8	22.5±0.57	17.5±0.87	25.9±3.55	29.91±1.30	33.63±0.21
10	28.7±1.22	12.45±1.05	36.25±1.11	33.9±1.32	37.21±0.29

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12 24	33.1±0.5 44.7±0.41	26.6±4.10 35.2±0.62	41.6±1.92 52.1±0.74	41.8±0.30 57.08±0.41	43.24±1.92 62.31±1.87”

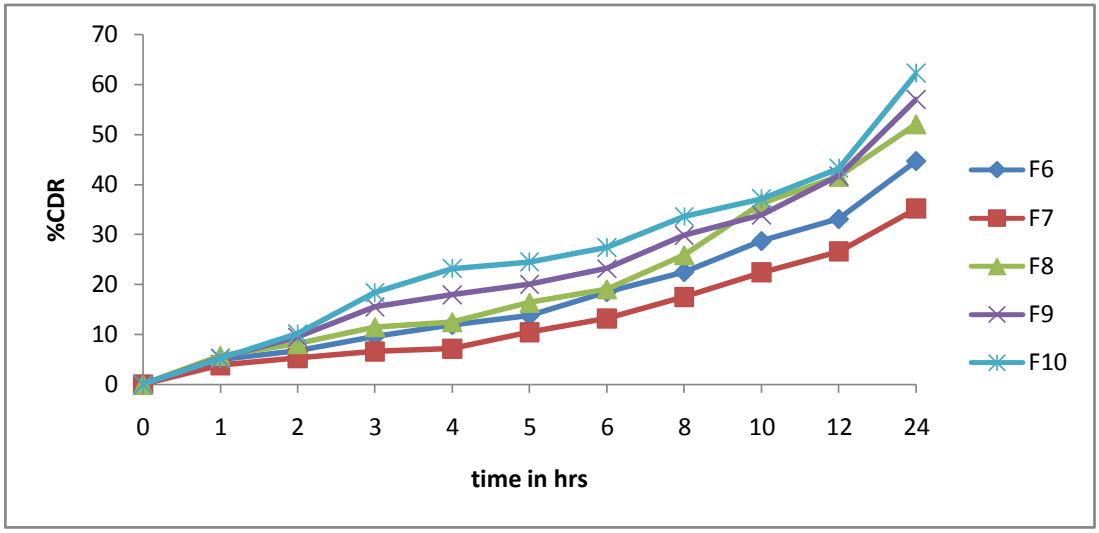

FIG 5. CUMULATIVE PERCENT RELEASE OF LENALIDOMIDEFROM TRANSDERMAL PATCHES F6-F10

➢ **EX VIVO PERMEATION STUDIES THROUGH RAT ABDOMINAL SKIN FROM TRANSDERMAL PATCHES**

The results of ex vivo skin penetration of the patches containing lenalidomide. The formulations (6.9 cm2) F5 and F9 had the largest cumulative levels, considerably different than the lowest values recorded in ERL100(F1) and ERS100(F7) formulations at 24hrs.

Increased drug release and penetration in both series were found when the amount of HPMC increased in all formulations. The hydrophilic polymer is first disintegrated quickly when the patch comes in touch with the skin, resulting in the buildup of high concentrations of medicine on the cutaneous surface and leading to saturation of the skin at all times with medication molecules.

Maximum flow was seen with formulation F5. However, the needed flow was not produced with these formulas. Studies in literature showed the idea of using drug permeation enhancers as they help drug penetration through the skin. As permeation boosters oleic acid and d-limonene have been employed.

The most cumulative amoune of drug permeability was found in formulations C3(12 percent D-Limonene), D3 (12 percent oleic acid) these formulae showed the necessary flow.

- **The fluxes obtained for formulations C3 is 128.6 which are in agreement with the target flux. Hence the formulation C3 was found to be optimized and best when compared to that of the remaining formulations.**

Ex vivo data for optimized F5, C3 and D3 formulations in several kinetic models were fitted (zero order, first order and Higuchi model and Peppas model). The first-order R2 (0.876, 0.946 and.935) values were higher than the first-order R2 (0.845, 0.073 and 0.889) values and the Higuchi (0.956, 0.966 and 0.941) values were higher than the first-order and zero-order R2 values.

A slope value of 0.45 to 1 suggests an abnormal behaviour, according to peppa model. (Non-Fickian). The 'n' values are 0.822, 0.746 and 0.731 correspondingly in formulas F5, C3 and D3. It also shows that, after non-Fickian

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diffusion, the liberating mechanism from the optimal formulations (anomalous behavior).The results of drug penetration through rat abdomen skin from transdermal patchs in lenalidomide confirmed that lenalidomide is released from the formulation and penetrated through the skin of the rat.

Table 10."CUMULATIVE PERCENTAGE OF LENALIDOMIDE PERMEATED FROM TRANSDERMAL PATCHES (A SERIES)

TIME (HRS)	CUMULATIVE PERCENTAGE OF DRUG PERMEATED, MEAN ± S.D (N=3)				
	F1	F2	F3	F4	F5"
1	4.3±1.43	3.01±1.76	4.08± 1.78	43.2±1.09	7.3±1.45
2	6.3±2.22	5.88±1.92	6.01±2.37	5.1±2.07	9.7±1.90
3	7.9±2.10	6.4±0.92	8.5±2.03	8.3±1.55	14.9±2.08
4	10.8±1.20	8.01±0.89	10.8±2.18	10.4±1.87	19.1±2.78
5	12.3±0.92	10.5±1.25	12.0±1.35	15.8±0.98	21.3±1.67
6	14.5±1.25	14.9±1.84	16.9±1.11	20.9±0.99	27.2±0.56
8	15.1±1.73	16.8±1.11	18.3±1.90	22.4±1.89	33.4±1.23
10	16.5±0.83	18.09±0.92	20.1±0.98	25.1±1.45	40.02±1.09
12	17.8±0.98	29.9±0.89	25.1±1.12	27.4±2.09	46.1±2.01
24	21.1±1.25	35.4±1.56	28.3±2.07	35.2±2.34	**92.08±1.45**

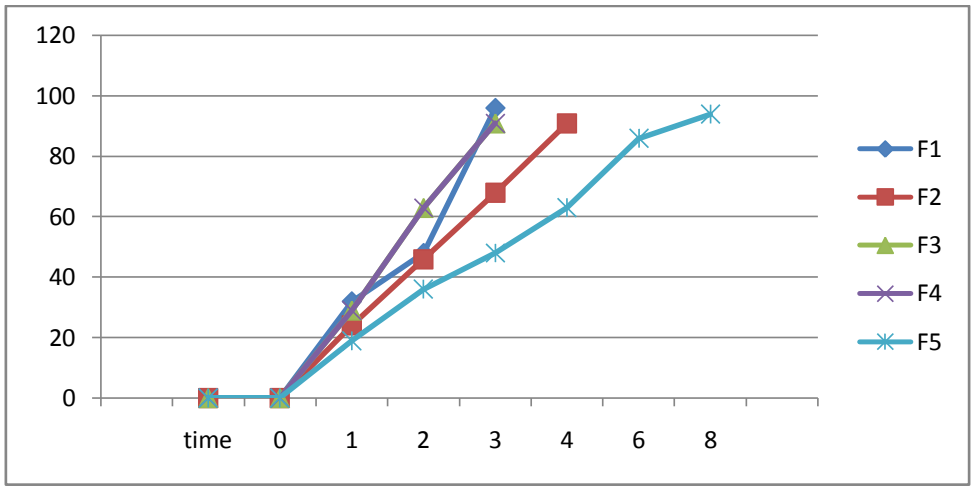

FIGURE 6: CUMULATIVE PERCENTAGE OF LENALIDOMIDE PERMEATED FROM TRANSDERMAL PATCHES (A SERIES)

TABLE 11. CUMULATIVE PERCENTAGE OF LENALIDOMIDE PERMEATED "FROM TRANSDERMAL PATCHES (B- SERIES)

TIME (HRS)	CUMULATIVE PERCENTAGE OF DRUG PERMEATED, MEAN ± S.D (N=3)				
	F6	F7	F8	F9	F10"

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1	3.99±1.92	3.51±1.22	5.91±0.99	4.6±2.09	5.3±1.86
2	4.5±0.78	4.9±2.66	7.5±0.78	6.02±1.79	6.9±2.35
3	5.9±0.45	5.4±2.02	9.2±1.77	8.7±1.90	9.08±2.09
4	6.6±1.23	7.9±1.23	10.8±1.44	12.9±2.45	12.08±1.58
5	9.5±1.99	9.6±1.99	15.9±1.56	19.02±2.45	15.7±1.20
6	10.9±1.67	12.1±1.45	17.3±2.09	21.9±1.89	21.9±0.85
8	14.5±0.89	14.8±2.09	20.9±2.03	26.5±1.57	25.01±1.84
10	18.3±0.99	17.9±2.66	23.5±1.22	31.1±1.01	28.2±0.47
12	24.5±1.99	21.01±1.22	25.9±1.24	36.9±0.901	33.8±1.94
24	34.5±2.08	25.01±1.90	31.3±1.89	**42.08±1.46**	38.2±1.36

TABLE 12 .CUMULATIVE PERCENTAGE OF LENALIDOMIDE PERMEATED FROM TRANSDERMAL PATCHES (C1-C3)

TIME (HRS)	**CUMULATIVE PERCENTAGE OF DRUG PERMEATED MEAN ± S.D (N=3)**		
	C1	C2	C3”
1	5.3±1.89	8.8±1.34	9.1±1.17
2	7.01±2.23	12.9±0.97	12.8±1.90
3	9.9±2.12	16.1±1.34	25.6±2.01
4	12.5±1.45	20.5±1.23	30.8±1.45
5	14.9±1.67	23.4±0.67	38.1±1.11
6	17.8±1.90	26.6±0.55	43.8±1.23
8	23.09±1.99	33.3±0.97	51.9±0.35
10	31.8±2.89	42.6±1.67	62.8±0.93
12	40.3±0.98	51.8±1.23	69.09±1.23
24	53.1±1.56	62.8±1.11	**93.1±1.45**

TABLE 13. CUMULATIVE PERCENTAGE OF LENALIDOMIDE PERMEATED FROM TRANSDERMAL PATCHES (D1-D3).

“TIME (HRS)	**CUMULATIVE PERCENTAGE OF DRUG PERMEATED, MEAN ± S.D (N=3)**		
	D1	D2	D3”
1	6.6±1.01	8.8±0.78	9.8±1.11
2	9.9±0.97	11.9±1.20	11.6±1.23
3	11.8±1.22	15.1±1.01	14.1±0.97
4	13.3±2.01	18.8±0.99	17.9±1.98
5	16.6±1.62	22.2±0.96	21.8±2.02
6	20.01±0.92	27.6±0.89	27.7±2.34
8	26.8±1.11	35.5±1.54	38.3±1.89
10	33.1±1.99	42.1±1.76	49.9±0.99
12	42.8±1.34	50.9±1.09	58.6±1.35
24	51.1±0.87	60.5±1.97	**69.9±1.67**

- **KINETIC MODELS FOR OPTIMIZED FORMULATIONS**

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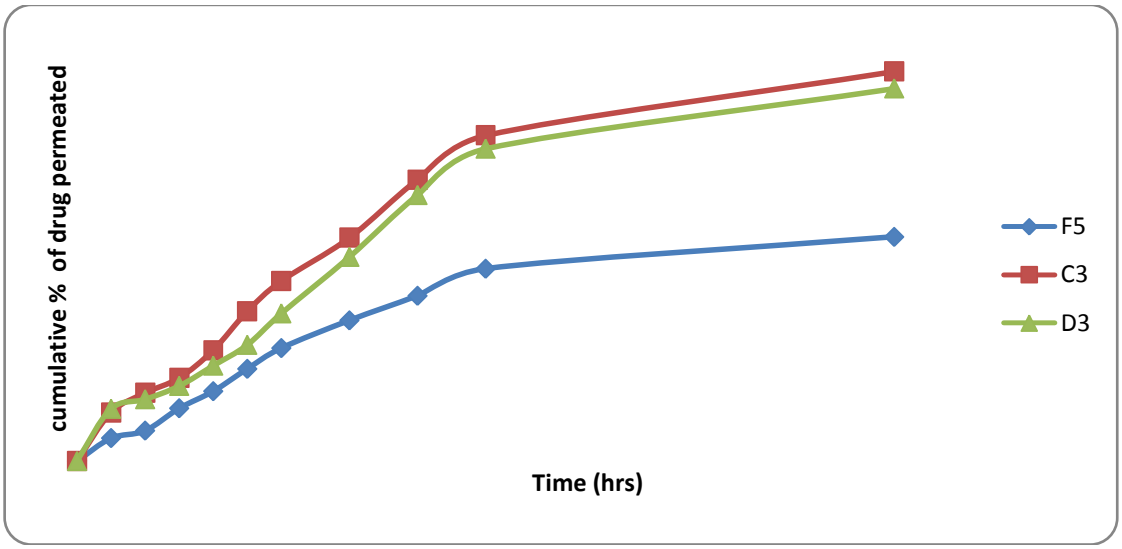

FIGURE 7."ZERO ORDER MODEL (CUMULATIVE PERCENT OF DRUG PERMEATED VS TIME)"

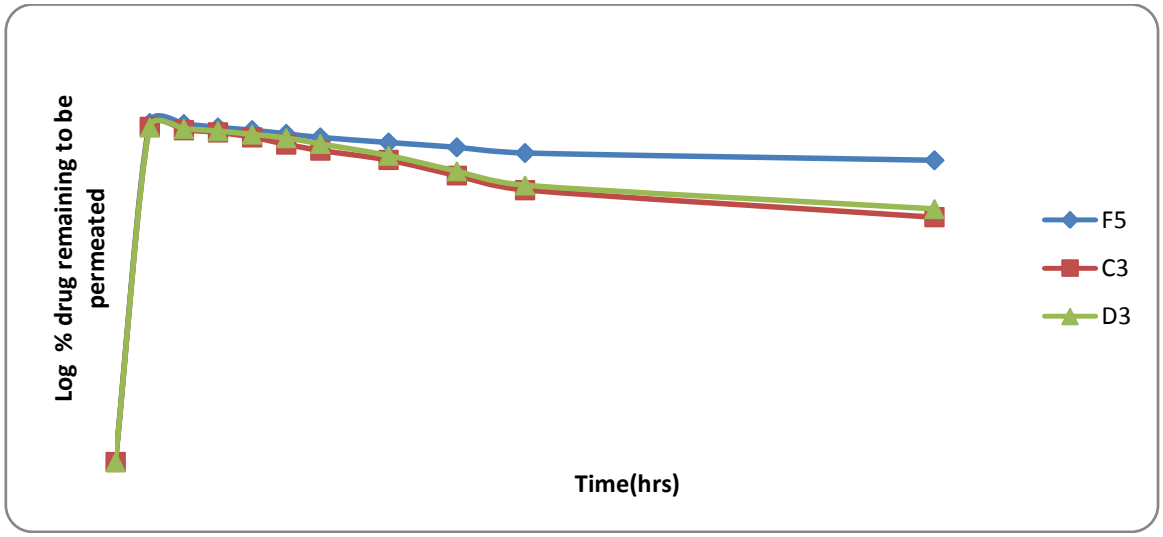

FIG. 8. FIRST ORDER MODEL (LOG PERCENTAGE DRUG REMAINING TO BE PERMEATED VS TIME)

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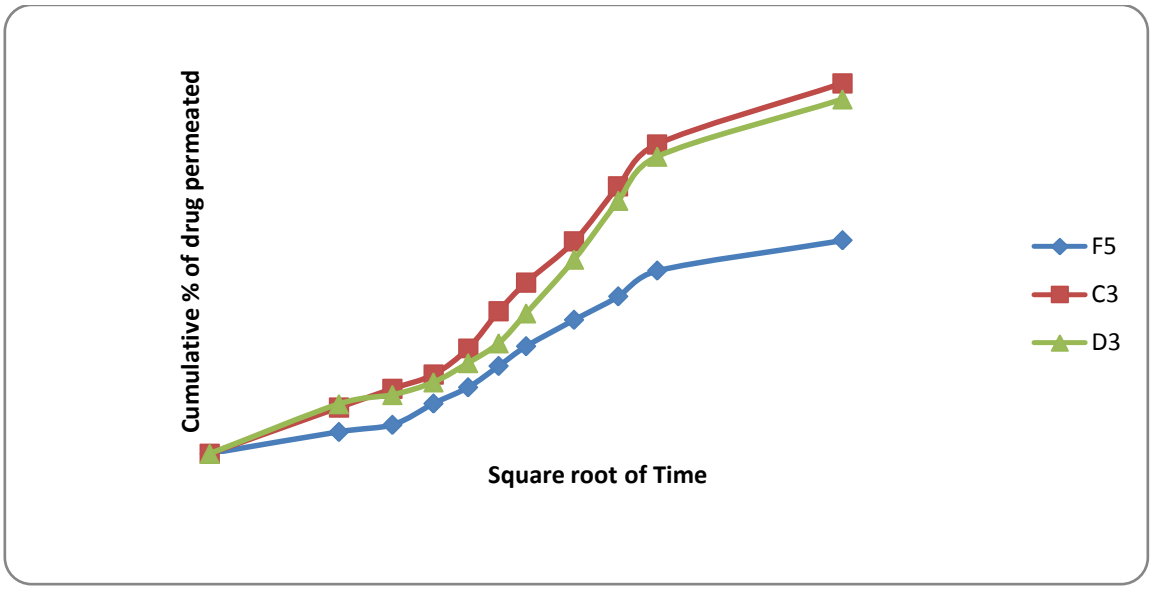

FIG. 9. HIGUCHI MODEL
(CUMULATIVE PERCENTAGE OF DRUG PERMEATED VS SQUARE ROOT OF TIME)

TABLE 12. CORRELATION COEFFICIENTS OF KINETIC MODELS OF OPTIMIZED FORMULATIONS

"FORMULATION CODE	ZERO ORDER	FIRST ORDER	HIGUCHI MODEL	PEPPAS MODEL	'N' VALUE (PEPPAS MODEL)
F5	0.845	0.876	0.939	0.956	0.822
C3	0.873	0.946	0.945	0.966	0.746
D3	0.884	0.935	0.926	0.941	0.731"

IV. CONCLUSION-

It was contemplated that the TDDS patches with ERL 100 AND HPMC E15 showed better release than patches with ERS 100 and HPMC E15. The formulations comprising d-LIMONENE (12%) was found to meet the required flux. The transdermal patches of Lenalidomide with required flux could be prepared with suitable mechanical properties; further studies are recommended to find their therapeutic utility in humans by pharmacokinetic and pharmacodynamic studies.

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