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Research Article

FORMULATION DEVELOPMENT AND EVALUATION OF MATRIX TYPE LIDOCAINE TOPICAL PATCH FOR LOCAL ANESTHETIC

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ABSTRACT

Objective: The objective of the present study was to develop a more patient, elegant, stable, good adhesion and convenient dosage form, namely drug in the adhesive topical patch containing Lidocaine as a local anesthetic.

Material and method: For preparation of a topical patch of Lidocaine with the help of penetration enhancer which gives good adhesion and maintained up to 12 hours delivery. Topical patch to adhere for 12 hours with help of different adhesive and select adhesive based on delivery of Lidocaine. Compatible excipients with Lidocaine and polymer were selected for stability of formulation. Other excipients were also added for stabilizing the blend and final topical patch. After finalization of the formulation, evaluate the formulation as per the evaluation parameter of topical patch. Final formulation is also tested for identifying the delivery of Lidocaine from the patch, also charged for three months stability to know the self-life of the formulation.

Results: Formulated patch had been evaluated for weight variation, thickness, moisture content, drug content, degradation product, adhesion study, dissolution study and in-vitro diffusion study. Three month stability study of the final formulation was carried out and results of stability study were found satisfactory showing the stability of the formulated topical patch.

Conclusion: Based on evaluation of topical Lidocaine patch, it was concluded that final formulation of Lidocaine is adhered and deliver in 12 hours and stable for 3 month in accelerated condition.

Keywords: Topical patch, Lidocaine, Release liner, Non-Woven backing film, penetration enhancers, matrix stiffener.

INTRODUCTION

Day by day, human body is becoming less defensive against microbial attack and people become more susceptible to illness. Different type of drugs used to prevent and cure the illness. The drug has been administrated via various routes like oral, sublingual, transdermal, rectal, parental, topical, inhalation etc. Effective and safe will be the need for therapeutic products that can address for chronic pain, metabolic disorders and cognitive impairment [(1)]. Post herpetic neuralgia is a disease in which peripheral neurons discharge spontaneously and have lowered activation thresholds, and exhibit an exaggerated response to stimuli. Treatments used in an attempt to reduce post herpetic neuralgia include tricyclic antidepressant (e.g. amitriptyline- an unlicensed indication), antiepileptic (e.g. gabapentin) and analgesics, as well as topical treatments such as capsaicin, Lidocaine. However, such treatments may only provide partial pain relief, and tolerability can be a problem, particularly in older patients. Versatis (Grunenthal, Ltd), a topical preparation of Lidocaine formulated in a plaster, has recently been licensed for treating patients with post herpetic neuralgia. Topical Lidocaine reduces peripheral nociception sensitization and central nervous system hyper excitability, and may benefit patients with post herpetic neuralgia.

Apart from other dosage forms, topical or transdermal route gives better advantages for local pain management [3, 4]. Topical or transdermal drug delivery can be defined as the application of the formulation to the skin to directly treat the local or/and systemic disorders with the intent of containing the pharmacological or other effect of the drug. Mainly three types of drug delivery systems are delivering the drug via the skin. Local delivery can be defined as the application of a drug-containing formulation to the skin to directly treat cutaneous manifestations of a general disease. Regional delivery, in contrast, involves the application of a drug to the skin for the purpose of treating diseases or alleviating disease symptoms in deep tissues beneath the application and transdermal delivery involves the application of a drug to the skin to treat systemic disease and is aimed at achieving systemically active levels of the drug [2]. The objective of the present study was to develop a more patient, elegant, stable, good adhesion and convenient dosage form, namely drug in the adhesive topical patch containing Lidocaine as a local anesthetic.

Factors affecting topical permeation [5, 6]

There are various factors that affect the topical permeation of drug, these are:

1. Physicochemical properties of drug molecule like Partition co-efficient, pH and permeation concentration.
2. Physicochemical properties of drug delivery system like Release characteristics, composition of drug delivery system and enhancement of transdermal permeation.
3. Physiological and pathological conditions of skin
4. Drug metabolism and drug loss while permeation through skin

Topical Patch Design

Flynn and Cleary provide the information regarding to characteristics, design, development, properties, and manufacturing of a variety of the transdermal system [7]. Adhesive transdermal systems consist as polymer coated laminates. It has three layers, backing film, adhesive matrix layer and protective release liner. The outer surface of the patch is the top of the backing layer and contains product particulars. A backing film serves several important functions in a transdermal drug delivery system and is an integral part of the system. The backing film provides mechanical support to the drug-adhesive matrix formulation. It provides physical integrity of the system by maintaining the physical dimensions and shape of the formulation. The backing also prevents direct contact of the patch formulation with the environment. The backing layer itself is made from sheets of polymer and must adhere strongly to the adhesive layer below it. The release liners are typically used in transdermal systems for at least two purposes. First they act as a protective covering for the transdermal system during the product shelf -life and are removed prior to the patch application by the patient. Second, they can act as substrates for the coating process. The release liner lies are also made from polymeric sheets and must have minimal ability to bind to the adhesive layer. This is required to remove the prior application of the topical patch. To remove easily before application, Polyester or polyethylene liner is coated with silicon or fluorocarbon polymer[8, 9]. Other than backing and liner, transdermal patch manufactured by Presser Sensitive adhesives, Semi permeable or supporting membrane, Active pharmaceutical ingredients, Tackifiers Penetration enhancers and other excipients like anti-oxidant, preservative, filler, humectants, fragrance, crystal inhibitor, solubility enhancers, protective film, overlay, matrix stiffener, solvents, matrix softeners, surfactants, plasticizers.

MATERIAL AND METHOD:

Development of transdermal patch:

1. Solubility study of penetration enhancers and solvents [10, 11]:

Penetration enhancers are to improve the penetration of the drug and also increase the solubility of dry matrix. Solvents are used to solubilize the Lidocaine in blend and also useful to facilitate coating. To know the solubility of Lidocaine in solvent or penetration enhancers, excess quantity of Lidocaine above the solubility is added in individual penetration enhancers and solvents and put in sonication for 2 hrs. After sonication individual solutions are filtered and analyze with the help of HPLC to measure the saturated solubility of Lidocaine in individual solvents and penetration enhancers. It will be easy to select penetration enhancer and solvent after identification of solubility of Lidocaine. Results of solubility are attached in table 1. The solubility studies of Lidocaine show that Lidocaine is very soluble in various permeation enhancers and solvents. The highest solubility was found in Oleyl Alcohol Di Propylene Glycol, Propylene

Glycol, and Oleic Acid.

2. Drug-Excipient Compatibility Study [12]:

When we mix two or more excipients with each other & if they are affect adversely on the physical, chemical, safety, efficacy of the product then they are said to be incompatible. The objectives of this study were to maximize stability of dosage form and to avoid any unexpected problems during or after formulation up to expiry period. Traces of monomers are present in polymer which can be potential cause of in-compatibility with Lidocaine. So this study was performed to determine any physical as well as chemical change in the drug when kept in contact with various monomers. For the evaluation of compatibility, the drug was mixed with various excipients in 1:1 ratios. This mixture was kept in glass vials than properly capped and sealed with Teflon tape. Two vials of each mixture were kept at room temperature (25˚C) and in the oven at 40°C for a one month period. After every week till one month, the vials were withdrawn and sample mixture was assayed for drug content/related substances. Results of reactivity are attached in tables 2.

BQL: Below quantification limit

As the results shown in table 2, Lidocaine found to be compatible with Oleyl alcohol, Triacetin, Mineral oil, Oleic acid and other excipients. So this permeation enhancers and excipients were used for further study.

3. Selection of pressure sensitive adhesive:

A. Saturated Solubility Study of Lidocaine in PSA Polymers (Crystallization Study) [10, 11]: Solubility of drug molecules in polymer is a critical issue for developments of transdermal patch. A patch should be given in such a way that patch has a drug loading above the solubility limit in order to obtain zero order release kinetics. The objective of this study was to determine the saturation solubility of Lidocaine in acrylate and polyisobutylene (PIB) pressure sensitive adhesives (PSA) using crystallization studies.

For identify the solubility of Lidocaine in polymer, Mix the Lidocaine and adhesive using lab size remi stirrer to achieve drug concentration of 2.5, 5, and 10% w/w in dry matrix of 100 GSM. The prepared patches were observed for crystallization under light microscope (100X) for three month at different time intervals and observations are as in table 4. Based on the above results, Gelva-373, Aqueous gelva and duro tak 4287 PSA polymers were selected for further study and 8.9% of Lidocaine concentration.

B. Selection of polymer Based on adhesion data:

After the solubility of API in polymer, Adhesion of the patch is also critical. Adhesion of the patch includes peel strength, tack property, shear strength and release force. Peel adhesion (15, 16, 17) is the force required to remove a patch from a test substrate. Tack property is the force required to pull a probe away from an adhesive at a fixed rate. Shear strength is the measurement of cohesive strength of an adhesive polymer and Release force is the force required to detach or remove release liner prior to use of patch. To measure the adhesion of the patch, Lidocaine and adhesive mixed well using stirrer to achieve drug concentration of 5% in dry matrix. Patches were prepared using 600 µm knife gaps at 60°C for 50 min. The prepared patches were studied for the following adhesion parameters.

Peel strength:

Attach the test patch on the steel plate of LLOYD (Make AMETEX). Adhere patch on the steel plate in such way that about 1 inch portion of the patch should not adhere. Now, roll the roller on it for two-three times. Allow it to stand for 1 minute. Fix the steel plate on instrument and attach the 1 inch portion on upper jaw. Peel at 180˚ using 300 mm/min cross head speed and 50 Newton load cell. Repeat same procedure for other five patches and report it in table 5.

Tack properties:

Take one patch and cut it size of 1 inch square. Remove the release liner and apply on test panel of LLOYD (Make AMETEX) such way that adhesion side remain upward direction toward hole. Load the cell on instrument and start machine at speed of 610 mm/min to bring contact of probe to adhesive site of patch. After 1 second contact time, remove probe from adhesive at same speed. Note force (maximum) required for remove the probe from patch. Repeat same procedure for other five patches and report it in table 5.

Shear strength:

Cut all patches with 0.5 inch width. Remove liner from one end and apply the patch on the test panel of shear tester (Make: CHEM. INSTRUMENT) with 0.5*0.5 inch area. Roll the roller on it and allow standing for 15 min. The other end was attached with hook and applied weight on the hook and

Table 1: Solubility of Lidocaine in different enhancers and solvents

Permeation Enhancers	Solubility (mg/ml)	Permeation Enhancers	Solubility (mg/ml)
Mineral Oil	77.75	Ethyl Acetate	37
Isopropyl Marystate	285	Heptane	488
Ethyl Oleate	263	Ethanol	226
Capric Capryl Triglyceride	374	Di Propylene Glycol	827
Glycerine	23	Toluene	232
Oleyl Alcohol	718	Phosphate Buffer,7.4 pH	210
Oleic Acid	781	Propylene Glycol	859

Table 2: Reactivity of Lidocaine with Permeation Enhancers

Excipients	Impurity	Sampling Period				
		Initial	1week	2week	3week	4week
Talc	A	BQL	BQL	BQL	BQL	BQL
	B	BQL	BQL	BQL	BQL	BQL
Colloidal	A	BQL	**0.02**	**0.03**	**0.02**	**0.05**
Silicon Dioxide	B	BQL	BQL	BQL	BQL	BQL
Glycerin	A	BQL	BQL	BQL	BQL	BQL
	B	BQL	BQL	BQL	BQL	BQL
Tween 80	A	BQL	BQL	BQL	BQL	BQL
	B	BQL	BQL	BQL	BQL	BQL
Kaolin	A	BQL	**0.16**	BQL	**0.01**	**0.03**
	B	BQL	**0.02**	BQL	BQL	BQL
Oleyl Alcohol	A	**0.08**	**0.17**	**0.39**	**0.55**	**0.56**
	B	**0.05**	**0.01**	**0.04**	**0.03**	**0.03**
Oleic Acid	A	**0.04**	**0.07**	**0.02**	**0.05**	**0.06**
	B	**0.08**	**0.11**	**0.1**	**0.08**	**0.07**
Propylene	A	**0.2**	**0.23**	**0.15**	**0.23**	**0.22**
Glycol	B	**0.04**	**0.03**	**0.02**	**0.03**	**0.03**
Ethyl Oleate	A	BQL	BQL	**0.05**	BQL	BQL
	B	BQL	BQL	BQL	BQL	BQL
Mineral Oil	A	BQL	**0.11**	BQL	**0.08**	**0.07**
	B	BQL	**0.05**	BQL	**0.07**	**0.07**

Table 3: Characteristics of PSA polymers

Sr. No.	Polymers	Solvent Composition	% Solids	Viscosity (cps)
1	Duro-Tek-608 A	Heptane	38	8000
2	HMW PIB	Heptane	-	-
3	Gelva-737	Ethyl Acetate, Ethanol, Toluene	32.5	1100
4	Gelva-9073	Ethyl Acetate, Ethanol, Hexane, IPA	32.5	4000
5	Aqueous Gelva	Water	65.5	1280
6	Duro-Tak-4287	Ethyl Acetate	39	8000
7	Duro-Tak-2510	Ethyl Acetate	40	4250
8	Bio-PSA-4302	Heptane	60	500
9	Bio-PSA-4102	Ethyl Acetate	60	350

Table 4: Crystallization study of Lidocaine in different PSA polymers [13, 14]

Polymer	% Drug	Sampling					
		Initial	3 Days	2 Week	1 Month	2 Month	3 Month
LMW PIB	2.5	-	-	+	+	+	+
	5.0	-	+	+	+	+	+
	10.0	-	+	+	+	+	+
HMW PIB	2.5	-	-	-	-	+	+
	5.0	-	-	+	+	+	+
	10.0	-	-	+	+	+	+
Duro-Tek -4287	2.5	-	-	-	-	-	-
	5.0	-	-	-	-	-	-
	10.0	-	-	-	-	-	-
Gelva -9073	2.5	-	-	-	-	-	-
	5.0	-	-	-	-	-	-
	10.0	-	-	-	-	-	-
Gelva -737	2.5	-	-	-	-	-	-
	5.0	-	-	-	-	-	-
	10.0	-	-	-	-	-	-
Aqueous Gelva	2.5	-	-	-	-	-	-
	5.0	-	-	-	-	-	-
	10.0	-	-	-	-	-	-
Bio-PSA -4102	2.5	+	+	+	+	+	+
	5.0	+	+	+	+	+	+
	10.0	+	+	+	+	+	+
Bio-PSA -4302	2.5	+	+	+	+	+	+
	5.0	+	+	+	+	+	+
	10.0	+	+	+	+	+	+

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Table 5 : Peel, Tack, shear and release force data of different polymer

No.	Peel at 180° angle (N/inch)			Tack property (N/18.89cm)		
	Aqueous Gelva	Gelva -737	Duro-Tak -4287	Aqueous Gelva	Gelva -737	Duro-Tak -4287
Average	4.48	3.47	1.28	1.46	1.3	0.46
S.D.	0.13	0.29	0.23	0.09	0.1	0.11
Minimum	4.3	3.1	1.1	1.4	1.2	0.3
Maximum	4.6	3.8	1.7	1.6	1.4	0.6
No.	**Shear Strength (min)**			**Release force (gf/inch)**		
	Aqueous Gelva	**Gelva -737**	**Duro-Tak -4287**	**Aqueous Gelva**	**Gelva -737**	**Duro-Tak -4287**
Average	41.4	34.2	12.6	29	25.8	6.18
S.D.	4.2	2.9	1.5	2.7	2.4	1.2
Minimum	35	31	11	25	23	4.5
Maximum	46	38	15	32	29	7.2

Table 6: *Ex-vivo* permeation of Lidocaine for selection of pressure sensitive adhesive

Sr. No.	Time (hrs.)	Innovator	Aqueous Gelva	Gelva -737
1	0	0	0	0
2	3	4.28	2.52	1.72
3	6	2.23	1.32	1.1
4	9	5.34	2.61	1.95
5	12	**6.85**	3.84	2.17

Table 7: Formulation with different penetration enhancers

Sr. No.	Ingredients	%Solid (%w/w)			
		F-9	**F-11**	**F-12**	**F-13**
1	Lidocaine	8.98	8.98	8.98	8.98
2	Oleyl Alcohol	*5*	-	-	-
3	Triacetin	-	*5*	-	-
4	Mineral Oil	-	-	*5*	-
5	Oleic Acid	-	-	-	*5*
6	Tween-80	*0.7*	*0.7*	*0.7*	*0.7*
7	Talc	*25*	*25*	*25*	*25*
8	Aqueous Gelva	60.3	60.3	60.3	60.3
	Total	**100**	**100**	**100**	**100**

Table 8: Comparison of skin flux (mcg/cm^2/hr) between different Permeation enhancers.

Sr. no.	Time (hrs.)	Innovator	5% Oleyl Alcohol	5% MO	5% O.Acid	5% Triacetine
1	0	0	0	0	0	0
2	3	4.28	3.46	2.98	3.02	2.77
3	6	2.23	1.74	1.84	1.74	1.71
4	9	5.34	4.28	3.43	4.13	3.21
5	12	6.85	*5.15*	4.20	4.71	4.05

Table 9: Comparison of Skin Flux between different concentrations of Oleyl Alcohol(O.Alcohol)

Sr. No.	Time (hrs.)	Innovator	5% O.Alcohol	7.5% O.Alcohol	10% O.Alcohol	12.5% O.Alcohol
1	0	0	0	0	0	0
2	3	4.28	3.46	3.67	4.19	5.11
3	6	2.23	1.74	1.74	2.37	3.02
4	9	5.34	4.28	5.33	5.27	6.26
5	12	6.85	*5.15*	5.41	6.75	8.12

Table 10: Composition of final formulation of Lidocaine topical patch

Raw Materials	Dry matrix, (% w/w)	Wet matrix, (% w/w)
Lidocaine	*1.5*	*0.83*
Oleyl Alcohol	*--*	*11.10*
Triacetin	*2.00*	*1.33*
Mineral Oil	*5.00*	2.78
Oleic Acid	*2.00*	1.11
Tween-80	*8.00*	4.44
Talc	*26.00*	*28.39*
Aqueous Gelva	*55.50*	*50.02*
Total	**100.00**	**100.00**

Table 11: Thickness of drug matrix of fabricated topical patches

S. No.	Sample	Thickness (Micron)
1	Liner	*55-65*
2	Backing	420-480
3	Backing + Liner	*475-545*
4	Total Patch	1175-1240
5	Matrix weight	690-700

Table 12: Uniformity of Weight

Sr. No	Total patch Weight(g)	Dry matrix weight (g)
1	16.786	14.256
2	16.797	14.267
3	16.532	14.002
4	16.526	13.996
5	16.668	14.138
6	16.675	14.145
7	16.52	13.99
8	16.495	13.965
9	16.615	14.085
10	16.73	14.2
Mean	**16.6344**	**14.1044**
minimum	**16.495**	**13.965**
Maximum	**16.797**	**14.267**

Table 13: Assay/Drug content/Content uniformity of Lidocaine transdermal system

Sr. no	Drug Content (% w/w)	Sr. No	Drug Content (% w/w)	Results	
1	101.98	**6**	99.45	**Mean**	100.073
2	100.3	**7**	100.34	**Minimum**	98.23
3	99.45	**8**	100.97	**Maximum**	101.98
4	98.23	**9**	100	**RSD**	0.98
5	100.12	**10**	99.89	**%AV**	2.34

Table 14: Adhesion Study

Sample No.	180⁰ Peel, (N/inch)	Tack Force, (N)	Release force, (gf)	Shear, (minutes)
1	2.921	1.222	7.754	9.6
2	2.380	1.29	9.47	8.5
3	2.197	1.218	10.41	9.6
4	2.365	1.253	8.39	9.1
5	2.845	1.264	9.94	8.9
Avg.	**2.5426**	**1.2494**	**9.1928**	**9.14**
Min.	**2.197**	**1.218**	**7.754**	**8.5**
Max.	**2.921**	**1.29**	**10.41**	**9.6**

Table 15: In-Vitro drug release or dissolution study

Time (hr.)	Cell-1	Cell-2	Cell-3	Cell-4	Cell-5	Cell-6	Mean	SD	MIN.	MAX.
0	0.00	0.00	0.00	0.00	0.00	0.00	**0.0**	**0.0**	**0.0**	**0.0**
0.5	20.40	21.00	22.70	17.10	19.50	17.00	**19.6**	**2.3**	**17.0**	**22.7**
3	54.10	53.80	53.00	55.10	53.90	55.60	**54.2**	**0.9**	**53.0**	**55.6**
6	73.00	71.00	73.60	72.10	75.00	74.60	**73.2**	**1.5**	**71.0**	**75.0**
12	95.60	93.10	92.90	97.30	96.80	98.80	**95.7**	**2.4**	**92.9**	**98.8**
14	99.90	103.50	102.50	96.60	99.50	98.20	**100.0**	**2.6**	**96.6**	**103.5**

Table 16: In-Vivo drug release or skin flux study

	Cumulative penetration µg/cm2				
Time in hrs.	**Cell-1**	**Cell-2**	**Cell-3**	**Average**	**Std. deviation**
0	0.0	0.0	0.0	0.0	0.0
3	38.6	27.7	23.8	30.0	7.7
6	95.4	76.1	63.0	78.2	16.3
9	157.2	128.6	107.3	131.0	25.0
12	208.3	171.2	144.4	174.6	32.1

Table 17: Skin flux data

Skin Flux µg/cm2/h					
Time in hrs.	**Cell-1**	**Cell-2**	**Cell-3**	**Average**	**Std. deviation**
0	0.0	0.0	0.0	0.0	0.0
3	12.9	9.2	7.9	10.0	2.6
6	18.9	16.1	13.1	16.0	2.9
9	20.6	17.5	14.8	17.6	2.9
12	17.0	14.2	12.3	14.5	2.4

Table 18: Stability results

Test details		**Initial**	**1 Month**	**2 Month**	**3 Month**
% Assay Mean, (90 - 110 % of label claim)		101.6	102.7	102.6	101.3
% Drug Release:	30min	31.0	36.0	33.0	33.2
USP Apparatus : V	3hrs.	82.0	89.0	83.0	87.0
Medium :1.4 pH SGF Buffer	12hrs:	108.0	107.0	105.0	108.9
RPM : 100					
Temperature :32.0 ± 0.5 ° C					
Patch Size : 7.94 sq.cm					
Volume : 1000 ml					
No of patches : 6					
Degradation Products: % known product at RRT 0.3, (NMT 1.0%)		0.09%	0.10	0.16%	0.16%
% Unknown product at RRT 0.4, (NMT 1.0%)		<0.05%	<0.05%	<0.05%	<0.05%
% Total Degradation, (NMT 3.0%)		0.08%	0.10%	0.16%	0.16%

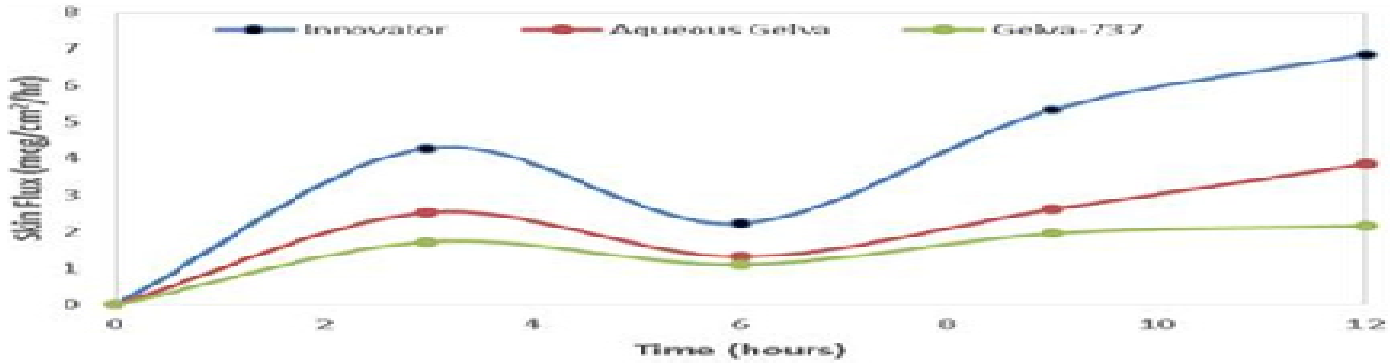

Figure 1: Skin flux between Gelva-737 and Aqueous Gelva

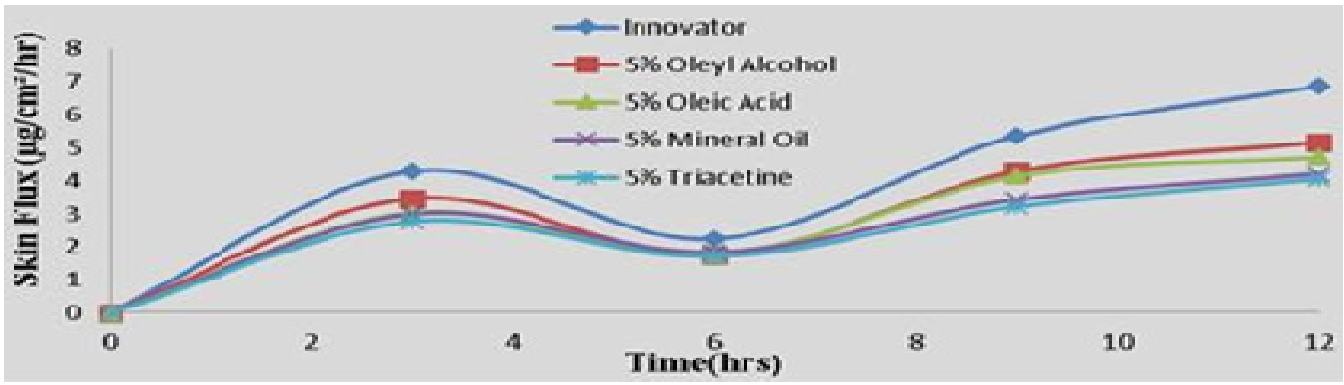

Figure 2: Comparison of skin flux from different permeation enhances

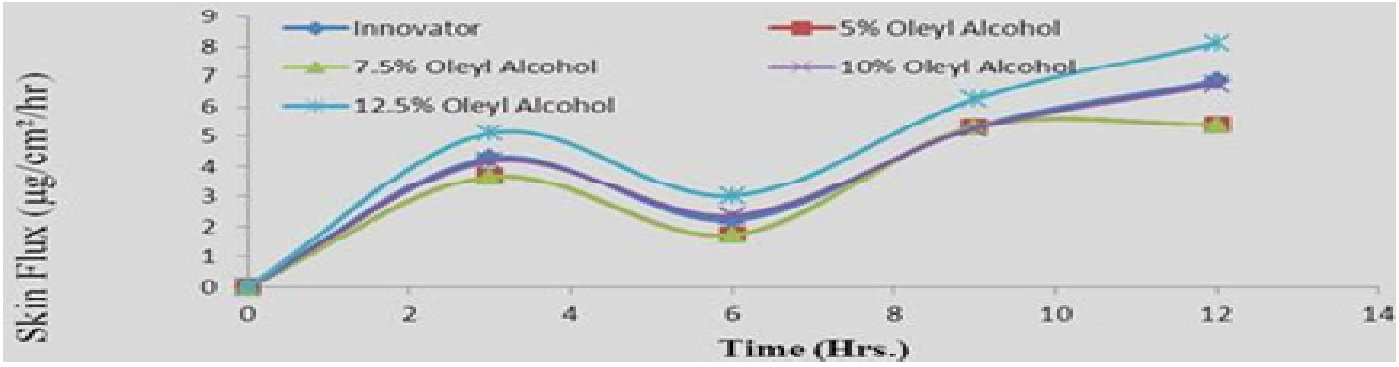

Figure 3: Comparison of skin flux from different concentrations of OleylAlcohol

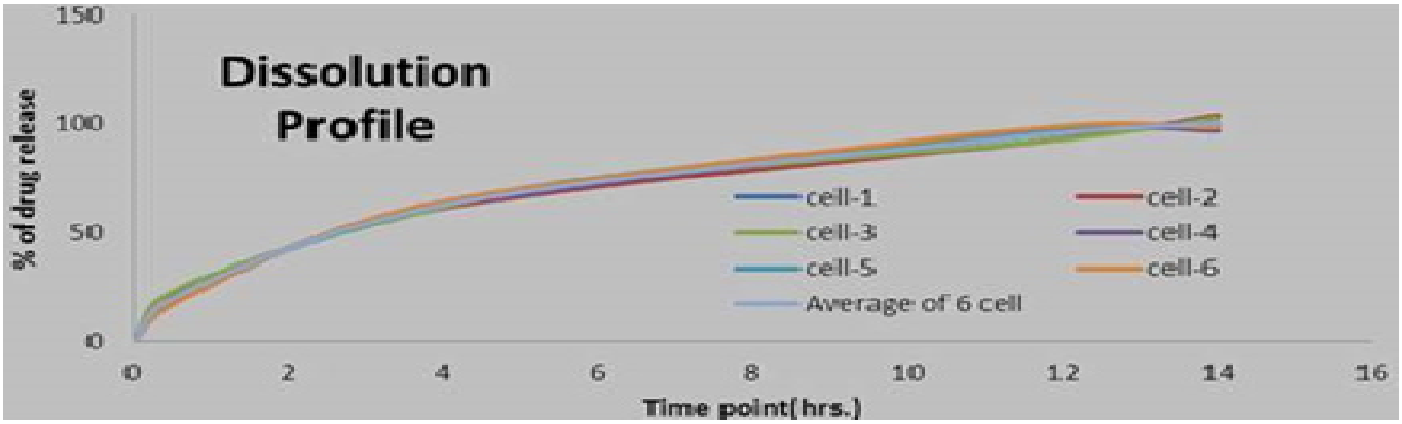

Figure 4: Dissolution profile

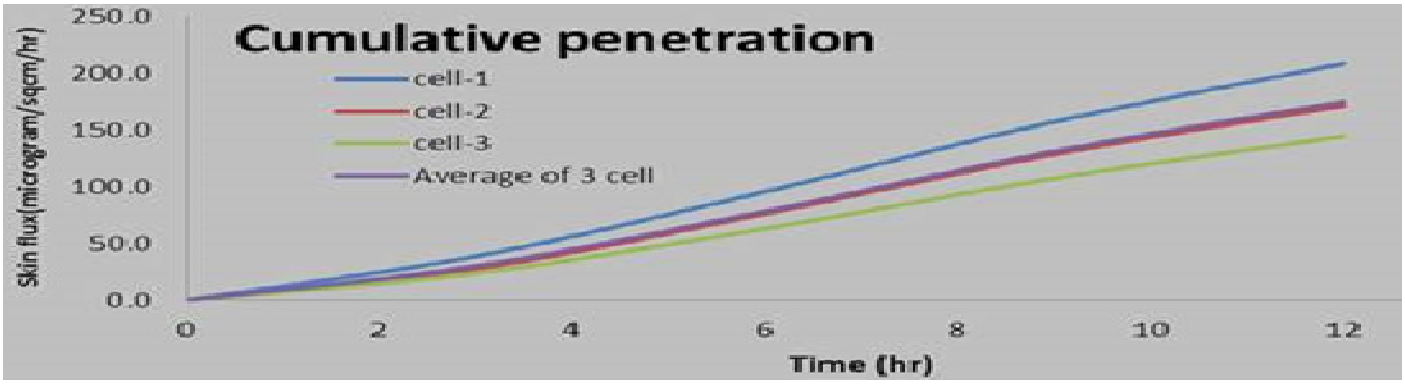

Figure 5: In-vitro cumulative penetration

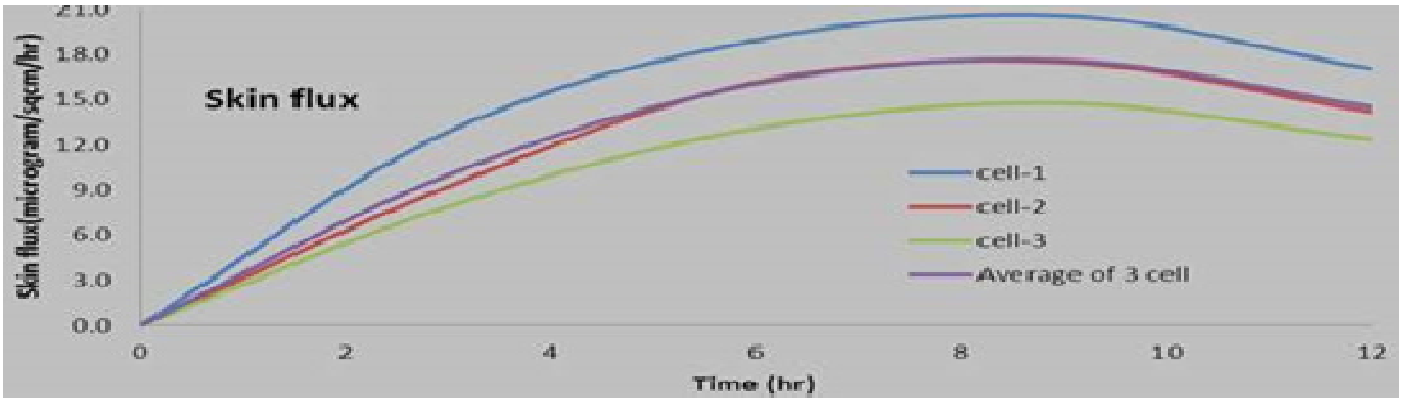

Figure 6: In-vitro skin flux

measure time to fall down patch. Repeat same procedure for other five patches and report it in table 5.

Release Force:

Attach double-sided adhesive tape to the surface of steel panel of LLOYD (AMETEX). Adhere test patch on double-sided adhesive tape in such way liner remains outside. Attach the liner with movable jaw using cello tape. Peel at 180° using 300mm/min cross head speed and 50 newton load cell. Repeat same procedure for other five patches and report it in table 5.

From the observations in table 5, it was found that there were no significant differences in adhesion parameters among the patches which prepared from Aqueous Gelva and Gelva-737. But patches prepared from the PSA adhesive Duro-Tak-4287 show poor adhesion property, so this polymer was not selected for further study. Aqueous Gelva and Gelva-737 selected for further study.

C. Selection of pressure sensitive adhesive based on ex-vivo permeation

The objective of this study was to investigate the effects of various PSAs on the in ex-vivo permeation of Lidocaine across the hairless human cadaver skin using modified Franz type diffusion cells at 32±0.5 °C. The human cadaver skin was cut into desired size of 7.94 cm^2 and clamped between the receptor and donor compartments so that the dermal side of the skin faced the receiver fluid. The release liner was removed from the patch (7.94 cm^2 size) and the drug releasing surface was pressed on the skin with the adhesive side facing the stratum corneum. The receptor compartment was filled by the diffusion medium (phosphate buffer pH 7.4) through sampling port taking care to remove all the air bubbles. The contents were stirred by the small magnetic beads. At suitable time intervals (0, 3, 6, 9, 12 hour), 1ml aliquots of diffusion medium were collected at and filtered through Whatman® filter grade 41, suitably diluted and the amount of Lidocaine diffused through the skin membrane was then determined by HPLC. Fresh diffusion medium of the same volume (1ml), which was pre-warmed at 32±0.5 °C, was replaced into the diffusion cell after each withdrawal. The study was continued up to 12 hours and reported in table 6 and figure 1 (17, 18, 19). From the results, it was concluded that Lidocaine in aqueous polymer shows more skin flux compare to gelva-737. So this polymer was selected as pressure sensitive adhesive for further study.

4. Selection and optimization of Permeation Enhancer (Based on Ex-vivo permeation study)

The objective of this study was to investigate the effects of various permeation enhancers like Oleyl Alcohol, Triacetin, Oleic Acid and Mineral oil on the Ex vivo permeation of Lidocaine across the skin membrane using Franz diffusion cells at 32±0.5°C. Formulation of different batches is listed in table 7.

By using the above Formula, patches were made which contained different penetration enhancer. Then performed Ex-vivo permeation study of this patches and results reported in table 8 and figure 2 and in figure 5.9, 5.10.

From the results, it was concluded that Lidocaine in 5% Oleyl Alcohol shows more skin flux compare to other permeation enhancer. So this permeation enhancer was selected for further study. After selection of penetration enhancer, Oleyl alcohol concentrations need to optimize. To optimize the oleyl alcohol different concentration patch were made and do flux study. Results are reported in table 9 and figure 3.

From the results, it was concluded that Lidocaine in 7.5% Oley Alcohol shows comparative better skin flux. So 7.5% concentration of permeation enhancer was used for further trials.

5. Addition of smoothing agent (Glycerin)

When more than 5% of oil was added, the blend became thick. But the blend was difficult to coat. So some smoothing agent was required to make the blend smooth and can be coated easily. From the literature 5% glycerine was selected as smoothing agent.

6. Addition of surfactant: Aqueous Gelva is Gelva Multi-polymer Emulsion (GME).

When we added Lidocaine solution in olayl alcohol in this polymer, polymer became separated due to change in oil concentration. So we required to add some surfactant to stabilize the system. From the literature, 5% Tween 80 was selected as surface active agent.

7. Optimization of Matrix Stiffening Agent:

When patches were prepared by using above formula it was found that matrix was not sufficient stif means matrix somewhat soft. So lagging was observed in all patches. An essential component of the transdermal patch is stiffener.

Based on expriment from 0-40% of talc and 0-10% CSD, 26% talc was selected due to below 26% lagging was observed and above 26% patch was not adhere properly.

8. Final formation of matrix type Lidocaine transdermal patch

After selection of all ingredients and concentration (Table 9), accurately weighed Lidocaine was solubilize in permeation enhancers solution in a 500ml stainless steel beaker. Dispensed quantity of talc was mix with Lidocaine solution. After proper mixing of talc, adhesive solution was added to the above mixture and mixed properly using electric stirrer to prepare homogenous mixture. Tween-80 was mixed into above uniform dispersion of polymer. The patch was prepared by coating the above mixture on release liner (Silicone coated polyester film) and allowed to dry in oven at 70oC for 30 min on coater (Make: Mathis) and laminate with non-woven backing film on laminator (Make: Cheminstrument®). After formation of laminate, cut the patch as per in the size of 140 cm2 and evaluate the patch for different parameters.

EVALUATION OF FINAL PATCH

1. Patch Thickness: The thickness of the drug-containing adhesive matrix was determined by measuring the thickness of the whole patch (adhesive matrix with backing membrane and release liner) and subtracting the thickness of the backing membrane and release liner. The average thickness was determined using a digital caliper (Micrometer MI-1000, Cheminstruments®).

2. Uniformity of Weight: Weight variation was studied by individually weighing 10 randomly selected individual patches and calculating the average weight. The individual weight should not deviate significantly from the average weight.

3. Assay/Drug content/Content uniformity of Lidocaine transdermal system (Patch): In transdermal formulation, mean of content uniformity is considered as an assay of the formulation and calculate drug content based on label claim and mean of content uniformity. Below is the method for identification of the content uniformity.

For sample preparation: Remove the liner of 10 individual patches and place the patch in individual volumetric flask containing 500ml of diluent in such that matrix side faced upwardly. Shake for one hour on a mechanical shaker to extract the Lidocaine. Filter the extract in a test tube. Dilute 5 ml of the filtrate to 20 ml with ethyl acetate. Filter the solution and drug content estimated by Agilent® HPLC system supported by Chromeleon® software.

For mobile phase preparation: mix about 9 volumes n-Hexane with 1 volume of ethanol in one liter glass bottle.

For standard preparation: Dissolve about 45.1mg of USP Lidocaine, accurately weighed in 10mL of ethyl acetate in a 250mL volumetric flask, and makeup the volume with ethyl acetate having a known concentration of about 0.18mg/ml of Lidocaine.

Separately inject equal volume (5 micro liters) of a diluent, standard preparation and sample preparation into a HPLC system, record a chromatogram and measure responses for a major peaks and also the retention time of the major peaks. Drug content of the transdermal formulation is calculated based on assay of the patch and average assay of 10 patches was determine for individual patch assay is called content uniformity of the patch.

4. Adhesion Study: Adhesion test include peel strength, tack property, shear strength and release force. Adhesion study of prepared final patches was performed by using procedure given in above section of adhesion.

5. In-Vitro drug release or dissolution study: The in-vitro drug release study of the patch is essential to ensure whether drug release from the matrix and available to skin for constant delivery. In transdermal formulation, in-vitro drug release or dissolution is not a product performance test or critical quality attributes but dissolution is to see the product character stick or product quality test. Although several apparatus and procedures have been used to study in vitro release characteristics of trans-dermal patches, current pharmacopeia apparatus include the paddle over disc assembly method (USP apparatus 5), the rotating cylinder (USP apparatus 6), the reciprocating disk (USP apparatus 7), and a paddle over extraction cell method.

There are various methods available for determination of drug release rate of TDDS. But this test was performed as only quality test parameter. The dissolution study was conducted using USP apparatus-5 (Electrolab® TDT-06P, paddle -type) with addition of a disc. The fabricated patch of 140 cm2 is to be cut into 20 cm2 was placed against a glass disc (delivery side up) retained with the stainless-steel

screen and exposed to 1.4 pH SGF buffer. All dissolution studies were carried out at 32 ± 0.5 °C and 100 ± 5 rpm, with each dissolution jar carrying 900 ml of the 1.4 pH SGF buffer. 5 ml aliquots of dissolution medium sample was withdrawn at various time intervals and replaced with 5 ml of the 1.4 pH SGF buffer. Withdrawn were appropriate diluted and analyzed by HPLC.

6. In-Vivo drug release or skin flux study:

The objective of this study was to know the amount of active penetrate through human cadaver skin and cumulative permeation of the final prepared patch. The Ex-vivo drug release experiment was carried out by using Franz type modified diffusion cell. The diffusion study is essential to investigate the mechanism of drug transport from the stratum corneum to the systemic circulation. Several designs of in-vitro diffusion apparatus are in existence, these are:

1. Horizontal diffusion cell
2. Vertical diffusion cell
3. Flow through diffusion cell
4. Continuous diffusion cell
5. Fluid circulation diffusion cell
6. Non circulation diffusion cell

Most widely used diffusion cells are Franz and K-C type. The K-C cell which is modified form of Franz diffusion cell has an effective receptor volume of 12 ml and skin surface area is 3.14cm^2. Skin (pig, mouse, human cadaver or any artificial membrane) is mounted between donor and receptor compartment. The receptor solution is then agitated by a small magnetic bead at a constant rate of 100-200 rpm. To simulate the in-vivo conditions receptor cell is covered with a jacket in which previously warm water flows at definite temperature to provide a temperature of 32oC at the membrane surface. The excised human cadaver skin was cut into desired size of 7.94 cm^2 and clamped between the receptor and donor compartments so that the dermal side of the skin faced the receiver fluid. The release liner was removed from the patch (7.94 cm^2 size) and the drug releasing surface was pressed on the skin with the adhesive side facing the stratum corneum. The receptor compartment was filled with the specified volume by the diffusion medium (phosphate buffer pH 7.4) through the sampling port taking care to remove all the air bubbles. The contents were stirred by smaller magnetic beads and continuously stirred at about 200 RPM to keep them well mixed. At suitable time intervals, 1ml aliquots of diffusion medium were collected at and filtered through Whatman® filter grade 41. Suitably diluted and the amount of Lidocaine diffused through the skin membrane was then determined by HPLC. Fresh diffusion medium of the same volume (1ml), which was pre-warmed at 32±0.5 °C, was replaced into the diffusion cell after each withdrawal. The study was continued up to 12 hours. Each study was performed in triplicate (n=3) and the mean value was used to calculate the permeability of drug through the skin.

***7.* Stability Study of Final Patch:** Stability testing of drug products begins as a part of drug discovery and ends with demise of compound or commercial product. FDA and ICH specifies the guidelines for stability testing of new drug products, as a technical requirement for registration of pharmaceuticals for human use (ICH Guidelines). The stability studies of the formulated transdermal patches were carried out on prepared patches at different temperature and humidity according to ICH guidelines: 25 ± 2°C (60%RH) and 45 ± 2°C (75%RH) a period of 3 months in paper pouch having 7 micron aluminum layer. Then samples were withdrawn and analyzed for physical evaluation, assay, drug release, adhesion and degradation products.

RESULTS AND DISCUSSIONS:

1. Thickness of drug matrix of fabricated topical patches

Total patch thickness of transdermal Lidocaine is 1175-1240 micron with 55-65 micron liner and 420-480 micron backing film. Matrix after drying is having thickness approx. 700 microns. According to USFDA guidelines for topical formulation of Lidocaine, total matrix weight, area of the final cut patch and total amount of active ingredients are similar compared to already exist in US market innovator formulation.

2. Uniformity of Weight:

Total patch weight of transdermal Lidocaine is 16.495-16.797 gram with 1.33 gram of backing weight and 1.20 gram of liner weight. Matrix after drying is having weight approx. 14grams. According to USFDA guidelines for topical formulation of Lidocaine, total matrix weight, area of the final cut patch and total amount of active ingredients are similar compared to already exist in US market innovator formulation.

3. Assay/Drug content/Content uniformity of Lidocaine transdermal system (Patch):

Prepared final patches comply with content uniformity test. Assay of all 10 randomly selected patches was found to be between 90-110 %w/w. % total degraded product of Lidocaine topical patch was found to be 0.00% w/w. Acceptance value of Lidocaine transdermal patch is 2.34 and according to US Pharmacopeia below 15% AV is accepted for further study. Similarly standard deviation is 0.98 and below 5.0% SD is accepted for further study, so Lidocaine formulation was evaluated for further adhesion and stability study.

4. Adhesion Study:

From above results, it can be concluded that prepared final patches shown good adhesion value. This adhesion value was sufficient to keep patch 12 hr. on skin and easily remove from the skin without leaving residue on skin.

5. In-Vitro drug release or dissolution study

We performed dissolution of patch in medium where it was sufficient soluble to maintained sink condition. From the results of dissolution study, we can conclude that patch give control drug release and not dose dumping or any uneven drug release observed. Thus prepared patch show control drug release and permeability is rate limiting step.

6. In-vitro skin flux

After 12 hrs. the cumulative permeation of Lidocaine from Final Patch and Innovator was found to be 55.25µg/cm² and 56.18µg/cm² respectively. After 12 hours the cumulative permeation of Lidocaine from Final Patch and Innovator was found to be 6.67µg/cm² and 6.85µg/cm² respectively. From the results, it was concluded that Final Patch shown comparative cumulative permeation and skin flux with Innovator.

7. Stability Study of Final Patch:

The samples of optimized final patch were kept in accelerated condition (40^0C/75% RH) for two month. Then samples were withdrawn and analyzed for physical evaluation, assay, drug release, and degradation products. The results are given in below table 17.

DISCUSSION:

The procured sample of Lidocaine was characterized by I.R., UV, HPLC and melting point studies. All the observed data were matched with the reported data of the Lidocaine. Hence it was inferred that the procured drug sample was of pure Lidocaine and hence used for further studies. In the pre-formulation studies, drug solubility study, partition coefficient, thermogravimetric analysis, drug-monomer, drug-enhancer and drug-excipient compatibility and transmission and uptake study was carried out. Drug-excipients, drug-monomers and drug enhancer reactivity study and transmission and uptake study had been started and their final results are awaited. On the basis of pre-formulation studies, adhesive polymer, permeation enhancers and other excipients, and baking and the liner had been selected for the formulation. During the formulation design initial drug was mixed with polymer but it was not dissolved, so the drug was mixed with oleyl alcohol and premix was made and then premix was mixed with polymer and patch was made. On the basis of permeation and adhesion aqueous Gelva was selected as polymer to be used in the formulation. For the stability of the mixture tween-80 as surfactant was added in the formulation. Than talc was selected as matrix filler and it's also optimized for its concentration. Oleyl alcohol was selected as a permeation enhancer amongst four available ad its concentration was also optimized. In the above formula glycerin was added as a matrix stiffening agent. So, in this way the final formula was designed and can be used for final formula. Formulated patch had been evaluated for weight variation, thickness, moisture content, drug content, degradation product, adhesion study, dissolution study and in-vitro diffusion study. 3 month stability study of the patch was carried out and results of stability study were found satisfactory showing the stability of the formulated topical patch.

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