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FORMULATION AND EVALUATION OF TRANSDERMAL PATCH OF LIDOCAINE HCl FOR INSECT BITE

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ABSTRACT

Objective: Lidocaine needs to be administered frequently as it has poor oral bioavailability and it lacks prolong duration of action thus the study was aimed at to devise, develop, and analyze a matrix system transdermal formulation with Lidocaine HCl to give a sustained release effect of drug for chronic pains with a goal to enhance the bioavailability, avoid multiple administration thus improving the patient compliance. **Materials and Methods:** The different concentrations of different polymers of different grades such as HPMC K15, HPMC K100, Oleic acid, Eudragit RS100 and Patchouli oil were used in different conjuction to get optimized preparation of transdermal patches. Different hydrophilic and hydrophobic polymeric ratios resulted in plasticization with PEG 400 by the solvent casting method. The designed patches were then tested for their physico-chemical properties, including thickness, clarity, uniform drug content in patches and folding endurance. The improved formulation was then assessed by drug-excipient compatibility, in-vitro release study and kinetic modeling. **Results:** Folding endurance and clarity of al patches was satisfied. Spectroscopic techniques using the Fourier transform in the infrared and ultraviolet spectrum were used to rule out the interference of the polymers. In vitro release studies of Lidocaine were performed using a modified diffusion cell and phosphate buffer with a pH of 7.4, HCl loaded patches and it followed Higuchi and Korsmeyer Peppas model. In vivo drug release studies demonstrated the release up to 24h with release of 90.97% to 97.57%. **Conclusion:** The findings concluded that transdermal patches of Lidocaine HCl prepared by different grades of polymer were capable of exhibiting sustained release or controlled release of drug with defined stability. The developed patches had produced encouraging outcomes.

Keywords: Lidocaine HCl, Hydroxypropyl methylcellulose, In vitro permeation, Transdermal patches, Controlled release.

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INTRODUCTION

One of the drug delivery mechanisms is the transdermal drug delivery method, which uses the intact skin as route for the delivery of drug it contains which avoids the problems of gastric irritation, pH related factors, so that drug reaches the systemic circulation to provide its therapeutic effect **[1]**. Transdermal drug delivery approach is one of the delivery methods which uses the intact skin as the route of delivery of drug it contains in its system so that it can goes directly into blood stream without undergoing the liver metabolism which is a major factor in lowering the bioavailability of drugs thus leading to lowering the efficacy at desired dose **[2]**. It has many advantageous features over other conventional routes which lacks sustained effect and show fluctuations in peak plasma levels. It provides invasive method for drug delivery.it is a painless process as compared to the parental route which although bypass the first pass metabolism but does not give sustained effect and use multiple dosing and is painful and required skills to administer **[3]**.

It is user-friendly and enhances patient compliance. Patient can simply apply the patch on its own without need of assistance it is suitable for old age people and people who use multiple medicine on daily basis.it is cost effective.it avoids use of multiple dosing for maintaining plasma concentration.it delivers the drug at control rate leading to sustained effect **[4]**. It is a great option for treating the chronic diseases which requires dosing on daily basis. It is convenient to use for drugs causing gastric irritation or either unstable in the GIT acidic environment. The undesirable

effects can be reduced with the patch as it releases at control rate thus not reaching the peak levels instantly causing sudden adverse drug reaction, if the ADR reported the termination of patch is easy and quick.it is greater to use it for the drugs having narrow therapeutic window to minimize the chances of adverse effects. The potential candidate drugs to be formulated as patches must have shorter half-life, low oral bioavailability, low dose, low molecular weight **[5]**.

Patches of transdermal lidocaine has been used in the treatment of localized pain. Arthritis and Back pain are the commonly occurring diseases worldwide. Lidocaine transdermal patches are used to treat back pain, arthritis, muscle pain and strains. It relieved neuropathic pain by blocking Na-channels in the area of damaged nociceptors. Transdermal lidocaine patches are used as an alternative to post-operative opioids therapy as a postoperative analgesic. It is also used to alleviate pain linked with cannula insertion **[6]**. Lidocaine is an anesthetic which acts locally and is amide type. Orally administered Lidocaine possess low bioavailability due to high rate of liver metabolism .IM injection of lidocaine is absorbed quickly and completely in all tissues particularly in kidneys, heart, liver tissues. The Volume of distribution is nearly 1000ml/kg of body wight.51% of drug binds to protein. Immediately effective after IV route but to maintain plasma concentration between therapeutic range it needs to be administered frequently which is inconvenient and painful **[7]**.

Patches of transdermal lidocaine have been used as a gold standard therapy in the treatment of localized pain. Arthritis and Back pain are the commonly occurring disease worldwide. Lidocaine transdermal patches are used to treat back pain, arthritis, muscle pain and strains. Patches of lidocaine approved by FDA are used as a 1st line therapy to treat postherpetic neuralgia **[8]**. The main aim of developing this system is due to its ability to release a drug in a sustained manner to maintain a flat blood level profile which helps in bridging a gap between dose intervals such as once daily dosing of orally administered drugs and once a week or longer dosing drugs addressed by depot injection and involves in achieving optimal blood level. Patches of TDDS bypasses the skin barrier and improved the delivery of hydrophilic drugs and macromolecules. TDDS has less systemic toxicity and high specificity for cutaneous viral disease **[9]**.

MATERIALS AND METHODS

Materials

Lidocaine HCL, Ethyl cellulose, Eudragit RS-100, HPMC K15, Oleic acid, Patchouli oil, Hydroxy propyl methylcellulose (HPMC K100), Polyvinyl pyrrolidone (PVP K30) were purchased from sigma Aldrich and PEG-400, Dibutyl phthalate Dichloromethane, Propylene Glycol, Chloroform and Methanol all these ingredients were purchased from Merck Pakistan. All the chemicals used were of analytical grade and Distilled water was used throughout.

Method

The Drug loaded Patch was prepared by Solvent casting Method. In order to create a transparent solution, the polymers were precisely weighed, dissolved in a solution of water and methanol, and set aside. Drug was dissolved in the aforementioned solution and thoroughly mixed to produce a clear solution. Polyethylene glycol (PEG) 400 had a plasticizing effect. and propylene glycol was employed to improve permeability. The uniformly formed solution was poured into a petri dish, greased with glycerin, and allowed to dry for 24 to 48 hours at room temperature. To prevent the solvent from quickly evaporating, an inverted funnel was placed on top of the petri dish. The dried patches were removed after 24 hours and kept in a desiccator for future analysis. Formulation design was given in **Table 1**.

Table 1: Formulation design for lidocaine patches.

Formulations Ingredients	**F1**	**F2**	**F3**	**F4**	**F5**
Lidocaine HCL (mg)	50	50	50	50	50
HPMC K100 (mg)			130		
Propylene Glycol (ml)					0.142
HPMC K15 (mg)		885		796	425
PVP 30 (mg)			130		425
PEG 400 (ml)	1.2	7		0.25	0.285
Patchouli Oil (%)			0.25 %		
Eudragit RS 100 (mg)		65			
Ethyl cellulose (mg)	950			199	
Dibutyl phthalate (ml)	1.3				
Dichloromethane (ml)				20	
Ethanol (ml)				20	
Methanol (ml)					10

PRELIMINARY STUDIES OF SELECTED DRUG

Preliminary studies were conducted to assess the physiochemical properties of the selected drug Lidocaine HCL.

Crystallinity

A pinch of drug powder was added on slide and covered with coverslip. The slide was observed under a compound microscope.

Hygroscopicity

Required amount of Lidocaine was taken on the petri dish. The sample was exposed to the environment at room temperature. Petri dish wash heated with the help of oven at 80℃ for 15 minutes. Then the sample was weighed again and the difference was calculated. LOD was calculated with the help of following formula: = (initial W – final W / initial W) x 100

Melting Point

The Temperature was set between 0.1oC-350o C The sample of drug was placed on slide and placed in chamber of apparatus. It started noticing the melting point by observing the sample through naked eye or through lens. The temperature was recorded at which melting begun and at which the last crystal disappeared.

Angle of Repose

A weighed amount of powder was taken. The amount of powder was passed through 10 mesh sieves. The assembly of the funnel was blocked by thumb and transferred the powder into the funnel. The height of the funnel was adjusted as that about 6.4mm gap was maintained between the bottom of the funnel stem peak/top of the powder. The angle of repose when the powder was emptied from the funnel. The outer edge of the pile was taken on blank paper with pencil and found out diameter of the pile. The height of the pile was measured using two rulers. The angle of repose was measured from radius and height.

EVALUATION OF PREPARED TRANSDERMAL PATCHES

Physical Characterization

Folding Endurance

Until it broke, a strip of a specified size (2 cm x 2 cm) was cut uniformly and folded repeatedly in the same spot. The quantity of folds the film could withstand at the same location without breaking determined its folding endurance.

Thickness

Using a digital Vernier Caliper of Tricle Brand, the patch thickness was measured three times, and the mean value was computed.

Clarity

It was determined by the percentage of light passed through the deviates from the incident beam less than 2.5 degrees.

Chemical Characterization

Calibration Curve

Calibration curve also known as a standard curve, is a general method for determining the concentration of a substance in an unknown sample by comparing the unknown to a set of standard samples of known concentration. All dilutions were run on spectrophotometer and absorbance was noted. A calibration curve was drawn by using Microsoft excel **[10]**.

In-Vitro Dissolution Analysis

900 ml of 6.8 pH buffer was taken in the Apparatus Basket. Patch of 2cm by 2cm was attached to the paddle of the apparatus. 1ml of first sample was taken after 30 minutes. 1ml of second sample was taken after another 30 minutes and Remaining 4 samples were taken with the interval of 1 hour. 9ml of buffer was added in each of the sample to makeup to 10ml. Then all these samples were run on the UV spectrophotometer and the readings were taken from the UV spectrophotometer **[11]**.

Kinetic Modeling of Dissolution Data

Kinetic analysis of the in-vitro release data to ascertain the kinetic modelling of drug release, data from in vitro drug release were fitted. to zero order, first order, Higuchi, and Korsmeyer- Peppas equations to ascertain the pattern of drug release of Lidocaine HCL from transdermal patches **[12]**.

Content Uniformity of the Patches

The drug uniformity in all patches were evaluated .10 % of patch was taken and added in 10 ml of buffer. It was heated and stirred continuously for 30 minutes. Then kept aside for 24 hours. After 24 hours, the centrifugation was performed. Supernatant was taken and observed on the UV Spectrophotometer **[13]**.

Differential Scanning Colorimetry

A differential scanning calorimeter was used to conduct DSC tests, and 10 mg of the material was placed in an aluminum pan for the experiment. After the pan had been sealed, a DSC heating/cooling/heating cycle (first heating, first cooling, and second heating) was used to scan the temperature between 40°C and 180°C at a rate of 10°C/min while nitrogen gas flowed at a rate of 30 mL/min. Following the method, the Pyris application automatically created a heat flow vs temperature graph **[14]**.

Fourier-transform Infrared Spectroscopy

A FT-IR 8400S Shimadzu spectrophotometer was used to record FT-IR spectra in the 4000-400 cm-1 range for 30 times for pure drugs, drug mixtures, and pure drug polymer mixtures. The compatibility of these spectra was examined **[15]**.

Stability Studies

For the purpose of determining the stability of the manufactured patches, lidocaine patches with 4%

PVA backing membrane were kept in a sealed container and kept at various temperatures for 90 days, including 4 °C, ambient temperature, and 45 °C. Investigations were done on the drug's content and outward looks **[16]**.

RESULTS

The preformulation studies were required for development of any formulation to establish the purity and compatibility of the active substance.

The crystals of the drug were monoclinic under microscope. LOD was less than 1% which meant that the drug (lidocaine) was non-hygroscopic. The Melting Point of the lidocaine powder was 68.5 ˚C. The angle of repose was found to be 37 degree which indicated that powder was passable that way hung up.

POST FORMULATION

The transdermal patch batches all displayed thickness variation ranging from 0.16 to 0.19 mm, demonstrating that all patches were of uniform thickness. All of the factorial design patches' folding endurance values were >200, which was deemed satisfactory. Every patch was clear.

Kinetic Modelling Dissolution Analysis

To determine the kinetic modelling of drug release, kinetic analysis of the in-vitro release data must be performed. To determine the pattern of Lidocaine HCL drug release from transdermal patches, in vitro drug release data was fitted to zero order, first order, Higuchi, and Korsmeyer-Peppas equations. Attempts have been made to describe drug release characteristics by a model function utilizing various kinetics (zero order, first order, and Higuchi square-root model, Peppas) given in **Table 3**.

Percentage release was also determined on excel by using UV absorbance data given in **Figure 1**. F5 showed maximum percentage release with 96.95 % after 24 hrs.and F2 showed second heights release 90.42%. Other preparations showed release not less than 75 which showed the results to be within limits.

Table 2: Physical characterization**.**

Physical Characterization Parameters	**Results**
Crystallinity	Monoclinic
Melting Point	68.5 ºC
Hygroscopicity	Non-Hygroscopic
Flow Properties	Passable Flow

Table 3 Kinetic modeling.

	F1	**F2**	**F3**	**F4**	**F5**
k0	3.797	5.193	4.303	3.976	4.157
Rsqr_adj	0.6306	0.5178	0.2868	0.9595	0.4931
AIC	51.3024	57.8015	56.2081	40.1381	53.6772
MSC	0.7103	0.4437	0.0523	2.9196	0.3938
k1	0.070	0.133	0.093	0.064	0.084
Rsqr_adj	0.9384	0.9858	0.8412	0.9446	0.9220
AIC	38.7593	33.1417	45.6959	42.3206	40.5749
MSC	2.5021	3.9665	1.5541	2.6079	2.2655
kH	15.253	21.115	17.620	14.907	16.856
Rsqr_adj	0.9628	0.9396	0.9000	0.8325	0.9770
AIC	35.2326	43.2619	42.4530	50.0677	32.0195
MSC	3.0060	2.5208	2.0174	1.5011	3.4877
kKP	13.830	20.744	19.882	5.806	17.207
n	0.539	0.507	0.451	0.867	0.492
Rsqr_adj	0.9598	0.9277	0.8891	0.9665	0.9727
AIC	36.4959	45.2462	43.9033	39.5243	33.9585
MSC	2.8255	2.2373	1.8102	3.0073	3.2107

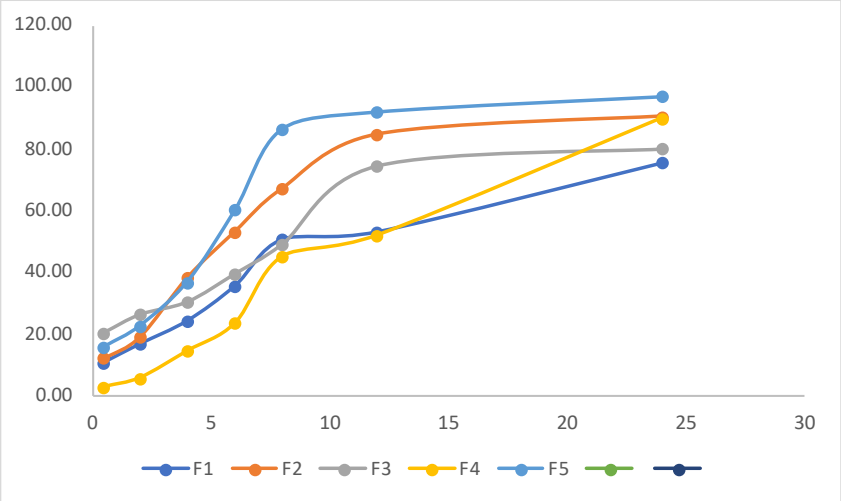

Figure 1: Percentage release data of formulations.

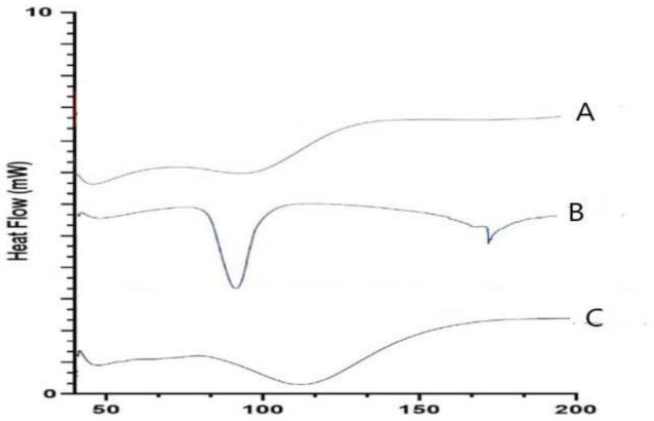

Figure 2: Differential scanning colorimetry analysis thermogram A= HPMCK 100, B=Lidocaine HCL, C= Optimized Formulation.

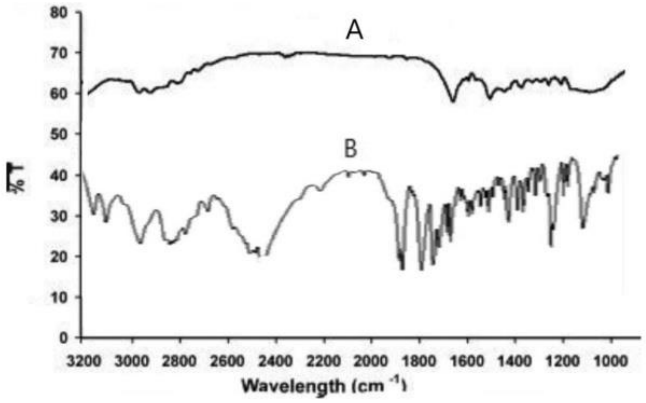

Figure 3: Fourier-transform Infrared Spectroscopy A= Optimized Formulation, B= Lidocaine HCl.

Content Uniformity of Patches

The drug content of transdermal patches was found to be in the range of 90.97% to 97.57%.

Differential Scanning Colorimetry

In DSC thermogram of optimized formulation no extra peak was noted during the entire scan except a single wide band. Showed in (**Figure 2)**.

Fourier-Transform Infrared Spectroscopy

The FTIR spectrum of Lidocaine HCL pure drug shows: 3500 cm^{-1} (OH stretching and bonding intermolecular H), 3000 cm^{-1} (aromatic CH stretch and alkene), 1750 cm^{-1} (CO stretch acid group), 1600 cm -1 (NH bending present in quinolones), 1500 cm^{-1} (CO stretch carbonyl group), 1250 cm^{-1} (OH bending), and 1050 cm^{-1} (stretching the group CF). There was no considerable variation in dosage stability and used excipients. Individual peaks of lignocaine HCl were clearly established without any interaction of excipients used in Lidoderm Patch formulation (**Figure 3)**.

Stability Studies

For three months, the lidocaine patch was held at 4 °C, ambient temperature and 45 °C, accelerated settings. After three months of research, lidocaine patches exhibited good stability and should be stored at low temperatures to preserve their characteristics.

DISCUSSION

Preliminary Studies of Selected Drug

The preformulation studies were performed before formulation development and various parameters namely Crystallinity, melting point, Powder flow properties, Hygroscopicity were determined and found to be within the range. Crystals of lidocaine were monoclinic, and were observed under microscope. Lidocaine free base was not hygroscopic showed that the Lidocaine purchased was free from impurities and the Active substance was compatible enough to be formulated **[17]**. The melting point of lidocaine is between 68 and 69 ˚C. It is exceedingly resistant to heat, acid, and alkali in aqueous solutions, although hydrolysis is anticipated to cause it to break down. The formulations were properly dried in an oven at 50 °C for 24 hours to reduce the moisture content, which decreased the likelihood of drug hydrolysis and produced results that were very similar to those reported in the literature **[17]**.

Post Formulation Studies

The manufactured Lidocaine HCL patches displayed homogenous drug content, a smooth surface, an elegant appearance, a consistent weight and thickness, no obvious cracks, and good folding endurance. The thickness was observed to rise with an increase in polymer content and ranged from 0.16 to 0.19 mm. These parameters were all within allowable ranges **[18]**.

Kinetic Modelling Dissolution Analysis

F1 Formulation followed Higuchi and Korsmeyer Peppas Model (n=0.539) showing concentration independent release (non-Fickian release). F2 formulation followed First order model and supported Dissolution phenomena for the release of drug. F3 formulation followed none of the models. F4 followed Zero order model for the release of drug from the patch which showed diffusion phenomena of release with following KP model (n=0.86) which further explain release by diffusion-dissolution mechanism. F5 formulation followed Higuchi model therefore the release of drug pattern is conc independent and also followed Korseymere Peppas with n=0.492 which showed the drug release was anomalous and diffusion-dissolution both mechanisms were followed **[19]**.

Content Uniformity of Patches

The patches' homogeneous drug content demonstrated that the drug was distributed equally across each patch. Transdermal patches had a drug concentration ranging from 90.97% to 97.57%. It was evident from the data that the drug was distributed correctly in all formulations. These variables were all inside allowable bounds **[20]**.

Differential Scanning Colorimetry

As seen, an endothermic peak of lignocaine hydrochloride was achieved at 83.27 °C that is associated with the drug's behaviour during phase transitions. At 75.82°C, the powder started to melt. Likewise, DSC thermograms of lidocaine and HPMC showed patterns that were similar to those described in the literature **[20]**.

Fourier-Transform Infrared Spectroscopy

FTIR spectrum for formulation was developed to evaluate the compatibility of the active substance with polymers used. A mixture of Lidocaine and HPMC K100 doesn't show a doublet or any changes to the other peaks that indicate interactions between the drug a polymer; therefore, HPMC K100 may not bind the Lidocaine ionically or covalently, accounting for the burst release of Lidocaine from HPMC K100.There was no considerable variation in dosage stability and used excipients. Individual peaks of lignocaine HCl were clearly established without any interaction of excipients used in Lidoderm Patch formulation **[20]**.

Stability Studies

Particularly in 45 °C conditions, these patches' physical appearance was a little darker. After storage, the drug content in the patches marginally decreased. The drug content percentages were acceptable at 4 °C and ambient temperature, with more than 90% of the drug remaining from the original formulation. Lidocaine, however, lost up to 16% after three months of storage at 45 C. These could be the result

of patches' flat and thin nature, which could promote greater interaction between the environment and the medicine in the matrix polymers **[21]**.

CONCLUSION

It was concluded from the studies that transdermal patch of Lidocaine HCL prepared with different grades of polymer are capable of exhibiting Controlled release with stability. It was concluded patch containing HPMC and PVP showed promising and optimized outcomes.

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