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ASSESSMENT ON TOPICAL DRUG DELIVERY SYSTEM FOR PAIN RELIEF: EFFICACY AND PATIENT ADHERENCE

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ABSTRACT

Topical hydrogels of Bupivacaine HCl were developed using co-solvents and penetration enhancers. The optimized hydrogels exhibited desired consistency, homogeneity, spreadabiltity and stability. Since, the polymers were water soluble; consequently, water washable gels were formed and offered benefits like ease of application and ease of removal.

Keywords: Topical Preparation, Pain, Bupivacaine, Nano Emulsion.

INTRODUCTION

Pain is most often grouped by the kind of damage that causes it. The two main types are pain caused by tissue damage (also called nociceptive pain) and pain caused by nerve damage (also called neuropathic pain). A third category is psychogenic pain, which is pain that is affected by psychological factors. Psychogenic pain most often has a physical origin either in tissue damage or nerve damage. But the pain gets worse or lasts longer because of things like fear, depression, stress, or anxiety. In some cases, pain comes from a psychological condition.

Pain is also classified by the type of tissue that's involved or by the part of the body that's affected. For example, pain may be referred to as muscle pain or joint pain. Or a doctor may ask you about chest pain or back pain.

Certain types of pain are referred to as syndromes. For instance, myofascial pain syndrome refers to pain that starts in trigger points in the body's muscles. Fibromyalgia is an example.

Pain is a phenomenon that may vary in intensity, location, time pattern, and quality. It is the most common symptom for which patients seek medical attention. Distinguishing between different types of pain is critical for proper treatment; it is classified by its duration into acute and chronic pain. Chronic pain may depend upon its source of production: nociceptive pain is transmitted by nociceptors from the site of injury or tissue damage (for example, inflamed joints in arthritis) while neuropathic pain is initiated or caused by a primary lesion or dysfunction in the nervous system (further subdivided into central and peripheral, involving the central and peripheral nervous systems, respectively); while the visceral pain involves the internal organs and mixed pain is of mixed origin.

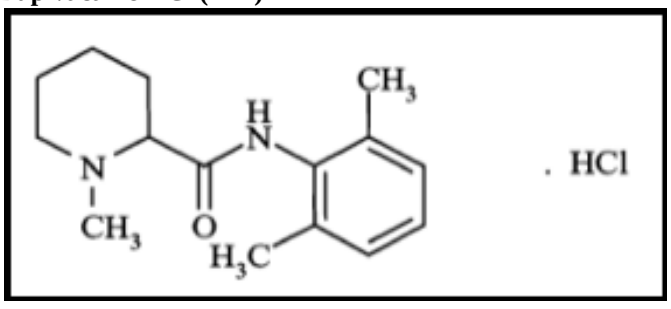
MATERIALS AND METHODS

Preformulation and Standardization of Drugs

Preformulation is an exploratory activity that begins early in drug development. Preformulation studies are designed to determine the compatibility of excipients with the active substance for a biopharmaceutical, physicochemical, and analytical investigation in support of promising experimental formulations. These studies are conducted to form the basis for the rational of formulation design. Data from preformulation studies provide the necessary groundwork for formulation attempts.

The selected drugs and excipients were standardized as per respective pharmacopeial specifications, or as per the manufacturers' specifications**.** The Certificates of Analysis provided by the suppliers in case of gift samples have been duly included in the appropriate sections**.**

Bupivacaine HCl (MH)



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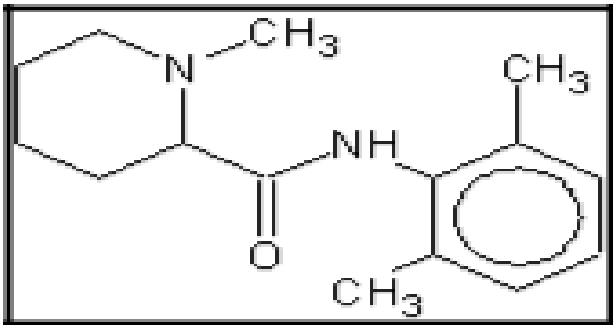
Chemical Name: - (±)-1-Methyl-3′, 6′ pipecoloxylidide monohydrochloride
Molecular Formula: - $C_{15}H_{33}N_3O$. HCl
Molecular Weight: - 383.81
Appearance: A white crystalline powder
Solubility: Freely soluble in water and methanol, very slightly soluble in methylene chloride.
Melting point: 355 - 363^{0}C with partial decomposition

Bupivacaine Base (MB)



Chemical Name: - N-(3, 6-dimethylphenyl)-1-methylpiperidine-3-carboxamide
Molecular Formula: - $C_{15}H_{33}N_3O$
Molecular weight: - 346
Appearance: Odourless, white powder
Solubility: Water solubility is 7000 mg/L. It is soluble in alcohol, methanol, chloroform, acetone and phosphate buffer pH 6.8.

Melting point: 149-153°C
Standardization of Drugs and Excipients
Monographic Evaluation of Bupivacaine HCl, Bupivacaine Base and Lidocaine HCl

Bupivacaine base and its hydrochloride salt were procured from Hagzhou Verychem Science and Technology Co. Ltd. China. Both the drug forms were standardized as per USP monograph; purity and identity were checked with Certificates of Analyses provided by supplier. Lidocaine HCl was procured as a gift sample from Gufic Biosciences Limited, Mumbai. It was standardized as per monograph and purity and identity were checked with Certificate of Analysis provided by supplier. Bupivacaine HCl, Bupivacaine Base and Lidocaine HCl were tested for the following-

Appearance:

Colour of drugs was observed visually.

Solubility:

Solubility was checked in alcohol, methanol, chloroform, acetone and phosphate buffers of different pH.

Identification tests:

Infrared spectrum of drugs was investigated using FTIR Infrared Spectrophotometer using potassium disk method. Spectrum was scanned over the wave number range 4000-400 cm^{-1}.

Loss on drying:

Drug (1gm) was weighed and dried in an oven at 100°C- 105°C to constant weight for 4 hours. The weight was again recorded.

Melting point:

This was determined using melting point testing apparatus.

Assay:

Percent drug content was considered as mentioned in Certificate of Analysis of drug obtained from the suppliers and confirmed by the analytical method described in later section.

RESULTS AND DISCUSSION
UV–visible spectrophotometric method for estimation of Bupivacaine HCl, Bupivacaine base and Lidocaine HCl for drug assay in semisolid dosage forms

In the present work, U.V spectrophotometric method for the quantitation of Bupivacaine HCl and base and Lidocaine in topical dosage form was developed for routine analysis. The method was developed by using phosphate buffer solution pH 6.8 and methanol as solvents as the drug showed good solubility in both the solvent systems. In proposed method, absorption maxima was obtained at 263 nm for Bupivacaine base & HCl and 264 nm for lidocaine and the calibration curve obeyed Beer-Lambertz law in the concentration range of 100-450 µg/ml with correlation coefficient (r^2) of 0.9999 and 0.9998 in phosphate buffer pH 6.8 and methanol respectively. The developed method was validated according to ICH guidelines for validation of analytical procedures. Limit of detection was found to be 20 µg/ml and limit of quantification was 60 µg/ml for Bupivacaine HCl and base. The low values of percentage relative standard deviation showed that the developed method was precise. All statistical data proved validity of proposed method, which can be applied for assay of Bupivacaine. Although the proposed method was found to be linear, precise and accurate, it is not very sensitive for the quantification of Bupivacaine from *in vitro*/*ex vivo* diffusion media. Hence a more sensitive HPLC method was developed for the analysis of Bupivacaine HCl and base from topical formulations.

Analytical Method Development and Validation for Quantification of Bupivacaine from *In vitro* diffusion media

The initial mobile phases tried were based on published data on Bupivacaine as shown in Table 2.25. However a well resolved peak of drug could not be obtained. The developed mobile phase used for the quantitation of Bupivacaine from the diffusion media

consisted on acetonitrile: phosphate buffer solution pH 6.8 (6:4 v/v). The validation was carried out to demonstrate the suitability of the developed method for quantitation of Bupivacaine from the *in vitro* diffusion media i.e., the method should be sensitive enough to detect low concentrations of the active and should be repeatable and linear. The analytical method was validated for linearity and precision.

Linearity:

The linear regression coefficients for the constructed calibration curves of Bupivacaine demonstrated linearity with r^2 value greater than 0.999.

Precision:

Intra-day and Inter-day precision of Bupivacaine analyzed at three different concentrations showed % RSD values < 2 as shown in Table 2.27 and 2.28. This indicated that the developed method for quantification of drug from the *in vitro* diffusion media was precise.

Thus, an analytical method for *in vitro* diffusion studies was developed and found to be selective, sensitive, linear and precise.

Analytical Method for extraction of drug from Porcine Ear Skin.

Bupivacaine could be easily extracted from the porcine ear skin using tissue homogenizer for homogenizing the skin sample and methanol as solvent for extraction since the drug has excellent solubility in methanol. The suitability of the method was further verified by performing the detailed validation of the method as per ICH guidelines.

Specificity:

The control skin sample HPLC spectra were compared with HPLC spectra from Bupivacaine spiked skin sample. The retention time of the drug was recorded at 5.8 min. In the chromatogram of the skin extracts, skin components did not interfere with the peak of interest (Fig 2.23 and 2.24). Since no interference between the drug and skin matrix components was observed in the HPLC spectra, the method was proved to be selective and specific.

Linearity:

Calibration curve constructed for Bupivacaine by plotting the graph of concentration versus Bupivacaine area was found to be linear in the range of 2.0 to 10µg/ml as shown in the Fig 2.25. The analytical method showed a regression coefficient greater than 0.999 on all the three days. Thus the linear regression analysis demonstrated acceptability of the method for quantitative analysis of Bupivacaine in the skin samples.

Intra-day and Inter-day Precision:

The observed lower values of relative standard deviation, lower % RSD values <2, at both, intra-day and inter-day analysis indicated the method to be precise. It showed the acceptability of the method with adequate intra-day and inter-day precision (Table 2.29 & 2.30).

Repeatability:

SD, % RSD and SE displayed low variance for three separate days for Bupivacaine as shown in the Table 2.31. This demonstrates the method to be repeatable for the analysis of Bupivacaine from the skin homogenate.

Recovery:

The recovery was calculated from the Bupivacaine concentration with the non skin sample and compared with the spiked skin homogenate. The mean recovery of Bupivacaine was 96.34%, 98.45% and 97.59% at concentrations of 2.0, 8.0 and 10.0 µg/mL respectively (Table 2.32). The average recovery over the entire analytical range was 97.46%. From the recovery rates, it can be concluded that the extraction procedure provided a reliable quantitative determination of the drug in skin extracts.

Pharmacokinetic Studies

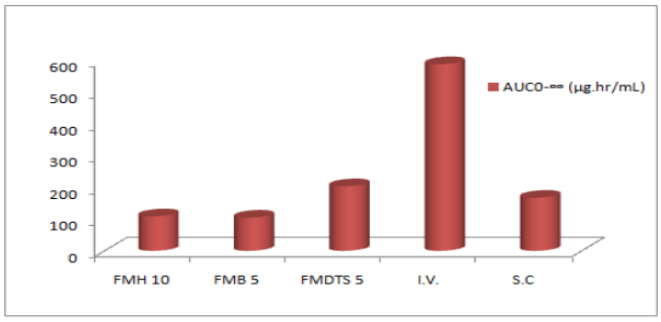
Pharmacokinetic studies of topical Bupivacaine formulations in Bupivacaine provided information on the extent, rate and duration of Bupivacaine absorption from the formulations through the skin.

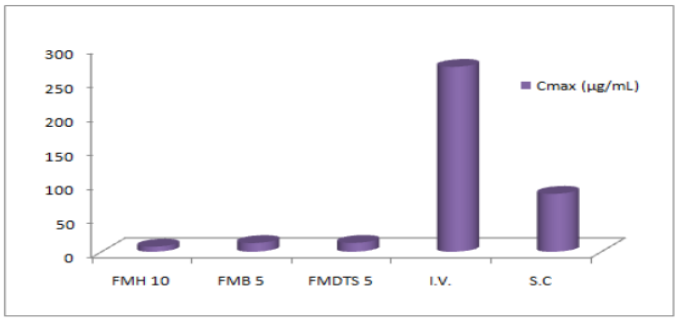
A non-compartmental model was applied. The plasma concentrations of Bupivacaine from various test formulations at different time intervals were subjected to pharmacokinetic analysis. Pharmacokinetic parameters like C_{max}, t_{max}, AUC were calculated from the conc. Vs time plot (Table 4.17). Trapezoidal rule was employed to calculate AUC. The C_{max} of the test formulations was 7.53 µg/mL, 12.83 µg/mL and 13.06 µg/mL for FMH 10, FMB 5 and FMDTS 5 Bupivacaine topical formulations respectively. For FMDTS 5, T_{max} to reach C_{max} was 13.05 h and was the highest amongst other formulations tested. The $AUC_{0-\infty}$ (µg.hr/mL) values was in the following order, FMDTS 5> FMB 5> FMH 10. For Bupivacaine administered intravenously and subcutaneously, C_{max} of 272 µg/mL at T_{max} 0.8 h and C_{max} of 85.2 µg/mL at T_{max} 0.33 h respectively were observed in rabbits.

Pharmacokinetic Parameters Calculated for Test Formulations and I.V and S.C Bupivacaine formulations.

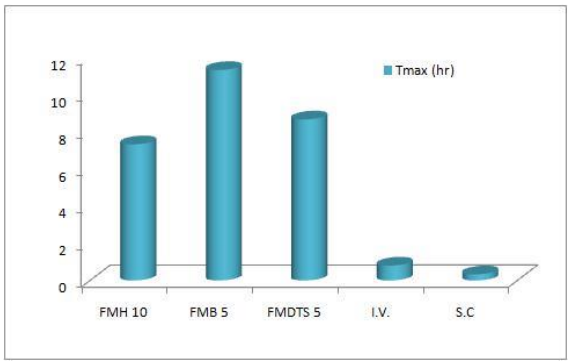
PK Parameters	FMH 10	FMB 5	FMDTS 5	I.V.	S.C
$AUC_{0-\infty}$ (µg.hr/mL)	108.67	104.67	203.33	588	167.2
C_{max} (µg/mL)	7.53	12.83	13.06	272	85.2
T_{max} (hr)	7.33	11.33	8.67	0.8	0.33

Figure 1 : Comparative Pharmacokinetic Profiles a) AUC0-∞ , µg.hr/mL b) Cmax ,µg/mL and c) Tmax, hr of Test formulations vs I.V & S.C Bupivacaine.





(c)



CONCLUSION

Nano emulsion system composed of oleic acid as oil, Smix of labrasol: Transcutol P and distilled water have been proposed for topical delivery of Bupivacaine. A topically applied nano emulsion is expected to penetrate the stratum corneum and exist intact in the honey layer. Once it enters into the stratum corneum, nano emulsions may simultaneously alter both the lipid and the polar pathways. Greater drug penetration Novel metered dose topical spray formulations of Bupivacaine base were developed using different polymers. Solution spray formulations were developed and filled in containers with metered dose spray pumps to provide propellant free delivery. The metered dose topical spray of Bupivacaine base will prove as an alternative to conventional topical delivery for relief of neuropathic pain.

Topical delivery of Bupivacaine via various formulation approaches has been investigated in the present research work. Novel clear, stable, hydrogels, nano emulsion based gels and metered dose film forming sprays of Bupivacaine base and its pharmaceutically acceptable HCl salt at 5% and 10% concentrations respectively for topical delivery has been developed and optimized. The formulations were developed to modulate the drug diffusion and accumulation at the intended site to exhibit the desired response.

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