RESEARCH ARTICLE

Creation and Expansion of Bioadhesive Transdermal Gel of Levobupivacaine Loaded Nanoparticles for Enhancement of Anesthetic Effect

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Received: 16th March, 2024; Revised: 23rd May, 2024; Accepted: 02nd August, 2024; Available Online: 25th September, 2024

ABSTRACT

The present research work aimed to prepare a bioadhesive gel containing Levobupivacaine-loaded nanoparticles (NPs) to improve local anesthesia as transdermal patches were patient-friendly and easy to therapy. This study focuses on developing a The NPs were created using the ionotropic gelation method and assessed for particle charge, vesicle size and its distribution, and surface morphology. The improved NPs were incorporated into a gel and evaluated for their physicochemical assets. Among the NPs, NP4 was identified as the best based on its physicochemical properties. The NG-6 bioadhesive gel formulation stood out as the top gel among those tested. The NG-6 gel exhibited superior skin permeation ended 14 hours compared to other NPs. This bioadhesive transdermal gel with Levobupivacaine nanoparticles offers a promising approach to enhancing anesthetic effects.

Keywords: Bioadhesion, Gel, Levobupivacaine, Local anesthesia, nanoparticles, permeation.

International Journal of Drug Delivery Technology (2024); DOI: 10.25258/ijddt.14.3.08

How to cite this article: Choudhary RK, Patil A, Gadekar RA, Dharmamoorthy G. Creation and Expansion of Bioadhesive Transdermal Gel of Levobupivacaine Loaded Nanoparticles for Enhancement of Anesthetic Effect. International Journal of Drug Delivery Technology. 2024;14(3):1306-1311.

Source of support: Nil.

Conflict of interest: None

INTRODUCTION

Transdermal drug delivery systems (TDDS) are a revolutionary approach to medication administration that offer significant advantages over traditional methods. By delivering drugs directly through the skin, TDDS provides a non-invasive, convenient, and user-friendly way to achieve consistent therapeutic effects. These systems ensure high patient compliance due to their ease of application and the ability to avoid the discomfort and inconvenience associated with injections or oral medications. TDDS also minimizes the risk of gastrointestinal issues and first-pass metabolism, enhancing drug bioavailability and reducing side effects. Furthermore, they allow for controlled and sustained drug release, maintaining stable plasma levels over extended periods. This approach is particularly beneficial for patients requiring long-term therapy, providing a steady dose of medication and improving overall treatment outcomes.[1]

Topical local anesthetic gels are a convenient and effective means of providing localized pain relief by numbing specific areas of the skin and mucous membranes. These gels are commonly used in various medical, dental, and cosmetic procedures to reduce discomfort and pain. The primary active ingredients in these gels are local anesthetics such as lidocaine, benzocaine, or prilocaine, which work by blocking nerve signals in the targeted area. The application of topical anesthetic gels is straightforward, involving the direct application of the gel to the skin or mucosal surface. The onset of numbness typically occurs within minutes, making these gels ideal for quick, temporary relief. They are widely used in minor surgical procedures, wound care, dental treatments, and cosmetic interventions like laser hair removal and tattoo application. One of the significant advantages of topical anesthetic gels is their non-invasive nature, which enhances patient comfort and compliance. These gels can also be used to alleviate chronic pain conditions such as neuropathic pain, providing relief without the need for systemic medications that may have broader side effects. Formulating these gels requires careful consideration of factors such as pH, viscosity,

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and bioadhesive properties to ensure optimal efficacy and patient comfort. Advanced formulations may incorporate nanoparticles (NP) or other delivery systems to improve the penetration and sustained release (SR) of the anesthetic agent, further improving the therapeutic effect.[2]

NP drug delivery technology represents a ground-breaking advancement in the field of medicine, offering significant improvements in the delivery, efficacy, and safety of therapeutic agents. This technology involves the use of NPs, tiny units of size from 1 to 100 nm, as carriers for drugs, which can enhance the delivery of active pharmaceutical ingredients to targeted sites within the body. One of the primary benefits of NP drug delivery systems is their aptitude to improve the bioavailability of drugs. Many therapeutic agents, especially those that are poorly soluble in water, face challenges in reaching their intended site of action at therapeutic concentrations. NP can encapsulate these drugs, protecting them from degradation and facilitating their absorption into the bloodstream. This encapsulation can also enable controlled SR of the drug, reducing the frequency of treating and refining patient acquiescence. NP can be contrived to target specific tissues or cells, which is particularly advantageous in dealing with ailments like tumors. By modifying the surface properties of NPs with ligands or antibodies, they can be directed to bind to specific receivers on the exterior of tumors, delivering the drug precisely where it is needed and minimizing damage to healthy tissues.[3]

The versatility of NP drug delivery systems spans a wide range of applications, including gene therapy, vaccine delivery, and the handling of chronic illnesses *viz*., diabetes and heart disorders. Various types of NPs, such as liposomes, dendrimers, polymeric NPs, and metal NPs, offer distinct advantages and can be customized to meet the specific needs of the therapeutic agent and the disease being addressed. Furthermore, the small size of NPs allows them to cross biological barriers that larger particles cannot, such as the blood-brain barrier, making them particularly useful in treating central nervous system disorders. Despite the numerous advantages, there are challenges associated with NP drug delivery technology, including issues related to scalability, stability, and potential toxicity. Ongoing research and development are focused on overcoming these hurdles to fully realize the potential of NPs in clinical applications.[4,5]

Levobupivacaine (LBV), an enantiomer of bupivacaine, is a local anesthetic known for its prolonged duration of action and lower cardiotoxicity compared to its racemic counterpart. As a transdermal gel, LBV presents an innovative and effective method for delivering local anesthesia. This delivery system harnesses the benefits of transdermal administration, including enhanced patient compliance, consistent drug discharge, and minimized systemic side effects. The formulation of LBV into a transdermal gel involves incorporating the drug into a gel matrix that can adhere to the skin. This gel matrix often contains bioadhesive polymers that enhance the gel's ability to stay in contact with the skin for extended periods, allowing for SR of the drug. The bioadhesive assets ensure that the gel remains localized at the application site, providing a controlled release of LBV directly into the underlying tissues.[6] One of the key advantages of using a transdermal gel for LBV delivery is the ability to bypass the gut and first-pass metabolism, which can degrade the drug and reduce its efficacy. By applying the gel directly to the skin, the drug is absorbed through the dermal layers, reaching the targeted tissues more effectively and maintaining a steady therapeutic concentration over time. The formulation process typically involves optimizing several parameters to ensure the gel's efficacy and stability. These parameters include size, zeta potential (ZP), loading, and its morphology. The ionotropic gelation method is often used to prepare NPs of LBV, which are then incorporated into the gel.[7] This method ensures that the NPs are uniformly distributed within the gel matrix, allowing for consistent drug release. The physicochemical assets of the gel, such as clarity, pH, bioadhesive strength, LBV content, and viscosity, are critical factors that influence its performance. Additionally, *ex-vivo* skin permeation studies are conducted to evaluate the rate and extent of LBV absorption through the skin.

MATERIALS AND METHODS

Materials

LBV was sourced from Neon Laboratories Limited, Bengaluru, India. Chitosan, Tripolyphosphate (TPP), acetic acid, folic acid, carbopol 934, methylparaben, and triethanolamine were acquired from Fischer Scientific, India.

Preparation of NPs

LBV-chitosan NPs were synthesized using the ionotropic gelation method. Initially, chitosan was dissolved in a CH_3COOH solution and stirred at room temperature. This chitosan solution was then mixed with a 1% v/v tween-80, and the LBV, dissolved in acetone, was added dropwise to the liquid phase to form an o/w emulsion in continuous rousing. TPP was gradually added to the emulsion in various concentrations as a cross-linking agent. The mixture was left overnight to ensure complete evaporation of the organic solvent.[8] NPs resulted from the interaction of TPP's negative charge with chitosan's positive amino groups. They were isolated using a cooling centrifuge at -80°C and 20,000 rpm for 15 minutes. The HPLC analysis of the supernatant quantified the free LBV content shown in Table 1.

Preparation of NP gel

To prepare NP gel, Carbopol 934 was dissolved in 100 mL of water along with methylparaben (0.5% w/w). The solution was stirred until a clear, translucent gel formed. The pH was then attuned to 7 with triethanolamine, and the gel was left at for a day to stabilize. Finally, the LBV-loaded NP was gently incorporated into the gel by swirling[9] show in Table 2).

Assessing of NPs

Vesicle size, ZP, and PDI

All parameters were evaluated using a Zetasizer. The NP suspension was mixed with water and mixed for 20 minutes

Table 1: Configuration NP of LBV

Trials	*Contents*						
	LBV (mg)	*Chitosan (mg)*	*Acetone (mL)*	*Acetic acid (3%) (mL)*	*Tween 80 (mL)*	*TPP (mg)*	*Water (mL)*
NP-1	50	25	1	15	0.2	0.5	100
NP-2	50	50	1	15	0.4	1.0	100
NP-3	50	75	1	15	0.6	1.5	100
NP-4	50	100	1	15	0.8	2.0	100

Table 2: Formulae of the gel

Ingredient	*NG-1*	*NG-2*	*NG-3*	*NG-4*	*NG-5*	*NG-6*
LBV-NP (% w/w)	1	1	1	1	1	1
Carbopol 934 (% w/w)	0.5	1	1.5	2	2.5	3
Methylparaben (mg)	0.25	0.25	0.25	0.25	0.25	0.25
Triethanolamine (mL)	15	15	15	15	15	15
Water (mL)	100	100	100	100	100	100

using a sonicator to achieve homogeneous dispersion. Subsequently, this suspension was placed in a zeta sizer and analyzed accordingly.[10]

LBV filling effectiveness

After centrifugation, the LBV concentration in the supernatant solution was assessed using HPLC. This analytical method allows for precise quantification of LBV, ensuring accurate measurement of its concentration in the samples (E.q.1).[11]

$$Drug\ loading\ efficiency = \frac{(target\ loading - unloaded\ LBV)}{target\ loading} X100 \quad (1)$$

SEM analysis

By scanning a focused electron beam across the sample's surface, SEM generates high-resolution images that reveal the topographical details at a micro- to nanoscale level. This method not only provides insights into the physical characteristics, such as particle size distribution and shape irregularities, but also aids in understanding the surface roughness, porosity, and overall structural integrity of the NP. Therefore, SEM is essential for the comprehensive characterization and quality assessment of nanomaterials intended for various applications, including drug delivery systems.[12]

Assessing transdermal gel

Appeal

All the gels underwent visual inspection to assess their physical appearance, including the detection of foreign particles or aggregates. This evaluation was conducted using both dark and white backgrounds to enhance contrast and visibility. By examining the formulations against these backgrounds, any anomalies such as particulate matter, discoloration, or irregularities in texture could be readily identified. This visual inspection step is crucial in ensuring the overall quality and consistency of the formulations before proceeding with further characterization and testing.[13]

pH of the gels

A calibrated digital pH meter was used and the pH of the gel was determined. This process ensures accurate measurement of the pH of the gel, which is crucial for understanding its acidity or alkalinity and for ensuring consistency in formulation characteristics.[14]

LBV content

To determine the total LBV content in the NP gel formulation, approximately 100 mg of the gel was mixed in 5 mL of ethanol. This solution was then diluted with additional ethanol to reach a total volume of 25 mL, ensuring proper solubility and uniformity. UV-visible spectrophotometry was employed to analyze the diluted solution. In this case, it allows precise measurement of the LBV content present in the formulation. This method is crucial for pharmaceutical analysis and quality control, providing essential data to ensure the consistency and potency of the NP gel product.[15]

Viscosity

The viscosity of the NP gel was assessed using a Brookfield digital viscometer equipped with spindle no. 6 rotating at 5 rpm. The viscosity observations were noted to characterize the flow behavior and consistency of the gel, giving crucial evidence for its formulation and application as a TDDS.[16]

Bioadhesive strength

A biological membrane was initially securely affixed to a small glass slide by glue tape. This membrane-slide assembly was carefully placed at the bottom of a 100 mL beaker. Next, the beaker containing the membrane-slide assembly was placed inside a larger 500 mL glass beaker. To this pH 6.8 buffer was added until it covered the membrane, ensuring an environment conducive to the experiment. Approximately 1 g of the gel formulation under evaluation was stuck to the bottom surface of the membrane. A preload weight of 100 g was placed on a slide on top of the gel layer to promote adhesion. This preload was maintained for 10 minutes to allow sufficient time for the gel to adhere firmly to the biological membrane. After the preload period, the force essential to separate the gel from the membrane was carefully measured using appropriate instrumentation. Multiple measurements were conducted to ensure accuracy, and an average value was calculated from these measurements. This average force value provided a quantitative assessment of the bioadhesive strength of the gel formulation, indicating its ability to adhere to biological surfaces under specified conditions. This methodological approach is crucial in pharmaceutical and biomedical research for evaluating the adhesive properties of formulations intended for topical or mucosal application, providing essential data for product development and quality control.[17]

LBV skin permeation test (*ex vivo*)

A Franz diffusion cell was used with rat skin that was nourished with a saline solution maintained at 6-8°C and positioned between the two sections of the diffusion cell. Gels containing LBV ≈ 50 mg were lightly placed on the skin. In the receptor cubicle of the diffusion cell, pH 6.8 buffer served as the release medium, with temperature carefully kept at a constant 37 ± 0.5°C and agitation set at 30 rpm. Sampling of 0.5 mL was conducted for 1-hour. Following each sample removal, an equivalent volume of media was included to ensure a constant sink condition and assessed at 230 nm to accurately quantify the amount of LBV that had permeated through the membrane. This method enabled precise evaluation of LBV permeation characteristics under controlled experimental conditions, essential for assessing its potential as a TDDS.[18]

RESULTS

Characterization of NP's

The ionotropic gelation tactic proved to be highly suitable for preparing LBV-NP. The LBV loading efficiency ranged from 14.35 ± 0.02 to 24.28 ± 0.05%, while the particle sizes varied between 358 ± 0.98 to 178 ± 0.51 nm. The Polydispersity Index (PDI) values indicated a uniform size spreading within the NPs suspension. Additionally, the ZP ranges from 23.88 ± 0.04 to 27.41 ± 0.05 mV shown in Table 3.[19]

Surface morphology

The NP4 was observed to be spherical, smooth, and free from cracks shown in Figure 1. Based on these characteristics, the NP4 was selected as the optimized NP and subsequently used in the formulation of the transdermal gel.

Table 3: Categorization of LBV-NP

Formulation	*DL (%)*	*PSD (nm)*	*ZP (mV)*	*PDI*
NP1	14.35 ± 0.02	358 ± 0.98	23.88 ± 0.04	0.29 ± 0.01
NP2	16.69 ± 0.03	200 ± 0.08	24.71 ± 0.07	0.32 ± 0.01
NP3	19.17 ± 0.04	278 ± 0.62	24.72 ± 0.08	0.22 ± 0.01
NP4	24.28 ± 0.05	178 ± 0.51	27.41 ± 0.05	0.24 ± 0.01

Values in mean ± SD; n = 3

Physicochemical evaluation of transdermal gel

The results of various physicochemical assets are as follows shown in Table 4.

The gels exhibited distinct characteristics based on their composition and intended application. The LBV-NP appeared cloudy and non-transparent due to the presence of LBV-loaded NPs, whereas those gels with Carbopol 934 polymer maintained clarity and transparency. All the gels maintained a neutral pH range (7.0 ± 0.01–7.5 ± 0.02), ensuring compatibility for skin application without irritation. There was a clear relationship pragmatic amid LBV content and Carbopol 934 concentration, with the NG-6 formulation showing the highest LBV content due to its higher polymer concentration. The viscosity of the gel formulations ranged from 7889 ± 14.62 to 13269 ± 12.25 cps, indicating suitability for topical LBV delivery. Additionally, bioadhesive strengths ranged from 1562 ± 7.16 to 2428 ± 2.31 dyne/cm², showing a linear correlation with polymer concentrations. These findings highlight the critical role of polymer concentration in influencing both the physical properties and performance characteristics of the gel formulations, essential for optimizing their efficacy and application in pharmaceutical formulations.[20]

LBV permeation (*ex-vivo*) study

Show in Figure 2 illustrates the relative LBV permeation across a mucosa. The NG-6 formulation demonstrated superior skin

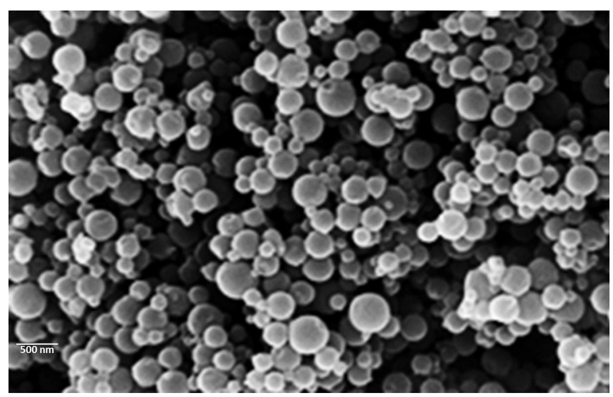

Figure 1: SEM of NP

Table 4: Assets of LBV-NP loaded gel

Trails	*Appeal*	*Clearness*	*pH*	*LBV amount (%)*	*Viscosity (cps)*	*Mucoadhesive strength (dyne/cm^2)*
NG-1	Foggy	No clear	7.1 ± 0.01	89.20 ± 2.65	7889 ± 14.62	1562 ± 7.16
NG-2			7.5 ± 0.02	91.11 ± 3.67	9585 ± 10.27	1695 ± 9.17
NG-3			7.0 ± 0.02	93.50 ± 4.87	10254 ± 16.64	1958 ± 8.18
NG-4			7.3 ± 0.04	97.89 ± 1.15	11658 ± 18.54	2125 ± 4.15
NG-5			7.2 ± 0.02	98.57 ± 3.25	12953 ± 26.35	2232 ± 6.25
NG-6			7.4 ± 0.02	99.89 ± 2.36	13269 ± 12.25	2428 ± 2.31

NG: Nano gel

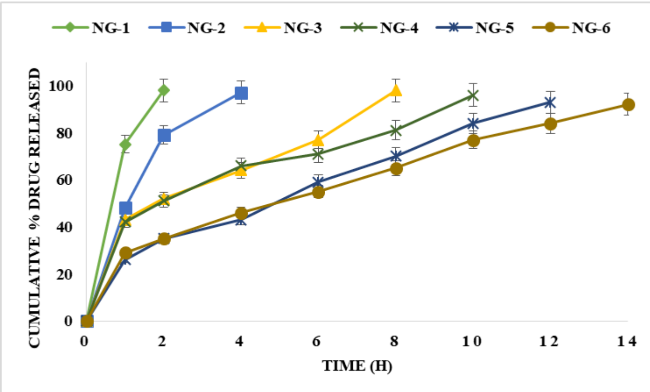

Figure 2: *Ex vivo* permeation of NGs through rat skin membranes

permeation characteristics over 14 hours when associated to other formulations.[21-25]

DISCUSSION

The present study signifies a comprehensive exertion aimed at enhancing the effectiveness of LBV through the development of a bioadhesive transdermal gel incorporating LBV-loaded NPs. Chitosan, a biocompatible polymer renowned for its suitability in drug delivery systems, was chosen for its ability to form NPs via the ionotropic gelation method. This tactic capitalizes on the electrostatic communication amid the amino groups of chitosan and the tripolyphosphate (TPP), resulting in the formation of NPs with desirable physicochemical properties.

The loading efficiency of LBV into these chitosan NPs was found to be directly proportional to the concentration of chitosan used during formulation. Higher concentrations of chitosan facilitated greater encapsulation of LBV, ensuring efficient LBV loading and uniform distribution within the NPs. This step is crucial for optimizing drug delivery systems, as it enhances the bioavailability and therapeutic efficacy of LBV, which is pivotal for achieving sustained pain relief in clinical applications.

In formulating the transdermal gel, Carbopol 934 polymer was selected owing to its biocompatibility and versatility in pharmaceutical formulations. Known for its excellent adhesive properties and ability to form clear and stable gels, Carbopol 934 ensures optimal contact with biological membranes, facilitating enhanced LBV absorption and prolonged release. The choice of Carbopol 934 enables the gel to adhere effectively to skin or mucosal surfaces, offering ease of application and improved patient compliance.

Our formulations demonstrated that increasing the concentration of Carbopol 934 correlated with higher LBV content, indicating a more efficient incorporation of LBV-loaded NPs into the gel matrix. This optimization not only enhances formulation stability but also extends the duration of LBV release, achieving sustained therapeutic levels necessary for effective pain management.

Furthermore, the permeation profile of LBV through the skin membrane was significantly prejudiced by the concentration of Carbopol 934 in the gel formulation. Higher concentrations of Carbopol 934 effectively controlled the rate of LBV permeation, ensuring an SR profile that is crucial for maintaining prolonged anesthetic effects. This characteristic is particularly advantageous in local anesthesia, where prolonged pain relief is desired without the need for frequent applications.

CONCLUSION

In conclusion, the innovative bioadhesive transdermal gel incorporating LBV nanoparticles presents a compelling advancement in enhancing anesthetic effects compared to traditional delivery systems. Continued research into its clinical applications is essential to validate its safety, efficacy, and potential therapeutic benefits in practical medical settings. Clinical investigations should encompass a range of parameters to evaluate the performance of the LBV nanoparticle-loaded bioadhesive gel. Key aspects include assessing its pharmacokinetics to determine the absorption, distribution, metabolism, and excretion of LBV from the gel following transdermal application. Pharmacodynamic studies are essential to elucidate the onset, duration, and intensity of the anesthetic effect achieved by the formulation. Moreover, comparative clinical trials against existing local anesthetic formulations would provide valuable insights into the superiority of the LBV nanoparticle-loaded gel in terms of efficacy, safety, and patient comfort. These trials could involve diverse patient populations to assess the formulation's performance across different demographic and clinical conditions. In addition to efficacy and safety, investigations into the formulation's tolerability and potential adverse effects are crucial. Detailed studies should be conducted to monitor skin irritation, allergic reactions, and any systemic effects associated with prolonged use of the gel. Furthermore, the economic feasibility and practical applicability of the LBV nanoparticle-loaded bioadhesive gel in clinical settings should be evaluated. This includes considerations such as ease of application, storage stability, and cost-effectiveness compared to conventional local anesthetic formulations.

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