Journal of Neonatal Surgery
ISSN(Online): 2226-0439
Vol. 14, Issue 18s (2025)
https://www.jneonatalsurg.com

OPEN ACCESS

Optimization and formulation of dissolvable microneedle patch loaded with venlafaxine

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Cite this paper as: Deepak Kumar*, Naresh Kalra, (2025) Optimization and formulation of dissolvable microneedle patch loaded with venlafaxine. *Journal of Neonatal Surgery*, 14 (18s), 759-766.

ABSTRACT

The objective of this work was to prepare and optimize dissolvable microneedle formulations loaded with venlafaxine. PVA (2.5 - 20 % w/v) along with or without 20% w/v chitosan were used to prepare the microneedles by casting aqueous solution in the molds. The microneedle patches were evaluated for physical appearance, surface pH, weight uniformity, drug content, moisture content and uptake, insertion capability, mechanical strength, in vitro dissolution capability and in vitro release. Among the ten formulations developed F8, F9 and F10 presented sharp needles whereas the ones with lower PVA ratio had blunt needles and were very plastic to be cast as microneedles. The surface pH ranged from 5.33 to 5.63 suggesting skin compatibility. Venlafaxine loaded microneedle patch was prepare using 5.0%w/v PVA and 20% chitosan. The drug content in the microneedle patch was 97.18%. venlafaxine released in a biphasic manner from the microneedles with an initial burst release within 3 hours releasing about 50% of drug. The burst release could be due to the dissolved microneedle tips in the dermis. After the initial rapid release, the release was found to be prolonged for more than 24h. This biphasic release profile would be able to effectively manage both acute and chronic pain conditions. The results led us to conclude that microneedle patches could be easily prepared using simple casting method and also present effective loading of venlafaxine for managing acute and chronic pain with single application.

Keywords: Microneedle, venlafaxine, pain, controlled release, optimization

1. INTRODUCTION

In recent years, various drug delivery systems have been developed which provide sustained release therapy via a sub-dermal insert[1]. Systems have been disclosed which also provide drug delivery systems suitable for transdermal drug administration. Many of the anti-inflammatory and anti-nociceptive drugs possess the properties necessary to be effective in a transdermal drug delivery system. The properties include high potency, proper physic-chemical characteristics, good dermal penetration and lack of dermal irritation.

Venlafaxine is a serotonin and norepinephrine reuptake inhibitor prescribed for management of depression and chronic pain. The oral absorption of the drug is high (92%) still it has an absolute oral bioavailability of the drug is around 45%. The peak plasma levels of venlafaxine are attained in 2-3 hours of immediate release oral formulations. It has a protein binding of 27-30% and 87% drug is excreted in urine[2]. The elimination half-life ($t_{1/2}$) for the parent compound is 5 hours[3]. The prolonged use of drugs like venlafaxine have been associated with abuse and dependency tendencies. Hence alternate delivery routes that are patient compliant and help in targeted therapy for pain need to be developed for venlafaxine. Transdermal delivery of venlafaxine has been found to improve its bioavailability in the treatment of diabetic neuropathy[4]. The literature shows that microneedles can be applied transdermally as patch and they possess the ability to target the site of action reaching the deeper layers of dermis[5-10]. Several studies have shown the role of dissolvable microneedles in enhancing bioavailability of the loaded drugs[11-15]. Studies have also revealed the fabrication of long acting transdermal delivery systems by incorporating of drug loaded nanoparticles in the polymeric microneedles[16-19]. Hence formulation as dissolvable microneedle patches present excellent approach for formulating venlafaxine as a transdermal delivery system, thereby reducing the dose of the drug.

2. MATERIAL AND METHODS

Venlafaxine was purchased from Yarrow Pharmaceuticals, Mumbai; Resin and hardener were procured from local market; poly vinyl alcohol (PVA) and chitosan was purchased from Himedia and all other required chemicals were obtained from CDH and Loba Chemie. The polymer, chemicals and reagents were used as obtained. Freshly distilled water was used throughout wherever required.

Preformulation study

The procured venlafaxine was studied for its organoleptic features, melting point, partition coefficient, solubility profile and loss on drying.[20,21]

The calibration curve of venlafaxine was prepared by using methanol as the solvent. 5mg venlafaxine was dissolved in 5 mL of the methanol and further diluted to obtain solutions of 10, 20, 30, 40 and 50 µg/mL concentration. These standard solutions were analyzed for their absorbance at 276 nm using a UV-visible spectrophotometer. The calibration curve of concentration against absorbance was plotted and the equation for the calibration curve for calculated.

Preparation of microneedle mold

The molds required for fabrication of the microneedle were prepared using resin and hardener purchased from local market (Emseal). The resin and hydrate material taken in a 1:1 ratio and mixed well properly by hand mixing. The mixed preparation was placed into a micro centrifuge tube of 1.5ml quantity and the upper surface area of tube had been evenly distributed. It was then pierced with micron sized needle tip to get array mold. After preparation of mold arrays, they were dried for 48 hours at room temperature for formation of hard solid molds[22].

Optimization of microneedle patch

PVA was dissolved in distilled water by heating on magnetic stirrer at 80°C for 20 min. Chitosan was dissolved in 2 mL of 2%v/v acetic acid. The chitosan solution was added to the PVA solution (Table 1). The prepared polymer gel solution was transferred into micro-molds and immediately centrifuged at 1500 rpm for 10 minutes for even and uniform distribution and to remove the air spaces. After completion of the process the micro centrifuge tube was removed from the centrifuge and dried for 2 days and then kept in freezer for 30 minutes at 4 °C for easy separation of microneedle patch from the micro molds. The fabricated patches were peeled off from the molds using forcep, stored in butter paper in desiccators[23].

The formulated microneedle patches were evaluated for proper formation of needles, mechanical properties, insertion capability and dissolution of needles to optimize the polymer ratio.

Table 1. Formulation Table

Formulation	PVA (% w/v)	Chitosan (% w/v)	Drug (mg)	Water (mL)
F1	2.5	-	2	5
F2	5	-	2	5
F3	7.5	-	2	5
F4	10	-	2	5
F5	20	-	2	5
F6	2.5	20	2	5
F7	5	20	2	5
F8	7.5	20	2	6
F9	10	20	2	6
F10	20	20	2	8

3. EVALUATION OF THE MICRONEEDLE PATCHES

Physical appearance

The formulated venlafaxine loaded microneedle patch was evaluated for homogeneity, clarity, color, and proper formation of needle

Uniformity of weight test

The microneedle patches were subjected to mass variation by individually weighing each formulated patch and checking the weight of patch against the average weight of the formulated patches. Measurement of patch weight was carried out using a calibrated analytical balance. The determination was carried out for each formulation in triplicate.

Surface pH
The surface pH of the microneedle patches was measured using a calibrated pH meter. In a test tube, 1 mL of distilled water and microneedle patch was kept at room temperature (25 ± 2°C) for 2 h. The water from the test tube was decanted and the wet patch was used for surface pH analysis. The pH electrode was placed at three different places at the swollen part of the patch for calculating the average pH.

Percent moisture content
The prepared microneedle patches were weighed individually and kept in desiccators containing fused calcium chloride at room temperature for the duration of 24 hours. After 24 hours, the films were re-weighed and the percentage moisture content was determined by the given formula

$$\%\ moisture\ content = \frac{Initial\ patch\ weight}{Final\ patch\ weight}\ x\ 100$$

Percent moisture uptake
The prepared microneedle patches were weighed individually and kept in desiccators containing buffer solution at room temperature for the duration of 24 hours. After 24 hours, the films were re-weighed and the percentage moisture content was determined by the given formula

$$\%\ moisture\ uptake = \frac{Initial\ patch\ weight}{Final\ patch\ weight}\ x\ 100$$

Mechanical Properties
The mechanical strength of microneedle patches against static forces was measured by placing different weights over the patches. The microneedle patches were placed on a solid platform needle upward, onto which weights of 50 g, 500 g, and 1000 g were placed gently on the top of each patch, respectively. After 5 min, the weights were removed, and morphological changes were evaluated.

Insertion capability
The fabricated microneedle patches were manually pushed into 8 stacked parafilm layers as a skin stimulant for 30 s and observed under a microscope to study the insertion efficiency and microneedle insertion depth[24]. The insertion was expressed in the number of pores created in each parafilm layer.

Dissolution Test of microneedle patches using Agarose Gel
The microneedle patches were applied on to agarose gel 3% (w/v) serving as a skin simulant. A weight of 500 g was placed above the microneedle patches, and patches were removed after predetermined times of 15, 45, 120, 180 and 210 seconds. The patches were visualized before and after dissolution using a microscope camera[25].

Preparation and evaluation of venlafaxine loaded microneedle patch
PVA (5.0 %w/v) was dissolved in distilled water by heating on magnetic stirrer at 80°C for 20 min. Chitosan was dissolved in 2 mL of 2%v/v acetic acid. The chitosan solution was added to the PVA solution. The required quantity of venlafaxine (20 mg) was dispersed in 1 mL distilled water and added to the polymer solution. The prepared polymer gel solution containing venlafaxine was transferred into micro-molds and immediately centrifuged at 1500 rpm for 10 minutes for even and uniform distribution and to remove the air spaces. After completion of the process the micro centrifuge tube was removed from the centrifuge and dried for 2 days and then kept in freezer for 30 minutes at 4 °C for easy separation of microneedle patch from the micro molds. The fabricated patches were peeled off from the molds using forcep, stored in butter paper in desiccators.

Drug content test
The fabricated microneedle patches were dissolved in 10 ml phosphate buffer and were placed on vortex shaker for 1 h to dissolve completely the patches. The resultant solutions were filtered through the whatman paper and then 0.1 mL solution was withdrawn into another volumetric flask (10 mL) and dilution was made up to 10 mL using methanol. The absorbance of this solution was observed at 276 nm using UV-Visible spectrophotometer and the drug content was calculated.

***In-Vitro* Drug Release Studies**
The fabricated microneedle patches loaded with the drug were soaked in 10 mL of PBS pH 7.4, and maintained at 37°C (50 rpm) in a rotary incubator. At predetermined time intervals, 0.5 mL of the release medium was sampled and was replenished immediately with the same volume of fresh prewarmed PBS (37°C), maintaining sink condition throughout the experiment. Then, drug concentration was determined using a UV–Vis spectrophotometer at a wavelength of 276 nm by diluting with methanol[26].

4. RESULTS AND DISCUSSION

Preformulation study

The procured venlafaxine was studied for preformulation characters and the results are reported in Table 2.

Table 2. Observed properties of venlafaxine

Property	Observation
Color	White
Odor	Odorless
Appearance	Crystalline powder
Melting point	217-218°C
Solubility	Soluble in water, methanol, ethanol, chloroform and 0.1N HCl; insoluble in 0.1N NaOH
Partition coefficient	0.264
LOD (%)	0.30 %

The absorption maximum of venlafaxine in methanol was found to be 276 nm and the calibration curve was prepared for a range of 10-50 µg/mL (Figure 1).

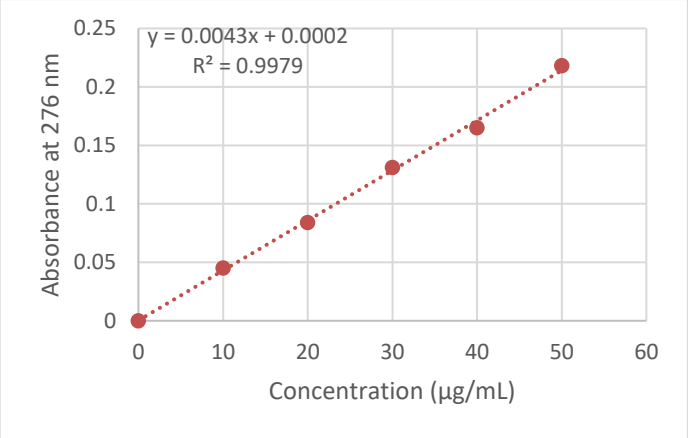

Figure 1. Standard curve of Venlafaxine

Compatibility study of Venlafaxine, PVA and Chitosan by FT-IR

In order to confirm the compatibility of the drug and the excipients, a physical mixture of PVA, chitosan and venlafaxine was subjected to FT-IR analysis. The spectrum was observed for the occurrence of stretching and bending vibrations. The spectra of the mixture exhibited all the peaks of the pure drug as well as some peaks due to the functional groups of the excipients. No peak of the pure drug was removed though the position of the peak changed marginally due to the vibrations of the functional groups of the excipients (Figure 2).

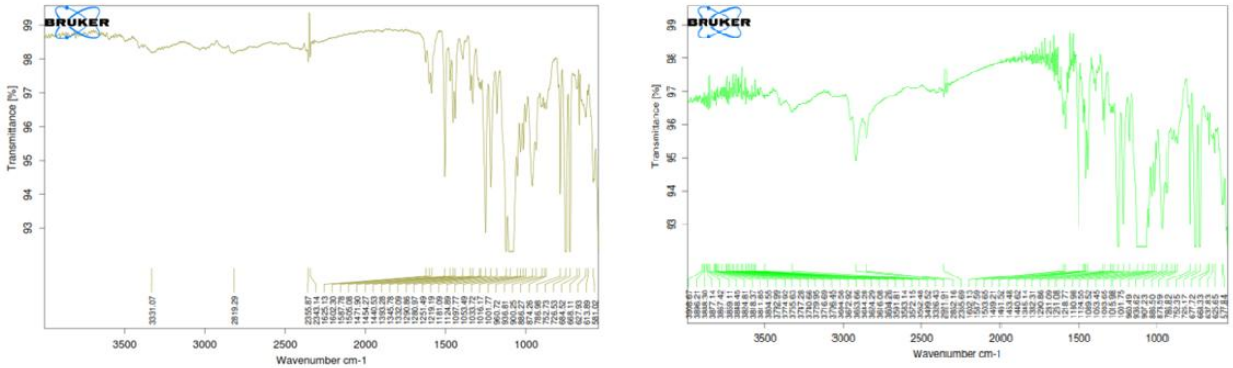

Figure 2. FT-IR spectra of (A) Venlafaxine (B) PVA+chitosan+Venlafaxine

Fabrication of microneedle patches

In order to study the most optimum amount of PVA to obtain microneedles of desired mechanical strength and penetration, various concentrations of PVA (2.5 - 20% w/v) with or without 20% w/v chitosan were used to fabricate microneedle

patches. The molds prepared using resin and hardener were utilized to cast the microneedle patches (Figure 3). Additionally a recent study using Chitosan-PVA blend for fabrication of microneedle patch to deliver perindopril has reported no skin irritation of the patch[27].

Figure 3. Microneedle patches

5. EVALUATION OF THE MICRONEEDLE PATCHES

Physical appearance

F1-F6 were found to be colorless, soft, blunt while F7-F10 where whitish, sharp needles. The homogeneity, clarity and needle shape was visualized for each formulation and the formulations were homogenous. It could be seen from the results that without chitosan the patches were blunt whereas lower ratio of chitosan and PVA led to smooth and highly plastic patches making them unsuitable to be microneedle patches. On increasing the concentration of PVA in the blend, the patches displayed the sharpness strength for formulation as microneedle patches.

Weight uniformity, pH and moisture

The weight variation of each formulation was performed by weighing the individual formulation in triplicate and the ability of the mold to produce microneedle patches of consistent size and weight. The formulations F5, F9 and F10 presented a weight variation of more than 10% whereas the variation was less than 7.5% in all other formulations. The surface pH of the microneedle patches were studied using the reported method to assess the compatibility of the patches with skin. The surface pH was unaffected by the concentration of the PVA and addition of chitosan in the patches. The surface pH ranged from 5.33 to 5.63 suggesting skin compatibility. The moisture uptake and content of the microneedle patches was also found to increase with an increasing concentration of PVA and addition of chitosan in the formulations. The moisture content and uptake ranged from 6.53 to 8.24 % and 5.77 to 7.46% respectively (Table 3).

Table 3. Weight uniformity, pH and moisture in microneedle patches

Formulation	Weight Variation (%)	Surface pH	Moisture content (%)	Moisture uptake (%)
F1	2.58	5.33	6.53	5.77
F2	3.17	5.37	6.67	5.92
F3	3.11	5.38	6.84	6.01
F4	5.26	5.41	6.99	6.13
F5	16.4	5.53	7.08	6.21
F6	4.23	5.38	7.14	6.29
F7	3.13	5.42	7.33	6.54
F8	3.27	5.45	7.45	6.88
F9	14.3	5.52	7.79	7.05
F10	26.3	5.63	8.24	7.46

Mechanical strength of microneedle patches

The microneedle patches were tested for their ability to withstand the pressure applied for application to skin. Weights of increasing magnitude were placed on the microneedles patches and the needle shape was visualized. The results suggest that the microneedle patches produced using 5.0, 7.5 and 10% PVA with 20% chitosan presented the highest mechanical strength and could retain the shape of the needle even on pressure applied by 1000g weight. This suggests that blend of 20% w/v chitosan with 5.0, 7.5 and 10% w/v PVA were the most suitable for having microneedle patches of sufficient strength to withstand the pressure of application.

Insertion capacity and dissolution of microneedle patces

To evaluate the ability of the microneedle patches to get inserted in to the skin, commercial parafilm was used as the skin simulating membrane. The film was folded in 8 layers of 140 µm each and the microneedle patch was pressed by thumb on the parafilm layers. The layers were separated and visualized for the formation of holes (insertion). It was found that the microneedle patches prepared using 20% w/v chitosan and 5.0, 7.5 and 10% w/v PVA were able to produce all 10 impressions (all needles inserted) whereas the other microneedle patches could not produce impressions due to all the needles in the first layer. This suggests that the approximate insertion capability of the microneedle patches was 140µm.
The dissolving capability of the polymeric tips affects the release rate of drug from microneedle patches. Agarose gel was used as the simulating material in place of the biological tissue and it was found that the microneedle tips dissolved around 18% within 20 seconds of insertion into agarose gel. Within 347 seconds the entire microneedle tip was found to disappear suggesting a complete dissolution of the microneedle tip. The good water solubility of PVA-chitosan blend could be attributed to the rapid dissolution of the microneedle tip.

Venlafaxine loaded microneedle patches

Considering the physical appearance, weight variation, mechanical strength, insertion capability and dissolvability of the formulated microneedle patch, **F8** was selected as the optimized microneedle patch formulation for preparation for preparing venlafaxine loaded microneedles.
The microneedle patches exhibited sharp needles, the patch was white, homogenous and opaque with surface pH of 5.58. The weight variation was 3.45% and the moisture loss and uptake were 7.39% and 6.74% respectively. The drug content in the microneedle patches was found to be 97.18%.

***In vitro* release of venlafaxine from the microneedle patches**

The release of venlafaxine from the optimized microneedle patches was studied in phosphate buffer using dialysis bag method.

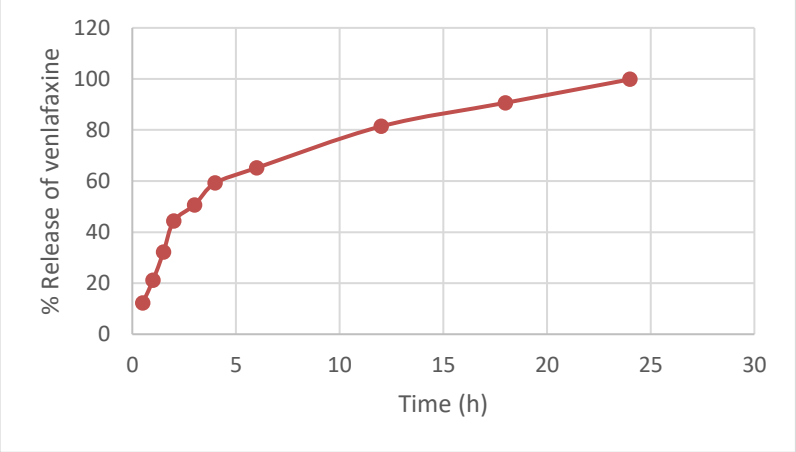

Figure 4. Cumulative release of venlafaxine from microneedle patches

As visible from the graph of release (Figure 4), venlafaxine released in a biphasic manner from the microneedle patches with an initial burst release within 3 hours releasing about 50% of drug. The burst release could be due to the dissolved microneedle tips in the dermis. After the initial rapid release, the release was found to be prolonged for more than 24h. This biphasic release profile would be able to effectively manage both acute and chronic pain conditions. Previously it has been reported in a study that use of highly water soluble matrix (carboxymethylcellulose) for preparation of microneedles to quick release (almost 100%) within 1 h whereas highly lipophilic matrix (Eudragit S100) resulted in release of only 25-30% drug in 96 h, suggesting that the polymer type has an influence on the release of incorporated drug[15].

6. CONCLUSION

The present investigation was undertaken with an objective to produce an alternate delivery system for Venlafaxine, a drug used in chronic pain management to reduce its dose and produce controlled action. The results obtained from the

study reveal that microneedle patches could be easily prepared using simple casting method and also present effective loading of venlafaxine. The microneedle patches were able to release 50% drug within 3 hours and sustain the release of venlafaxine for more than 24 hours thus being helpful for management of both acute and chronic pain. Further in vivo studies are required for studying the effect of the prepared microneedle patches on the pharmacokinetics of venlafaxine.

7. ACKNOWLEDGEMENTS

The authors are thankful to RB Science, Bhopal for utilizing their facilities to carry out a part of the research work.

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