RESEARCH ARTICLE

Comparison between Ethylcellulose and Polymethacrylate Topical Nanosponges Loaded with Butenafine Hydrochloride

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ABSTRACT

In this study, nanosponges (NS) loaded with butenafine hydrochloride (a broad-spectrum benzylamine antifungal agent) were successfully prepared by emulsion solvent diffusion method using ethylcellulose or polymethacrylate as retarder polymers. PVA was used as a stabilizer. NS 18 formulations were formulated with various ratios of 1:1, 1:2, and 1:3 (%, w/w), using different PVA concentrations of 0.25, 0.5, and 0.75 (%, w/w). The prepared formulations were tested for particle size in terms of diameter, which ranged from (73.6 ± 15.4–991 ± 11.2 nm) for ethylcellulose NS, and from (116 ± 0.96–1439.6 ± 237.4 nm) for polymethacrylate NS. The entrapment efficiency of the selected formulas (F1, F10) were (74.12 ± 2.60%) and (72.89 ± 1.41%). The selected formulas F1 and F10 were also evaluated for their polydispersity, yield, and *in-vitro* drug release. The release of BFNS powder in F10 (90.42 ± 1.81%) was higher than that of ECNS F1 powder (78.53 ± 3.24%) within 24 hours. Evaluation tests of the scanning electron microscope (SEM), Fourier transform infrared ray (FTIR), and powder X-ray diffraction (PXRD) confirmed the NS' spherical and porous features, the absence of any drug polymer interaction, and the stability of the drug in the delivery system. The two formulas of F1 and F10 were found to exhibit prolonged drug release, which minimizes side effects and dosing frequency of BF drug application.

Keywords: Hydrochloride, Ethylcellulose, Nanosponges, Butenafine.

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INTRODUCTION

Owing to their uncontrolled drug release, conventional local dosage forms (*e.g.,* ointments and creams) are characterized by low affectivities and, consequently, more side effects. These two disadvantages have encouraged conducting research-works aiming at developing more advanced systems of controllable drug release *via* particle-delivery carriers such as microspheres, liposomes, and nanoparticles.[1] In this research field, particular attention has been drawn to nanosponges (NS), especially because they allow predictable, precise, and targeted drug release.[2-4] Due to their nanoporous structure, NS easily provides an advantageous topical drug delivery carrier for many active pharmaceutical ingredients, such as local anesthetics, antifungals, and anti-acne agents.[3-5] The advantages of NS are numerous since they cause no irritation, allergy, toxicity, nor mutagenicity, all being safety factors. As delivery particulates of a wide variety of ingredients, they offer cost-effective, self-sterilizing extended-release. In addition, NS structures have enhanced thermal, physical, and chemical stability.[6-9]

Butenafine hydrochloride is a benzylamine derivative, [1-(4-*tert*-butylphenyl)-*N*-methyl-*N*-(naphthalen-1-ylmethyl) methanamine; hydrochloride] as shown in Figure 1, with a molecular weight of 353.9 and is practically insoluble in water drug with log P~5.85. It is the first representative of a new class of antifungal agents. As a broad-spectrum antifungal agent, butenafine has proven to be effective in the treatment of tinea pedis, corporis, cruris, toe-nail onychomycosis, pityriasis versicolor, and seborrheic dermatitis caused by *Malassezia sp.*,

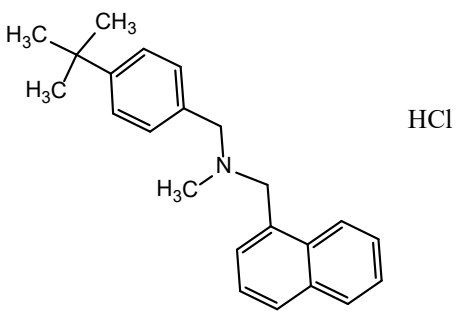

Figure 1: Chemical structure of butenafine hydrochloride[11]

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with the common side effects of irritation and burning sensation at the site of application.[10-12]

This study aims to prepare and evaluate butenafine HCl NS (BFNS) carrier for dermal delivery using ethylcellulose (EC) or polymethacrylate (Eudragit) and their comparison.

MATERIALS AND METHODS

Materials

HCl and EC were supplied by Hangzhou Hyper Chemicals Limited, Hangzhou, China. Eudragit RS 100 was obtained from Evonik Rohm GmbH, Darmstadt, Germany. Polyvinyl Alcohol 14000 was supplied by Thomas Baker (Chemicals) Pvt. Ltd. Mumbai, India. All the chemicals used were of analytical grade.

Methods

Preparation of NS

BFNS were prepared by the emulsion solvent diffusion method as proposed by Sharma and Pathak in 2011. The organic phase consists of 200 mg butenafine hydrochloride, with the retarder (EC or Eudragit RS100) were dissolved in different volumes of dichloromethane or acetone as seen in Table 1. The aqueous phase consisting of polyvinyl alcohol (an emulsifying or stabilizing agent) was dissolved in warm water. The organic phase was gradually added into the aqueous phase and stirred mechanically at 1000 rpm for 2 hours at room temperature to remove the organic solvent from the mixture.[5]

NS formed were collected by vacuum filtration, dried at 40°C, and stored in a tightly closed container. Different variables (ratios of butenafine hydrochloride and the retarder, PVA concentrations, stirring speed, type, or volume of organic phase) were used for preparing NS that was evaluated for particle size, entrapment efficiency, and yield percentage.

Percentage Yield

BFNS obtained after drying were weighed. The percentage yield value was calculated according to the formula:[13,14]

$$\%yield = \frac{weight\ of\ nanosponge}{Total\ weight\ of\ solids\ added} \times 100$$

Entrapment Efficiency (EE%)

The UV spectrophotometric method was used to estimate the entrapment efficiency of BFNS. Batches of NS were selected and placed in 30 mL of BPS. Butenafine HCl was extracted by centrifuging at 1000 rpm for 30 minutes, then filtered and analyzed after proper dilution. Percentage entrapment was calculated as:[15,16]

$$\%EE = \frac{original\ drug\ content\ in\ NS - drug\ content\ in\ supernatant}{original\ drug\ content\ in\ NS} \times 100$$

Particle Size and Size Distribution

Particle size and polydispersity index (PDI) determination were obtained using the Nano Brook 90Plus particle size analyzer, which uses dynamic light scattering (DLS) to measure the intensity of light scattered by the molecules in the sample as a function of time.[17]

In-vitro Dissolution Profile of NS

In a pre-treated dialysis bag (Schuchardt dialysis membrane MWCO 12,000 Da) that is cut off, an aqueous dispersion of NS (10 mL) is placed in a dissolution test USP apparatus Type II. An environment of 100 rpm and 34 ± 0.5°C in 500 mL, 5.5 pH phosphate buffer was used.[18,19]

Table 1: Formulation variables of butenafine HCl NS

ID	*Butenafine HCl g*	*EC g*	*Eudragit RS 100 g*	*PVA g*	*DCM mL*	*Acetone mL*	*Stirring speed rpm*
F1	0.2	0.2	-	0.5	20	-	1000
F2	0.2	0.2	-	0.5	40	-	1000
F3	0.2	0.2	-	0.5	-	20	1000
F4	0.2	0.4	-	0.5	20	-	1000
F5	0.2	0.4	-	0.25	20	-	1000
F6	0.2	0.4	-	0.75	20	-	1000
F7	0.2	0.4	-	0.5	20	-	500
F8	0.2	0.4	-	0.5	20	-	1500
F9	0.2	0.6	-	0.5	20	-	1000
F10	0.2	-	0.2	0.5	20	-	1000
F11	0.2	-	0.2	0.5	40	-	1000
F12	0.2	-	0.2	0.5	-	20	1000
F13	0.2	-	0.4	0.5	20	-	1000
F14	0.2	-	0.4	0.25	20	-	1000
F15	0.2	-	0.4	0.75	20	-	1000
F16	0.2	-	0.4	0.5	20	-	500
F17	0.2	-	0.4	0.5	20	-	1500
F18	0.2	-	0.6	0.5	20	-	1000

Zeta Potential (ZP) Measurement

The selected formula's ZP was determined using The Malvern zetasizer UK.[20]

X-Ray Powder Diffraction (PXRD)

Shimadzu XRD-6000 PXRD was used to test the crystalline nature of the substances in the solid-state. Diffractograms of butenafine HCl powder and the selected formulas were obtained.[21]

Scanning Electron Microscope (SEM)

A Vega/TESCAN SEM was used to study morphology, the surface topography of the prepared NS, the difference in morphology state of the pure drug, and the selected formulas.[22]

Fourier Transform Infrared Spectroscopic Analysis

The FTIR analyzer was used to study the compatibility between butenafine hydrochloride and the excipients in the selected formulas by using FTIR-8300 Shimadzu, Japan.

Statistical Analysis

The statistical analysis of the results were performed using GraphPad Prism version 8.4.3 at level of significance $p < 0.05$.

RESULTS AND DISCUSSION

Particle Size Analysis and PDI Measurement

The effect of different variables on the particle size and PDI was investigated using nine formulas for each retarder. Formulas' mean particle size in terms of diameter ranged from (73.6 ± 15.4- 991 ± 11.2 nm) for EC NS, and from (116 ± 0.96-1439.6 ± 237.4 nm) for Eudragit NS. Table 2 below offers the particle size, standard error (SE), and PDI for the variables affecting different formulas.

Variables Affecting Formulas

Effect of Drug to Polymer Ratio

In formulas F1, F4, and F9, the increase of EC-polymer-to-drug ratios (1:1, 2:1, and 3:1) translated into an increase in particle size. The highest to lowest cline of increase was in F9, followed by F1 and F4. Mean of particle size increase between F4 and F1, and between F4 and F9 was significant (*p-value* < 0.05), but insignificant between F1 and F9. The same results were obtained by Sharma *et al*. (2011).[5]

A proportional increase in nanoparticle size was measured in formulas: F10, F13, and F18, at an ascending cline, with an insignificant increase in Eudragit-to-drug ratios (1:1, 2:1, and 3:1; *p-value* > 0.05). Similar results were reported by Kiliçarslan *et al*. (2008) and Pandav and Naik (2014).[23,24]

Effect of Polyvinyl Alcohol (PVA) Concentration

During NS preparation, PVA molecules have the function of stabilizing the emulsion nano-droplets by preventing those droplets from aggregating with one another. An exact amount of PVA molecules is required to surround the droplets' organic/aqueous interfacial area. The smallest particle size was obtained from (0.5%) PVA in F4 (EC), and F14 (Eudragit), respectively. The increase in the amount of PVA from (0.5%) to (0.75%) in F6 (EC) showed an insignificant increase (*p-value* > 0.05) in the particle size, while the decrease of that amount to (0.25%) in F5 caused a significant increase (p <0.05) in particle size. This result corresponds with those reported by Kemala *et al.* (2012). With the Eudragit, a direct proportional increase in concentration to particle size was obtained in F14, F13, and F15. This increase in particle size was insignificant between F14 and F13 (*p-value* > 0.05), but significant between F14 and

Table 2: Particle size, PDI of different butenafine HCl NS formulas

ID	*Butenafine HCl g*	*EC g*	*Eudragit RS 100 g*	*PVA g*	*DCM mL*	*Acetone mL*	*Stirring Rpm*	*Particle Size ± SEM nm*	*PDI*
F1	0.2	0.2	-	0.5	20	-	1000	311.6 ± 48.4	0.005
F2	0.2	0.2	-	0.5	40	-	1000	756.8 ± 156.2	0.8225
F3	0.2	0.2	-	0.5	-	20	1000	502.3 ± 16.2	0.3724
F4	0.2	0.4	-	0.5	20	-	1000	83.7 ± 8.9	0.091
F5	0.2	0.4	-	0.25	20	-	1000	651 ± 106.7	0.005
F6	0.2	0.4	-	0.75	20	-	1000	606 ± 58.3	0.376
F7	0.2	0.4	-	0.5	20	-	500	991 ± 11.2	0.005
F8	0.2	0.4	-	0.5	20	-	1500	73.6 ± 15.4	0.273
F9	0.2	0.6	-	0.5	20	-	1000	391.80 ± 58.5	0.005
F10	0.2	-	0.2	0.5	20	-	1000	279.8 ± 41.4	0.005
F11	0.2	-	0.2	0.5	40	-	1000	192.7 ± 4.1	0.4561
F12	0.2	-	0.2	0.5	-	20	1000	116 ± 0.96	0.1494
F13	0.2	-	0.4	0.5	20	-	1000	373.3 ± 83.7	0.005
F14	0.2	-	0.4	0.25	20	-	1000	123.7 ± 7.1	0.005
F15	0.2	-	0.4	0.75	20	-	1000	484.1 ± 14.4	0.1779
F16	0.2	-	0.4	0.5	20	-	500	1439.6 ± 237.4	0.191
F17	0.2	-	0.4	0.5	20	-	1500	146.7 ± 2.6	0.3661
F18	0.2	-	0.6	0.5	20	-	1000	464.2 ± 98.1	0.005

F15 (*p-value* < 0.01). Similar results were reported by Shoaib, *et al.* (2018) for naproxen and ibuprofen NS. [25,26]

Effect of Internal Phase Solvent Type

Organic solvents play a crucial role in NS preparation due to their functionality in dissolving the drug and polymer, ensuring the initial thermodynamic equilibrium with the external phase, plus the organic solvent's eventual diffusion and evaporation to form the NS. This diffusion and eventual evaporation are mainly dependent upon its boiling point.[27]

On comparing F1 (EC NS) and F10 (Eudragit NS) prepared with dichloromethane with F3 EC NS (prepared with 20mL acetone), there was an insignificant increase (*p-value* > 0.05) in particle size and PDI. However, F12 (Eudragit NS, also prepared with acetone) showed a significant decrease (*p-value* < 0.05) in particle size and an increase in PDI. In this connection, acetone's higher boiling point (at 56°C) rendered slower evaporation than DCM's boiling point (at 39°C), also slowing the NS partitioning process, hence the higher PDI in F3 and F12. [28,29]

Effect of Stirring Speed

In both ECNS (F7, F4, F8) and Eudragit NS (F16, F13, F17), the respective increase in stirring speed from 500 rpm to 1000 and 1500 rpms caused a decrease in mean particle size. In ECNS, the significance level of this decrease in particle size was at *p value* < 0.0001, while in Eudragit NS, the significant decrease was at *p value* < 0.05. Srinivas *et al.* (2013) described this effect to the polymer's adherence to the stirrer's paddle due to the high turbulence created within the aqueous phases.[30]

ZP Measurement

In BFNS, ZP were 0.0382 and -0.0688 for F1 and F10, respectively.

The ZP of the aqueous dispersion describes the stability of the prepared NSs. The ZP of BFNSs of 0.0382 and (-0.0688) do not correspond with Smoluchowski (1916) values of (ZP ≥ ±30 mV), which are indicative of the stable dispersion for hard spheres, not soft NSs particles. Consequently, owing to the soft nature of NS, ZP calculated by the conventional hard-sphere method does not reflect the state of agglomeration or stability of our soft NS particles, which were intended to be eventually collected as a dry powder.[31,32]

Dissolution Profile of Butenafine-Loaded NS Powder

Drug-release profiles for the ECNS and Eudragit NS selected formulas are indicated in Figure 2.

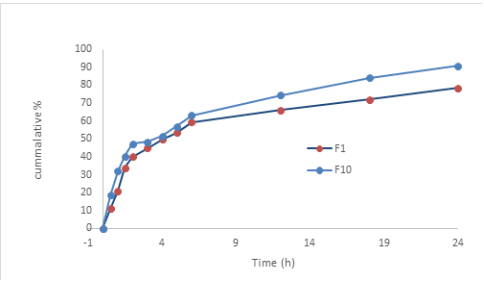

Figure 2: BF Release Profile for F1 (ECNS) and F10 (Eudragit NS)

The release of BFNS powder in F10 (90.42 ± 1.81%) was higher than that of ECNS F1 powder (78.53 ± 3.24%) within (24) hours, as shown in Figure 2. This result is ascribable to the low particle size in F10, which increased the surface area and enhanced the contact between particles and dissolution medium.[24]

Drug EE%

The results showed that the EE% for each 100 mg of NS powder in formulas F1 and F10 was 74.12 and 72.89%, respectively.

FTIR Spectroscopic Analysis

The FTIR spectrum of pure BF and BFNS powder is shown in Figure 3. The results showed that the characteristic peaks of BF (sharp stretching aromatic C-H stretching 3046.01 cm^{-1}, C–CH_3 peaks at 2959.23 cm^{-1}, C=C aromatic peak at 1605.45 cm^{-1}, and C–N stretching peaks at 1216.77 and 550–950 cm^{-1} aromatic bending), present in the pure drug and NS formulations which show that there is no chemical interaction between the drug and other excipients. BF F1 F10

SEM

SEM scanning showed that the pure drug particles obtained a random-shaped surface, with a large particle size as revealed in Figure 4. On the other hand, the SEM of F1 powder in Figure 5 showed finely spherical, smooth, and porous NS particles. Ahmed *et al.* (2021) reported the same results.[15]

PXRDA

As shown in Figure 6, The PXRDA patterns of pure powder BF revealed highly intense diffraction peaks, highlighting its crystalline nature. However, these diffraction peaks were of lower intensity in the powder pattern, as seen in Figures 7 and 8. This result is indicative of the BF powder's amorphous state. This same result was reported by Rao *et al.*[33,34]

CONCLUSION

On the basis of the results described above, the implemented emulsion solvent diffusion method in the prepared formulas of both EC and Eudragit NS showed successful drug-entrapment and prolonged release of BF for 24 hours. These results function in minimizing the side effects and dosing frequency of BF drug application.

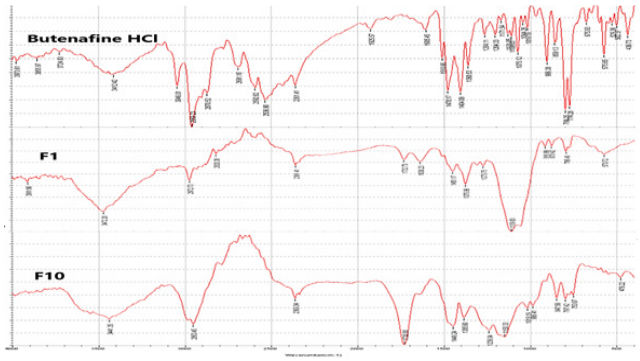

Figure 3: FTIR Spectrum of Pure BF, F1 (ECNS Powder), and F10 (Eudragit NS Powder)

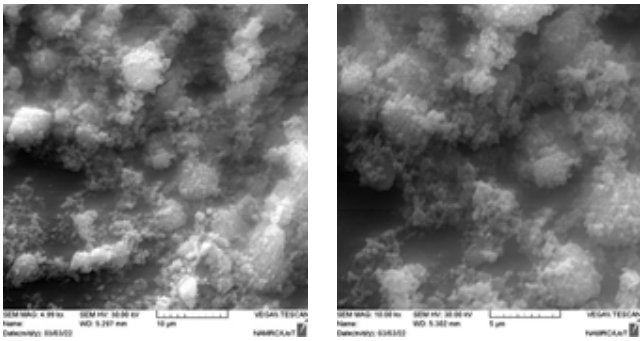

Figure 4: SEM of Pure Drug, at 10.00 Kx Magnification

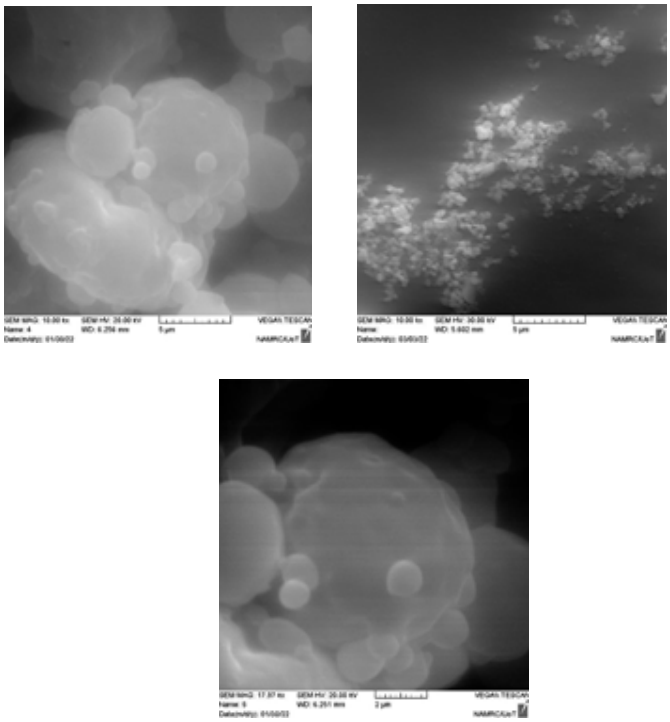

Figure 5: SEM of F1, F10 at 10.00Kx and F1 at 17.97Kx

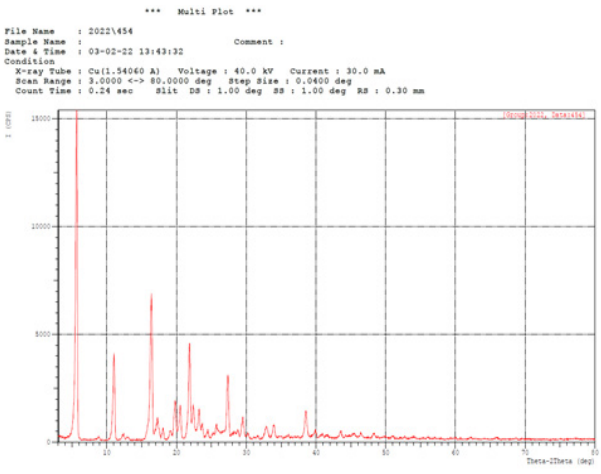

Figure 6: PXRD of Pure Drug

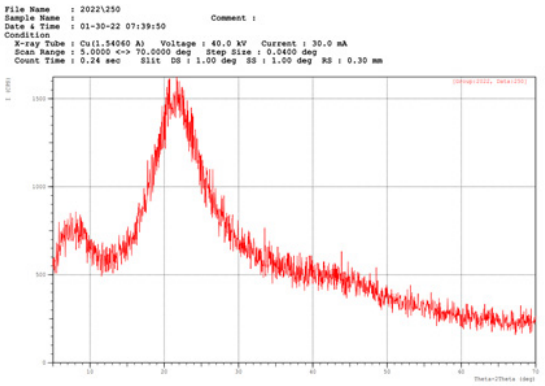

Figure 7: PXRD of Formula F1

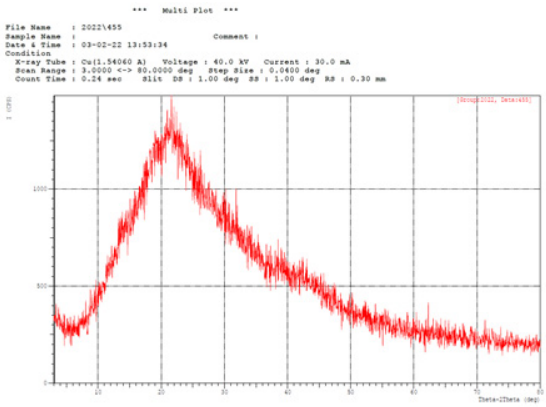

Figure 8: PXRD of Formula F10

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