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Solubility enhancement of ebastine through natural solid dispersion: formulation and pharmacokinetics

Shaimaa Nazar Abdal-Hammid[1], Hussein K. Alkufi[2,*], Zahraa Kareem Hussein[3], Ahmed H. Salman[4]

[1]Department of Pharmaceutics, College of Pharmacy, University of Baghdad, Baghdad, Iraq
[2]Department of Pharmacognosy, College of Pharmacy, University of Thi-Qar, Nasiriyah, Iraq
[3]Wasit Health Directorate, Ministry of Health and Environment, Wasit, Iraq
[4]Department of Pharmaceutics, College of Pharmacy, Al-Bayan University, Baghdad, Iraq

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*** CORRESPONDING AUTHOR:**
Hussein K. Alkufi, Department of Pharmacognosy, College of Pharmacy, University of Thi-Qar, Nasiriyah, Iraq; e-mail: husseinalkufi21@utq.edu.iq

ABSTRACT

Natural solid dispersion (NSD) is a clever pharmaceutical technology technique that is used in order to improve the physicochemical characteristics of pharmaceuticals, such as their solubility and dissolution. Ebastine (EBS) is a medication used for the treatment of pruritic skin problems and the symptoms of allergic illnesses, such as rhinitis. The aim of this work was to improve the solubility and rate of dissolution of EBS by using an NSD system. Utilizing solvent evaporation as a preparation technique, eight EBS formulations were created as solid dispersions through the use of two natural polymers, namely sodium alginate (SA) and xyloglucan, at various drug to polymer ratios (1:0.5, 1:1, 1:2, and 1:3). The produced formulations were assessed for their *in vivo* pharmacokinetics, their solubility, and their dissolution. According to our results, the employed polymers improved the drug solubility. In comparison to pure EBS, the optimal formula (EBS:SA at a 1:1 ratio) exhibited a significant increase in solubility. Additional analysis of the ideal formula revealed that EBS is amorphous. *In vivo* experiments in rats revealed a superior pharmacokinetic performance in terms of bioavailability of the ideal formula compared to pure EBS. It may be inferred that the NSD can be used in order to address the issue of EBS solubility under the chosen conditions, which may lead to improved EBS bioavailability.

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1. Introduction

The adoption of natural solid dispersion (NSD) is a smart way of improving a drug's absorption rate and solubility[1]. Solid dispersion (eutectic mixture) is the term used when a drug (hydrophobic component) is disseminated in an inert carrier or matrix (hydrophilic part) in a solid state. Ebastine (EBS) helps with pruritic skin problems and the symptoms of allergic conditions including rhinitis; it is a prodrug that undergoes significant first-pass metabolism allowing it to produce carebastine (an active metabolite of carboxylic acids). Carebastine is responsible for almost all of the H_1-antihistaminic activity, and is more potent than the parent medication. The administration is performed orally. The disadvantage of this molecule is that it is mostly hydrophobic, which results in reduced water solubility and lower medication bioavailability[2]: in fact, it is sparingly soluble in methanol, practically insoluble in water, and highly soluble in methylene chloride. With a pKa of 8.8 and a logP of 7.64, it is a basic compound with a tertiary amine group. According to the Biopharmaceutics Classification System, it falls within class II[3]. The aim of this work was to create an NSD of EBS by using natural polymers in varying ratios, so as to improve its solubility and bioavailability.

2. Methodology

2.1. Production of EBS solid dispersion formulas

We employed solvent evaporation in order to create NSDs of EBS. To create a transparent solution, 500 mg of the medication were dissolved in 25 mL of methanol. The natural polymers xyloglucan (XG) and sodium alginate (SA) were then suspended in the medication solution. The drug to carrier ratios of 1:0.5, 1:1, 1:2, and 1:3 were used in order to mix the drug and the carriers. NSD1–NSD4 represent EBS:SA formulas, while NSD5–NSD8 represent EBS:XG formulas. At room temperature, the suspension was continuously agitated with a magnetic stirrer until all of the solvent had evaporated. For additional assessments, the produced NSDs were placed in a desiccator with calcium chloride for at least 24 h after passing through a #20 sieve[4].

2.2. Assessment of EBS solid dispersion formulas

2.2.1. Study of saturation solubility and *in vitro* dissolution and solubility

Excess NSD formulations were added to distilled water in simple tubes in order to measure the saturation solubility of prepared NSDs in water through the use of a water bath shaker for 48 h, at 25°C. The USP type II dissolution device was filled with precisely weighed samples equal to 5 mg of EBS. Pure drugs and NSDs with the highest solubility values were the subjects of an *in vitro* dissolution assessment. At 37°C (±0.5°C), 1,000 cc of 0.1 N HCl (pH 1.2) and a paddle speed of 100 rpm were used for this assessment. After filtering, a 5-mL sample was obtained at 10, 15, 20, 30, 40, 50, and 60 min. The samples were then evaluated spectrophotometrically at the designated λ_{max} of EBS and were replaced with an equivalent volume of fresh dissolution media. Subsequently, the plotting of the drug dissolution profiles was undertaken[5,6].

2.2.2. Study of *in vivo* pharmacokinetics

We assessed the pharmacokinetic properties of the pure EBT suspension and of the NSD suspension in male Wistar rats. Rats were randomly assigned into two groups (A and B), each consisting of three rats (n=3). All animals received the samples orally. In each session, the EBT dosage was 10 mg/kg of body weight. Every rat received ether anaesthesia. A nasogastric tube was used in order to administer the optimized formula diluted with water and the pure EBT suspension. The tail vein was used in order to obtain blood samples at 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, 24, 48, and 72 h after the administration. Centrifugation (Centurion Scientific, Chichester, UK) was performed on the blood samples (that were collected in heparinized plastic tubes) for 5 min at 1,500 rpm. For additional assessments, the plasma was carefully pipetted out and kept at -20°C in Eppendorf plastic tubes. We centrifuged equal amounts

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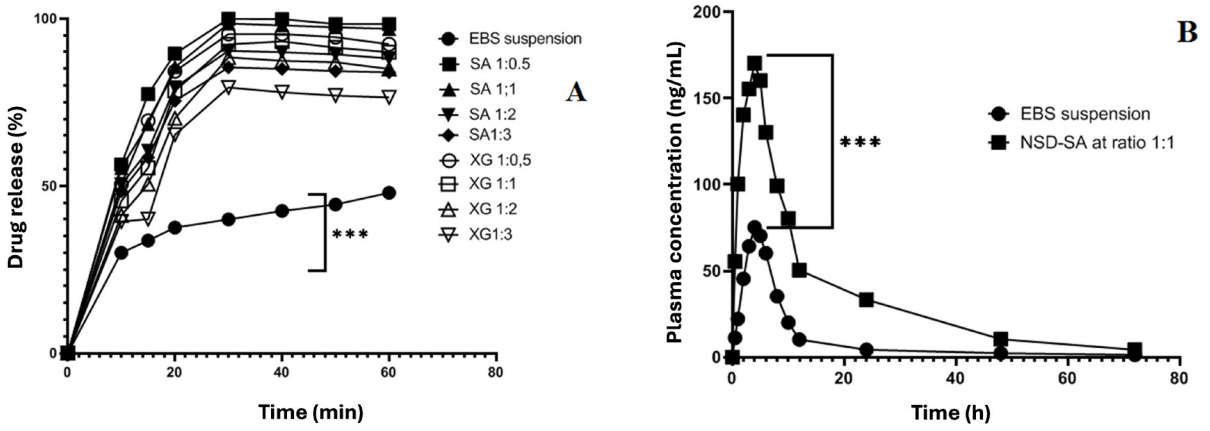

Figure 1. *(A): Dissolution profiles of the herein employed EBS suspension and of various NSDs. (B): Mean plasma concentration-time profile for carebastine following the oral administration of an EBS suspension and of the optimized NSD formula (EBS:SA at a 1:1 ratio). After 4 h, the C_{max} of the EBS suspension was 75.33 ng/mL, while the C_{max} of the EBS:SA NSD (at a ratio of 1:1) indicated a peak plasma concentration of 170.32 ng/mL. Compared to the oral suspension that exhibited an area-under-the-curve (AUC) value of 701.9 ng/mL/h, the optimized formula had a considerably greater AUC of 2,541.33 ng/mL/h. Abbreviations used: EBS, ebastine; NSD, natural solid dispersion; SA, sodium alginate; XG, xyloglucan.*

of absolute methanol and plasma for 5 min at 10,000 rpm. Drying the supernatant involved applying a nitrogen stream at -40°C. To acquire the supernatant for subsequent analysis using Knauer HPLC (Germany), the obtained residue was reconstituted with methanol and centrifuged at 10,000 rpm. Acetonitrile, methanol, and ammonium acetate buffer (20:30:50) made up the mobile phase. The HPLC with a C-18 column (4.6 x 250 mm) used a flow rate of 1 mL/min and a wavelength of 257 nm in order to evaluate the levels of carebastine, while samples that included 1.0 mg/mL of cetirizine hydrochloride acted as internal standard. The column's temperature remained constant at 40°C. The final sample and standard concentrations (40 μg/mL) were prepared. The samples were injected for elution after the baseline was established. The maximum plasma concentration (C_{max}), the time to attain the C_{max} (T_{max}), and the area-under-the-curve (AUC_{0-t}) were all determined by using the Microsoft Excel PKSolver (2016) software.

3. Results and Discussion

EBS is sparingly soluble in methanol, nearly insoluble in water, and insoluble in 0.1-N HCl. Our findings concurred with those of earlier studies[7,8]. All assessed formulations exhibited superior dissolving rates in 0.1-N HCl, as shown in Figure 1A. Compared to XG, SA dissolves better in water. This implies that it can more readily envelop drug particles in a hydrated layer, potentially aiding in their dispersion and disintegration in the aqueous medium. Based on the earlier findings, the NSD of EBS:SA at ratio of 1:1 improved the EBS dissolution and solubility. As a result, this NSD was examined further *in vivo*.

Following the administration of a single oral dose, the concentration of EBT in the rat plasma was measured (Figure 1B). EBT underwent substantial first-pass metabolism to become carebastine; its active metabolite. The AUC's findings, which are based on variations between comparable items, were statistically significant. Carebastine was measured, since the concentration of EBS in the plasma was not found. The *in vivo* pharmacokinetic assessment of carebastine confirmed that the EBS:SA NSD (at a ratio of 1:1) significantly increases the bioavailability of EBT. The significant

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absorption across transmucosal membranes may have contributed to the high C_{max} value observed (Figure 1B). The developed optimized formula resulted in a considerable increase in the AUC value. When compared to pure EBT, the optimized formula's oral bioavailability rose about 2.95 times. The solubility of EBS in natural polymers may be the cause of the observed increase in the oral absorption rate. The absorption across the mucosal membranes was improved by the released NSD. Together, these elements improved EBT's bioavailability. Previously, the NSD approach has been used for the improvement of the transdermal delivery of the therapeutic compounds[9,10].

4. Conclusion

The present study's findings demonstrate that the NSD method, which makes use of natural polymers such as SA and XG, is effective in improving the poor solubility of EBS. However, when compared to XG, the SA polymer with a drug to SA ratio of 1:1 appeared to be the superior carrier. Using the solvent evaporation method, the optimized formula with the EBS:SA of 1:1 ratio appeared to be the best one for increasing the solubility, the dissolution, and the bioavailability of EBS.

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Conflicts of interest

None exist.

ORCIDs

0000-0002-6650-1997 (S.N. Abdal-Hammid); 0000-0001-6977-6737 (H.K. Alkufi); 0009-0002-8280-0513 (Z.K. Hussein); 0000-0001-7343-2064 (A.H. Salman)

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