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A Nanoemulsion Drug Delivery System for An Aqueous Insoluble Drug

▪ Ultrasonication technique for Ramipril preparation ▪

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Abstract: Nanoemulsions have emerged as potential drug delivery systems for most hydrophobics in recent pharmaceutics. An angiotensin converting enzyme inhibitor, ramipril, of its kind has demonstrated relatively low aqueous solubility and bioavailability. This preferred medicine for hypertension and congestive heart failure has exhibited intense drug interactions leading to multiple side effects. Focusing on these facts, we intended to raise an essential oil based nanoemulsion comprising of cinnamon oil, tween 80 and water by ultrasonication. Stability studies were performed to delineate the best formulation. Droplet size analysis using dynamic light scattering technique and electrical conductivity was measured in characterizing the internal physico-chemical state of the emulsion. The optically clear and low-viscous formulation with enhanced solubility and minimum droplet size diameter would pose a definite promise in improving the significance of this sparingly soluble drug.
Keywords: Ramipril, drug delivery,nanoemulsion, droplet size.

Introduction and Experimental:

The role of nanotechnology in drug delivery systems have shown remarkable advance in present pharmaceutical research. Among these, we placed our focus on nanoemulsions which could be defined as isotropic, thermodynamically stable, transparent or translucent with mean droplet diameters in the range between 50 to 1000 nm [1]. These generally employ high shear stress or mechanical extrusion to improve stability and bioavailability of drugs and also protects from any degradation. The uniform nano-sized spherical droplets produce large interfacial area with unusual elastic behavior that influences easy transport of drug and causes sustained and targeted drug delivery [2,3]. One such drug, ramipril (an active inhibitor of angiotensin converting enzyme) is chosen in this study based on its poor physico-chemical properties [4].

Preparation of Nanoemulsion

Based on the good solubilization of ramipril (Morepen Laboratories, India) in cinnamon oil (Sigma), i.e., 80.25 ± 0.04 mg/ml [5], a nanoemulsion was formulated by ultrasonication.

Stability

Stability studies followed the protocol of Shafiq et al which comprised of heating-cooling cycle, centrifugation and freeze-thaw cycle [6].

Measurement of pH and Conductivity

The pH and conductivity (25 °C) of the formulations were measured using a calibrated pH meter (Hanna Instruments Inc., USA) and conductivity meter (Elco CM 180) respectively.

Droplet size distribution and Polydispersity Index

The size distribution of the optimized formulation was determined by dynamic light scattering [90Plus Particle Size Analyzer-Brookhaven Instruments, USA].

Results and Discussion:

Preparation of Drug-loaded Nanoemulsion

A coarse emulsion was formulated using drug solubilized oil and tween 80 at varying ratios of 1:1, 1:2, 1:3 (i.e., 6:6:88; 6:12:82; 6:18:76) respectively followed by appropriate dilution with water (v/v) at 500 rpm in room temperature. In our case, a known quantity of drug was initially solubilized in 6% of cinnamon oil. This coarse emulsion was broken to fine droplets by subjecting to 20 kHz sonicator (Ultrasonics, USA) of 750 W with the probe diameter being 13 mm. Drug-loaded oil-in-water nanoemulsion was thus formed due to the presence of surfactant with a higher HLB value. We followed similar methodology from our previous literatures [7,8].

Stability Studies

All drug-loaded cinnamon oil based system subjected to sonication period of 10, 20 and 30 min respectively was checked for stability as shown in Table 1. Only the formulations B3, C2 and C3 have passed through all stress tests and thus chosen for further optimization.

Conductivity and pH

The conductivity and pH of the selected system are determined and shown clearly in Table 2. There was increase in both conductivity and pH measurement in comparison with its blank counterparts. The results of blank counterparts were previously published in our literatures.

Droplet size and Polydispersity Index

It was seen that the formulation C3 had the minimized droplet size diameter with low polydispersity index. Lower the polydispersity, more stable would be the formulation comparatively. Hence, C3 was chosen as the optimized formulation owing to its small droplet size, low polydispersity index, lower surfactant concentration and better stability that would improve good permeation with reduced gastrointestinal irritation.

Table 1. Thermodynamic stability studies of all drug-loaded cinnamon oil-based formulations.

Formulations	Sonication (min)	Centrifugation	Heating cooling	Freeze thaw	Inference
A1	10	-	-	-	Failed
A2	20	+	-	-	Failed
A3	30	+	+	-	Failed
B1	10	+	-	-	Failed
B2	20	+	-	-	Failed
B3	30	+	+	+	Passed
C1	10	+	+	-	Failed
C2	20	+	+	+	Passed
C3	30	+	+	+	Passed

Table 2. Physicochemical characterization of nanoemulsions after a sonication period of 30 min.

Formulation Code	Mean droplet diameter (nm)*	Polydispersity index*	pH*	Conductivity (mS)*
B3	261.5 ± 3.06	0.249 ± 0.12	4.58 ± 0.04	0.159 ± 0.06
C2	101 ± 3.12	0.234 ± 0.09	5.06 ± 0.08	0.148 ± 0.08
C3	74.5 ± 2.47	0.212 ± 0.08	5.32 ± 0.06	0.129 ± 0.04

*Mean ± S.D. (n=3)

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