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Original Article

Novel expandable gastro retentive system by unfolding mechanism of levetiracetam using simple lattice design – Formulation optimization and *in vitro* evaluation

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ABSTRACT

The aim of the present study was to develop and characterize a novel expandable gastro-retentive dosage form (GRDF), based on unfolding mechanism. The dosage form consists of a drug loaded the polymeric patch, folded into a hard gelatin capsule. Gastro retention obtained from unfolding and swelling of the patch and its adhesion to the gastric mucosa. Therefore in this work, a gastro retentive patch of levetiracetam was developed using simple lattice design considering concentration of Hydroxy Propyl Methyl Cellulose, Carbopol 934P and Xanthan gum as independent variables. A response surface plot and multiple regression equations were used to evaluate the effect of independent variables on dependent variables such as mucoadhesive strength (g/cm^2) and t_{90} (h). The prepared patches were evaluated for weight and thickness variation, mechanical properties, *in vitro* drug release and unfolding behavior. The absence of drug-polymer interaction and uniform drug dispersion in the polymeric patches was revealed by FT-IR, DSC, XRD and SEM. The results indicates, the novel GRDF based on unfolding mechanism can be alternative for other mucoadhesive dosage forms which will provide sustained release for 12 h.

1. Introduction

Oral delivery of drugs is the most preferred route of drug delivery, due to ease of administration, patient compliance, and flexibility in formulation. Conventional immediate oral dosage forms provide a specific drug concentration in the systemic circulation with limited control over drug delivery but limited in retention of the dosage form in the stomach [1]. The several approaches are currently used to retain the dosage form in the stomach. These include bioadhesive systems, swelling and expandable systems, floating systems and other delayed gastric emptying devices [2]. An alternative strategy is to combine bioadhesion with the ability to expand by unfolding and swelling. Gastro retentive drug loaded polymeric films was previously investigated and the effect of shape, folding pattern and polymer characteristics on gastric retention has been studied [3]. Klausner et al., initiated the research on expandable gastro-retentive dosage form (GRDF), investigated on Riboflavin and Levodopa expandable GRDFs [4,5]. Darandale et al., designed controlled release gastro-retentive mucoadhesive dosage form of Furosemide by unfolding mechanism [6]. Levetiracetam is an antiepileptic drug with good bioavailability, rapid achievement of steady state concentration after oral administration. Besides it also has a relatively short elimination half-life 6 h. A drug with a short half-life requires frequent dosing and this makes levetiracetam an ideal candidate for extended release formulation [7–9]. The purpose of this research is to develop a novel expandable gastro-retentive dosage form, based on unfolding mechanism using levetiracetam as a model drug. The work was aimed to develop gastro retentive patch using various hydrophilic mucoadhesive polymers like cellulose derivative (HPMC), acrylic acid derivative (Carbopol 934P) and natural gum (Xanthan gum). Ethyl cellulose which is hydrophobic in nature is used as rate retarding polymer in all formulation. In simple lattice design, three factors were evaluated by taking individual concentration and changing their concentrations simultaneously. In this

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work gastro retentive patches were developed using simple lattice design considering concentration of HPMC, Carbopol and Xanthan gum as independent variables. The mucoadhesive strength (g/cm^2) and time for 90% drug release (t_{90}) were selected as responses (Dependent variables). The constraints are to be set on responses and to optimize the best formulation.

2. Materials and methods

Levetiracetam was obtained as a gift sample from Molecules Drugs and Research Laboratory, Chennai, India. Hydroxy Propyl Methyl Cellulose, Carbopol, Xanthan Gum, Ethyl Cellulose, Propylene Glycol were procured from Aurobindo Labs, Hyderabad, India. All other reagents used were of analytical grade.

2.1. Analytical method

The Ultra-violet spectrum of levetiracetam was recorded in the range of 200–400 nm in the solution of 0.1 N hydrochloric acid (pH 1.2). The wave length of maximum absorption (λ_{max}) in this range was found and the standard calibration curve was prepared at the wavelength 210 nm [10].

2.2. Preparation of different formulations of gastro retentive patch

The gastro-retentive patch was fabricated by solvent casting technique [11] by using different matrixing agent such as HPMC (A), Carbopol 934P (B), Xanthan gum (C). Hydrophobic polymer ethylcellulose was added commonly in all formulation in order to produce integrity and sustain effect. In polymeric solution the required amount of polymers were dissolved in distilled water and ethyl cellulose solution prepared with ethanol was added. Drug solution of levetiracetam was prepared in distilled water. Then the drug solution was incorporated into the polymer solution, propylene glycol used as a plasticizer and mixed thoroughly in the magnetic stirrer. Finally, this solution was transferred into a rectangular plate and kept for 24 h at room temperature for drying. After drying, the patches were stored in desiccators. Totally seven formulations F1, F2, F3, F4, F5, F6, and F7 were prepared using Simple lattice design. F1, F2, F3 (A, B, C) were prepared with individual concentration of which produces sufficient viscous solution selected from preliminary trails. F4, F5, F6 (AB, AC, BC) were prepared with half of the individual concentration and F7 (ABC) prepared with one third of all the factors (A, B, C). The equilateral triangle representing simple lattice design for 3 components, HPMC (A), Carbopol 934P (B) and Xanthan gum(C) (Fig. 1 & Table 1).

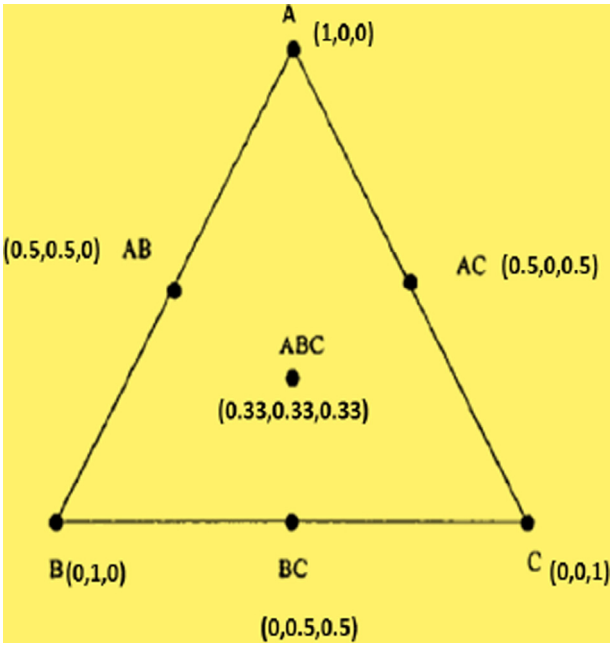

Fig. 1. Equilateral triangle representing simple lattice design for 3 components (A, B and C).

2.3. Characterization of gastro retentive patches

2.3.1. Weight variation

A weight variation test was conducted for ten patches (1 cm × 1 cm). The patches were weighed individually and their average weights and standard deviations were calculated [9]. The mean ± SD (n = 3) values were shown in Table 2.

2.3.2. Thickness

Patch thickness was determined by optical microscopy by taking transverse sections from different points within a patch and observing under ×100 magnification. The mean and standard deviation were calculated [12]. The mean ± SD (n = 3) values were shown in Table 2.

2.3.3. Folding endurance

The number of times the patch could be folded at the same place till it broke gave the value of folding endurance [11]. The values were shown in Table 2.

2.3.4. Swelling behavior

Swelling of Patches was examined in triplicates in 0.1 N HCl (pH 1.2) according to the following procedure. After recording the initial weight of the patch (W_1), it was immersed in 0.1 N HCl (pH 1.2) buffer solution maintained at 37 ± 0.5 °C. The weight at end of 120 min was recorded (W_2). The swelling index was determined by using the formula [13]. The mean ± SD (n = 3) values were shown in Table 2.

$$(W_2 - W_1)/W_1 \times 100$$

2.3.5. In vitro bioadhesion

Bioadhesion studies were carried out working on the principle of double beam physical balance [14]. The intestinal mucosa excised and washed, was tied tightly with the mucosal side upwards, using a thread over the protrusion in the Teflon block. It reaches the surface of the mucosal membrane and keeps it moist. This was then kept below left-hand setup of the balance. The patch was then stuck with a little moisture, onto the lower surface suspended from the left-hand side of the balance and was brought in contact with the mucosa placed on a block by removing the 5 g weight from the right pan of the balance. The balance was kept in this position for 3 min and then slowly weights were added to the right pan, till the patch separated from the mucosal surface. The excess weight on the pan i.e., total weight minus 5 g is forced required to separate the patch from the mucosa. This gave the mucoadhesive strength of the patch in g/cm^2. The mean ± SD (n = 3) values were shown in Table 2.

2.3.6. Unfolding study

The rectangular shaped patches were cut and folded in the zigzag manner before insertion into the hard gelatin capsule (size 00). Capsules were prepared and subjected to an *in vitro* dissolution

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