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Research paper

Montmorillonite-alginate microspheres as a delivery vehicle for oral extended release of Venlafaxine hydrochloride

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ABSTRACT

Extended release of drugs is extremely essential for patients who require medicinal treatment round the clock. Depressed patients are one of such patients who suffer from recurrent and chronic disorder requiring long-term treatment. The treatment for such disease lies in the use of anti-depressants. Venlafaxine hydrochloride (VF) is an effective third generation drug which is capable of inhibiting the reuptake of serotonin, norepinephrine and dopamine. This highly water soluble drug (534 mg/ml) has a short steady state elimination half-life of 4–5 h due to which this drug needs to be administrated 2 to 3 times in a day in order to maintain its required concentration in the blood plasma. The present study aimed at developing montmorillonite (Mt) alginate (ALG) biopolymeric composites as micro beads with 97% encapsulation efficiency for an oral extended release of VF. These micro beads were synthesized using in situ ion-exchange followed by ionotropic gelation technique. The *in - vitro* release profile of pure drug shows a rapid burst release followed by 100% cumulative release within 5.5 h and 3.5 h in the gastric and intestinal fluid respectively. Whereas, the *in - vitro* release profile of VF from Mt biopolymeric beads show substantially less burst release with cumulative release of 20% (over a period of 26 h) and 22% (over a period of 29 h) in the gastric and intestinal fluid respectively. The presence of clay not only reduces the burst effect but also results in extended release of drug. Thus, there is possibility of making a formulation for oral extended release dosage forms for Venlafaxine with better patient compliance as repeated intake (every 3–4 h) of drug will not be necessary.

1. Introduction

Depression patients generally require long–term treatment due to recurrent and chronic disorder behavior. The major symptoms of this disorder are feeling of guilt, hopelessness and lack of interest/pleasure in variety of activities. This psychological disorder has become a severe social problem which has gained concern across the world. The treatment for such disease lies in the use of anti-depressants [7,35,41].

Venlafaxine [1-{2-(dimethylamino)-1-(4-methoxyphenyl)-ethyl} cyclohexanol hydrochloride] is an effective third generation drug which is capable of inhibiting the reuptake of serotonin, norepinephrine and dopamine (drugs.com, [16,17,34]). This highly water soluble drug (534 mg/ml) has a short steady state elimination half-life of 4–5 h due to which this drug needs to be administrated 2 to 3 times in a day in order to maintain its required concentration in the blood plasma. The dose of VF ranges from 75 to 350 mg/day [21,22,72], . The drug formulations available in market includes immediate-release formulations which results side effects including nausea, insomnia, weakness and drowsiness and the extended release formulations which is expected to improve patient compliance and convenience in comparison VF immediate release, serious side effects of extended release formulation still persists suicide risk, especially in younger patients [14,44,50,66]. Moreover these formulations do not extend enough to cover time period as recommended [43]. These factors generate the need for better oral drug delivery vehicles for extended release of VF.

Several methods like pellet technique [38,65], adsorption and coating [44]; chitosan hydrogels [48], thermoplastic granulation [49] and tablets [1,15,51] microbeads [19,39] have been evaluated for the controlled release of VF. The microbeads technique using alginate seems interesting for extending the release of VF in systemic circulation by increasing the amount of drug available in gastrointestinal tract (GIT) as VF gets readily absorbed from upper GI tract.

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Sodium alginate (ALG), which are linear copolymers of b-D-mannuronate (M) and a-L-guluronate (G) residues in (1–4)-linkage, arranged in a blockwise pattern along the linear chain, have been widely used a delivery vehicle for extended release of various therapeutic agents [6,10,68]. The distinctive properties of ALG namely biodegradability, biocompatibility and nontoxicity make it a suitable carrier for drug delivery. Interestingly, Ca-cross linked ALG is pH sensitive. It is stable in low pH but swells and disintegrates in weakly basic solutions. This indicates that Ca-cross linked ALG systems have a great possibility to remain intact in gastric fluid (pH 1.2) and disintegrate in intestinal fluids (pH 7.4). Due to this property ALG has been used in many biomedical applications, mostly in the form of beads or matrix. However, the tensile properties of pristine ALG beads are poor. Hence to improve physical properties of ALG modifications with inorganic material like montmorillonite (Mt) can prove to be favorable for extended release preparations involving ALG.

Mt, a naturally occurring layered alumino silicate, has emerged as an attractive inorganic matrix which has gained a lot of importance from the researchers [9,25–27,31–33,53,57–61,67,69]. Mt possesses large specific surface area and large cation exchange capacity [5,54,55]. Also it belongs to GRAS (Generally Recognized as Safe) list of FDA-USA approved excipient material for drug delivery. The negative charge of alginate carboxyl groups can interact electrostatically with the positively charged sites existing at the edges of Mt [29,30,36,37,45]. Hence, combination of ALG and Mt are expected to decrease the drug release rate by increasing the drug adsorption capacity in the matrix.

A few reports on combination of Mt and ALG for the controlled release of proteins, vitamins, drugs like diclofenac, irinotecan, PPN [23,28–30,36,47,73]are available but to the best of our knowledge no report is present involving Mt and alginate micro beads for extended release of VF.

In view of the above facts, the objective of this work was to synthesize a delivery vehicle using Mt-ALG beads as host for extended release of VF with possibility of better patient compliance with intake of less number of doses.

2. Materials and methods

2.1. Materials

Montmorillonite KSF (Mt) was obtained from Sigma Aldrich (USA), Sodium Alginate (analytical grade, Sisco research laboratory), Venlafaxine hydrochloride (purity >98%) was gift sample from Ami life sciences Pvt. Ltd. Analytical grade ethyl acetate, hydrochloric acid, potassium chloride, sodium hydroxide, potassium dihydrogen phosphate, calcium chloride were obtained from MERCK (India). HPLC grade methanol, acetonitrile and water were obtained from MERCK (India).

2.2. Synthesis

2.2.1. Synthesis of VF-ALG beads and Mt-VF-ALG beads

In this study, Alginate-drug beads were prepared using ion gelation process. Initially 200 mg of sodium alginate (5 ml double distilled water) was dissolved and agitated on a magnetic stirrer for 30 min (REMI instruments). To this solution 20 mg drug was added and again stirred for 2 h. The resulting solution was then filled in a syringe and added into a 100 ml of 0.1 M $CaCl_2$ solution drop wise with constant stirring. The produced beads were allowed to harden by leaving them in $CaCl_2$ solution for 30 min and thereafter filtered washed twice with double distilled water. The supernatant and the beads thus obtained were used for the estimation of drug encapsulation efficiency. The beads were air dried and were further characterized using appropriate analytical techniques. The first step in the synthesis of Mt- drug-ALG beads involved preparation of alginate - Mt aqueous dispersion by addition of Mt dispersion in the aqueous solution of sodium alginate followed by same procedure as discussed above for the synthesis of VF-ALG beads (see Fig. 1).

2.2.2. Quantitative estimation of VF in $CaCl_2$ medium

The aqueous sample solutions of pure VF were prepared and their corresponding absorbance value was measured at 225 nm. A calibration graph was constructed to ensure the validity of Lambert-Beer's law for quantitative estimation of VF in the synthesized samples.

Quantitative estimation of the drug in each synthesized composite bead was calculated from the supernatant obtained after removal of beads using the standard calibration graph Fig. 2.

2.2.3. Stock solutions

Stock solution of 50 ppm VF (100 ml) was prepared in 0.1 M calcium chloride solution. This solution was diluted with 0.1 M calcium chloride solution to obtain standard solutions of 1.0–30.0 ppm concentration range.

The area under the peak as a function of concentration of the drug was found to be linear with the slope of 3.4×10^{-2} in the concentration range of 1–25 ppm at 225 nm ($R^2 = 0.9994$) Fig. 2. Hence for all the estimations, concentration of VF was kept below 30 ppm.

2.2.4. In-vitro release conditions

The drug release kinetics under in vitro conditions was performed using USP six stage dissolution rate test apparatus (DISSO 8000, Lab India, India) with the dialysis bag technique [25,26]. Simulated gastric fluid was prepared by mixing 250 ml of 0.2 M HCl and 147 ml of 0.2 M KCl (buffer solution of pH 1.2). Simulated intestinal fluid was prepared by mixing 250 ml of 0.1 M KH_2PO_4 and 195.5 ml of 0.1 M NaOH (buffer solution of pH 7.4). Dialysis bags were equilibrated overnight with the dissolution media prior to experiments. A known amount of sample is placed in the dialysis bag containing 5 ml of dissolution medium. The drug loaded dialysis bag was placed into the receptor compartment containing 500 ml dissolution medium (with constant stirring, 80 rpm) maintained at 37 ± 0.5 °C. An aliquot (5 ml) was withdrawn at regular interval of time followed by replenishment with equal volume of dissolution medium to maintain same volume and composition of the dissolution medium. The extracted aliquots were analyzed for its drug content using UV spectrometer and HPLC (calibration plot of standard drug solutions were prepared in the same releasing media).The above mentioned procedure is repeated for every sample (pure VF, VF- ALG beads and Mt-VF-ALG beads) in simulated gastric fluid and simulated intestinal fluid.

2.3. Characterizations

Powder X-ray diffraction (PXRD) patterns of samples were recorded on an X-ray diffractometer (Pan Analytical, Germany) using Cu Kα radiation ($\lambda = 1.5418$) generated at 40 kV and 40 mA as X-ray source 2–40° (2θ) and step angle 0.02°/s. Scanning electron microscopic images coupled with Energy dispersive X-ray analysis (SEM-EDX) of the samples mounted on a stub and coated with gold in a vacuum evaporator were recorded using a JEOL JSM-6610LV with electron energy of 15 kV. FTIR spectra was recorded with an FTIR spectrophotometer (Perkin Elmer, Spectrum BXFTIR Spectrometer) using the KBr (Merck, Germany) disc method.

Thermal analysis were carried out using TGA 2050, Perkin Elmer, samples were purged with dry nitrogen at a flow rate of 10 ml/min and temperature was raised from 20 to 700 °C at a rate of 5 °C/min.