Formulation and evaluation of Pregabalin microspheres

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Abstract

Microspheres play a very important role as particulate drug delivery system because of their small size and other efficient properties. Microspheres are characteristically free flowing solid powders, which consist of proteins or synthetic polymer, which are biodegradable in nature. The present study aimed to formulate and evaluate Pregabal in microspheres. Ionotropic gelation technique was employed for microsphere preparation using different ratios of ethyl cellulose polymer and drug. Prepared microspheres were evaluated for drug entrapment efficiency, micromeritic characters and *In vitro* drug release. The particle size of all the formulations were ranged between 152.2 to 142.9 µm. The entrapment efficiency was ranged between 78.95 to 82.14 %. Stability studies showed almost negligible changes in particle size, entrapment efficiency and drug release throughout the study period.

Keywords: Pregabalin, FTIR studies, Sodium alginate, Ionotropic gelation technique, *In vitro* drug release studies

Introduction

Microspheres are defined as solid, approximately spherical particles ranging in size from1to1000µm.They are made up of polymeric, waxy or other protective materials such as synthetic polymers (PLA, PGA) and modified natural polymers [1]. Pregabalin (S) - 3 - amino methyl hexanoic acid, is a structural analogues of γ-amino butyric acid (GABA). They constitute an important group of compounds that are used in the treatment of epilepsy and neuropathic pain. Pregabalin has been studied for use in a variety of disorders, including monotherapy in refractory partial seizures, diabetic neuropathy, surgical dental pain and other pain syndromes, postherpetic neuralgia, and social anxiety disorders [2]. The aim of this study was to prepare microspheres containing Pregabalin by ionotropic gelation method to achieve a controlled drug release profile and to study the effect of different formulation variables such as drug: polymer ratio and particle size, encapsulation efficiency, and its *In vitro* release behavior.

Materials

Pregabalin was obtained from Micro labs, HYD. Sodium alginate and tragacanth were procured from Synpharma Research Labs, Hyderabad, and other chemicals the reagents used were of analytical grade.

Methodology

Drug and excipient compatibility studies [3]

Drug excipients compatibility studies were performed to know the compatibility of excipient with drug at accelerated conditions. The study was conducted by preparing homogenous mixture of excipients with drug and filled in HDPE bags and LDPE bags. Glass vials were exposed to 600 C and 400C/75 %RH for 4 weeks and LDPE bags were exposed to 400C±75 %RH for 4 weeks. Samples were observed periodically for any physical change.

Preparation and evaluation of Pregabalin Microspheres

Selection of polymers for preparation of Microspheres

Polymers were used as excipients for drug formulations, and cellulose derivatives were also used for the formulation of Microspheres. In the present study, for the preparation of Microspheres of Pregabalin.

Preparation method of Microspheres [4]

Microspheres containing Pregabalin as a core material were prepared by Ionotropic gelation technique method.

Formulation table

Table 1: Preparation of Pregabalin Microspheres

Ingredients	F1	F2	F3	F4
Drug	75	75	75	75
Sodium alginate	250	500	-	-
Tragacanth	-	-	250	500

Evaluation of Microspheres [5, 6, 7]

Yield of Microspheres

The yield of Microspheres was calculated from the amount of Microspheres obtained divided by the total amount of all non-volatile components

$$\% \text{ Yield} = \frac{\text{Actual weight of the Microspheres}}{\text{Total weight of all non-volatile components}} \times 100$$

Particle size and shape

The particle size of the Microspheres was measured by optical microscopy. The eyepiece micrometer was calibrated using a stage micrometer and the calibration factor was used further in the calculation of the size of Microspheres. The Microspheres were finely spread over a slide and visualized under an optical microscope using an eyepiece micrometer. About 50 readings were taken at random and the mean ± standard deviation was calculated. The shape of the Microspheres was visualized and the photographs were taken with the aid of a binocular microscope.

Surface morphology of the Microspheres

The surface morphology of the Microspheres was studied with the aid of a Scanning Electron Microscope (SEM).

Drug entrapment efficiency (DEE)

The amount of drug entrapped was estimated by crushing 50 mg of Microspheres using mortar and pestle, and extracting drug with aliquots of 7.4 pH buffer repeatedly. The extract was transferred to a 100 ml volumetric flask and the volume was made up using7.4 pH buffer. The solution was taken in a beaker and sonicated in a bath sonicator for 2 hours. The solution was filtered and absorbance was measured after suitable dilutions spectrophotometrically at 280 nm against an appropriate blank.

The amount of drug entrapped in the Microspheres was calculated using the following formula –

$$\text{DEE} = \frac{\text{Amount of drug actually present}}{\text{Theoretical drug load expected}} \times 100$$

***In vitro* drug release study [8]**

In vitro drug studies were carried out for all formulations in Franz diffusion cell. Microspheres equivalent to 10 mg of Pregabalin were poured into1 ml aliquots were withdrawn at a predetermined intervals and equal volume of dissolution medium was replaced to maintain sink conditions. The necessary dilutions were made with 7.4 pH buffer and the solution was analyzed for the drug content spectrophotometrically using UV-Visible spectrophotometer (Lab India) at 272 nm against an appropriate blank. Three trials were carried out for all formulations. From this cumulative percentage drug was calculated and plotted against function of time to study the pattern of drug.

Stability studies [9]

The success of an effective formulation can be evaluated only through stability studies. The prepared Pregabalin Microspheres placed on plastic tubes containing desiccant and stored at ambient conditions, such as at room temperature, 40±2ºc and refrigerator 2-8ºc for a period of 3 months.

Results and Discussion

FT-IR Spectrum of Pregabalin

FT-IR Spectra of Pregabalin and F2 formulation were recorded. All these peaks have appeared in formulation and physical mixture, indicating no chemical interaction between Pregabalin and polymer. It also confirmed that the stability of drug during microencapsulation process.

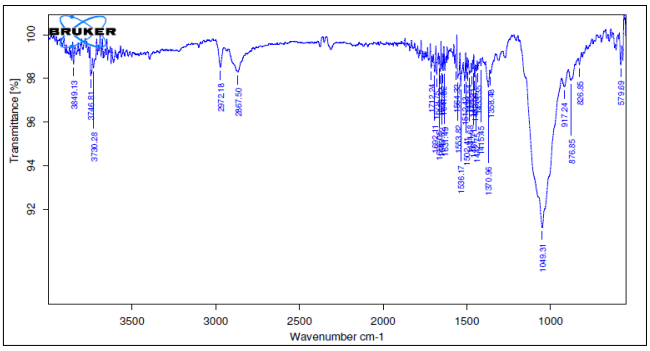

Fig 1: FTIR Studies of Pregabalin

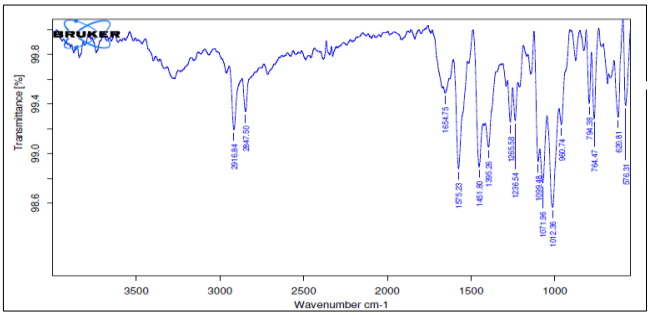

Fig 2: FTIR Studies of optimized formulation

Formulation and Evaluation of sustained release Microspheres of Pregabalin

Optimization of formulation variables

Therefore, the optimized conditions for the formulation of sustained release microspheres were:

Results of the evaluation parameters of formulated sustained release microspheres

The prepared sustained release microspheres were evaluated for various parameters such as yield, drug entrapment efficiency, particle size, and *In vitro* drug release. And effect of preparation and process variables such as drug polymer ratio, speed, type of polymer and combination of polymers on particle size, yield, entrapment efficiency, and *in-vitro* release of Pregabalin from sustained microspheres were also studied.

Table 2: Evaluation parameters of microspheres

Formulation code	%yield	Particle size	Drug Entrapment Efficiency
F1	81.26	125.2	79.83
F2	83.93	130.7	82.14
F3	80.12	142.9	78.95
F4	79.25	139.3	81.56

***In vitro* drug release studies**

Table 3: Cumulative %drug release for all formulations

TIME (hours)	F1	F 2	F3	F4
0	0	0	0	0
1	13.85	14.22	11.46	12.85
2	27.12	24.93	26.14	23.15
3	37.06	38.14	35.80	42.18
4	48.15	46.55	43.42	40.54
5	57.55	67.82	56.23	60.15
6	67.26	74.93	70.18	72.94
7	82.95	84.79	81.96	83.17
8	92.12	97.54	93.47	94.58

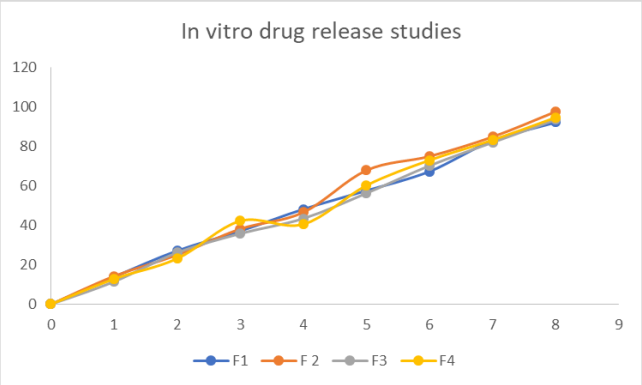

Fig 3: Cumulative percentage drug released Vs Time Curves of microspheres F1–F4 in P^H 7.4 buffer.

Here, keeping drug ratio constant and varied polymer ratio as the polymer concentration increases viscosity; this influences the interaction between disperse phase and dispersion medium that affects the size distribution of particle. And F2formulation shows good results when compared to other formulations.

Above graph indicates that %Drug release of F2 formulation shows better drug release when compared with other formulation.

Stability Study

There was no significant change in physical and chemical properties of the formulation F-2 after 3 Months. Parameters quantified at various time intervals were shown;

Table 4: Results of stability studies of optimized formulation F-2

Formulation Code	Parameters	Initial	1st Month	2nd Month	3rd Month	Limits as per Specifications
F-2	25^0C/60%RH % Release	97.54	97.12	96.37	95.78	Not less than 85 %
F-2	30^0C/75% RH % Release	97.54	97.02	96.48	95.84	Not less than 85 %
F-2	40^0C/75% RH % Release	97.54	97.15	96.30	95.24	Not less than 85 %

Characterization of microspheres

Surface topography by scanning electron microscopy (SEM)

Figure shows SEM photograph of optimized microspheres at 100× magnification, at 1000× magnification. SEM photographs showed discrete, spherical microspheres. SEM Photographs also showed the presence of drug crystal on the surface of microspheres revealing that the microspheres were having some rough surface**.** The drug crystals on microspheres were may be due to the presence of un entrapped drug in dispersion medium.

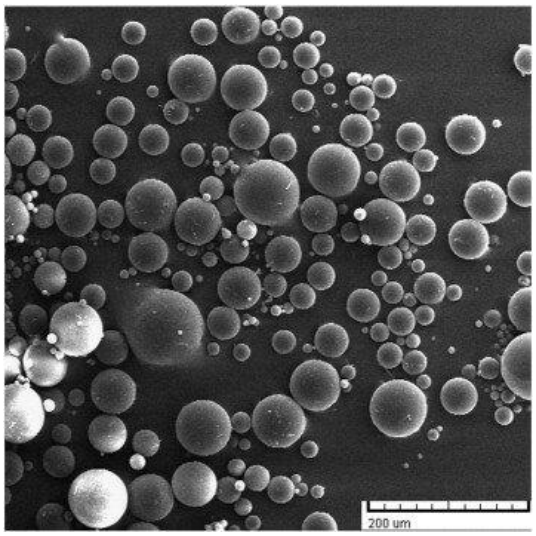

Fig 4: SEM photograph of Pregabalin microspheres

Conclusion

Pregabalin microsphere with Tragacanth and sodium alginate were successfully prepared by using ionotropic gelation technique. More than 80% yield was observed. The microspheres were freely flowing spherical in nature. The entrapment efficiency of sodium alginate microsphere was more as compared to other formulation. The entrapment efficiency increased with increase in drug concentration in both of die microspheres. The formed microspheres had smooth surfaces. IR spectroscopic study indicated no interaction of drug with polymer as well as no degradation of drug during preparation. The release of the drug ms satisfactory in both cases. The release was retarded up to 8 hrs. From all above results it can be here by concluded that the methods used for preparation were most suitable, no degradation occurred and release was prolonged to 8 hrs. Microspheres were found to be stable at room temperature. Finally it can be concluded that sustained release microspheres of Pregabalin can be prepared with ease and required release qualities can be controlled by varying the concentration of polymer.

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