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Formulation and Evaluation of Sustained Release Microspheres of Gabapentin by Solvent Evaporation Technique

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A B S T R A C T

Sustained release microcapsules of gabapentin, was developed to reduce the frequency of drug administration, ease of dose adjustment and improve patient compliance. In this study, sustained release microcapsules of gabapentin was prepared by solvent evaporation techniques using Eudragit RL/RS as polymer and particle size, encapsulation efficiencies and in vitro release of the fabricated microcapsules were evaluated. The results showed that the encapsulation efficiencies were desired for all the formulations of microcapsules developed. Particle sizes of the microcapsules were influenced by the concentration of Eudragit and stirring speed. From the results of the in vitro study shows that the desired release rate is achieved by the combination of Eudragit RL and Eudragit RS.

Keywords: Gabapentin, Sustained release, Eudragit

A R T I C L E I N F O

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1. Introduction

Conventional oral drug administration does not usually provide ratecontrolled release or target specificity. In many cases, conventional drug delivery provides sharp increase in drug concentration often achieving toxic level and following a relatively short period at the therapeutic level of the drug concentration eventually drops off until re-administration. In order to obtain maximum therapeutic efficacy, it becomes necessary to deliver an agent to the

target tissue in the optimal amount for the required period of time, thereby causing less toxicity and minimal side effects1. Natural polymers such as polysaccharides and its derivatives are widely used in pharmaceutical and food industry as biodegradable and biocompatibility. Alginate and pectin are the most extensively studied polysaccharides and has shown great potential as a drug carrier and large number of applications such as binding, thickening, emulsifying, gelling agent etc2. Microparticulate drug delivery systems are considered and accepted as a reliable one to deliver the drug to the target site with specificity, to maintain the desired concentration at the site of interest without untoward effects3. Microencapsulation is a useful method which prolongs the duration of drug effect significantly and improves patient compliance. Eventually the total dose and few adverse reactions may be reduced since a steady plasma concentration is maintained4.Gabapentin is used as an anticonvulsant to treat epilepsy, and currently is also used to relieve neuropathic pain 5. The Gabapentin has a biological half-life in the terminal phase (t1/2) of 5-7 h and the usual oral dosage regimen is 300mg7 taken two to three times a day, which necessitates dosing of immediate release formulations every 6 h. The aim of present study was to develop sustained release pharmaceutical formulation to reduce the dosing frequency and minimize the peak-to-trough fluctuations. Methacrylate copolymers (Eudragits) have recently received increased attention for modified dosage forms because of their inertness, solubility in relatively non-toxic solvents and availability of resins with different properties (14-16). Eudragit® RS and Eudragit® RL polymers are copolymers of poly (ethylacrylate, methyl-methacrylate and chlorotrimethyl ammonioethyl methacrylate), containing an amount of quaternary ammonium groups between 4.5-6.8% and 8.8-12% for RS and RL, respectlively [17]. The copolymer Eudragit RS PM® differs from Eudragit® RS 100 in that it contains 0.5% talc. Eudragit® RS and Eudragit® RL are insoluble in water and digestive juices, but they are permeable and both have pH-independent release profiles. The permeability of Eudragit® RS and RL in aqueous media is due to the presence of quaternary ammonium groups in their structure; Eudragit® RL has a greater proportion of these groups and as such is more permeable than Eudragit® RS.

2. Materials and Methods

Gabapentin (MSN pharmaceuticals, Hyderabad), Eudragit RS, Eudragit RL (S.D fine chemicals, India) were obtained from commercial sources. All other reagents used were analytical grade.

Methods

Preparation of microspheres

Gabapentin microspheres were prepared by solvent evaporation technique. Various proportions of polymers like Eudragit RS and Eudragit RL were dissolved in acetone. Gabapentin was powdered and dispersed in polymer solution. This solution was added slowly to a jacketed flask containing 300ml of petroleum ether and light liquid paraffin (40:60 w/w) and 1% w/w span 80 under constant stirring (400, 500 and 750 RPM). After evaporation of acetone, the microspheres formed were collected by filtration in vacuum, washed 3-4 times with 50ml of petroleum ether each and dried at room temperature for one day.

Table 1

Batch no	Drug (g) Gabapentin	Eudragit RS(g)	Eudragit RL(g)	Stirring speed (rpm)
1	0.3	0.3	---	600
2	0.3	0.3	---	900
3	0.3	--	0.3	600
4	0.3	0.6	---	600
5	0.3	0.6	---	900
6	0.3	0.9	---	600
7	0.3	0.9	---	900
8	0.3	---	0.6	600
9	0.3	----	0.6	900
10	0.3	---	0.9	600
11	0.3	---	0.9	900
12	0.3	0.4	0.25	900
13	0.3	0.5	0.2	900
14	0.3	0.8	0.1	900

Fourier Transform Infrared Spectroscopy (FTIR)

The drug-polymer interactions were studied by infrared spectroscopy to confirm the presence of any interaction between the polymer and drug. The polymer and drug were finely ground with KBr to prepare the pellets under a hydraulic pressure 600psi and spectra scanned between 500 and 3500cm-1.

Particle Size Analysis: [5]

Particle sizes of micro spheres were measured by a particle size analyzer. For this analysis, the sample was prepared by suspending 50mg of microspheres in 5ml of filtered distilled water containing 2% w/v of Tween 80 and then sonicating in a water bath for 3 mins to prevent aggregation between microspheres. The particle size was expressed as the volume mean diameter in micrometer.

Determination of Yield and Drug Content: [6,7]

The yields of the formulations were calculated by the ratio between the experimental weight of product and the sum of the weight of all components, discounting the weight of acetone and span 80. To determine the drug content, the microspheres were powdered and content equivalent to 30mg of gabapentin was transferred into 100ml volumetric flask. The contents was dissolved by using 0.01M sodium hydroxide solution and made up to 100 ml. From the above solutions, 5ml was diluted to 50ml using the 0.01M sodium hydroxide solution. The resulting solution was measured the absorbance at 210nm. The amount of gabapentin present in the fabricated microspheres was calculated by the reference standard of gabapentin

Microspheres morphology by scanning electron microscopy (SEM):

The morphology of the Microspheres surfaces was investigated using scanning electron microscopy. Microspheres were spread on a carbon double-adhesive layer on a metal holder and gold-coated using Ion-Sputtering device (100 and 50 A0 thickness respectively). The coated samples were then observed under a scanning electron microscope at 10Kv.

***In-vitro* Release** [8,9]

The release pattern of the gabapentin microspheres were determined by using USP XXV dissolution test apparatus. 900 ml of dissolution medium (0.1N HCl) was taken and maintained at the temperature of 37±5˚ C. gabapentin microspheres was accurately weighed and taken in each basket and rotated at 100 rpm. 5ml of sample was withdrawn at each time interval and made up to 100ml with dissolution medium. Absorbance was measured at 210 nm and the percentage release was calculated.

Kinetics of the *in-vitro* drug release

The kinetic parameters for the *in vitro* release of gabapentin were determined and then analyzed in order to find the drug release. Zero, first order kinetics, Higuchi diffusion and Mayer peppas were investigated**.**

3. Results and Discussion

The present study was taken to formulate and evaluate sustained release microspheres of gabapentin by solvent evaporation method. Various batches were made and these formulations are shown in table 1. When drug and polymer ratio was too low (1:1), no spherical particles were obtained. These results indicates that the amount of solid, thus the viscosity of the inner phase is and important factor for the formulation of microspheres. Spherical particles were obtained, when the polymer and drug ratio was increased (2:1, 3:1) at stirring speed 750rpm. But the shapes of particles in the above ratio were irregular. The average size of the microspheres was found as 250µm in all the formulations. The particle size distribution and mean particle size of the microspheres are shown in the fig.1. The yield of microspheres and encapsulation efficiencies were high for all the formulations and were not affected by the type of polymer and drug polymer ratio and stirring speed. The *in-vitro* releases of the drug from microspheres were studied at pH 1.2 using USP XXIV basket method. The results are given in the fig .2 and fig.3. From this study, it shows that the release rates were very slow in Eudragit RS and the release rate is fast in the microspheres made by Eudragit RL. So the combination of the polymers Eudragit RS and Eudragit RL gives desired release of drug from the microspheres.

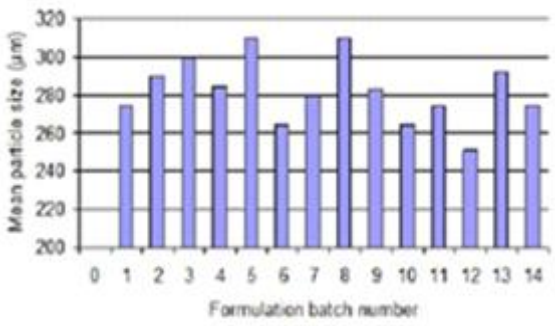

Figure 1

Table 1

Formulation Code	Particle size (µm)	% Yield	Swelling ratio	Entrapment efficiency	Drug Content
F1	1239.5±2.3	56±1.52	218±1.14	73.53+1.54	97.56±1.11
F2	1120±2.21	73±1.22	220±1.13	83.23+1.84	98.52±1.15
F3	1143.4±1.42	76±1.56	234±1.15	86.97+1.2	96.71±1.2
F4	1223.2±0.9	83±1.11	242±1.2	90.76+0.33	99.88±2.1
F5	1172.5±1.3	80±1.12	244±1.5	90.57+0.58	98.31±1.45
F6	1153±2.8	70±1.15	260±1.51	95.49+1.05	98.39±1.35
F7	1228.6±1.7	75±1.2	265±2.54	87.18+0.1	98.37±1.65
F8	1276±2.35	79±1.4	272±1.25	82.73+0.43	98.19±1.05
F9	1353.8±1.8	81±1.1	293±1.33	81.46+0.31	99.58±1.35

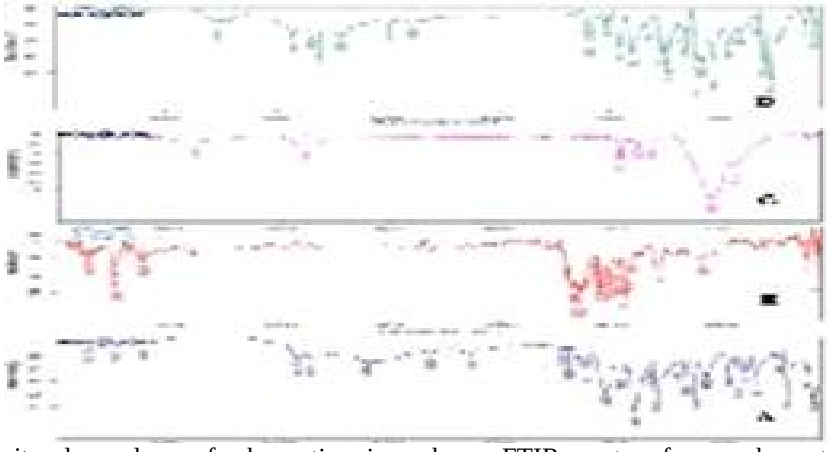

Figure 2: *In-vitro* drug release of gabapentin microspheres. FTIR spectra of pure gabapentin and polyme.

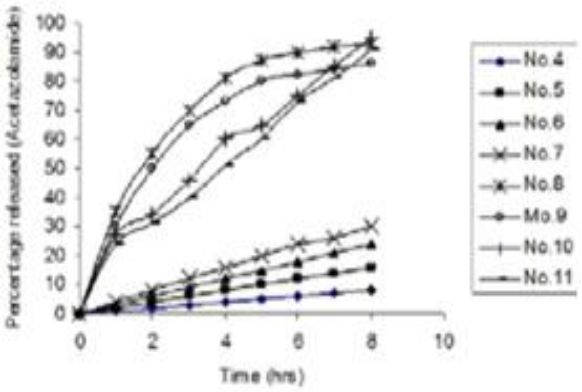

Figure 3

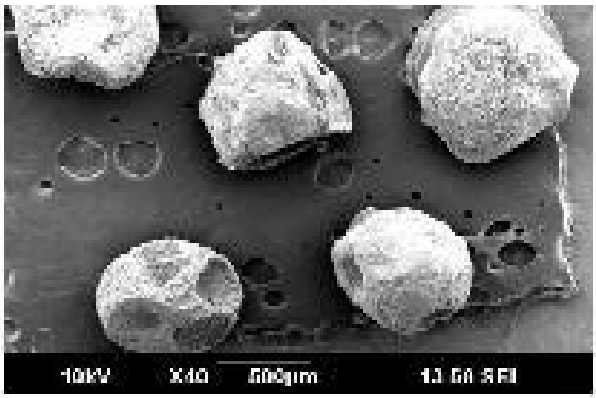

Figure 4: SEM of gabapentin microspheres

Table 2: Kinetics of gabapentin drug release from microspheres.

Formulation code	Zero order r^2	First order $_r2$	Higuchi's $_r2$	Korsmeyer Peppas
F1	0.926	0.864	0.986	0.659
F2	0.937	0.849	0.959	0.628
F3	0.952	0.792	0.951	0.57
F4	0.978	0.856	0.910	0.641
F5	0.954	0.837	0.944	0.619
F6	0.852	0.942	0.972	0.758
F7	0.884	0.886	0.969	0.71
F8	0.901	0.903	0.961	0.696
F9	0.928	0.925	0.964	0.723

4. Conclusion

The sustained release microspheres of gabapentin were successfully developed by solvent evaporation technique using Eudragit as polymers. From this study it is concluded that the drug polymer ratio and stirring speed were important for obtained desired spherical particles. The yield and encapsulation efficiencies are found to be high in all the

formulations. The release rate of gabapentin from the microspheres were depending upon the amount and type of polymers used. Microspheres containing Eudragit RS gives very slow release of drug whereas the desired release rate is achieved by combination of the Eudragit RS and Eudragit RL.

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