



Development and Evaluation of Pulsatile Release Capsules of Divalproex Sodium

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ABSTRACT

Aim of the present work was to formulate and evaluate pulsatile drug delivery system to achieve timed release of divalproex sodium which is a GABA transaminase enzyme inhibitor. General treatment of epilepsy and migraine disorders requires multiple dosing in order to maintain the plasma concentration of the drug. The pulsatile drug delivery system in the form of pulsing cap approach is attempted. The Pulsatile delivery system is capable of delivering drug when and where it required most. The pulsatile release of the drug was obtained by the cross linking of capsule body with formaldehyde to make it significantly insoluble. In order to sustain the release, HPMC, xanthan gum and eudragit were used as polymer plug with physical mixture of drug and diluents (dicalcium phosphate) in the ratio of 1:1:1. When the empty capsules were subjected to various physico-chemical tests, the results were found to be complied with the pharmacopoeial standards. The drug loaded capsules were evaluated for weight variation, content uniformity, disintegration and *in-vitro* dissolution. The formulation F2 (xanthan gum based) has showed 99.28% of drug release at the end of 12hrs and the other results were found to be satisfactory. Release kinetics indicated that the formulations followed Higuchi's model and exhibited non-fickian release mechanism. The capsules were found to be stable after subjecting to the stability studies.

Keywords: pulsatile release, divalproex sodium, HPMC, xanthan gum, eudragit.

INTRODUCTION

Pulsatile systems are gaining a lot of interest as they deliver the drug at the right site of action at the right time thus providing spatial and temporal delivery and increasing patient compliance. These systems are designed according to the circadian rhythm of the body. The pulsatile effect^{1,2} i.e., the release of drug as a "pulse" after a lag time has to be designed in such a way that a complete and rapid drug release should follow the lag time. Such systems are also called time controlled, as the drug released is independent of the environment. These systems are beneficial for the drugs having high first-pass effect, drugs administered for diseases that follow chronopharmacological behavior, drugs having specific absorption site in GIT, targeting to colon, and cases where night time dosing is required. In recent years considerable attention has been focused on the development of pulsatile drug delivery system. Oral controlled drug delivery systems are generally used due to convenient dosage form & it also releases drug in constant or variable rates^{3,4}. In these systems drug release generally occurs within therapeutic window for prolonged period of time, hence shows sustained release of drug from dosage form.

Epilepsy is a common chronic neurological disorder that is characterized by recurrent unprovoked seizures. These seizures are transient signs and/or symptoms due to abnormal, excessive or synchronous neuronal activity in the brain⁵.

Divalproex sodium is a stable compound, comprised of sodium valproate which is connected to valproic acid with

a coordinate bonding. It has been administrated in various conditions such as seizures, bipolar disorder, and migraine headaches⁶

The present investigation was aimed at developing PULSINCAP drug delivery system containing divalproex sodium with various polymers which give immediate as well as sustained release of the drug from the hard capsules cross linked with formalin.

MATERIALS AND METHODS

Divalproex sodium was obtained as gift sample from ROAQ Chemicals Pvt. Ltd. Vadodara. Dicalcium phosphate, HPMC, xanthan gum and eudragit were obtained from SD Fine chem. Ltd, Mumbai.

Preparation of Cross-Linked Gelatin Capsule

Formaldehyde treatment

About 100 hard gelatin capsules of size '0' were taken. Their body was separated from the cap and placed on a wire mesh. 25 ml of 37% formaldehyde solution was taken in a beaker and kept in an empty glass desiccators and to this 2.5 g of potassium permanganate was added. On the top of beaker a wire mesh containing the body of the capsule was kept and immediately the desiccator was tightly closed and sealed. The body of the capsule was made to react with formaldehyde vapours for 12 hrs. Then they were removed and kept on a filter paper and dried for 48 hrs to ensure completion of reaction between gelatin and formaldehyde vapors. Afterwards the capsules were kept in an open atmosphere, to facilitate removal of residual formaldehyde. These



capsule bodies were capped with untreated cap and stored in a polythene bag for further use.

Evaluation of formaldehyde treated capsules

The size '0' capsules chosen, had transparent body with red colored cap. They were lockable type, odourless, soft and sticky when touched with wet hand.

After treating with formaldehyde, there were no significant changes in the capsules except for the stickiness. The body of the capsule was hard and non-sticking even when touched with wet hand.

Solubility tests for formaldehyde treated capsules

The empty hard gelatin capsules were stirred vigorously in 100 ml of dissolution medium taken in 250 ml beaker, with magnetic stirrer.

The dissolution medium was buffers of different pH. The time at which the capsule dissolves or forms a soft mass was noted.

Physical characteristics of capsule bodies

Variation in dimensions between formaldehyde treated and untreated capsules were studied. The length and diameter of capsules were measured before and after formaldehyde treatment using caliper.

Chemical test

Qualitative test for free formaldehyde

Standard formaldehyde solution: Dilute a suitable volume of formaldehyde solution with water to give a solution containing 20 µg/ml of formaldehyde.

Sample solution: 25 formaldehyde treated bodies were cut into small pieces and taken into a beaker containing distilled water (40 ml). This was stirred for 1 hr with a magnetic stirrer, to solubilize the free formaldehyde. The solution was filtered into a 50 ml volumetric flask, washed with distilled water and volume was made up to 50 ml with washings.

Procedure

To 1 ml of sample solution in a test tube, add 4 ml of water and 5 ml of acetyl acetone solution, place the test tube in a water bath at 40°C for 40 min, at the same time reference solution is placed in the same manner using 1 mL of standard formaldehyde solution.

The sample solution is not more intensely colored than the standard solution inferring that less than 20 µg/mL of free formaldehyde is present in 25 capsules body.

Formulation of pulsatile release capsules

An accurately weighed quantity of divalproex sodium (125mg) was mixed with the diluent dicalcium phosphate in the ratio of 1:1 and kept separately. The different polymers were selected for the plugs and maintained the composition with respect to drug and diluent was 1:1:1 as shown in the table 1.

Filling of capsules

Hard gelatin capsules size '0' with formaldehyde treated body and untreated cap was taken for filling. The physical mixture of drug and diluents equivalent to 125mg of divalproex sodium was accurately weighed and filled into the treated bodies; this forms the second dose of the drug.

The quantity of the polymer was weighed and filled above the physical mixture, then pressed with a glass plunger. Similarly the first dose of the drug was filled into the untreated cap.

Finally the cap was locked into the capsule body and stored in tightly packed container for further studies.

Evaluation of drug loaded capsules

Various physico-chemical properties such as weight variation, content uniformity, disintegration and dissolution studies were determined on prepared capsules.

Weight variation

Ten capsules were selected randomly from each batch and weighed individually for weight variation. The test requirements are met if none of the individual weights are less than or more than 10% of the average.

Content uniformity

Ten capsules were weighed and average weight was calculated.

The content of all the capsules were emptied and powder equivalent to 100 mg of drug was dissolved in pH 7.4 phosphate buffer and the volume was made up to 100 ml with pH 7.4 phosphate buffer.

The solution was kept in sonicator for 1 hr. From the stock solution, 1ml solution was taken in 10 ml volumetric flask and the volume was made with pH 7.4 phosphate buffer. Solution was filtered and absorbance was measured spectrophotometrically at 210 nm against pH 7.4 phosphate buffer as a blank.

Disintegration test

Six capsules were placed in each of the six tubes of the basket. Perforated plastic discs were then placed on the top of the capsules and the buffer (pH 1.2) was used as dissolution media. Then the disintegration apparatus was operated and test was carried out for all the formulations.

In-vitro release profile

Dissolution studies were carried out by using rotating basket method where pH 1.2 buffer was used as dissolution medium for first 2hrs, followed by pH 7.4 buffer for 10 hrs. 5 ml of the sample was withdrawn from dissolution media at an interval of 1 hr and same amount replaced with fresh buffer. The absorbance was measured spectrophotometrically at 210 nm.



Drug release kinetics

The results of *in-vitro* release profile obtained for all the formulations were plotted in modes of data treatment as follows:-

Zero- order Kinetic model – Cumulative % drug released versus time.

First- order Kinetic model – Log cumulative % drug remaining versus time.

Higuchi's model- Cumulative percent drug released versus square root of time.

Korsmeyer equation/Peppas's model- Log cumulative % drug released versus log time.

Stability studies

The selected formulations were packed in an air tight polythene bag and stored at 60 °C and 45 °C for a period of 3 and 10 weeks respectively.

The samples were withdrawn at the end of 5th, 8th and 10th week in case formulations stored at 45 °C and 1st, 2nd and 3rd week the sample was collected in case of formulations stored at 60°C. All the samples were evaluated for any physical change, drug content, disintegration time and *In vitro* dissolution test.

RESULTS AND DISCUSSION

The pulsatile release capsules of divalproex sodium were obtained by cross linking of empty capsules by formalin treatment in order to modify the solubility of gelatin capsules.

All the empty capsules were of lockable type, odourless, soft and sticky when touched with wet finger. After formalin treatment, there were no significant changes in the capsules except for the stickiness. The body of the capsules was hard and non-sticky even when touched with wet hand.

Solubility tests for formaldehyde treated capsules

When the capsules were subjected to solubility studies in buffers of different pH, it was found that both the body and cap of untreated capsules dissolved within fifteen minutes whereas body of treated capsules remained intact even after 12 hrs.

Evaluation of formaldehyde treated capsules

The formaldehyde treated and untreated capsules were evaluated for the determination of physical characteristics like capsule length, diameter etc and the minor differences were found between the treated and untreated capsules. The results are tabulated in table 2.

Table 1: Formulation Development

Formulations	Drug: Polymer: Diluent (1:1:1)		
F1	Divalproex sodium	HPMC	Dicalcium phosphate
F2	Divalproex sodium	Xanthan gum	Dicalcium phosphate
F3	Divalproex sodium	Eudragit	Dicalcium phosphate

Table 2: Physical characteristics of capsule bodies

Parameter	Untreated body	Treated body
Capsule length (mm)	21.7	21.13
Diameter of capsule body (mm)	7.26	6.98
Length of capsule body (mm)	17.5	16.8
Percent moisture (%)	16.05	13.51

Table 3: Results of content uniformity

Formulations	Drug content (%)	Weight variation (mg)	Disintegration (min)	
			Untreated	Treated
F1	98.71	401.66 ± 6.5	14	No change
F2	99.56	406.66 ± 5.5	15	No change
F3	98.41	402.00 ± 7.0	14	No change

Qualitative test for free formaldehyde

The formaldehyde treated capsules were tested for the presence of free formaldehyde. It was found that the sample solution was not more intensely colored when compared with standard solution indicating that less than 20 µg of free formaldehyde was present in capsules.

Evaluation of drug loaded capsules

Weight variation

The results of weight variation test was found to be below 10% of all the capsules when complied with the USP specifications indicating that all the capsules were of uniform weight. Hence all formulation batches pass the test. The results are shown in the table 3.



Content uniformity

All the formulations were evaluated for their drug content uniformity according to the procedure to determine the amount of drug in all the formulation. The maximum percentage of drug is 99.56% in F2 formulation and minimum percent of 98.41% in F3 formulation. The results are shown in the table 3.

Disintegration test

The results of disintegration showed that all the capsules were disintegrated within 15 minutes, whereas the bodies of formalin treated capsules were remain intact. The results were shown in table 3.

In-vitro release profile

The dissolution test was carried out using 1.2 pH buffer for the first 2 hrs followed by 7.4 pH buffer for the next 10 hrs. The results showed that the formulations F1, F2 and F3 exhibited the release of the drug in 98.61%, 99.39% and 96.76% respectively at the end of 12 hrs. The formulation F2 containing xanthan gum as polymer plug showed maximum release at the end of 12 hrs. The release profile of all the formulation were shown in the Figure(1)

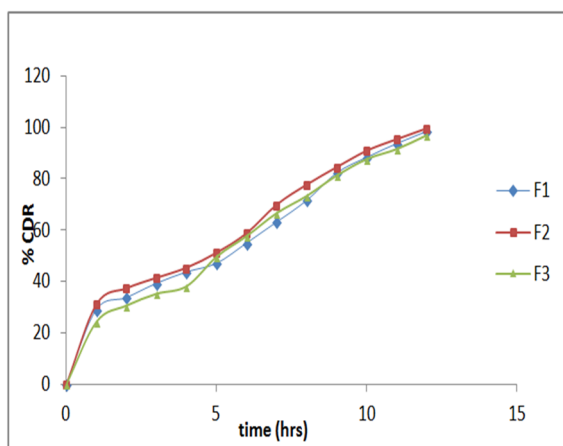


Figure 1: *In-vitro* release profile of various formulations

Drug release kinetics

The regression values of zero order kinetics of pulsatile release capsules of formulations F1, F2 and F3 were 0.9668, 0.9594 and 0.9778 respectively, and the first order kinetics were 0.7784, 0.8887 and 0.8036 respectively. When subjected to Higuchi's model, R^2 value for F1, F2 and F3 were found to be 0.9621, 0.9672 and

0.9544 respectively. Korsmeyer-peppas model showed R^2 value of 0.9535, 0.9331 and 0.9259 respectively for F1, F2 and F3 and 'n' value ranges from 0.5092 to 0.6069 indicating that the drug release was by non-fickian release mechanism.

Stability Studies

The stability studies showed that there was no significant changes in content estimation, disintegration time and dissolution profile.

CONCLUSION

The present work is an attempt to develop pulsatile release capsules of divalproex sodium where the body of the capsule is made insoluble by the treatment of formaldehyde to obtain pulsatile release of the drug. The second dose of the drug was filled into the insoluble body followed by polymer plug and the first dose was filled into the soluble cap. The polymer plugs used were HPMC, xanthan gum and eudragit. The results of evaluation tests were found to be satisfactory and all the values comply within the pharmacopoeial standards. *In-vitro* release profiles showed the drug release at the end of 12 hrs. When the *in-vitro* release data were fitted into kinetic models, it was found to follow Higuchi's model and drug release was by non-fickian mechanism.

REFERENCES

1. Sameer Sharma, Atmaram pawar, "Low density multiparticulate system for pulsatile release of meloxicam", *Int.j.pharm*, 313(1-2), 2006, 150-158.
2. Rathod Shruti. "Colon targeted pulsatile drug delivery: A Review", *Pharmainfo net*, 5(2), 2007, 33-66.
3. Shweta Arora, Ali.J, Alaka Ahuja, Sanjula Baboota and Qureshi.J, "Pulsatile drug delivery system: An approach for controlled drug delivery", *Indian. Pharm. Sci*, 688(3), 2006, 295-300.
4. Sachin Survase, Neeraj Kumar. "Review of pulsatile drug delivery: Current scenario", *CRIPS2007*; 8(2), 27-33.
5. Manivannan R, Balasubramaniam A, Parthiban KG, Gandhi R, Senthilkumar B and Senthilkumar N. Formulation Development And Evaluation Of Divsodium Extended Release Tablet. *Int J Pharm & Pharmaceutical Sci*. 2(3), 2010, 83-85.
6. Monajjemzadeh F, Hamishehkar H, Zakeri-Milani P, Farjami A and Valizadeh H. Design and Optimization of Sustained-Release Divalproex Sodium Tablets with Response Surface Methodology. *American Association of Pharm Sci*. 2012.

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