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FORMULATION AND EVALUATION OF EXTENDED RELEASE MATRIX TABLETS OF LEVETIRACETAM

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ABSTRACT

For extended release drug delivery systems, the oral route of drug administration has, by far received more attention as it is natural uncomplicated, convenient and safer route. Matrix tablets composed of drug and release retarding material (e.g. polymer) offer the simplest approach in designing the extended release system. Long-term adherence to anti-epilepsy drug (AED) regimens is frequently suboptimal. Poor adherence to therapy is associated with a number of negative consequences, including an increase in patient seizures and mortality. The present study was aimed to study the effect of Chitosan and Sodium Alginate on the release rate Levetiracetam for the preparation of extended release formulations. Matrix Tablets were prepared by wet granulation method and subjected for Physiochemical and *in-vitro* evaluation tests. The results were shown that the prepared were found to be within the pharmacopeial limit and with good release characteristics.

KEYWORDS: Levetiracetam, Chitosan, Sodium Alginate, Extended release, Matrix Tablets.

INTRODUCTION

The oral route is the most popular route used for administration of drugs, which is due in part to the ease of administration and to the fact that gastrointestinal physiology offers more flexibility in dosage form design than most other routes. The terms Sustained release, prolonged release, modified release, extended release or depot formulations are used to identify drug delivery systems that are designed to achieve or extend therapeutic effect by continuously releasing medication over an extended period of time after administration of a

single dose.[1]

Epilepsy is defined as the repeated occurrence of sudden, excessive and/or synchronous discharges in cerebral cortical neurons resulting in disruption of consciousness, disturbance of sensation, movements, impairment of mental function, or some combination of these signs. The terms epilepsy, seizure and convulsion are not synonymous. A seizure always is a symptom of abnormal function in the central nervous system (CNS) rather than a disease in itself. A seizure discharge may be initiated in an entirely normal cerebral cortex by a variety of acute insults, such as withdrawal from alcohol, low blood sodium, or certain toxins. Seizures are to be distinguished from epilepsy, which is a chronic condition in which seizures occur repeatedly due to an underlying brain abnormality which persists between seizures. A convulsion is a forceful involuntary contraction of skeletal muscles. A convulsion is a physical manifestation of a seizure, but the term is inappropriate as a synonym for epilepsy when epilepsy may consist only of a temporary alteration of conscious-ness or sensation.[2]

MATERIALS AND METHODS

The drug Levetiracetam [3,5-diamino-6-(2,3-dicholorophenyl)-1,2,4-Triazine] was received as a gift sample from cadchem laboratories, Chandigarh , India. Acetone LR from SD finechem ltd, Mumbai. Hydrochloric acid and Methanol from Merck, Mumbai. All the other materials like Chitosan, Sodium lauryl sulphate, Sodium chloride, Potassium chloride, Lactose monohydrate, Potassium Dihydrogen Orthophosphate and Talc were purchased from Central drug house, New Delhi.

Preparation

Tablets were prepared by Wet Granulation method. In this method Chitosan and Sodium alginate are used as Matrix former and Lactose as diluents.[3] Taking into account various formulation variables like drug and polymer concentration seven formulations were prepared, named as F1, F2, F3, F4, F5, F6 and F7. All the formulations were characterized for their physiochemical parameters and in-vitro release studies.

Ingredients used in formulation

S.NO	INGREDIENTS	FORMULATION (mg)						
		F1	F2	F3	F4	F5	F6	F7
1	Levetiracetam	200	200	200	200	200	200	200
2	Chitosan	200	100	100	100	100	100	90
3	Lactose	100	200	100	100	50	75	50

4	Purified water	q.s	q.s	q.s	q.s	q.s	q.s	q.s
5	Talc (2%)	10	10	10	10	10	10	10
6	Sodium alginate	-	-	100	-	100	75	100
7	Microcrystalline cellulose	-	-	-	100	50	50	60
	Total	510	510	510	510	510	510	510

Preformulation Studies

Powder was evaluated for organoleptic characters and identified by using UV and FT-IR analysis. Drug- Excipient compatibility study was carried out by FT-IR studies. The solubility of Levetiracetam was studied in buffers of different pH range (pH 1.2, pH 6.8 and pH 7.4) at room temperature, by shake flask method.[4]

Evaluation Parameters

Physio-Chemical Characteristics

The prepared tablets were subjected to various tests to measure the various parameters like Weight variation, Hardness, Friability and Thickness. The tests were carried out as per Indian Pharmacopoeia and the observed values were checked for the pharmacopoeial limits where ever applicable.[5]

Drug Content Determination

About 3 tablets were powdered in a mortar and powder equivalent to 100 mg of Levetiracetam was taken in a 100 ml volumetric flask. The powder was dissolved in a minimum volume of methanol and then volume was further adjusted with methanol. The solution was filtered through whatmann filter paper (No.1). Then the solution was further diluted as per requirement and analyzed spectrophotometrically at 275 nm.[6]

Swelling-Index Determination

The extent of Swelling was measured in terms of % weight gain by the tablet. Three tablets from each formulation were kept in Petri dishes containing pH 6.8 phosphate buffer. At the end of one hr tablets were withdrawn, soaked with tissue paper, and weighed. At the end of second hr the process was repeated and weights of tablets were noted. Then for every 2 hr. weights of tablets were noted, and the process was continued till the end of 12 hrs.[7] Percent weight gain by tablet was calculated by using the following formula;

Swelling Index (SI) = {(Mt-Mo)/Mo} x 100, Where, S.I = Swelling Index

Mt= weight of tablet at time t Mo= weight of tablet at time t=0

In-vitro Dissolution Test

The in vitro dissolution study was carried out using USP Type 2 dissolution apparatus. The study was carried out in 900 ml of 0.1N HCl buffer (pH 1.2) for first 2 hours and then 900 ml of phosphate buffer (pH 6.8) from 3 to 12 h. The dissolution medium was kept in thermostatically controlled water bath, maintained at 37+0.5□c. The pre-weighed tablet was then introduced into the dissolution jar and the paddle was rotated at 75 rpm. At different time intervals, 5 ml sample was withdrawn and analyzed spectrophotometrically at 274 nm for the drug release. At each time of withdrawal, 5 ml of fresh corresponding medium was replaced into the dissolution flask.[8]

RESULTS AND DISCUSSION

Drug-Excipient compatibility was carried out by FT-IR analysis. Initially the IR spectrum of pure drug was obtained. After that various admixtures of drug with other excipients like Guar gum, HPMC, MCC and Lactose were prepared and IR Spectra were obtained. The obtained spectra of physical admixtures were observed for major peaks of drugs. The results of this observation were concluded that there is no interaction between the drug (Lamotrigene) and other excipients**.**

All the formulated tablets met the pharmacopoeial standard of uniformity of the weight, percentage friability, thickness and drug content. The values were within the limit.

Drug Content Determination

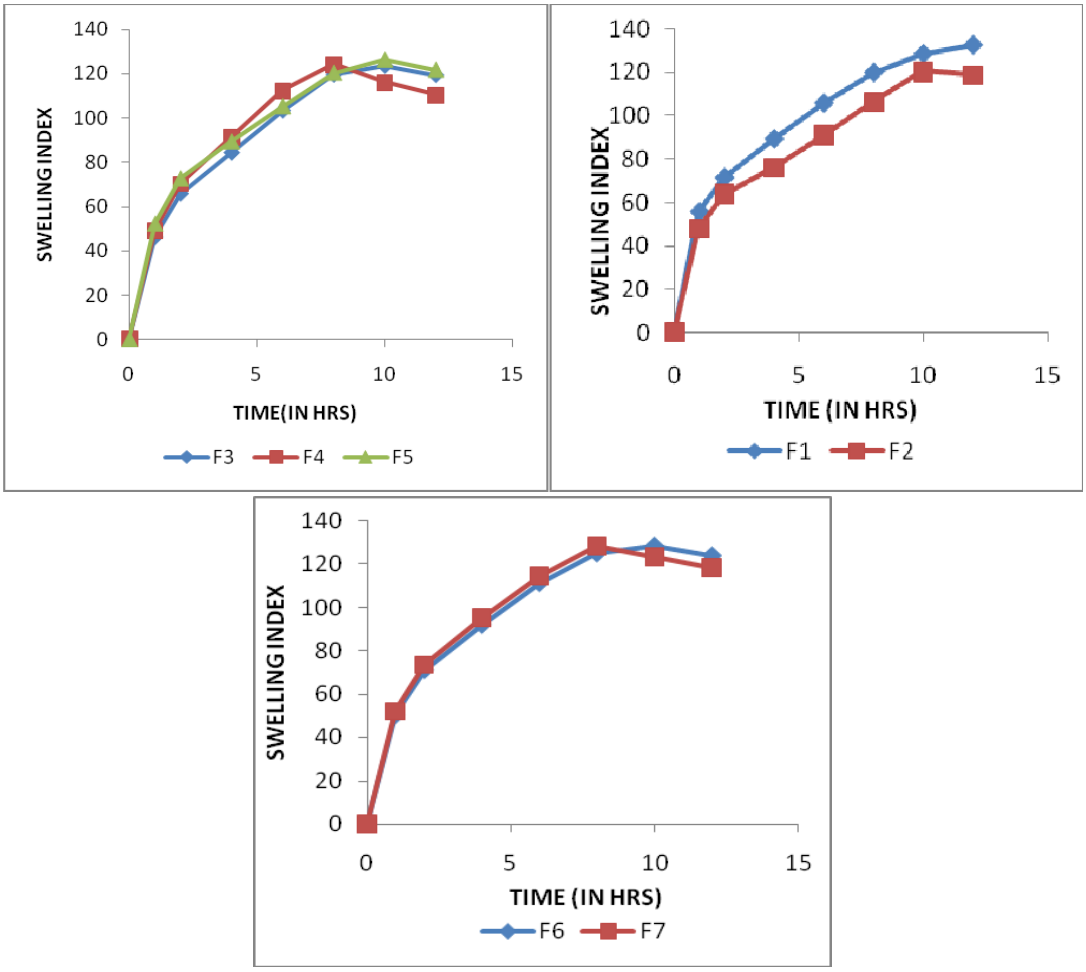
Formulationcode no	F1	F2	F3	F4	F5	F6	F7
Drug content*	99.93 ±0.87	99.88 ±0.52	100.79 ±0.33	101.69± 1.24	99.29± 0.76	101.34± 1.15	100.51± 0.74

Physical parameters of Levetiracetam matrix tablets

Formulations	Average weight (mg)	Hardness (Kg/cm^2)	Friability (%)	Thickness (mm)
F1	511.2±2.263	6	0.33	4.3
F2	509.35±3.372	6	0.21	4.3
F3	510.53±2.192	6	0.13	4.2
F4	511.13±1.311	6	0.18	4.3
F5	512.11±1.863	6	0.23	4.2
F6	509.66±2.312	6	0.17	4.2
F7	510.73±2.341	6	0.12	4.2

The results of swelling behavior study of Lamotrigene matrix tablets were shown in the Figure. Except in the case of F1 (Drug: Polymer used in the ratio of 1:1), the swelling was

reduced after 8 hrs (F4, F7) or after 10 hrs (F2, F3, F5 and F6). In case of F1 there was no reduction in swelling index even up to 12 hrs. This may be due to the fact that the gum content is higher in it and hence a thicker rigid swollen matrix layer. In case of other formulations (F2-F7) depending upon the quantity of microcrystalline cellulose and lactose, the swelling index was reduced, due to the erosion of swollen gel layer.

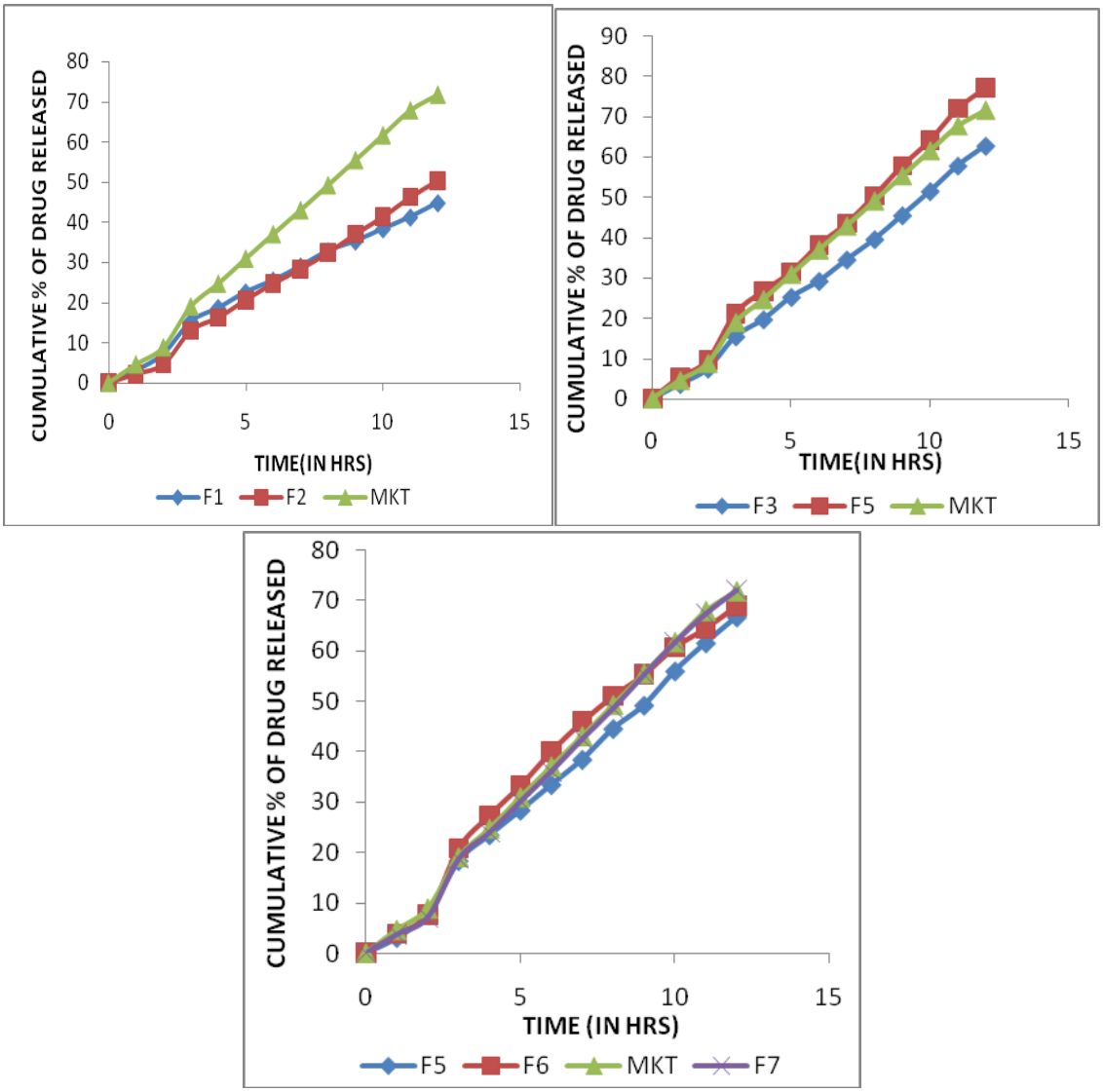


Graphical representation of swelling behavior of Levetiracetam Matrix Tablets

Fig. Swelling behavior of Levetiracetam Matrix Tablets F1,F2, F3,F4,F5, F6 & F7.

All the formulations showed a low drug release in 0.1N HCl buffer (3-9% of drug) due to low solubility of Levetiracetam in the acid medium (pH 1.2).But the drug release in third hour was more when the dissolution medium was changed to phosphate buffer (pH 6.8) from acid buffer. This may be due to the fact that the drug released from the matrix may get accumulated in the surface of tablet in first two hours because of low solubility of drug in the acid medium and when the medium was changed to phosphate buffer, the drug may get released suddenly because of high solubility or high sink condition obtained. Similar results have been reported in the previous studies.[9] After that a sustained and drug release in the

range of 50% to 72% was displayed by all the formulations. Various kinetic models were used to describe the release kinetics of all formulations. All the formulations were found to follow zero-order than first order. The release profiles of all formulations and marketed product were analyzed by statistically (student-t test) and by model independent approach (difference factor, f1 and similarity factor, f2).



DISSOLUTION PROFILES OF FORMULATIONS & MARKETED PRODUCT

CONCLUSION

Extended release matrix tablets of Levetiracetam were prepared by wet granulation method. The pre- compression parameters like bulk density, tapped density, Carr's index and Hausner's ratio of granules were found to be within the limit and the results indicated that the granules were with good flow properties. Various kinetic models were used to describe the release kinetics of all formulations. All the formulations were found to follow zero-order

than first order. The release profiles of all formulations and marketed product were analyzed by statistically (student-t test) and by model independent approach (difference factor, f1 and similarity factor, f2). From the FT-IR analysis of pure drug and physical admixtures of drug with other excipients, it was found that there was no interaction between Levetiracetam and other excipients. From the above results, it was concluded that Chitosan may be used as a matrix former for the preparation of extended release matrix tablets of Levetiracetam, either alone or in combination with sodium alginate and with other excipients like microcrystalline cellulose and lactose.

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