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DESIGN AND EVALUATION OF LEVETIRACETAM EXTENDED RELEASE PELLETS

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ABSTRACT

The purpose of the present investigation was to prepare oral Pellets of levetiracetam with a view to reduce the frequency of dosing and to attain steady state drug levels in addition to masking the bitter taste and faint odor of drug. Levetiracetam is a second-generation antiepileptic agent useful in the treatment of partial onset and myoclonic seizures, which has short plasma half-life of 7 ± 1 hour in adults along with bitter taste and faint odor. Pelletization is one of the suitable drug delivery system for such drug candidate. Preformulation studies were carried out to rule out any drug-polymer interactions by FTIR technique, Pellets were prepared by using Extrusion- Spheronization process. and coating is carried out using FBD, Stability studies were carried out for the optimized formulation for a period of 90 days at 40 ±2 °C and 75 ± 5% relative humidity. mean particle size ranged from 989µm to 1011µm and percentage yield ranged from 93.34-98.12 % In the in vitro release studies initial burst release was observed from all the formulations. The most satisfactory formulation released drug for 24hours. SEM studies of the most satisfactory formulation showed that the pellets were spherical. The data obtained from in vitro release showed highest correlation with Higuchi model and the drug release was found to be Zero order.

KEYWORDS: Levetiracetam, Pellets, FTIR, Extrusion- Spheronization, Release kinetics, SEM.

INTRODUCTON

A Drug may be defined as an agent, intended for use in the diagnosis, mitigation, treatment, cure or prevention of disease or disorder in man or in other animals

Drugs are rarely administered in their original pure state. They are administered in different dosage forms after converting them in to a suitable formulation every dosage form is a combination of the drug and different kinds of nn-drug components (polymers) also called as additives, they are used to give a particular shape to formulation and to increase stability.

Drug Delivery Systems

The treatment of acute diseases or chronic illness has been achieved by delivery of drugs to the patients for many years. A number of oral dosage forms are available. Some are liquids (e.g., syrups, elixirs, tinctures, suspensions, and emulsions), whereas the most common ones are solids (e.g., tablets & capsules). Tablets and like modified-release dosage forms have been developed to release the drug at a controlled rate. The purpose is generally either to avoid contact with gastric fluids (acidic environment) or to prolong drug input in systemic circulation.capsules are generally formulated to release the drug immediately after oral administration to hasten systemic absorption. These are called immediate- release products. Other products like modified-release dosage forms have been developed to release the drug at a controlled rate. The purpose is generally either to avoid contact with gastric fluids (acidic environment) or to prolong drug input in systemic circulation.\

These drug delivery systems include tablets, Parenteral, suspensions, creams, ointments, liquids and aerosols. Today these conventional drug delivery systems are widely used. The term drug delivery can be defined as techniques that are used to get the therapeutic agents inside the human body.

1. Conventional Drug Delivery system
2. Controlled Drug Delivery system

1. Conventional Drug Delivery System

These therapies require periodic doses of therapeutic agents. These agents are formulated to produce maximum stability, activity and bioavailability. For most drugs, conventional methods of drug administration are effective, but some drugs are unstable or toxic and have narrow therapeutic window. Conventional forms often cause problems to the patient, because

they maintain therapeutic drug level for only brief duration. This gives rise to sharp fluctuations of drug levels in plasma and in tissue. In such cases, a method of continuous administration of therapeutic agent is desirable to maintain fixed plasma levels.

To overcome these problems, controlled drug delivery systems were introduced into the market. These delivery systems have a number of advantages over traditional systems such as improved efficiency, reduced toxicity and improved patient convenience. The goal of controlled drug delivery systems is to improve the effectiveness of drug therapies. Conventional dosage forms are rapidly absorbed, with the ascending and descending portions of the concentrations versus time curve reflecting primarily the rate of absorption and elimination, respectively. Because of the rapid rate of absorption from conventional dosage forms, drugs are usually administered more than once daily, with the frequency being dependent on biological half life ($t_{1/2}$) and duration of pharmacological effect.

Disadvantages of conventional drug delivery system

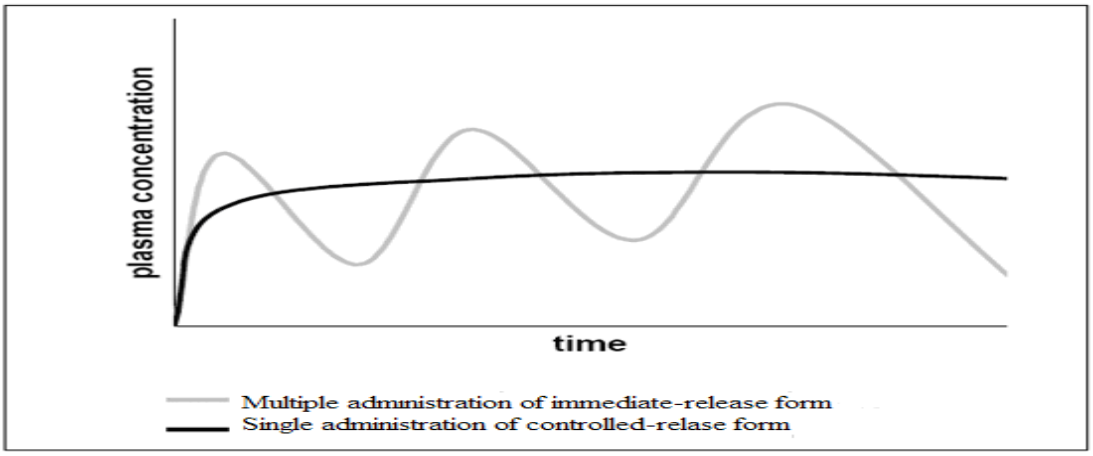
- ✓ In Conventional oral drug delivery systems, there is little or no control over the release of the drug and effective concentration at the target site can be achieved by intermittent of excessive doses.
- ✓ The dosing pattern in Conventional dosage forms results in constantly changing, unpredictable and often sub-therapeutic plasma concentrations, leading to marked side effects in some cases.
- ✓ The rate and extent of absorption of drug from conventional formulations may vary greatly, depending on the factors such as physicochemical properties of the drug, presence of excipients, various physiological factors such as the presence or absence of food. pH of the gastrointestinal motility and so on.

1. Controlled release drug delivery system

Oral route still remains the most popular for drug administration by virtue of its convenience to the patient. A sizable portion of orally administered dosage forms, so called conventional, are designed to achieve maximal drug bioavailability by maximizing the rate and extent of absorption. Whilst such dosage forms have been useful, frequent daily administration is necessary, particularly when the drug has a short biological half life. This may result in wide fluctuation in peak and trough steady-state drug levels, which is undesirable for drugs with marginal therapeutic indices. Moreover, patient compliance is likely to be poor when patients need to take their medication three to four times daily on chronic basis. Fortunately, these

shortcomings have been circumvented with the introduction of controlled release dosage forms. These dosage forms are capable of controlling the rate of drug delivery, leading to more sustained drug levels and hence therapeutic action as outlined in Fig.1.

During past few decades, significant advance have been made in the area of controlled release as evidenced by an increasing number of patents, publication, as well as commercial controlled release products for the delivery of variety of pharmaceutical compounds. With a controlled release formulation a predictable and reproducible release rate can be achieved, at the target site for desired duration. This results in optimum biological response, prolonged efficacy, decreased toxicity as well as reduction in required dose levels as compared to the conventional mode of delivery (Wilding *et al*., 1991).



Schematic drawing of plasma concentration-versus-time profiles following administration of three immediate-release dosage forms versus one single controlled-release dosage form

The first truly effective oral drug delivery system, the "Spansule" was introduced in the 1950s. This prolonged release system was marketed by SmithKline & French Laboratories and consisted of small coated beads placed in a capsule (*US Patent* No. 2738303).

Matrix tablets which were prepared by compressing granules to form matrices appeared in 1959 (*British Patent* No. 808014). The inherent drawback of the matrix system is its first order release behavior. For most controlled dosage forms zero order release may be the "holy grail". To overcome the inherent preponderant first order release behavior with continuously diminishing release rate from matrix systems, geometry factors have been utilized to compensate for the increasing diffusional distance and decreasing area at the penetrating

diffusion front generally encountered in matrix system. Geomatrix is a delivery device, in the form of a multi-layer tablet, proposed for constant drug release. It consists of matrix core, containing the active ingredient, and one or two impermeable or semi-permeable polymeric barriers compressed on one or both faces of the core. These barrier layers provide a modulation of the drug dissolution profile; they reduce the release rate from the tablets and are shown to be effective in obtaining zero order release (Colombo *et al*., 1989; Colombo *et al*., 1990; Colombo *et al*., 1992; Conte *et al*., 1992; Conte *et al*., 1993; Conte *et al*., 1994).

A geomatrix system has few advantages. A conventional high-speed tableting machine can be used to produce geomatrix tablets with a high degree of product consistency and uniformity. This system can be applied to a wide range of drug molecules, including some with poor water solubility and can target the site of release. The major advantage of this system being its ability to control the rate of drug diffusion throughout the release process, ensuring 100% release of the active drug. Moreover, the geomatrix technologies can improve drug efficacy and enhance patient compliance.

Advantages and disadvantages of controlled release delivery system

Controlled release technology may provide increased clinical value as well as extended product life. The advantages of an ideal controlled release dosage form over an immediate release product include improved patient compliance due to a reduced dosing frequency, a decreased incidence and/or intensity of the side effects, greater selectivity of pharmacological activity and more prolonged therapeutic effect as well as an increase of cost effectiveness.

However, the controlled release dosage forms also possess some disadvantages. Potential disadvantages of controlled release dosage form include the possibility of dose dumping, less facile dose adjustment, increased potential for hepatic first-pass metabolism, possible delay in onset of action and possibly poor system availability.

MATERIALS AND METHODS

Drugs and Chemicals

Levetiracetam(Hetero Pharmaceuticals Ltd, Hyderabad, India.), Hydroxypropyl methyl cellulose(Molychem Ltd, Mumbai, India) Microcrystaline cellulose(S.D. Fine Chemicals Pvt Ltd, Mumbai), Polysorbate 80(Molychem Ltd, Mumbai, India) Crpss povidone(S.D.Fine Chemicals Pvt Ltd, Mumbai) Cross caramellose sodium (S.D. Fine Chemicals Pvt Ltd, Mumbai)Tri ethyl cetrate(S.D. Fine Chemicals Pvt Ltd, Mumbai), Propylene

glycol(Molychem Ltd, Mumbai, India), Acrylic acid*(*S.D. Fine Chemicals Pvt Ltd, Mumbai), Magnesium oxide(S.D. Fine Chemicals Pvt Ltd, Mumbai), Sodium hydroxide*(*S.D. Fine Chemicals Pvt Ltd, Mumbai

Methods

Preformulation study

Levetiracetam was characterized for organoleptic properties vis. State, color,odor,taste. Micromeritics properties like Bulk density, Tapped density, Carr's index, Hausner ratio, Angle of repose were determined as per official methods. Solubility was determined in different media like in water, 0.1 N HCl, Acetate buffer pH 4.5, and phosphate buffer pH 6.8 (Lachman,).

Interferance study

Interference study was performed to check whether the drug is compatible with excipients or not. The drug and excipients must be compatible with one another to produce a product that is stable, efficacious, attractive and easy to administer and safe. Drug- Excipients compatibility studies were performed by physical observation. Physical observation of sample was done every month for any color change or lumps formation and also Drug - Excipients compatibility studies were performed by FTIR (Fourier transform infrared) spectroscopy. FTIR spectra were obtained on a Perkin-Elmer using the KBr Disc Method (2 mg sample in 200 mg KBr) and Nujol Mull Technique. The scanning range was 4000 to 450 cm^{-1}, the resolution was $1cm^{-1}$. FTIR absorption spectra of pure drug and all the Excipients were carried out.

Formulation of Levetiracetam

Core pellets was prepared by extrusion and spheronization method. The required quantity of levetiracetam was weighted and sifted through sieve 30, Microcrystalline cellulose, disintigrant (crosspovidone or crosscarmelose sodium), sodium carbonate, sodium lauryl sulphate, hydroxyl propyl methyl cellulose were weighted accurately and sifted through sieve, and blend was prepared. Antitacking agents talc and magnesium steareate were passed through sieve 60 Hydroxyl propyl methyl cellulose was dissolved in purified water. And It is used as granulating fluid for granulation. The required quantity of Hydroxyl propyl methyl cellulose, PVPK30, and plasticizer were weighed and dispersed in purified water with the help of overhead stirrer for over a period of 10 min. Pigment suspension was prepared by dissolving magnesium oxide \ titanium dioxide, color, in a sufficient volume of purified water

by using homogenizer. The pigment suspension was added in HPMC solution then specified volume of Isopropyl alcohol was added and continuous stirring for another 5 minutes Prepared coating suspension was sprayed on core pellets in fluid bed processor. The coating was carried out with the help of bottom spray. The coating was continuous until 5% build up was achieved.

Composition of Levetiracetam Pellets

INGREDIENTS	F1	F2	F3	F4	F5	F6	F7	F8
Levetiracetam	500g	500 g	500 g	500g	500 g	500 g	500 g	500g
Microcrystaline cellulose	2.5%	5%	7.5%	10%	15%	20%	25%	2.5%
Lactose mono hydrate	2.5%	5%	7.5%	10%	15%	20%	25%	2.5%
Polysorbate 80	-	-	-	-	1%	2%	3%	2.5%
Sodium luryl sulphate	-	1%	2%	3%	-	-	-	2.5%
Cross Povidone	-	-	-	-	2.5%	5%	7.5%	2.5%
Cross caramellose sodium(ccs)	-	2.5%	5%	7.5%	-	-	-	2.5%
HPMC	1%	1%	1%	1%	1%	1%	1%	1%
Sodium carbonate	5%	5%	5%	5%	5%	5%	5%	5%
Binder solution	5%	10%	15%	20%	25%	30%	35%	40%
Total weight	555g	597.5 g	640 g	682.5g	697.5 g	765 g	832.5 g	605g

Binder solution : HPMC + Purified water

Micromeritics evaluation

Micromeritic properties of granules like bulk density, tapped density, Angle of repose, Carr's index, and Hausner's ratio were measured and compared with the micromeritics property of API.

Physical evaluation of levetiracetam

Extended Release tablets prepared were evaluated for the following official parameters: Weight variation, hardness, thickness, friability and drug content were measured.

In-vitro Dissolution Study

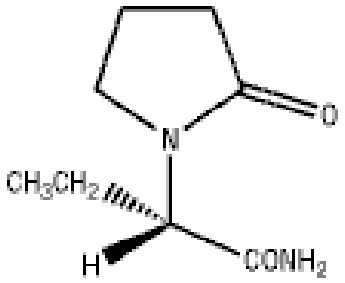
The USP type II rotating Paddle method was used to study the drug release from the Capsule Containing pellets. The capsules were kept in sinkers for stopping floating property. The dissolution medium contained 900 ml of phosphate buffer pH 6.8. The release study was performed at 37 ± 0.5^0 C, with a rotation speed of 50 rpm. Aliquots (5ml each) were withdrawn at regular time intervals and replaced with fresh medium. The samples were filtered, after making appropriate dilutions with phosphate buffer pH 6.8 and were analyzed U.V spectrophotometrically at 217 nm.

Dissolution Parameters

Apparatus	USP Type II(Paddle)
Medium	pH 6.8 Phosphate buffer
Quantity	900ml
R.P.M	50 rpm
Temperature	37 ± 0.5^0c

Kinetics for Drug Release

To find out the mechanism of drug release from hydrophilic matrices, the *in-vitro* dissolution data of each formulation with different kinetic drug release equations. Namely Zero order: $Q=K_0t$; Higuchi's square rate at time: $Q=K_Ht^{1/2}$ and Peppas: $F=K_mt^n$, where Q is amount of drug release at time t, F is Fraction of drug release at time t, K_0 is zero order kinetic drug release constant, K_H is Higuchi's square root of time kinetic drug release constant, K_m is constant incorporating geometric and structural characteristic of the films and n is the diffusion exponent indicative of the release mechanism. The correlation coefficient values (r^2) indicate the kinetic of drug release was zero order. The mechanism of drug release was by peppas model indicates the non fickian release and super case II transport evidenced with diffusion exponent values (n).



Levetiracetam

Stability study

The formulation F5 was selected and the stability studies were carried out at accelerated condition of $40^oC\pm2^0C/75\pm5\%$ RH conditions, stored in Thermolab. The pellets were analyzed periodically for their physical appearance and *in-vitro* drug release.

Study	Storage condition	Minimum time period covered by data at submission
Long term	25°C ± 2°C/60% RH ± 5% RH or 30°C ± 2°C/65% RH ± 5% RH	12 months
Intermediate	30°C ± 2°C/65% RH ± 5% RH	6 months
Accelerated	40°C ± 2°C/75% RH ± 5% RH	6 months

Product identification

PARAMETER	STANDARD	OBSERVED
Appearance	Full White	Full White
Texture	Amorphus	Amorphus
Solubility	Freely soluble in water	Freely soluble in water
State	Solid	Solid
Melting point	112-115^{0}c	112^{0}c
% Purity	99.99%	98%
λ max	217nm	217nm

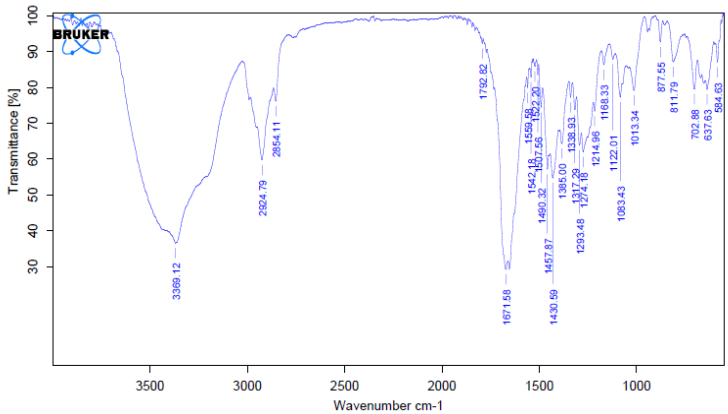
Micromeritic parameters

API (Levetiracetam)	Obtained values
Angle of repose	43.72^0
Bulk density gm/cc	1.565
Tapped density gm/cc	1.621
True density gm/cc	1.415
Particle size µm	13.20
Carr's index	27.74
Compressability index	27.36
Hausner's ratio	2.74
Drug content (%)	98.3

Analytical Observation

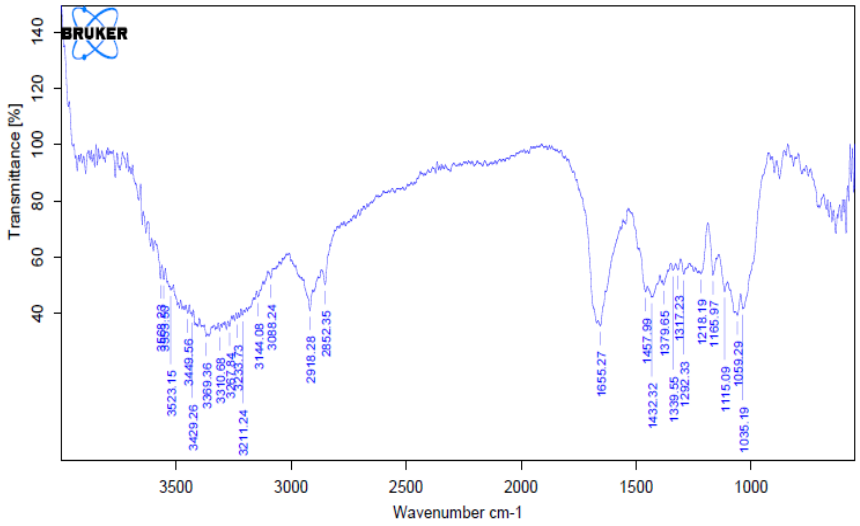
Drug - Excipients compatibility studies were performed by FTIR (Fourier transform infrared) spectroscopy. FTIR spectra were obtained on a Perkin Elmer using the KBr disc method (2 mg sample in 200 mg KBr) and Mull technique method (nujol). The scanning range was 4000 to 450 cm-1 and the resolution was 1 cm^{-1}. FTIR absorption spectra of pure drug and all the excipients and the combination of drug and polymer were shows no significant interaction between drug and polymers.

LEVETIRACETAM



Spectra: FTIR spectra for Levetiracetam

LEVETIRACETAM FORMULATION



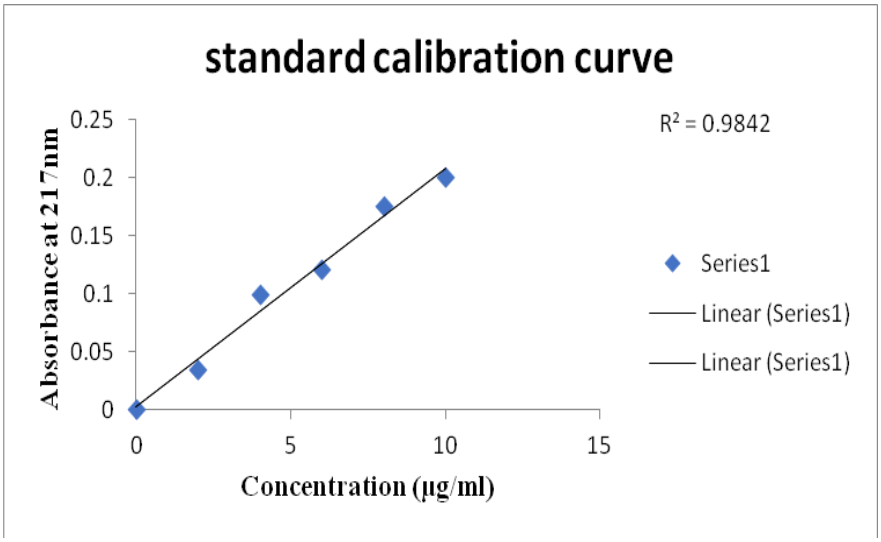
Spectra:FTIR spectra for Levetiracetam Formulation

CONSTRUCTION OF STANDARD CALIBRATION CURVE

- **Construction of Calibration Curve in 6.8 pH phosphate buffer**

Concentration (µg/ml)	Absorbance (217 nm)
0	0.000
2	0.0345
4	0.0996
6	0.1205
8	0.1760
10	0.2003

Calibration curve data for levetiracetam in 6.8 pH phosphate buffer

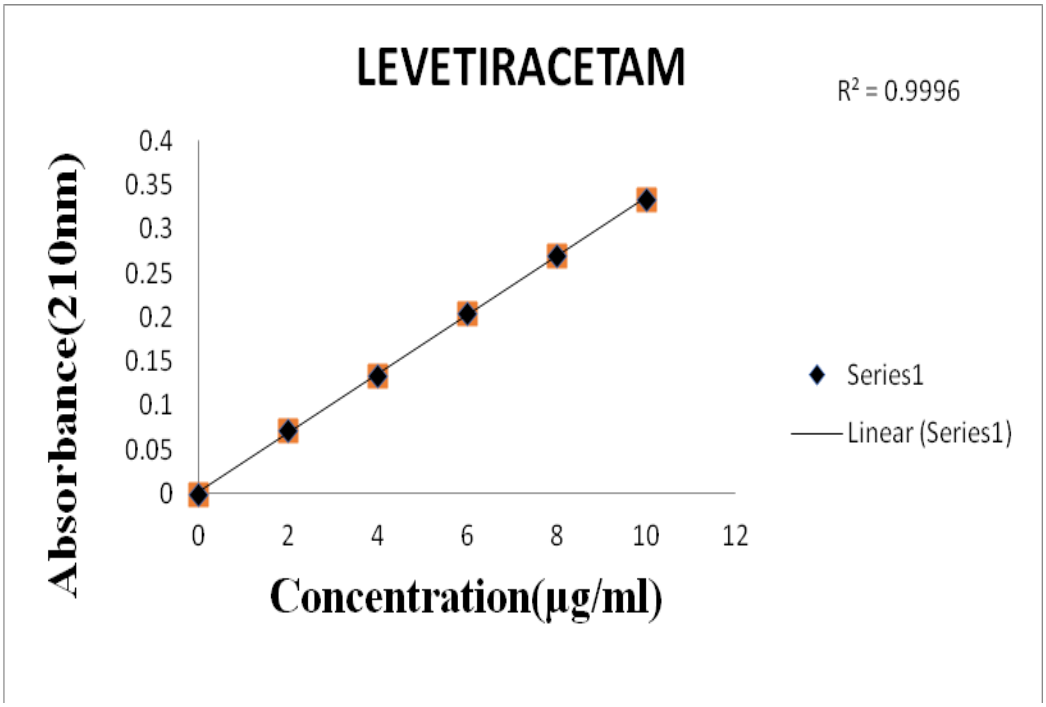


Calibration curve of Levetiracetam in 6.8 pH posphate bufer

➢ **Construction of Calibration Curve in 0.1 N HCl**

Concentration (µg/ml)	Absorbance at (217 nm)
0	0.000
2	0.072
4	0.134
6	0.205
8	0.271
10	0.334

Calibration curve data for levetiracetam in 0.1 N HCl



Calibration curve of Levetiracetam in 0.1 N HCl

Physico- chemical Evaluation of Extended release pellets

Formulation Cod	Weight variation (mg)	Thickness (mm)	Friability (%)	Drug Content (%)
F1	754	1.11	0.31	97.44
F2	757	1.16	0.46	96.89
F3	754	1.24	0.66	98.36
F4	755	1.20	0.48	98.10
F5	756	1.18	0.55	98.72
F6	753	1.23	0.67	97.65
F7	756	1.28	0.43	98.43
F8	754	1.16	0.64	98.28

STABILITY STUDIES FOR OPTIMISED FORMULA

Stability studies were carried out for the optimized formulation under specified conditions

ASSAY

Time	Test (%)	Temperature 40°C / 75% RH
0 Days	Assay	98.6
15 Days	Assay	98.4
30 Days	Assay	98.3
45 Days	Assay	98.1
60 Days	Assay	98.1

Stability of Assay for the optimized formula

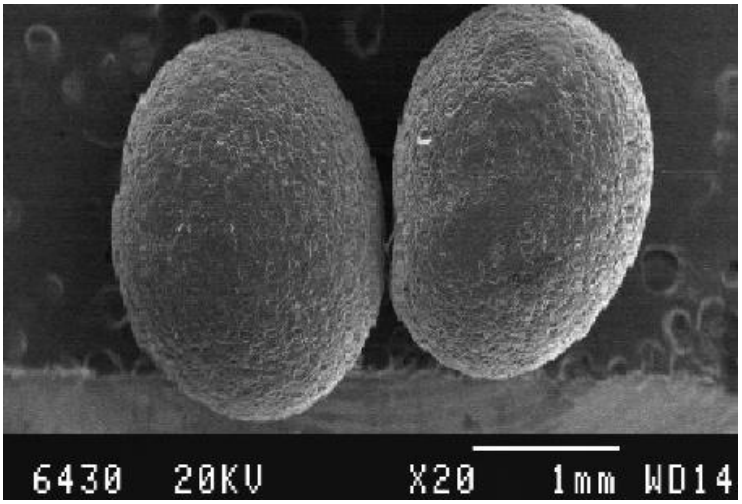
PHYSICAL APPEARANCE & IN-VITRO DRUG RELEASE

PARAMETER	0 DAYS	15 DAYS	30 DAYS	45 DAYS	60 DAYS
Physical Appearance	No Change	No Change	No Change	No Change	No Change
In-Vito Drug release	98 %	96.9 %	96.6%	96.5%	96.2%

Stability of physical appearance & in-vitro drug release for the optimized formula

SEM (Scanning Electron Microscope)

SEM photomicrograph showed that the pellets were spherical in nature and had a smooth surface when they cured after 24 hrs at 40 °C.The amount of surface drug determined by loose surface crystal study was found to be minimal



SEM photo graph of Pellets

SUMMARY AND CONCLUSION

- The present study was to formulate and evaluate Extended release pellets of Levetiracetam.
- The formulation process was carried out by using extrusion % sphironization technique and with the help of FBD for coating.

- Levetiracetam is a BCS Class I drug, it is highly soluble in water and have a short half life is 7±1 hr, also having bitter taste ,faint odour and it requires high amount of doses in chronic state of Epilepsy (500-3000 mg/day).
- To treat the chronic conditions repeated administration of drug is necessary, this may leads to patient non-compliance.
- The better compliance of the patient may achieved by minimising the dosage regimen by means of modified drug delivery systems.
- The present study extended release formulation is modified release drug delivery system which may increase the half life of the drug.
- To minimise the dose dumping prone by modified release dosage forms when use large doses multiple unit particulate system is benfecial.
- That's why I used to prepare pellets more over pellets are an optimum dosage form for overcoming dysphagia, a problem common in gastric and pediatric population as well as in case f un cooperative patients or un availability of water.
- In addition, the enhanced distribution of pellets reduces the probability of in creased topical API concentration and thus local irritation effects on the GI mucosa are reduced
- By the palletisation mask the bitter taste and faint odour and also increase the better appearance to patients by using different colours
- This study includes preformulation of drug & excipients, formulation, evaluation % stability studies.
- The core matrix pellets of Levetiracetam was prepared by using extrusion & sphironization method and further subjected to coating with extended release polymers Ethyl cellulose .
- The concentration between 10-30% give the better extended drug release and 20% concentration shows the better in-vitro drug release.
- During the coating plastisizers like TEC, PG are used for good film forming capacity.
- Extended release coated pellets were evaluated for assay, dissolution and F5 was optimised.

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