Research Article

DEVELOPMENT AND IN VITRO CHARACTERIZATION OF EXTENDED-RELEASE TABLETS OF LEVETIRACETAM

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ABSTARCT

The aim of the present study was to develop an extended-release formulation of Levetiracetam to maintain constant therapeutic levels of the drug for over 12 hrs. Various grades of polymethacrylate polymers and ethyl cellulose were employed as polymers. Levetiracetam dose was fixed as 500 mg. Total weight of the tablet was considered as 900 mg. Polymers were used in the concentration of 60, 90 and 180 mg concentration. All the formulations were passed various physicochemical evaluation parameters and they were found to be within limits. Whereas from the dissolution studies it was evident that the formulation (F6) showed better and desired drug release pattern i.e.,96.10 % in 12 hours. It followed zero order release kinetics mechanism.

Keywords: Levetiracetam, Eudragit RL 100, Eudragit Rs 100, Ethyl cellulose, extended-release tablets.

INTRODUCTION

ORAL DRUG DELIVERY

Most conventional oral drug products, such as tablets and capsules, are formulated to release the active drug immediately after oral administration, to obtain rapid and complete systemic drug absorption. Such immediate-release products result in relatively rapid drug absorption and onset of accompanying pharmacodynamic effects. However, after absorption of the drug from the dosage form is complete, plasma drug concentrations decline according to the drug's pharmacokinetic profile. Eventually, plasma drug concentrations fall below the minimum effective plasma concentration (MEC), resulting in loss of therapeutic activity. Before this point is reached, another dose is usually given if a sustained therapeutic effect is desired. An alternative to administering another dose is to use a dosage form that will provide sustained drug release, and therefore maintain plasma drug concentrations, beyond what is typically seen using immediate-release dosage forms.

The term modified-release drug product is used to describe products that alter the timing and/or the rate of release of the drug substance. A modified-release dosage form is defined "as one for which the drug-release characteristics of time course and/or location are chosen to accomplish therapeutic or convenience objectives not offered by conventional dosage forms such as solutions, ointments, or promptly dissolving dosage forms as presently recognized". Several types of modified-release drug products are recognized:

1. *Extended-release drug products*. A dosage form that allows at least a twofold reduction in dosage frequency as compared to that drug presented as an immediate-release (conventional) dosage form. Examples of extended-release dosage forms include controlled-release, sustained-release and long-acting drug products.

2. *Delayed-release drug products*. A dosage form that releases a discrete portion or portions of drug, at a time or at times other than promptly after administration, although one portion may be released promptly after administration. Enteric-coated dosage forms are the most common delayed-release products.

3. *Targeted-release drug products*. A dosage form that releases drug at or near the intended physiologic site of action. Targeted-release dosage forms may have either immediate- or extended-release characteristics.

Modified-release drug products are designed for different routes of administration based on the physicochemical, pharmacologic and pharmacokinetic properties of the drug and on the properties of the materials used in the dosage form. Several different terms are now defined to describe the available types of modified-release drug products based on the drug release characteristics of the products.

Route of Administration	Drug Product	Examples	Comments
Oral drug products	Extended release	Diltiazem HCl extended release	Once-a-day dosing.
	Delayed release	Mesalamine delayed- release	Coated for drug release in terminal ileum.
	Oral mucosal drug delivery	Oral transmucosal fentanyl citrate	Fentanyl citrate is in the form of a flavored sugar lozenge that dissolves slowly in the mouth.
Transdermal drug delivery systems	Transdermal therapeutic system (TTS)	Clonidine transdermal therapeutic system	Clonidine TTS is applied every 7 days to intact skin on the upper arm or chest.
	Iontophoretic drug delivery		Small electric current moves charged molecules across the skin.
Ophthalmic drug delivery	Insert	Controlled-release pilocarpine	Elliptically shaped insert designed for continuous release of pilocarpine following placement in the cul-de-sac of the eye.
Parenteral drug delivery	Intramuscular drug products	Depot injections	Lyophylized microspheres containing leuprolide acetate for depot suspension.
		Water-immiscible injections	Medroxyprogesterone acetate (Depo-Provera®)
	Subcutaneous drug products	Controlled-release insulin	Basulin is a controlled-release, recombinant human insulin delivered by nanoparticulate technology.

ORAL CONTROLLED RELEASE DRUG DELIVERY SYSTEMS

Oral ingestion is traditionally preferred route of drug administration, providing a convenient method of effectively achieving both local and systemic effects. In conventional oral drug delivery systems, there is very little control over release of drug. The effective concentration at the target site can be achieved by intermittent administration of grossly excessive doses, which in most situations, often results in constantly changing, unpredictable and often sub or supra therapeutic plasma concentrations leaving the marked side effects.

Oral controlled release drug delivery is a system that provides continuous oral delivery of drugs at predictable and reproducible kinetics for a predetermined period throughout the course of GI transit and also the system that target the delivery of a drug to a specific region within the GI tract for either a local or systemic action.

An ideal oral drug delivery system should steadily deliver a measurable and reproducible amount of drug to the target site over a prolonged period. Controlled release (CR) delivery system provides a uniform concentration or amount of the drug at the absorption site and thus, after absorption allow maintenance of plasma concentrations within a therapeutic range, which minimizes side effects and also reduces the frequency of administration.

In order to overcome the drawbacks of conventional drug delivery systems, several technical advancements have led to the development of controlled drug delivery system that could revolutionize method of medication and provide a number of therapeutic benefits.

Advantages of Controlled Drug Delivery Systems:

- Maintenance of plasma drug concentration within an optimal therapeutic range for prolonged duration of treatment.
- More consistent and prolonged therapeutic effect is observed.
- Maximization of efficiency-dose relationship.
- Employ less total drug than that in combined conventional dosage forms.
- Reduction of adverse side effects.
- Minimization of the need for frequent dose intake.
- Improved patient compliance.
- Improves control of condition i.e., reduced fluctuation in drug level.
- Minimize or eliminate local side effects
- Minimize drug accumulation with chronic dosing.
- Make use of special effects, e.g. Sustained-release aspirin for morning relief of arthritis by dosing before bed time.
- Economy i.e. reduction in health care costs. The average cost of treatment over an extended time period may be less, with lesser frequency of dosing, enhanced therapeutic benefits and reduced side effects.

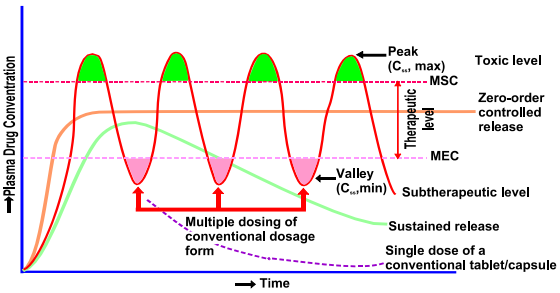


Fig 1.1 - A hypothetical plasma concentration-time profile from conventional multiple dosing and single doses of sustained and controlled delivery formulations. (MSC = maximum safe concentration, MEC = minimum effective concentration).

Disadvantages of Controlled Drug Delivery Systems:

- Increased variability among dosage units.
- Poor in vitro – in vivo correlation.
- Toxicity due to dose dumping may occur when more than usual fraction is being released.
- Retrieval of drug is difficult in case of toxicity, poisoning or hypersensitivity reactions.
- More rapid development of tolerance.
- Need for additional patient education and counselling.
- Reduced potential for dose adjustment of drugs normally administered in varying strengths.

SELECTION OF DRUG CANDIDATE FOR SUSTAINED RELEASE DOSAGE FORM

The physio - chemical properties of the drug such as pKa, partition coefficient, biological half-life, molecular weight, dose of the drug etc., have to be considered before selection.

Characteristics of drugs suitable for formulation as Sustained Release Products

1. Exhibit moderate rates of absorption and excretion.
2. Uniform absorption throughout the gastrointestinal tract.
3. Administered in relatively small doses.
4. Possess good margin of safety.
5. Used for treatment of chronic therapy.

Characteristics of drugs unsuitable for formulation as Sustained Release Products

1. Not effectively absorbed in the lower intestine (Riboflavin).
2. Absorbed and excreted rapidly i.e. short biological half lives, less than one hour (Penicillin G, Furosemide).
3. Long biological half lives greater than 12 hours (Diazepam, Phenytoin).
4. Large doses required, 1gm (Sulphonamides)
5. Drugs with low therapeutic index (Phenobarbital, Digoxin).
6. Precise dosage titrated to individuals required (anticoagulants)
7. No clear advantage for sustained release formulation (griseofulvin)

METHODOLOGY

Analytical method development:

a) Determination of absorption maxima:

A solution containing the concentration 10 µg/ ml drug was prepared in 0.1N HCl and pH 6.8 Phosphate buffer UV spectrums was taken using Double beam UV/VIS spectrophotometer. The solution was scanned in the range of 200 – 400.

b) Preparation calibration curve:

100mg of Levetiracetam pure drug was dissolved in 100ml of 0.1 N HCl (stock solution)10ml of solution was taken and make up with100ml of 0.1 N HCl (100µg/ml).from this 10ml was taken and make up with 100 ml of 0.1 N HCl (10µg/ml). The above solution was subsequently diluted with 0.1N HCl to obtain series of dilutions Containing 5,10,15,20,25,30,35 and 40µg/ml of Levetiracetam per ml of solution. The absorbance of the above dilutions was measured at 298 nm by using UV-Spectrophotometer taking 0.1N HCl as blank. Then a graph was plotted by taking Concentration on X-Axis and Absorbance on Y-Axis which gives a straight line Linearity of standard curve was assessed from the square of correlation coefficient (R^2) which determined by least-square linear regression analysis. The above procedure was repeated by using pH 6.8 phosphate buffer solutions.

Pre-formulation parameters

The quality of tablet, once formulated by rule, is generally dictated by the quality of physicochemical properties of blends. There are many formulations and process variables involved in mixing and all these can affect the characteristics of blends produced. The various characteristics of blends tested as per Pharmacopoeia.

Angle of repose:

The frictional force in a loose powder can be measured by the angle of repose. It is defined as, the maximum angle possible between the surface of

the pile of the powder and the horizontal plane. If more powder is added to the pile, it slides down the sides of the pile until the mutual friction of the particles producing a surface angle, is in equilibrium with the gravitational force. The fixed funnel method was employed to measure the angle of repose.

Bulk density:

Density is defined as weight per unit volume. Bulk density, is defined as the mass of the powder divided by the bulk volume and is expressed as gm/cm^3. The bulk density of a powder primarily depends on particle size distribution, particle shape and the tendency of particles to adhere together. Bulk density is very important in the size of containers needed for handling, shipping, and storage of raw material and blend. It is also important in size blending equipment.

Tapped density:

After carrying out the procedure as given in the measurement of bulk density the cylinder containing the sample was tapped using a suitable mechanical tapped density tester that provides 100 drops per minute and this was repeated until difference between succeeding measurement is less than 2 %.

Measures of powder compressibility:

The Compressibility Index (Carr's Index) is a measure of the propensity of a powder to be compressed. It is determined from the bulk and tapped densities. In theory, the less compressible a material the more flowable it is. As such, it is measures of the relative importance of inter-particulate interactions. In a free- flowing powder, such interactions are generally less significant, and the bulk and tapped densities will be closer in value.

Formulation development of Tablets:

All the formulations were prepared by direct compression. The compositions of different formulations are given in Table 6.3.The tablets were prepared as per the procedure given below and aim is to prolong the release of Levetiracetam . Total weight of the tablet was considered as 900mg.

Procedure:

1) Levetiracetam and all other ingredients were individually passed through sieve no ≠ 60.
2) All the ingredients were mixed thoroughly by triturating up to 15 min.
3) The powder mixture was lubricated with talc.
4) The tablets were prepared by using direct compression method.

Table 2: Formulation composition for tablets

All the quantities were in mg

Evaluation of post compression parameters for prepared Tablets

The designed formulation tablets were studied for their physicochemical properties like weight variation, hardness, thickness, friability and drug content.

Formulation No.	Levetiracetam	Eudragit RL 100	Eudragit RS 100	Ethyl cellulose	Mag. Stearate	Talc	MCC pH 102
F1	500	60			9	9	QS
F2	500	90			9	9	QS
F3	500	180			9	9	QS
F4	500		60		9	9	QS
F5	500		90		9	9	QS
F6	500		180		9	9	QS
F7	500			60	9	9	QS
F8	500			90	9	9	QS
F9	500			180	9	9	QS

Weight variation test:

To study the weight variation, twenty tablets were taken and their weight was determined individually and collectively on a digital weighing balance. The average weight of one tablet was determined from the collective weight. The weight variation test would be a satisfactory method of deter mining the drug content uniformity. Not more than two of the individual weights deviate from the average weight by more than the percentage shown in the following table and none deviate by more than twice the percentage.

Hardness:

Hardness of tablet is defined as the force applied across the diameter of the tablet in order to break the tablet. The resistance of the tablet to chipping, abrasion or breakage under condition of storage transformation and handling before usage depends on its hardness. For each formulation, the hardness of three tablets was determined using Monsanto hardness tester and the average is calculated and presented with deviation.

Thickness:

Tablet thickness is an important characteristic in reproducing appearance. Tablet thickness is an important characteristic in

reproducing appearance. Average thickness for core and coated tablets is calculated and presented with deviation.

Friability:

It is measured of mechanical strength of tablets. Roche friabilator was used to determine the friability by following procedure. Preweighed tablets were placed in the friabilator. The tablets were rotated at 25 rpm for 4 minutes (100 rotations).

Determination of drug content:

Tablets were tested for their drug content. Ten tablets were finely powdered quantities of the powder equivalent to one tablet weight of Meloxicam were accurately weighed, transferred to a 100 ml volumetric flask containing 50 ml water and were allowed to stand to ensure complete solubility of the drug. The mixture was made up to volume with water. The solution was suitably diluted and the absorption was determined by UV –Visible spectrophotometer. The drug concentration was calculated from the calibration curve.

In vitro drug release studies

Dissolution parameters:

Apparatus -- USP-II, Paddle Method
Dissolution Medium -- 0.1 N HCl,
p H -- 6.8 Phophate buffer
RPM -- 50
Sampling intervals (hrs)- 0.5,1,2,3,4,5,6,7,8,10,11,12
Temperature -- 37°c ± 0.5°c

As the preparation was for floating drug release given through oral route of administration, different receptors fluids are used for evaluation the dissolution profile.

Procedure:

900ml 0f 0.1 HCl was placed in vessel and the USP apparatus –II (Paddle Method) was assembled. The medium was allowed to equilibrate to temp of 37°c ± 0.5°c. Tablet was placed in the vessel and the vessel was covered the apparatus was operated for 2 hours and then the medium 0.1 N HCl was removed and pH 6.8 phosphate buffer was added process was continued from upto 12 hrs at 50 rpm. At definite time intervals of 5 ml of the receptors fluid was withdrawn, filtered and again 5ml receptor fluid was replaced. Suitable dilutions were done with receptor fluid and analyzed by spectrophotometrically at 298 nm using UV-spectrophotometer.

Application of Release Rate Kinetics to Dissolution Data:

Various models were tested for explaining the kinetics of drug release. To analyze the mechanism of the drug release rate kinetics of the dosage form, the obtained data were fitted into zero-order, first order, Higuchi, and Korsmeyer-Peppas release model.

RESULTS AND DISCUSSION

The present study was aimed to developing extended-release tablets of Levetiracetam using various polymers. All the formulations were evaluated for physicochemical properties and invitro drug release studies.

Analytical Method

Graphs of Levetiracetam were taken in Simulated Gastric fluid (pH 1.2) and in p H 6.8 phosphate buffer at 298 nm and 294 nm respectively.

Table 3: Observations for graph of Levetiracetam in 0.1N HCl (298nm)

Concentration [µg/l]	Abs
5	0.104
10	0.205
15	0.302
20	0.411
25	0.503
30	0.608
35	0.710
40	0.808

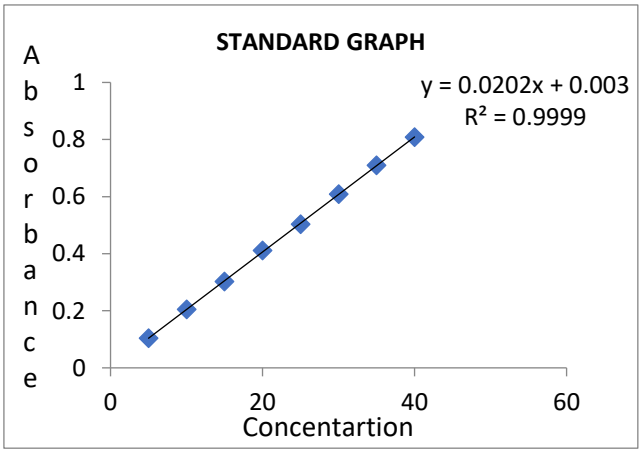
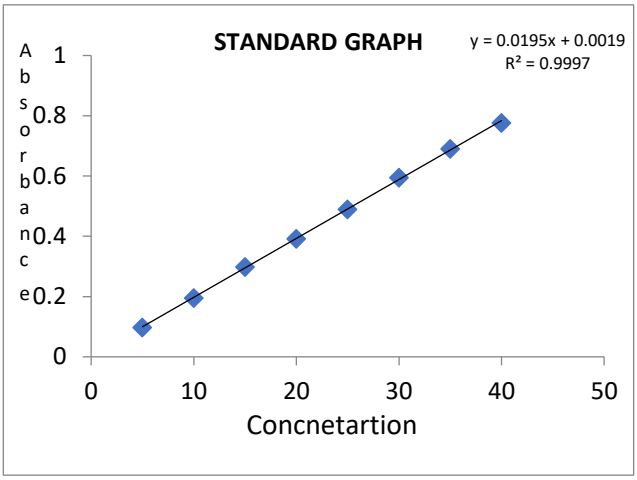


Figure 1: Standard graph of Levetiracetam in 0.1N HCl

Table 4: Observations for graph of Levetiracetam in p H 6.8 phosphate buffer (294nm)

Conc [µg/l]	Abs
5	0.098
10	0.195
15	0.298
20	0.392
25	0.490
30	0.595
35	0.690
40	0.776

Figure 2: Standard graph of Levetiracetam p H 6.8 phosphate buffer (294nm)



Preformulation parameters of powder blend

Formulation Code	Angle of Repose	Bulk density (gm/ml)	Tapped density (gm/ml)	Carr's index (%)	Hausner's Ratio
F1	25.11	0.49±0.04	0.54±0.04	16.21±0.06	0.86±0.06
F2	25.67	0.52±0.09	0.52±0.04	16.87±0.05	0.98±0.05
F3	25.54	0.50±0.05	0.58±0.05	17.11±0.01	0.64±0.03
F4	25.43	0.51±0.06	0.54±0.07	17.67±0.08	1.12±0.04
F5	25.34	0.52±0.03	0.57±0.03	16.92±0.04	1.2±0.08
F6	24.22	0.53±0.04	0.56±0.06	17.65±0.09	1.06±0.09
F7	25.18	0.54±0.06	0.59±0.04	16.43±0.05	0.76±0.03
F8	24.22	0.58±0.04	0.67±0.02	17.97±0.02	1.15±0.09
F9	25.05	0.55±0.08	0.5 2±0.03	17.54±0.09	1.17±0.02

Table 5: Pre-formulation parameters of Core blend

Tablet powder blend was subjected to various pre-formulation parameters. The angle of repose values indicates that the powder blend has good flow properties. The bulk density of all the formulations was found to be in the range of 0.43±0.07 to 0.58±0.06 (gm/cm3) showing that the powder has good flow properties. The tapped density of all the formulations was found to be in the range of 0.57 to 0.69 showing the powder has good flow properties. The compressibility index of all the formulations was found to be ranging between 16 to 18 which shows that the powder has good flow properties. All the formulations have shown the Hauser ratio ranging between 0 to 1.2 indicating the powder has good flow properties.

Quality Control Parameters For tablets:

Tablet quality control tests such as weight variation, hardness, and friability, thickness, and drug release studies in different media were performed on the compression coated tablet.

Formulation codes	Weight variation(mg)	Hardness(kg/cm2)	Friability (%loss)	Thickness (mm)	Drug content (%)
F1	912.5	4.5	0.50	6.8	99.76
F2	905.4	4.5	0.51	6.9	99.45
F3	898.6	4.4	0.51	4.9	99.34
F4	910.6	4.5	0.55	6.9	99.87
F5	909.4	4.4	0.56	6.7	99.14
F6	910.7	4.5	0.45	6.5	98.56
F7	902.3	4.1	0.51	6.4	98.42
F8	901.2	4.3	0.49	6.7	99.65
F9	898.3	4.5	0.55	6.6	99.12

Invitro quality control parameters for tablets

All the parameters such as weight variation, friability, hardness, thickness and drug content were found to be within limits.

In-Vitro Drug Release Studies

Table 7: Dissolution Data of Levetiracetam Tablets Prepared with Eudragit RL 100 In Different Concentrations

TIME (hr)	CUMULATIVE PERCENT DRUG DISSOLVED (n=3±SD)		
	F1	F2	F3
0.5	25.5	20.1	16.4
1	46.7	39.4	26.7
2	76.5	55.3	34.6
3	98.4	75.3	42.4
4		87.3	55.4
5		99.4	67.4
6			85.4
7			91.5
8			97.3

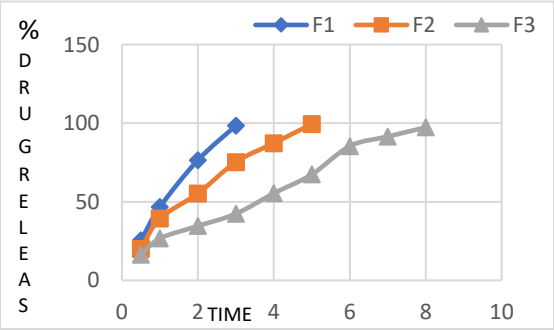


Fig 4: Dissolution profile of Levetiracetam (F1, F2, F3 formulations).

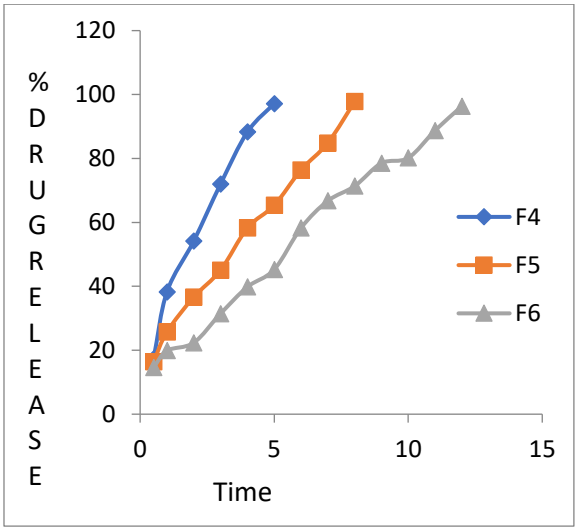


Fig5: Dissolution profile of Levetiracetam (F4, F5, F6 formulations)

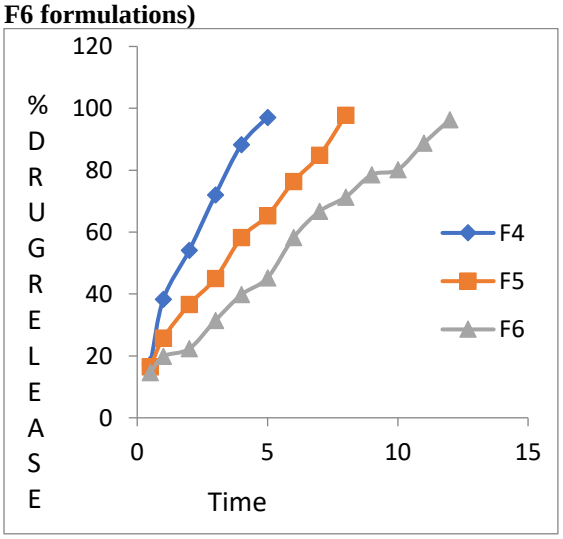


Table 8: Dissolution Data of Levetiracetam Tablets Prepared with Eudragit RS 100 In Different Concentrations

TIME (hr)	CUMULATIVE PERCENT DRUG DISSOLVED (n=3±SD)		
	F4	**F5**	**F6**
0.5	17.25	16.42	14.62
1	38.26	25.73	19.86
2	54.16	36.63	22.35
3	72.01	45.04	31.45
4	88.26	58.25	39.80
5	97.10	65.33	45.25
6		76.41	58.24
7		84.84	66.73
8		97.80	71.34
9			75.52
10			82.17
11			87.10
12			96.10

Table 9: Dissolution Data of Levetiracetam Tablets Prepared with Ethyl cellulose In Different Concentrations

TIME (hr)	CUMULATIVE PERCENT DRUG DISSOLVED (n=3±SD)		
	F7	**F8**	**F9**
0.5	10.4	9.4	8.5
1	16.5	15.6	14.5
2	28.6	21.4	18.4
3	39.5	36.7	23.4
4	48.5	42.4	28.2
5	59.4	49.6	34.8
6	69.2	55.3	40.2
7	74.5	60.3	44.8
8	82.3	72.8	50.4
9	87.78	83.52	63.34
10	98.78	88.65	69.27
11		96.56	74.86
12			79.97

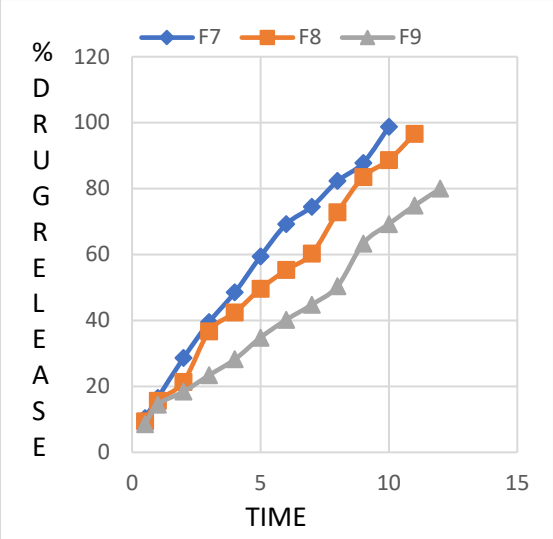


Fig 6: Dissolution profile of Levetiracetam (F7, F8, F9 formulations)

From the dissolution data it was evident that the formulations prepared with Eudragit RL 100 as polymer were unable to retard the drug release up to desired time period i.e., 12 hours.

Whereas the formulations prepared with Eudragit RS 100 retarded the drug release in the concentration of 180 mg showed required release pattern i.e., retarded the drug release up to 12 hours and showed maximum of 96.10% in 12 hours with good retardation.

The formulations prepared with Ethyl cellulose showed more retardation even after 12 hours they were not shown total drug release. Hence, they were not considered.

CONCLUSION

The aim of the present study was to develop an extended-release formulation of Levetiracetam to maintain constant therapeutic levels of the drug for over 12 hrs. Various grades of polymethacrylate polymers and ethyl cellulose were employed as polymers. Levetiracetam dose was fixed as 500 mg. Total weight of the tablet was considered as 900 mg. Polymers were used in the concentration of 60, 90 and 180 mg concentration. All the formulations were passed various physicochemical evaluation parameters and they were found to be within limits. Whereas from the dissolution studies it was evident that the formulation (F6) showed better and desired drug release pattern i.e.,96.10 % in 12 hours. It followed zero order release kinetics mechanism.

REFERENCE

1. Leon Shargel, Susanna Pong, Andrew B.C., Applied Biopharmaceutics and Pharmacokinetics, Modified-Release Drug Products, Pg 515 Fifth Edition, 2004

2. Chien Y.W., Controlled- and modulated-release drug-delivery systems. Encyclopedia of pharmaceutical technology. New York, Dekker, pgs 281-313, 1992.

3. J. R. Robinson, S. P. Eriksen, Theoretical formulation of sustained-release dosage forms. *J Pharm Sci.* 1966

4. Gilbert S. Banker, Christopher T. Rhodes, Modern Pharmaceutics, Sustained - and Controlled -release drug-delivery systems, Pg 505 Fourth Edition, 2002

5. Leon Lachman, The Theory and Practice of Industrial Pharmacy, Sustained Release Dosage Forms, pgs 430-431, Third Edition, 1987

6. Gilbert S. Banker, Christopher T. Rhodes, Modern Pharmaceutics, Sustained - and Controlled -release drug-delivery systems, Pgs 505-506 Fourth Edition, 2002

7. Gilbert S. Banker, Christopher T. Rhodes, Modern Pharmaceutics, Sustained - and Controlled -release drug-delivery systems, Pgs 507-508 Fourth Edition, 2002

8. Gilbert S. Banker, Christopher T. Rhodes, Modern Pharmaceutics, Sustained - and Controlled -release drug-delivery systems, Pgs 510-511 Fourth Edition, 2002

9. Leon Shargel, Susanna Pong, Andrew B.C., Applied Biopharmaceutics and Pharmacokinetics, Modified-Release Drug Products, Pg 535 Fifth Edition, 2004

10. http://www.pharmainfo.net/reviews/floating-drug-delivery-systemsan-approach-gastro-retention

11. http://www.initium.demon.co.uk/relfick.htm

12. Leon Shargel, Susanna Pong, Andrew B.C., Applied Biopharmaceutics and Pharmacokinetics, Modified-Release Drug Products, Pg 534 Fifth Edition, 2004

13. Gilbert S. Banker, Christopher T. Rhodes, Modern Pharmaceutics, Sustained - and Controlled -release drug-delivery systems, Pg 513 Fourth Edition, 2002

14. Korsmeyer RW, Gurny R, Doelker E, Buri P. Peppas NA. Mechanisms of solute release from porous hydrophilic polymers. *Int J Pharm*. 1983

15. Alfred Martin, Textbook Of Physical Pharmacy, Pgs 285 – 289, Fifth edition

16. Leon Shargel, Susanna Pong, Andrew B.C., Applied Biopharmaceutics and Pharmacokinetics, Modified-Release Drug Products, Pg 526 Fifth Edition, 2004

16a. Physicians Desk Reference, 62nd edition, Pgs 1715-1717

17. http://www.boomer.org/c/p3/c24/c2404.html