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Research Article

FORMULATION DEVELOPMENT AND EVALUATION OF MEMBRANE-MATRIX HYBRID SYSTEM TO SUSTAIN THE DRUG RELEASE FROM PELLETS LOADED WITH LEVETIRACETAM

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ABSTRACT

The objective of the present work was to design and develop Membrane-matrix hybrid sustained release pellets of Levetiracetam for the treatment of epilepsy. Levetiracetam is an anti Epileptic drug used in treatment of Seizures in adults and pediatric patients. Levetiracetam has short biological half life (7±1hr), so to prolong the biological half of the drug by finding a capable dosage form to release the drug gradually in sustained manner and to minimize the side effects. This research was carried out for development of drug loaded oral Sustained-release pellets by membrane – matrix hybrid technology of water soluble drug Levetiracetam (LEV), using blend of Carbopol® 974P and Octadecanol as drug release-modifying agents, Micro crystalline cellulose (MCC) (Avicel pH 101) as principal spheronization agent, and Sodium carbonate used to control pH (carbonate solutions neutralize acids, producing only carbon dioxide and water)., HPMC and Calcium chloride were used as blenders, HPMC, Methacrylic acid copolymers (Eudragit® L30D-55, Eudragit® NE30D), Ethyl cellulose and Chitosan were used as coating polymers. **Methods:** LEV formulations were developed by the pelletization technique, and drug loaded pellets are characterized with regard to the drug content, size distribution, Scanning Electron Microscopy (SEM), Differential Scanning Calorimetry, and Fourier Transform InfraredSpectroscopy (FTIR). Stability studies were carried out for the optimized formulation for a period of 60 days at 40 ± 2 °C and 75 ± 5% relative humidity. **Results and major conclusion:** The drug content was in the range of 93.34-98.12 %. The mean particle size of the drug loaded pellets was in the range 1024 to 1087µm. SEM photographs and calculated sphericity factor confirmed that the prepared formulations were spherical in nature. The compatibility between drug and polymers in the drug loaded pellets was confirmed by FTIR studies. Stability studies indicated that pellets are stable. Drug release was sustained for more than 10 hrs and mechanism of the drug release followed by Fickian diffusion. It may be concluded that F8 is an ideal formulation for once a day administration.

Keywords: Pelletization, Microporous membrane, Release kinetics, SEM.

INTRODUCTION

Levetiracetam (LEV) is an antiepileptic drug (AED) with favourable pharmacologic characteristics and demonstrated activity in improving seizure control. It was synthesized in the early 1980s during a follow-up chemical program aimed at identifying a second-generation nootropic drug, and initial pharmacologic studies with LEV explored its ability to facilitate cholinergic neurotransmission. In 1991, pivotal clinical studies were initiated in epilepsy patients as adjunctive therapy in refractory partial onset seizures. In November 1999, the FDA approved LEV as a new AED. LEV tablet was approved in India in April 2005 as adjunctive therapy in treatment of partial onsetseizures in adults with epilepsy.

There has been increasing evidence that besides partial seizures in adults and paediatric patients, LEV may also be useful in patients with generalized absence or myoclonic seizures, in patients with Lennox-

Gastaut syndrome. It has become one of the most frequently prescribed new drugs for the treatment of partial seizures.

The major objective of the present work is to design and develop Membrane-matrix hybrid sustained release pellets for the treatment of epilepsy. The present study sustained release formulation is modified release drug delivery system which may increase the half life of the drug and for overcoming dysphasia, a problem common in gastric and paediatric population as well as in case of un cooperative patients or un availability of water.

MATERIALS AND METHODS

Materials

Levetiracetam was obtained from Hetero Pharmaceuticals Ltd, Hyderabad, India. Hydroxypropyl methyl cellulose, Octadecanol, Carbopol were supplied by Molychem Ltd, Mumbai, India. Lactose monohydrate, Sodium carbonate, Talc, Magnesium oxide, Potassium di hydrogen ortho phosphate, Sodium hydroxide were supplied by S.D. Fine Chemicals Pvt Ltd, Mumbai. Polyvinyl pyrrolidine K30 was supplied from Oxford Ltd, Mumbai, India.Isopropyl alcohol was supplied from Samir Tech. Chem Pvt Ltd, Vadodara. Hydrochloric acid was obtained from Qualigens fine chemicals, Mumbai.

Preparation of levetiracetam matrix pellets

HPMC and calcium chloride ($CaCl_2$) were employed as binders. They were separately dissolved in purified water to provide a 2% solution before use. Levetiracetam, Carbopol® 974P, octadecanol, microcrystalline cellulose and Na_2CO_3 were blended uniformly. The mixture of the powder and 2% HPMC and $CaCl_2$ solution were mixed until a wet mass was obtained. This wet mass was then transferred to a screw drive extruder (WL 350, Wenzhou, China) which had a rotation speed of 30 rpm/min. The extrudates were cut into smaller cylinders by the knives fixed inside the roller and further processed in a spheronizer rotated at a speed of 48 rpm. A 15min spheronization time were used to prepare the pellets. After spheronization, the pellets were placed in an oven at 40°C and allowed to dry thoroughly. The formulations of matrix pellet are shown in Table 1 below. The dried pellets were screened and the 20–24-mesh fraction was collected for further study.

Solubility

The solubility of LEV was found that it was freely soluble in water and also found that the solubility in some of organic solvents. The results are a follows

Water - 104.72g/100ml, Chloroform - 65.3g/100ml

Methanol - 53.6g/100ml, Ethanol - 16.5g/100ml, Acetonitrile - 5.7g/100ml

Composition of Levetiracetam Pellet Formulations

Table 1: Composition of binder solution

Formulation number	HPMC (%)	$CaCl_2$ (%)	Purified water (ml)
F1	0.5	1	Q.s
F2	1	0.5	Q.s
F3	1	1	Q.s
F4	1	1.5	Q.s
F5	1.5	1	Q.s
F6	2	1	Q.s
F7	1	2	Q.s
F8	2	2	Q.s
F9	2	2.5	Q.s
F10	2.5	2	Q.s
F11	2	3	Q.s
F12	3	2	Q.s

Table 2: Composition of Levetiracetam core pellets

COMPOSITION	FORMULATIONS											
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
LEV	76%	76%	76%	76%	76%	76%	76%	76%	76%	76%	76%	76%
Carbapol	-	2%	4%	6%	-	-	-	2%	2%	2%	4%	6%
Octadecanol	-	-	-	-	2%	4%	6%	2%	4%	6%	2%	2%
Sodium carbonate	2%	2%	2%	2%	2%	2%	2%	2%	2%	2%	2%	2%
Microcrystalline cellulose	22%	20%	18%	16%	20%	18%	16%	18%	16%	14%	16%	14%
Binder solution	0.5:1	1:0.5	1:1	1:1.5	1.5:1	1:2	2:1	2:2	2:2.5	2.5:2	3:2	2:3

COATING OF DRUG-LOADED MATRIX PELLETS

HPMC, Methacrylic acid co- polymer, Ethyl Cellulose, Chitosanwere used for preparation of coating solution. From all these Ethyl Cellulose is suitable polymer for coating the pellets. Purified water is used for the preparation of coating solution.To prevent agglomeration after mixing, the coating polymers dispersions were first diluted with an equal volume of purified water. The polymer dispersions were then blended by stirring for at least 60 min and mixed with 500 g of LEV matrix pellets. Three dispersion coating levels were applied which involved a weight gain of 10%, 20% and 30%. All the coating processes were performed using a fluidized bed coater (FD MP-10, Powrex Co., Ltd., Japan). The coated pellets were cured overnight in an oven with an air-circulating fan at 40°C and stored in a desiccator before initiating the dissolution studies. For 657.89mg of pellets required 20% concentration of Ethyl cellulose coating solution for coating of pellets.

Drug – Excipients Compatibility Studies

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 ofpure drugand all the Excipients.

Evaluation of levetiracetam Capsules Containing SR Pellets

Weight variation

Formulated 20 capsules were weighed collectively and individually for all batches. From the collective weight, average weight was calculated by using Digital Balance. The percent weight variation was calculated by using the following formula.

$$\%\ \text{Weight Variation} = \frac{\text{Average Weight} - \text{Individual Weight}}{\text{Average Weight}} X 100$$

Thickness

The Thickness of the pellet was measured by using Verniercaliper and the average Thickness in mm was calculated.

Friability

The Roche friability test apparatus was used to determine the friability of the pellets. The percentage friability was calculated according to the following formula.

$$\%\ \text{Friability} = \frac{\text{Initial Weight} - \text{Final Weight}}{\text{Initial Weight}} X\ 100$$

***In-vitro* drug release studies**

The USP type II rotating Paddle method was used to study the drug release from the Capsule Containing pellets. The capsule was 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 100 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.

Table 3: Dissolution Parameters

Apparatus	USP Type II(Paddle)
Medium	0.1 N HCl/ 6.8 posphate buffer
Quantity	900ml
R.P.M	100 rpm
Temperature	37±0.5^{0}c
Time	Up to 12hr

In-vitro drug release kinetics

The obtained data were fitted into mathematical equation zero order, first order, higuchi model and korsemeyer equation/ peppa's model in order to describe the kinetics and mechanism of drug release from the matrix formulations.

RESULT AND DISCUSSION

The formulations Carbopol and Octadecanol contain MCC as a principleshironizing agent prepared by Extrusion and sphironization technique. These formulations were subjected to drug release studies in varied dissolution media namely, 0.1N HCl (for 2 hr) and P^H 6 phosphate buffer(till the end).

The uncoated core matrix pellets containing carbopol (2%), octodecanol (2%), Mcc (18%) with binder solution 2:2 ratio shows better release.

The uncoated matrix pellets were coated with different sustained release coating materials like HPMC, Methacrylic acid co-polymer, thyl cellulose and Chitosan with the concentrations of 10%,20% and 30% respectively. These formulations were subjected to drug release studies in varied dissolution media namely, 0.1N HCl (for 2 hr) and PH 6 phosphate buffer (till the end).

Binder solution was prepared by using HPMC and Calcium chloride with different concentrations and observed that 2:2 ratio was optimised.

Sustained release coating solution was prepared by using HPMC, Methacrylic acid co-polymer, Ethyl cellulose and Guargum with different concentrations and observed that 20% concentration of ethyl cellulose solution shows better sustained drug release.

The coated matrix-membrane pellets containing Ethylcellulose 20% concentration shows better release uto 18hrs among all formulations.

FTIR Studies

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).

From the FTIR spectra, it was concluded that similar characteristic peaks with minor difference for the drug and their formulation. Hence, it appears that therewas no chemical interaction between the drugs and excipients used**.**

The scanning range was 4000 to 450 cm-1 and the resolution was 1 cm^{-1}. FTIR absorption spectra ofpure drugand all the excipients used like HPMC, $CaCl_2$, carbopol, Octadecanol, Sodium carbonate, MCC, Methacrylic acid co-polymers and the combination of drug and polymer were shows no significant interaction between drug and polymers. The graphs obtained were shown

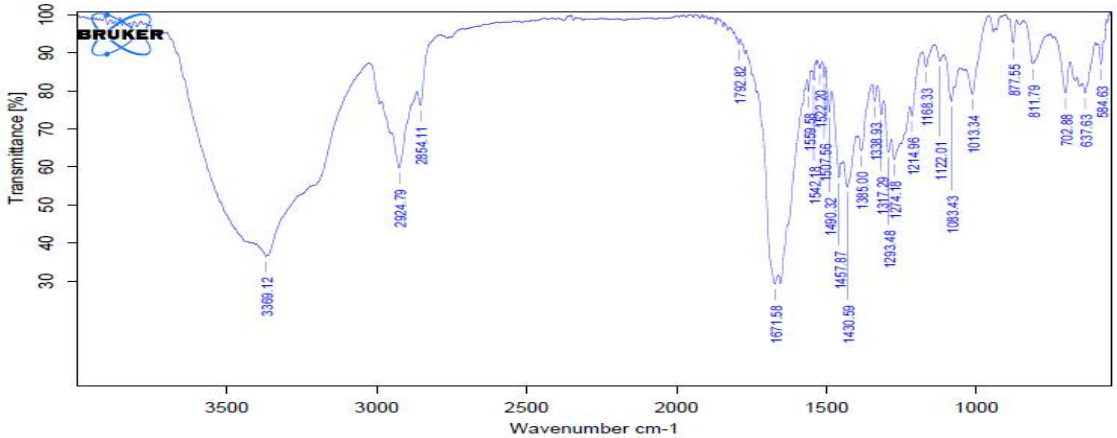

Fig. 1: FTIR spectrum of Levetiracetam

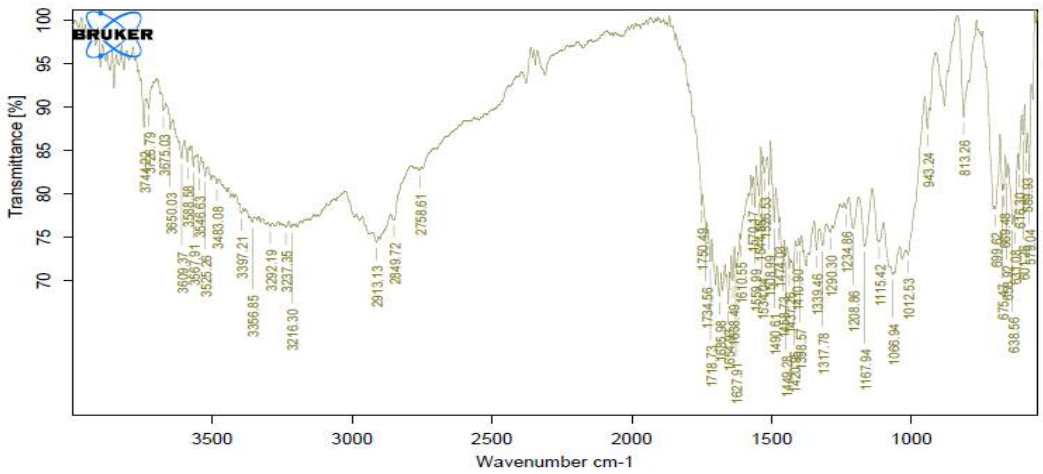

Fig. 2: FTIR spectrum of Levetiracetam sustained release formulation

Table 4: Physico- chemical Evaluation of Sustained release pellets

FORMULATION	WEIGHT VARIATION (mg)	THICKNESS (mm)	FRIABILITY (%)	DRUG CONTENT (%)
F1	789	1.24± 0.06	0.48± 0,01	97.44
F2	787	1.20± 0.06	0.54± 0.01	96.89
F3	790	1.15± 0.06	0.57± 0.01	98.36
F4	789	1.13± 0.06	0.46± 0.01	98.10
F5	789	1.25± 0.06	0.35± 0.01	98.72
F6	789	1.17± 0.06	0.56± 0.01	97.65
F7	791	1.16± 0.06	0.61± 0.01	98.43
F8	**789**	**1.18± 0.06**	**0.54± 0.01**	**98.28**
F9	789	1.22± 0.06	0.43± 0.01	97.22
F10	788	1.18± 0.06	0.56± 0.01	98.16
F11	789	1.14± 0.06	0.32± 0.01	99.01
F12	787	1.17± 0.06	0.57± 0.01	98.24

In vitro release studies

Comparison of *in vitro* drug release profiles of different formulations are shown in Fig. 3, 4, 5 andthe data is shown in Table 5.

Table 5: Dissolution studies for coated tablets

Time (hr)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
0.5	5.5	3.8	7.8	34.4	8.2	6.2	1.2	**2.1**	3.4	5.1	3.7	4.6
1	8.4	6.8	10.4	47.5	10.6	7.3	1.4	**3.7**	7.8	8.1	7.1	6.6
2	17.0	8.3	19.8	62.9	26.3	10.7	2.1	**6.5**	8.3	30.3	8.3	8.1
3	22.4	20.2	33.1	80.6	33.0	17.4	3.4	**8.3**	10.2	44.1	17.4	19.2
4	47.7	28.9	44.1	96.7	40.2	23.6	4.7	**11.1**	14.2	56.4	23.2	28.5
5	78.9	52.2	52.5		46.8	28.2	5.6	**17.8**	16.9	46.8	28.3	39.5
6	92.9	81.2	63.4		57.8	35.5	7.1	**24.4**	21.4	60.1	41.5	46.9
7		89.9	70.3		73.2	43.2	8.6	**28.7**	27.4	72.6	47.6	57.7
8		98.0	78.6		79.5	51.0	10.2	**36.7**	33.5	80.2	62.7	63.4
9			84.6		87.3	61.6	12.3	**42.9**	37.8	92.1	69.9	67.4
10			92.1		98.0	80.2	16.0	**48.2**	44.7	99.1	82.6	78.5
11			101.5			87.9	17.5	**55.4**	51.2		96.7	83.4
12						97.9	19.5	**62.2**	54.5			91.8
13								**66.9**	57.5			95.1
14								**75.1**	58.1			
15								**81.5**	57.4			
16								**85.2**	58.3			
17								**91.8**				
18								**97.7**				

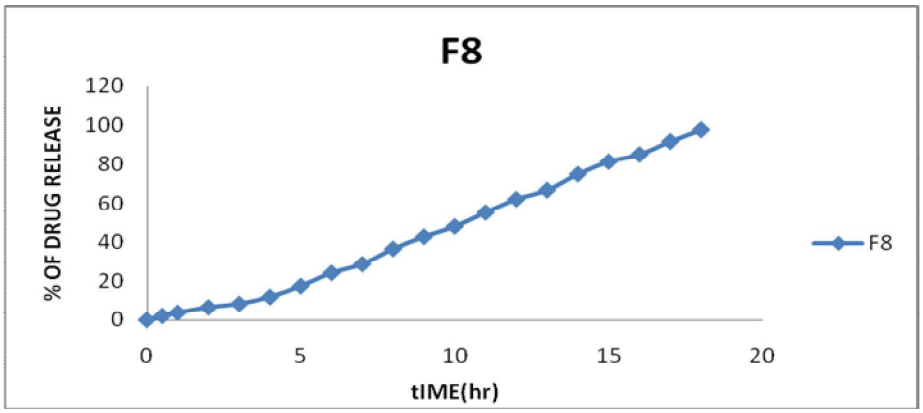

Fig. 3: Percentage of drug release studies from F8 coated pellet

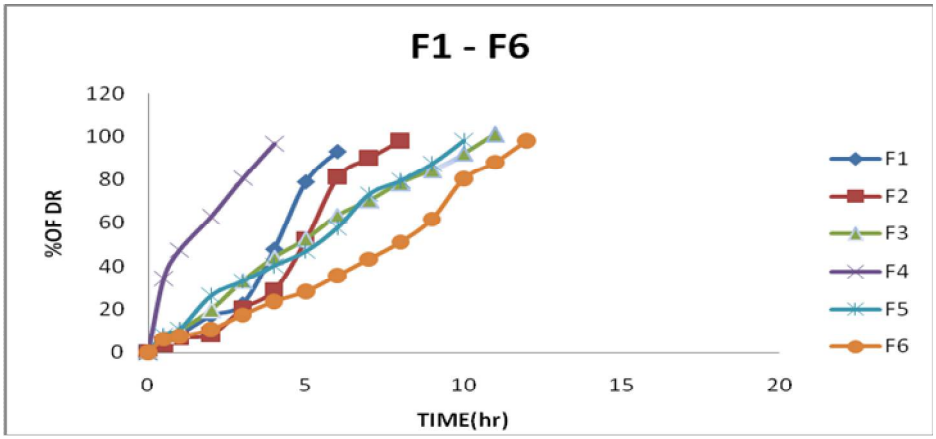

Fig. 4: Comparative*In-vitro* Drug release graphs for formulation F1 – F6

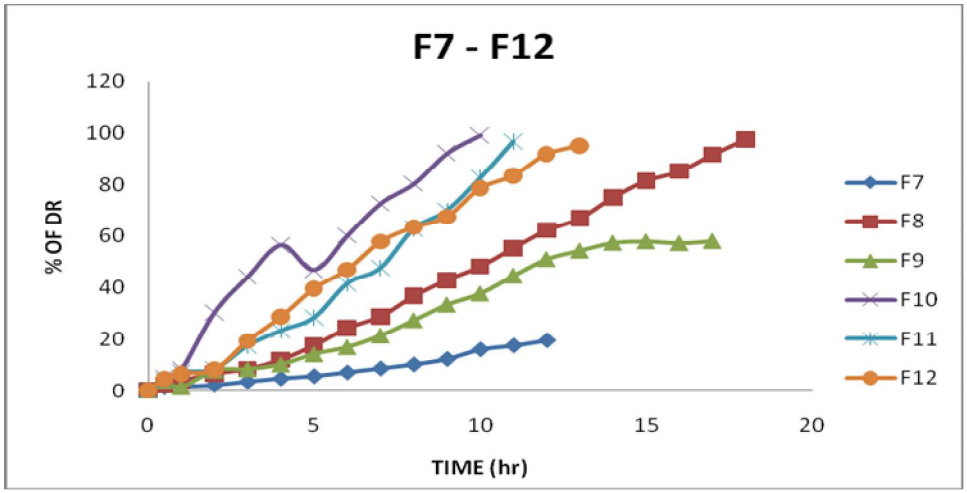

Fig. 5: Comparative*In-vitro* Drug release graphs for formulation F7 – F12

SEM Analysis

SEM photomicrograph Fig. 6, 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.

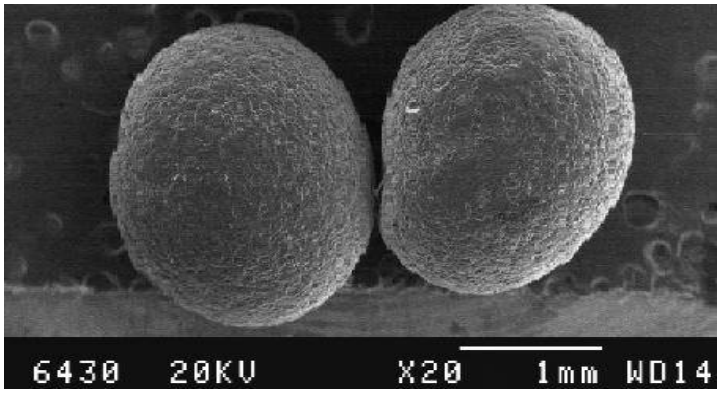

Fig. 6: SEM photograph of LEV pellets

Kinetic drug release studies

The kinetics of the drug release was evaluated by drug release rate modelsnamely Zero order, First order.

The mechanism of drug release was evaluated byHiguchi kinetics and Peppas drug release.

The optimised formula follows zero order drug release with peppas mechanism.

Table 6: Kinetic drug release studies for SR pellets F1-F12

Formulation	Zero order	First order	Higuchi	Peppas
F1	0.933	0.793	0.774	0.952
F2	0.945	0.781	0.798	0.941
F3	0.992	0.941	0.956	0.761
F4	0.923	0.903	0.996	0.212
F5	0.991	0.781	0.936	0.728
F6	0.966	0.826	0.839	0.816
F7	0.978	0.697	0.859	0.918
F8	**0.990**	**0.953**	**0.885**	**0.953**
F9	0.972	0.958	0.996	0.905
F10	0.963	0.739	0.943	0.776
F11	0.973	0.715	0.844	0.867
F12	0.992	0.891	0.926	0.868

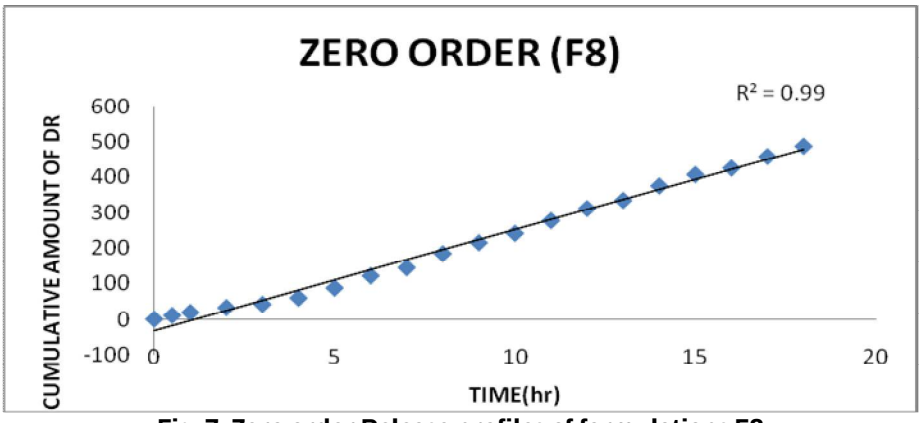

Fig. 7: Zero order Release profiles of formulations F8

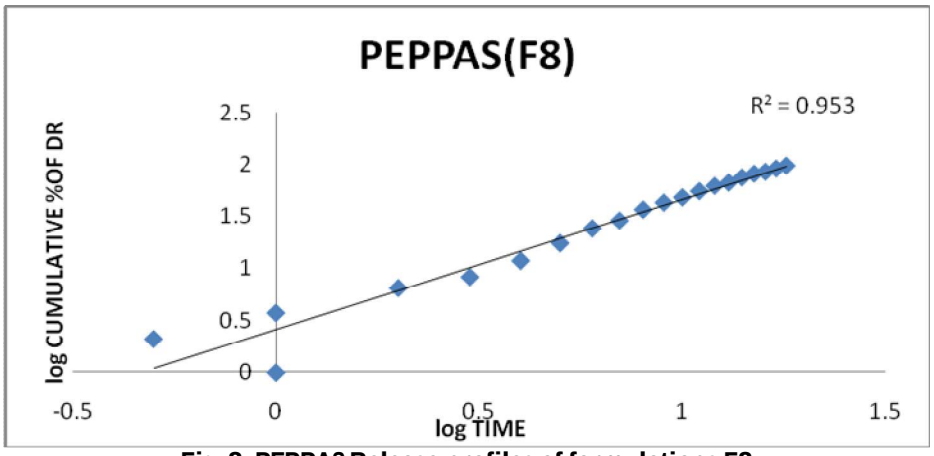

Fig. 8: PEPPAS Release profiles of formulations F8

Stability Studies of Optimized Formulation F8

Table 7: Stability studies of optimised formulation F8

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%
Assay	98.6%	98.4%	98.4%	98.1%	98.1%

Stability studies were carried out for optimized formula for 60 days at 40ºC / 75% RH,after stability study there was no physical change was observed, also found that assay of the formulation was 98.1 % and in-vitro drug release is 96.2%.

Optimized formulation **F8** was kept for stability studies and observed that there was no significant change in Physical appearance, *In-vitro* drug release profile and assay after 0, 15, 30 and 60 days. It shows that formulation **F8** was stable.

CONCLUSION

The present study was to development of membrane-matrix hybrid sustained release pellets loaded with 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 minimizing the dosage regimen by means of modified drug delivery systems.The present study sustained release formulation is modified release drug delivery system which may increase the half life of the drug. To minimize the dose dumping prone by modified release dosage forms when use large doses multiple unit particulate system is beneficial.That's why it's better to prepare pellets more over pellets are an optimum dosage form for overcoming dysphasia, a problem common in gastric and pediatric population as well as in case of uncooperative patients or unavailability of water.In addition, the enhanced distribution of pellets reduces the probability of increased 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..The core matrix pellets of Levetiracetam was prepared by using extrusion & sphironization method and further subjected to coating with sustained release polymers (HMC, Methacrylic acid co-olymer, Ethyl cellulose & Chitosan).The concentration between 10-30% give the better sustained drug release and 20% concentration of Ethyl cellulose shows the better in-vitro drug release.Sustained release coated pellets were evaluated for assay, dissolution and forformulation **F8** was optimized.

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