INTERNATIONAL JOURNAL OF ENGINEERING TECHNOLOGY AND SCIENCES (IJETS) Vol.6 (1) Dec 2016 DOI: http://dx.doi.org/10.15282/ijets.6.2016.1.9.1059

Formulation and Evaluation of Pregabalin Loaded Eudragit S100 Nanoparticles

B. Senthilnathan[1]*, A.Maheswaran[1], K. Gopalasatheeskumar[1], K. Masilamani[1], Raihana Z Edros[2]

[1]Jaya College of Paramedical sciences, College of Pharmacy, Thiruninravur, Chennai – 602024 Tamilnadu, India.

[2]Department of Pharmaceutical Engineering, University Malaysia Pahang, Lebuhraya Tun Razak, 26300 Gambang, Kuantan, Pahang Darul Makmur, Malaysia

sen03mpharm@gmail.com

Abstract: ***In this work, polymeric nanoparticles containing Pregabalin was prepared and optimized the ideal concentration of polymer based on its in vitro release profile for a period of 24hrs.The nanoparticles were prepared by solvent displacement method using various concentrations of Eudragit S100 (EPNP1-EPNP5). The prepared nanoparticles were characterized for its particle size, zeta potential, drug content, entrapment efficiency and invitro drug release profile. The preformulation study results confirmed the compatibility between the drug and other excipients used in the formulation. The optimized formulation was selected based on its particle size, entrapment efficiency and in vitro drug release profile. The formulation which contains 300mg of Eudragit S100 (EPNP5) was selected as optimized concentration for the controlled release of Pregabalin for a period of 24hrs.***

Index Terms- Pregabalin, Eudragit S100, Polymeric nanoparticles, Zeta potential, Encapsulation efficiency.

I. INTRODUCTION

The aim of the present work is to develop a controlled release formulation for an antiepileptic drug Pregabalin which is considered as one of the primary drug used in the treatment of neuropathic pain and epilepsy. [1]

Pregabalin on continuous usage (150 – 600mg/day), is reported to cause severe adverse effects including dizziness, drowsiness, blurred vision, increased appetite, euphoria, constipation, vomiting, erectile dysfunction etc and it is required to be taken three times a day.[2-5] These biological situation demand the formulation of Pregabalin loaded Eudragit S100 nanoparticles to achieve controlled release for a period of 24hrs which in turn reduces the complications of dose size, dosing frequency, adverse effects and improves better patient compliance.

The biological half-life of Pregabalin is 6 hrs, it needs to be taken frequently in order to maintain the steady state blood level concentration. This can be overcome by formulation of controlled release nanoparticles of Pregabalin.

To achieve the objectives the plan is executed to formulate controlled release Pregabalin nanoparticles using Eudragit S100.

II. MATERIALS AND METHODS

2.1Materials Used

Pregabalin , Eudragit S100 and Poloxamer were purchased from Sigma Aldrich. Ethanol was purchased from Chemika-Biochemika-Reagents, Mumbai. All other chemicals and reagents used were of analytical grade.

2.2Methods

2.2.1Preparation of Pregabalin loaded Eudragit S100 nanoparticles

Solvent displacement method was adopted for the preparation of Pregabalin loaded nanoparticles using various concentration of Eudragit S100 as polymer.[6,7,8] Eudragit S100 in various concentrations were dissolved with 20ml of ethanol in a beaker. Pregabalin 100mg was dissolved in a 25ml of distilled water. The drug solution was then injected to the above polymeric solution under magnetic stirring. The solution was stirred up to 2 hrs until end point is attained. The water and ethanol was evaporated under reduced pressure and final volume is adjusted to 50ml. Several batches namely (EPNP1, EPNP2, EPNP3, EPNP4, EPNP5) were formulated by changing the drug and polymeric ratio and the effect of polymer concentration on the encapsulation efficiency, particle size and *in vitro* drug release were studied.

Table 1: Formula used for the preparation of Pregabalin loaded Eudragit S100 nanoparticles

S.No	Trials	Pregabalin (mg)	Eudragit S100 (mg)	Poloxamer (mg)	Ethanol (ml)	Purified Water (ml)
1.	**EPNP1**	100	100	200	20	20
2.	**EPNP2**	100	150	200	20	20
3.	**EPNP3**	100	200	200	20	20
4.	**EPNP4**	100	250	200	20	20
5.	**EPNP5**	100	300	200	20	20

2.2.2 Characterization Studies

2.2.2.1 Particle size and Surface charge

Surface charge is important in adhesion and interaction of particle with cells.[7] The zeta- potential is used to measure the cell surface charge density. It can be measured using Malvern zeta sizer. The prepared nanoparticles were evaluated for their particle size and surface charge by photon correlation spectroscopy (PCS) using zetasizer. [9]

2.2.2.2 Drug content

2.2.2.2.1 Standard Preparation

100mg of Pregabalin standard was weighed accurately and transferred into a 25ml volumetric standard flask and dissolved with 5ml of pH 6.8 phosphate buffer. 1ml of this solution was diluted with 25 ml with pH 6.8 phosphate buffer.

2.2.2.2.2 Sample Preparation

Weighed accurately Pregabalin nanoparticles equivalent to 100mg of Pregabalin and transferred in to a 25 ml standard flask. The sample was dissolved with 5 ml of pH 6.8 phosphate buffer and diluted to 25 ml with pH 6.8 phosphate buffer.1ml of this solution was diluted to 25ml with buffer solution.

Then the standard and sample absorbance was measured at 210 nm using a UV-Visible spectrophotometer. The percentage of drug content was calculated.

$$\text{Drug content (\%)} = \frac{\text{Weight of drug in nanoparticles X 100}}{\text{Weight of nanoparticles}}$$

2.2.2.3 Entrapment Efficiency

The drug loaded nanoparticles were exposed to centrifugation at 15000 rpm for 30 min.[10, 11] The supernatant liquid was separated and 1ml of this solution was diluted with water and the absorbance was measured at 210 nm. The amount of Pregabalin un-entrapped in the supernatant was calculated. The amount of Pregabalin entrapped was determined by subtracting amount of free un-entrapped Pregabalin from the total amount of Pregabalin taken for the preparation.

The formula used to calculate entrapment efficiency was given below [12]

$$\text{Drug entrapment(\%)} = \frac{\text{mass of drug in nanoparticles x100}}{\text{mass of drug used in formulation}}$$

2.2.2.4 In vitro release

In vitro release studies were performed for 24hrs by using the Franz diffusion cell. [13-16] The prepared Pregabalin nanoparticles formulations equivalent to 100mg of Pregabalin were placed inside a dialysis membrane and immersed in pH 6.8 phosphate buffer. At predetermined time intervals the sample was withdrawn and the amount of Pregabalin released was determined by measuring the absorbance at 210 nm using a UV-Visible spectrophotometer. From the absorbance values the cumulative percentage drug release was calculated.

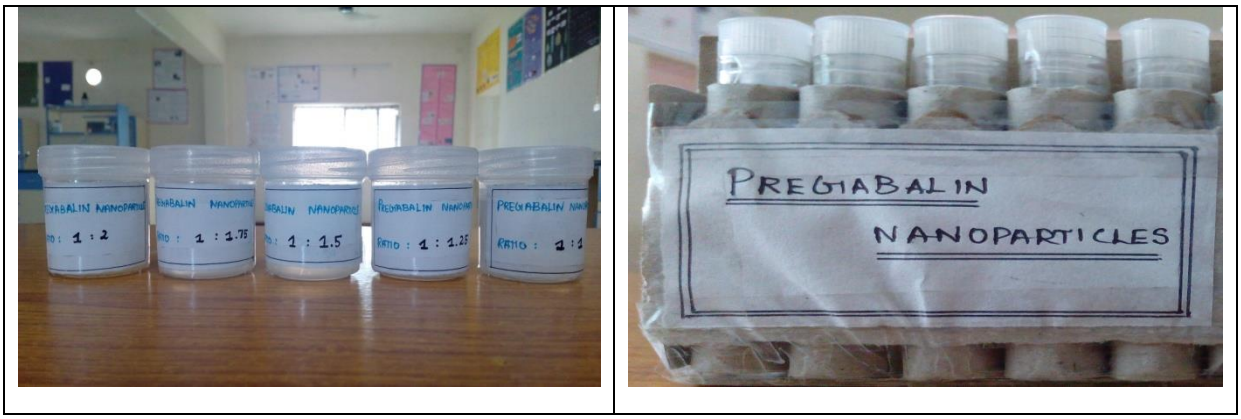


Figure.1-2. pregabalin loaded eudragit s 100 nanoparticles (EPNP1-EPNP5)

III. Result and Discussion

3.1 Drug content and entrapment efficiency

Particle size and entrapment efficiency of the Pregabalin nanoparticles (EPNP1- EPNP5) were increased with increasing Eudragit S100 concentration.[12] This may be due to high amount of availability of Eudragit S100 to encapsulate the drug, upon increasing the Eudragit S100 content, number of layers coated the drug was increased, this resulted in increased particle size and entrapment efficiency. Further increase in the Eudragit S100 concentration (EPNP5), there is no much increase in the entrapment efficiency due to the availability of the drug to be incorporated is low which is not enough for further encapsulation of drug by Eudragit S100.

Table 2: Drug content and entrapment efficiency Particle size and zeta potential of Pregabalin nanoparticles.

Trials	Zeta potential (mV)	Particle size (nm)	Entrapment Efficiency (%)	Drug Content (%)
EPNP1	4.75	187.0	72.46±0.24	99.67±0.08
EPNP2	10.6	663.4	77.89±0.08	99.56±0.24
EPNP3	6.33	129.8	86.47±0.09	99.38±0.31
EPNP4	1.73	139.7	90.83±0.15	99.62±0.27
EPNP5	0.277	117.3	95.07±0.45	99.71±0.19

Table 3: *In vitro* release studies of Pregabalin nanoparticles

S.NO	TIME (Hrs)	% CUMULATIVE DRUG RELEASE				
		EPNP1	**EPNP2**	**EPNP3**	**EPNP4**	**EPNP5**
1	0.5	25.56± 0.08	22.46± 0.09	18.45± 0.45	13.37± 0.64	11.38± 0.31
2	1	43.67± 0.34	40.58± 0.31	35.53± 0.27	30.75± 0.15	22.45± 0.27
3	6	75.57± 0.12	71.79± 0.19	67.85± 0.76	61.44± 0.40	54.29± 0.38
4	12	98.54± 0.34	93.72± 0.38	81.36± 0.28	73.65± 0.29	68.76± 0.17
5	16	98.51± 0.27	98.57± 0.19	92.49± 0.38	85.73± 0.17	80.47± 0.28
6	20	98.48± 0.55	98.54± 0.17	98.56± 0.11	93.42± 0.53	91.39± 0.26
7	24	98.47± 0.32	98.52± 0.21	98.55± 0.28	98.57± 0.64	99.58± 0.08
mean±S.D, n=3						

3.2 In- vitro drug release

From the *in vitro* drug release study results, the maximum percentage drug release (99.58± 0.08) at the end of 24hrs was observed with trial EPNP5 which contains 300 mg of Eudragit S100.

Below 300 mg of Eudragit S100 concentration as in the case of trials EPNP1, EPNP 2,EPNP 3 and EPNP 4, the maximum percentage drug release 98.54± 0.34, 98.57± 0.19,98.56± 0.11and 98.57± 0.64were obtained at the end of 12, 16,20 and 24hrs respectively which was not desirable.

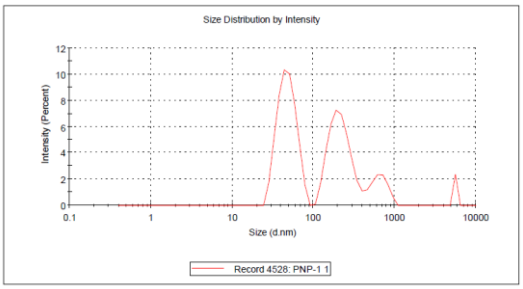
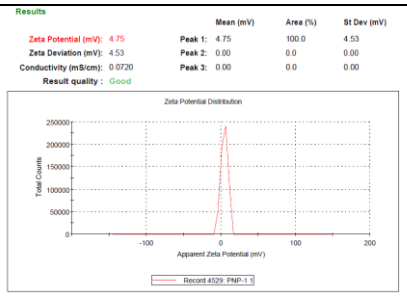
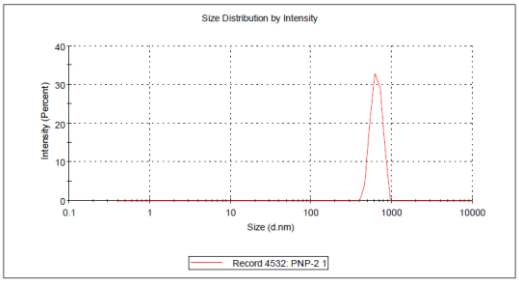
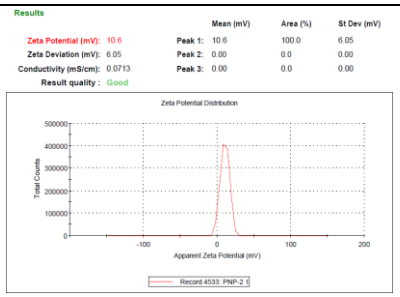
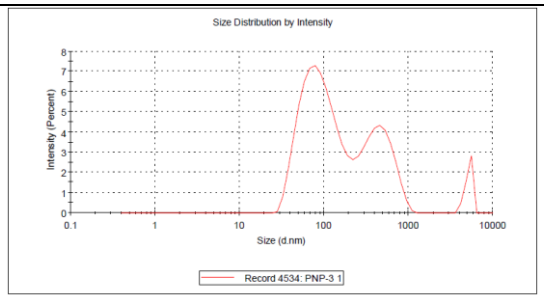
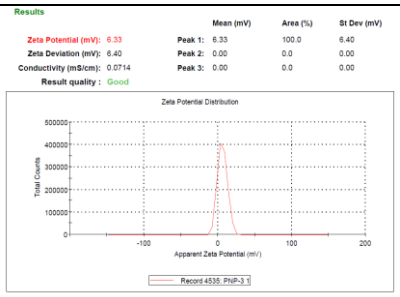
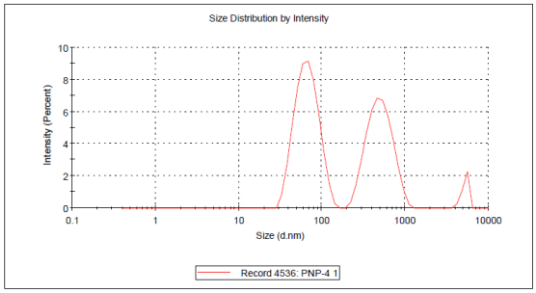
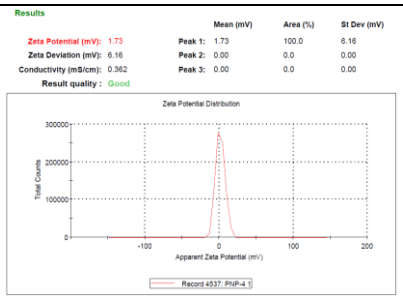
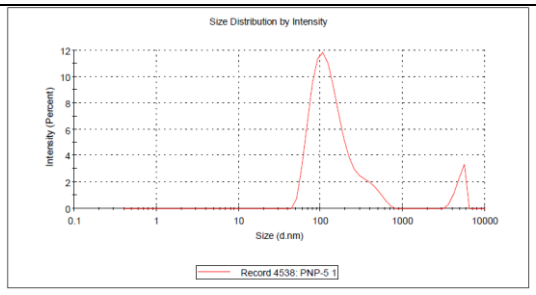
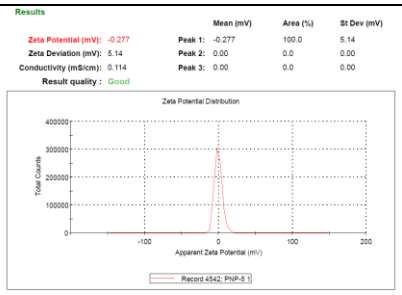
Sample ID	Particle size	Zeta potential
EPNP1		
EPNP2		
EPNP3		
EPNP4		
EPNP5		

Figure.3-12. Particle size and Zeta potential

Beyond 250 mg of Eudragit S100 concentration, reduction in drug release was observed in the case of trial EPNP5. The maximum percentage drug release for EPNP5 was found to be 99.58± 0.08at the end of 24hrs were obtained.

From the *in vitro* drug release data for EPNP1- EPNP5, it was observed that increase in Eudragit S100 concentration delays the drug release due to increased particle size and reduced surface area available for drug release.

From all the formulations, EPNP5 was selected as best formulation due to its ideal particle size (nm), high entrapment efficiency (95.07±0.45%) and desirable drug release (99.58± 0.08% at 24 h).

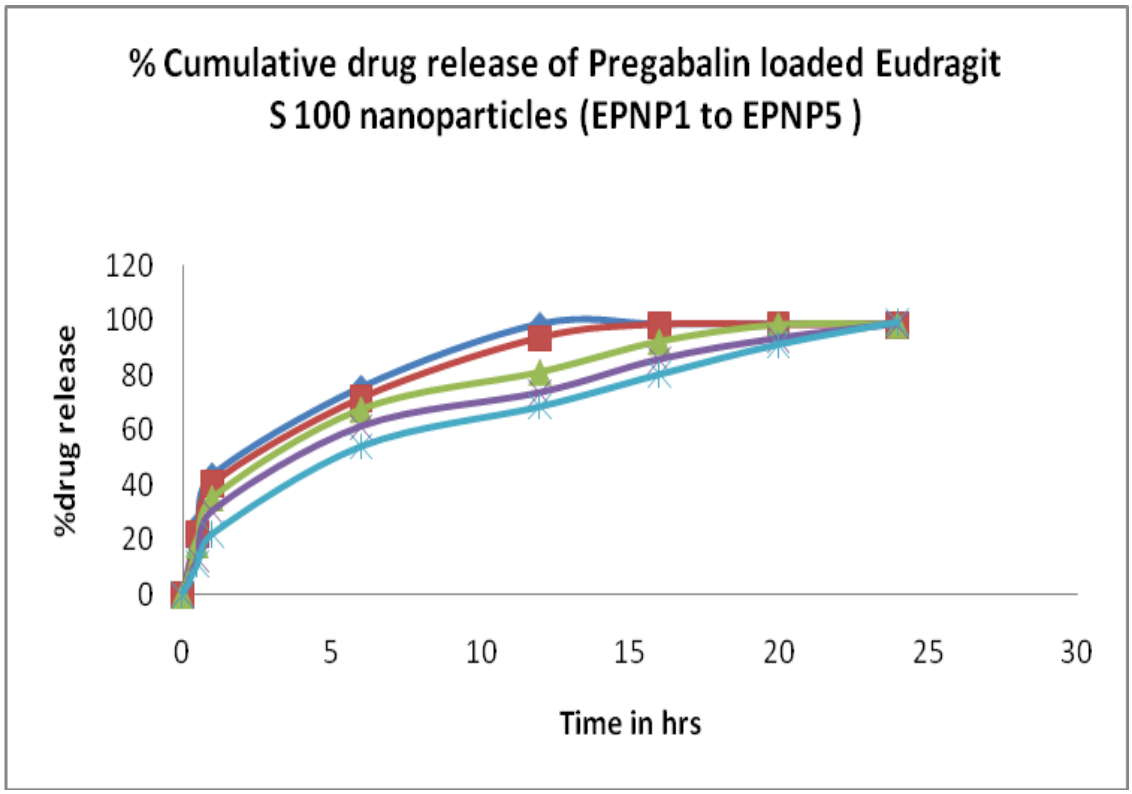


Fig. 13 % Cumulative drug release of Pregabalin loaded Eudragit S 100 nanoparticles (EPNP1 to EPNP5)

IV. CONCLUSION

In the present study Eudragit S100 nanoparticles containing Pregabalin was prepared by solvent displacement technique. The effect of increase in polymer concentration in various parameters like particle size, zeta potential, entrapment efficiency and *in vitro* release profile were studied. The results showed that the *in vitro* drug release for EPNP1, EPNP2, EPNP3, EPNP4 and EPNP5 were found to be 98.47± 0.32, 98.52± 0.21, 98.55± 0.28, 98.57± 0.64 and 99.58± 0.08 respectively. Based on the *in vitro* drug release profile of Pregabalin nanoparticles formulations (EPNP1-EPNP5) EPNP5 was selected as the best formulation in which the particle size was 117.3nm and drug:polymer in the ratio of 1:3 (Pregabalin 100mg:300mg of Eudragit S100).The *in vitro* % drug release of EPNP5 formulation was 99.58± 0.08 and it was found to be suitable formulation for the epileptic patient to manage the symptoms of epilepsy. Hence it can be concluded that the newly formulated Pregabalin loaded Eudragit S 100 nanoparticles may be ideal and effective to control the epilepsy by allowing the drug to release continuously for 24 hrs.

References

1. Nagarajan E, Shanmugasundaram P, Ravichandiran V, Vijayalakshmi A, Senthilnathan B, Masilamani K. "Development and Evaluation of Chitosan Based Polymeric Nanoparticles of an Antiulcer Drug Lansoprazole", Journal of Applied Pharmaceutical Science 5 (04):20-25.2015.
2. Anusha R, Somasundaram I, Ravichandiran V, Kausalya J, Joseprakash, D Senthilnathan B, "Effect of Cholesterol and Surfactant Concentration On Solid Lipid Nanosuspension Of Ropinirole Hydrochloride", Journal of Pharmacy Research" 4(6),1606-1609.2011.
3. Senthilnathan B, Ameerkhan H, Aswini S, Abirami M, Bharath T, Ajithkumar T and Maheswaran A "Review on various approaches on preparation, Characterisation and applications of polymeric Nanoparticles", World Journal of Pharmaceutical Research 4(6):645-663.2015.
4. Karpagavalli L, Senthilnathan B, Maheswaran A, Narayanan N. "Formulation and evaluation of Aceclofenac nanocapsules", Invent Rapid:NDDS 4:1-6.2015.
5. ChizobaEkezie FD, Suneetha J, Uma Maheswari WK, Prasad TNVKV. "Zinc nanoparticulated bitter gourd extract: in-vitro anti-diabetic efficacy", *International Journal of Science and Nature*, 6(4):687-692.2015.
6. Antal I, Kubovcikova M, Zavisova V, Koneracka M, Pechanova O, Barta A. "Magnetic poly(D,L-lactide) nanoparticles loaded with aliskiren: a promising tool for hypertension treatment", *Journal of Magnetism and Magnetic Materials* 380 280–284.2015.
7. Fargnoli AS, Mu A, Katz MG, Williams RD , Margulies KB, Weiner DB, Yang S Bridges CR. "Anti-inflammatory loaded poly-lactic glycolic acid nanoparticle formulations to enhance myocardial gene transfer: an in-vitro assessment of a drug/gene combination therapeutic approach for direct injection", *Journal of Translational Medicine* 2014, 12:171.2014.
8. Reddy AS, Sailaja AK "Preparation characterization of aspirin loaded ethylcellulose nanoparticles", *WJPPS*. 3(6):1781-1793.2014.
9. Sagar SJ, Aparna V B "Formulation characterization of aspirin loaded ethylcellulose nanoparticles". *WJPPS* 3(6):1781-1793.2014.
10. Kumar GP, Razdan BK, Meenakshi B "Formulation and evaluation of nanoparticles containing aetemisinin HCL", *International Journal of Research and Development in Pharmacy and Life Sciences*, 3(2):925-934.2014.
11. Lokhande AK, Sathyendra, Kulkarni R ,"Formulation and evaluation of Glipizide loaded nanoparticles", *IJPPS*, 05(04):147-151.2013.
12. Srinivas P, Pragna S. "Formulation and evaluation of moxifloxacin HCL ocular nanoparticles" *IJND*. 3(2):105-113.2012.
13. Naik JB, Mokale VJ "Formulation and evaluation of Repaglimide nanoparticles as sustained release carriers", *IJPS*, 1(5):259-266.2012.
14. Kesarkar R, Oza G, Pandey S, Dahake R, Mukherjee S, Chowdhary A, Sharon M "Gold nanoparticles: effective as both entry inhibitors and virus neutralizing agents against HIV", Scholars Research Library, *J. Microbiol. Biotech. Res.*, 2 (2):276-283.2012.
15. Choi SW, Kim JH "Design of surface-modified poly (d,l-lactide-co-glycolide) nanoparticles for targeted drug delivery to bone", *J Control Release*, 122:24–30.2007.

Kawashima Y, "Nanoparticulate systems for improved drug delivery", *Adv Drug Deliv Rev* 47:1–2.2001.