EUROPEAN JOURNAL OF BIOMEDICAL AND PHARMACEUTICAL SCIENCES
http://www.ejbps.com

ISSN 2349-8870
Volume: 9
Issue: 3
336-342
Year: 2022

FORMULATION DEVELOPMENT AND EVALUATION OF NANOPARTICLES OF VALSARTAN BY EMULSIFICATION METHOD

Ulsa Chandra Babu[1], V Jhansi Priya Marabathuni[1] and Naidu Narapusetty*[1]

Department of Pharmaceutics, Bellamkonda Institute of Technology & Science, Podili. A.P-523240.

***Corresponding Author: Naidu Narapusetty**
Department of Pharmaceutics, Bellamkonda Institute of Technology & Science, Podili. A.P-523240.

Article Received on 10/01/2022 **Article Revised on 30/01/2022** **Article Accepted on 20/02/2022**

ABSTRACT
Valsartan is an antidepressant which functions pharmacologically as a selective serotonin reuptake inhibitor. Though it is in the same class as other SSRI drugs, it is most often used to treat obsessive-compulsive disorder. As biological half life of drug is 15.6 hrs and belongs to BCS class II. To overcome with these problems, Nanoparticles of Valsartan were formulated by using Ethyl Cellulose, Eudragit RS 100 & Eudragit Rl 100 as a polymer by emulsification method. Among all the 9 formulations F6 formulation is optimized, as it shows maximum drug release at the end of 12hrs which suits the controlled release drug delivery system criteria as per our studies, having acceptable particle size, SEM and Zeta potential value. From the drug release kinetics of F8 formulation of Valsartan Nanoparticles dispersion it was concluded that the F8 formulation follows Zero order drug release with super case II transport mechanism.

KEYWORDS: Valsartan, Nanoparticles, particle size, SEM and Zeta potential.

INTRODUCTION
Valsartan[6] is an orally active nonpeptide triazole-derived antagonist of angiotensin (AT) II with antihypertensive properties. Valsartan selectively and competitively blocks the binding of angiotensin II to the AT1 subtype receptor in vascular smooth muscle and the adrenal gland, preventing AT II-mediated vasoconstriction, aldosterone synthesis and secretion, and renal reabsorption of sodium, and resulting in vasodilation, increased excretion of sodium and water, a reduction in plasma volume, and a reduction in blood pressure.

Structure

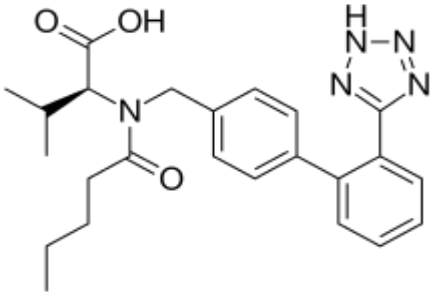


Figure 1: Chemical Structure of Valsartan.

Experimental work
Materials: Valsartan from Spectrum labs, Ethyl cellulose from Signet Chemical Corp., Mumbai, Eudragit RS 100, Eudragit RL 100 from sigma Aldrich Mumbai.

Instruments: Digital balance form Essae-Teraoka ltd, DS-852j, UV Spectrophotometer from PG Instruments T60, FTIR Spectrophotometer from Shimadzu -8400 S and pH meter from Hanna Instruments, Italy.

Pre-formulation studies
The goals of pre-formulation studies are

- To evaluate the drug substance analytically and determine its necessary characteristics
- To establish its compatibility with different excipients.

Spectroscopic study
Identification of pure drug
Solubility studies
Solubility of Valsartan was carried out in different solvents – like 0.1N HCL, 6.8pH buffer and 7.4 pH buffer. Saturated solutions were prepared by adding excess drug to the vehicles and shaking on the shaker for 48 hr. at 25°C under constant vibration. Filtered samples (1ml) were determined spectrophotometrically at 250 nm.

Drug-Excipient Interactions Studies: There is always possibility of drug- excipient interaction in any formulation due to their intimate contact. The technique employed in this study is IR spectroscopy.
IR spectroscopy is one of the most powerful analytical techniques, which offers possibility of chemical identification. The IR spectra was obtained by KBr pellet

method. (Perkin-Elmer series 1615 FTIR Spectrometer).

Determination of UV spectrum of Valsartan

10mg of Valsartan was dissolved in 2-3ml of 7.4pH buffer then makeupto10ml with 7.4 pH buffer so as to get a stock solution of 1000 µg/ml concentration. From the above stock solution pipette out 1ml of the solution and makeup the volume to 10ml using 7.4 pH buffer to get the concentration of 100µg/ml concentration. From this stock solution pipette out 1ml of the solution and makeup the volume to 10ml using 7.4 pH buffer to get the concentration of 10µg/ml concentration, this solution was scanned under UV Spectroscopy using 200-400nm.

Preparation of Calibration Curve of Valsartan[5-10]

Standard calibration curve of Valsartan using 7.4 pH Buffer

Method

10 mg drug was taken accurately in 10ml volumetric flask. It was dissolved in few ml of methanol and make up the volume upto the mark with 7.4 pH buffer to gives 1000 µg /ml. The standard stock solution was then serially diluted with 7.4 pH buffer to get 2 to 12 µg/ml of Valsartan. The absorbance was measured against 7.4 pH buffer as blank at 232 nm using UV spectrophotometer. The absorbance values were plotted against concentration (µg/ml) to obtain the standard calibration curve.

Method of Preparation of Nanoparticles

Valsartan Nanoparticles were prepared by emulsification method. In this method Polymer was dissolved in organic solvent (methanol). Drug is dispersed in this solution. Then this mixuture emulsified in an aqueous phase containing surfactant (polyvinyl alcohol) make an oil in water emulsion by using mechanical stirring, or sonication. After formation of emulsion the organic solvent evaporate by increased the temperature and reduced pressure with continuous stirring.

Formulation code	Drug: polymer	Ratios	Concentration of PVA (%w/v)
F1	Drug : Ethyl cellulose	1:1	2
F2	Drug : Ethyl cellulose	1:2	2
F3	Drug : Ethyl cellulose	1:3	2
F4	Drug : Eudragit RS 100	1:1	2
F5	Drug : Eudragit RS 100	1:2	2
F6	Drug : Eudragit RS 100	1:3	2
F7	Drug : Eudragit RL 100	1:1	2
F8	Drug : Eudragit RL 100	1:2	2
F9	Drug : Eudragit RL 100	1:3	2

Evaluation parameters of Nanoparticles Valsartan[10-12]

The Nanoparticles was evaluated for various parameters

1. Entrapment efficiency
2. Particles size analysis
3. Zeta potential
4. In-vitro drug release studies
5. SEM(Scanning electron microscopy)

Zeta potential

There are three ways by which a solid particle (colloid) dispersed in a liquid media can acquire a surface charge. First, by the adsorption of ions present in the solution. Second, by the ionization of functional groups on the particle's surface. Third, due to the difference in dielectric constant between the particle and the medium. Attention should be paid to the formation of electric double layer at the solid-liquid interface. The zeta Potential is defined as the difference in potential between the surface of the tightly bound layer (shear plane) and the electro-neutral region of the solution. The potential gradually decreases as the distance from the surface increases.

As the concentration of electrolyte increases in the medium, the zeta potential falls off rapidly due to the screening effect of the counter ions (Figure 2). The zeta potential cannot be measured directly; however, it can be calculated using theoretical models and from experimentally determined electrophoretic mobility data. The theory is based on electrophoresis and can be expressed as:

$$\mu = \zeta\varepsilon/\eta$$

Where (µ) is the electrophoretic mobility, (ε) is the electric permittivity of the liquid, (η)
Is the viscosity and (ζ) us the zeta potential.

RESULTS AND DISSUASION

Preformulation studies

Solubility studies

Saturation solubility was carried out at 25^0C using 0.1N HCL, 6.8 and 7.4 phosphate buffer, ethanol, and methanol.

Table 8.1: Solubility Studies Data of Valsartan.

Solvent	Solubility (µg/ml)
Methanol	2.25
Ethanol	1.45
1.2 pH buffer	0.676
7.4 pH buffer	0.652
6.8 pH buffer	0.737

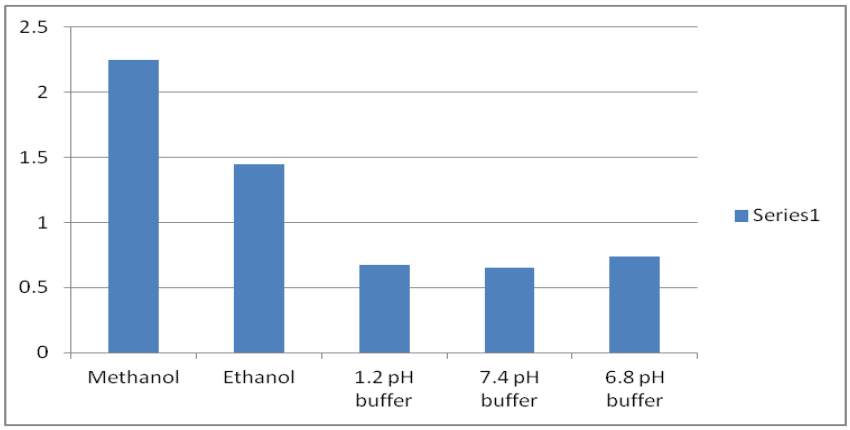


Fig. 8.1: Solubility Chart.

DISCUSSION

From the above conducted solubility studies in various solvents we can say that methanol shows highest solubility than other solvents.

Determination of absorption maximum (λmax)

Determination of Valsartan λ-max was done in pH 7.4 buffer medium for accurate quantitative assessment of drug dissolution rate.

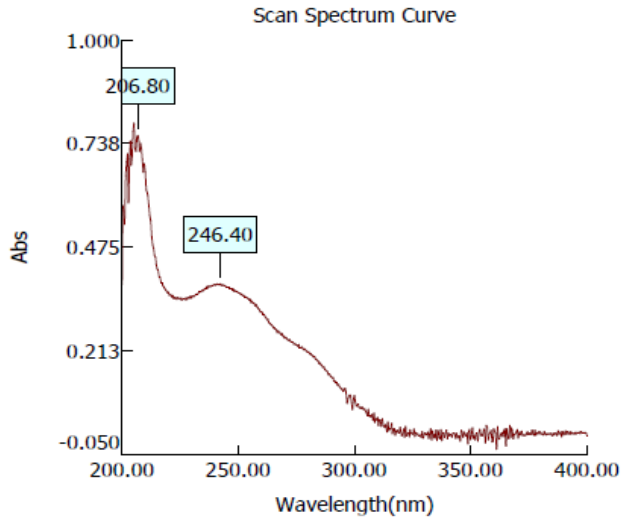


Fig. 8.2: UV Spectrum of Valsartan.

Standard Calibration curve of Valsartan

Table 8.2: Calibration curve of Valsartan in 7.4 pH buffer.

Concentration (µg/ml)	Absorbance
0	0
2	0.108
4	0.214
6	0.325
8	0.433
10	0.535
12	0.634

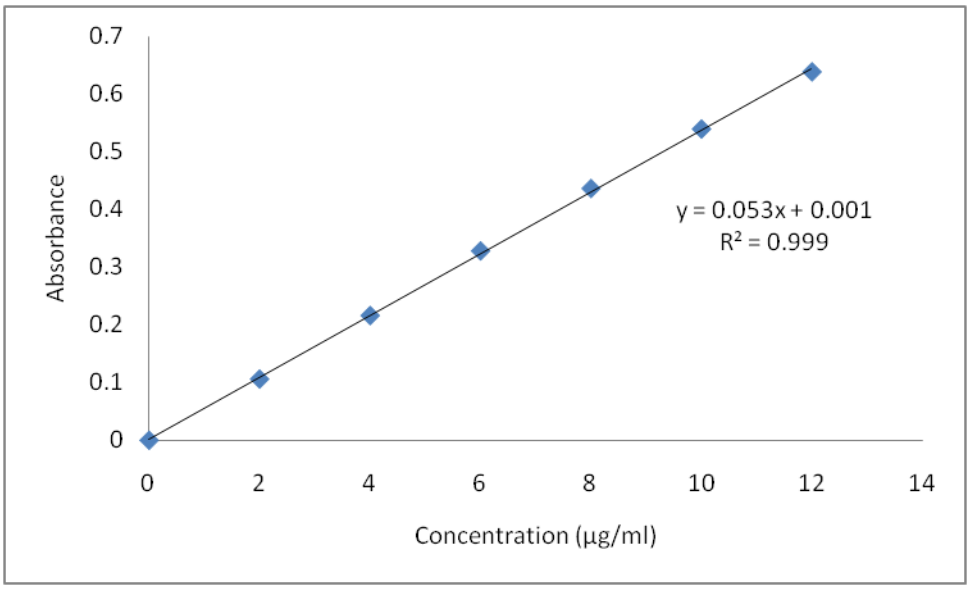


Fig. 8.3: Calibration curve of Valsartan in 7.4 pH buffer.

Drug and Excipients compatibility studies

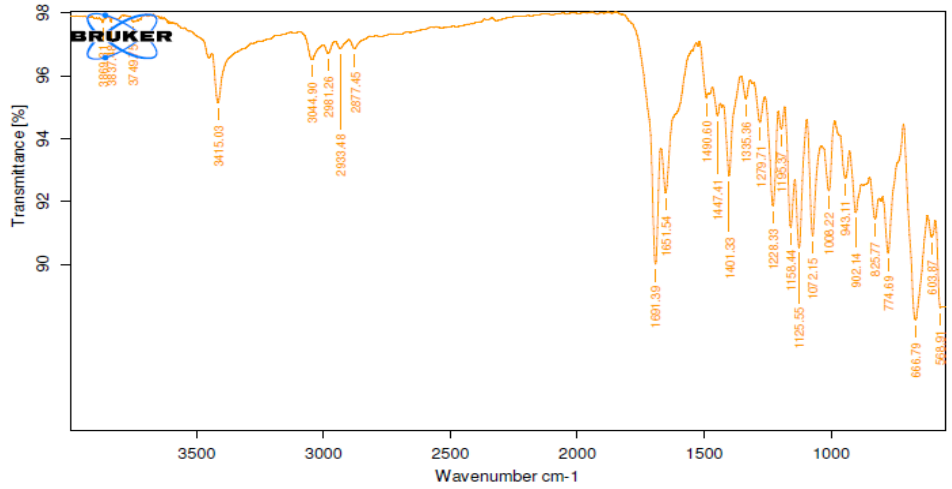


Fig. 8.4: FTIR of Pure Drug.

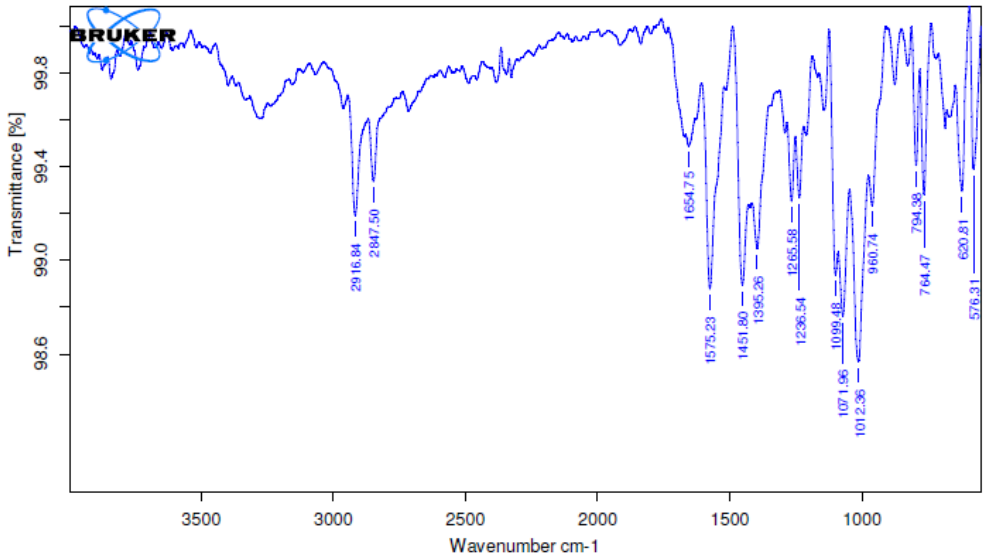


Fig. 8.5: FTIR of Drug + Excipients.

Drug entrapment efficacy

Table 8.3: Drug Entrapment efficacy.

Formulation code	% EE
F1	95.31
F2	96.47
F3	97.23
F4	98.43
F5	96.43
F6	95.08
F7	96.43
F8	95.36
F9	98.13

Scanning Electron Microscopy

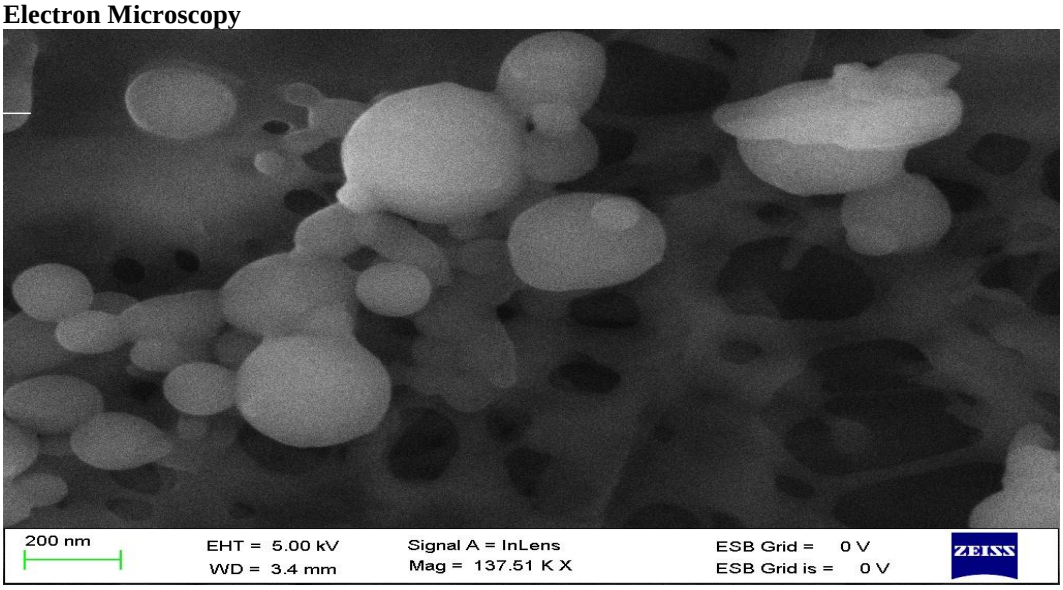
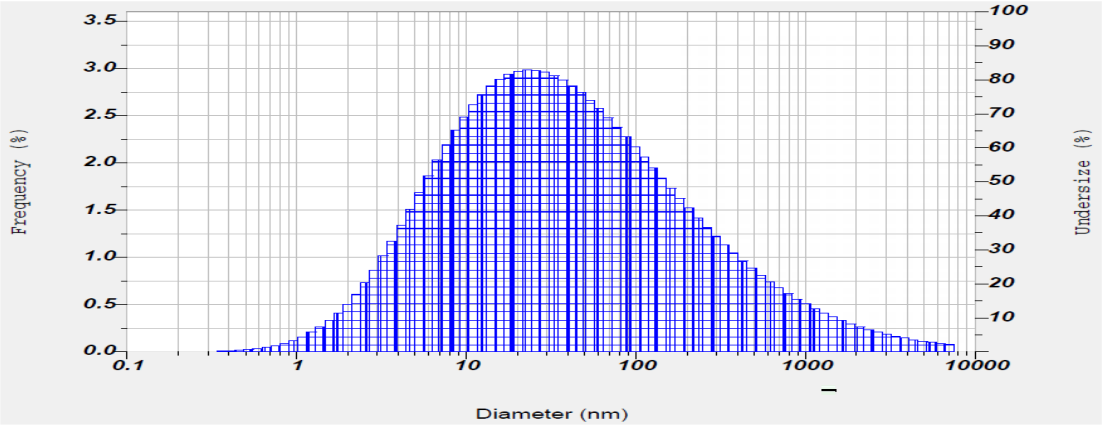
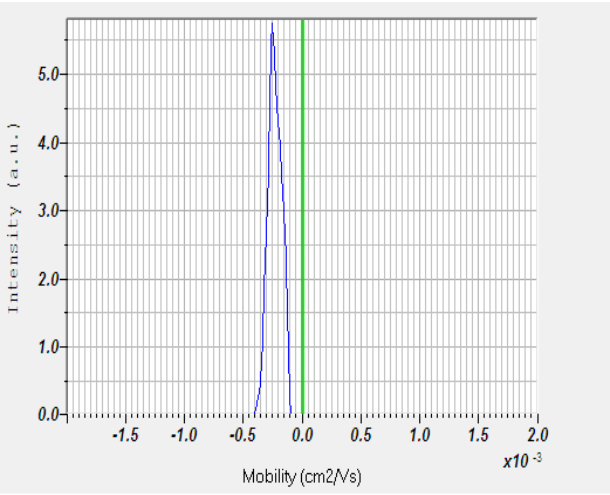


Fig. 8.6: SEM Image of Optimized Nanoparticle formulation.

Particle size analysis



Zeta Potential: The measurement itself is a particle electrophoresis, the particle velocity is determined via the doppler shift of the laser light scattered by the moving particles. The field strength applied was 20 V/cm. The electrophoretic mobility was converted to the zeta potential in mV using the Helmholtz-Smoluchowski equation. At standard measuring conditions (room temperature of 25 °C, water) this equation can be simplified to the multiplication of the measured electrophoretic mobility (µm/cm per V/cm) by a factor of 12.8, yielding the ZP in mV.



Measurement Results

Date	: 29, February 2020
Measurement Type	: Zeta Potential
Sample Name	: np-zeta
Temperature of the Holder	: 25.2 °C
Dispersion Medium Viscosity	: 0.892 mPa·s
Conductivity	: 0.096 mS/cm
Electrode Voltage	: 3.8 V

Calculation Results

Peak No.	Zeta Potential	Electrophoretic Mobility
1	-29.7 mV	-0.000231 cm2/Vs
2	--- mV	--- cm2/Vs
3	--- mV	--- cm2/Vs

Zeta Potential (Mean)	: -29.7 mV
Electrophoretic Mobility Mean	: -0.000231 cm^2/Vs

Invitro diffusion studies of Valsartan nanoparticles

Table 8.4 Invitro diffusion studies of Valsartan nanoparticles.

Time (hrs)	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
1	36.15	40.18	45.46	39.42	34.15	40.81	27.31	22.63	28.49
2	53.16	50.45	57.71	46.98	42.87	46.97	39.52	37.49	36.05
3	67.49	58.08	66.18	58.05	54.98	50.18	51.18	50.02	48.18
4	80.52	70.98	72.31	70.46	66.52	58.51	65.08	62.31	59.17
6	95.75	81.08	85.18	79.32	77.42	65.19	75.98	75.53	65.79
8		97.35	92.21	91.05	83.16	73.94	94.75	91.49	72.43
10			98.42		95.21	82.05		98.61	85.19
12						98.05			96.19

DISCUSSION[13-14]

All the 9 formulations of Valsartan nanoparticle dispersion were subjected to drug release studies.

Formulations F1, F2, F3 containing the ethyl cellulose as polymer. F1 shows 95.75% drug release at the end of 6hrs. Where as F2 formulation shows 97.35% drug release at the end of 8hrs. While the F3 formulation shows 98.42% drug release at the end of 10hrs. As the concentration of polymer increasing drug release time is increased. So further trails were performed using Eudragit RS 100 with same proportions.

Formulations F4, F5, F6 containing the Eudragit RS 100, F6 formulation shows maximum drug release at the end of 12hrs. while Formulation F7, F8, F9 containing Eudragit RL 100, in which F7 formulation shows 94.75% drug release at the end of 8th hour and F8, F9 shows 98.61%, 96.19% drug release at the end of 10, 12hrs.

Among all the 9 formulations F6 formulation is optimized, as it shows maximum drug release at the end of 12hrs which suits the controlled release drug delivery system criteria as per our studies.

Further drug release kinetics were performed to F6 formulation.

Table 8.5: *in-vitro* drug release mechanism of best formulation.

Batch Code	Zero Order R^2	First Order R^2	Higuchi R^2	Peppas R^2	Peppas n
F6	0.967	0.864	0.972	0.676	1.235

From the drug release kinetics of nanoparticles dispersion it was concluded that the formulation F6 shows 97.365 of drug release at the end of 12th hour. It follows zero order release and follows super case II transport mechanism.

CONCLUSION

Based the results concluding that, From the invitro studies we can say that formulation F6 shows best drug release of 98.05% within 12 hrs to release the drug.

The drug release from the Nanoparticles was explained by the using mathematical model equations such as zero order, first order, and equation methods. Based on the regression values it was concluded that the optimized

formulation F6 follows Zero order drug release with super case II transport mechanism.

REFERENCES

1. Sovan Lal Pal, Utpal Jana, P. K. Manna, G. P. Mohanta, R. Manavalan, Nanoparticle: An overview of preparation and characterization, Journal of Applied Pharmaceutical Science, 2011; 1(6): 228-234.
2. Gayatri Khosla, Lakshmi Goswami, Preeti Kothiyal, Sayantan Mukhopadhyay, Nanoparticles: A Novelistic Approach for CNS disorders, Journal of Advanced Pharmaceutical Sciences, 2012; 2(2): 220-259.
3. Abhilash M., Potential applications of Nanoparticles, International Journal of Pharma and Bio Sciences, 2010; 1(1): 1-12.
4. Nagavarma B. V. N., Hemant K. S. Yadav, Ayuz A., Vasudha L.S., Shivakumar H.G, Different techniques for preparation of polymeric nanoparticles – A Review, Asian Journal of Pharmaceutical and Clinical Research, 2012; 5(3): 1-8.
5. A. R. Mullaicharam, Nanoparticles in drug delivery system, International Journal of Nutrition, Pharmacology Neurological Diseases, 2011; 1(2): 103-121.
6. Joachim Allouche, Synthesis of Organic and Bioorganic Nanoparticles: An Overview of the Preparation Methods, Springer-Verlag London, 2013; 27-30.
7. S. Tamizhrasi, A. Shukla, T. Shivkumar, V. Rathi, J. C. Rathi, Formulation and evaluation of Lamivudine loaded polymethacrylic acid nanoparticles, International Journal of PharmTech Research IJPRIF, 2009; 1(3): 411-415.
8. VJ Mohanraj and Y Chen, Research Article Nanoparticles – A Review, Tropical Journal of Pharmaceutical Research, 2006; 5(1): 561-573.
9. Saikat Das, Rinti Banerjee and Jayesh Bellare., Aspirin Loaded Albumin Nanoparticles by Coacervation: Implications in Drug Delivery, Trends Biomater. Artif Organs, 2005; 18(2): 1-10.
10. Lakshmana Prabu S, Shirwaikar AA, Shirwaikar A, Kumar A., Formulation and evaluation of sustained release microspheres of rosin containing Aceclofenac, Ars Pharm, 2009; 50(2): 51-62.
11. Choi, H.K., Jung, J.H., Ryu, J.M., Yoon, S.J., Oh, Y.K. and Kim. C.K., Development of insitu gelling and mucoadhesive acetaminophen liquid suppository, Int. J Pharm, 1998; 165: 33-44.
12. Aejaz A, Azmail K, Sanaullah S and Mohsin A., Formulation and in vitro evaluation of Aceclofenac solid dispersion incorporated gels, International Journal of Applied Sciences, 2010; 2(1): 7-12.
13. Marabathuni VJ, Dinesh P, Ravikumar R, Yamini P, Kiran PS, Hussain SP, Rao CM. Chitosan based sustained release mucoadhesive buccal patches containing amlodipine besylate (AMB). Asian Journal of Research in Pharmaceutical Science. 2017; 7(2): 97-104.
14. Marabathuni VJ, Bhavani M, Lavanya M, Padmaja K, Madhavi N, Babu P, Rao CM. Formulation and evaluation of mouth dissolving Tablets of carbamazepine. Asian Journal of Pharmacy and Technology, 2017; 7(3): 137-43.