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Research Article

FORMULATION AND EVALUATION OF TRIPTANS NANOPARTICLES FOR RAPID RELIEF FROM MIGRAINE

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ABSTRACT

The aim of this study was to prepare and evaluate the triptans nanoparticles such as Zolmitriptan, Naratiriptan, Frovatriptan and Almotriptan by using nanoprecipitation method with Eudragit L-100 as carrier. Using poloxamer 188 (PX) and poly vinyl alcohol (PVA) as stablizers and different drugs to polymers ratios (1:1, 1:2 and 1:3) were compared. The particle size and zeta potential of the Eudragit L-100 nanoparticles were analyzed by HORIBA scientific nano Partica, nanoparticle analyzer SZ-100 and a zetasizer and the morphological structure was visualized by scanning electron microscopy (SEM). The mean particle size of the nanoparticles was found to be 28-120 nm with zeta potential of about +21mV and Entrapment efficiency (EE) of 69.1% to 89.5%. The drug loaded nanoparticles were found to exhibit a spherical shape and have a smooth surface and the completion of the reaction was confirmed by IR spectra. The drug and polymer ratio of 1:3 (A3) with 1% PVA as stabilizer showed particle size of 28.3 nm and polydispersity index of 0.55 and zeta potential of -21.0 mV. The drug and polymer ratio of 1:3 (A6) with 1% poloxamer 188 as stabilizer showed particle size of 81.3 nm and polydispersity index of 0.35 and zeta potential of -18.5 mV. We have concluded that the drug and polymer ratio of 1:3 in present of PVA as stabilizer showed the best results for all the drugs and it can be an appropriate method for preparing nanoparticles as a delivery vehicle for triptans.

KEYWORDS: *Triptan; Eudragit L-100; Nanoparticles; Nanoprecipitation.*

INTRODUCTION

A migraine is a complex neurological condition that involves several changes in the body, including the dilation (widening) of blood vessels, inflammation, and activation of pain receptors. [1, 2]

Triptans also called serotonin 5-hydroxytryptamine (5-HT) receptor agonists, are help to relieve migraine and other migraine symptoms, such as nausea, vomiting, and sensitivity to light, noise, and motion and also certain other headaches, but they do not prevent migraine attacks. Since triptans work by temporarily constricting (narrowing) dilated or widened blood vessels, they should not be taken by people with certain conditions, including coronary artery disease or angina (chest pain), and peripheral vascular disease. People who have a heart attack or stroke, have uncontrolled high blood pressure, or have migraines that are accompanied by weakness or paralysis in an arm or leg, vertigo, ringing in the ears, or speech difficulties, should also avoid triptans. [3]

Triptans have at least three modes of action. These anti-migraine mechanisms are:

1. vasoconstriction of pain producing intra cranial extracerebral vessels by a direct effect on vascular smooth muscle.
2. inhibition of vasoactive neuropeptide release by trigeminal terminals innervating intracranial vessels and the dura mater. The trigeminocervical complex has 5-HT_{1D} receptors that bind dihydroergotamine and triptans in humans.
3. neurotransmission within the trigeminocervical complex in the brain stem and upper cervical spinal column. Rizatriptan has central trigeminal antinociceptive activity. Other possibilities of triptans in antimigraine effects are modulation of nitric oxide dependent signal transduction pathways, nitric oxide scavenging in the brain, and sodium dependent cell metabolic activity. [4]

Triptans may be taken subcutaneously, orally as tablets, capsules, or quick dissolving wafers, or intranasally as a spray. They significantly reduce pain within two hours for most people. In case of mild and less frequent migraine attacks, could be try other pain relievers can be used, including; nonsteroidal anti-inflammatory drugs (NSAIDs), such as acetaminophen, aspirin, ibuprofen, or naproxen or combination products that contain acetaminophen, aspirin, and caffeine. In general, triptans have proved to be effective for migraine attacks associated with moderate to severe pain intensity. [5]

MATERIALS AND METHODS

Materials:

Triptans were received as a gift sample from Apotex Research Private Limited, Bangalore. Eudragit L-100 was from Sigma Aldrich Pvt. Ltd. Poloxamers 188 and PVA was from Apotex India Pvt Ltd, Mumbai. Ethanol was obtained from Merck specialties private limited- world, Mumbai. Tween 80 were procured from Alpha Chemika, Mumbai.

Methods:

Drug excipient compatibility study:

Drug-excipient interaction plays a vital role in the release of the drug from the formulation. Fourier transform infrared spectroscopy (FTIR) has been used to study the physical and chemical interactions between drug and the excipients used. Here weighed amount of drug or physical mixture of drug and polymer (1:1) was mixed with 100mg of potassium bromide (dried at 40-50°C) the mixture was taken and compressed under 10-ton pressure in a hydraulic press to form a transparent pellet. The pellet was scanned by IR Spectrophotometer.

Preparation of triptan-loaded eudragit L-100 nanoparticles:

The Eudragit L-100 nanoparticles containing the drug Almotriptan (A) were prepared by nanoprecipitation method. [6-8]\

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The accurately weighed amount of drug (Almotriptan) and eudragit L-100 in different ratios (1:1, 1:2, 1:3) were dissolved in 2 ml of ethanol. The internal organic phase solution was slowly injected into 10 ml of the external aqueous solution containing 1% of stabilizer (Poloxamer 188 / PVP) and 0.02ml Tween 80 and the mixtures were continuously stirred at 500 rpm using a mechanical stirrer (Remi Motors- RO-123, RPM 4000) at room temperature for 50 minutes, Subsequently, the pH was adjusted to 5.5 with the help of a required amount of 0.1N, NaOH.

Internal organic phase solutions are always composed of solvents, making the drug and eudragit L-100 soluble completely, and the external aqueous phase comprises aqueous solution with surfactant in it. The surfactant can penetrate into the Almotriptan nanoparticles during the nanoprecipitation process to form a stable nanoparticle delivery system. Ethanol was completely removed by rotary vacuum evaporation under a water bath at 32°C. The nanoparticles formed were centrifuged using a refrigerated centrifuge (Eppendorf Centrifuge 5430R) at 11,000 rpm for 60 minutes. The supernatant was separated and analyzed. The Almotriptan nanoparticles were collected, washed three times with distilled water and freeze dried.

The best formulation procedure has been repeated with the Zolmitriptan (Z), Naratriptan (N) and Frovatriptan (F).

Characterization of Eudragit L-100 Nanoparticles:

Shape and surface morphology:

The shape and surface morphology of the Eudragit L-100 nanoparticles was visualized by scanning electron microscopy (LEO-430 Cambridge and U.K). The samples were prepared by lightly sprinkling nanoparticles on double-sided adhesive tape on an aluminum stub. The stubs were then coated with gold to a thickness of 200 to 500 Å under an argon atmosphere using a gold sputter module in a high vacuum evaporator. The samples were then randomly scanned and photomicrographs were taken at different magnifications with SEM.

Particle size and Zeta potential measurement:

Particle size was measured with the help of HORIBA Scientific Nano Partica, nanoparticle size analyzer SZ-100. For the determination of particle size, samples were prepared by tenfold dilution of 1ml of the nanoparticulate suspension with distilled water. The analysis was carried out in triplicate.

The average particle size and polydispersity index and Zeta potential were measured by HORIBA scientific nano Partica, nanoparticle analyzer SZ-100.

Drug entrapment efficiency:

The entrapment efficiency of the formulation was determined upon the centrifugation of a fixed quantity of the aqueous nanoparticulate suspension (about 2ml) at 11000 rpm for 60 minutes at 4°C. (SIGMA 3-18K, Sartorius). The absorbance of the unencapsulated drug in the supernatant was evaluated using a UV-VIS spectrophotometer (UV-1800 Pharma Spec, Shimadzu) using a calibration curve with plain Eudragit L-100 nanoparticles (ENPs) as the blank which had also been prepared and treated similarly to the drug-loaded nanoparticles excluding the drug. The analysis was carried out in triplicate and the mean was taken. The drug entrapment of the nanoparticles was calculated by the following equation.

$$\%Drug\ entrapment\ efficiency = \frac{Initial\ amount\ of\ the\ drug\ added\ -\ Amounth\ of\ drug\ in\ supernatant}{Initial\ amount\ of\ drug\ added} \times 100$$

RESULTS AND DISCUSSION

The IR spectrum of pure drug was found to be similar to the standard spectrum of Triptans which was in compliance with I.P. standards. [10]

Drug-excipients compatibility study was carried out by FTIR technique and it shows that there is no interaction between Triptans and other excipients used as all the characteristic peaks of the drug remained unchanged when mixed with excipients. (**Figures 1, 2, 3, 4 & 5**).

Shape and Surface Morphology:

The shape and surface morphology of the Almotriptan-loaded Eudragit L-100 Nanoparticles (E-NP) were visualized by scanning electron microscopy (SEM). It was revealed that the nanoparticles are round in shape and have a smooth surface. (**Figures 6 & 7**)

Particle size and Zeta potential measurement of nanoparticles:

The particle size and zeta potential of the eudragit L-100 nanoparticles were analyzed by HORIBA scientific nano partica, nanoparticle analyzer SZ-100 and a zetasizer.

The values for the average particle size, zeta potential, and polydispersity index are tabulated. **(Table 2)**

The drug and polymer ratio of 1:3 (A3) with 1% PVA as stabilizer showed particle size of 28.3 nm and polydispersity index of 0.55 and zeta potential of -21.0 mV.

The drug and polymer ratio of 1:3 (A6) with 1% poloxamer 188 as stabilizer showed particle size of 81.3 nm and polydispersity index of 0.35 and zeta potential of -18.5 mV.

The drug and polymer ratio of 1:3 showed the best results for all the drugs. **(Figures 8 & 9)**

Formulation "A3" of Almotriptan nanoparticles is selected as optimum formulation, and the procedure has been repeated with the Zolmitriptan (Z), Naratriptan (N) and Frovatriptan (F). **(Table 3)**.

Entrapment efficiency:

Entrapment efficiency of the triptan-loaded eudragit L-100 nanoparticles was determined and the data is shown in Tables 2 & 3.

Among all the formulations, A3 showed an average drug entrapment efficiency of 89.7±0.7%, which is highest amongst all the formulations.

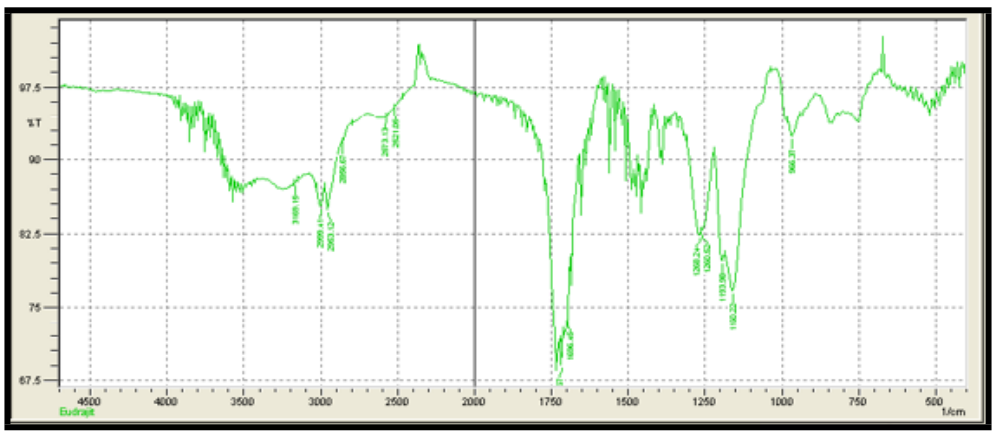

Fig. 1: FTIR SPECTRA OF EUDRAGIT L100 (PURE DRUG)

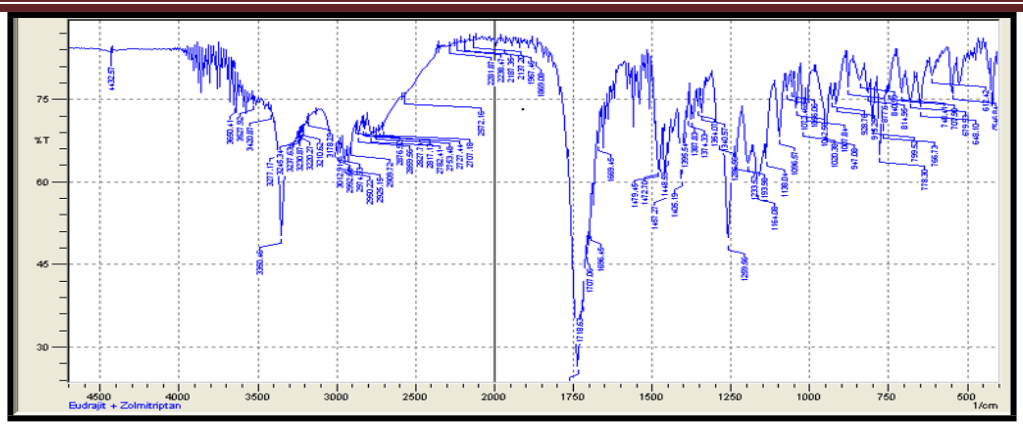

Fig. 2: FTIR SPECTRA OF EUDRAGIT L100 + ZOLMITRIPTAN

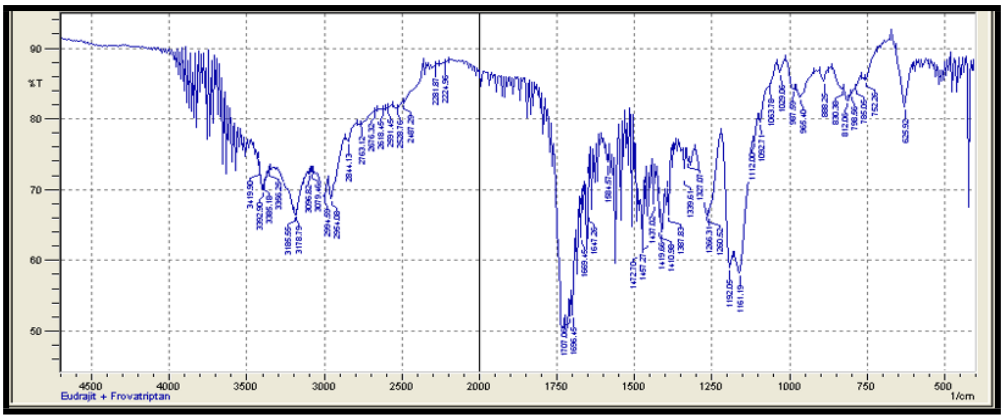

Fig. 3: FTIR SPECTRA OF EUDRAGIT L100 + FROVATRIPTAN

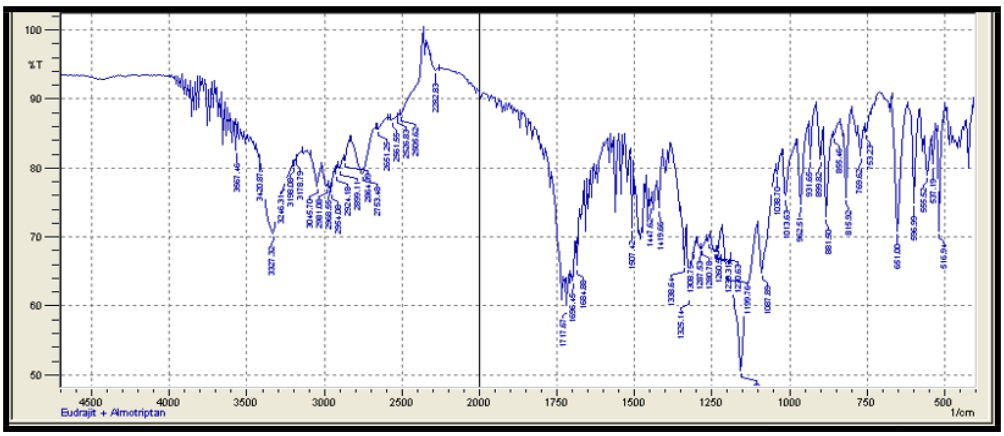

Fig. 4: FTIR SPECTRA OF EUDRAGIT L100 + ALMOTRIPTAN

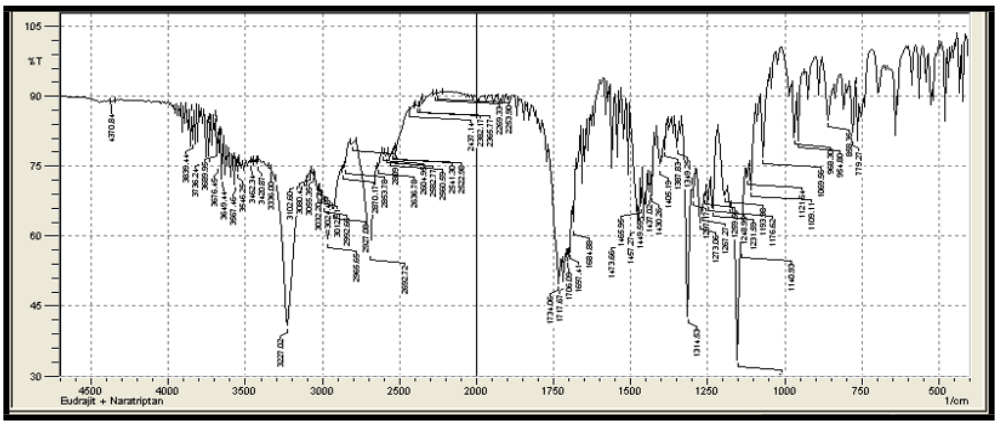

Fig. 5: FTIR SPECTRA OF EUDRAGIT L100 + NARATRIPTAN

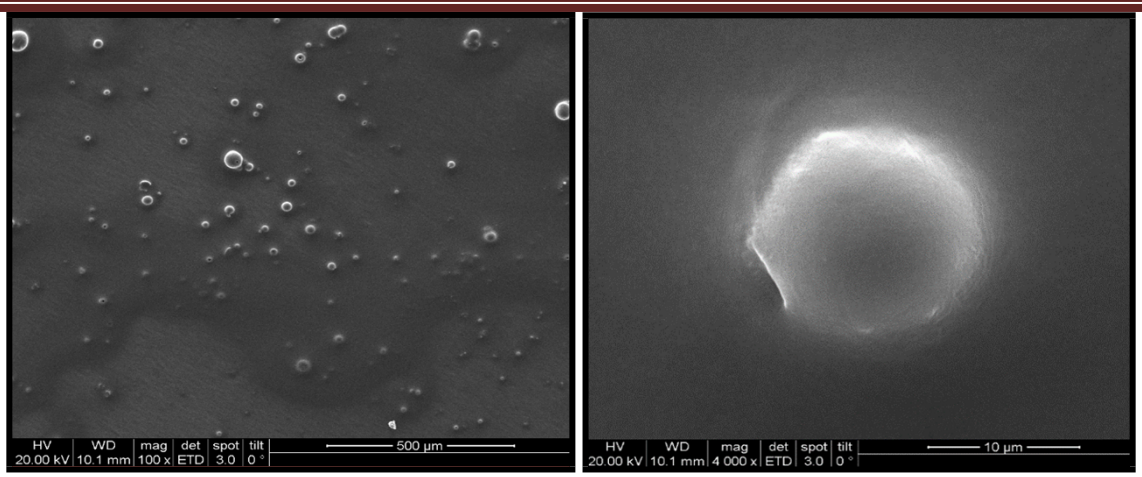

Fig. 6, 7: APM Images of Drug loaded ET-NP

Table No. 1: Experimental control factors for Triptan-Loaded Eudragit L-100 nanoparticles formulation

S. No	Ingredients	A1	A2	A3	A4	A5	A6
	Internal phase						
1	Drug: Polymer Concentration	1:01	1:02	1:03	1:01	1:02	1:03
2	Ethanol (ml)	2	2	2	2	2	2
	External phase						
1	Tween 80 (ml)	0.02	0.02	0.02	0.02	0.02	0.02
2	Water (ml)	10	10	10	10	10	10
3	PVA (%)	1	1	1	-	-	-
4	Poloxamer 188 (%)	-	-	-	1	1	1

Table No. 2: Data for Particle Size, Entrapment Efficiency, Zeta Potential, Polydispersity Index, formulation of Almotriptan

Formulation	Average Particle Size ± S.D	Zeta Potential ± S.D	Polydispersity Index ± S.D	Entrapment Efficiency ± S.D
1.Almotriptan (A1)	71.5 ± 9.8	-20.1 ± 1.0	0.38 ± 0.28	72 ± 0.4
2.Almotriptan (A2)	30.6 ± 1.6	-20.7 ± 0.6	0.43 ± 0.32	85 ± 1.7
3.Almotriptan (A3)	28.3 ± 2.9	-21.0 ± 0.1	0.55 ± 0.24	89 ± 0.7
4.Almotriptan (A4)	120.7 ± 2.6	-16.6 ± 1.4	0.39 ± 0.14	67 ± 1.7
5.Almotriptan (A5)	87.5 ± 3.5	-19.7 ± 2.3	0.23 ± 0.19	69 ± 1.3
6.Almotriptan (A6)	81.3 ± 6.6	-18.5 ± 0.2	0.35 ± 0.14	75 ± 1.5

N=3; Values are mean ± standard deviation

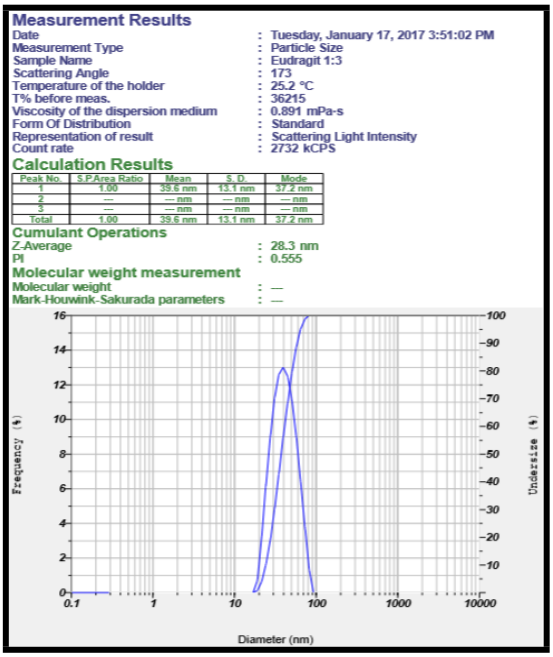

Fig. 8: Particles size Measurement of Nanoparticles

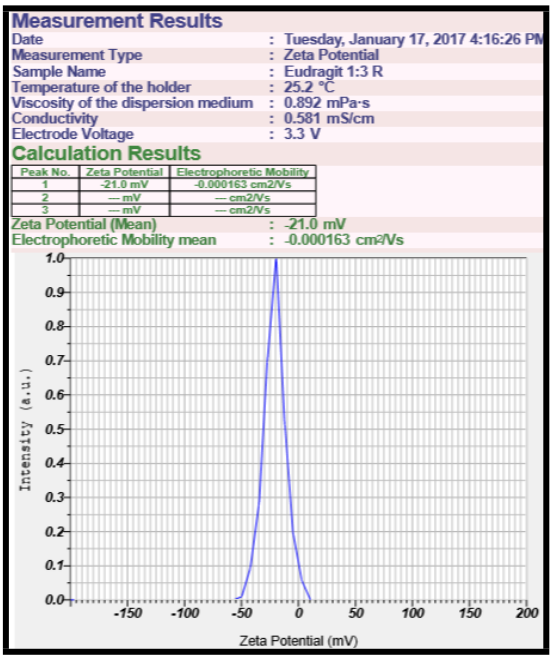

Fig. 9: Zeta Potential Measurement of Nanoparticles

Table No. 3: Data for Particle Size, Entrapment Efficiency, Zeta Potential, Polydispersity Index, of Zolmitriptan (Z), Naratriptan (N) and Frovatriptan (F).

Formulation	Average Particle Size ± S.D	Zeta Potential ± S.D	Polydispersity Index ± S.D	Entrapment Efficiency ± S.D
1.Zolmitriptan (Z)	47.5 ± 4.5	-20.1 ± 0.6	0.49 ± 0.23	88 ± 1.1
2.Naratriptan (N)	59.5 ± 2.4	-22.2 ± 0.7	0.50 ± 0.14	80 ± 1.7
3.Frovatriptan (F)	45.5 ± 5.7	-21.1 ± 0.1	0.34 ± 0.17	79 ± 0.4

N=3; Values are mean ± standard deviation

CONCLUSION

Nanoparticles were prepared with nanoprecipitation technique. It is a rapid and easy technique mainly used for poorly soluble drugs. The nanoparticles were formed spontaneously. Nanoparticles were characterized by particle size distribution, zeta potential analysis, drug entrapment efficacy, polydispersity index, surface morphology and the preformulation studies such as, IR spectra studies.

The entrapment efficiency of Almotriptan, Zolmitriptan, Naratriptan and Frovatriptan was found to be 89.7±0.1%, 88±0.1%, 80±0.7%, 79±0.4% and particle size is 28.3nm, 47.5nm, 59.5nm, 45.5nm respectively.

The mean zeta potential for Almotriptan, Zolmitriptan, Naratriptan and Frovatriptan was found to be -21.0 mV, -20.1 mV, -22.2 mV, -21.1 mV respectively.

FTIR technique shows that there is no interaction between the triptans and other excipients used as all the characteristic peak of the drug are remained unchanged when mixed with excipients.

The drug and polymer ratio of 1:3 (A3) with 1% PVA as stabilizer showed particle size of 28.3 nm and polydispersity index of 0.55 and zeta potential of -21.0 mV.

The drug and polymer ratio of 1:3 (A6) with 1% poloxamer 188 as stabilizer showed particle size of 81.3 nm and polydispersity index of 0.35 and zeta potential of -18.5 mV.

The shape and surface morphology of the drug-loaded eudragit L-100 nanoparticles (A3) was visualized by scanning electron microscopy (SEM). The nanoparticles were spherical in shape and have a smooth surface.

So it was concluded that the drug to polymer ratio of 1:3 with 1% PVA as stabilizer showed the best results for all the drugs and it can be suggested that nanoprecipitation method is appropriate for preparing nanoparticles as a delivery vehicle for triptans.

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