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FORMULATION AND IN-VITRO EVALUATION OF RIZATRIPTAN BENZOATE SOLID LIPID NANOPARTICLES FOR THE TREATMENT OF EPILEPSY

Vipin Singh Yadav*, Dr. Shamim, Mrs. Muskan Bhardwaj

IIMT College of Medical Sciences Ganga Nagar Meerut, U.P., India.

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***Corresponding Author**
Vipin Singh Yadav
IIMT College of Medical Sciences Ganga Nagar Meerut, U.P., India.

ABSTRACT

Epilepsy is one of the most common neurological disorders that affects people of all ages. The majority of people diagnosed with epilepsy may be alive Seizures-free life with appropriate antiepileptic drugs. In this context, this review provides up-to-date information on the various botanical ingredients that may: Treatment of different types of seizures via different signaling pathways in preclinical studies. The purpose of this review is to help you focus About the potential of anti-Epilepsy drugs and the pharmacology of various plant components Reasonable rationale for its use as an alternative treatment. The solid-lipid nanoparticles (SLNs) are a new class of nanocarriers which are based on the combined properties of fatty emulsion, liposomes and polymeric particles. The SLN comprises of the nanosized range spherical solid lipid particles. These lipid-based particles are capable of providing sustained release of their constituents and can exhibit targeted drug delivery if administered parenterally. The desired drug which is to be encapsulated into the nanostructured lipid carriers was firstly dispersed or dissolved either into the melted lipid which was solid at the room temperature or into the mix of an oil (liquid lipid) and a melted solid fatty. Then the resulting solid product was milled with the help of ball mill or mortar pestle up to the size of 50-100 micron. The product was characterized by X-ray diffraction (XRD). The polydispersity index and particle size of product obtained from the cold HPH technique are more as that of the hot HPH method.

KEYWORDS: Epilepsy, Seizures, emulsion, lipids.

INTRODUCTION

DRUG DELIVERY SYSTEMS

The drugs having problems related to their solubility and bioavailability are intended to be delivered through any novel delivery system to overcome the shortcomings and get the desired therapeutic effect on the body. The various techniques involved in enhancing the properties of drug involve precipitation, micronization, nanonization, use of surfactants or drug coating. Other than these conventional methods, active attempts are being made to upgrade the drug efficacy by encapsulating the drug into suitable nano carriers as drug delivery systems. The efficacious implementation of nanoparticles as drug delivery system depends on upon various factors such as penetration capacity of the system through a number of physiological as well as anatomical barriers, the sustained release of their constituents and their ability to remain stabilized in nanometer size range also. However, the shortage of the variety of safe polymers, which could get the regulatory approval along with the high cost of the available polymers have made it more difficult for the application in nanoparticles formulation for clinical medicines. To conquer these limitations, lipid has been used in place of polymers to act as a delivery system, especially in case of lipophilic active constituents and these lipid-based nanoparticles are known as the Solid-Lipid Nanoparticles (SLNs) which are drawing more and more attention of the researchers. The lipid matrix made in the SLNs are prepared by the physiologically tolerated fat content which results in the decrease in the potential risk of chronic or acute toxicity which can occur in case of polymeric nanoparticles. The SLNs are considered to be the favourable systems of drug delivery in advanced era of submicron-sized emulsions of lipid in which the solid lipid is being used in place of the liquid lipid (oil). These solid-lipid nanoparticles exhibit several properties like nano ranged size, larger surface area, increased drug loading and the interfacial interaction of phases. These systems have the capability to enhance the therapeutic performance of the pharmaceutically active materials.

SOLID LIPID NANOPARTICLE FOR ORAL DELIVERY

The lipid nanoparticles made with the solid matrix have emerged as an efficient carrier of drug for the enhancement of oral bioavailability and GI absorption of many poorly soluble drugs, chiefly the lipophilic ones. This system can also be used for the sustained release and are being considered and studied for their abilities to deliver the drug orally. The lipids chosen for the nanoparticles preparations should be biocompatible, biodegradable as well as physiological which minimizes the risk of toxicity associated with the polymeric

nanoparticles. Along with that, the solid matrix results in the enhanced stability of the formulation as compared to other nano-carrier liquid preparations. Such nanoparticles preparations can be carried out using various techniques and it is easy to move up from lab scale production to industrial scale production during the process. It was observed that the solid lipid nanoparticles provide improved drug entrapment efficiency as well as bioavailability and oral absorption were also enhanced in the oral administration.

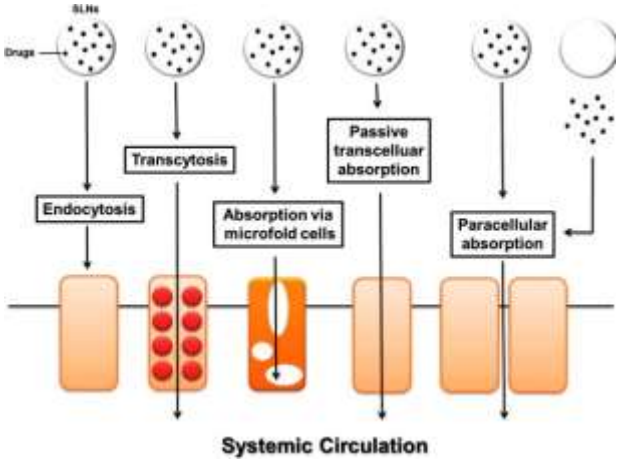


Fig. 1: Solid lipid nanoparticles reaching systemic circulation via oral route.

Fig 1.1 shows the various pathways which could be followed by SLNs to reach into systemic circulation via oral route.

Due to several combinations of lipids and their morphologies, the chemical and physical characteristics of these lipid-matrix based systems can get very complicated. The drug solubility is dependent upon their morphologies, the morphology interconversions with respect to time and their chemical structure along with the digestion of lipids all should be observed and kept in mind to get the desired results.

The perks of lipid-based formulations cover

- The improved GI absorption and reduced instability of the lipophilic, poorly soluble drugs.
- Feasible reduction or withdrawal of several processing operations and steps like selection of salt, determination of a steady crystalline form of the API, taste-making, coating and tedious process of clean-ups while manufacturing any cytotoxic or very potent drug products.
- Reduced chances of food-drug interactions.

- Comparative ease in manufacturing due to the use of easily available tools and equipment.

The in-vivo outcome of SLNs depends primarily on the route of administration and the process of distribution i.e. the biological material adsorbing on the surface of particles and the SLN constituents desorbing in the biological atmosphere. Solid lipid nanoparticles consist of physiological lipids or related waxes which helps in the transportation pathways and the metabolism process to be carried out with more ease and hence assure the in-vivo journey of the carrier to a greater extent. The process of lipid digestion in the body is shown in Fig. 1.2.

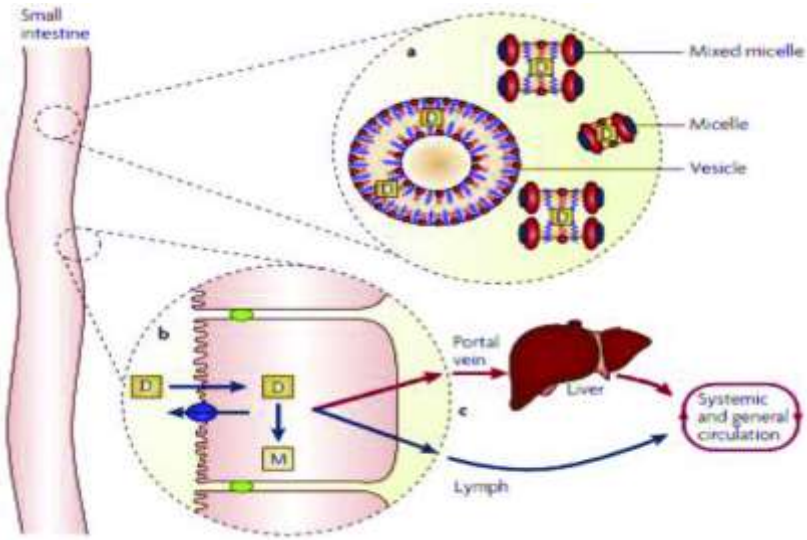


Fig. 2: Digestion of lipid and process of drug solubilisation in small intestine.

Lipases are the most significant enzymes for the degradation of solid lipid nanoparticles and are present in many tissues and organs. Lipases produce free fatty acids and fractional glycerides by splitting the ester linkage. They need to get activated by an oil or water interface which leads to the opening of the catalytic centre. The in-vivo studies show that SLNs with different compositions show different velocities of degradation by the pancreatic lipase enzyme. Every oral route solid lipid nanoparticle formulation either involves any aqueous dispersion or they are loaded in any conventional dosage form such as capsules, tablets or pellets. The environment of stomach supports the aggregation of particles because of the high ionic strength and acidity. It is quite possible that the food present in the stomach will have a great effect on the performance of the SLNs, although no such experimental proof or data have been found yet as per our knowledge.

Solid Lipid Nanoparticles (SLNs)

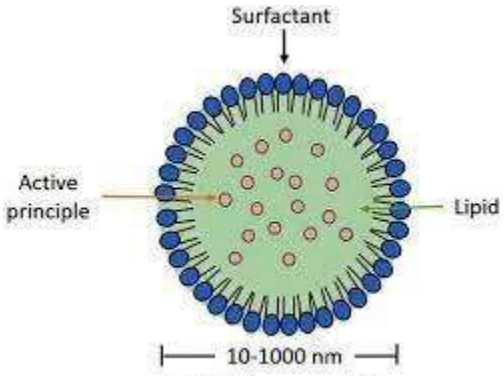


Fig. 3: Structure Of SLN.

The SLNs are made of the hydrophobic core of lipid which remains solid at room temperature and has the phospholipid monolayer coating over it. The hydrophobic solid core consists of the drug which is dispersed or dissolved into the solid matrix of the lipid and the phospholipid hydrophobic chains gets embedded into this solid lipid matrix. This system has the capacity to carry both hydrophilic as well as hydrophobic drugs and diagnostics in it. The structure of SLN is shown in the fig.1.3.

The solid lipid nanoparticles consist of the combined properties of fat emulsion, liposomes and polymeric nanoparticles. They possess several advantages such as non-toxic nature, better bioavailability, chemically stability from hydrolysis, biodegradability, coalescence, physical stability and efficient lipophilic drug carrier.

The main difference between the liposomes and the lipid emulsion is that the basic structure of lipid emulsion consists of a neutral hydrophobic oil core covered with a amphiphilic lipid monolayer while the liposomes comprises of the amphiphilic phospholipid bilayer as outer covering and has aqueous chamber inside. The solid lipid nanoparticles can be administered through many routes as shown in Fig.1.4 and their in-vivo activity depends on these routes of administrations.

Advantages of SLNs

- SLNs exhibits much better stability and gives better scope of upgradability as than that of the liposomes.
- The lipid matrix of the SLNs consists of the physiological lipid which lowers the risk of either acute or chronic toxicity.
- The SLNs possesses long term and high physical as well as chemical stability.

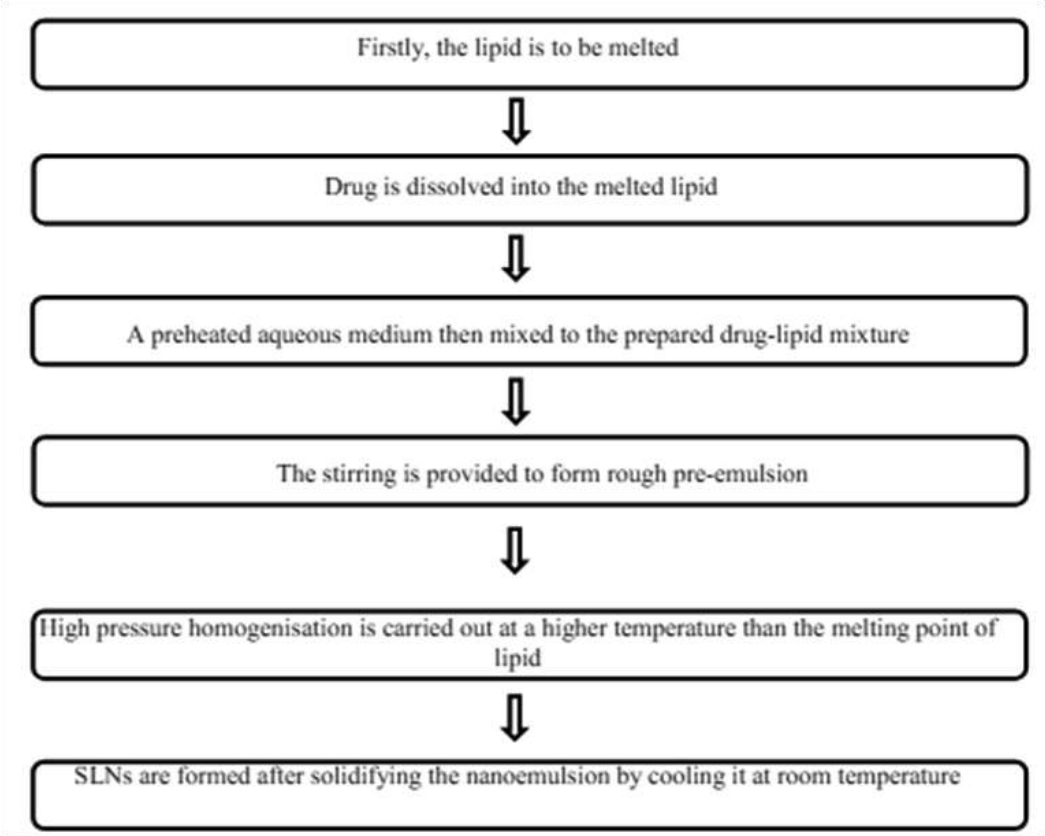
- The manufacturing of solid lipid nanoparticles is comparatively easier than the preparation of bipolymeric nanoparticles.
- The solid lipid nanoparticles have good control over the release kinetics of the entrapped active component.
- SLNs are capable of improving the bioavailability of the incorporated bioactive compound.

Methods of Preparation of SLNs

There are several production methods through which we can achieve the solid lipid nanoparticles at large scale production -:

1. **High Pressure Homogenisation:** HPH is an influencial and reliable technique for the preparation of solid lipid nanoparticles. In this approach, the high-pressure homogenizers thrust the liqiuid at a very high pressure of 100-2000 bar through a slender gap of few microns range size. This elevates the fluid to very high velocity of over 1000Km/h on a very short distance. The very high shear stress and cavitation forces produced by these conditions leads to the disruption of particles to submicron range At first, the HPH technique was adopted for the formulation of solid lipid nano-dispersions.

2. **Hot High Pressure Homogenisation**



The desired drug which is to be encapsulated into the nanostructured lipid carriers, was firstly dispersed or dissolved either into the melted lipid which was solid at the room temperature or into the mix of an oil (liquid lipid) and a melted solid lipid. Now, in the hot homogenization process, the hot lipid melt having the dissolved drug would be dispersed into a hot solution of surfactant with continuous and vigorous stirring. The temperature must be maintained 5-10 ○C higher than the melting point of the solid lipid or the whole lipid blend. Now this preemulsion should be treated under the high pressure homogenizer regulated to the same temperature as earlier and the cycles as three cycles adjusted at 500 bar or two cycles adjusted at 800 bars. The technique in mainly used in case of lipophilic and poorly soluble drugs. Since, the operating time and heat exposure time is short, some heat sensitive or thermolabile drugs can also be safely handled. But this techniques is not useful in case of hydrophilic drug incorporation into SLNs as the higher fraction of drug content in water at the time of homogenization will lead to low entrapment efficiency.

Epilepsy

Epilepsy is one of the oldest known illnesses in Humanity and still the most common neurological condition that affects people of all age's definitely. Estimated50 million people worldwide have been diagnosed with epilepsy. Higher in developing countries than in developed countries Countries with low economic status and limited Access to Health Care. Our understanding Pathophysiology of epilepsy is advancing Dramatically in the last 30 years, especially Their cell physiology and genetics. Drug treatment Epilepsy has made remarkable progress with it. Since 1978, many new antiepileptic drugs have been introduced. However, the improvement in clinical outcomes. It was below expectations. Up to 1/3 Patients with persistent or unacceptable seizures. Epilepsy is an ancient illness that has been historically described from the time of the ancient Babylonians to the present day. Epilepsy is characterized by an unpredictable frequency of seizures, but epilepsy is a common neuropathy that affects people of all ages. In fact, epilepsy presents with bimodal onset, most commonly in childhood and adulthood (Institute of Medicine2012). However, it is also a series of illnesses with varying severity, very different types and causes of seizures, and different effects on individuals and their relatives. In addition to living with epilepsy and its seizures and coexisting health conditions, the challenges faced by millions of people with epilepsy include access to quality health care and learning about health care. And as a response to stigma and general public misunderstandings, including coordination, dosing, professional independent living, and other community services. In this way, epilepsy puts a

great deal of strain on individuals, families and society as a whole.

The purpose of this review is to help you focus About the potential of antiepileptic drugs and the pharmacology of various plant components Reasonable rationale for its use as an alternative treatment. To understand seizures and epilepsy, you need to fully understand the official terminology and nomenclature used to describe seizures and epilepsy. According to the International League Against Epilepsy (ILAE), which is responsible for terms and nomenclature related to seizures and epilepsy, seizures are defined as abnormal electrical damage due to a network of neurons.

Epilepsy Types

1. Generalized epilepsy
2. Focus epilepsy
3. Unknown whether systemic epilepsy or partial epilepsy

DRUG AND EXCIPIENTS PROFILE

Drug Name: Rizatriptan Benzoate

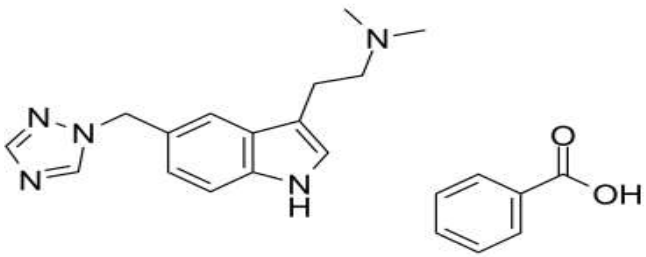


Fig. 4: Structure of RZT Benzoate.

Source: Synthetic.

Description: White to off-white colour powder.

Chemical Name

2 benzoic acid; *N*,*N*-dimethyl-2-[5-(1,2,4-triazol-1-ylmethyl)-1*H*-indol-3-yl] Ethan amine.

M.W: 391.5g/mole.

M.F: $C_{22}H_{25}N_5O_2$.

M.P: 178-180ºC.

Solubility: 42mg/mL in H2O.

Purity: > 99%.

Storage: Stored at room temperature.

Pharmacokinetic Data

Protein binding: 14%.

Half-life: 2-3hours.

pH range: 7.2.

pkaValue:9.56

Oral bio-availability: 40s%

Nature: Hydrophobic.

Identification: 220–400nm in UV spectrophotometer.

Route of administration: oral

Dose: 5mg, 10mg.

Dosage form: tablets

Therapeutic categories

It is a selective agonist of serotonin (5-hydroxytryptamine; 5-HT) type 1B and 1D receptors.

Use

Rizatriptan is used to treat migraines.

It helps to relieve headache, pain.

Excipient Name

1. Tween 20
2. Stearic acid
3. Span 80

RESULTS AND DISCUSSION

The purpose of this review is to help you focus About the potential of antiepileptic drugs and the pharmacology of various plant components Reasonable rationale for its use as an alternative treatment. To understand seizures and epilepsy, you need to fully understand the official terminology and nomenclature used to describe seizures and epilepsy. According to the International League Against Epilepsy (ILAE), which is responsible for terms and nomenclature related to seizures and epilepsy, seizures are defined as abnormal electrical damage due to a network of neurons.

Preformulation Studies

1. **Melting Point Determination:** The melting point of Rizatriptan Benzoate, API was found to be 178-181℃.
2. **Solubility Study:** RZB was practically insoluble in water, slightly soluble in Chloroform and freely soluble in Methanol and Ethanol.
3. **Calibration curve of Rizatriptan Benzoate**

Table 1: Standard Calibration Curve of RZT Benzoate.

S. No.	Concentration (µg/ml)	Absorbance (226nm)
I.	02	0.194
II.	04	0.340
III.	06	0.582
IV.	08	0.691
V.	10	0.844

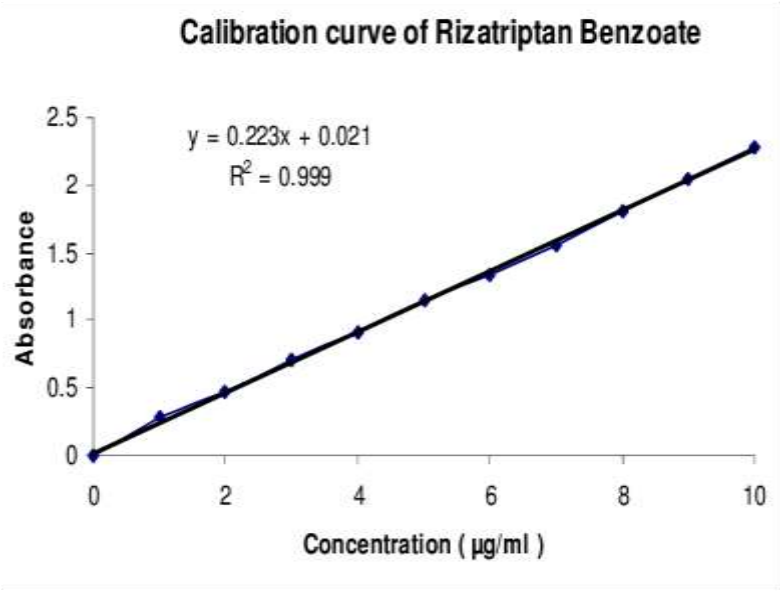


Fig. 5: Standard Calibration Curve of RZT Benzoate.

4. Physical drug Excipients Compatibility Studies

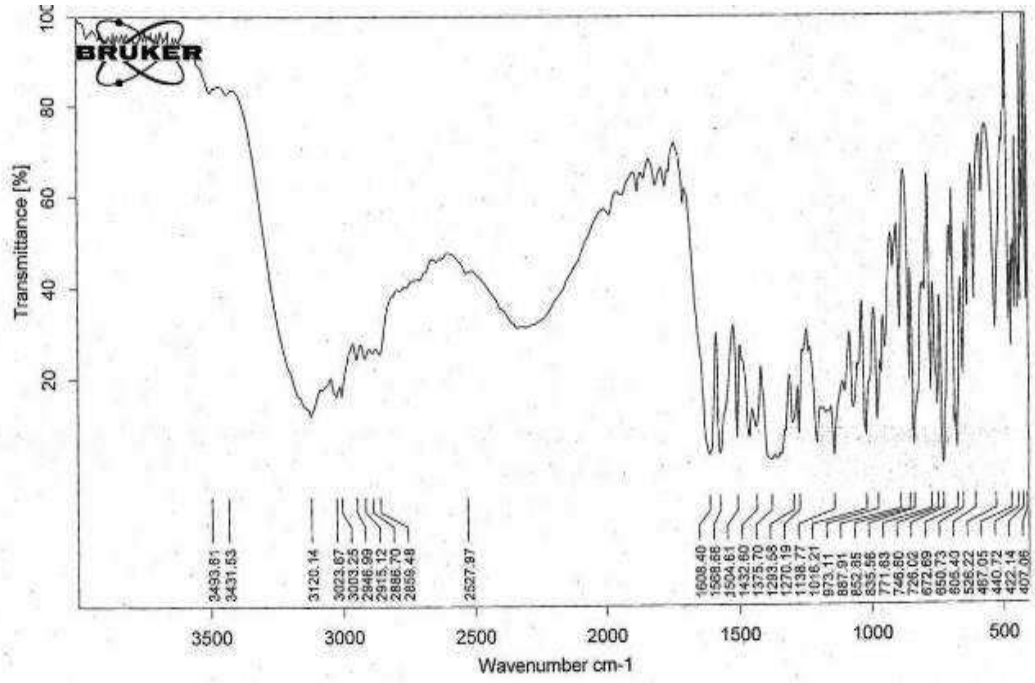


Fig. 6: FTIR spectra of RZT Benzoate.

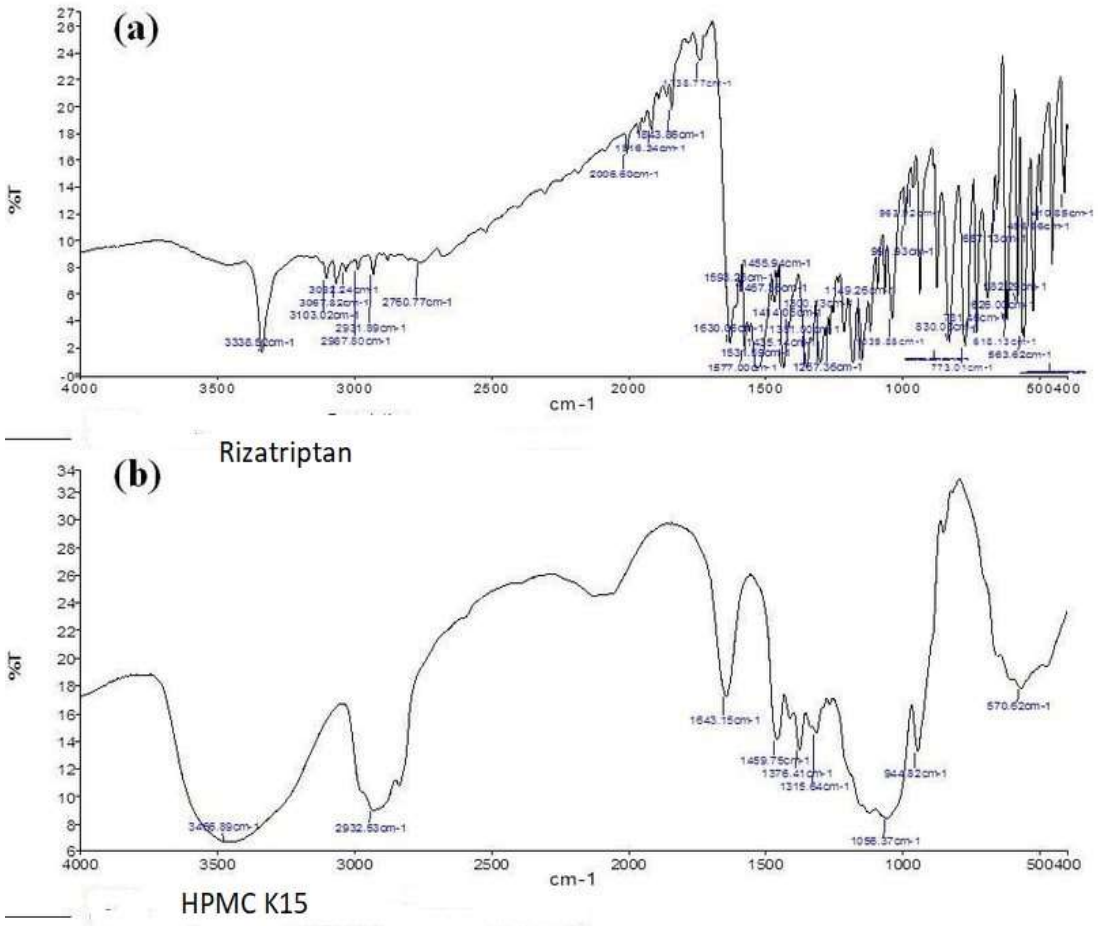


Fig. 7: FTIR Spectra of RZT Benzoate + Gleceryl Monostearate.

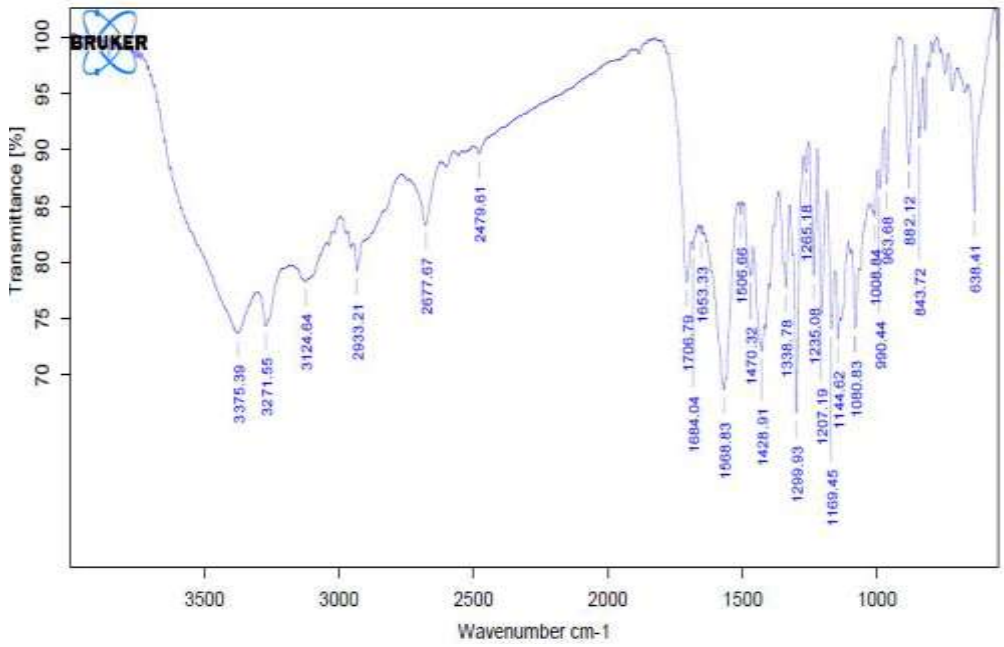


Fig 8: FTIR spectrum of Rizatriptan Benzoate+ Stearic acid.

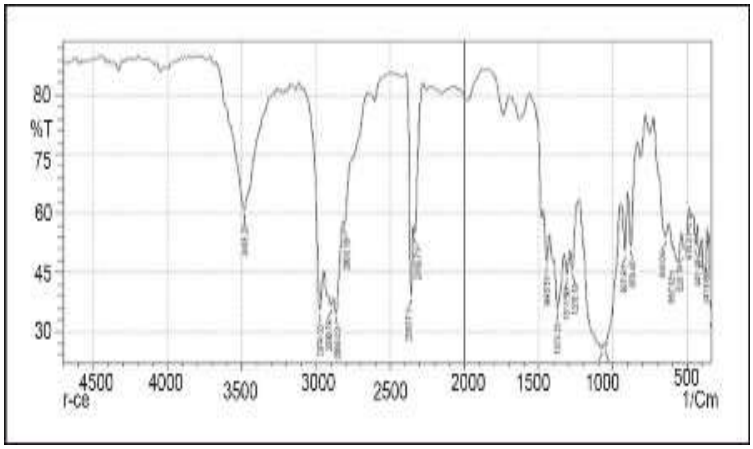


Fig. 9: FTIR spectrum of Rizatriptan Benzoate +Polysorbate 80 & Span 80.

Discussion FTIR Spectroscopy

The FTIR spectra of pure drug Rizatriptan Benzoate show design due to Nitrogen-Hydrogen extending at 3141.42/cm, Carbon=Oxygen extending at 1631.03/cm and C=Carbon stretching at 1451.0/cm. These assay were meeting the arrive values. The FTIR scope of optimised formulation F5 (Rizatriptan Benzoate +Material) reveal peak N-H stretching at 3214.70/cm, Carbon=Oxygen extending at 1634.05/cm, C=C stretching at 1546.09/cm.

CONCLUSION

Rizatriptan, a hydrophilic drug was successfully incorporated into SLNs by modified solvent injection method. The formulated Rizatriptan loaded SLNs were in nanometric range with

spherical structure. The release of drug from SLNs best-fitted Higuchi equation and the possible mechanisms for the drug release might be diffusion of the drug from the matrix and matrix erosion resulting from degradation of lipids. This experiment confirmed the evidence that solvent injection technique was a simple, available and effective method. The in- vitro drug release of F5 formulation was found to be 44.50% over 10 hours in controlled manners, hence the present study was a successful attempt to formulation of Rizatriptan by SLN system. The main purpose of formulating this formulation have been based on the enhancement of absorption of the drug in the systemic circulation. Overall, the findings suggest that Rizatriptan Benzoate SLNs hold promise as a viable therapeutic option for epilepsy, offering improved drug delivery characteristics and potentially enhancing patient compliance and treatment outcomes. Further study is necessary to investigate the exact mechanism related to findings of the study.

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