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FORMULATION DEVELOPMENT AND EVALUATION OF TOPICAL DRUG DELIVERY SYSTEM

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Abstract
Topical delivery has been developed for variety of disease and disorders. The treatment of skin diseases additionally as musculoskeletal disorders may well be advantageous from topical administration obtaining a substantial reduction in oral side effects with improved patient compliance. Many anti-inflammatory drugs are poorly water soluble and Nano suspension is that the techniques which is employed to enhance this characteristic, so anti-inflammatory drugs are chosen as a model for this study. Rizatriptan is employed to treat migraines. It helps to alleviate headache, pain, and other migraine symptoms (including nausea, vomiting, and sensitivity to light/sound). Prompt treatment helps you come back to your normal routine and should decrease your need for other pain medications. Rizatriptan belongs to a category of medicine called triptans. It affects a specific natural substance (serotonin) that causes narrowing of blood vessels within the brain. It's going to also relieve ache by affecting certain nerves inside the brain. Rizatriptan don't prevent future migraines or lessen how often you get migraine attacks the improved adoption of topical medication in current years has been impressive. this can be largely thanks to the very fact that the medication has proven to own more advantages than drawbacks. After all, the skin is right for drug administration, because it produces both systematic and native effects. Call it a life-changing medical innovation. Topical drug delivery systems have surely changed the way we glance at medication. More and more medical institutions and health practitioners are adopting this kind of medication in an endeavor to boost their services to patients.

Keyword: Rizatriptan, Migraine, Topical drug.

INTRODUCTION

Topical drug delivery system

Topical drug administration may be a localized drug delivery system anywhere within the body readily accessible organs on frame for topical administration and is main route of topical drug delivery System.Topical drug delivery system include an outsized sort of pharmaceutical dosage form like semi Solid Liquid preparation, sprays and solid powders. most generally semi-solid preparation for topical drug delivery include Ointment, gels and Creams.

Nanoemulgel:

Nanoemulgel is understood because the formulation of Nano emulsion based hydrogel by the

addition of the Nano emulsion system intergraded into hydrogel matrix which influence a higher skin permeation. Nano emulsion may be a promising alternative to extend drug delivery system penetration and targeting poorly Soluble drugs by increasing its absorption through the skin . Better retention time of drug within the topographic point and eventually end in fewer side effects. Nano emulsion improve the permeation of drug through skin, which intergrade the interest of researchers, additionally the little size of particles, the more amount of drug, is ready to be incorporated within the formulation, which subsequently increase the thermodynamics towards the skin.

Objectives: -

- To design a stable topical nanoemulgel of Rizatriptan Benzoate that will effectively release drug for prolong period time.
- Reduce the frequency of dosing by preporing formulation for prolong release and thus improves patient compliance.
- To predict the solubility, permeability and stability profile of Rizatriptan Benzoate.
- Eliminate the drawback of emulsion and gel by forming emulgel.
- To study the invitro study of Rizatriptan Benzoate emulgel.
- To improve the solubility of poorly soluble drug usin high speed homogenization method for preparing nano emulgel.
- To study compatibility of Rizatriptan Benzoate with polymer.

NEED:

Drug delivery through the skin to the circulation is convenient for variety of clinical conditions because of which there has been a substantial interest during this area Rizatriptan is employed to treat migraines. It helps to alleviate headache, pain, and other migraine symptoms (including nausea, vomiting, and sensitivity to light/sound). Prompt treatment helps you come back to your normal routine and should decrease your need for other pain medications. Rizatriptan belongs to a category of medicine called triptans. It affects a particular natural substance (serotonin) that causes narrowing of blood vessels within the brain. it should also relieve pain by affecting certain nerves within the brain.Rizatriptan doesn't prevent future migraines or lessen how often you get migraine attacks.

EXPERIMENTAL WORK

Preformulation Study

The basic development work encompasses Preformulation work and the subsequent dosage form development of any dosage form with a new or old drug candidate, it is essential that certain fundamental physical and chemical properties of the drug molecule and other derived properties of the drug be determined. This provides a framework for the drug combination with pharmaceutical excipients in the dosage form. This first learning phase is known as Preformulation.

Organoleptic Properties:

The drug sample of Rizatriptan was evaluated for its organoleptic properties such as appearance, color, and odor.

Melting Point:

The melting point of the drug was determined by using open capillary method using the melting point apparatus. The melting point done in triplicate.

Solubility:

The solubility of Rizatriptan was checked in different solvents: Water, acetonitrile, ethanol.

Ultraviolet - Visible Spectroscopy:

Determination of Maximum absorbance: (λ max)

The UV spectrum of Rizatriptan was obtained using UV Shimadzu. Correctly weighed 10 mg of the drug was dissolved in adequate quantity of methanol. Stock solutions (100µg/ml) of Rizatriptan were prepared in acetonitrile. The UV spectrums were noted in the range 200-400 nm by UV-Visible double beam spectrophotometer. The wavelength of maximum absorption (λ max) was determined.

Determination of Beer's Lambert's Plot:

Standard Calibration Curve of Rizatriptan in Acetonitrile

Accurately weighed 10 mg Rizatriptan and transferred to 10 ml volumetric flask. The volume was made up to 10 ml with acetonitrile and sonicated for 5 min. to produce stock solution of 100 µg/ml. Working standard solutions of strengths 2-10 µg/ml were made from the stock solution by appropriate dilutions. The above solutions were analyzed by UV spectrophotometer at λ max 229 nm.

Solubility Determination of Rizatriptan

Determination of solubility of drug in different Oils, Surfactants, Cosurfactants: The solubility of Rizatriptan in various oils, surfactants was determined by adding an excess amount of drug to 5 ml of selected oils, surfactants, separately in 10 ml capacity stopper vials, and mixed using a vortex mixer. The mixtures were then kept on magnetic stirrer for 48 hours at 40±0.5°C (RAJ 305-C). Further kept for 24 hours at room temperature to reach equilibrium. The equilibrated samples were centrifuged at 3000 rpm for 15 min followed by filtration through a 0.45-µm membrane filter. The filtrates were diluted with methanol and Rizatriptan solubility was subsequently quantified by UV.

FTIR spectroscopy

The IR spectrum of Rizatriptan was recorded at wave number 4000 to 50cm^{-1} using Fourier transforms infrared spectrophotometer (Mode- FTIR, Bruker). Method used for analysis was ATR. The methods above measure the infrared spectrum for powder samples mixed in a medium such as KBr or liquid paraffin. However, ATR technique is able to measure powder samples directly. Attenuated Total Reflection (ATR) method involves pressing the sample against high refractive index prism and measuring the infrared spectrum using infrared light that is totally internally reflected in prism.

Drug excipients compatibility study:

Drug excipients compatibility was performed by liquid FTIR. It was performed by mixing drug with excipients like oil, surfactant and polymer in equal proportion and then IR spectrum was noted for mixture using NaCl cell. Small amount of the mixture was placed on the sample cell, the cell was then fitted in sample holder, spectra were recorded with FTIR instrument and the spectral analysis was done.

Formulation and Development of Nanoemulsion

Full Factorial Design:

For the present work 3^2 full factorial designs was selected. It has been summarized in Table 14. In this design, 2 factors were evaluated each at 3 levels and experimental trials were performed at all 9 possible combinations as reflected in table no. 15. The 2 independent variables selected remained Almond oil (x1) and Speed of homogenizer **(x_2).**

Formulation code	Coded values		Coded Values	
	X_1	%	X_2	RPM
F1	**1**	**0.3**	**1**	**25000**
F2	**1**	**0.3**	**0**	**20000**
F3	**1**	**0.3**	**-1**	**15000**

F4	**0**	**0.2**	**1**	**25000**
F5	**0**	**0.2**	**0**	**20000**
F6	**0**	**0.2**	**-1**	**15000**
F7	**-1**	**0.1**	**1**	**25000**
F8	**-1**	**0.1**	**0**	**20000**
F9	**-1**	**0.1**	**-1**	**15000**

Table 01: Experimental Design as per 32 Full Factorial Designs

Variables	**Code**	**Factor**
Independent	**X1**	Almond Oil
	X2	Speed of homogenizer
Dependent	**Y1**	% *in- vitro* drug release

Table 2: Variables in optimization study

Formulation code	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
Ingredients					%				
Rizatriptan (w/w)	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1
Almond Oil (v/v)	0.3	0.3	0.3	0.2	0.2	0.2	0.1	0.1	0.1
Tween 80 (v/v)	0.525	0.525	0.525	0.525	0.525	0.525	0.525	0.525	0.525
Propylene glycol (v/v)	0.175	0.175	0.175	0.175	0.175	0.175	0.175	0.175	0.175
Methyl Paraben (w/w)	0.003	0.003	0.003	0.003	0.003	0.003	0.003	0.003	0.003
Propyl Paraben (w/w)	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001
BHT	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01
Water (v/v)	10	10	10	10	10	10	10	10	10

Table 3: Composition of Nanoemulsion formulation as per 32 full factorial designs

Method of preparation for Nanoemulsion

The quantities of drug and other ingredients were weighed by calculating equivalent amounts as per table 11 and formulations were prepared in following manner.

Cleaning of glassware and container: All the glassware were washed with H2O so sterilized by drying at 160-1650c for 1 hr. in hot air oven.

Preparation of aqueous phase 'A': Accurately weighed quantity of propanediol was added into water (800c).

Preparation of Oil phase 'B': Weighed quantity of sweet almond oil and tween 80 mixed together by maintaining hot condition, simultaneously accurately weighed quantity of Rizatriptan was added into it then adding of methyl paraben, propyl paraben and BHT in it.

Incorporation of solution 'A' in dispersion 'B': Both the phases were mixed properly with the assistance of high Homogenizer maintaining the respective rpm.

Preparation of gel:

Sr. No.	**Ingredients (% w/w)**	**Quantity**
1	Carbopol 934	0.1%
2	Triethanolamine	0.01%
3	Water (q.s.)	10

Table 4: Composition of gel

The weighed quantity of carbopol 934 was mixed in water (400c) further addition of triethanolamine to take care of the required pH range of the answer. The uniformity within the stirring was maintained and so the gel was kept within the refrigerator for twenty-four hrs.

Preparation of Emulgel:
Further incorporation of nanoemulsion containing 0.1% drug was incorporated to get emulgel.
Filling to container:
The formulation was transferred into previously cleaned and dry containers.

Evaluation of Nanoemulsion
Appearance:
The prepared nanoemulgel formulations were inspected visually for his or her colour, homogeneity, consistency and pH. The pH values of one% aqueous solutions of the equipped Gellified Emulsion were measured by a pH meter.

Scanning Electron Microscopy:
The morphology of nanoemulsion may be determined by scanning microscopy (SEM). SEM gives a three- dimensional image of the partical. The samples are observed at appropriate accelerating voltage, usually 20 kV, at different magnifications. An honest analysis of surface morphology of disperse innovate the formulation is obtained through SEM. Image analysis software, is also employed to get an automatic analysis results of the form and surface morphology.

Particle Size Analysis
Formulated Nanoemulsion should be analysed for his or her hydrodynamic particle size. Generally, just in case of nanoemulsion dynamic light scattering method used for the measurement of particles and further particle size distribution.

Zeta potential measurements
Zeta potential for nanoemulsion was resolute using zetasizer hsa 3000 (Malvern instrument Ltd., UK). Samples were placed in clear disposable zeta cells and results were recorded. Before placing the fresh sample, cuvettes were washed with the methanol and cleaned using the sample to be measured previously each experimentation.

Entrapment efficiency:
Entrapment efficiency is defined because the percentage amount of drug which is entrapped by the Nanoemulsion. For the determination of entrapment efficiency, the unentrappped drug was first separated by centrifugation at 15000 rpm for half-hour. The resulting solution was then separated and supernatants liquid was collected. The collected supernatants were then diluted appropriately with methanol and estimated using UV visible spectrophotometer at 229 nm.

Evaluation of Nanoemulsion based Gel:
Determination of pH
pH of the formulation was firm by using digital pH meter. pH meter electrode was washed by H2O and so dipped into formulation to live pH and this process was repeated 3 times.

Measurement of viscosity
The viscosity of the formulated batches was resolute employing a Brookfield Viscometer (RVDV-I Prime, Brookfield Engineering Laboratories, and USA) with spindle 63. The formulation whose viscosity was to be determined was added to the beaker and was allowed to calm down for 30 min at the assay temperature (25±1ºC) before the measurement was taken. Spindle was lowered perpendicular in to the middle of emulgel taking care that spindle doesn't touch bottom of the jar and rotated at a speed of fifty rpm for 10 min. The viscosity reading was noted.

Spreadability
To determine spreadability of the gel formulations, two glass slides of ordinary dimensions were selected. Formulation whose spreadability was to be determined was placed over one slide and

therefore the other slide was placed over its top such the gel is sandwiched between the 2 slides. The slides were pressed upon one another so on displace any air present and also the adhering gel was wiped off. the 2 slides were placed onto a stand specified only the lower slide is held firm by the other fangs of the clamp allowing the upper slide to slide off freely by the force of weight tied thereto. 20 gm weight was tied to the upper slide carefully. The time taken by the upper slide to completely detach from the lower slide was noted.

S = M. L/T

Where, M = weight tied to upper slide

L = length of glass slides T = time taken to separate the slides

Drug content study

Drug content study was done to work out the quantity of the drug present within the certain quantity of the formulation. Took 1 g of the formulation into 10 ml volumetric flask added methanol in it and shake well and frame the quantity with methanol. The Volumetric flask was kept for two hrs. And shaken well in a very shaker to combine it properly. the answer was versed the paper and filtered the mixer then measured absorbance by using spectrophotometer at 229 nm.

In-vitro Drug release study

The in vitro drug release studies of the Emulgel were applied on Diffusion cell using egg membrane. This was compressed carefully to at least one end of the hollow glass tube of dialysis cell. Emulgel (1gm) was useful on to the surface of egg membrane dialysis membrane. The receptor chamber was crammed with freshly prepared PBS (pH 7.4) solution. Total amount of gel filled within the tube to solubilize the drug. The receptor chamber was stirred by magnetic stirrer. The samples (1ml aliquots) were collected at suitable amount sample were analyzed for drug content by UV visible spectrophotometer at 229 nm after appropriate dilutions. Cumulative corrections were made to get the full amount of drug release at when interval. The cumulative amount of drug release across the egg membrane was resolute as a function of your time. The preferred shares drug release was calculated using standard calibration curve.

Release kinetics of selected formulation

To examine the drug release kinetics and mechanism, the cumulative release data were fitted to models representing Zero order (cumulative % drug release v/s. time), First order (log cumulative % drug retained v/s. time), Higuchi model (cumulative % drug retained v/s. Square root of time).

Optimization Study

All experiments were performed in triplicates. All data are reported as mean ± standard deviation (SD) and the groups were compared using ANOVA, with $p<0.05$ considered statistically significant.

Accelerated stability studies of Emulgel

Stability studies are performed by guidelines. The organized emulgels were full in aluminum collapsible tubes (5 g) and subjected to strength learns at 5°C, 25°C/60% RH, 30°C/65% RH, and 40°C/75% RH and 60

± 2° for a period of 3 months. Tests were pulled back at 15-day time between times and surveyed for physical appearance, pH, rheological properties and pharmaceutical substance.

RESULT AND DISCUSSIONS

Preformulation study:

Organoleptic properties:

Rizatriptan was studied for its organoleptic properties such as appearance, colour and odour. The result shows the details of organoleptic properties of Rizatriptan were found to be similar as mentioned in literature.

Drug	Properties	Observed Results
Rizatriptan	Appearance	Crystalline powder
	Colour	White to pale yellow
	Odour	Slight Odour

Table 5: Organoleptic properties of Rizatriptan

Melting Point:

The melting point of compound was measured and reported as follows:

Drug	Observed Value	Reported Value
Rizatriptan	155-156^{0}c	152-156^{0}c

Table 6: Melting Point of Rizatriptan

All the physical properties of the drugs were within the limit of reported standards which assures the purity of the drug samples.

Solubility

Solubility of Rizatriptan has been tabulated in the following table:

Solvent	Solubility
Water	Insoluble
Methanol	Soluble
Acetonitrile	Soluble
DMSO	Soluble
Ethanol	Soluble

Table 7: Solubility of Rizatriptan

Solubility and its solubility features were utilized for the UV spectroscopy and drug content.

Ultraviolet – Visible Spectroscopy study:

Determination of (λ_{max}) of Rizatriptan in Methanol:

The UV spectrum of Rizatriptan solution (100µg/ml) scanned between 400-200 nm using UV spectrophotometer exhibited wavelength of absorbance maxima at 229 nm. λmax of Rizatriptan in Methanol has been shown in the following figure 1.

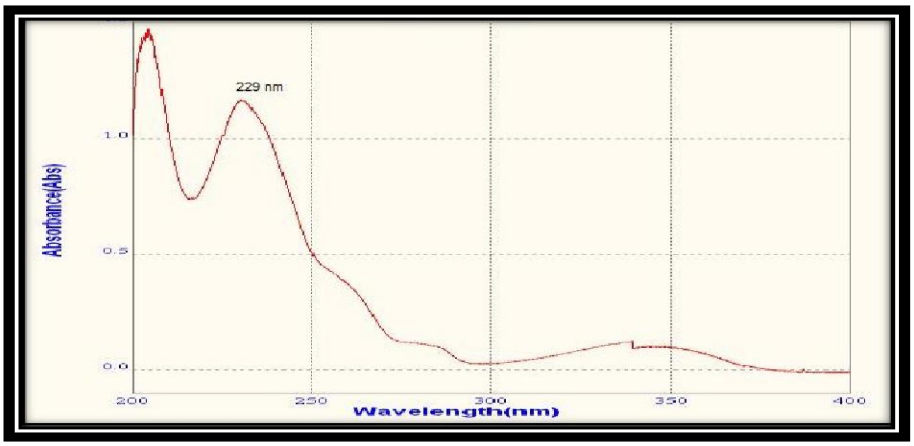

Figure 1: Ultraviolet Spectra of Rizatriptan in Methanol

Calibration of Rizatriptan in Methanol

Calibration curve of Rizatriptan was performed in methanol as Rizatriptan is soluble in methanol. Methanol solution of drug was very clear and readily analysed by the UV visible spectrophotometer. The calibration curve was found to be linear in the concentration range of 100

µg/ml given in following table.

Sr. No.	Conc.(ppm)	Absorbance
1	2	0.272
2	4	0.46
3	6	0.678
4	8	0.894
5	10	1.144

Table 8: Calibration Curve of Rizatriptan in Methanol

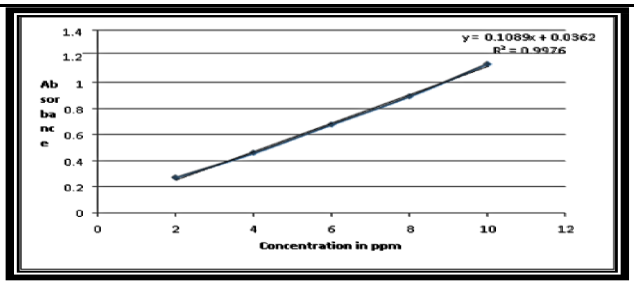

Figure 2: Calibration curve of Rizatriptan in Methanol

Solubility determination of Rizatriptan:

Solubility study of drug in different oils:

Sr. No.	Oils	Solubility
1	Castor oil	10.33
2	Oleic acid	12.3
3	Almond oil	31.03
4	Liquid paraffin	9.33
5	Isopropyl myristate	20.66

Table 9: Solubility of Rizatriptan in different oils:

Solubility of Rizatriptan in different oils was determined and indicated in above table.

Solubility determination of Rizatriptan in surfactants and co-surfactant

Sr. No.	Excipients	Solubility (mg/ml)
1	Tween 20	28.03
2	Span 20	3.02
3	**Tween 80**	**37.33**
4	Span 80	30.41
5	**Propylene glycol**	**35.66**

Table 10: Solubility of Rizatriptan in different surfactants and cosurfactant

Fourier Transform Infrared Spectroscopy

The FTIR spectrum of Rizatriptan has been shown in figure 3. The major peaks observed and corresponding functional groups are given in Table. The spectrum shows characteristic peaks for Rizatriptan

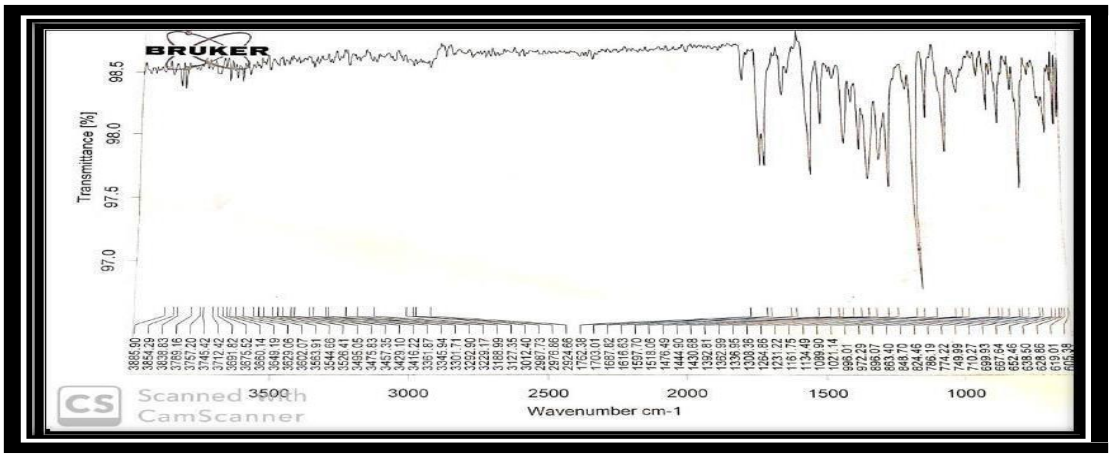

Figure 3: Representative IR spectrum of Rizatriptan

Sr. No.	Functional groups	Observed values (cm-1)	Standard values (cm-1)
1	NH Stretch	3495.05	3500-3100
2	C=O Stretch	1703.01	1725-1705
3	C-O Stretch	1264.86	1300-1000
4	C-H Bending	1444.9	1450-1375
5	C=C	1616.63	1680-1600
6	S=O	1362.99	1375-1300

Table 11: Functional groups present in I.R. of Rizatriptan

The absorption bands shown by Rizatriptan are characteristics of the groups present in its molecular structure. The presence of absorption bands corresponding to the functional groups present in the structure of Rizatriptan confirms the identification and purity of the Rizatriptan sample used in the study.

Compatibility study

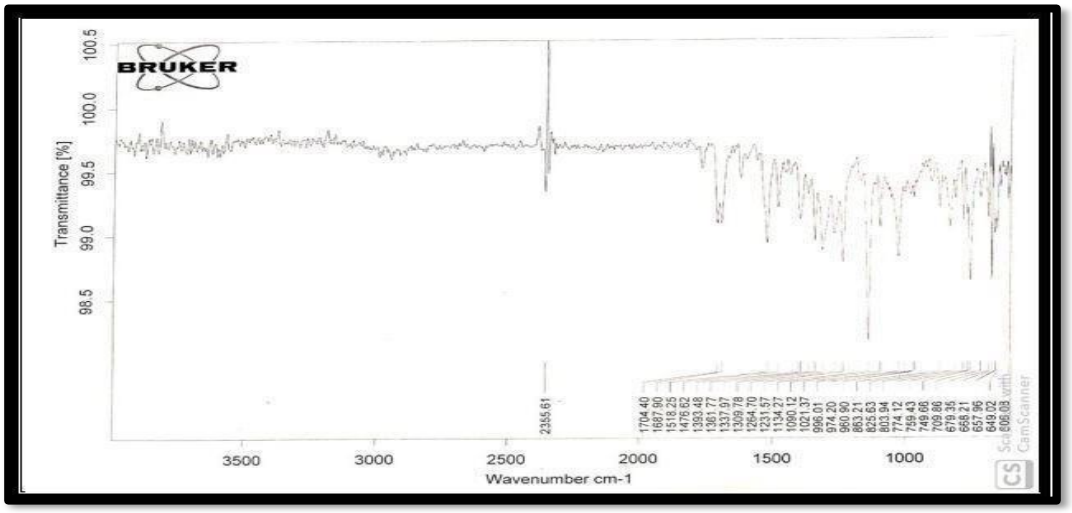

Fig 4: FTIR of Physical Mixture Table

Functional group	Pure drug	Physical mixture
NH Stretch	Yes	Yes
C=O Stretch	Yes	Yes
C-O Stretch	Yes	Yes

C-H Bending	Yes	Yes
C=C	Yes	Yes
S=O	Yes	Yes

Table 12: Interpretation of FTIR Spectrum of physical mixture

Formulation, Development and evaluation of Topical Nanoemulgel of Rizatriptan:

The various formulation prepared by 3^2 Full factorial design have been shown in following figure.

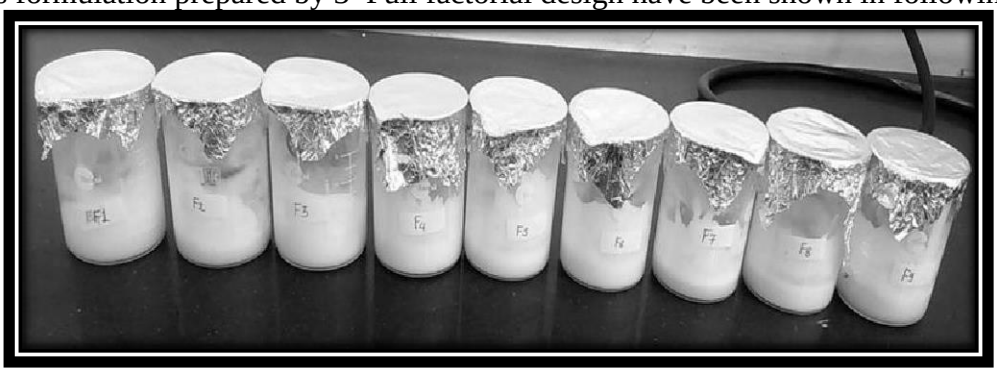

Figure 5: Formulation of F1 to F9 batch

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