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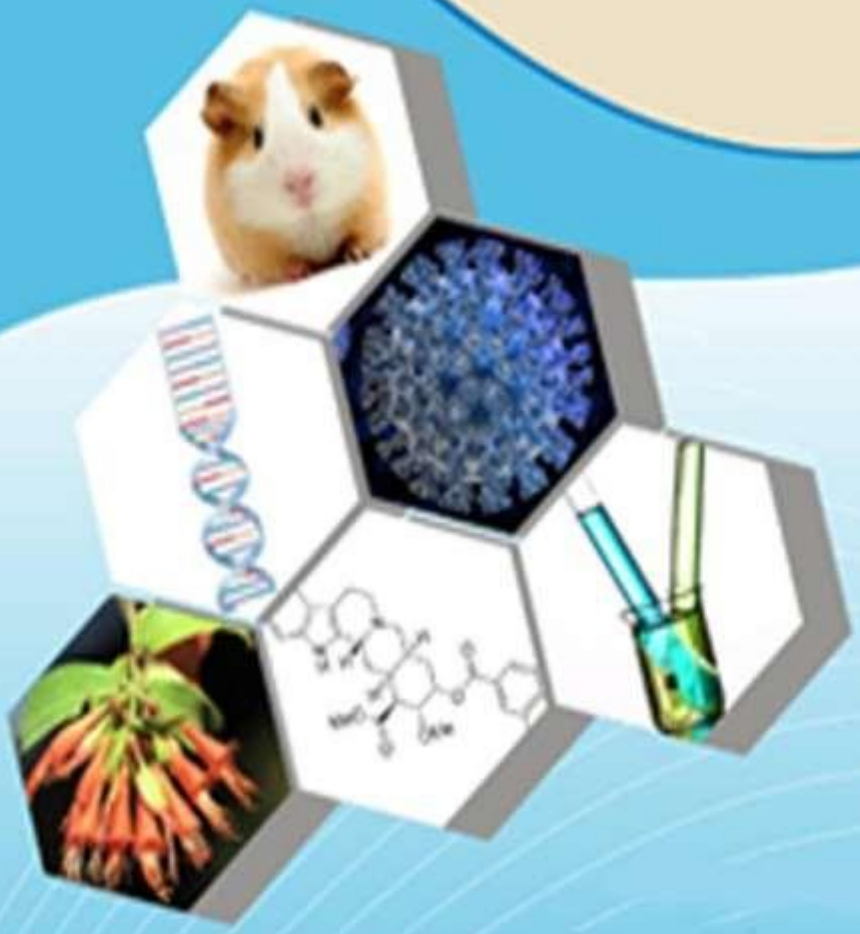

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Formulation And Evaluation Of Ordoispersible Tablet Of Frovatriptan

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INTRODUCTION

The necessity for easy dosage techniques has increased during the last two decades. Because of this, the pharmaceutical wholesale sector has expanded by over 350 firms, while the medical devices sector has expanded by over 1,000. The value of the market for these goods is projected to reach $60 billion by 2005, up from $14.20 billion in 1995.When considering patient compliance, usability, safety, and the capacity to accommodate a broad range of pharmacological options, oral administration is preferable (1, 2). Manufacturing expenses are reduced for inert oral delivery systems since sterile processing is not required. New oral delivery systems have emerged in recent years in an effort to boost drug adherence. These methods think about the pharmacological and chemical properties of drugs. Recent developments in technology have made computer-aided 3D printing (3DP) of tablets and electrostatic deposition and coating of pharmaceuticals possible. Fast-dissolving drug-delivery devices have been an option for children and the elderly who have difficulty swallowing pills, capsules, and syrups since the late 1970s. rapid dissolving pills, rapid dissolve tablets, and quick melt tablets all refer to the same kind of medicine. The different dosing strategies are equivalent in theory and practice. Some solid oral dosage forms are intended to dissolve quickly in the mouth to facilitate quicker absorption. Pills and capsules might be difficult for the elderly to swallow because of dysphagia. Dysphagia is linked to conditions such as HIV/AIDS, thyroid ectopy, cerebral palsy, and radiation therapy to the head and neck.

LITERATURE REVIEW

Rabeprazole sodium, a sublingual drug used to treat acid peptic disease, was created by Sindhu Abraham et al.32. The pills were made using a wet granulation method, and their active ingredients were the polymers risperidone and croscarmellose sodium. All timothy dispersions had a hardness

between 3 and 4kg/cm2, with the middle being the most common. All formulations were determined to have a friability percentage of less than 0.6%. It was discovered that the quantity of the active ingredient in each tablet was consistent across all lots and forms. around 97.37% to 100.51 % of its theoretical value. It was shown that the wetting time and disintegration time were extremely sensitive to the concentrations of risperidone and croscarmellose sodium. The effects of increasing the Amlodipine Besylate load in fast-dissolving sublingual tablets by utilizing several disintegrants were studied by Vineet Bharadwaj et al. 33. In this research, we employed super disintegrants Kallidin CL (2%), Ac-Di-Sod (4%) and Sodium starch glycolate (6%) at various doses. When compared to the other super disintegrants evaluated, the Ac-Di-Sol-prepared tablet? formulation showed a much quicker in vitro disintegration time of 16 seconds.

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Fast-dissolving sublingual glipizide tablets were developed and tested in research by Rajat Sharma et al.34. In this research, the powerful disintegrant risperidone was utilized. Scientists examined the pills' hardness, friability, and rate of wetting to determine how long it took for the tablets to disintegrate in water. Wet granulation was used to create the tablets. Tablets made by sublimation were better to those made using vacuum-pressurization of Naphthalene grains. Bhanja et al.35 created and refined the hypertension drug perindopril sublingual tablets. The perindopril tablets also included inactive components such risperidone, sodium saccharin, mannitol, microcrystalline cellulose, talc, and magnesium stearate, and they were manufactured using the direct compression process. The best formula, f4, decreased the in vitro disintegration time from 198 seconds to 98 by shortening the wetting time to 45 seconds and increasing the water absorption ratio to 55. After 12 minutes, medication availability was 99.88% when utilizing the super disintegrant Risperidone.

AIM AND OBJECTIVE

Aim of the study:

The purpose of this research was to determine the best super-disintegrant formulation for the fast dissolving of sublingual Rizatriptan tablets. Secondary symptoms of migraines include nausea, vomiting, and sensitivity to light. A lot of folks have severe discomfort on one side of their head alone. Because of first-pass metabolism and limited bioavailability (45%), oral dispersible dose formulations are less effective. Sublingual pills work more rapidly than orally dissolving medications. The triptan class of medications is now the gold standard for treating migraines. In this nation, sumatriptan has been the most successful pharmaceutical product. In comparison to Sumatriptan, Rizatriptan is favoured since its efficacy may be achieved with just 10mg of the drug rather than 100mg. The purpose of this research was to find a way to speed up the dissolve of sublingual tablets of Rizatriptan. Fast-acting sublingual tablet dose was developed for the following reasons: One target was to create sublingual tablets of Rizatriptan with an optimized chemical makeup for rapid dissolving. The goal is to assess how well the tablets' function. Third, we want to investigate the dissolution of finished tablets in vitro. Ingestion of a tablet that has been manufactured and stability evaluated in accordance with ICH specifications. 5. To increase patient engagement by generating positive associations with dental treatment. Sixth, to use sugar substitutes to sweeten the medicine.

.PLAN OF WORK

It was suggested that the study be broken up into the following phases: Preparatory formula research: Since the greatest dissolution was seen at a pH value of 6.8, this is the value utilized in the phosphate buffer calibration curve. The absence of drug-excipient interaction was shown by FTIR tests. Evaluation of the effectiveness and safety of direct-compression medications: Compositional Powder Analysis by

- Angle of repose
- Bulk density
- Tapped density
- Compressibility index
- Haurn's ratio

Sublingual tablets that dissolve quickly: The following research was undertaken to determine how different excipient types and amounts affected the physiochemical and in vitro release behaviour of fast dissolving sublingual tablets: A tablet is made by compressing the medicine together with any other ingredients. Report on rapid-release sublingual tablets

1. Thickness
2. Hardness
3. Friability
4. Weight variation
5. Drug content
6. Wetting time
7. Disintegration test
8. In vitro release studies
9. Stability studies

MATERIALS AND METHODS

MATERIALS:

Table 1: List of Materials

S.No	Name of chemicals	Manufacturer
1.	Frovatriptan	Taj pharmaceuticals limited, India
2.	Crospovidone	Jiaozuo yuanhai fine chemicals, Japan
3.	Croscarmellose sodium	Amish drugs & chemicals, Ahmadabad.
4.	Low substituted hydroxy propyl Cellulose	Shin-etsu chemicals co ltd. Japan.
5.	Mannitol	Merck, India.
6.	Aspartame	S.D. fine chemicals, Mumbai.
7.	Magnesium st earate	Harish chemicals Pvt Ltd., Ahmadabad
8.	Potassium dihydrogen ortho phosphate	Qualigens fine chemicals Pvt Ltd., Mumbai
9.	Sodium hydroxide pellets	Qualigens fine chemicals Pvt Ltd., Mumbai
10.	Hydrochloric acid	Qualigens fine chemicals Pvt Ltd., Mumbai
11.	Kbr IR grade	Qualigens fine chemicals Pvt Ltd., Mumbai

S.No	Name of the equipment	Make
1.	Electrical balance	SHIMADZU Scientific Instruments, Japan
2.	Single rotary tablet compression machine	Cadmach machinary Co PVT Ltd.India
3.	Hardness tester	Monsanto, St. Louis
4.	Friabilator	Roche friabilator
5.	Dissolution apparatus	Minicon equipments Pvt Ltd
6.	Micro syringe	Eonpipette(Bio Era)
7.	Hot air oven	Minicon equipments Pvt Ltd
8.	Kbr ster apparatus	Lasco equipment Pvt Ltd, Canada
9.	Bulk density test apparatus	Vargo instruments corporation, Mumbai
10.	UV	SHIMADZU Scientific instruments, Japan
11.	FTIR	SHIMADZU Scientific instruments, Japan

DRUG PROFILE& EXCIPIENTS PROFILE

DRUG PROFILE FROVATRIPTAN54: Name of drug:Rizatriptan

Molecular formula: C14H17N3O

Molecular weight: 269.345 g/mol

Chemical name: (6R)-6-(methylamino)-6,7,8,9- tetrahydro-5Hcarbazole-3-

Carboxamide Chemical structure:

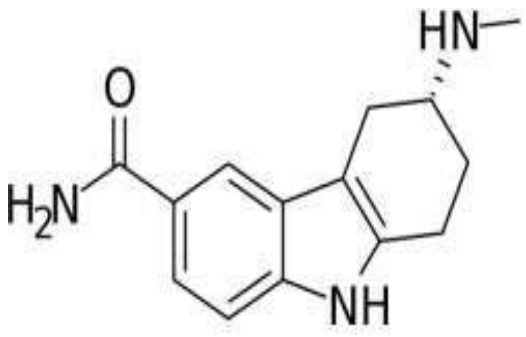

Fig 1: Chemical structure of Frovatriptan

Category:

Preventative medication for migraines that acts as a vasoconstrictor, an anti-inflammatory serotonin agonist, and a selective serotonin reuptake inhibitor.

Bioavailability: 45%

Protein binding: 14%

Half-life: 2-3hrs

Melting Point: 170-180◦C

BCS Classification: Category III (Extremely Immiscible)

Mechanism of action: It has been hypothesized that the antimigraine effects of triptans are due to their ability to inhibit Dural vasodilation and inflammation by activating presynaptic 5-HT1D receptors. The cellular excitability in the trigeminal nucleus is directly affected by the lack of 5-HT1B/1D receptors in the brainstem.vasoconstriction of the meningeal, Dural, cerebral, or pial arteries due to agonism of the vascular 5-HT1B receptor.

Pharmacokinetics:

Absorption is rapid after oral administration. The drug's bioavailability is about 45%. Rizatriptan's bioavailability is the same regardless of whether or not it is taken with meals. When Rizatriptan is taken with food, its peak plasma concentration is postponed for an additional hour. The pace at which the body absorbs substances is unaffected by a migraine.

Metabolism:

Rizatriptan is metabolized in part by monoamine oxidase. The MAO-A isoenzyme catalyses the conversion of indoleacetic acid to an inert metabolite. Inactive metabolites are also produced at a rather high rate. Truly little amounts of the active metabolite N-monodactyl-Rizatriptan (14% in the plasma) have been identified, but it nevertheless has the same pharmacological effects as the parent medication.

Excretion:

Only around 14% of an oral dose of froventriptan is removed in the urine as unmodified medication, whereas 51% is excreted as the Indole acetic acid metabolite.

Adverse effects:

Coronary artery spasms have been related to a wide range of symptoms, including heart attacks, ventricular tachycardia, hearing loss, sensitivity to light, muscular soreness, and even diarrhoea.

Advantage:

Rizatriptan (10 mg) is equivalent to Sumatriptan (100 mg).

EXCIPIENT PROFILE

MANNITOL55:

Pearlite, D-mannite, mannite, manage, manna sugar, and E421 are all synonyms for the same substance.

Structure:

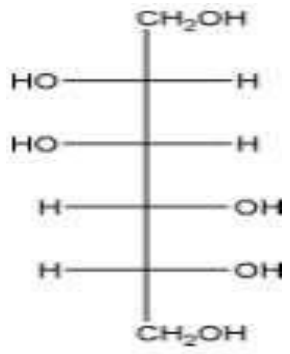

Fig No: 2Structure of Mannitol

Empirical formula: C6H14O6

Molecular weight: 182.17.

Chemical name: D-Mannitol

Functional category: Tonicity agent, flavour for lyophilized medicines, tablet, and capsule diluent.

Applications:

Added to pills to increase their weight by 10–90% by weight. Since it does not absorb moisture, it may be used with things that would otherwise be damaged by high humidity. Because of its low melting point, pleasant taste, and pleasant texture, it is ideal for use in the manufacture of chewable tablets. When given intravenously, mannitol may be used as an osmotic diuretic, as a diagnostic tool for kidney function, as an additional therapy for acute renal failure, and as a treatment for intracranial hypertension, cerebral enema, and increased intraocular pressure.

Description:

It is a hexahydro alcohol that may be found attached to mannose in two different forms (sorbitol and mannitol). White, crystalline, and doorless granules or powder are the most frequent forms of mannitol. In terms of sweetness, it falls between that of glucose and sucrose, and it lingers on the tongue and palate. Alcohol crystals, when seen via a microscope, take on the appearance of orthorhombic needles. Polymorphism is a very genuine phenomenon.

Melting point: 166–168o C.

Solubility: Freely soluble in water, practically insoluble in ether.

Stability and storage conditions:

Both dry and diluted mannitol are very stable in water. It is resistant to oxygen at room temperature and weak acids and bases without the need for catalysts. Keep it unopened and in a cold, dry location.

Incompatibilities:

When the mannitol solution (at 25% w/v) comes into contact with plastic, it begins to precipitate. Two different concentrations of sodium cephalin in mannitol (20% w/v)—2 mg/ml and 30 mg/ml—are incompatible. The sugar alcohol interacts poorly with mannitol infusions and may generate compounds with metals including aluminium, copper, and iron.

Non-proprietary names: CROSPOVIDONE56

BP: Crospovidone,

PhEur: Crospovidonum,

USPNF: Crospovidone

Synonyms: Polyvinylpyrrolidone and cross-linked povidone are two examples of chemicals that may serve as cross-linking agents. Other examples are Polyvinylpyrrolidone (Polycladose XL-10) and 1- and 2-vinylpyrrolidone.

Chemical name: 1- Etheny1-2 pyrrolidinone homopolymer

Empirical formula: [C6H9NO] n

Molecular weight: >1000000

Functional category: Tablet disintegrant

Description:

Risperidone is a fine, white, or off-white powder that may be easily poured. Totally or Almost Odourless and Tasteless

Solubility: Water and most organic solvents are not going to be able to dissolve this.

Typical properties:

Acidity / Alkalinity pH :5.0-8.0(1%w/v aqueous slurr

Density : 1.22 g/cm3

Bulk density : Polyplasdone XL10 – 0.416 g/cm3

Moisture content:About 60 percent is the maximum rate at which moisture may be absorbed. The highest allowable level of Polycladose XL-10 45 is 5%.

Compressibility (Car index): Polycladose XL -10-30%

Particle size distribution: Less than 74 am for Polycladose XL-10

Specific surface Area:

Polycladose XL-10, 1.2-1.4m2 per gram Since it absorbs moisture from the air, risperidone needs to be stored in an airtight container.

Application in pharmaceutical formulation or technology:

Risperidone concentrations between 2% and 5% are indicated to help in the disintegration and solubilization of tablets made by direct compression or wet and dry granulation. In a short length of time, it demonstrates a high capillary activity and hydration capacity with a low propensity to produce gels. The pace at which tablets break down depends critically on the particle size of the risperidone used. Larger particles tend to disintegrate more quickly than smaller ones. In this case, risperidone's solubility may also be enhanced.

Incompatibilities:

When used at recommended doses, risperidone does not interact negatively with other medicinal drugs. In the presence of a lot of water, risperidone may create a molecular adduct with several other compounds.

MAGNESIUM STEARATE57

Non-proprietarynames:

BP:Magnesium stearate

PhEur: magnesii

stearas USPNF; Magnesium stearate.

Synonyms : E572, Hyqual, magnesium octadecenoate

stearic acid Chemical name : Octadecanoic acid magnesium

Salt Empirical formula : C36H70MgO4

Structural formula : [CH3 (H2)16COO] 2

Mg Molecular weight : 591.27

Functional category : Tablet and capsule lubricant

Flow ability : Poorly flowing, cohesive powder

Melting point : 88.5C

Moisture content : 3.85%.

Applications in pharmaceutical formulation or technology:

Magnesium stearate is used in a wide variety of cosmetics, foods, and medicines. Concentrations between 0.2% and 5% are common when it is used as a lubricant in the manufacturing of capsules and tablets.

Description:

Magnesium stearate is an invincible, white powder that is very fine in consistency. It smells and tastes different from other things, but in a subtle way. The acicular trihydrate and the lamellar dihydrate of a lubricating hydrate have been isolated. It doesn't dissolve well in water, alcohol, or 95% ether ethanol, although it does dissolve in heated benzene and 95% ethanol.

METHODOLOGY

PREFORMULATION STUDIES:

The term "reformulation" is used to describe the study of the physical and chemical characteristics of the therapeutic component, both alone and in combination with the excipients. The fundamental goal of reformulation testing is to provide the formulator with information that will aid in the creation of a stable, bioavailable, and commercially viable dosage form. The following information is crucial. Stability of Solids in Ambient Conditions SolubilityIn vitro The drug-excipient stability research is the most crucial piece of prep work for a tablet formulator. Creating physical mixes of the medication and excipients components at varied proportions allows us to undertake a reformulation

profile analysis. Because the likelihood of detecting a physical or chemical interaction is maximized regardless of whether the ratio is what would be expected for the final dose form, it is employed. Translucent glass cells or vials are used for the analysis. Over the course of a month, the sample vials were exposed to a broad range of temperature and humidity conditions.

ANALYTICAL METHODS

Preparation of pH 6.8 buffer solution:

Water is added to a volumetric flask that holds 1000 millilitres and contains 6.8 grams of potassium dihydrogen orthophosphate and 0.94 grams of sodium hydroxide.

Preparation of stock solution:

One hundred millilitres of distilled water were added to a volumetric flask holding one hundred milligrams of pure medication. One millilitre of this solution is diluted to 10 millilitres in a volumetric flask. Using a 10 ml volumetric flask, dilute 1 ml of this to 10 ml to get a solution with a concentration of 10 g/ml.

Calibration curve of Rizatriptan in pH 6.8 buffer solution:

One millilitre, two millilitres, three millilitres, four millilitres, five millilitres, six millilitres, and seven millilitres of distilled water are added to the stock solution until a total volume of 10 millilitres is achieved. You may then calculate the absorbance at 226 nm by using a UV spectrophotometer. Peak areas recorded at different concentrations are compared in Table No. 8 and Figure No. 8 to show that concentration and absorbance are linearly related. Compatibility Studies Researchers employed infrared spectral matching to check for chemical reactions between the drug and excipients. First, the necessary quantity of potassium bromide is added, and the drug and excipients are mixed by hand (1:1). We were able to compress around 100mg of this mixture using 10 tons of hydraulic pressure, resulting in a transparent pellet. The range of 4000-400cm-1 was used for the analysis using a SHIMADZU FTIR Spectrophotometer. The IR spectra of the pure drug and excipients were compared to those of the finished product, allowing for the identification of peaks.

COMPATABILITY STUDIES

Using an infrared spectral-matching technique, scientists looked for evidence of a chemical reaction between the drug and the excipients. Physically mixing the drug and excipients (1:1) and then adding the necessary quantity of potassium bromide. We were able to compress around 100mg of this mixture using 10 tons of hydraulic pressure, resulting in a transparent pellet. It was examined between 4000-400cm-1 using a SHIMADZU FTIR Spectrophotometer. The IR spectra of the isolated drug and excipients were compared to those of the combined substance to determine whether or not any peaks were present.

FORMULATION & EVALUATION FORMULATION STEPS FOR SUBLINGUAL TABLETSS (DIRECT COMPRESSION)

Direct compression was used to make the fast-dissolving sublingual tablets of 5mg rizatriptan (no granules were created). Consistent with the make-up shown in Table No. 8. Making tablets using direct compression required the following steps: sifting, dry-blending, greasing, and crushing.

Sieving:

Each ingredient, including the active one, was sieved through a #40 mesh screen before being mixed together.

Dry Mixing:

To guarantee that the drug's active component was evenly distributed throughout the mixture, all of the ingredients were placed in a plastic bag and shaken for 5 minutes.

Lubrication:

The granules and magnesium stearate were well mixed after being shaken in a plastic bag for five minutes.

Compression:

Finally, the powder mixture was compressed into 100mg tablets using 7mm flat shaped punches in single rotating tablet compression machines.

EVALUATION OF SUBLINGUAL TABLETS

The composition of the tablets was analysed with respect to the following aspects. After the tablets were made, they were examined for everything from aesthetic quality to performance.

Thickness:

After formulation, the thickness of rizatriptan fast dissolving sublingual tablets was measured using a digital vernier calliper.

Uniformity of weight:

Twenty pills were measured for their total and average weights. The group's total weight was added together to determine a mean value. We determined the acceptable range for pill weight by comparing individual samples to the mean. The weight of individual 200 mg tablets did not vary by more than 10% or by less than -7.5%.

Hardness test:

The tablet's hardness was measured using a Pfizer hardness tester. When the bottom plunger was pressed against the tablet, the result was 0. A plunger was forced against a spring, shattering the tablet, by rotating a threaded bolt. The spring tension may be read via a gauge in the barrel. The tablet's hardness was measured using a Pfizer hardness tester. When the bottom plunger was pressed against the tablet, the result was 0. A plunger was forced against a spring, shattering the tablet, by rotating a threaded bolt. The spring tension may be read via a gauge in the barrel. The tablet's hardness was measured using a Pfizer hardness tester. When the bottom plunger was pressed against the tablet, the result was 0. A plunger was forced against a spring, shattering the tablet, by rotating a threaded bolt. The spring tension may be read via a gauge in the barrel. The tablet's hardness was measured using a Pfizer hardness tester. When the bottom plunger was pressed against the tablet, the result was 0. A plunger was forced against a spring, shattering the tablet, by rotating a threaded bolt. The spring tension may be read via a gauge in the barrel.

Friability test:

We reweighed the twenty pills after the machine had been spun a hundred times. The degree of friability was calculated using the following formula:

The grindability of an item may be determined by dividing the finished weight by the original weight. X100

Disintegration test:

A machine designed to smash tablets was tested for its efficiency. One pill was placed in each of the basket rack's six tubes, and the entire thing was submerged in water kept at 37°C2°. The pills were fed into the machine, and it ran until every last one of them was destroyed.

Drug content:

We obtained 5mg of Rizatriptan powder by crushing and weighing 10 tablets, which we then diluted to a final concentration of 5mg/ml in mobile phase using a 10ml standard flask. After the initial volume of 5 mL was reached, an additional 5 mL of mobile phase was added.

Wetting time:

Scientists in this experiment measured the amount of time it took for a tablet to get completely soaked with water by placing it between two sheets of absorbent paper in a dish. After letting the paper absorb the 6.8-pH phosphate buffer, the dish washed. The length of time it took for water to permeate the whole tablet through the wet absorbent material was measured. The results are shown in Table No. 12. Proportion of substances absorbed: After being folded in half, the tissue paper was placed in the petri dish containing the 6 ml of buffer pH 6.8. The tablet was placed on the wet tissue to maximize its ability to soak up moisture. Tablets are weighed after being submerged in water. The following equation was used to get the water absorption ratio, R.

RESULTS AND DISCUSSION

A rizatriptan calibration curve at a phosphate buffer pH of 6.8 is shown in the table below. The efficiency of the treatment was verified by the UV analysis. Standard solutions of rizatriptan in medium have an absorbance that linearly increases with concentration from 0 to 7 g/ml (see Graph No. 8). Figure 8 depicts the phosphate buffer's straight-line coefficient at a pH of 6.8. Table 8 displays the results of rizatriptan calibration in phosphate buffer (pH 6.8).

S.No	Concentration (µg/ml)	Absorbance
1	0	0.00
2	1	0.14
3	2	0.26
4	3	0.39
5	4	0.52
6	5	0.66
7	6	0.77
8	7	0.90

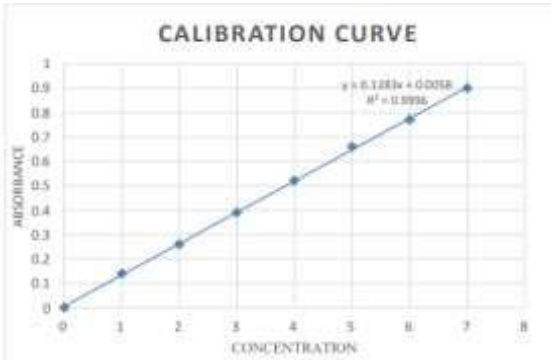

Figure 3: Standard curve of Frovatriptan

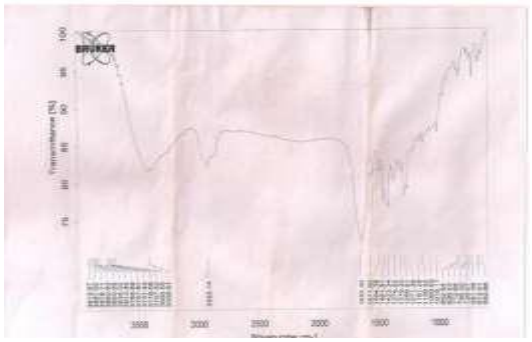

Figure 4: FTIR spectrum of Rizatriptan

Reformulation studies:

Drug –Polymer compatibility studies by FTIR:

No clear drug-polymer interaction was seen in the FTIR spectra of rizatriptan, risperidone, L-HPC, croscarmellose sodium, or their combinations. Figures 9, 10, 11, and 12 show rizatriptan, risperidone, croscarmellose sodium, L-HPC, and a drug/polymer combination.

Figure 5: FTIR spectrum of Frovatriptan+ Crospovidone

Figure 6: FTIR spectrum of Frovatriptan + Croscarmellose sodium

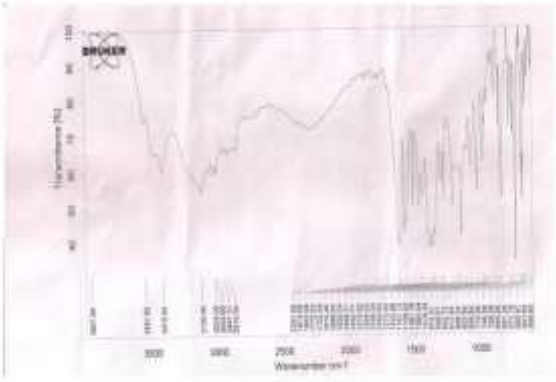

Figure 7: FTIR spectrum of Frovatriptan + L-HPC

FTIR analysis of pure Rizatriptan and excipients revealed maximal activity in both. This result suggested that there was no chemical interaction between the two.

CONCLUSION:

Reformulation studies were conducted on the medication's active pharmaceutical component, Rizatriptan. The findings of a drug excipients compatibility study indicated that Rizatriptan was compatible with the chosen excipients. Rapid dissolving sublingual tablets of 100mg Rizatriptan were created by mixing croscarmellose sodium, risperidone, and L-HPC as super disintegrants at concentrations of 3%, 4%, and 5%, respectively. Ten distinct formulations were developed by adjusting the quantities of several super disintegrants. Although F-10 was the most efficient, F-3 was chosen because of its superior flavour and smoother consistency. There are 5 milligrams of risperidone and 87 milligrams each of mannitol, aspartame, and magnesium stearate in F-3. The active component is the 5 milligrams. The F-3 formulation was also assessed for stability. The formulation has undergone extensive testing, and it has performed well across a range of physicochemical criteria. The release study and computational simulations led researchers to the

conclusion that the innovative formulation could be able to avoid the body's first metabolism.

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