**Anti-Migraine Fast Dissolving Tablets of Rizatriptan Benzoate**

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Received: 15-04-2023; Revised: 23-06-2023; Accepted: 02-07-2023; Published on: 15-07-2023.

**ABSTRACT**

Rizatriptan Benzoate is potent anti migraine drug having agonist activity at the 5-hydroxytryptamine (5-HT) 1B and 5-HT 1D receptor. It commonly used for relief of headaches in treatment of migraine. Conventional tablets of RZT are not capable of rapid action, which is required for immediate relief from migraine pain. Nevertheless, RZT elicits several adverse effects and RZT nasal sprays have a limited half-life, requiring repeated doses that could cause patient noncompliance or harm to the nasopharynx and cilia.

**Keywords:** Fast Dissolving tablets, Rizatriptan Benzoate, Migraine, Taste Mask.

**INTRODUCTION**

**Migraine**

Migraine is a primary headache disorder characterized by recurrent headaches that affect moderate to severe. Typically, episodes have an effect on one side of the head, are pulsating in nature, and last from many hours to a few days. Associated symptoms could include nausea, vomiting, and sensitivity to lightweight, sound, or smell. The pain is mostly created worse by physical activity, though regular exercise could have prophylactic effects. Up to common fraction of individuals affected have aura: usually a short amount of visual disturbance that signals that the headache can presently occur. Sometimes, aura will occur with very little or no headache following, however not everyone has this symptom.

Migraine is believed to be due to a mix of environmental and genetic factors. Concerning common fraction of cases run in families. Changing hormone levels may also play a job, as migraine affects slightly a lot of boys than girls before puberty and 2 to a few times a lot of girls than men. The danger of migraine typically decreases throughout pregnancy and when menopause. The underlying mechanisms aren’t totally familiar. They are, however, believed to involve the nerves and blood vessels of the brain.

Globally, approximately 15 % of people are affected by migraine. Within the world Burden of disease Study of 2010, it absolutely was ranked because the third most prevalent disorder within the world. It most frequently starts at pubescence and is worst throughout time of life. As of 2016, it’s one amongst the most common causes of incapacity. An early description in line with migraines is contained BC Ebers papyrus, written around 1500 BC in ancient Egypt.¹

**Signs and symptoms**

Migraine usually presents with ending, repeated severe headache related to involuntary symptoms. concerning 15–30% of individuals living with migraine experience episodes with aura, and that they conjointly frequently experience episodes while not aura. The severity of the pain, period of the headache, and frequency of attacks are variable. A migraine lasting longer than 72 hours is termed standing migrainosus. There are four attainable phases to a migraine, though not all the phases are essentially experienced:

- The prodroma, that happens hours or days before the headache
- The aura that immediately precedes the headache
- The pain phase, conjointly called headache part

The postdrome, the effects experienced following the end of a migraine attack Migraine is related to major depression, manic-depressive psychosis, anxiety disorders, and obsessional compulsive disorder. These psychiatric disorders are about 2–5 times a lot of common in folks while not aura, and 3–10 times a lot of common in people with aura.²
Cause
The underlying causes of migraines are unknown. However, they're believed to be associated with a combination of environmental and genetic factors. They run in families in concerning two-thirds of cases and barely occur due to one factor defect. Whereas migraines were once believed to be a lot of common in those of high intelligence, this doesn't seem to be true. Variety of psychological conditions are associated, as well as depression, anxiety, and bipolar disorder, as are several biological events or triggers.

Medication
Preventive migraine medications are considered effective if they reduce the frequency or severity of the migraine attacks by at least 500th. thanks to few medications being approved specifically for the preventative treatment of migraine headaches; several medications like beta-blockers, anticonvulsive agents like topiramate or metallic element valproate, antidepressants like amitriptyline and calcium channel blockers like flunarizine are used off label for the preventative treatment of migraine headaches. Guidelines are fairly consistent in rating the anticonvulsants topiramate and divalproex/sodium valproate, and therefore the beta blockers propranolol and beta-adrenergic blocker as having the highest level of proof for first-line use for migraine prophylaxis in adults. Propranolol and topiramate have the simplest proof in children; but, proof only supports short profit as of 2020.5

Antiemetics
Triptans
Triptans like sumatriptan are medications used to stop an active migraine headache (an abortive medication). Triptans are the initially counseled treatments for those with moderate to severe pain from an acute migraine headache or those with milder symptoms who don't respond to easy analgesics. Triptans are shown to be effective for each pain and nausea in up to 75th of individuals. There are completely different ways or routes of administration to require sumatriptan as well as oral (by mouth), injectable (subcutaneous), rectal, nasal spray, and oral dissolving tablets.

For people with migraine symptoms like nausea or vomiting, taking the abortive drugs orally or through the nose could also be tough. All route of administration are shown to be effective at reducing migraine symptoms, however, nasal and injectable hypodermic administration could lead to a lot of side effects. The adverse effects related to body part administration haven't been well studied. Some folks could notice that they respond to one kind of sumatriptan higher than another.

Most side effects are gentle, as well as flushing; but, rare cases of myocardial ischemia have occurred. They're thus not counseled for people with upset, World Health Organization have had a stroke, or have migraines that are in the course of medical specialty problems. Additionally, triptans ought to be prescribed with caution for those with risk factors for vascular disease. Whereas traditionally not counseled in those with basilar migraines there aren't any specific evidence of harm from their use during this population to support this caution. Triptans aren't habit-forming, however could cause medication-overuse headaches if used over ten days per month.

Sumatriptan does not stop different migraine headaches from beginning within the future. For increased effectiveness at stopping migraine symptoms, a combined medical care that features sumatriptan and naproxen could also be suggested.6

Rizatriptan Benzoate5

Chemical Name:

Benzoic acid; \(N,N\)-dimethyl-2-{[1,2,4-triazol-1-ylmethyl]-1H-indol-3-yl]ethanamine

Chemical Formula:

\( C_{22}H_{29}N_{5}O_{2} \)

Chemical Structure:

\[ \text{Chemical Structure Image} \]

Molecular Weight: 391.5 g/mol

CAS No.: 144034-80-0

Melting Point: 178-180 °C

Log P: 1.67

Appearance: White colored amorphous powder with odorless characteristics

Solubility: Soluble in organic solvents such as ethanol, DMSO, and dimethyl formamide

Drug Class: Selective serotonin receptor agonists

BCS Class: BCS class III drug

Description:
Rizatriptan Benzoate is the benzoate salt form of rizatriptan, a member of the triptan class agents with...
anti-migraine property. Rizatriptan benzoate selectively binds to and activates serotonin (5-HT) 1B receptors expressed in intracranial arteries, and to 5-HT 1D receptors located on peripheral trigeminal sensory nerve terminals in the meninges and central terminals in brain stem sensory nuclei. Receptor binding results in constriction of cranial vessels and inhibition of nociceptive transmission, thereby providing relief of migraine headaches. Rizatriptan benzoate may also relieve migraine headaches by inhibition of pro-inflammatory neuropeptide release.

Pharmacodynamics:

Rizatriptan is a selective agonist of serotonin (5-hydroxytryptamine; 5-HT) type 1B and 1D receptors. It is structurally and pharmacologically related to other selective 5-HT1B/1D receptor agonists and has only a weak affinity for 5-HT3A, 5-HT3D, and 5-HT7 receptors and no significant affinity or pharmacological activity at 5-HT2, 5-HT3 or 5-HT2 receptor subtypes or at alpha1-, alpha2-, or beta-adrenergic, dopamine1-, dopamine2-, muscarinic, or benzodiazepine receptors. This action in humans correlates with the relief of migraine headache. In addition to causing vasoconstriction, experimental data from animal studies show that Rizatriptan also activates 5-HT1 receptors on peripheral terminals of the trigeminal nerve innervating cranial blood vessels, which may also contribute to the antimigrainous effect of Rizatriptan in humans.

Mechanism of Action:

Three distinct pharmacological actions have been implicated in the antimigraine effect of the triptans:

(1) stimulation of presynaptic 5-HT1D receptors, which serves to inhibit both dural vasodilation and inflammation;
(2) direct inhibition of trigeminal nuclei cell excitability via 5-HT1B/1D receptor agonism in the brainstem and
(3) vasoconstriction of meningeal, dural, cerebral or pial vessels as a result of vascular 5-HT1B receptor agonism.

Absorption:

Rapid following oral administration. Bioavailability is 45%. Food has no effect on the bioavailability of rizatriptan. However, administering rizatriptan with food will delay by 1 hour the time to reach peak plasma concentration. The rate of absorption is not affected by the presence of a migraine attack.

Volume of Distribution:

140 L
110 L

Protein Binding: 14 %

Routes of Elimination:

Approximately 14% of an oral dose is excreted in urine as unchanged rizatriptan while 51% is excreted as indole acetic acid metabolite, indicating substantial first pass metabolism.

Half Life: 2-3 hours

Fast Dissolving Tablet

A fast dissolving tablet is defined as a solid dosage form that may disintegrates into smaller granules that slowly dissolve within the mouth. The disintegration time for quick dissolving tablet varies from many seconds to over a minute depending on the formulation and the size of the tablet. A quick disintegrating or dissolving system or tablet is outlined as a solid dosage form that may disintegrate or dissolve at intervals 30 seconds, within the mouth leading to a solution or suspension while not administration of water. The quick disintegrating tablets are similar with quick dissolving tablets; soften in mouth tablets, rapimelts, Porous tablets, Orodispersible, fast dissolving or rapidly disintegrating tablets.  

Difficulties with Existing Oral Dosage Form

Patient might suffer from tremors thus they need difficulty to require powder and liquids. In dysphasia physical obstacles and adherence to an esophagus might cause gastrointestinal ulceration. Swallowing of solid dosage forms like tablet and capsules and turn out difficulty for young adult of incomplete development of muscular and nervous system and old patients suffer from dysphasia. Liquid medicaments (suspension and emulsion) are packed in multidose container; thus achievement of uniformity within the content of every dose could also be difficult. Buccal and sublingual formation might cause irritation to oral membrane, thus patients refused to use such medications value of products is main factor as channel formulations are most expensive and discomfort.

Ideal Characteristics of Fast Dissolving Delivery System

Mouth-feel

Mouth-feel is critical, and patients ought to receive a product that feels pleasant. Any large particles from the disintegrating pill that are insoluble or slowly soluble in secretion would result in an unpleasant gritty feeling. This could be overcome by keeping the bulk of the particles below the detectable size limit. In some cases, certain flavors will an improved mouth-feel perception, leading to a product that’s perceived as being less gritty, even if the sole change is that the flavor. Effervescence is adscititious to assist disintegration and improve mouth-feel by reducing the “dryness” of a product.

Hygroscopicity

Several quick dissolving dose forms are absorptive and can’t maintain physical integrity beneath normal conditions of temperature and humidness. They have protection from humidness that calls for specialized product packaging.
**Friability**

In order to permit quick dissolving tablets to dissolve within the mouth, they're made of either terribly porous or soft wrought matrices or compressed into tablets with terribly low compression force, that makes the tablets friable and/or brittle that are difficult to handle, usually requiring specialized peel off blister packing. To overcome this downside, some companies introduced additional strong kinds of quick dissolving tablets, like Wowtab by Yamanouchi Shadlee and meninges Solve by CIMA labs. Excipients balance the properties of the actives in fast-melting tablets. This demands an intensive understanding of the chemistry of those Excipients to prevent interaction with the actives. Determinative the cost of those ingredients is another issue that must be addressed by formulators.

The role of excipients is very important within the formulation of fast-melting tablets. These inactive food-grade ingredients, when incorporated within the formulation, impart the specified Organoleptic properties and products effectiveness. Excipients are general and may be used for a broad vary of actives, except some actives that need masking agents.

**Super disintegrants**

A disintegrant is an excipient that is added to a tablet or capsule mix to assist within the breakup of the compacted mass once it’s place into a fluid environment.

**Advantages**

Effective in lower concentrations, less effect on compressibility and flowability more practical intragranularly.

Some super disintegrants are:

- **Sodium Starch Glycolate** (Explotab, primogel) employed in concentration of 2-8 zip & optimum is 4-dimensional.
- **Mechanism of Action:** rapid and intensive swelling with minimal gelling.

- **Microcrystalline cellulose** (Synonym: Avicel, celex) employed in concentration of 2-15% of tablet weight. And Water wicking Cross-linked

- **Povidone** (crosopovidone) (Kollidone) employed in concentration of 2-5% of weight of pill.

- **Mechanism of Action:** Water wicking, swelling and probably some deformation recovery. Rapidly disperses and swells in water, however does not gel even once prolonged exposure. Greatest rate of swelling compared to different disintegrants.

- Larger area to volume quantitative relation than different disintegrants. Low-substituted hydroxyl group propyl polyose, that is insoluble in water. Rapidly swells in water. Grades LH-11 and LH-21 exhibit the greatest degree of swelling. Bound grades may also give some binding properties whereas retaining disintegration capability. Counsell concentrated 1-5% **Croscarmellose sodium**:

- **Mechanism of Action:** Wicking due to fibrous structure, swelling with token gelling. Effective Concentrations: 1-3% Direct Compression, 2-4%.

**Wet Granulation**

**Gas producing disintegrants**

Gas producing disintegrants are used particularly wherever further rapid disintegration or promptly soluble formulation is needed. They need conjointly been found important once poor disintegration characteristics have resisted different ways of improvement. Care should be taken throughout tab belongings, significantly on wetness level. Composition relies upon constant principles as those used for effervescent tablets, the foremost common being mixtures of acid & salt acids and carbonates or bicarbonates. In several instances lower concentration is used with gas manufacturing disintegrants than are needed by different disintegrating agents. Certain peroxides that release oxygen are tried, however they are doing not perform still as those releasing carbon dioxide.

**Conventional Technique:**

1. Freeze drying technique
2. Tablet molding technique
3. Spray drying technique
4. Direct compression technique
5. Sublimation technique
6. Mass extrusion technique

**Freeze Drying Technology (Zydis Technology)**

Lyophilization can be used to prepare tablets that have terribly porous open matrix network into that saliva rapidly moves to disintegrate preserved mass when it’s placed in mouth. The drug is entrapped in a water soluble matrix which is freeze dried to supply a unit which rapidly disperses when placed in mouth. Aside from the matrix and active constituents, the ultimate formulation might contain alternative excipients that improve the method characteristics or enhance the standard of final product. These embrace suspending agents, wetting agents, preservatives, antioxidants, colours and flavors. The popular drug characteristics for freeze drying formulations are water insoluble, low dose, with chemicals stable, little particle size and tasteless. Corveleyen and Remon investigated the influence of varied formulation and method parameters on the characteristics of rapidly disintegrating tablets in preserved form using hydrochlorothiazide as a model drug. They need ended that maltodextrins are helpful within the formulation of quick dissolving tablets created by freeze drying. Dehydration is comparatively expensive and time intense producing method. Other drawback includes fragility, that build of
standard packing tough and poor stability throughout storage beneath stressful condition.

**Tablet Molding**

In this technology, water-soluble ingredients are used so tablet disintegrate and dissolve rapidly. The powder mix is moistened with a hydro alcoholic solvent and is wrought in to tablet using compression pressure under employed in standard tablets compression. The solvent is then removed by air-drying. Moulded tablets have a porous structure that enhances dissolution. Two problems commonly encountered are mechanical strength and poor style masking characteristics. Using binding agents like plant product, tree or poly vinyl pyrrolidone will increase the mechanical strength of the tablet. To overcome poor taste masking characteristic Van Scoik incorporated drug containing distinct particles, that were formed by spray congealing a molten mixture of alter vegetable oil, baking soda, lecithin, polyethylene glycol and active ingredient into a two based tablet triturate form.

**Spray Drying**

Spray dryers are wide employed in pharmaceuticals and biochemical processes. Due to process solvent is gaseous rapidly; spray drying will produce highly porous, fine powder. Spray drying will be used to prepare chop-chop disintegrating tablets. This system relies on a particulate support matrix that is prepared by spray drying a liquid composition containing support matrix and alternative parts to create an extremely porous and fine powder. This is often then mixed with active ingredients and compressed into tablets.

**Direct Compression method**

In this methodology, tablets are compressed directly from the mixture of the drug and excipients with none preliminary treatment. The mixture to be compressed should have adequate flow properties and cohere stressed so creating pretreatment as wet granulation unnecessary. Few medications will be directly compressed into tablets of acceptable quality. A sort of disintegrant and its proportion are of prime importance. The opposite factors to be thought of are particle size distribution, contact angle, pore size distribution, tablet hardness and water absorption capability. The disintegrant addition technology is value effective and easy to implement at industrial level.

**Sublimation Technique**

The basis of this system is to feature inert solid ingredients that modify promptly, (e.g. camphor, ammonia carbonate, hydrocarbon, urea, ester etc) to alternative tablet excipients and therefore the mixture is then compressed into tablets. Volatile material is then removed via sublimation that generates a porous structure.

**Mass-Extrusion (Mass-Extrusion)**

This technology involves softening the active mix using the solvent mixture of soluble synthetic resin glycol and methanol and sequent expulsion of softened mass through the extruder or syringe to induce a cylinder of the product into even segments using heated blade to create tablets. The dried cylinder also can be wont to coat granules for bitter medication and thereby come through taste masking.

**Patented Technologies:**

Rapid-dissolving characteristic of FDTs is usually attributed to quick penetration of water into tablet matrix leading to its quick disintegration. Many technologies are developed on the idea of formulation aspects and completely different processes and patented by many pharmaceutical companies. Patented technology is represented below:

**Zydis technology**

Zydis formulation may be a distinctive freeze-dried tablet during which drug is physically entrapped or dissolved among the matrix of quick dissolving carrier material. Once zydis units are place into the mouth, the freeze-dried structure disintegrates in a flash and doesn’t need water to help swallowing. The zydis matrix consists of the many materials designed to attain variety of objectives. To impart strength and resilience throughout handling, polymers like gelatin, dextran or alginites ar incorporated. These form a shiny amorphous structure that imparts strength.

**Orasolv technology**

Orasolv technology has been developed by CIMA labs. During this system, the active medicinal drug is taste covert. It conjointly contains the bubbling disintegrating agent. Tablets are made by direct compression technique at low compression force so as to minimise oral dissolution time. Conventional blenders and tablet machine is employed to supply the tablets. The tablets created are soft and friable and prepacked in specially designed choice and place system.

**Durasolv technology**

Durasolv is that the patented technology of CIMA labs. The tablets created by this technology carries with it a drug, fillers and lubricating substance. Tablets are prepared by using typical tableting instrumentation and have sensible rigidity. These will be packed into typical packaging system like blisters. Durasolv is an applicable technology for product requiring low amounts of active ingredients.

**Wow tab technology**

Wow, tab technology is patented by Yamanouchi Pharmaceutical Co. WOW means that “Without Water”. During this method, a mix of low moldability saccharides and high moldability saccharides is employed to get a rapidly melting strong tablet. The mixture of high and low moldability is employed to supply tablets of adequate hardness.
Flash dose technology

Flash dose technology has been patented by Fuisz. Nurofen melt let, a new type of Advil as melt-in-mouth tablets, prepared using flash dose technology is that the 1st industrial product launched by Biovail Corporation. Flash dose tablets carries with it a self-binding shear form matrix termed as floss. Shearform matrices are prepared by flash heat process.15

Flashtab technology

The flashtab technology is one more fast-dissolving/disintegrating tablet formulation. Prographarm laboratories have patented the flashtab technology. It utilizes most of constant excipients as in typical compressed tablets. A disintegrating agent and a swelling agent are employed in combination with coated drug particles during this formulation to supply a tablet that disintegrates within the mouth in but one minute.16

Oraquick technology

K. V. S. pharmaceuticals have a patent over this technology. It utilizes taste masking microsphere technology referred to as micromask, that provides superior mouth feel over taste masking alternatives, vital mechanical strength, and fast disintegration/dissolution of the product. Any quite solvents aren't used by taste masking method. Thus it leads to superior and quick economical production.

Advatab technology17

Advatab tablets disintegrate quickly within the mouth, generally in less than 30 seconds, to permit for convenient oral drug administration while not water. Advatab is distinct from different FDT technologies because it may be combined with Eurand’s complimentary particle technologies like its world leading Microcaps® taste masking technology and its Diffucaps®, controlled release technology.

Nanocrystal technology

For fast dissolving tablets, elan's proprietary nanocrystal technology will modify formulation and improve compound activity and final product characteristics. Decreasing particle size will increase the surface area that results in a rise in dissolution rate. This will be accomplished predictably and with efficiency using nanocrystal technology.

CONCLUSION

The FDSSs were found to be thin and showed fast disintegration, satisfactory dissolution and acceptable physico-mechanical characteristics. The bitter taste of rizatriptan benzoate could be successfully masked by using combination of flavor. Therefore, the FDSSs containing rizatriptan benzoate is considered to be potentially useful for treatment of migraine where improved patient compliance and convenience is expected.

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Source of Support: The author(s) received no financial support for the research, authorship, and/or publication of this article.

Conflict of Interest: The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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