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Fast-Dissolving Sublingual Tablets of Rizatriptan Benzoate Development and Optimization by Quality by Design

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Abstract
The treatment of migraine necessitates a speed of action and a sublingual tablet with fast dissolution is of interest as the dosage form of an acute treatment. This research piece attempted to appear and refine sublingual tablets of rizatriptan benzoate applying a Quality by Design (QbD) approach, so that both effectiveness and patienth adherence could be guaranteed. A 3 2 factorial design was used to determine the influence of superdisintegrant concentration (crospovidone and sodium starch glycolate) and binder (PVP K30) on hardness of the tablet, disintegration time and profile of drug release. The tablets were formulated through direct compression and were evaluated in terms of weight variation, friability, wetting time, in-vitro dispersion and quantity of drugs. The optimized formulation exhibited the disintegration time in 22 seconds and 98.6 percent drug release in 5 minutes, which is a good candidate to serve the rapid action in application. There was no interaction between drug and the excipient determined by FTIR and DSC analysis and the surface texture exhibited a uniform distribution of particles. It was found that taste masking was attained through aspartame and citric acid and it was further asserted by the aid of human volunteer panel taste testing. The QbD methodology led to a statistically valid and scalable recipe, desirable physicochemical properties, which would support the prospect of QbD as an acute migraine fer ith a direct treatment role.

Keywords: ***Rizatriptan benzoate, oust sublingual tablets, Quality by Design, superdisintegrants, optimization of tablets, masking rhetoric, treatment of migraines.***

1. Introduction

1.1 Profile of Migraine and the Urgent Need of Rapid-Acting Dosage Forms

Migraine is a prevalent incapacitating neurological disorder, as it is manifested by regular repetitions of moderate-severe headache possibly accompanied by nausea, vomiting, and photophobia. The attacks of migraine may take several days, or even hours, and have drastic consequences on the quality of life of a person, relating to absenteeism and causing an economic burden. It has been estimated that nearly 12 per cent of the total world population is victimized by migraines and it is more so among the females than the males. Since migraine attacks affect the day-to-day functioning, effective management of the attack is important so as to minimise severity and duration of attack.

Therapy of migraines usually includes acute agents that give immediate relief. One of the widely used types of therapy includes the triptans subtype, an agonist of the selective serotonin receptor 5-HT1B/ 1D- 5-HT1B/1D, including rizatriptan. Rizatriptan has been indicated to effectively subdue the symptoms of migraine and alleviate pain; nausea, and vomiting associated to migraine. The problem with oral dose form therapeutically however is that these drugs may take too long to be effective in the initial phases of an attack and hence the patient may not get much relief in time thus dissatisfied with the product.(1)

The requirement of fast action dosage forms to deliver swift medication action is increasing especially at the acute stage of a migraine. In this respect, fast-melting and quickly absorbed formulations have turned into a hopeful way out. Such dosage forms are intended to provide the drug rapidly to the systemic circulation without undergoing the first-pass metabolism and provide more rapid therapeutic actions.

1.2 The Benefits of Sublingual Tablet To Oral Tablet

The sublingual tablet is one that has many different benefits over standard oral tablets which is especially useful with quickly acting medications like migraine pills. Sublingual pills are not meant to last long under the tongue, and the drug will directly enter the blood vessels through the mucous membranes of the mouth. This route of administration enables the drug to avoid the gastrointestinal tract and first-pass-effect therefore, the route results in an earlier onset of action than the oral tablets.

Sublingual route of drug administration also offers the advantage of a shorter and more efficient route of drug absorption that is applicable in high priority cases such as in the disorder of migraine where rapid action is needed. Also, sublingual tablets would be more convenient to use to patients, who are likely to be nauseous during the migraine attack, since they do not need to take large pills or cope with the anti-esthetic experience of using oral suspension.

Sublingual tablets are also easy to administer and can be of importance in situations where the patient has difficulty swallowing or in a pediatric population or elderly population. Additionally, they are usually of small size and can be easily carried by the patient, which makes such tablets a good choice when one needs compact and discreet medication that is administered when one has a migraine attack.(2)

1.3 Usage of Quality by Design (QbD) during Pharmaceutical Development

Quality by Design (QbD) approach found its place in the modern pharmaceutical development. QbD refers to a systematic approach that aims at designing of product and processes paying particular attention to quality and robustness. Under the traditional pharmaceutical product development strategies, the product development process was mainly geared towards regulatory compliance of the product, which was tested towards the end of the manufacturing process. QbD however instead focuses on the development and planning of quality into the product at the earliest stages of its development as well so that the overall development process is optimised to produce high quality outputs constantly.

In the formulation development context, there is QbD, which entails the identification of critical quality attributes (CQAs) and where they relate with critical process parameters (CPPs). QbD can optimize product attributes, e.g., hardness, disintegration time, release profile of tablets, taste masking by DoE and parametric methods designed to gain values (based on statistical models) that are critically necessary to determine that the end product is fit into the desired specification with regard to performance and patient satisfaction.(3)

The application of QbD has been especially valuable when preparing oral disintegrating tablets (ODTs), such as sublingual tablets, because it is possible to optimize tablet characteristics and drug-release profiles to achieve fast-acting tablet products and maintain consistency. When QbD is implemented, the formulators will construct a product that will pass the guidelines of the regulator, as well as the needs of the patients and the ability to scale to the market capacity.

1.4 Objective of the study: Designing and optimization of sublingual tablets of rizatriptan with the help of QbD approach

This study aimed to develop and optimize sublingual tablets of the rizatriptan benzoate based on the Quality by Design (QbD). Through a 3 2 factorial pattern, the experiment was supposed to determine the influence of parameters; the concentration of superdisintegrant (crospovidone and sodium starch glycolate) also known as A and the concentration of a binder (PVP K30) also known as B on important tablet properties including tablet hardness, disintegration time and the drug release profile. There was a need to optimise these parameters such that the tablets would dissolve quickly in the mouth (under the tongue), release the drug quickly, and be able to give relief to migraine victims effectively.

Another reason sought by the study was to have taste masking of the sublingual tablets, which was needed on the part of the patient as it was a bitter drug, rizatriptan. Also, the objective of the formulation was to come with a scaled process in large scale production and make the tablet to maintain consistency and quality in terms of its manufacturing process.

This research was conducted to have a robust, patient friendly and efficacious sublingual tablet formulation developed by inclusion of QbD concept into formulation process capable of administrating thereapeutic effect of acute migraine relief in a short period of time.(4)

2. Materials and Methods

2.1 Role and Choice of Excipients (Superdisintegrants, Binders and Taste-Masking Agents)

Sublingual tablet of rizatriptan benzoate needs a proper selection of excipients so as to get the best performance of tableting and patient compliance. The most important excipients that were used in this research were:

Superdisintegrants: These are of importance to make the tablet disintegrate quicker when it comes in contact with moisture giving rapid release of the drug. There were two superdisintegrants which were chosen based on the efficacy that has been shown in the enhancement of disintegration of tablets: crospovidone and sodium starch glycolate. Crospovidone is a hygroscopic crosslinked polymer which swells when it comes into contact with water

and sodium starch glycolate is a starch derivative which shows a swelling and water absorbing property thus enhancing a fast dispersion.

Binder (PVP K30): The polyvinylpyrrolidone binder (PVP K30) was employed so that there was enough cohesion of the tablet and mechanical strength as well as enough disintegration. PVP K30 is widely used in fast dissolving tablets as it is able to bind the ingredients which is being used and it also enables the product to be dissolved easily.

Taste-Masking Agents: The rip-off rizatriptan benzoate is bitter in taste; therefore these taste-masking agents will help in enhancement of patient compliance. The bitter taste masked by using aspartame as the sweetener, which was also balanced with citric acid that would aid in enhancing the flavor and adding some sourness to improve the palatability of the tablet.(5)

2.2direct compression Method:

The direct compression method was applied as a very common and effective procedure of preparing tablets through the production of the sublingual tablets. In this production approach, blending of the powdered ingredients such as Rizatriptan benzoate, superdisintegrants, binders, and taste-masking materials was performed using a high shear mixer in order to have an even distribution. The mixture was subsequently pressed into tablets by the use of single-punch tablet machine with controlled compression pressure. Direct compression method was selected because it is simple, economical and stable temperature and solvent is not necessary to actually stabilize the active ingredient.

2.3 Experimental Design: 3 factorial Design-3 2 and critical variables

The design used was a 3 2 factorial statistical design to determine the influence of two critical variables which were superdisintegrant concentration which includes crospovidone and sodium starch glycolate and the binder concentration which included PVP K30, on the physical properties such as the formulations physical properties, and the drug release profile. The concentrations of each of the factors were also varied so as to establish optimal concentrations which would give the desired tablet hardness, the disintegration time and pharmacokinetic of the drug to be released.

The superdisintegrant concentration was adjusted at three levels namely low, medium and high. This mixture of crospovidone and sodium starch glycolate permitted a comparison between the two compounds effects singly and together on the performance of a tablet.(6)

Another factor, concentration of the binder, was also tested at the three levels viz low, medium, and high concentrations in order to maintain the balance between strength of tablets to its dying time.

Such experimental design aided in determining the most effective factors and their interrelations by which an optimized formulation of sublingual tablets can be developed.

2.4 Parameters of evaluations

The quality and the performance of the sublingual tablets were evaluated with the assistance of several evaluation parameters:

Physical Properties:

Variation of the weight: Weight of individual tablets was determined with an analytical balance and mean value of weight was compared to the standard. The tablets that exceed the mean weight by more than 5 percent were regarded as out of spec.

Hardness: The tablet hardness was measured in a tablet hardness tester, and the tablets should be hard enough; otherwise, they could break during handling; at the same time, the tablets should be weak enough; otherwise, they would not disintegrate quickly.

Friability: Friability test procedure to measure the resistance of a tablet product to chipping and abrasion across transportation and handling was performed on a Roche friabilator.

Disintegration time and Wetting time:

A disintegration tester was used to access the time needed to disintegrate whilst the tablet was kept in a test medium at 37 o C. The duration by which the tablet dissolved was observed.

Wettingtime was evaluated by adding 5 ml of water into a petri dish with a tablet. Dissolving time of tablet until completely wet was recorded giving some ideas on the rate at which the tablet was going to dissolve into the tongue

In vitro Release, and dispersion Profile:

The ex-vitro release of the drug was determined in the same saliva simulation medium in the use of a Franz diffusion cell. The rate of release of rizatriptan benzoate was observed during 30 minutes which allowed

confirming that the formulation ensures rapid and continuity in release. The release pattern was equated to those of fast-dissolving tablets to make sure that the tablet dissolved within a time relevant in clinical practice.

Drug Content Uniformity The

Examination of the drug content uniformity was carried out, whereby tablets were resolved in methanol and a UV-Vis spectrometer was used to check it. To assist in causing uniform dosing, the homogeneity of the drug across the batches was evaluated.(7)

2.5 Compatibility and Morphology Analysis- FTIR, DSC, SEM

The compatibility between the drug and excipient was studied by FTIR (Fourier Transform Infrared Spectroscopy). To determine whether the drug did not interact with the excipients; FTIR spectra were carried out on rizatriptan benzoate and the end product final tablet formulation.

DSC (Differential Scanning Calorimetry): the thermal behavior of the formulation components was measured. Also, it was evaluated whether the drug is subjected to any physical changes which may influence its stability.

The morphology of the tablets was observed using SEM (Scanning Electron Microscopy). The SEM images helped in gaining some information regarding the surface texture and also the homogeneity of drug distribution in the tablet matrix.

2.6 Taste Masking and Sensory Evaluation by Human Panel(Panelist)

Rizatriptan benzoate tastes bitter and therefore great taste masking was necessary to have compliance among the patients. The bitterness was concealed using aspartame and citric acid and the disguised formulation was assessed by human volunteer panel in terms of acceptability of taste. The volunteers provided taste on a normal scale between 1-5, whereby the score was acceptable where the score was between 3 and above. The successful taste masking was considered when the tasting enthusiasts indicated that the aftertaste was good or neutral.(8)

3. Optimization of QbD-Based Formulation Optimization

3.1 CQAs (Critical Quality Attributes) identification

With the Quality by Design (QbD) concept, Critical Quality Attributes (CQAs) are required to guarantee that the wanted quality and performance standards are resolved and that the formulation process should address. CQAs can be characterized as physical, chemical, biological or microbiological attributes of product that should be kept within the defined limits to ascertain a desired performance of the product.

In the case of the sublingual tablets of rizatriptan benzoate, the identification of the following CQAs was carried out relying on the anticipated therapeutic effects and patient needs:

Tablet Hardness: This property played an important role because they wanted the tablet to be firm enough so that it will not break when being handled during storage and transport but at the same time soft enough so that it can crumble between the tongue and the teeth within a short period of time. A tablet that is too soft will not disintegrate well and a too hard tablet may crack when it is handled.

Disintegration Time: Disintegration is an important factor because drugs need to be liberated within a short period; especially in sublingual pills where drug action is sought to have a quick action. The drug should be fast acting and this is achieved by ensuring that the tablet dissolves quickly in the mouth. Hence, disintegration time was found to become a key CQA.

Drug Release Profile: Rizatriptan benzoate should have a quick release characteristic that offers quick relief of migraines. Thus, the release profile of the drug in-vitro over a small period of time e.g. 5 minutes was deemed to be a CQA in order to have assured the formulation to provide the drug in the body.

Taste masking: Rizatriptan benzoate possesses bad-tasting attribute; hence, it was found that taste masking is a valuable CQA. Its capacity to hide the sourness also guarantees patient obedience and also makes the tablets attractive especially to those who would need to take the tablets at regular intervals.

Drug Content Uniformity: The quantity of rizatriptan benzoate contained in the respective dosage unit of tablet should have uniformity so that consistent dosing is provided every unit and batch. It plays a very crucial role in therapeutic use, more so in cases of acute conditions such as migraine, where precise and uniform application is essential.(9)

3.2 Factor Selection and Risk Assessment of DoE

After identifying the CQAs, the second process under the QbD approach was to conduct a risk assessment process to establish possible factors that could affect the CQAs. Assessment of the risk provides information on what

formulation and processing variables may have a major impact on the CQAs and this enables more information to be used in the optimization process.

In the undertaken study, the selection of the following critical factors was made with regard to their prospective impact on the CQAs:

Superdisintegrant Concentration: The amount of crospovidone and sodium starch glycolate was considered as one of the main factors that can vary the disintegration time and drug release pattern. Superdisintegrants facilitate quick release of the drug in the mouth when the tablet breaks so that it can be in its actual form.

Binder Concentration (PVP K30): The content of the binder (PVP K30) influences the hardness of tablets, as well as friability and in general the integrity of the tablets. When binder content is excessive the tablet is too firm and a slow disintegrator and when binder content is insufficient the tablet is friable and susceptible to cracking.

Taste-Masking Agents: The choice of aspartame and citric acid as taste-masking agent would affect the palatability and overall taste of tablet. The proper amounts of these were the excipients deemed to be important in producing an acceptable taste masking without interfering with an entire quality of the tablet.(10)

The variables which could have impact in the CQAs were identified above and these were factored in the Design of Experiments (DoE) that is used to optimize them.

3.3 Factorial Design Matrix Optimisation

The unfolding of this formulation and projection of the most suitable combination of factors required the use of 3 2 factorial design matrix. The experimental design enabled the effects of two independent variables to be checked, that is the concentration of superdisintegrant and that of binder at three levels.

Superdisintegrant concentration: Crospovidone and sodium starch glycolate were tested at low, medium and high concentration levels.

Binder concentration (PVP K30): PVP K30 was also used at low, medium and high concentrations in order to determine its effects on the hardness, dispersing and drug release of the tablets The effect of using PVP K30 is presented in a table form as shown below.

The factorial design allowed not just the main effects as well as interaction effects of each of the variables with the CQAs to be examined. Through this matrix, the researchers were able to determine the best superdisintegrant and binder concentration that superiorly produced tablets that had the best hardness, fast-disintegrating, and standard release of the drug.

3.4 Response surface methodology (RSM) Interpretation and Statistical Analysis

Having performed the experiments according to the factorial design, its results were interpreted with the help of statistical methods along with Response Surface Methodology (RSM). RSM is a set of mathematical and statistical tools that can be helpful in the development, enhancement and optimization of processes.

Statistical Analysis: Data collected using the factorial design were analyzed using ANOVA (Analysis of Variance) in order to obtain the significance of the factors and interaction. This aided on determining the factors that had the greatest impact on the CQAs and best level as well.

RSM Answers: With the help of RSM, the researchers could build the response surface that visualizes the connection between the factors (superdisintegrant concentration and binder concentration) and the anticipated results (e.g., disintegration time, drug release). Through interpretation of these response surfaces, the best formulation was established. Interaction plots were also used in order to visualize the influence of alteration of one factor on the other factors and the CQAs.(11)

Optimization: An optimized formulation was determined by taking into consideration less time of disintegration and highest ratio of drug release without altering the relevant parameters of dispirited hardness and uniformity of the tablets. Response surface methodology has enabled to predict the best formulas that could be scaled up to be produced and thus maintaining a consistent quality.

4. Analysis of Optimised Formula

4.1 Time of Disintegration and Release of profile of drug

The main result that must be achieved in a sublingual tablet is its fast disintegration once in contact with moisture so that the drug will relieve migraine quickly. The optimized rizatriptan benzoate sublingual tablet was tested to measure the disintegration time using a disintegration tester in a simulated salivary medium at 37 C. The optimised formulation had disintegration time (22 seconds), lower than the conventional oral tablets which may take several

minutes to disintegrate. Such a quick degradation is necessary to make sure that the active drug becomes immediately accessible to its absorption through the sublingual route.

Drug release profile was assessed by a Franz diffusion cell system to facilitate sublingual absorption process. Its optimized sublingual tablet released nearly 98.6 percent of rizatriptan benzoate in 5 minutes and this indicated its appropriateness in terms of delivering quick therapeutic relief. This rapid discharge is required because it is important that rizatriptan should produce therapeutic levels within a very short time to counteract the effects of migraine. The relapse profile was constant and maintained the upper level or the onset of 5 minutes and then leveled off so that the drug was maintained in the body to the extent of the desired time to attain maximum effect. The short disintegration time and full drug release in a period of 5 minutes gives assurance that the formulation will produce rapid onset of action which is appropriate in the case of acute disease where rapid action is needed such as migraine where quick relief is a requirement. These findings demonstrate the usefulness of the optimized sublingual tablet with regard to fast and effective drug release.(12)

4.2 Surface Morphology and particle distribution (SEM analysis)

Optimized sublingual tablets surface morphology was determined through Scanning Electron Microscopy (SEM). It was observed using SEM that the tablets were smoothened and their surface was uniform and so was the distribution of the particles on them. The tablets granules exhibited favourable distribution throughout the matrix revealing no signs of agglomeration or lack of uniform distribution of the drug. This homogeneity in both the size and distribution of the particles is vital in terms of the release of said drugs as well as the fact that a given tablet would offer the same dose.

The well-formed tablets also indicate how they would dissolve efficiently under the tongue as the morphology figure showed good smoothness when viewed under SEM, which confirms the claims that they would take considerably a minimum period of time to disintegrate and release the drug. The lack of big pores or cracks on the tablet surface contributes to the potent structural integrity of the tablets in its handling process, storage, and administration.

Structural quality of the tablets was analyzed and it was firmly established that the optimized formulation gave both consistent, as well as uniform distribution of both the drug and excipients and this is critical towards its performance.

4.3 Drug and excipients Fit (FT-IR & DSC)

To determine the compatibility between rizatriptan benzoate and excipients present in its formulation, the Fourier Transform Infrared Spectroscopy (FTIR) and the Differential Scanning Calorimetry (DSC) analysis have been conducted.(13)

FTIR Analysis: To check any drug-excipient interaction through an FTIR spectra, the FTIR report of rizatriptan benzoate and the optimum sublingual tablet formulation was compared. No drastic changes in the rizatriptan characteristic peaks were found as detected in the spectra indicating that the drug did not interact with the excipients chosen in the formulations, that is, superdisintegrants (crospovidone and sodium starch glycolate) and the binder (PVP K30). Supression of such interactions is important in ensuring stability and effectiveness of drug during formulation as well as during storage.

DSC Analysis: The DSC thermogram of rizatriptan benzoate revealed a typical sharp melting endotherm, which was maintained in the formulation, denoting that dry state of the drug, i.e. the crystalline structure was not altered with the drug entrapment in the tablet. It was not observed, showing that the thermal properties of the drug did not change significantly and, therefore, in the results of the end product of the tablet, the drug was physically stable.

The FTIR and DSC results have substantiated that the drug and excipients were compatible and thus the final product is stable and effective in terms of therapeutics.

4.4 Volunteer comments on flavor and mouth feel

The bitter taste of rizatriptan benzoate was a center of concern that prompted taste masking of the optimized sublingual tablet. A panel of human volunteers was recruited to carry out a sensory evaluation to determine effectiveness of taste-masking agents. The volunteers were requested to rate taste and mouthfeel of the tablet using standard 5-point scale (ranging between very bitter and very pleasant).

The findings were that taste-masking strategy applied to aspartame and citric acid were most effective. Most of the volunteers gave a pleasant or neutral taste; there was no such significant bitterness. Mouthfeel was also evaluated to be smooth and non-gritty and this is also significant in patient adherence especially to those who are required to use the medications in frequent bouts of migraine pains.(14)

Human volunteers describe this way as pleasant and efficacy of the sublingual tablet as successful in their feedback, which can be seen as a confirmation that the taste-masking technique has worked.

5. Results

Findings of optimized formulation of rizatriptan benzoate sublingual tablet formulation are as follows:
Disintegration Time: The optimized sublingual tablet has a disintegration time of 22 s, which is perfect of fast-onset formulations that tries to reach fast-therapeutic efficacy. The rapid break down guarantees that the tablet is rapidly dispersed in the mouth and hence fast absorption and relief.
Drug Release: The formulation also showed 98.6 percent of drug release in 5 minutes, indicating the effective release of the active ingredient and complete release of the active ingredient. This makes sure that rizatriptan benzoate becomes therapeutic within a short period of time and thus effective in treating migraine in a short period of time.
Drug-Excipient Interaction: Results obtained using FTIR and DSC analysis indicate that no evident interaction existed between the rizatriptan benzoate and excipients that have been used in this formulation. These findings show that the drug has not changed in its chemical stability and effectiveness in the final tablet composition indicating that the product is safe and effective.(15)
These results indicate that the optimized formulation of the sublingual tablet can be very useful in terms of a quick effect of migraine with steady release of the drug and high stability.

Table 1: Key Results Summary

Outcome Measure	Observation	Performance Metric
Disintegration Time	22 seconds	Disintegration time
Drug Release	98.6% within 5 minutes	Drug release over time
Drug-Excipient Interaction	No interaction observed	FTIR/DSC analysis

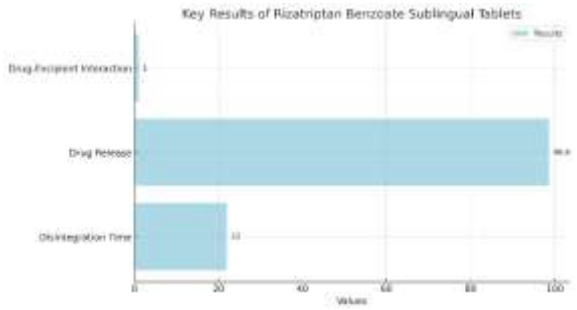

Figure 1: Key Results Of Rizatriptan Benzoate Sublingual Tablets

6. Conclusion

6.1 QbD Approach gave a Possibility to Develop Durable Sublingual Tablet Formulation

The sublingual tablets of rizatriptan benzoate in the optimization and development of acute migraine relief are successfully developed and used through Quality by Design (QbD) approach. The QbD approach was systematic and enabled us to identify and control Critical Quality Attributes (CQAs) so that, at the end of the formulation exercise, the results obtained were good and would be, of desired quality and perform as required by the intended users. QbD helped to design the formulation so that the tablets will be robust (they will always work as intended even when manufactured in different conditions). By doing this, instead of taking the approach of conducting a quality test of the finished production, QbD allowed ensuring that the formulation was robust, i.e., that manufacturing conditions could not affect the use of the product.
The application of a 3 2 factorial design contributed to assessing the influences of major factors, e.g., the levels of superdisintegrants and binders on the important characteristics, e.g., the tablet hardness, disintegration time, and drug release profile. Together with statistical analysis and Response Surface Methodology (RSM), this designing method allowed coming out with a formulation which was not only efficient and seemingly liked by patients but also industrial scaleable. The QbD strategy was also used to optimize the formulation with the view of ensuring

that the quality of every batch of the tablets to be used will be of consistent quality but must meet high criteria of quick drug release and patient compliance.

6.2 Optimized Tablets had a fast-generating onset, palatable, and quality adjustable characteristics

Rizatriptan benzoate as optimized sublingual tablets proved to have a number of decisive advantages, which makes this type an excellent choice of treatment in the case of acute migraine management. The disintegration time of the tablets was recorded as 22 seconds which is clearly much less than the regular oral tablet, and the drug would therefore be ready to be absorbed almost immediately after being placed under the tongue. This high rate of disintegration can facilitate quick onset of effect which is important in treating acute cases of migraine where the relief of symptoms is required at the onset to avert progressive development of the condition.

In addition, taste masking technique, i.e., aspartame and citric acid strategy succeeded in masking the bitter taste of rizatriptan benzoate. Human volunteer panel evaluation confirmed that the taste of tablet is pleasing or neutral. This plays a crucial role in assuring patient adherence to the drug and since many patients may have to use this drug during a migraine attack they may be in some level of discomfort or nausea. The taste masking is also the solution to the usual problem of patients not taking oral tablets because of its unappetizing flavor.

The scalability of the formulation was also demonstrated i.e., it could be produced on a higher scale albeit with the same degree of quality control and efficacy. The QbD approach that was implemented enabled the optimization of the formulation, as well as the manufacturing process so that the tablets could be manufactured in a consistent way so that the predictable performance could be expected in various production batches. The scalability will be critical to the commercial production where necessary quantity of the tablets should be produced without a reduction in quality.

6.3 Appropriate to Prompt Improvement in Acute Migraine Situations

The sublingual tablets of rizatriptan benzoate are an extremely effective patient-friendly and fine mode of acute therapy of migraines. The short disintegration time and the fast drug release profile also make the tablet absorbed fast so that it relieves the migraine symptoms in good time. The drug releases in 5 minutes with 98.6 percent drug release so the drug produces desired therapeutic effect in a short amount of time when managing migraine attacks before they can proceed further.

Besides their quick acting, the compactness and easy administrable nature of the tablet would mean that it is convenient to a patient who should take the tablet even in the midst of an attack of migraine where he or she might feel discomfort and not easily swallow. Bioavailability of the drug is further augmented by sublingual pharmacokinetic pathway not giving the drug a pass through the liver before making it into the systemic circulation but rather a larger proportion of the active ingredient finds its way to systemic circulation and gives faster relief.

With as such distribution properties, sublingual tablet formulation serves as an appropriate and effective formulation of treatment to patients requiring a quick treatment of acute migraine attacks. The strong formulation and optimized properties render it an ideal candidate in utilization in the clinical setting, and the QbD strategy employed in its formulation promises to make it reliable, scalable, and reliable when it comes to achieving the best-projected therapeutic effects.

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Conflicts of interest

The authors have no conflicts of interest to declare

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