https://doi.org/10.15218/zjms.2024.021

Effect of kyron T-134 and crospovidone as a fast disintegrating agent on formulation properties of fast dissolving tablet containing ketorolac and rizatriptan using direct compression method

Received: 12/09/2022 Accepted: 06/11/2022

Rawand Sirwan Izzalddin [1*] Nozad Rashid Hussein [1]

Abstract

Background and objective: Fast dissolving tablets (FDTs) are "they are uncoated tablets that are supposed to be placed in the mouth and dispersed quickly before being swallowed" within minutes. This study aimed to formulate and evaluate a combination of ketorolac and rizatriptan as orally fast-dissolving tablets using the most common and easiest method to treat migraine attacks with or without aura. To investigate the effects of various types of diluents and super disintegrants on wetting time, water absorption ratio, disintegration, and dissolution time of combined drugs (ketorolac and rizatriptan) as oral dissolving tablets prepared by direct compression technique.

Methods: Pre-formulation experiments were carried out in order to rule out any physicochemical interactions between the two medications (ketorolac and rizatriptan) as well as between each drug and its excipients. Four different formulations of fast-dissolving tablets with different types and ratios of diluents and super disintegrants were created using the direct compression technique in order to improve the formulation. Organoleptic characteristics, weight variation, thickness, friability, hardness, disintegration duration, wetting duration, water absorption ratio, drug content, *in-vitro* dissolution, stability, and comparison tests have all been characterized.

Results: According to FT-IR, the two drugs and excipients exhibit no physicochemical interactions. The ideal formula F4 contains crospovidone and Kyron T-134 at optimal concentrations of 2.5% and 2.5%, respectively, and provides the majority of pharmaceutical drugs to be released within the first five minutes, a strong stability profile, the shortest wetting time with the fastest disintegration time (10 sec), and a pleasant flavor (strawberry flavoring agent).

Conclusion: Kyron T-134 with Crospovidone in a (1:1) ratio provided rapid disintegration. Ketorolac tromethamine and rizatriptan benzoate may be made into fast-dissolving oral tablets using Kyron T-134 and Crospovidone. Improving migraine compliance is a reasonable goal.

Keywords: Ketorolac tromethamine; Rizatriptan benzoate; Direct compression method; Kyron T-134; Crospovidone; Fast Dissolving Tablet.

Introduction

Dysphagia, or difficulty swallowing, affects roughly 35% of the population as a whole, as well as 30-40% of the elderly in institutions and 18-22% of all long-term care facility residents.[1] The size, surface, shape, and flavour of tablets and hard gelatin capsules are the most common concerns concerning difficulties ingesting them, in order of frequency of complaints. Easy-to-swallow dosage forms are especially important for geriatric and pediatric patients, as well as travellers who may not have easy access to water. Patients with migraines typically experience a moderate to severe headache that is throbbing and localized to one side of the head, requiring

[1] Department of Pharmaceutics, College of Pharmacy, Hawler Medical University, Erbil, Iraq.
Correspondence: rawandpharmacist91@gmail.com

https://doi.org/10.15218/zjms.2024.021

a fast-acting drug with little gastric discomfort. Rizatriptan is a medication that belongs to a class of pharmaceuticals called selective serotonin receptor agonists. It works by constricting blood vessels in the brain, inhibiting the production of certain natural compounds that produce pain, nausea, and other migraine symptoms, and preventing pain signals from being delivered to the brain.[2] Ketorolac is a nonsteroidal anti-inflammatory drug (NSAID) used to treat migraines and provide a morphine-like action.[3] The success of this treatment is determined by the aetiology of the migraine. Because migraine is a disease characterized by acute attacks of severe pain, the preparation of these combined drugs is clinically beneficial for patients with migraine. Furthermore, improving patient compliance and reducing pharmacological adverse effects are equally essential because patients who take these two medications in their ordinary oral solid dosage forms may experience local gastric irritation, delayed and insufficient absorption as a result of poor bioavailability.[4] The United States Food and Drug Administration (USFDA) defines a fast dissolving tablet (FDT) as a solid dosage form containing a pharmaceutical drug or active ingredient that, when placed on the tongue, dissolves quickly, usually in a matter of seconds.[5] After being degraded in saliva, FDTs generate a solution or suspension that the patient may easily take. Part or all of the drug might be absorbed within the oral cavity which provides a rapid onset of action and relieves the headaches quickly, or it may go to the stomach in a solution form that is ready for absorption. Although the solution form minimizes epigastric pain caused by ketorolac. Compared to the conventional table, the bioavailability of the medications are greatly improved in this situation.[6]

A fast-dissolving with adequate structural integrity to be more stable, an exquisite look, better disintegration, the suitable hardness, and the optimal drug release profile may be created using direct compression method, which is also simplest, cheapest, and most appropriate approach.[7,8]

The aim of this study is to prepare a fast-dissolving tablet containing combined drugs (ketorolac and rizatriptan) to treat acute migraine attacks by combining two of the super-fast disintegrating agents (kyron T-134 and crospovidone) to provide rapid dissolution of the drugs in the mouth.[9] According to the NICE guideline, and as documented in many articles and trials, the use of triptans in combination with NSAIDs is recommended,[10,11] as the combination of these two drugs, through different mechanisms of action, rapidly relieves severe migraine attacks. Triptans (rizatriptan) increase serotonin levels,[12] through the selective activation of the 5-hydroxytryptamine1 receptor subtype,[13] whereas NSAID's (ketorolac) block COX-enzymes. As a result of blocking the COX enzyme, the pain is more effectively reduced as the COX enzyme is physiologically responsible for the production of pain mediators.[14] Ketorolac is considered a morphin-like action analgesic for the management of moderate to severe pain.[15]

Methods

Pre-formulation studies

To exclude un wanted interaction, Ketorolac and rizatriptan drug powders and the main other ingredients were subjected for FT-IR analysis (Jasco FT/IR-4600), both separately and in combinations as a physical mixture.

Melting point

Using electrical melting point equipment, the capillary tube method was used to determine the melting points of rizatriptan and ketorolac (Stuart, Copley Scientific, UK).

Determination of λ_{max} (maximum absorbance) of drugs

A solution of 10 µg/ml of both ketorolac and rizatriptan was scanned separately using a UV-spectrophotometer at

https://doi.org/10.15218/zjms.2024.021

a wavelength ranging from 200-400 nm using water as a blank. The lambda max of ketorolac and rizatriptan were determined (USP, 2010).

Determination of calibration curve of drugs

A stock solution of 100 µg/ml of ketorolac and rizatriptan separately are prepared by dissolving 10 mg of ketorlac and 10 mg of rizatriptan in 100 ml of water. Series concentration were prepared from the stock solutions using 10 ml volumetric flask and then volume made up with distilled water to the level. The solutions were analysed by UV-spectrophotometer at the lambda max.[16]

Preparation of fast dissolving tablet

Ketorolac (10 mg) and rizatriptan (5 mg) oral disintegrating tablets in four distinct formulations were created utilizing the direct compression method (Table 1), two different diluents, three different super disintegrants, and a combination of two super disintegrants. Citric acid and sodium saccharine were added to cover up the flavor, while magnesium stearate served as a lubricant and aerosil served as a gladient. Except for magnesium stearate, which was added afterwards and combined for an additional 2–5 minutes, all materials were fully blended for 10 minutes after passing through a sieve (mesh #30). Using a multi-rotary tablet compression machine, the powder mixture was crushed into tablets using 6.5 mm round-shaped flat punches to produce 100 mg-sized tablets.[7,8]

Table 1 Formulations ketorolac (10mg) combined with rizatriptan (5mg) orally disintegrating tablets

Excipients	F1 (mg)	F2 (mg)	F3 (mg)	F4 (mg)
Ketorolac	10	10	10	10
Rizatriptan	5	5	5	5
Mannitol DC (400)	57.8	65.8	-	45.8
MCC 102	20	10	76.8	30
Crospovidone	3	-	-	2.5
Kyron-T134	-	5	-	2.5
Sodium starch glycolate	-	-	4	-
Flavouring agent (strawberry)	1	1	1	1
Sodium Saccharin	1.2	1.2	1.2	1.2
Citric Acid	0.5	0.5	0.5	0.5
Magnesium stearate	1	1	1	1
Aerosol	0.5	0.5	0.5	0.5
Total % (w/w)	**100**	**100**	**100**	**100**

https://doi.org/10.15218/zjms.2024.021

Evaluation of fast dissolving tablets

Visual inspection (Organoleptic evaluation)

An "elegant" dosage form that will increase consumer acceptability. A visual inspection test was employed to regulate the general look of a tablet, which includes: tablet size, tablet shape, tablet color, presence or absence of an odor, presence or absence of a taste, and surface texture.

Hardness (Crushing strength)

The amount of pressure needed to compress the tablet and break it can be used to measure hardness.[17] The tablet breaking force tester-USP (Electrolab) was used to test 10 tablets at random from each formulation. The hardness was measured in Newtons (N), and the mean and standard deviation values were computed.

Friability (Resistance to abrasion)

The ability of the tablets to survive abrasion during packing, handling, and transportation may be assessed using a friability test as represented in equation 1. 20 tablets (6.5 g) were put into the friabilator chamber, which revolved for 4 minutes at 25 rpm.[18]

Thickness and diameter

Tablet thickness is a shape parameter, it is affected by mass and volume variation of each sample. Tablet thickness and diameter were measured by using Vernier Calliper (Instotech).[19]

Weight variation

The average weight of ten tablets was determined after a random selection of them. Calculations were made to determine how each tablet's weight varied from the average weight (European Pharmacopeia, 2017).

Wetting time and water absorption ratio

Wetting time is an important factor that provides insight into the tablet's disintegration characteristics; a shorter wetting time suggests a speedier breakdown. Ten milliliters of water heated to 37 °C + 0.5 were put to a petri dish with five circular tissue sheets each measuring 10 cm in diameter. The amount of time it took for the tablet's upper surface to become wet was measured by gently placing it on the tissue paper surface. The same method used for measuring wetting time was used to calculate the water absorption ratio. The tablet's original weight (Wb) was recorded before it was placed in the petri dish. After being wet, the tablet was removed and reweighed (Wa). The water absorption ratio (R) was determined according to equation 2.[20]

$$\text{Friability \%} = \frac{W\,(\text{initial}) - W\,(\text{final})}{W\,(\text{initial})} \times 100 \quad \text{..... Eq.(1)}$$

$$R = \frac{W_a - W_b}{W_b} \times 100 \quad \text{..... Eq.(2)}$$

Where R = water absorption ratio; W_a = weight of the tablet after absorption; W_b = weight of the tablet before absorption.

https://doi.org/10.15218/zjms.2024.021

Disintegration test

The disintegration time of FDTs containing ketorolac and rizatriptan was measured using the disintegration tester-3 USP (electrolab) and 900 ml of distilled water at 37 °C + 0.5.[21]

***In-vitro* dissolution studies**

The dissolution studies for optimum formulations of FDTs were carried out using USP type II dissolution test apparatus (USP) and distilled water (D.W) as the dissolution medium (USP). The FDTs were placed in a dissolution vessel containing 600 ml for ketorolac, 900 ml for rizatriptan by D.W, for each drug separately. The temperature was kept at 37 °C 0.5 and the mixture was stirred at 50 rpm for 15 minutes (USP). Samples (5 ml) were collected periodically at different time intervals (2, 4, 6, 8, 10, 12.5 and 15 min) and replaced with fresh dissolution medium. The absorbance was determined spectrophotometrically at 322 nm and 225 nm for ketorolac and rizatriptan, respectively and separately (USP, 2010).

Drug content

Ten tablets were chosen at random, weighed, and powdered to equal 10 mg of ketorolac and 5 mg of rizatriptan separately, which were then diluted in water and filtered using Whatman filter paper. Using water as a blank, a UV Spectrophotometer was used to determine the amount of ketorolac in the solution at 322 nm and rizatriptan at 225 nm separately.[22]

Effect of temperature and humidity on the stability of the prepared FDTs during storage

The manufactured FDTs of formulation F4 were submitted to stability studies to determine the impact of temperature and humidity on the stability of the main parameters, including disintegration and drug release profile. The tablets were kept in a stability chamber (NEWTRONIC) for three months at two different temperatures and relative humidity levels, 25 °C with the relative humidity of 60% ± 5 and 40 °C with the relative humidity of 75% ± 5 for three months.

Comparability study

In this study, manufactured FDTs (F4) containing (kyron T-134 combined with crospovidone) as a super-fast disintegrant were compared to commercialized melatonin FDTs containing (croscarmellose) as a super disintegrant that was received as a gift from (Pharma Natural Company) in terms of disintegration time, as this characteristic is a critical element of FDTs.

Statistical analysis

The Microsoft Excel 2013 t-test and ANOVA were used for statistical analysis. The difference was considered to be statistically significant when P <0.05 and non-significant when P >0.05. A mean and standard deviation were used to express the values in the data.

Results

Determination the melting point of drugs

Ketorolac and rizatriptan powder have recorded melting values of 164 C and 178 C, respectively. This is quite close to the reported ranges for rizatriptan and ketorolac, respectively. 162-165 C° and 178-180 C°.

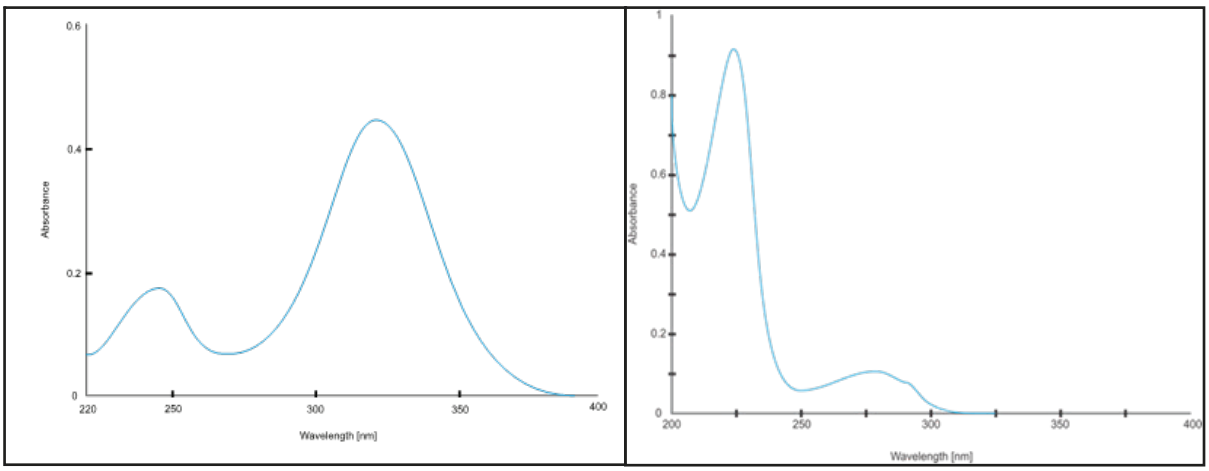
Determination of λ_{max} (maximum absorbance) of drugs

Ketorolac and rizatriptan had maximal absorbance at 322 nm and 225 nm, respectively. as seen in Figure 1.

Determination of calibration curve of drugs

After determining the calibration curve for both drugs, the linear relationship of absorbance versus concentration was determined and plotted, and a regression equation was obtained. as seen in Figure 2.

https://doi.org/10.15218/zjms.2024.021



a b

Figure 1 The UV spectrum of ketorolac (a) and rizatriptan (b) in water

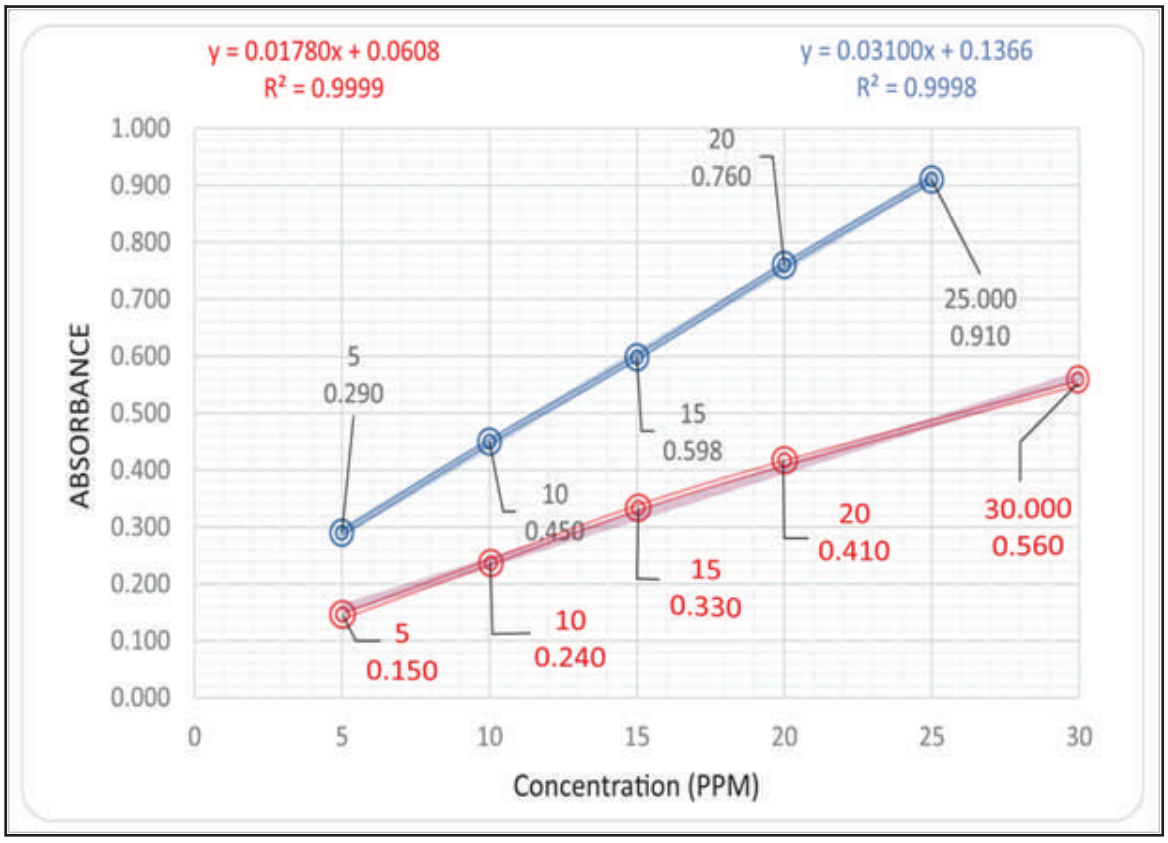


Figure 2 Calibration curve of ketorolac (upper line) and rizatriptan (lower line) in water

https://doi.org/10.15218/zjms.2024.021

Fourier transforms infrared (FTIR) studies

The FT-IR spectra for the drugs and ingredients showed no loss of the main functional groups, which are responsible for the pharmacological action and water solubility between ketorolac and rizatriptan, and each drug with Kyron T-134 and crospovidone. Figure 3 shows a section of this research.

The results showed that all the formulations had acceptable weight uniformity and friability (less than 1%), as seen in Table 2.

Table 2 Weight variation and friability test of FDTs

Formulation type	Weight variation (mg)*	Friability %
F1	99.33 ± 1.04	0.31
F2	100.52 ± 1.37	0.26
F3	101.32 ± 1.28	0.38
F4	100.33 ± 1.67	0.25

*Data are expressed as means ± S.D, n = 10

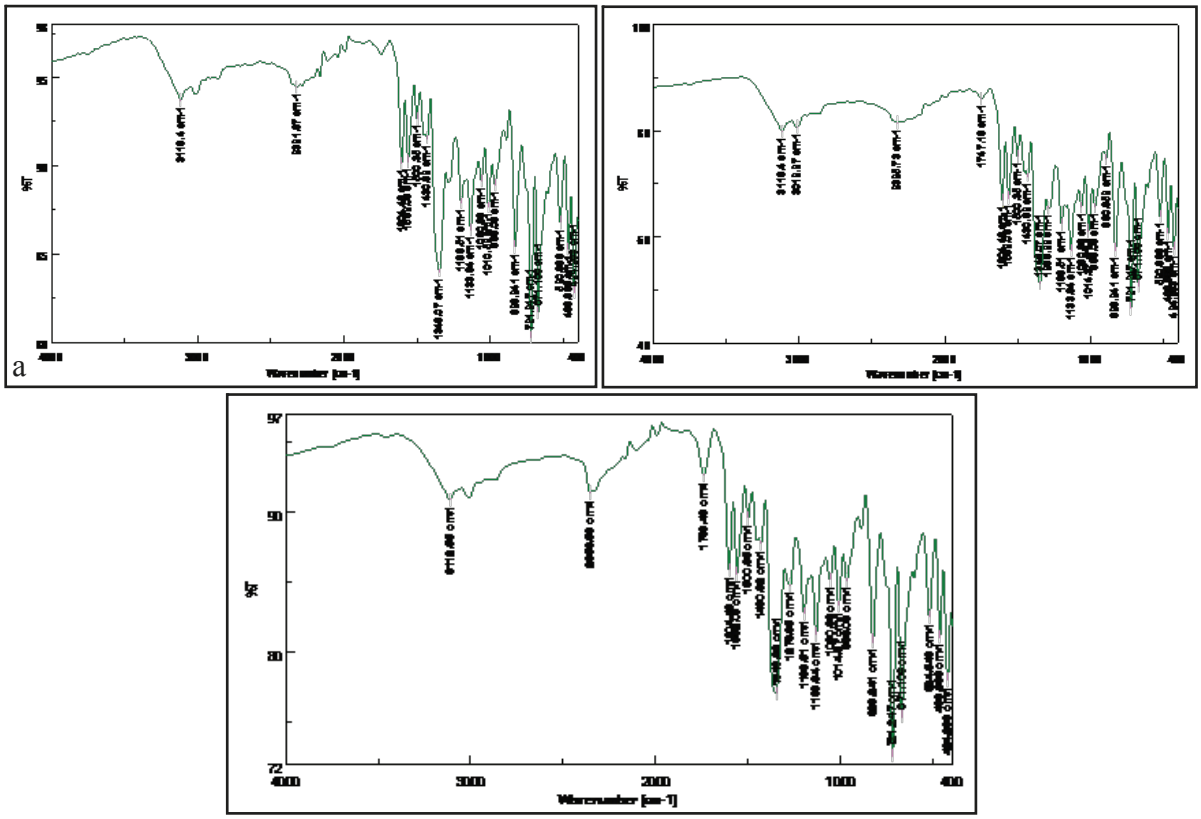


Figure 3 FTIR spectra of ketorolac alone (a), rizatriptan alone (b), ket-riz (c) Weight variation and friability test

https://doi.org/10.15218/zjms.2024.021

Thickness and hardness

The thickness of all formulations (F1-F4) ranged from 2.27 mm to 2.38 mm, and the hardness and the hardness of FDTs were in the range of 23 N to 37 N, and the highest hardness value was observed for the formulation (F3). As shown in Figure 4. Figure 5 shows the disintegration test of the prepared FDTs.

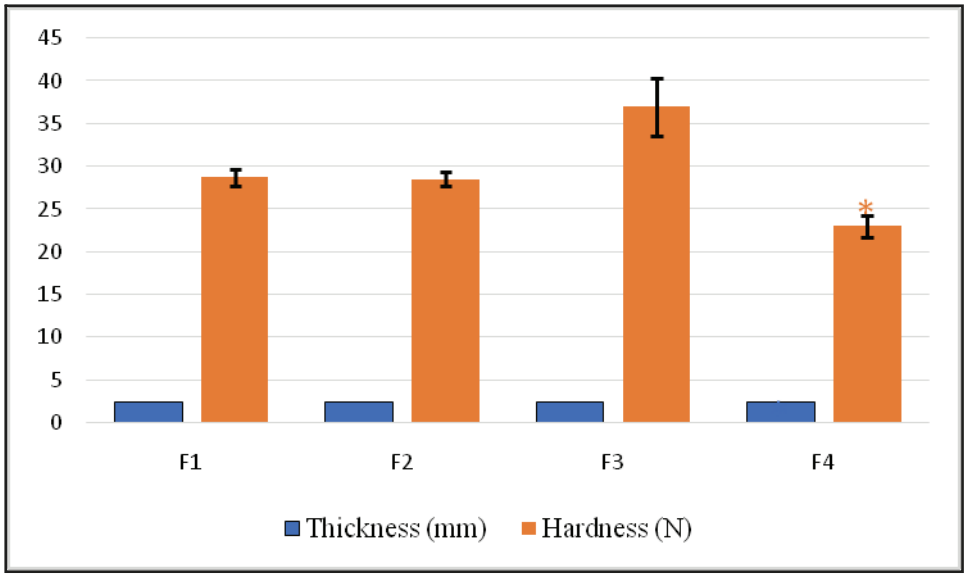


Figure 4 The thickness and hardness test of the prepared FDTs (mean±SD, *n*=10). The(*) indicates anon-significant difference in thickness for all formulation (*P* >0.05), while the (*) indicates a significant different in hardness of (F4),amongformulations of different super disintegrant and diluent types (*P* <0.05).

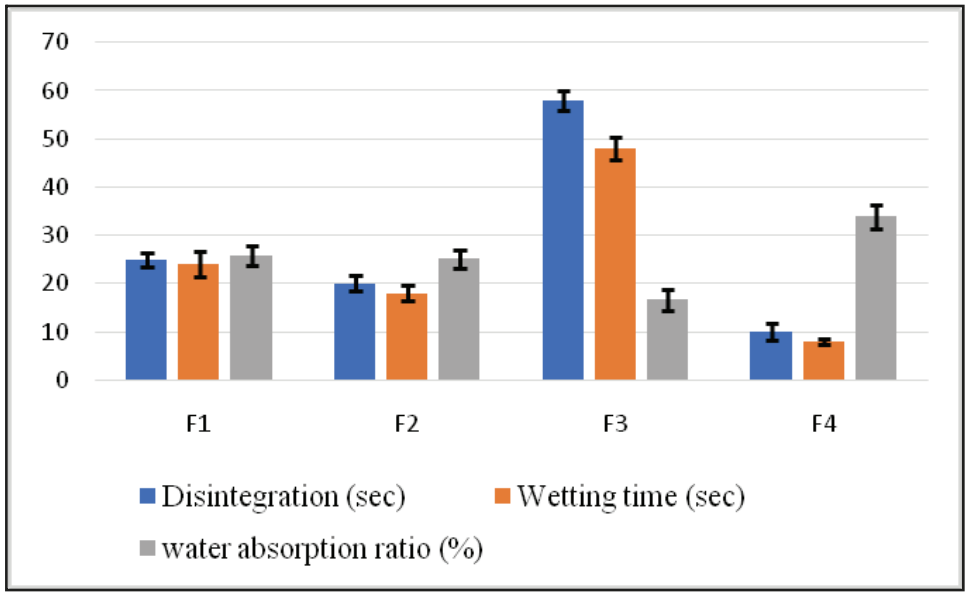


Figure 5 The disintegration test of the prepared FDTs (mean±SD, *n*=6 &3). The(*) indicates a significant different in disintegration time, wetting time and water absorption ratio of (F4), among formulations of different super disintegrant and diluent types (*P* <0.05).

https://doi.org/10.15218/zjms.2024.021

In-vitro dissolution test

The percentages of drug release for both drugs were within the acceptable range. is shown in Figures 6 and 7.

Drug content

As shown in Figure 8, the content of both drugs was within the pharmacopeial acceptable range (90%–110%).

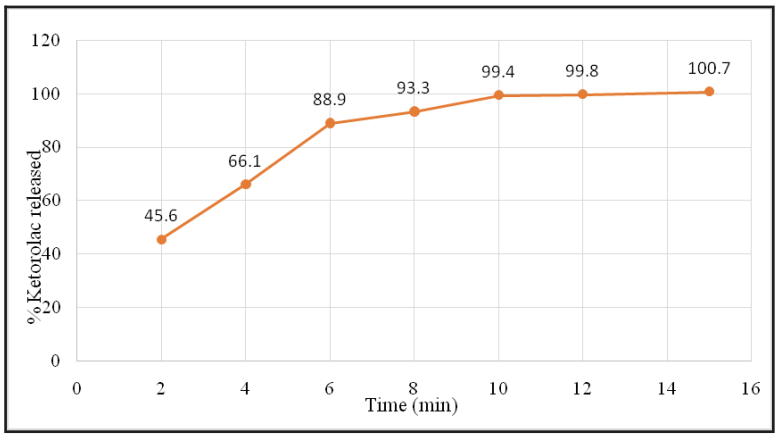


Figure 6 Percentage release of ketorolac from FDTs prepared with combining two different super disintegrants (Kyron T-134 + crospovidone)

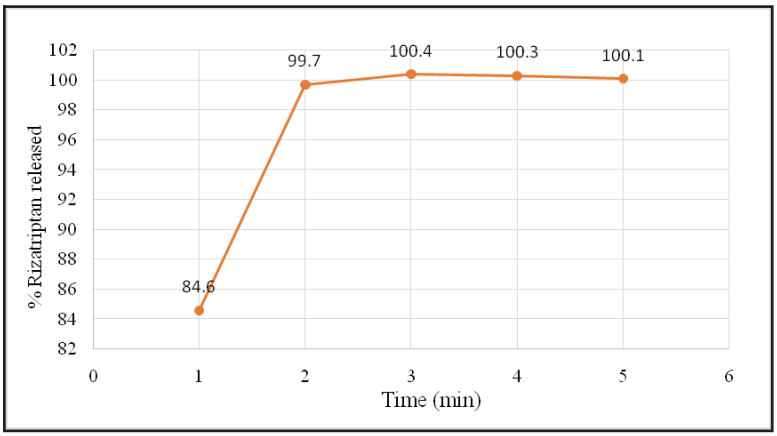


Figure 7 Percentage release of rizatriptan from FDTs prepared with combining two different super disintegrants (Kyron T-134 + Crospovidone)

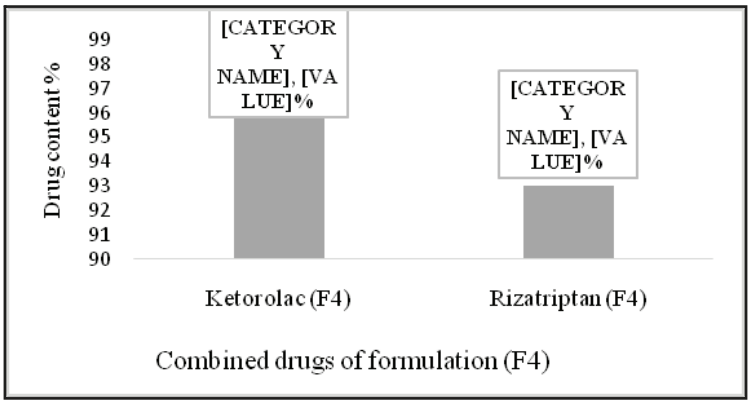


Figure 8 Drug content test for the prepared FDTs contain Ketorolac combined with rizatriptan

https://doi.org/10.15218/zjms.2024.021

Stability studies

The percentages of drug released and disintegrated time for during stability experiments after three months at various temperatures and humidity levels are shown in Figures 9 and 10, respectively.

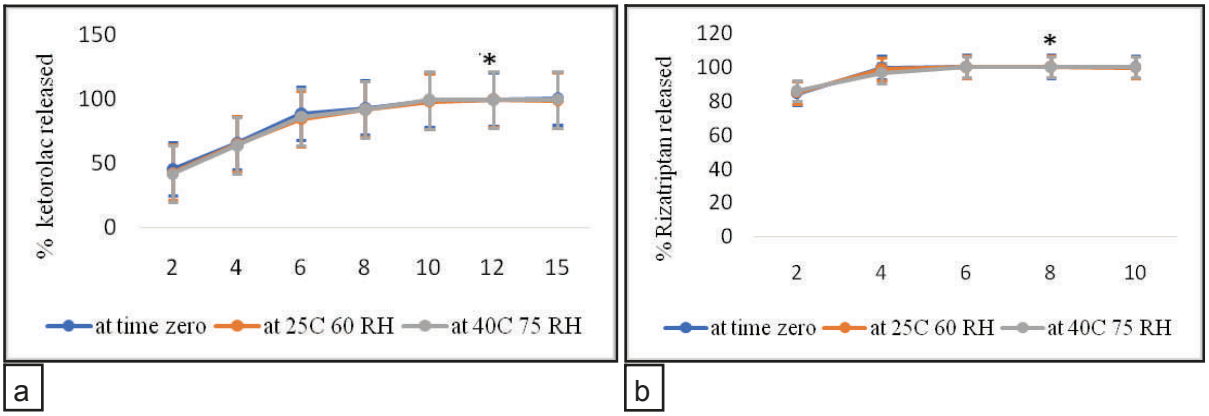


Figure 9 (a) represent the percentage of ketorolac FDTs released, and (b) represent the percentage of rizatriptan release during stability studies after three months at 25 °C, 60% ± 5 RH, and 40 °C, 75% ± 5 RH. The asterisks (*) indicate there is no significant difference in percent of release due to the effect of temperatures and humidity after three months. ($P > 0.05$).

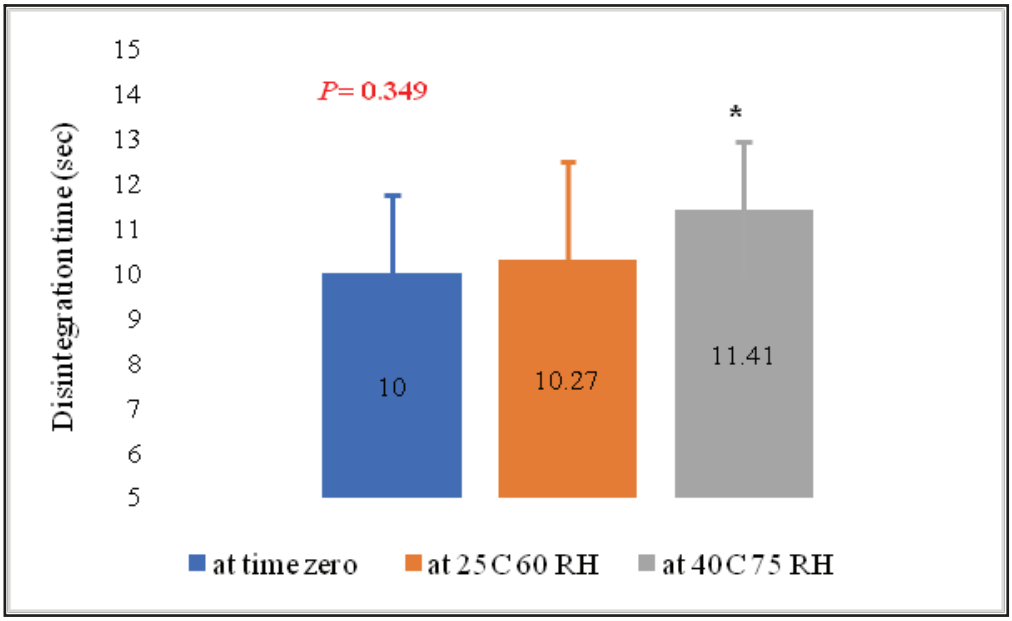


Figure 10 Disintegration time of the prepared FDTs during stability studies after three months, at 25 C°, 60% ± 5 RH and 40 C°, 75% ± 5 RH. The(*) indicate there is no significant difference in disintegration time by the effect of temperatures and humidity after three months. ($P > 0.05$).

https://doi.org/10.15218/zjms.2024.021

Comparability studies

As shown in Figure 11, the difference in disintegration time between prepared FDTs and marketed FDTs was 10 sec and 64.8 sec, respectively.

Discussion

The FT-IR spectra for the drugs and ingredients showed no loss of the main functional groups, which are responsible for the pharmacological action and water solubility between ketorolac and rizatriptan, and each drug with Kyron T-134 and crospovidone, as the main functional groups responsible for pharmacological effect, water solubility, and lipid penetration remained, based on their chemical structures, as shown in Figure 3.

The results showed that the general appearance of a tablet, which includes tablet size, tablet shape, tablet color, presence or absence of an odor, presence or absence of a taste, and surface texture to get an "elegant" dosage form to improve customer acceptance, was especially demonstrated in (F4). The reason might be the taste masking ability of Kyron T-134, which is utilized as a taste masking agent in addition to a super disintegrant agent, was connected with good masking flavor.[23]

All of the formulations have an acceptable hardness. The hardness of FDTs was in the range of 23 N to 37 N,[24] which indicates that the tablets had sufficient structural integrity to withstand handling without breakage. And the formulation showed the maximum hardness rating (F3). And the lowest hardness value was observed for the formulation (F4). Statistically, there was a significant difference at (P <0.05). In addition to that, this relatively low hardness range aids in rapid disintegration of the tablet upon placement in the mouth, as shown in Figure 4.

The friability of the prepared FDTs from different formulations was determined and the results showed that all the formulations had an acceptable value of friability (less than 1%), indicating the good mechanical resistance of the tablets for pressure, handling, transportation, manufacturing process, and storage. Generally, this test is run once, and a maximum loss of the mass is considered acceptable for most products if it is not more than 1% of the initial weight.[25]

The thickness of all formulations (F1-F4) were measured and it was ranged from (2.32 mm to 2.39 mm). The results were

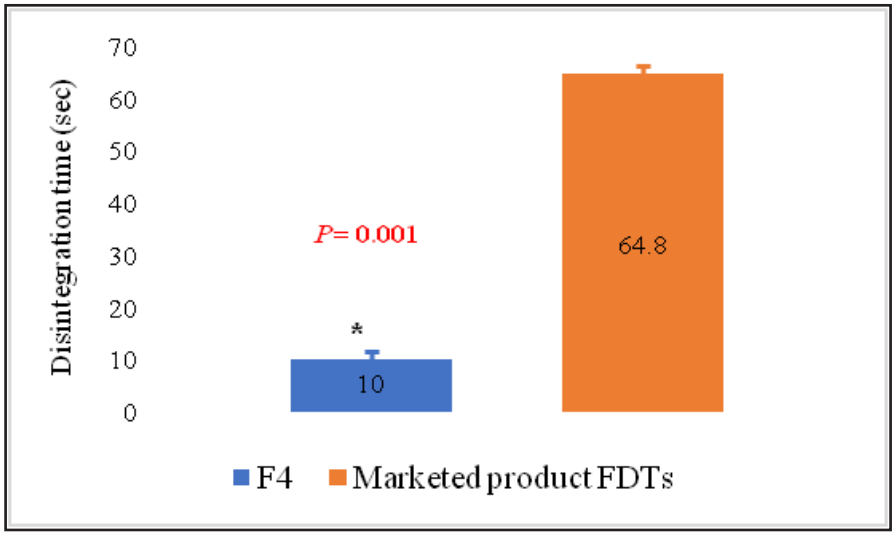


Figure 11 Disintegration time of the prepared FDTs versus marketed FDTs. The(*) indicate there is a significant difference in disintegration time between F4 and marketed product as FDTs (P <0.05).

https://doi.org/10.15218/zjms.2024.021

acceptable for all of the formulations as there was no significant variation in tablet thickness among them (*P* >0.05), This indicates constant die fill and compression force except.[26] As shown in Figure 4.

The results of weight variation were acceptable and indicated free flowability of the powder blend as we used the aerosil to improve the flowability of the formulations during the die filling process.[27]

All of the formulations disintegrated rapidly within an acceptable limit of (10 sec to 58 sec), fully satisfying the official requirements of disintegration within less than 3 minutes. The formulation (F4) had the shortest disintegration time compared to others, while formulation (F3) had the longest disintegration time. There was a statistically significant difference between them (*P* <0.05). This might be attributed to the combination of two types of efficient super disintegrants in the proper concentration, which aids the tablet to disintegrate properly within a short period of time.[28] As shown in Figure 5.

There was a statistically significant difference in the disintegration time between the formulations of different types of diluents (*P* <0.05), as shown in Figure 5. The formulations with the diluent MCC alone (F3) showed the longest disintegration time (58 sec), while the formulations containing both Mannitol and MCC, especially with a high amount of MCC (F4), showed the shortest disintegration time (10 sec). Because MCC may be attributed to its self-disintegration properties, MCC is frequently used as a disintegrant in wet granulation and dry compression processes. By accelerating tablet disintegration, it improves medication solubility. It also offers the maximum amount of disintegration force at low usage levels and uses two disintegration mechanisms—wicking and swelling—for faster disintegration.[29] Similar results were obtained by Pawar *et al. (2013),* who did a study on the effect of combining types of diluents on disintegration rate, and he demonstrated that MCC has a faster rate of disintegration than other diluents when mixed with mannitol that is water soluble. This may be explained by the high water solubility of mannitol, which might create holes in the matrix of the tablet; capillary action might then be in charge of the surrounding fluid's penetration into the matrix of the tablet and subsequent fast disintegration.[30]

As shown in Figure 5, there was a statistically significant difference in the disintegration time between the formulations of different types of super disintegrants (*P* <0.05). The formulation F4 (2.5% Kyron T-134 and 2.5% crospovidone) demonstrated the quickest disintegration time (10 sec), which was faster than Kyron T-134 and crospovidone when used alone (20 sec and 25 sec, respectively). Formulation (F3) provided the longest disintegration time (58 sec) when compared to the other formulations, in which sodium starch glycolate was used as a super disintegrant, as its swelling is accompanied by gelling, which may occult the tablet's pores and stop further water from penetrating the matrix.[31]

It is important to realize that the variations in the disintegration time between the formulations were related to the mechanism of action of their super disintegrants. Formulations containing crospovidone (Fl and F4) revealed the shortest disintegration time. This may be attributed to the porosity of particles, which provided a higher surface area and enabled them to absorb liquid into the core of the tablet quickly by capillary and swelling mechanisms to generate rapid volume expansion and fast tablet disintegration. In addition to that, crospovidone does not form a gel even at higher concentrations,[32] when combined with Kyron T-134, it disintegrates quickly because of its porous nature, which supports its wicking and swelling activity.[33]

As shown in Figure 5, wetting time is one of the most important characteristics for predicting how much fluid is required to break the tablet when put on the tongue.

All of the formulations were wetted within a reasonable limit of time (less than one minute).[9,34]

There was a statistically significant

https://doi.org/10.15218/zjms.2024.021

difference in wetting time between the formulations with different types of diluents. The shortest wetting time was observed for the formulations with the combination of mannitol with MCC (F4), which might be due to the porosity of MCC.[35] It has been reported that the wetting time is closely related to the inner structure and porosity of the tablets.[36] The same formulations revealed the least disintegration time, showing a great correlation between wetting time and disintegration time. As shown in Figure 5.

The results showed a statistically significant difference in the wetting time between the formulations of different types of super disintegrants (P <0.05), as shown in Figure 5. In the case of F4 (2.5% Kyron T-134 and 2.5% crospovidone), it demonstrated the shortest wetting time (8 sec), which was superior to both Kyron T-134 alone and crospovidone alone (18 sec) and (24 sec) respectively, which might be related to the fast absorption of water by Kyron T-134, which involves both wicking and swelling mechanisms.[33] Formulation F3, in which sodium starch glycolate was used as a super disintegrant, demonstrated the longest wetting time (48 sec) when compared to the other formulations, since its swelling is accompanied by gelling that could occlude the tablet and prevent further penetration of water into the tablet matrix.[31]

The water absorption ratio of the tablets from all of the prepared formulations was measured after 10 seconds (to ensure that the tablets remain intact to be weighed after absorption of water). The result showed that (F4) had the highest water absorption ratio, which was 33.95 sec in comparison to other formulations, and the result was statistically significant as (P <0.05). The results are shown in Figure 5.

The result was statistically significant (P <0.05) and demonstrated that the highest water absorption ratio was demonstrated in (F4), which was prepared using a combination of mannitol with a high amount of MCC as a diluent (due to the complementary effect of the swelling nature and water-solubility of the diluents respectively, compared with other formulations.[37,38] As shown in Figure 5.

The results demonstrated that the type of super disintegrant had a statistically significant impact on the water absorption ratio (P <0.05), particularly when two types of super disintegrants were combined (Kyron T-134 and Crospovidone) in F4. This combination produced a high-water absorption ratio due to the multi-mechanism of these two combined super disintegrants, as Kyron T-134 acts by both a swelling and wicking mechanism, and crospovidone also acts by a capillary and swelling mechanism.[33] As shown in Figure 5.

The drug content uniformity of the end product for both drugs (Ketorolac and Rizatriptan) was within the acceptable pharmacopeial limit and not less than 90%, indicating that the FDTs were manufactured correctly using the direct compression method (European Pharmacopeial, 2017). As shown in Figure 8.

The percentage of drug release of formulation (F4) was determined, and the results showed a good release percentage of both drugs, and the result was within the acceptable limits of (European Pharmacopeia, 2017). It is important to note that the dissolution test was performed by using deionized water as a dissolution medium (according to USP) and both of the drugs are water soluble. Figures 6 and 7 illustrate the release profiles of drugs from FDTs prepared using different diluents and super disintegrants. The results demonstrated an appropriate level of drug release. The free aqueous solubility of mannitol in water may be the reason. Considering the combined effects of two powerful super disintegrants (Kyron T-134 and crospovidone), which work through four different mechanisms as described in the study's disintegration part.[3,39,40]

The stability study showed no statistically significant changes in the hardness, friability, disintegration, or drug release of the examined tablets through the stability

https://doi.org/10.15218/zjms.2024.021

study at either storage conditions for three months. The optimized formulation (F4) was stored at 40 °C in a stability chamber with 75% ±5 relative humidity (RH) and at 25 °C with 60%±5 relative humidity (RH) (P >0.05), as shown in Figure 9 and 10.

In this study, the prepared FDTs (F4) were compared with the marketed melatonin FDTs (Pharma Natural Company) regarding disintegration time. Because disintegration rate is a critical characteristic in FDTs, (F4) had a disintegration time of (10 sec), while marketed melatonin FDTs had a disintegration time of (64.8 sec).

This significant difference in disintegration time (P <0.05) could be attributed to differences in the type and combination of diluents and super disintegrants used. In the (F4), Kyron T-134 combined with crospovidone was used as a super-fast disintegrant and MCC combined with mannitol was used as a diluent.

Furthermore, MCC has a disintegrating effect in addition to being a diluent,[29] whereas marketed melatonin FDTs only contain croscarmellose sodium as a super disintegrant and mannitol as a diluent.[33] The disintegration time for both of the FDTs is shown in Figure 11.

Conclusion

Ketorolac tromethamine and rizatriptan benzoate could be mixed together as fast dissolving oral tablets using Kyron T-134 and crospovidone as super-fast disintegrants using the direct compression method. Among the numerous diluents used, the combination of mannitol (45.8%) and microcrystalline cellulose (30%) as diluents and the combination of crospovidone (2.5%) and Kyron T-314 (2.5%) as super-fast disintegrants were the most successful formulas used in (F4) in this study. The disintegration impact of microcrystalline cellulose, in addition to its diluent function, was a key factor in exerting its action in this research. Because there is a strong connection between disintegration rate and the rate of drug release of drugs in orally dissolving tablets, the (F4) provided acceptable *in-vitro* drug release.

Funding

Not applicable.

Competing interests

The authors declare that they have no competing interests.

References

1. Jena GK, Patra CN, Rahman M, Beg S. Recent Advances in the Development of Modified Release Oral Dosage Forms in Pharmaceutical Drug Product Development and Process Optimization. App Acad Press 2020; 1:79–96.
2. Schmidt K, Berding T, Kleine-Borgmann J, Engler H, Holle-Lee D, Gaul C, et al. The beneficial effect of positive treatment expectations on pharmacological migraine prophylaxis. Pain 2022; 163(2):19–27. 10.1097/j.pain.0000000000002341
3. Nurathirah MN, Yazid MB, Norhayati MN, Baharuddin KA, Abu Bakar MA. Efficacy of ketorolac in the treatment of acute migraine attack A systematic review and meta□analysis. Acad Emerg Med 2022; 29(9):1118–31. https://doi.org/10.1111/acem.14457
4. Calandre EP, Slim M, Rico-Villademoros F. How does a physician decide which pharmacotherapeutic option to select for acute migraine attacks? Expert Opin Pharmacother 2022; 23(10):1129–33. https://doi.org/10.1080/14656566.2022.2060740
5. Rada SK, Kumari A. Fast dissolving tablets waterless patient compliance dosage forms. J Drug Deliv Ther 2019; 9(1):303–17. https://doi.org/10.22270/jddt.v9i1.2292
6. Dave V, Yadav RB, Ahuja R, Yadav S. Formulation design and optimization of novel fast dissolving tablet of chlorpheniramine maleate by using lyophilization techniques. Bull Fac Pharm Cairo Univ 2017; 55(1):31–9. https://doi.org/10.1016/j.bfopcu.2016.12.001
7. Bindal R, Indurkhya A. Formulation and Evaluation of Ketorolac Tromethamine Mouth Dissolving Tablets. J Drug Deliv Ther 2021; 11(1):60–4. https://doi.org/10.22270/jddt.v11i1.4502
8. Al-dhahir RK, Al-kotaji M. Formulation of orally disintegration tablets of cinnarizine by using direct compression method. Int J Appl Pharm 2019; 11(1):117. http://dx.doi.org/10.22159/ijap.2019v11i1.29599
9. Jain AA, Barhate SD. Formulation Optimization and Evaluation of Mouth Dissolving Tablet of Rizatriptan Benzoate by using Natural Super disintegrant. Asian J Res Pharm Sci 2019; 9(4):245. 10.5958/2231-5659.2019.00038.9
10. Diener HC, Holle-Lee D, Nägel S, Dresler T, Gaul C, Göbel H, et al. Treatment of migraine attacks and prevention of migraine Guidelines by the German Migraine and Headache Society and the German Society of Neurology. Clin

Transl Neurosci 2019; 3(1):2514183X1882337. https://doi.org/10.1177/2514183X18823377
11. Wang G, Tan T, Liu Y, Hong P. Drugs for Acute Attack of Pediatric Migraine A Network Meta-analysis of Randomized Controlled Trials. Clin Neurol Neurosurg 2020; 195:105853. https://doi.org/10.1016/j.clineuro.2020.105853
12. Negro A, Koverech A, Martelletti P. Serotonin receptor agonists in the acute treatment of migraine a review on their therapeutic potential. J Pain Res 2018; 11:515–26. 10.2147/JPR.S132833
13. Kempwade AA, Taranalli AD, Hiremath RD, Joshi SA. Formulation and Evaluation of Flexible Liposome Embedded In Situ Thermoreversible Intranasal Gel of Rizatriptan Benzoate. Indian J Pharm Sci 2022; 84(4):863–73. 10.36468/pharmaceutical-sciences.981
14. Abujbarah SM, Jogerst K, Kosiorek HE, Ahmad S, Cronin PA, Casey W, et al. Postoperative Hematomas in the Era of Outpatient Mastectomyls Ketorolac Really to Blame? Ann Surg Oncol 2022; 29(10):6395–403. https://doi.org/10.1245/s10434-022-12141-8
15. Babaie S, Taghvimi A, Hong JH, Hamishehkar H, An S, Kim KH. Recent advances in pain management based on nanoparticle technologies. J Nanobiotechnology 2022; 20 (1):290. https://doi.org/10.1186/s12951-022-01473-y
16. Smail SS, Ghareeb MM, Omer HK, Al-Kinani AA, Alany RG. Studies on Surfactants Cosurfactants and Oils for Prospective Use in Formulation of Ketorolac Tromethamine Ophthalmic Nanoemulsions. Pharmaceutics 2021; 13(4):467. https://doi.org/10.3390/pharmaceutics13040467
17. Ejeta F, Gabriel T, Joseph NM, Belete A. Formulation Optimization and *In Vitro* Evaluation of Fast Disintegrating Tablets of Salbutamol Sulphate using a Combination of Superdisintegrant and Subliming Agent. Curr Drug Deliv 2022; 19(1):129–41. https://doi.org/10.2174/1567201818666210614094646
18. RaheemA, Singh R, Hiremath A, Nayak S, KamathS, SK. Formulation and comparative evaluation of ondansetron hydrochloride mouth dissolving tablets in india. Int J Pharm Pharm Sci 2019; 57–64. http://dx.doi.org/10.22159/ijpps.2019v11i9.33840
19. Goh HP, Heng PW, Liew CV. Understanding die fill variation during minitablet production. Int J Pharm 2017; 534(1–2):279–86. https://doi.org/10.1016/j.ijpharm.2017.10.042
20. Kumar RS, Yagnesh TN. Synthesis characterization and evaluation of starch xanthate as a superdisintegrant in the formulation of fast dissolving tablets. Int J Appl Pharm. 2018;10(6):249. https://doi.org/10.22159/ijap.2018v10i6.29128
21. Shinkar DM, Aher PS, Kothawade PD, Maru AD. Formulation and in vitro evaluation of fast dissolving tablet of verapamil hydrochloride. Int J Pharm Pharm Sci 2018; 10(10):93. https://doi.org/10.22159/ijpps.2018v10i10.28714
22. Zhu C, Lal M. Preclinical Safety and Pharmacokinetics of Heat Stable Oxytocin in Sublingual Fast Dissolving Tablet Formulation. Pharmaceutics 2022; 14(5):953. https://doi.org/10.3390/pharmaceutics14050953
23. Garg A, Gupta MM. Taste masking and formulation developement & evaluation of mouth dissolving tablets of levocetrizine dihydrochloride. J Drug Deliv Ther 2013; 3(3):123–30. https://doi.org/10.22270/jddt.v3i3.514
24. Aslani A, Beigi M. Design formulation and physicochemical evaluation of montelukast orally disintegrating tablet. Int J Prev Med. 2016; 7(1):120. 10.4103/2008-7802.193097
25. Vlad RA, Antonoaea P, Todoran N, Rédai EM, Bîrsan M, Muntean DL, et al. Development and Evaluation of Cannabidiol Orodispersible Tablets Using a 23 Factorial Design. Pharmaceutics 2022; 14(7):1467. https://doi.org/10.3390/pharmaceutics14071467
26. Elsayed MM, Aboelez MO, Elsadek BE, Sarhan HA, Khaled KA, Belal A, et al. Tolmetin Sodium Fast Dissolving Tablets for Rheumatoid Arthritis Treatment Preparation and Optimization Using Box-Behnken Design and Response Surface Methodology. Pharmaceutics 2022; 14(4):880. https://doi.org/10.3390/pharmaceutics14040880
27. Carpenter A, Gupta MK, Jain NK, Sharma U, Sisodiya R. Formulation and development of fast dissolving tablet of metoclopramide an antiemetic drug. J Biomed Pharm Res 2019; 8(6). https://doi.org/10.32553/jbpr.v8i6.699
28. Nagar PK. SUPERDISINTEGRANTSCURRENT APPROACH. J Drug Deliv Ther 2014; 4(3):37–44. https://doi.org/10.22270/jddt.v4i3.831
29. Oraeluno JN, Obasi JC, Bamigbola EA, Joseph BA.Production and Evaluation of Disintegrant Properties of Microcrystalline Cellulose Derived from Saccharum officinarum L (Poaceae) in Metronidazole Based Formulation. Int J Pharm Sci Med 2021; 6(4):42–51. 10.47760/ijpsm.2021.v06i04.004
30. Pawar P, Bala R, Khanna S. Formulation and optimization of fast dissolving intraoral drug delivery system for clobazam using response surface methodology. J Adv Pharm Technol Res 2013; 4(3):151. 10.4103/2231-4040.116785
31. Pabari RM, Ramtoola Z. Effect of a Disintegration Mechanism on Wetting Water Absorption and Disintegration Time of Orodispersible Tablets. J Young Pharm 2012; 4(3):157–63. https://doi.org/10.4103/0975-1483.100021
32. Kuck J, Breitkreutz J. Impact of Lubrication on Key Properties of Orodispersible Minitablets in Comparison to Conventionally Sized Orodispersible Tablets. Eur J Pharm Biopharm. 2022; S0939641122001898. https://doi.org/10.1016/j.ejpb.2022.08.023
33. Bele MH, Derle DV. Mechanism of disintegrant action of polacrillin potassium Swelling or wicking? Acta Pharm Sin B 2012; 2(1):70–6. https://doi.org/10.1016/j.apsb.2011.12.002

34. Bhardwaj S, Jain V, Jat RC, Mangal A, Jain S. Formulation and evaluation of fast dissolving tablet of aceclofenac. Int J Drug Deliv 2010; 2(1):93–7. 10.5138/ijdd.2010.0975.0215.02017
35. Thoorens G, Krier F, Leclercq B, Carlin B, Evrard B. Microcrystalline cellulose a direct compression binder in a quality by design environment A review. Int J Pharm 2014; 473(1–2):64–72. https://doi.org/10.1016/j.ijpharm.2014.06.055
36. Yang B, Wei C, Yang Y, Wang Q, Li S. Evaluation about wettability water absorption or swelling of excipients through various methods and the correlation between these parameters and tablet disintegration. Drug Dev Ind Pharm 2018; 44(9):1417–25. https://doi.org/10.1080/03639045.2018.1453519
37. Postek E, Sadowski T. Assessing the Influence of Porosity in the Deformation of Metal. Ceramic Composites. Compos Interfaces 2011; 18(1):57–76.
38. Ohrem HL, Schornick E, Kalivoda A, Ognibene R. Why is mannitol becoming more and more popular as a pharmaceutical excipient in solid dosage forms? Pharm Dev Technol 2014; 19(3):257–62. https://doi.org/10.3109/10837450.2013.775154
39. Lourenco C, Keny R, Desouza C. Formulation and evaluation of rizatriptan Benzoate mouth disintegrating tablets. Indian J Pharm Sci 2010; 72(1):79. 10.4103/0250-474X.62253
40. Raina B, Sharma A, Bajwa PS. Formulation evaluation and optimization of fast disintegrating tablets of ketorolac tromethamine. J Pharm Investig 2018; 48(6):685–95. https://doi.org/10.1007/s40005-017-0366-0