RESEARCH ARTICLE

Development and Evaluation of Trazodone Hydrochloride Tablets for Oral Drug Delivery Technology

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ABSTRACT

Usually, conventional oral drugs such as tablets and capsules are formulated to rapidly release the active ingredient into the body when ingested orally. This facilitates speedy and complete assimilation of the medication into the circulatory system, resulting in a prompt onset of its effects. The term "modified release drug product" pertains to drugs that alter the timing and/or rate of drug component release. The objective of study was to develop and evaluate a matrix tablet that achieves prolonged release of trazodone hydrochloride. Trazodone hydrochloride is an orally administered novel antidepressant medication. Mood disorders, phobias, and social anxiety disorders are common indications for its usage. Two different forms of trazodone hydrochloride medications are now on the market: Rapid-release tablets and prolonged-release capsules. Effexor and Effexor XR are the brand names under which these drugs are marketed. Trazodone hydrochloride has a short biological half-life of 5 hours, which means that it is necessary to take 2 to 3 dosages each day. The optimal daily dose falls within the range of 75 to 450 mg/day. Trazodone hydrochloride is a kind of medicine used for long-term treatment of depression. Thus, to decrease the occurrence of dosing, we chose to develop straightforward and cost-effective sustained-release tablets of trazodone.

Keywords: Development, Evaluation, Oral platform drug, Delivery technology, Trazodone hydrochloride.

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INTRODUCTION

You require a partner in oral drug delivery systems with the technical expertise and a range of advanced technologies to offer sustained value in response to the growing demand for specialized and personalized oral pharmaceuticals. Many leading pharmaceutical companies worldwide depend on Evonik to develop, modify, and supply innovative and highly versatile oral drug delivery systems that may enhance and differentiate their small molecules and biologics. In addition to offering top-notch formulation services and being at the forefront of the oral functional excipient business for over six decades, we have developed a substantial collection of patent-protected, commercially feasible oral drug delivery systems that are available for restricted licensing.[1-3]

In addition, our extensive knowledge in matrix formulation, coating technologies, melt extrusion, and the development of multi-unit dosage forms allows us to address any specific medical or regulatory needs that demand advanced formulation solutions. The physicochemical characteristics of a certain administration method and the drug delivery channels themselves are crucial determinants that impact a treatment's immediate and prolonged biological outcomes. Each distribution approach has its own set of benefits and drawbacks, and each requires the development of a specific delivery vehicle. The oral mode of delivery is considered the most attractive compared to other routes because it is probable to produce solid formulations with extended shelf life, can be distributed continuously, is easy to administer, and can elicit a stronger immune response. Nevertheless, oral delivery has presented several challenges that have been the primary focus of study in the sector in recent years. The present study emphasizes the reasons why oral delivery has emerged as the most viable choice by providing a concise overview of several administration routes and their respective advantages and disadvantages.[4,5]

The current study discusses the most common problems with oral systems and lays out the most recent solutions for each of those problems. Over an extended time, the ideal drug delivery system should reliably and precisely administer a quantifiable medication dosage to the targeted area. By regulating the release of the drug from the absorption site, controlled-release devices keep plasma concentrations within the therapeutic range. This reduces negative consequences and simultaneously decreases the frequency of distribution. Extended-release products, designed for once or twice daily administration, gradually and consistently release active

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medicine into the body over 12 to 24 hours. Compared to immediate-release drugs, it has several benefits, including enhanced effectiveness in treating long-term diseases, fewer negative effects, more convenience, and higher patient adherence due to a simpler dosage regimen. These approaches dominate the medicine distribution market because of the aforementioned advantages. Drug delivery through intranasal, pulmonary, transdermal, vaginal, colon, and transmucosal routes, as well as controlled release, flavor masking, and oral fast-dispersing dosage forms are all areas that pharmaceutical companies are constantly inventing new platform technologies to address. To guarantee exact distribution of pharmaceuticals in terms of time and space, a complex drug delivery system employs cutting-edge technologies, including rate control, pulsatile release, and bio-responsive release.[6-8]

MATERIAL AND METHODS

Selection of Candidate Drug

A candidate drug is selected for the creation of a platform technology that is tailored to meet specific therapeutic needs, with an emphasis on attaining the best possible treatment adherence and advantages. Selection of appropriate medication is dependent on its pharmacokinetic characteristics, as well as its permeability and solubility parameters. To fulfill the precise drug and pharmacokinetic-pharmacodynamic (PK-PD) requirements, developing a drug delivery platform technology is imperative. Subsequently, this technique may be evaluated for other drugs belonging to same biopharmaceutics classification system (BCS) class or therapeutic class, with only minor modifications to the formulation being necessary.[9,10]

Selection of Polymers

The materials for controlling drug release include polymers from natural origins, chemically modified natural compounds, and synthetic compounds. Polymers can be used by themselves or with other substances, depending on the traits you want. The list is not comprehensive but serves as an initial point of reference for development endeavors.[11,12]

Design and Development of Platform Technology

Each medicine possesses distinct attributes that require specific considerations for the medication itself and its administration methods. The development of controlled-release formulations necessitates the incorporation of a clearly defined therapeutic rationale, the drug's biological characteristics, and its physicochemical properties. The primary rationale for a controlled-release product is that it must offer one or more advantages in terms of efficacy, safety, and patient compliance. The desired drug input rate and the pharmacokinetic characteristics of the medication dictate the formulation of controlled release products.[13]

Analytical Methodology

Preformulation

Preformulation data on the active chemicals are vital for formulation scientists during the process of developing stable, safe, and effective dosage forms. Acquiring this information can provide a rational basis for developing strategies, enhancing the chances of effectively producing a desirable product, and ultimately optimizing the product's quality and performance.[14-16]

Dissolution method development

after identifying a prototype formulation that encompasses appropriate process and composition parameters, it becomes imperative to examine the test variables. These variables include variations in pH, the influence of surfactants, agitation, ionic strength, and other factors. The key considerations for the dissolution evaluation are (a) ensuring the method's reproducibility, (b) maintaining sink conditions, (c) achieving a dissolution profile that meets a strict one-hour requirement to prevent dose dumping, and (d) ensuring that at least 75% of the drug is released during the final sampling interval to ensure complete release.[17,18]

In-vitro Evaluation of Drug Delivery System

Physico-chemical parameters

Physical characteristics of dosage form, with its visual appearance, dimensions, thickness, width, length, hardness, friability, and size distribution, must be evaluated. In addition, hydrological humidity level: The estimate can be performed by employing loss on drying or water content analysis using a Karl-Fischer titrator.

Dissolution studies

Conducting experiments in living organisms is essential for progressing and evaluating dosage formulations. Dissolution testing is a vital process employed to evaluate the efficacy of solid oral dosage forms, particularly those that need drug absorption to provide a therapeutic impact. Assessing the *in-vitro* characteristics and excellence of the product is very crucial.[19,20]

RESULT AND DISCUSSION

Selection of Candidate Drug

The freeze-drying method has been discovered to have the capacity to alter the rate at which drugs are released and demonstrate excellent stability and reduced fragility. Trazodone hydrochloride has a high solubility in methanol, with a 25 mg/mL concentration, resulting in a transparent and devoid-of-color solution. Heat may also dissolve in water at a concentration of 50 mg/mL by applying heat, resulting in a turbid and colorless solution. In addition, the product can dissolve in DMSO or in a solution of HCl (0.1 N)at a concentration of 7.4 mg/mL.

Selection of Polymers

Initial characterization was done for the selected excipients and the results were as follows:

Colloidal silicon dioxide

Insoluble in water. LoD is 1.5% w/w, bulk density is 0.035 g/mL.

Croscarmellose sodium

Insoluble in water. LoD is 7.0% w/w, bulk density is 0.529 g/mL.

Crospovidone

Insoluble in water. LoD is 3.5% w/w, bulk density is 0.30 g/mL.

Ethylcellulose

About 4 and 7 cps: Insoluble in water, soluble in isopropyl alcohol. LoD is 2.4, 2.1% w/w and bulk density is 0.4, 0.38 g/mL, respectively.

Glyceryl monostearate

Insoluble in water. Meting point is 56°C.

Hydroxypropyl cellulose

Soluble in water (1 in 2), 95% ethanol (1 in 2.5), methanol (1 in 2), dichloromethane (1 in 10). A 1% w/w water solution has a pH of 7.2. LoD is 2.3% dry weight. There is 0.5 grams per mL of bulk.

Hypromellose

5 cps: Soluble in water. 1% w/w aqueous solution has pH 6.5, LoD is 5.0% w/w. Bulk density is 0.341 g/mL.

Lactose monohydrate

Soluble in water (1 in 5.24). LoD is 0.5% w/w, bulk density is 0.57 g/mL.

Magnesium stearate

Insoluble in water. LoD is 6% w/w, bulk density is 0.159 g/mL.

Mannitol

Soluble in water (1 in 5.5). LoD is 0.3% w/w. Meting point is 167°C. Bulk density is 0.430 g/mL.

Meglumine

Soluble in water (1 in 1). pH of 1% w/v aqueous solution is 10.5, LoD is 1.0% w/w. Meting point is 130°C.

Methacrylic acid copolymer (Type C)

Eudragit L 30 D-55 is miscible in water. Soluble in intestinal fluid from pH 5.5

Microcrystalline cellulose

Insoluble in water. pH is 6, LoD is 7.0% w/w. Bulk density is 0.32 g/mL.

Poloxamer

Soluble in water, ethanol (95%). In a water solution with 2.5% w/v, the pH is 6.2.; Melting point is 54°C. Bulk density is 1.06 g/mL.

Polyethylene glycol

Soluble in water and alcohol. Bulk density is 1.13 g /mL.

Polysorbate 80

Soluble in water and ethanol. pH of 5% w/v aqueous solution is 7.0.

Povidone (PVPK 30)

Soluble in water. pH of 5% w/v aqueous solution is 5.0. Bulk density is 0.34 g/mL.

Sodium lauryl sulfate

Soluble in water. pH is 8.0 for 1% w/v aqueous solution. Melting point is 205°C.

Sodium starch glycolate

Gives a translucent suspension in water. pH is 4.0, LoD is 10.0% w/w. Bulk density is 0.81 g/mL.

Starch

Slightly soluble in cold water. pH is 5.8 for 10% w/v aqueous dispersion. LoD is 14.0 % w/w. Bulk density is 0.586 g/mL.

Sugar spheres

Slightly soluble in water. LoD is 4.0% w/w. Bulk density is 1.57 g/mL.

Talc

Insoluble in water. pH is 8.5 for a 20% w/v aqueous dispersion.

Titanium dioxide

Insoluble in water. LoD is 0.5% w/w. Meting point is 185°C. Bulk density is 0.51 g/mL.

Triethyl citrate

Soluble 1 part water to 15 parts acetone, ethanol (95%), propan-2-ol.

Comprehensive knowledge on excipients obtained by their characterization steered to the development of robust drug products, which was evident by their AST studies.

Analytical Methodology

Pre-formulation studies

Pre-formulation investigations are the initial stage in the logical creation of a pharmacological substance's dosage form. The purpose of preformulation research is to provide a comprehensive collection of data on the drug material, which can then be utilized in the development of the formulation. Preformulation refers to the examination of the physicochemical characteristics of a pharmacological ingredient both on its own and when coupled with other substances known as excipients. The following tests were conducted for pre-formulation research.

Organoleptic characteristics

Organoleptic characteristics were studied as Description, Taste, Color, Odor and reported in Table 1.

Solubility

The specified quantity of medication was introduced and dissolved in various solvents in order to determine the solubility of unrefined medication using the visual inspection

Table 1: Organoleptic characteristic

Property	*Result*
Description	Crystalline powder
Taste	Slightly bitter
Odor	Odorless powder
Color	Off-white powder

Table 2: Solubility of trazodone hydrochloride

Solvent	*Water*	*Alcohol*	*Methanol*	*Chloroform*	*PBS*		
					1.2	*6.8*	*7.4*
Solubility (mg/mL)	0.11 ± 0.02	11.21 ± 0.05	14.32 ± 0.11	0.12 ± 0.03	0.263 ± 0.008	0.343 ± 0.011	0.318 ± 0.012

technique. The surplus amount of medication was measured and added to a flask holding 10 mL of solvent. The flask was then placed on a water bath shaker and held at a temperature of 37°C for a duration of 72 hours. The solution that had been passed through a filter was examined using spectrophotometry at a wavelength of 235 nm. The result acquired from the trazodone hydrochloride medication indicates that it has a high solubility in methanol and alcohol and is insoluble in water and chloroform. Experiments were conducted utilizing various buffer solutions. The medication exhibits limited solubility in all buffers, with the highest solubility seen in PBS 6.8. Consequently, PBS 6.8 was chosen as the dissolving medium for the *in-vitro* dissolution investigation, as indicated in Table 2.

Determination of drug-polymer compatibility

- *Fourier-transform infrared spectroscopy*

KBr pellet method is employed within the 4000 to 400 cm^{-1} range to analyze IR spectra of pure medication. This is done utilizing a 3.3.4.1 fourier-transform infrared spectroscopy (FTIR) spectrophotometer and the KBr pellet method using a KBr press. The FTIR spectra of the drug in its pure form and the physical combination of the drug and polymer were analyzed. The functional groups observed in the physical combination of medicines and polymer were found to be consistent with peaks observed in pure drug mixtures. The physical combination exhibited strong peaks at 3420 cm^{-1} (N-H Stretching), 3290 cm^{-1} (O-H Symmetric Stretching), and 1500 to 1800 cm^{-1} (C=O, C=N, C-H Stretching) bending, as seen in Figure 1 and Table 3. The FTIR spectroscopic interpretation results indicated absenteeism of some interactions between drug combination and polymer since there were no observable alterations in the peaks. Therefore, the medication combination and chosen polymer exhibited compatibility with each other.

- *Differential scanning calorimetry*

Compatibility of pure medication and excipients was assessed using DSC-60, Shimadzu. Samples are hermetically sealed in a container and subjected to a temperature 40 to 300°C, a heating rate of 20°C/min. Continuous purging of nitrogen gas was performed. Figures 2 and 3 display the 3.3.4.2 differential scanning calorimetry (DSC) curves produced for pure trazodone hydrochloride, the reference sample, and physical mixture. The DSC thermograms of pure trazodone hydrochloride exhibited a distinct melting point at 210°C, but the thermogram of the powder combination, including the drug and excipients, had a melting peak at the same temperature. Consequently, the endothermic peak seen in both the pure medication trazodone hydrochloride and the physical combination occurred at the same temperature range, indicating that all the excipients are mutually compatible.

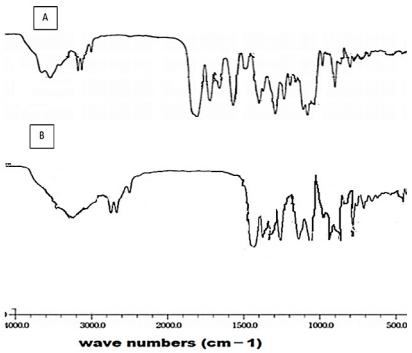

Figure 1: FTIR spectra of trazodone hydrochloride(A), physical mixture (B)

Table 3: FTIR spectrum interpretation of drug and physical mixture

The peak observed (cm-1)	*Interpretation*
1655.16	C = O Stretching
2928.80	C - H Stretching
3448.06	N - H Stretching
1292.52	C - N Stretching
3404.14	O - H Stretching
1326.01	C - O Stretching

Design and Development of Platform Technology

This technique is employed when the components may be mixed together and directly compressed in a tablet press, eliminating the need for any pre-processing of the materials. To succeed, the active substance must possess suitable physical and chemical characteristics, including favorable compatibility and little stickiness. Direct compression is commonly favored due to its straightforwardness and generally affordable nature; however, it may not always be technically viable. This technique involves the full blending of all the powdered excipients within a plastic bag. Following thorough blending, the powder was compressed into tablets. The tablet's weight was 400 mg, and the drug's dosage is 150 mg (Table 4).

***In-vitro* Evaluation of Drug Delivery System**

Pre-compression studies of powder blends

- *Bulk density*

The bulk density of medications and their formulations significantly influence their packing characteristics. According to the statement, bulk density levels below 1.2 gm/cm^3 indicate favorable flow, whereas values above 1.5 gm/cm^3 indicate unfavorable flow. According to the findings, bulk density values are less than 1.2 gm/cm^3. This indicates that the granules have good flow characteristics. Table 5 displays the values.

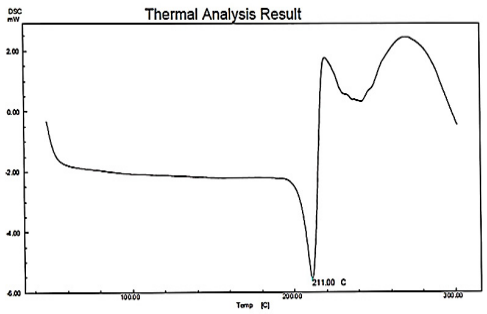

Figure 2: DSC of a reference sample

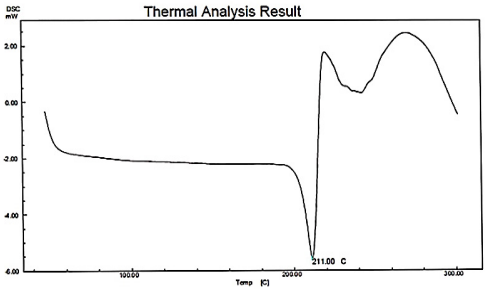

Figure 3: DSC of sample trazodone hydrochloride

- *Tapped density*

It is clear from the results that the granules have good flow properties based on the tapped density values. Results are displayed in Table 5.

- *Angle of repose*

Granules with an angle of repose of 40 degrees or less are free-flowing. Having an angle of repose higher than 40 degrees implies that the material is not flowing well. The fact that the angle of repose for different batches of granules is less than 40°C shows that they have good flow qualities, as can be seen in the table above. Results are displayed in Table 5.

- *Compressibility index or carr's index*

The granules are free-flowing if Carr's index is less than or equal to <10. Poor material flow is indicated by a Carr's index larger than less than 10. The above table shows that Carr's index for different batches of the granules is less than 10, which means that the granules have good flow qualities. Results are displayed in Table 5.

- *Hausner's ratio*

The granules have free-flowing characteristics if Hausner's ratio is less than or equal to 1.069. A Hausner's ratio higher than 1.35 suggests the material flow is inadequate. From the data in the table above, we can deduce that the granules have good flow qualities because Hausner's Ratio is less than 1.122 for all of the batches tested.

Table 4: Different formulations of trazodone hydrochloride (TH) oral dispersible tablets

Formulation code	*TH-1*	*TH-2*	*TH-3*	*TH-4*	*TH-5*	*TH-6*	*TH-7*
Drug mg	150	150	150	150	150	150	150
SSG mg	90	-	-	45	-	45	30
CCS mg	-	90	-	45	45	-	30
CP mg	-	-	90	-	45	45	30
Avicel PH102 mg	100	100	100	100	100	100	100
Mannitol mg	45	45	45	45	45	45	45
Sodium saccharin mg	10	10	10	10	10	10	10
Magnesium stearate mg	5	5	5	5	5	5	5
Mint flavor mg	q.s	q.s	q.s	q.s	q.s	q.s	q.s

Every Tablet wt. – 400 mg.

Post-compression studies of trazodone hydrochloride tablets

The compressed tablets were evaluated for physical properties and the results are tabulated in Table 6.

- *Hardness test*

It was found out how hard the tablets were in different batches. The hardness ratings of the several batches of the oral dispersible tablets are within the specified ranges, which suggests that they are of good strength. Results are displayed in Table 6.

- *Thickness test*

It was discovered that the mean tablet thicknesses ranged from 0.37 mm across all formulations, which is very consistent. Results are displayed in Table 6.

- *Friability test*

All instances of the oral dispersible tablets' friability ratings being less than 1% are deemed good. Results are displayed in Table 6.

- *Weight variation test*

All of these oral dispersible tablets passed the weight variation test since their percentage of weight variation was within the limitations set by the pharmacopeia. With small standard

Table 5: Pre-compression of powder blend

Formulation code	*TH-1*	*TH-2*	*TH-3*	*TH-4*	*TH-5*	*TH-6*	*TH-7*
Tapped density (gm/mL)	0.375	0.372	0.362	0.333	0.368	0.384	0.354
Bulk density (gm/mL)	0.334	0.346	0.328	0.312	0.333	0.352	0.326
Angle of repose (θ)	32.26	34.15	33.82	31.38	35.07	35.07	39.48
Carr's index (%)	10.93	6.98	9.39	6.30	9.51	8.33	7.90
Hausner's ratio	1.122	1.075	1.103	1.067	1.105	1.090	1.085

Table 6: Post-compression studies of trazodone hydrochloride oral dispersible tablets

Formulation code	*TH-1*	*TH-2*	*TH-3*	*TH-4*	*TH-5*	*TH-6*	*TH-7*
Hardness test (kg/cm)	2.45	2.34	3.42	2.92	2.65	3.23	2.86
Thickness test (cm)	0.37	0.37	0.37	0.37	0.37	0.37	0.37
Friability test (%)	0.164	0.228	0.236	0.267	0.224	0.254	0.253
% of Weight variation test	99.7	99.2	99.8	99.8	99.6	99.5	99.9
Estimation of drug content%	98.12	96.29	97.54	97.27	96.48	98.34	98.84

Table 7: Disintegration time and wetting time

Formulation code	*TH-1*	*TH-2*	*TH-3*	*TH-4*	*TH-5*	*TH-6*	*TH-7*
Disintegration time (sec)	25	23	32	22	25	23	20
Wetting time (sec)	17	16	17	15	15	16	14

deviation readings, it was determined that the weight of each tablet was consistent (Table 6).

Estimation of drug content

It is evident that the drug and excipients were mixed correctly because the drug content is within the permissible range in all batches. Results are displayed in Table 6.

- *Disintegration time study*

Table 7 displays the disintegration time (DT) for each formulation.

CONCLUSION

Throughout this investigation, a grand total of seven distinct formulations were developed, and formulation F6 demonstrated favorable outcomes. The tablets were prepared using the straightforward technique of direct compression. This technique entailed consolidating the medication and the excipients into a single stage using compression. This process ensures that tablet batches are consistently uniform. The findings demonstrated that the physicochemical parameters of excipients significantly influence their performance in tablet formation. The angle of repose, compressibility index, bulk, tapped density, and Hausner's ratio were all looked at to figure out the pre-compression qualities. The medicine powder normally flowed well most of the time. Of all the formulas, F6 had the most noticeable drug release profile compared to the new product. Such was the situation with the formulations that were examined. Consequently, formulation F6 was determined to be the most optimal formulation and more studies will be conducted to ensure the effective introduction of the product. The study's overall results demonstrated that tablets of trazodone hydrochloride exhibited a greater dissolution rate, resulting in an enhanced bioavailability of the medication. Taste-masked systems are designed to provide greater bioavailability and tolerance for people with chronic conditions. The analysis concluded that formulation F6 was deemed the optimal formulation.

REFERENCES

1. Pawar MA, Shevalkar GB, Vavia PR. Design and development of gastro-retentive drug delivery system for trazodone hydrochloride: a promising alternative to innovator's controlled-release tablet. AAPS PharmSciTech. 2022 Sep 7;23(7):251.
2. Shukla KV, Vishwakarma P, Pathak R. Formulation Development and Evaluation of Gastroretentive Floating Tablets of Trazodone Hydrochloride Using Natural Polymer. Journal of Drug Delivery and Therapeutics. 2019 Aug 15;9(4-s):451-6.
3. Jaiswal M, Dubey BK, Pandey GK, Yadav SK, Parkhe G. Formulation Development and Evaluation of Fast Dissolving Oral Film of Trazodone Hydrochloride. Journal of Drug Delivery & Therapeutics. 2019 Jul 2;9.
4. Sahu RK, Jain S, Kapoor V, Gupta N. Formulation, development and evaluation of fast dissolving oral film of antidepressant drug. Journal of Drug Delivery and Therapeutics. 2019 Aug 15;9(4-s):404-7.
5. Danielak D, Milanowski B, Wentowski K, Nogowska M, Kątny M, Rogowski P, Konwicki Ł, Puk E, Pieczuro J, Bawiec M, Garbacz G. Physiologically based dissolution testing in a drug development process—A case study of a successful application in a bioequivalence study of trazodone er formulations under fed conditions. Aaps Pharmscitech. 2020 Jul;21:1-1.
6. Elhesaisy N, Swidan S. Trazodone loaded lipid core poly (ε-caprolactone) nanocapsules: development, characterization and in vivo antidepressant effect evaluation. Scientific Reports. 2020 Feb 6;10(1):1964.
7. Das MK, Ghosal SK. Ex vivo and in vivo evaluation of transdermal formulation of trazodone hydrochloride. Acta Pol Pharm. 2008 Jul 1;65(4):481-6.
8. Teixeira MT, Sa-Barreto LL, Taveira SF, Gratieri T, Gelfuso GM, Marreto RN, Silva IC, Cunha-Filho M. The influence of matrix technology on the subdivision of sustained release matrix tablets. Aaps Pharmscitech. 2020 Jan;21:1-9.
9. Zeng F, Wang L, Zhang W, Shi K, Zong L. Formulation and in vivo evaluation of orally disintegrating tablets of clozapine/hydroxypropyl-β-cyclodextrin inclusion complexes. AAPS PharmSciTech. 2013 Jun;14:854-60.
10. Alexander A, Tripathi DK, Giri TK, Patel RJ. Technologies influencing rapidly disintegrating drug delivery systems: A review. International Journal of Pharma Professional's Research (IJPPR). 2014;5(2):1039-53.
11. Karhu D, Gossen ER, Mostertº A, Cronjé T, Fradette C. Safety, tolerability, and pharmacokinetics of once-daily trazodone extended-release. International journal of clinical pharmacology and therapeutics. 2011;49(12):730-43.
12. Mahapatra AK, Swain RP, Revathi B, Nirisha N, Murthy PN. Orodispersible tablets: a review on formulation development technologies and strategies. Research Journal of Pharmacy and Technology. 2013;6(9):941-53.

13. Kale P, Agrawal YK. Pharmacokinetics of single oral dose trazodone: a randomized, two-period, cross-over trial in healthy, adult, human volunteers under fed condition. Frontiers in Pharmacology. 2015 Oct 2;6:147145.
14. Jaśkowska J, Zaręba P, Drabczyk A, Kozak A, Madura ID, Majka Z, Pindelska E. New pharmaceutical salts of trazodone. Molecules. 2021 Feb 2;26(3):769.
15. Jia-Lian Z, Gong Y, Wen-Wen L, Qi-Zhi Z, Rong-Hua Z, Wen-Xing P. Pharmacokinetics of trazodone sustained-release tablets in healthy subjects: Three open-label, randomized crossover studies. International journal of clinical pharmacology and therapeutics. 2019 Oct 1;57(10):520.
16. Mittur A. Trazodone: properties and utility in multiple disorders. Expert review of clinical pharmacology. 2011 Mar 1;4(2):181-96.
17. García MS, Ortuño J, Albero MI, Cuartero M. Application of a trazodone-selective electrode to pharmaceutical quality control and urine analyses. Analytical and bioanalytical chemistry. 2009 Jul;394:1563-7.
18. Mujawar T, Ahmad S, Tajane P, Sable V, Gaikwad A, Tare H. Development and validation of ultraviolet spectrophotometric method for Saquinavir estimation in bulk and dosage form. Multidisciplinary Science Journal. 2023 Apr 9;5(2):2023020.
19. Kharate V, Kuchekar M, Harde M, Pimple B, Patole V, Salunkhe M, Wadgave P, Bhise M, Gaikwad A, Tare H. Development of Validated Stability Indicating HPTLC Method for Estimation of Febuxostat in Bulk and Tablet Dosage Form by Using QBD Approach. International Journal of Drug Delivery Technology. 2023;13(2):542-550.
20. Barde L, Suruse P, Agrawal S, Kalkotwar R, Sable V, Tare H. Design, Development And Fabrication Of Mouth-Dissolving Tablets Containing Extract of *Tribulus terrestris* for the Treatment of Hypertension. Int J App Pharm. 2023;15(3):234-41.