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Research

Formulation And Invitro Evaluation Of Quetiapine Fumarate Oral Dispersible Tablets Using Co-Processed Super Disintegrant Technique

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Abstract

Orally disintegrating tablets (ODTs) quickly break down or dissolve in the mouth without the need for water. The demand for orally disintegrating tablets (ODTs) has experienced a significant surge, leading to a substantial expansion of this field within the pharmaceutical business and academics. Orally dissolving tablets are becoming increasingly popular compared to regular tablets since they are convenient to administer and suitable for patients. This study aims to create orally disintegrating tablets of Quetiapine fumarate (QTP). The tablets were formulated using a novel technique called co-processed super disintegrates technology. The preparations were made using the direct compression approach. The optimal flow properties, such as angle of repose, bulk density, and tapped density, were demonstrated by the amalgamation of all the formulations. The produced tablets exhibited favorable post-compression characteristics and successfully met all quality control evaluation criteria according to the I.P limits. The QF4 formulation exhibited the highest drug release, specifically 99.21%, within a 30-minute timeframe. Therefore, it is regarded as the optimum formulation. The QF4 formulation includes second control point (CP2) as a highly effective disintegrant at a strength of 10 mg. The second control point (CP 2) consists of a mixture of CCS and CP in a ratio of 1:2. The current investigation showcased the capacity for swift assimilation, enhanced availability for the body to utilize, successful treatment outcomes, and adherence from patients. The rapid beginning of action and improved anti-psychiatric activity of QTP were observed in fast dissolving tablets made by utilizing combined super disintegrates technology of QTP.

Keywords: Quetiapine fumarate; Co processed super disintegrates; CCS and CP; dissolution rate; orally disintegrating tablets.

INTRODUCTION

Oral medication delivery is widely accepted, constituting 50-60% of total dose forms. Patient compliance, ease of administration, accuracy of dosage, self-medication, and pain avoidance are some of the benefits of solid dosage forms. However, swallowing challenges are common, especially when water isn't available, such as during motion sickness or coughing bouts. Oro-dispersible tablets break down rapidly when swallowed, catering to those with dysphagia and active lifestyles[1].

ODTs are commonly referred to by different terms, including "fast-melting, fast-dissolving, oral disintegrating, or oro disperse". As per the European Pharmacopoeia, "oro disperse" denotes a tablet that disperses quickly in the mouth before swallowing. Fast dissolving tablets break down swiftly upon tongue contact, enabling the medicine to dissolve or disperse in saliva. The rate of drug dissolution directly impacts absorption speed and the onset of clinical effect[2].

These pills don't need water to dissolve; they do it in a matter of seconds in saliva. The phrase was just accepted by the European Pharmacopoeia "Oro-dispersible tablet" for tablets that dissolve in the mouth in less than 3 minutes. Some ODTs in the market dissolve in under one minute or even 30 seconds. ODTs are made using methods like lyophilization, moulding, and direct compression. While lyophilization and moulding produce tablets that disintegrate rapidly, they may lack durability and be prone to crumbling. In contrast, tablets produced through direct compression exhibit reduced fragility but have a longer disintegration period[3]. There were some work done on orodispersible tablet formulations such as, orlistat[4], ondansetron[5], zolmitriptan[6], pantoprazol[7], Metformin HCL[8], levocetirizine dihydrochloride and Montelukast sodium[9].

Quetiapine fumarate (QTP) is crystalline powder that is white to off-white in colour and tastes bitter with a slight odor. Quetiapine acts on multiple neurotransmitter receptors, including the dopamine and serotonin receptors, to ameliorate the negative and positive symptoms of major depression and schizophrenia[10]. Our goal in developing these fast-solving Quetiapine fumarate tablets is to enhance the drug's bioavailability, disintegration rate, and overall disintegration profile in order to find the sweet spot for the co-processed super disintegrating agent's concentration.

MATERIALS AND METHODS

Chemicals

Quetiapine fumarate was obtained as a gift sample from Natco Pharmaceuticals, Hyderabad, India. Microcrystalline cellulose was purchased from Signet Chemical Corporation, Mumbai, India. Croscarmellose sodium and crospovidone were purchased from Cronus pharma specialities India Pvt Ltd. Magnesium stearate and talc were purchased from S D Fine Chem, Mumbai, India. All the used reagents and chemicals were of analytical grade.

Determination of absorption maxima

A UV-Visible double beam spectrophotometer (UV-3200, Lab India, India) is used to obtain the UV spectra of a phosphate buffer with a pH of 6.8 buffer solution containing 10 µg/ml of the QTP has been made. The 200-400 range was used to scan the solution[11].

Determination of drug-polymer compatibility by Fourier Transforms Infra-Red (FTIR) Spectroscopy[12]

To determine whether peaks were present or absent, the infrared spectra of the physical mixture and the pure drug were compared. The FTIR spectrometer (Bruker Alpha II FTIR Spectrometer, Mumbai, India) was used to evaluate the compatibility of the pure medication with the excipients. Using a mortar and KBr press, the solid powder sample was ground with an amount of KBr 100 times higher to create the potassium bromide pellets. After that, the finely ground powder was placed within a stainless steel mould and compressed under polished steel anvils at a pressure of about 10 tonnes per square inch. The spectra were acquired across a wave number range of 4000 to 400 cm-1.

Preparation of tablets

The table displays the formulation's direct compression technique of QTP Dispersible Tablet. The ingredients were measured using a scale. The necessary amount of medication and additive are carefully blended in a polybag. The mixture is compacted utilizing a rotary tablet machine with 10 stations, employing a 6mm flat punch and B tooling. The composition of each tablet consists of 200 mg of QTP together with additional medicinal components[13].

Table 1: The ingredients used in different tablet forms

Ingredients	QF1	QF2	QF3	QF4	QF5	QF6	QF7	QF8	QF9
QTP (mg)	200	200	200	200	200	200	200	200	200
CP 1 (mg)	20	40	60	-	-	-	-	-	-
CP 2 (mg)	-	-	-	20	40	60	-	-	-
CP 3 (mg)	-	-	-	-	-	-	20	40	60
Magnesium stearate (mg)	4	4	4	4	4	4	4	4	4
Talc (mg)	2	2	2	2	2	2	2	2	2
MCC (mg)	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs

Note: Total weight of QTP tablet is 300 mg.

Evaluation of post compression parameters for prepared Tablets[14]

A comprehensive analysis was conducted on the physicochemical parameters of the proposed tablet formulation, encompassing drug content, hardness, thickness, friability, and weight change.

In vitro Dissolution Study[15]

Lab India's model DS-800, a modified USP XXIII dissolving test apparatus, was used for the in-vitro release investigations. A dissolution fluid of 500 cc of pH 6.8 phosphate buffer was used in each experiment, with the conditions being 37°C, 50 rpm, and speed of rotation. Taking 5 ml samples of the dissolving liquid at 2 min intervals allowed us to monitor its concentration of QTP using absorbance measurements at 286 nm. A 5 ml volume of test media was removed at predetermined times and replenished with a 6.8 pH phosphate buffer throughout all experiments.

Release Kinetics[16]

The findings from the in-vitro diffusion investigation were used to investigate the drug release kinetics of QTP oro-dispersible tablets, including their order and mechanism. The zero order, first order, and Higuchi equations were among the kinetic models that were plotted; the Korsmeyer-Peppas equations were used to determine the release.

Stability Studies[17, 18, 19]

If a drug wants to be registered in the US, EU, or Japan, it must pass certain stability tests that are laid out in the ICH Guidelines, particularly the "Stability testing of new drug substance and products" (QIA). Stability studies for the present research conducted at 40^{o} C ± 2^{o}C/75% ± 5% RH for the made a selection and used it for three months.

RESULTS AND DISCUSSION

Calibration of QTP in phosphate buffer pH 6.8

A phosphate buffer solution with a pH of 6.8 was used to generate the QTP calibration curves. At 296 nm, the wavelength of maximum absorption, the absorbance was measured. When the concentration of QTP falls between the range of 5-25µg/ml, it follows Beer's rule. A correlation coefficient of 0.9971 has been computed. It was found that the standard curve correlation coefficient was getting close. Phosphate buffer QTP calibration plot with a pH of 6.8 was presented in Figure.

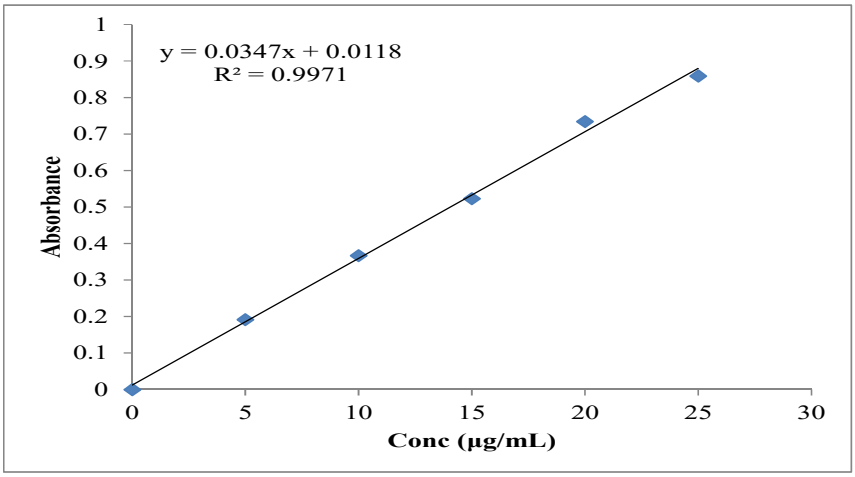

Fig 1: Standard graph of QTP 6.8 pH phosphate buffer

Drug and Excipient Compatibility Studies Using Fourier Transform Infrared Spectroscopy (FT-IR)

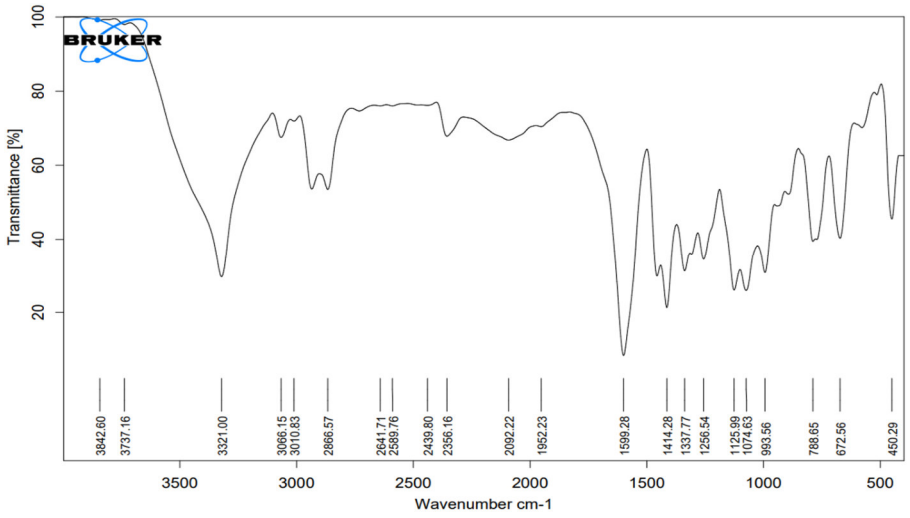

Fig 2: FTIR spectrum of QTP

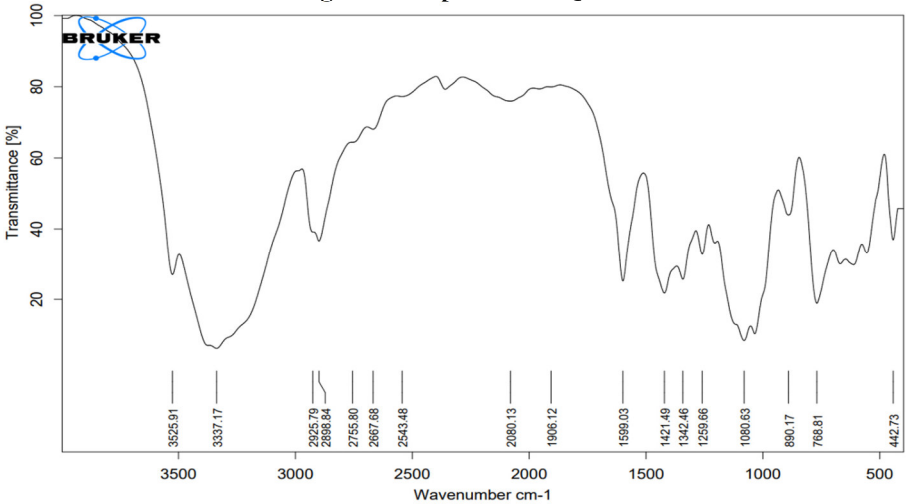

Fig 3: FTIR spectrum of optimized formulation.

The infrared spectral analysis of Quetiapine fumarate and its optimized formulation revealed characteristic absorption bands corresponding to various functional groups. In Quetiapine fumarate, OH stretching was observed at 3321 cm^{-1}, C-H stretching at 2866 cm^{-1}, C=O stretching at 1952 cm^{-1}, N-H bending at 1599 cm^{-1}, C-H bending in-plane at 1337 cm^{-1}, and C-C stretching at 1074 cm^{-1}. In the optimized formulation, slight shifts were noted, with OH stretching at 3337 cm^{-1}, C-H stretching at 2898 cm^{-1}, C=O stretching at 1906 cm^{-1}, N-H bending remaining unchanged at 1599 cm^{-1}, C-H bending in-plane at 1342 cm^{-1}, and C-C stretching at 1080 cm^{-1}. These results showed that there is no interaction between Quetiapine fumarate and the optimised formulation.

QTP Oral Dispersible Tablets Evaluation Criteria

Initial settings for compression

All formulas displayed in table 2; results showing angle of repose values between 19.09±0.34 and 24.18±0.38. Synthetic formulations with super disintegrants showed good flow properties, while natural formulations with super disintegrants exhibited good flow qualities, according to the results. A powder's flowability can be evaluated by looking at its bulk density. A bulk density of 0.47±0.03 to 0.49±0.05 g/ml was observed in the formulations. The tapping densities of the formulations ranged from 0.57±0.02 to 0.59±0.06 g/cm^3. Each formulation had a unique compressibility index, which ranged from 11.42±0.63% to 16.22±0.63%. Having a score below 16% is seen as a positive flow characteristic and compression propensity. The Hausner's ratio ranged from 1.05±0.04 to 1.18±0.12 for all the formulations. According to the results, the powder blends were ideal for manufacturing tablets because of their good flow properties.

Table 2: Parameters for pre-compression

Formulations	Bulk Density (g/cm^2)	Tap Density (g/cm^2)	Carr's Index (%)	Hausner's ratio	Angle Of Repose(Ɵ)
QF1	0.49±0.05	0.58±0.05	13.32±0.61	1.07±0.12	21.11±0.41
QF2	0.48±0.04	0.59±0.03	12.25±0.72	1.06±0.09	19.09±0.34
QF3	0.49±0.02	0.57±0.04	11.42±0.63	1.09±0.11	21.12±0.32
QF4	0.47±0.03	0.58±0.05	12.27±0.68	1.11±0.08	20.08±0.39
QF5	0.49±0.04	0.59±0.06	15.21±0.61	1.18±0.12	22.21±0.41
QF6	0.46±0.05	0.57±0.05	14.18±0.68	1.06±0.09	24.18±0.38
QF7	0.47±0.04	0.58±0.03	15.32±0.79	1.17±0.11	23.21±0.17
QF8	0.48±0.02	0.57±0.02	16.22±0.63	1.05±0.04	22.17±0.34
QF9	0.49±0.04	0.59±0.04	14.34±0.66	1.08±0.06	21.22±0.42

Post compression Parameters

The corresponding data is presented in Table 3. The findings indicated that the tablets' hardness fell within the range of 4.1±0.3 to 5.2±0.5 kg/cm^2, meeting the specified limitations set by IP. According to the findings, the thickness of the tablet ranges from 4.29±0.21 to 4.52±0.34. All of the formulas' average friability falls within the range of 0.45±0.04% to 0.71±0.07%, which is below 1% as required by the official IP standards. The disintegration duration of the formulated tablets ranged from 18.34±1.56 to 23.78±2.54 seconds. The drug content values of all the formulations ranged from 97.28±2.21 percent to 99.37±5.36 %.

Table 3: Post-Compression parameters:

F code	Weight variation (mg)	Hardness (kg/cm^2)	Thickness (mm)	Disintegration Time (sec)	Friability (%)	Assay (%)
QF1	294.8±3.4	4.1±0.3	4.51±0.24	18.34±1.56	0.49±0.04	97.28±2.21
QF2	296.4±5.5	4.3±0.4	4.34±0.27	19.56±1.42	0.51±0.06	98.42±4.18
QF3	297.5±4.1	4.8±0.5	4.41±0.35	21.27±2.32	0.57±0.07	98.34±3.29
QF4	301.7±5.6	4.4±0.4	4.48±0.42	20.32±2.27	0.45±0.04	99.37±5.36
QF5	299.3±4.2	4.9±0.6	4.52±0.34	22.37±2.49	0.68±0.05	98.24±4.22
QF6	302.2±5.5	4.7±0.3	4.42±0.33	21.11±2.31	0.51±0.04	97.38±6.42
QF7	301.2±3.8	4.6±0.6	4.29±0.21	20.67±1.52	0.49±0.03	99.25±5.31
QF8	298.5±4.9	5.1±0.4	4.38±0.23	23.21±2.41	0.69±0.06	98.43±3.12
QF9	303.4±3.9	5.2±0.5	4.48±0.22	23.78±2.54	0.71±0.07	99.35±6.26

Percentage of water absorbed and wetting time

The super disintegrant and diluent were tested for their water-absorbing capacities using the water absorption ratio. Table 4 displays the results for the water absorption ratio for each formulation. QF1, QF2, QF3, QF4, QF5, QF6, QF7, QF8, and QF9 had water absorption ratios of 74.42%, 72.57%, 86.31%, 99.59%, 78.33%, 84.51%, 87.42%, 77.38%, and 85.29%, respectively. A favourable link was seen between the super disintegrant concentration and the water absorption ratio, according to the results. Out of all the formulations tested, Formulation QF4, which contains CP2, showed the best water absorption ratio at 99.59%. A quick rise in tablet volume is caused by the rapid transport of water into the tablet by the high water absorption ratio of the QF4 formulation integrating CP2. The formulations QF1, QF2, QF3, QF4, QF5, QF6, QF7, QF8, and QF9 exhibited wetting times of 71.43, 70.38, 68.47, 56.24, 67.32, 62.46, 59.35, 62.53, and 68.66 seconds respectively.

Table 4: Wetting time

F code	Percentage of water absorbed	Wetting time
QF1	74.42±0.33	71.43±0.07
QF2	72.57±0.47	70.38±0.06
QF3	86.31±0.28	68.47±0.03
QF4	99.59±0.31	56.24±0.05
QF5	78.33±0.45	67.32±0.08
QF6	84.51±0.62	62.46±0.09
QF7	87.42±0.54	59.35±0.04
QF8	77.38±0.48	62.53±0.06
QF9	85.29±0.59	68.66±0.04

In vitro Dissolution studies

Figure 4-6 shows the results of dissolution profile. The dissolution profile range within a 30-minute timeframe ranged from 82.59 percent to 99.21 percent as seen in Appendices QF4 and QF6. There was a noticeable decrease in medication release in the formulation that included a natural super disintegrant, specifically gelatinized flour. The formulation containing QF3, QF4 and QF8 exhibited the highest drug release rate, reaching 98.01%, 99.21% and 98.34% dissolution within 30 minutes of the dissolution study. This result is in accordance with the guidelines set by the World Health Organization (WHO). Several factors, including rapid disintegration and increased wettability, contributed to acceleration drug release. Out of the 9 formulations, formulation 4 (QF4) was chosen as the best formulation due to its favourable characteristics, including a short disintegration time, the maximum time to wet, rapid water absorption, and medication release.

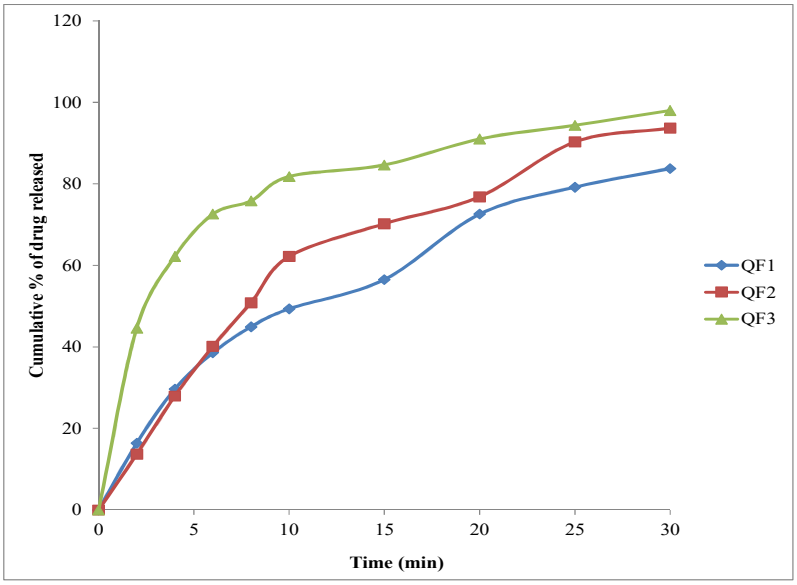

Fig 4: Graph of dissolution for formulations made using CP1 as a super disintegrant.

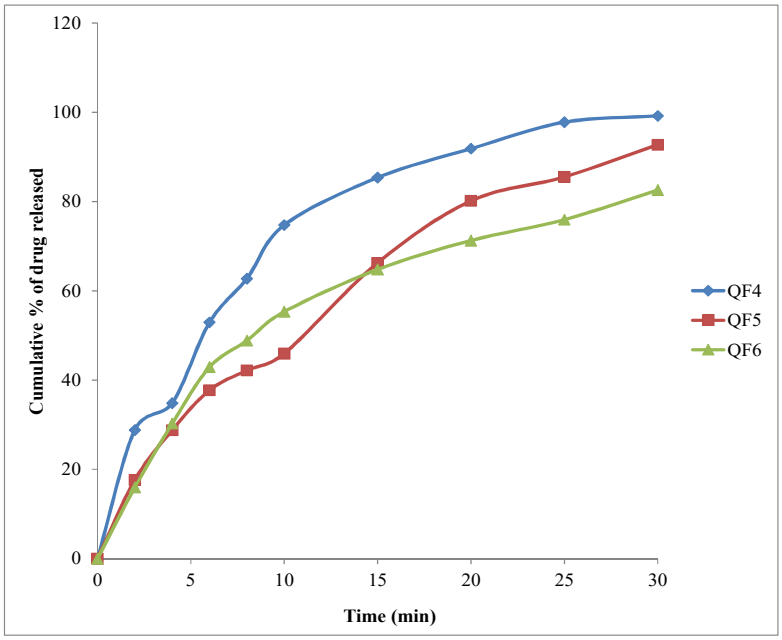

Fig 5: Graph of dissolution for formulations made using CP2 as a super disintegrant.

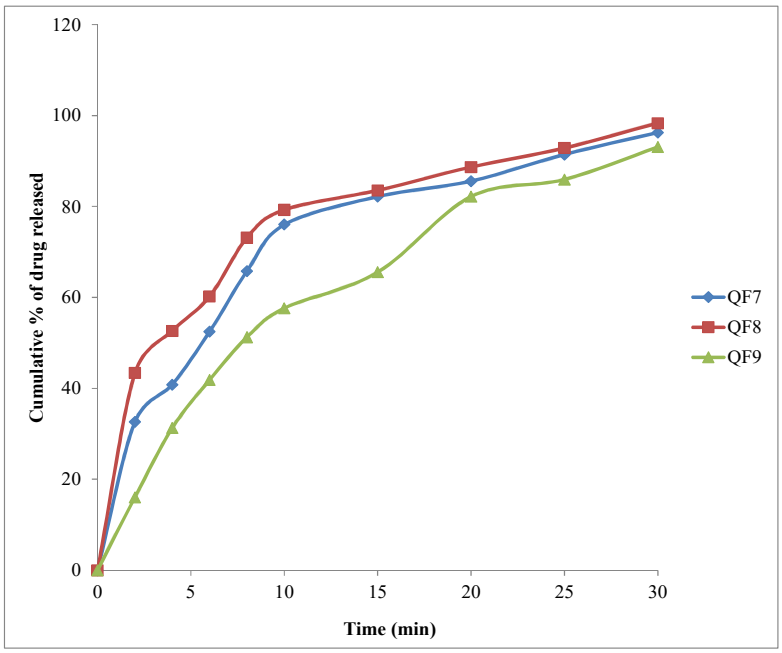

Fig 6: Graph of dissolution for formulations made using CP3 as a super disintegrant.

Based on the data shown in Figure 5, it is clear that the formulations containing super disintegrate CP2 exhibited superior drug release, reaching 99.21% within a 30-minute timeframe.

Utilizing Release Rate Kinetics for Dissolution Data

Various models were utilized to examine the drug release kinetics. A number of release of drug models, including First-order, Zero-order, Higuchi, and Korsmeyer-Peppas, were fitted to the collected data in order to investigate the mechanism of the dosage form's rate kinetics.

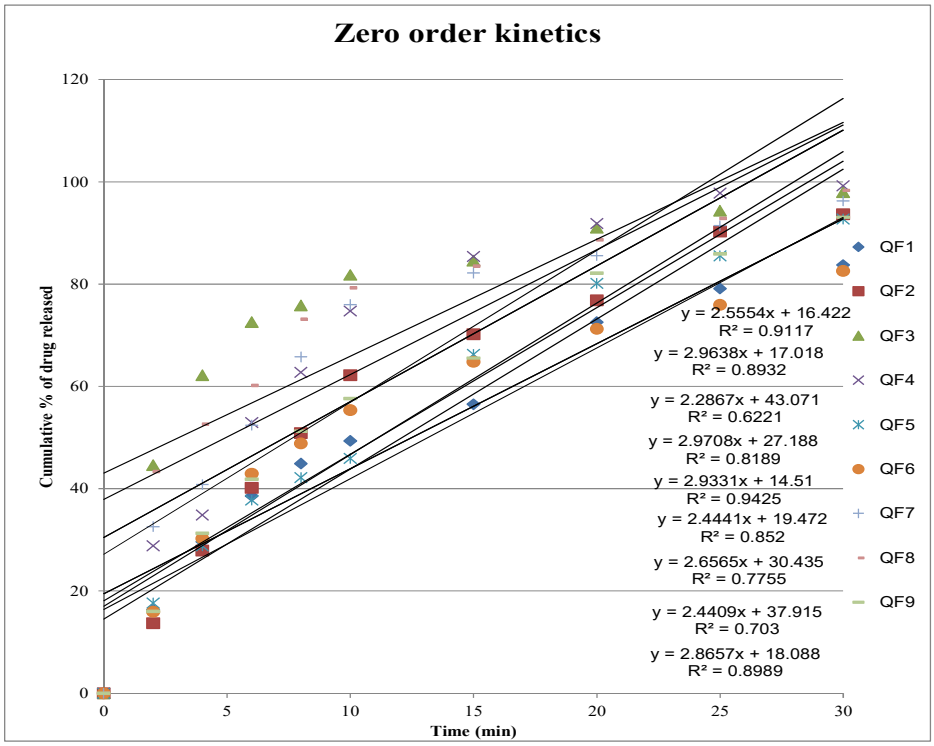

Fig 7: Zero order release kinetics graph of QTP formulations.

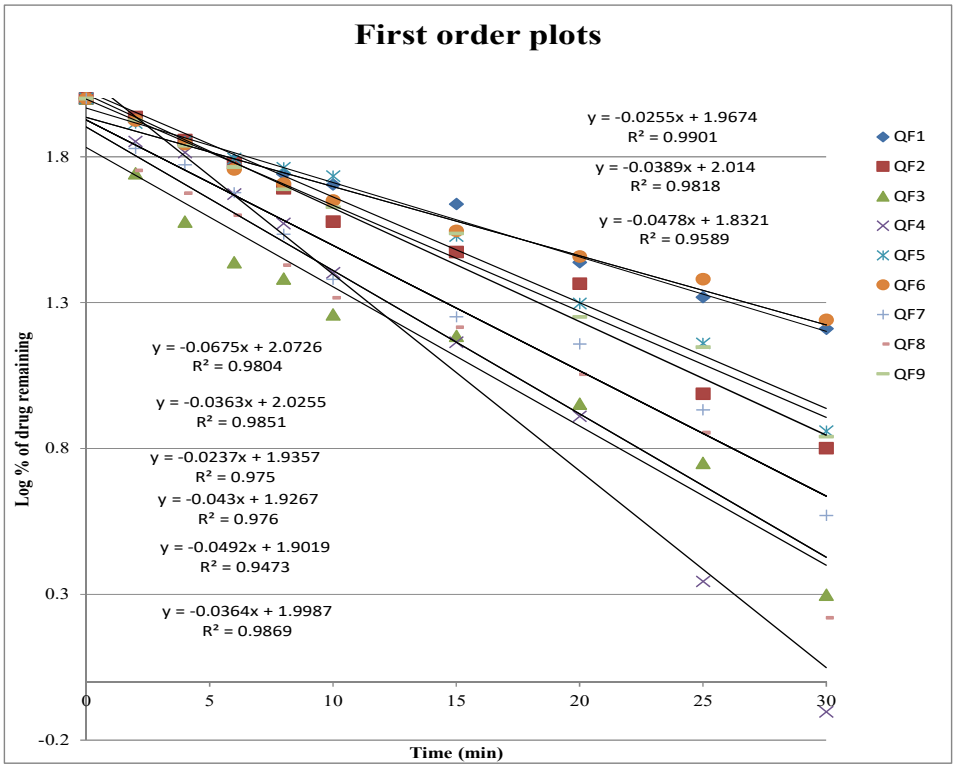

Fig 8: First order release kinetics graph of QTP formulations.

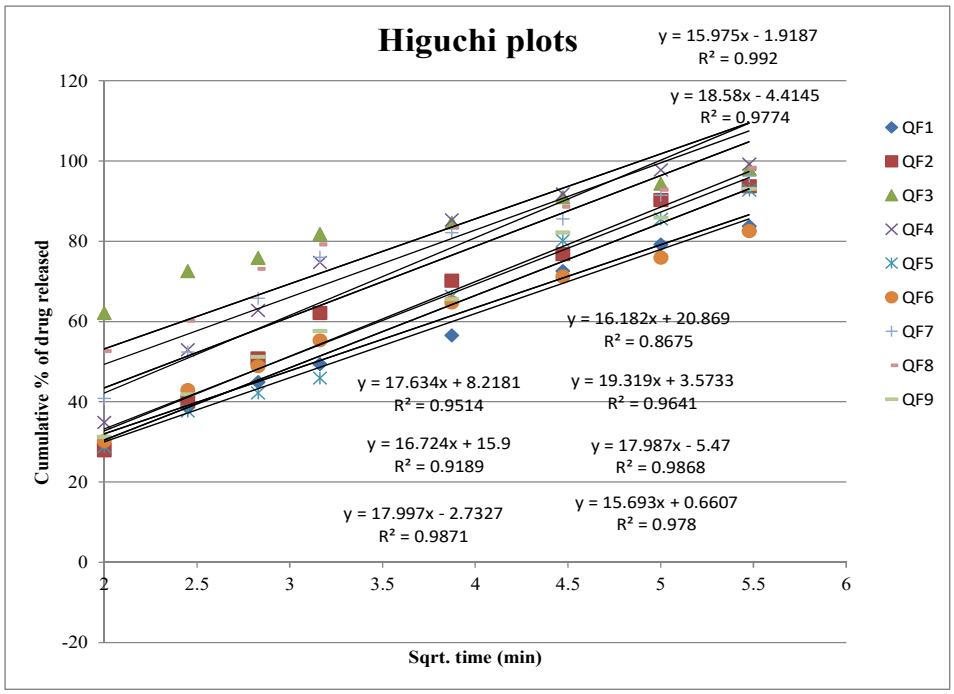

Fig 9: Higuchi release kinetics graph of QTP formulations.

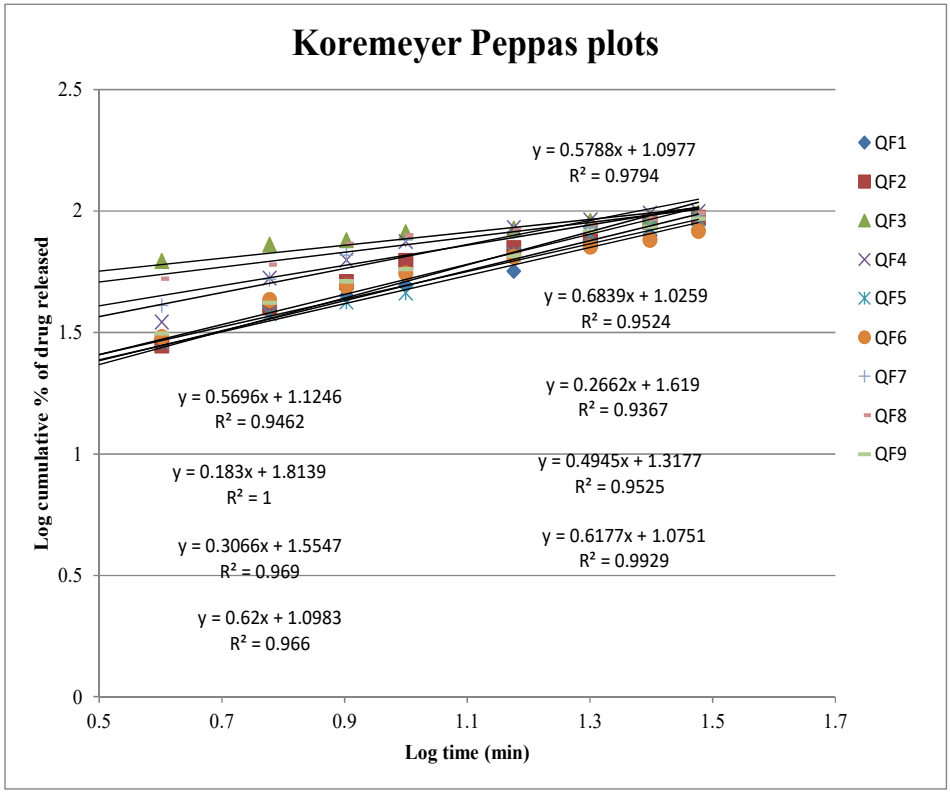

Fig 10: Korsmeyer-Peppas kinetics graph of QTP formulations.

Table 5: Dissolution kinetic's parameters data

Formulations	Zero order	First order	Higuchi	Korsmeyer-Peppas	
	R^2	R^2	R^2	n	R^2
QF4	0.8189	0. 9804	0.9641	0.4945	0.9525

The R2 values presented in the first-order kinetic graphs exceed 0.9, in contrast to the zero-order kinetic graphs, indicating that the drug release adheres to first-order kinetics. The regression equations of Higuchi plots provide R^2 values exceeding 0.9, indicating that drug release adheres to diffusion kinetics. The Korsmeyer-Peppas model is applicable when drug release entails many processes or when the precise mechanisms are indeterminate. The model can additionally ascertain if the release is governed by diffusion. Here "n" is between 0.45 and 0.89, it signifies that the drug is released through non-fickian diffusion process.

Selection of Best Formulation

Out of nine potential formulations, the one with the best combination of characteristics was selected: rapid drug release, short wetting time, high water absorption ratio, and minimal disintegration time. With a disintegration time of just 20.32 seconds, a drug release rate of 99.21% within 30 minutes, a water absorption of 99.59%, and a wetting time of just 56.24 seconds, Formulation QF4 stood out from the others. According to these considerations, the QF4 formulation is the best one to use.

Stability Studies

A three-month stability investigation was conducted on the QF4 [CP2] refined compounds in a controlled environment with a temperature of 40°C and a relative humidity of 75%. Further testing was conducted at 80°C in the fridge and 60°C in the incubator. Every thirty days, the tablets were tested for a variety of properties, including thickness, diameter, hardness, friability, weight change, content uniformity, and disintegration time. All of the metrics were within the predetermined range, and there was no discernible change from the original data. Measurements were taken every 30 days throughout the three-month in-vitro dissolving research. Exposure to elevated temperatures and controlled humidity levels had no effect on the release patterns.

SUMMARY AND CONCLUSION

Creating rapidly dissolving QTP tablets is the main goal of this study. The revolutionary co-processed super disintegrants technology was used to prepare the tablets. When compared to more traditional dosage forms, oro-dispersible tablets offer a feasible alternative that may hasten the onset of therapeutic effects. The direct compression technique was used to make QTP dispersible tablets. The ingredients in the mixture included pregelatinized crospovidone and croscarmellose sodium. The direct compression methodology was used to carry out the preparations. The flow characteristics, including angle of repose, bulk density, and tapped density, were all satisfactory in all of the formulations. All quality control assessment criteria were successfully met by the manufactured tablets, which demonstrated desirable post-compression qualities according to the I.P limits. With a maximal medication release of exactly 99.21 percent in just 30 minutes, the QF4 formulation was clearly the best option. With a dosage of 200 mg, the QF4 formulation includes CP2 as a powerful disintegrant. A mixture of CCS and CP in a 1:2 ratio makes up the second control point (CP 2).

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