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ORIGINAL RESEARCH

Quality by Design Formulation Approach for the Development of Orodispersible Tablets of Dexlansoprazole

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Purpose: Dexlansoprazole (DX) is a commercially available proton pump inhibitor (PPI). It is an oral delayed-release (DR) formulation that takes 1–2 h to reach the systemic circulation. To overcome the delayed onset of action of conventional formulation and patient inconvenience, orodispersible tablets (ODTs) have been formulated. Drug delivery systems, especially in elderly and frequent travelers, are limited by conventional dosage forms, and ODTs are an ideal dosage form for the fast onset of action and ease of administration for these patients and are more convenient than conventional tablets for patient compliance.

Methods: The formulation was optimized via Design Expert® software (version 13.0) and evaluated for in vitro and in vivo attributes. The ODTs were compressed by the most convenient method of compression, that is, direct compression, the formulation contains a combination of citric acid and sodium bicarbonate along with Kyron T-314® (polymer). Pre- and post-compression evaluations were performed, and a comparative pharmacokinetic study of the DX ODT was carried out in human volunteers.

Results: Drug plasma concentrations were analyzed at different time intervals through high-performance liquid chromatography (HPLC). PK Summit® software was used to calculate various pharmacokinetic parameters. The pharmacokinetic results revealed that the T_{max} of 0.4 h was significantly lower than that of conventional DX, indicating rapid onset of action. Stability studies indicated that the formulation was stable under both intermediate and accelerated conditions.

Conclusion: The ODTs exhibited good physical characteristics, with a pleasant taste and disintegrated rapidly in the saliva due to the addition of a superdisintegrant and an effervescent pair. Pharmacokinetics revealed a rapid therapeutic effect with good C_{max}. Furthermore, this formulation is cost-effective in terms of fewer manufacturing steps and a lower cost for excipients, along with a good stability profile.

Keywords: dexlansoprazole, ODT, polymer, FTIR, pharmacokinetic, stability

Introduction

Solid dosage forms are commonly more acceptable owing to their low cost, ease of administration, avoidance of complications, and more specifically, patient compliance. Tablets and capsules are more popular; however, the evident drawback related to this dosage form is its administration in the condition of dysphagia (difficulty in swallowing) in patients, who are in dire need of a convenient dosage form to fulfill these medical needs. Pharmaceutical scientists have developed oral dosage forms called orodispersible tablets (ODTs), which disintegrate soon after administration in the oral cavity within seconds(s) without the need for water. These factors improve drug dissolution as well as the onset of action, whereas pregastric absorption avoids the first-pass effect.[1] Owing to the disintegration of ODTs in the saliva, the dissolved/suspended drugs move down along the

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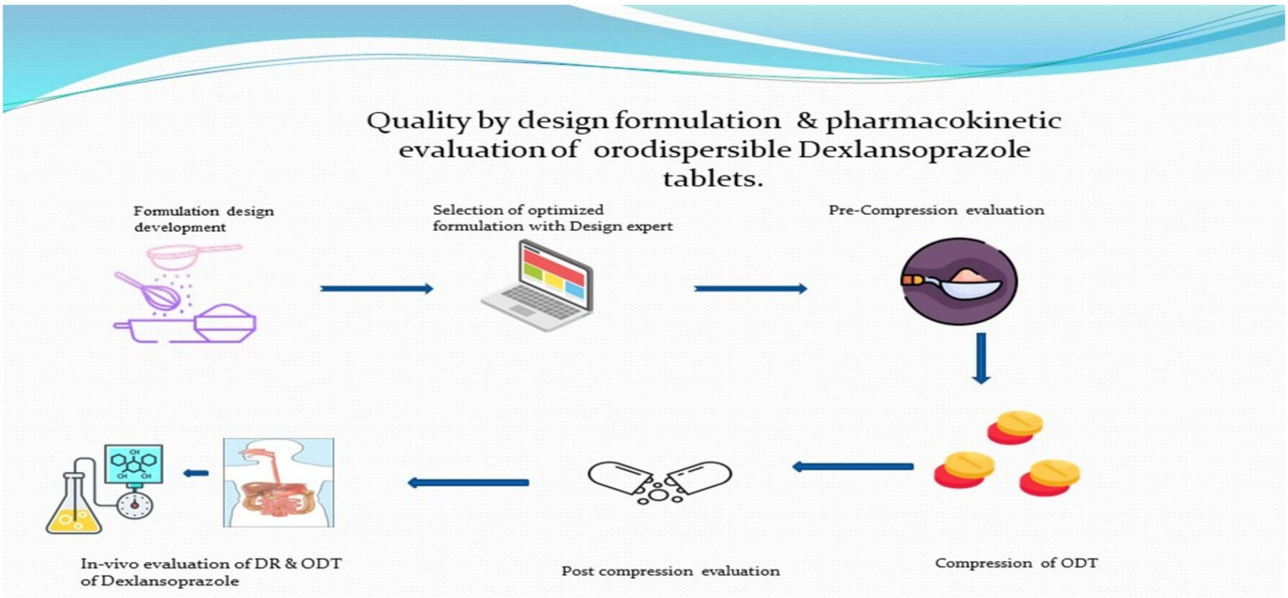
Graphical Abstract



saliva, and absorption starts at the mouth, followed by the pharynx and esophagus. They are gaining importance because of their convenience in administration and better taste due to the addition of taste-masking agents and flavors;[2] they also provide rapid relief to patients, especially geriatric and pediatric populations, which have various ingestion problems.

In recent years, ODT products have undergone rapid market growth, along with advancements in manufacturing technologies. The newest techniques produce ODTs with a pleasant taste, overcoming the limitations of previous ones. They can overcome the processing steps via direct compression technology, while the route of administration remains the same, and the clinical requirement to gain regulatory approval for the bioequivalent or generic version of the current oral dosage form is minimal.

Dexlansoprazole (DX) was used as the model drug in this study, it is a second-generation PPI that is more effective, faster in achieving acid suppression, and less dependent on CYP450 enzymatic metabolism.[3] It does not depend on the time of administration or gastric emptying. Hence, these benefits may lead to improvements in a patient's quality of life, demonstrating great promise in treatment.[4] It is 2-[(R)-[3-methyl-4-(2,2,2-trifluoromethoxy)pyridin-2-yl] methylsulfinyl]-1H-benzimidazole, as shown in Figure 1, with a molecular weight of 369.36g/mole.[5] It is a new-generation PPI prescribed for gastroesophageal reflux disease (GERD) and was registered by the US FDA in 2009.

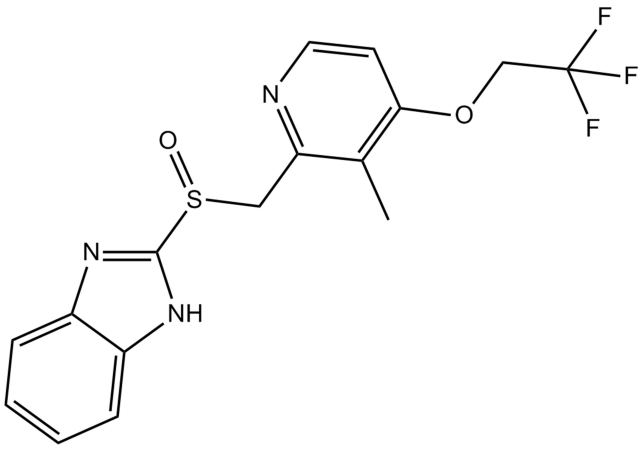


Figure 1 Chemical structure of dexlansoprazole.

To develop optimized ODT formulation[6], inert materials, such as polymer (a derivative of cross-linked polycarboxylic acid)[7] and effervescent pair[8] (sodium bicarbonate and citric acid), were used for the prompt disintegration and taste masking of the tablets. The acid–base reaction in contact with moisture in saliva produces sodium citrate, which helps to neutralize gastric acid.[9] Eleven trial formulations were suggested by software, which were subjected to pre- and post-compression evaluation as per official compendia, and the disintegration time and dissolution results were used to obtain the optimized formulation. Furthermore, the pharmacokinetic attributes of the optimized formulations were evaluated.

Materials and Methods

Materials

Dexlansoprazole was a kind gift from Metrochem API Pvt Ltd. Hyderabad, India. Mannitol was purchased from Rewine Pharmaceuticals, India, Lactose SD (Kerry Ingredients, India), sodium bicarbonate (GHCL-Lion, India), citric acid (Yixing-union Biochemical, China), magnesium stearate (Signet Chemicals, India), KyronT-314® (Corel Pharma, Gujarat, India), and orange powder (Gogia Chemicals, India).

All the chemicals used in the study were of HPLC and analytical grade. Acetonitrile (ACN) was purchased from Fisher Scientific UK, and ortho-phosphoric acid and trimethylamine (TEA) were purchased from Scharlau Chemie (Barcelona, Spain).

Instrumentation

Digital balance (Shimadzu, Japan), Mini Hobart mixer (Hobart Ohio, USA), rotary tablet machine (China), tablet thickness and hardness tester (Pharma Test GmbH, Germany), dissolution apparatus (Pharma Test GmbH, Germany), double beam ultraviolet (UV) visible spectrophotometer (Shimadzu1800, Japan), FTIR-Affinity (Shimadzu®, Japan), Double drum Friabilator (Pharma Test, Germany), Vortex mixer (Fisher Scientific®, USA), and HPLC system (Perkin-Elmer®, Norwalk, USA) consisted of a UV–VIS detector coupled with an online vacuum degasser, auto sampler and column oven, and a stability chamber (Shjianheng®, China) coupled with an online 24/7 graph recorder and monitor.

Methodology

Drug Excipient Compatibility Studies

FTIR studies were performed in the range of 400–4000cm^{-1} for the optimized formulation to determine the compatibility of DX with the excipients. The FTIR spectra (n = 3) of pure DX, excipients intended for use in the preparation of ODTs, and a mixture of DX and excipients were obtained.

Statistical Analysis of the Optimized Formulation

The factors of interest were screened prior to the experimental design. The inputs were quantities of citric acid, sodium bicarbonate, and polymer. The minimum and maximum quantities of sodium bicarbonate and citric acid were 30–70 mg, whereas the minimum and maximum quantities of the super disintegrant were 15–25 mg. The three variables are selected on the basis of their established role in the dispersion of various ODT formulations. The center points were added to assess the skeptical curvature effects in the design. The dependent variables were the disintegration time and dissolution profile. The full factorial design of (2^3) and a total of eleven combinations were used to prepare the DX ODT via the direct compression[10] technique. The responses, that is, disintegration time and dissolution rate, were determined[11] and recorded.

Preparation of ODT

ODTs were prepared via the direct compression technique.[12] Citric acid was crushed owing to its crystalline structure and passed through mesh #20. Sodium bicarbonate was heated at 120°C for 30 min, where a portion was converted to sodium carbonate at this high temperature and formed a layer, which resulted in the passiveness of the particle surface of sodium bicarbonate[13] resulting in improved flow ability. All the materials, except magnesium stearate, were blended in a laboratory-scale Hobart mixer for 10 min at 15 rpm after being passed through mesh #20. Magnesium stearate was blended with the powder mixture for 5 min after it was sifted through mesh # 40. The powder blend was compressed via

a ZP-19 compression machine fitted with round shallow concave punches. This process is illustrated in Figure 2, which provides a schematic representation of ODTs preparation.

Pre- and Post-Compression Evaluation

The developed formulation was evaluated for various quality attributes. The parameters assessed during the pre- and post-compression evaluations are presented in Figure 3.

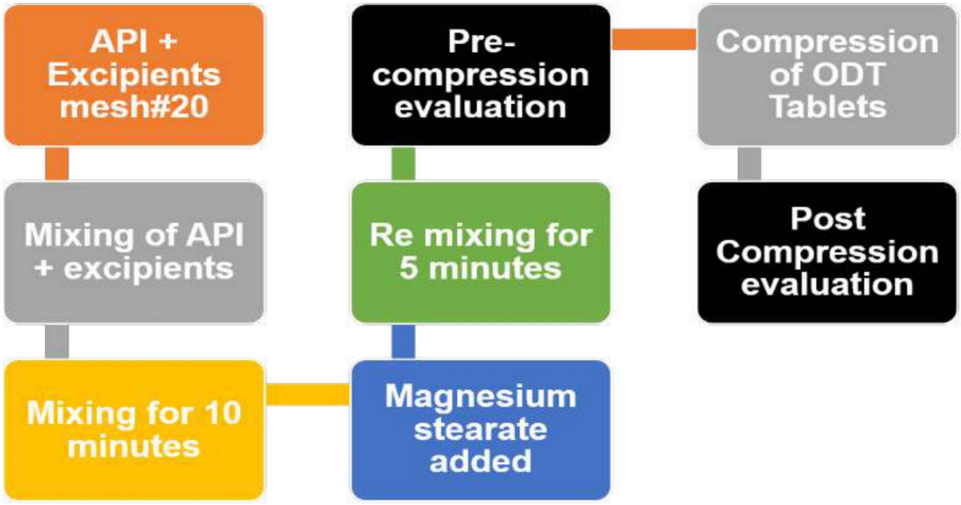


Figure 2 Schematic presentation of the process for preparation of ODT.

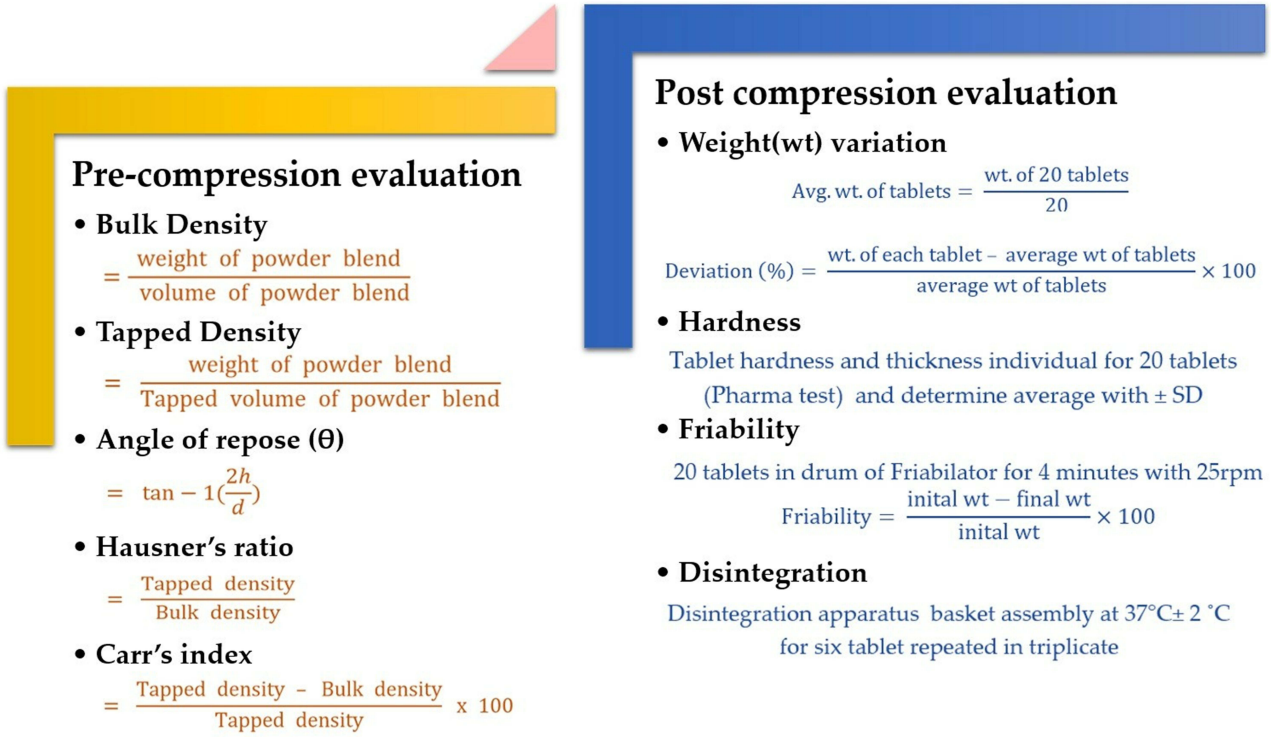


Figure 3 Pre- and post-compression evaluation parameters.

Disintegration Time

The DT of the ODTs was determined according to the USP procedure, and six tablets were placed in a basket immersed in water maintained at 37°C ± 2. The time taken by the tablets to disintegrate and disperse was recorded.

Oral DT was determined in human volunteers after fulfilling all the obligations of ethical approval certificate no. 501/EC-FLES-UOP/2022. The test was performed on six healthy male volunteers aged between 25 and 28 years. The volunteers were advised to rinse their mouths with fresh water (150 mL). A single tablet was kept on the upper tongue of each volunteer, the disintegration time was recorded, and the in vitro disintegration time was checked with a disintegration apparatus (USP). The mean disintegration time was recorded.[14,15]

The dissolution profiles of the DX ODT and DX DR formulations (commercial) were determined via a USP-I (basket-type) dissolution apparatus in 900 mL of phosphate buffer (pH 6.8) solution as the dissolution medium.[16]

A sample (5.0 mL) was withdrawn at predetermined time intervals (5, 10, 15, 30, and 60 min), replaced with fresh phosphate buffer maintained at 37 ±0.5°C to maintain sink conditions, and filtered through a 0.2 µm disposable filter. The drug content in each sample was quantified with a Shimadzu UV spectrophotometer at 285 nm.

Assay

The optimized DX ODT was assayed via HPLC with UV detection at 285 nm. The mobile phase was composed of acetonitrile (ACN) and 1% TEA in distilled water adjusted to pH 7 with orthophosphoric acid at 55:45 (ACN: water), and a Welchrom ® C18, 5 µm, 4.6 × 250 mm column was used. The samples were analyzed in triplicate with an injection volume of 20 µL.

Standard preparation: Accurately weighed 10 mg of DX working standard was placed in a 100 mL volumetric flask, 50 mL ACN was added, the mixture was vortexed,[17] and the volume was adjusted with the mobile phase to the mark.

Sample preparation: Twenty tablets were crushed and weighed, and an amount equal to 10 mg of DX was added to a 100 mL flask, ACN. (50 mL) was added, the mixture was sonicated, and then a final volume of 100 mL was made up of the mobile phase.

In vivo Evaluation

The pharmacokinetic parameters, ie, the highest concentration (C_{max}), time to peak drug concentration (T_{max}), area under the curve (AUC), half-life ($t_{1/2}$), clearance, and volume of distribution (Vd), of the optimized DX ODT were compared with those of commercial DX formulations in human volunteers.

Twelve healthy male volunteers aged 25–30 years, not on any medication, fasted for 8 h and had a body weight of 55–65 kg were selected. They were briefed about the drug administration procedure and drawn blood samples.[18] A single dose of DX (30 mg ODT) was administered to each of the twelve 8-hour fasted individuals in group A according to the instructions to keep the tablet on the tongue and not to ingest it[19] until it disintegrated completely. They were observed until the disintegration of the tablet was achieved.

The same procedure with the conventional dosage form was repeated with the same volunteers, eight-hour fasting after a one-week wash period; this time, they were advised to swallow the whole capsule with 200 mL of drinking water.

This study was approved by the Ethical Committee of the Department of Pharmacy, University of Peshawar, Ethical Certificate No. 501/EC-FLES-UOP/2022.

Sample Collection

Blood samples (3 mL) were withdrawn immediately before administration of the dose and after intervals of (1, 15, 30, 60,120,180, 240,300,360, 540, and 720) min in heparinized tubes. The plasma was separated by centrifugation at 5000 rpm for 10 min. These samples were stored at −20°C until analysis.

Drug Extraction From Plasma

Drug extraction from plasma was carried out via a liquid–liquid drug extraction procedure. The plasma samples were thawed at room temperature, 200 µL of plasma was collected in Eppendorf tubes, and 800 µL of ACN was added for protein precipitation. The samples were vortexed for five minutes and centrifuged for ten minutes at 5000 rpm, and the supernatant was collected, as shown in Figure 4. The same procedure was repeated once for the

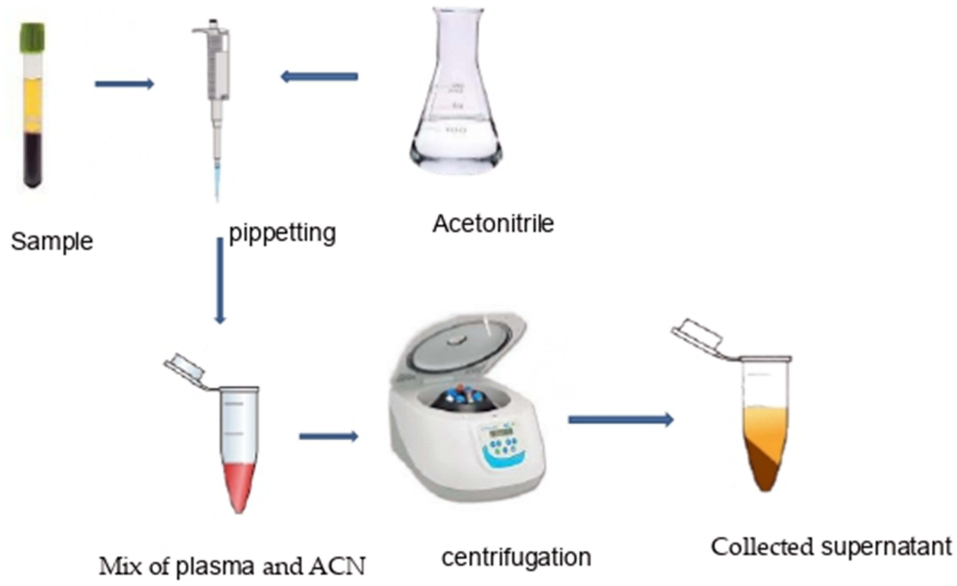


Figure 4 Schematic diagram of drug plasma extraction procedure.

sediment, and both supernatants were mixed. The DX content of the samples was analyzed via HPLC, as described in assay.

Calibration Curve

The calibration curve of the standard and spiked plasma samples was constructed in the concentration range of 0.5, 1, 2, 3, 4, and 5 µg/mL.

Stability Studies

Stability studies of the optimized DX ODT were carried out for six months as per the ICH guidelines for Zone IV at 40 ± 2°C and 75 ± 5% relative humidity (RH) for accelerated conditions and 30 ± 2°C and 60 ± 5% RH for intermediate conditions. The tablets were packed in an Alu-Alu blister pack with a base material of nylon 30 ± 10 µm, with the first laminate material as aluminum and the second laminate material as PVC. The density of both materials was 60 ± 10 µm, the densities of nylon, aluminum foil and PVC were 1.15 g/cm^3, 2.76 g/cm^{3,} and 1.38 g/cm^3 respectively. The moisture vapor transmission rate and oxygen transmission rate of <0.5 g/m^3/day were measured with an overall concentration of 290 ± 5 g/m^2.

Statistical Analysis of the Data

Statistical analysis of the data was performed via Minitab® (Minitab Inc., Version 17, PA16801; State College, PA, USA; 2017). A comparison of the data at different sampling points was carried out through a *t* test. Analysis of qualitative data and the preparation of tables and graphs were carried out via Microsoft Excel and OriginPro® 2024.

Results

Drug Excipient Compatibility Studies

FTIR analysis was conducted to determine the compatibility of the drug (DX) and excipients. The DX, excipients, and physical mixture (DX + excipients), as shown in Table 1 and Figure 5, were analyzed.

The distinctive peaks of DX in the physical mixture at 3448 (N-H stretching), 1637.36 (C=N stretching), 1358.097 (S=O stretching), 1466 (C-H bending), and 1244 cm^{-1} (C-N vibrations), as shown in Figure 5, were preserved, indicating that no interaction occurred between the DX and excipients.[20]

Table 1 Description of Samples for FTIR Analysis

Sample 1	Sample 2	Sample 3
Dexlansoprazole Pure	Mannitol, Sodium bicarbonate, Citric acid, Magnesium stearate, Lactose spray dried, Kyron T 314, Orange flavor powder	Dexlansoprazole, Mannitol, Sodium bicarbonate, Citric acid, Magnesium stearate, Lactose spray dried, Kyron T 314, Orange flavor powder

Preparation of ODTs and Statistical Analysis

ODTs were prepared via the direct compression method. The vital role of polymers is not only as a superdisintegrant and taste masking ingredient but also to improve dissolution through the formation of fine particles after tablet disintegration with a creamy taste, which is a desirable quality in ODTs.[21]

The combinations suggested by the software were subjected to statistical analysis, with a statistical significance of $p = 0.05$.

The powder blends of different trial formulations were compressed[22] on a ZP-19 compression machine, and the DT and dissolution rate results (Table 2) were used to select the optimized formulation. Three variables, sodium bicarbonate (A), citric acid (B), and polymer (C), were used in the study. The dissolution profile revealed that the factors B and C (citric acid and polymer) contributed to the dissolution of the DX individually and had a two-factor interaction, whereas factor A (sodium bicarbonate) had no individual impact but was involved in a two-factor interaction, as indicated in the half-normal plot.[23–25.]

The experimental results were investigated via a normal plot (Figure 6a) and a response surface plot of dissolution (Figure 6b).

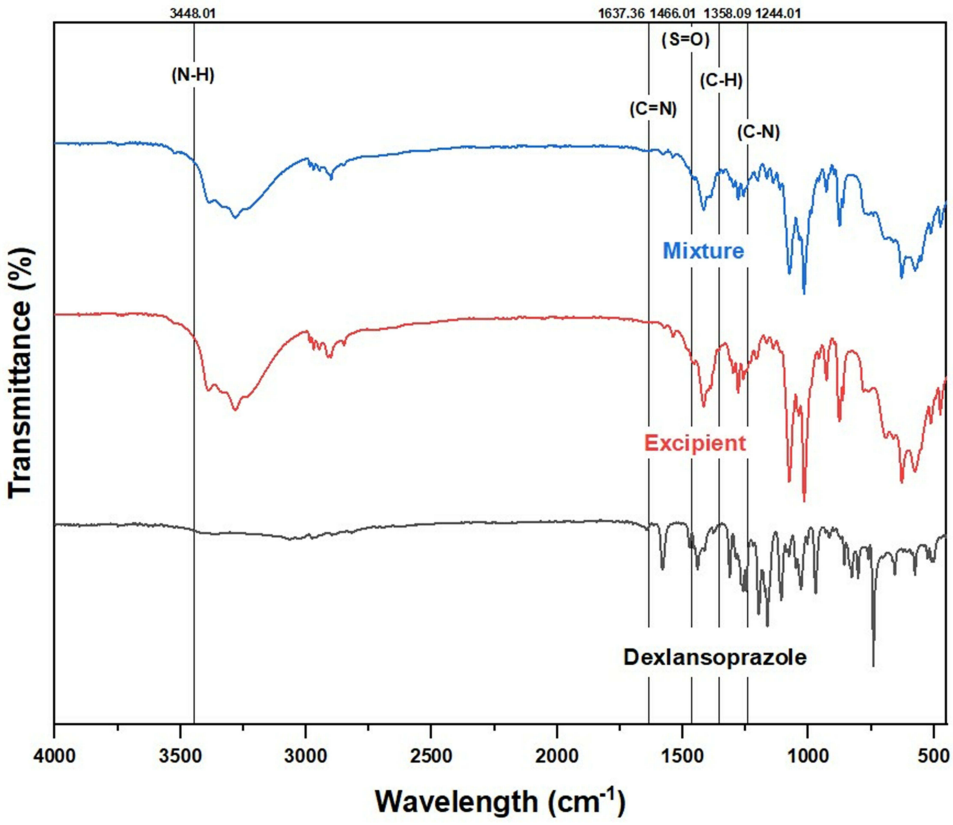


Figure 5 FTIR spectra of drug, excipients and its physical mixture.

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Table 2 Results of Disintegration and Dissolution Tests of Different Trials

S#	Sodium Bicarbonate (mg)	Citric Acid (mg)	Polymer (mg)	D.T (sec)	% Dissolution
1	70	70	15	76	66.1
2	70	30	15	69	64.3
3	50	50	20	58	77.3
4	30	70	15	66	84.9
5	70	70	25	51	89.8
6	30	30	15	65	68.8
7	50	50	20	53	71.1
8	50	50	20	59	73.7
9	30	30	25	61	79.1
10	70	30	25	63	87.4
11	30	70	25	58	84.4

The statistics in Table 3 show that the model F value of 21.84 implies that the model is significant, as evident in factors B (citric acid), C (polymer), AB (sodium bicarbonate and citric acid), and AC (sodium bicarbonate and polymer), which are significant model terms. The R^2 of 0.9562 indicated that the responses are well explained by the equation. The predicted R^2 of 0.8782 was in reasonable agreement with the adjusted R^2 of 0.9124, ie, with a difference of less than 0.2.

The linear regression model was recommended for the experimental data and final model equation, which demonstrated the relationship between the formulation variables and dissolution. The extent of each main factor's effect and the two-factor interaction's effect were evaluated via a normal plot of the residuals, which indicated that the data points were normally distributed in a linear relationship. The model suggested that, by increasing the concentrations of factors B and C, the dissolution of the drug increased, whereas factor A had no effect on drug dissolution. The interaction plot revealed a decrease in the dissolution rate when operating at a low level of factor A and with a low level of factor B and vice versa, whereas there was a significant increase in the dissolution rate when working at a low level of factor A with a high level of factor B. The model also revealed that the two means were statistically the same at a high level of factor A with high and low levels of factor B. The same findings in the design space were validated by the 3D response surface plot. The DT half-normal plot (Figure 7a) and response surface plot (Figure 7b) were analyzed to determine the profound effects of these factors. Factor C has significant effects individually, whereas factors A & B have no independent effect but are involved in two-factor interactions, as evident from the half-normal plot.

The ANOVA results and descriptive statistics of DT, as shown in Table 4, suggest the significance of the model (F value = 15.43), with C, AC, BC, and ABC as the significant terms. The lack of curvature reflected the goodness of fit of the model, with a lack of fit value of 7.91. The response disintegration was well described by the model equation, which is indicative of a high R^2 value of 0.9114. Additionally, the predicted R^2 of 0.6202 is in reasonable agreement with the adjusted R^2 of 0.8523.

As evident from the model equation, the individual and combined (interaction) effects of the polymer have a considerable effect on disintegration time.[26,27] The data and model suggested that the most significant effect on DT is factor C. DT is high when operating at a low level of factor C, and vice versa. There is no significant effect of factors A and B, which operate both at high and low levels. The interaction between factors A and C revealed that there was a significant increase in DT, when operating at a high level of factor A with a low level of factor C, and vice versa, whereas at a high level of factor C, there was no considerable effect.

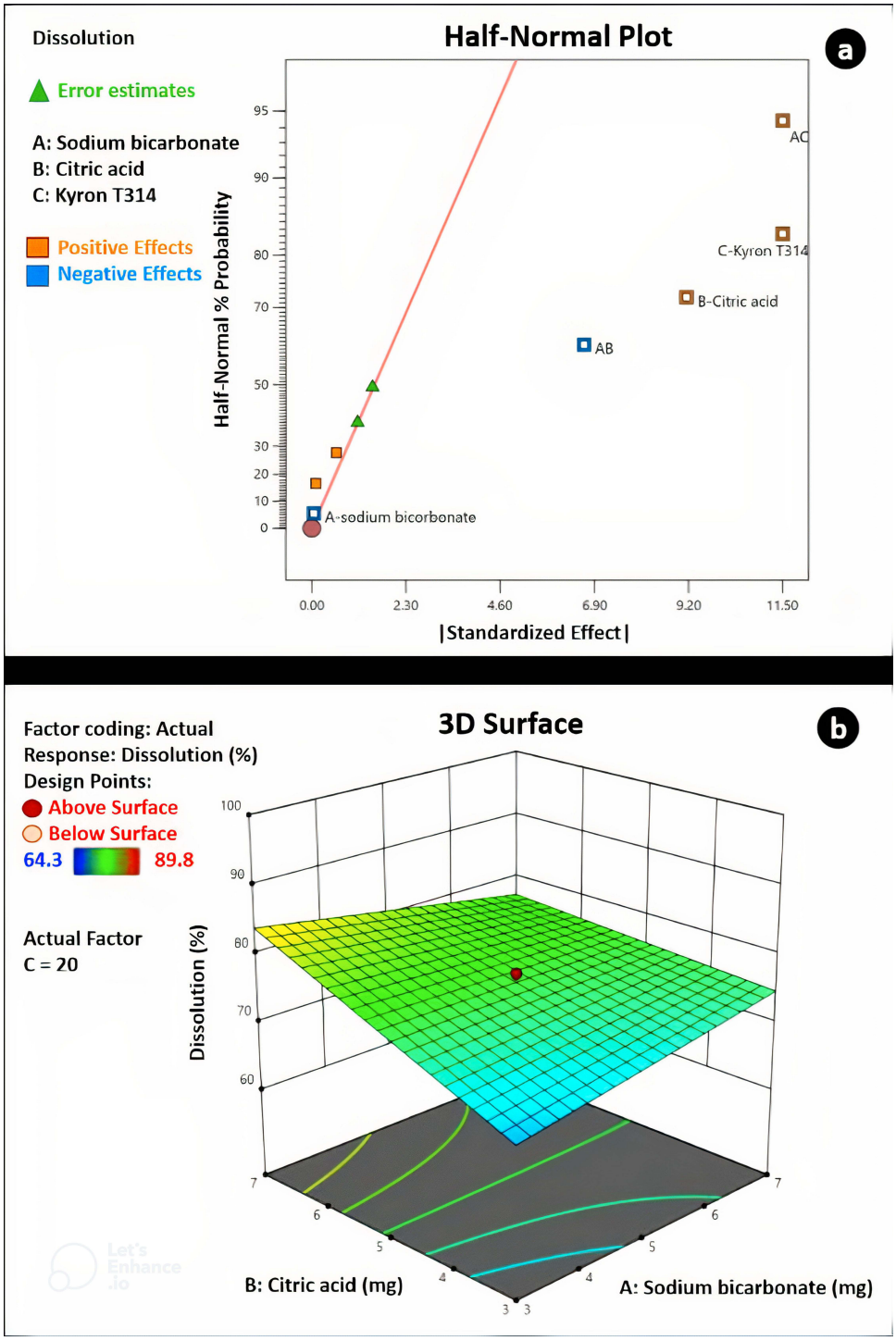

Figure 6 (**a**) Half normal plot of % dissolution, (**b**) response surface plot of % dissolution.

Optimization and Validation of the ODT Formulation

The optimized conditions for ODTs preparation within the specified range were determined via the developed regression model.[28–30] Among all the solutions recommended by the software, the one with the highest desirability was selected as the optimal solution for preparing the DX ODTs 30 mg formulation.[31] The optimized solutions selected for the preparation of ODTs with various amounts of factors A, B, and C were 7 mg, 3 mg, and 25 mg, respectively. The predicted values of the dissolution rate and DT were 86% and 56s, respectively. The confirmatory runs were performed in

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Table 3 ANOVA and Descriptive Statistics of Optimized DX ODT Dissolution

Source	SOS	DoF	MS	F-value	p-value
Model	784.9	5	156.98	21.84	0.0021
A	0.005	1	0.005	0.0007	0.98
B	165.45	1	165.45	23.3	0.0048
Polymer	264.5	1	264.5	36.8	0.0018
AB	88.45	1	88.45	12.31	0.0171
AC	264.5	1	264.5	36.8	0.0018
Residual	35.939	5	7.19		
Lack of Fit	16.55	3	5.52	0.569	0.6875
Pure error	19.39	2	9.69		
Cor total	82.83	10			
Descriptive Statistics					
Mean	75.99	Standard Deviation	2.68	% CV	3.53
R^2	0.9562	Adjusted R^2	9.124	Predicted R^2	0.8782

Abbreviations: SoS, sum of squares; DoF, degree of freedom; MS, mean square; A, sodium bicarbonate; B, citric acid; C, polymer.

triplicate. The observed values for dissolution and DT were 87.4% and 63s, respectively, which matched well with the predicted values, ie, within the 95% confidence intervals (Table 5). The optimized formulation is shown in Table 6.

Pre- and Post-compression Evaluation

Prior to compression, the optimized blend was evaluated for physical appearance,[32] loss on drying, bulk and tapped density, angle of repose, Carr's index, and Hausner's ratio.[33] The optimized formulation was compressed on a compression machine at 15 rpm and a compression force of 6 kN. After compression, the ODTs were evaluated for various characteristics, ie, weight variation, hardness, thickness, friability, disintegration time, dissolution, and assay (Table 7).

The disintegration time was fast, as expected, owing to the addition of an effervescent pair[34] and a polymer as a super disintegrant.[35,36] The polymer has potassium ionic functionality; it absorbs water and swells to weaken the intermolecular bond and entrance of water in the interparticle and intraparticle gaps, resulting in the breaking of tablets into fine particles.[37–39] The combination of an effervescent pair and a super disintegrant enhances the dispersion of the tablet in the saliva due to a synergistic effect and creates pressure inside the tablet to disperse, ultimately resulting in fast disintegration.

Dissolution studies of the ODTs and conventional formulations (DR) were carried out in phosphate buffer (pH 6.8),[40] as shown in Figure 8, as a result more than 80% of the drug released in 10 min compared with the steady release of the conventional formulation[41.] The addition of a superdisintegrant burst the tablet to assist in dissolution.[42]

Calibration Curves of Standard and Spiked Plasma

The calibration curves of the DX standard and spiked plasma were constructed in the concentration ranges of 0.5, 1, 2, 3, 4, and 5 µg/mL, as shown in Figure 9.

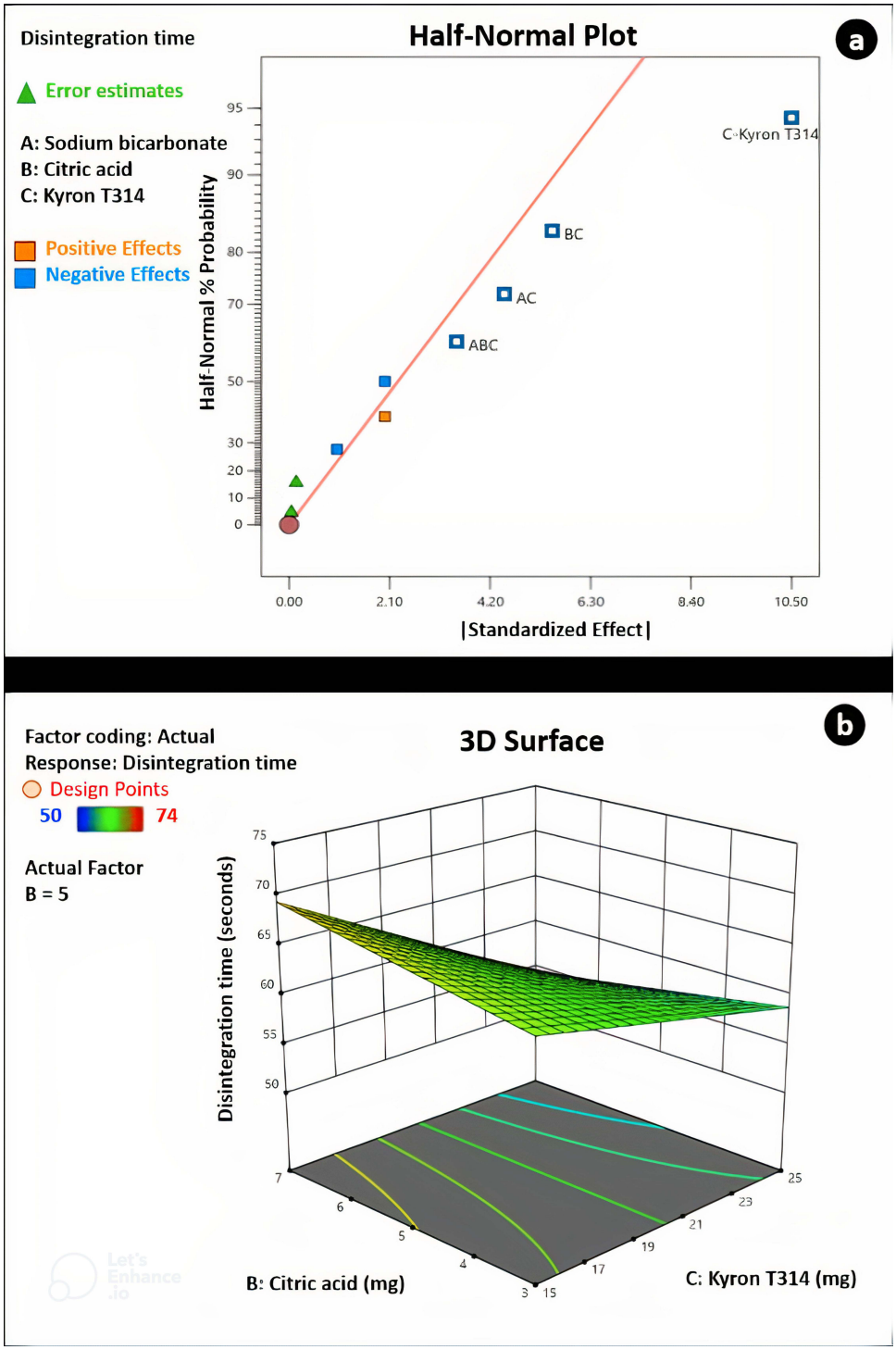

Figure 7 (**a**) Half normal plot of % D.T, (**b**) response surface plot of D.T.

Comparative in vivo Pharmacokinetic Study

The in vivo pharmacokinetic evaluation was performed via PK Solutions 2.0™ from Summit Research Services, Pharmacokinetics, and Metabolism Software CO 81401, USA, as shown in Table 8 and Figure 10.

The pharmacokinetic parameters were determined for the DX ODTs through HPLC analysis of the blood samples.[43] The DX ODTs disintegrated quickly, which resulted in a relatively high dissolution rate. The pH of the oral mucosa plays

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Table 4 ANOVA and Descriptive Statistics of Optimized DX ODT D.T

Source	SOS	DoF	MS	F-value	p-value
Model	346.00	4	86.50	15.43	0.0026
Polymer	220.50	1	220.50	39.33	0.0008
AC	40.50	1	40.50	7.22	0.0362
BC	60.50	1	60.50	10.79	0.0167
ABC	24.50	1	24.50	4.37	0.0815
Residual	33.64	6	5.16		
Lack of Fit	31.64	4	7.91	7.91	0.1154
Pure error	2.00	2	1.0000		
Cor total	379.64	10			
Descriptive Statistics					
Mean	61.82	Standard Deviation	2.37	% CV	3.83
R^2	0.9114	Adjusted R^2	0.8523	Predicted R^2	0.602

Abbreviations: SoS, sum of squares; DoF, degree of freedom; MS, mean square; A, sodium bicarbonate; B, citric acid; C, polymer.

Table 5 Confirmation of Two Variables Dissolution and Disintegration Time (95% Confidence)

Parameters	Predicted Mean	SD	N	SEP	95% Low	Mean	95% High
%Dissolution	86.2159	2.68082	3	2.74604	79.157	87.95	93.2748
Disintegration time	58.8182	2.36771	3	2.7626	53.2484	62.6667	64.388

Abbreviations: SD, standard deviation; SEP, standard error of prediction; N, number of experimental units.

Table 6 Optimized Formulation of Dexlansoprazole 30mg ODT

Ingredients	Weight/Table (mg)
Dexlansoprazole	30
Mannitol	250
Sodium Bicarbonate	70
Citric Acid	30
Magnesium Stearate	30
Lactose Spray Dried	30
Kyron T-314	25
Flavor Orange Powder	2.0

an important role in the partial absorption of DX from this site.[44] The relatively high bioavailability is linked to rapid disintegration and dissolution with increased absorption, as the in vivo results are correlated with the in vitro profile.[45]

The T_{max} (0.4 h) of DX indicated rapid absorption and fast onset of therapeutic effects,[46] whereas the higher C_{max} (0.83 μg/mL) resulted from increased absorption. The clearance of DX ODTs was measurably lower than that of

Table 7 Pre- and Post-Compression Results of DX ODT Formulation

Parameters	Mean ± SD
Physical Appearance	White powder
LoD %	2.11±0.058
Bulk Density(gm/mL)	0.51±0.02
Tapped Density (gm/mL)	0.60±0.046
Angle of Repose	23.63°±0.02
Carr's Index	15±0.58
Hausner's ratio	1.17±0.025
Weight variation (mg)	350±3.04
Hardness (kg/cm^2)	3.70±0.34
Thickness (mm)	12.0±0.04
Friability (%)	0.24±0.05
Disintegration time (seconds)	54.0±4.20
% Dissolution	96.31±0.06
Assay (%)	99.67±0.09

Abbreviations: LoD, loss on drying; SD, standard deviation.

conventional formulation, and the high Vd and low clearance resulted in high bioavailability. The addition of sodium bicarbonate to the formulation not only acts in effervescence but also plays a role in neutralizing the gastric pH,[47,48] which is also supported by the high MRT of ODT.[49.]

Stability Studies

The DX ODTs were packed in an Alu-Alu blister pack and kept in a Shjianheng stability chamber equipped with an online recorder at accelerated (40°C & 75% RH) and intermediate (30°C & 65% RH) storage conditions as per the ICH guidelines for Zone IV. The tablets were analyzed at intervals of one, three and six months,[50] and the data obtained are presented in Table 9.

The stability results clearly revealed that the optimized formulation is stable under both conditions and that all the parameters were well within this range.

Discussion

The ODT formulation was developed with a polymer that is a derivative of a cross-linked polymer of Polycarboxylic acids, as mentioned in USP/NF, and has the K+ ionic form. It is considered a superfast disintegrant as well as a dissolution modifier in tablet formulations. Owing to its high molecular weight, it does not absorb and is considered safe for use with no physiological action. The formulation was optimized through software, and the optimization focused on increasing the dissolution rate and decreasing the disintegration time. The addition of an effervescent pair added value to the disintegration time profile,[51] as evident from the results.

The pre- and post-compression data revealed that the powder blend has good flow from the hopper, as evident from Hausner's ratio (1.17), Carr's index (15), and the angle of repose (23.[63°]), which prevented any weight variation in the tablets during compression and resulted in quality tablets[52,] as evident from the weight variation results. The average

 https://doi.org/10.2147/DDDT.S515139

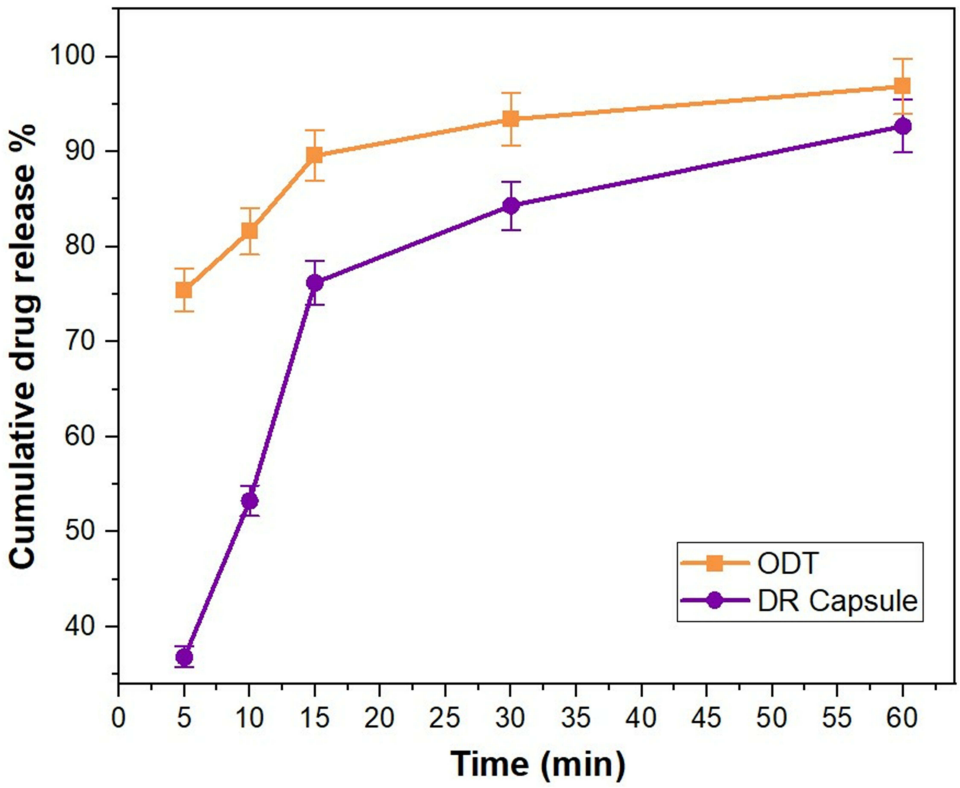

Figure 8 Drug release profile of ODT and commercial.

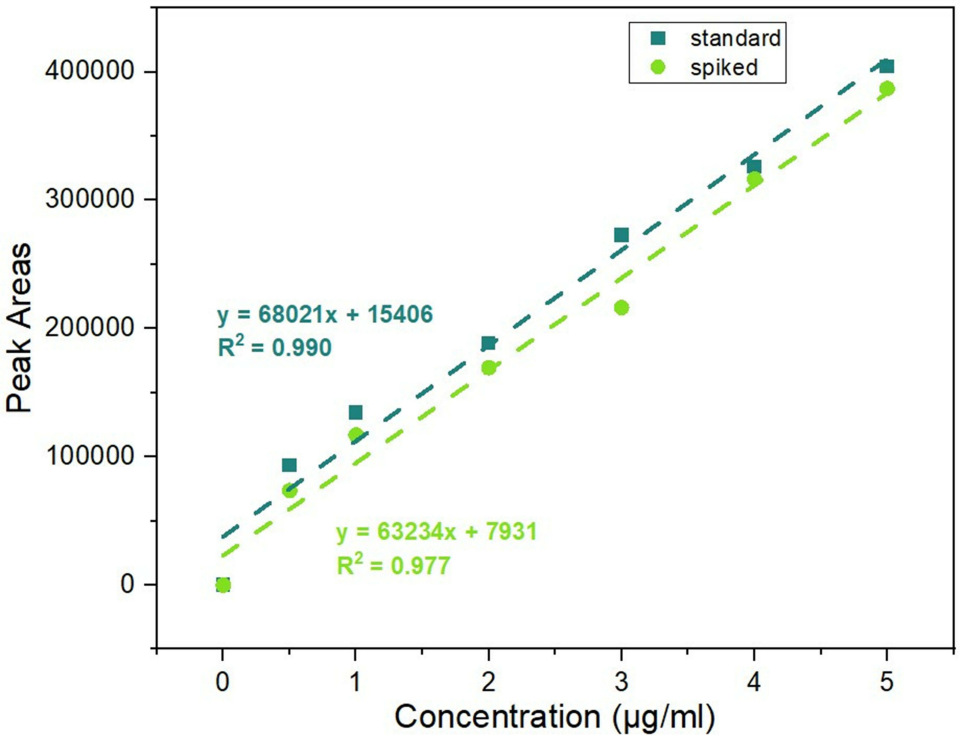

Figure 9 Calibration curve of standard and spiked plasma.

Table 8 Pharmacokinetic Results of ODTs and Commercial Formulations of DX

Pharmacokinetic parameters	ODT± SD	Commercial± SD	P-value
$T_{1/2}$ (h)	0.061±0.0014	1.757±0.0354	0.0156
C_{max} (µg/mL)	0.832±0.0073	0.659±0.0126	0.0092
T_{max} (h)	0.399±0.0065	5.124±0.0674	0.0164
$AUC_{(0-t)}$ (µg-h/mL)	3.186±0.0114	3.114±0.0192	0.0036
MRT (h)	7.799±0.0142	6.109±0.0241	0.0024
V/F (mg)/(µg/mL)	940.524±2.5341	463.668±3.945	0.0226
CL/F(mg)/(µg/mL)/h	121.967±0.511	160.164±1.487	0.0384

Abbreviations: C_{max}, concentration maximum; T_{max}, maximum time to reach C_{max}; AUC, area under the curve; MRT, mean residual time; V/F, volume of distribution; CL/F, plasma clearance; SD, standard deviation.

value of friability was also within the limits, ie, <1, demonstrating that the optimized formulation was robust enough to withstand handling and transportation, and no cracking/capping was observed in the tablet during compression.

As the formulation contains an effervescent pair, which is much more sensitive to moisture, the formulation and packaging process must be carried out at a controlled humidity <40% RH. The oral DT of the ODTs, as described in the methods section, was determined with healthy volunteers in triplicate, and the average result was 51 ± 3.9 s, whereas the time of 54 ± 4.20 s of disintegration in the basket assembly (USP apparatus) indicated that the ODTs had almost identical DT both in vivo and in vitro.

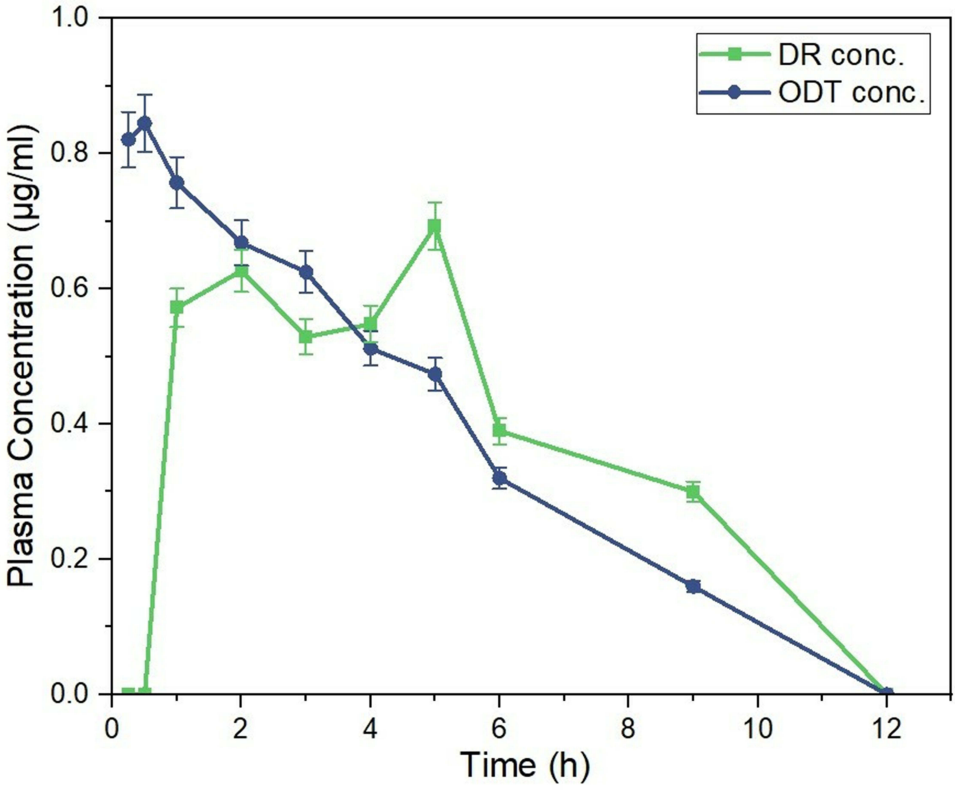

Figure 10 Concentration vs time curve of ODT and commercial formulations.

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Table 9 Results of Accelerated and Intermediate Stability Studies

Period	D.T (Water) Sec		D.T (Oral) Sec		Dissolution (NLT 75%)		Assay (90–100%)	
	Acc.	Int	Acc.	Int	Acc.	Int	Acc.	Int
Initial	48	54	63	61	97	99.5	99.5	98.5
After 1 month	51	49	59	60	96.8	98.3	98.7	97.6
After 3 months	50	47	65	63	96.8	98.1	97.6	96.8
After 6 months	56	46	55	59	96.4	97.8	97.6	96.3

Abbreviations: Acc, accelerated; Int, intermediate; D.T, disintegration time.

Dissolution studies in phosphate buffer (pH 6.8) revealed that more than 80% of the drug was released in 10 min, whereas the conventional formulations started a steady release as half of the drug was released comparatively. The dissolution profiles of the ODTs formulations revealed that the ODTs released the drug promptly. The fast release of was due to the swelling effect of the effervescent pair after contact with water, as it releases carbon dioxide to burst the tablet, while the addition of polymer assisted in the effervescence.

The interlinked effects observed in the pharmacokinetic parameters collectively contribute to its superior performance over conventional formulations. Rapid disintegration and dissolution lead to increased drug exposure to the oral mucosa, pharynx, and esophagus, facilitating enhanced absorption. This swift absorption, reflected by the significantly lower T_{max}, indicated expedited drug entry into the bloodstream. Consequently, the elevated C_{max} and Vd, alongside reduced clearance, ensures a more effective therapeutic response. Thus, each aspect, such as disintegration, absorption, T_{max}, C_{max}, Vd, and clearance, works in tandem to optimize the pharmacokinetic profile, culminating in improved clinical efficacy and patient outcomes.

The stability data indicate that the physical appearance, ie, color, shape, moisture content, assay, DT and dissolution results were within limits.

Limitations of the Study

The main limitation of the study is the duration of the stability study. In the present work, an accelerated stability study was conducted for the developed formulation as per the ICH guidelines. It is recommended that long-term real-time stability studies be conducted for the developed formulation of ODTs under specified storage conditions.

Conclusion

The prime objective of this study was the quality-by-design formulation development of orodispersible tablets of DX and its pharmacokinetic evaluation with the simplest method of direct compression to shorten the onset of action time of the drug and provide quick relief to the patient. Furthermore, as there are many manufacturing steps involved along with high cost to prepare conventional formulations, the direct compression method is less costly, with few manufacturing steps. The in vitro evaluation of ODTs demonstrated their effectiveness in terms of dissolution and disintegration.

The pharmacokinetic evaluation revealed that the shortest T_{max} (0.4 h) of the ODTs occurred because the commercial formulations have to pass the stomach intact and then disintegrate in the alkaline medium to deliver its contents for absorption. This was one of the objectives of this study to minimize $T_{max,}$ which results in the quick appearance of the drug in plasma, as evident from the pharmacokinetic data. The plasma concentration revealed that because of an increase in absorption, it has a higher C_{max} (0.83 μg/mL) than conventional materials do (0.65 μg/mL).

A study of the stability of the optimized formulations under accelerated and intermediate conditions for six months proved that the formulation is stable and has the ability to withstand environmental conditions.

Data Sharing Statement

The data are contained within the article.

Ethical Approval and Informed Consent

The study was approved by the Department of Pharmacy University of Peshawar ethical committee (501/EC-FLES-UOP /2022). Investigations were carried out following the rules of the Declaration of Helsinki of 1975. Informed consent was obtained via a consent form from each individual and briefed about the study.

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Disclosure

The authors have no relevant financial or nonfinancial interests to disclose.

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