Journal of Research in Pharmacy

Research Article

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The effect of different granulation amounts of kollicoat MAE 30DP® on ODT CQAs using risk assessment

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Received: 4 December 2025 / Revised: 21 April 2026 / Accepted: 6 May 2026

ABSTRACT: Orally disintegrating tablets (ODTs) improve patient compliance, but they present challenges in terms of masking the bitter taste of active pharmaceutical ingredients such as dexketoprofen trometamol (DEX). The study aimed to develop palatable DEX ODTs by granulating drug with Kollicoat MAE 30DP® to create a physical barrier. Using a quality by design (QbD) approach, an initial risk assessment identified Prosolv® ODT G2, Emdex®, and Magnasweet® MM100 and tablet compression pressure as critical variables. A Box-Behnken design was employed to prepare 26 formulations, systematically evaluating the impact of these variables across low and high polymer concentrations. The results showed that although high concentrations of Kollicoat MAE 30DP initially delayed the dissolution rate, this barrier effect did not affect the final extent of drug release. Disintegration was predominantly governed by compression pressure, which altered tablet porosity, whereas PROSOLV® ODT G2 significantly influenced the overall dissolution profile. By optimizing the superdisintegrant-to-binder ratio, high-polymer formulations successfully overcame the initial retardation, consistently exceeding an 85% cumulative release at 30 minutes.

KEYWORDS: Orally Disintegrating Tablet; Dexketoprofen Trometamol; Quality by Design Box-Behnken Design; Minitab; Granulation.

1. INTRODUCTION

Oral administration is consistently regarded as the most desirable administration route for drug delivery, despite the extensive developments achieved in alternative drug delivery systems. Oral administration remains the preferred delivery option due to high patient compliance and safety [1]. Consequently, solid oral dosage forms, particularly conventional tablets and capsules, represent the most widely utilized formulations [2]. However, a significant clinical challenge arises from the fact that paediatric, geriatric, physical impaired, and bedridden patients usually have difficulty swallowing, making the administration of these solid dosage forms with water highly problematic [3].

In recent years, numerous researchers and pharmaceutical companies have dedicated considerable resources to developing this therapeutic approach. Unlike traditional conventional tablets that must be swallowed whole, orally disintegrating tablets (ODTs) are specifically design to dissolve or disperse rapidly in the oral cavity upon contact with saliva. Consequently, this rapid disintegration process can lead to enhanced bioavailability by significantly improving cumulative drug release [4,5]. ODTs can be manufactured using a variety of methods, including freeze drying, molding, spray drying, direct compression (DC), cotton candy technology, and phase transition [6]. Among these, the DC method is considered the most straightforward and cost-effective approach. Because it typically requires no modification to conventional tabletting machinery, DC has emerged as the most widely adopted technique for ODT manufacturing on an industrial scale [7]. According to Food and Drug Administration (FDA) guidelines, ODTs are classified as relatively distinct tablets, clearly differentiated from traditional chewable or swallowed tablets. They are specifically designed to exhibit a disintegration time of 30 seconds or less under *in vitro* test conditions. Moreover, the FDA specifies key characteristics of ODT formulations, such as low tablet weight, small tablet size, and rapid disintegration [8].

The unpleasant taste of drugs is a critical issue in designing ODTs, which dissolve directly on the taste buds [9]. Therefore, the taste-masking is a mandatory approach for ODTs to mitigate unpalatable

How to cite this article: Pirincci Tok Y, Demiralp B., Al-Mohaya M., Ozsoy Y. The effect of different granulation amounts of kollicoat MAE 30DP® on ODT CQAs using risk assessment . J Res Pharm. 2026; 30(3): 957-974.

ISSN: 2630-6344

https://doi.org/10.12991/jrespharm.1835939

characteristics, such as bitterness and gritty mouthfeel [6]. Generally, taste masking strategies are classified into three main categories: changing taste perception via sugar-based excipients, forming a physical barrier, and altering drug solubility. Several approaches have been developed to mask the taste of pharmaceutical products, including the use of flavours and sweeteners, coating or granulation with hydrophilic vehicles, hot-melt granulation, inclusion complexation, and ion-exchange resin. Process like coating, granulation, and encapsulation effectively create a physical barrier between unpalatable drug and taste receptors in the oral cavity [10-12]. These approaches are often preferred as they can be easily incorporated into ODT manufacturing [13].

Considerable research efforts have recently been directed towards developing effective taste-masking strategies, especially for unpalatable drug molecules such as macrolide antibiotics, non-steroidal anti-inflammatory drugs (NSAID), analgesics, penicillins, antipsychotics, antihistamines, and chemotherapeutics [14]. Ketoprofen, a propionic acid derivative, is a widely prescribed NSAID with potent analgesic and antipyretic effects [15]. It exists naturally as a racemic mixture of S (+) and R (-) enantiomers. However, its pharmacological activity, specifically the inhibition of prostaglandin synthesis, is primarily attributed to the S (+) enantiomers, known as dexketoprofen[16]. Dexketoprofen trometamol (DEX) was improved as a water-soluble salt to improve its dissolution rate. While DEX is classified as Class I compound of the Biopharmaceutical Classification System, its intensely bitter and unpleasant taste necessitates effective taste masking for oral delivery [17].

Kollicoat® MAE 30DP is an anionic polymer [18] that functions primarily as an enteric coating agent while also offering pore-forming, taste-masking, film-forming capabilities for various dosage forms. It is known by several compendial names, such as Methacrylic Acid - Ethyl Acrylate Copolymer (1:1) Dispersion 30% (European Pharmacopoeia (Ph. Eu.)), Methacrylic Acid and Ethyl Acrylate Copolymer Dispersion (United States Pharmacopeia (USP)), and Methacrylic Acid Copolymer LD (Japanese Pharmaceutical Excipients). Because it dissolves at a pH above 5.5 it enables effective enteric protection and pH-responsive, targeted drug delivery in lower gastrointestinal tract [19]. In addition, Eudragit L100 – 55, which is also based on methacrylic acid and ethyl acrylate, is used for similar purposes, including taste masking [20] and enteric coating [21]. For example, Maniruzzaman et al. have implemented the hot melt extrusion process to propranolol HCI using Eudragit L 100 - 55 specifically for taste masking purpose [20].

The Quality by Design (QbD) approach systematically begins with establishing the Quality Target Product Profile (QTPP). The QTPP serves as a prospective summary of the essential quality characteristics of a drug product that must be achieved to ensure both safety and efficacy, ultimately forming the basis of the product's label[22]. According to the International Conference on Harmonisation Q8, risk assessment is a fundamental science-based process within quality risk management. It is employed to evaluate and identify which material attributes and process parameters potentially have an effect on critical quality attributes (CQAs) of product [23]. In order to systematically investigate these complex relationships, a Box-Behnken design was implemented. This is a widely recognised response surface methodology and was used as a second-order experimental design to mathematically model the interactions between independent variables [24].

The primary objective of the present study was to develop taste-masked formulation of DEX by preparing granules with Kollicoat® MAE 30DP. This polymer serves as a physical barrier against the bitter taste without compromising the rapid disintegration of the formulation. Furthermore, employing a QbD approach, the study systematically investigated the impact of various formulation and process variables on the CQAs of the product, specifically focusing on tablet friability, breaking strength, disintegration time, and the dissolution profile of the taste-masked DEX.

2. RESULTS

2.1. Identify the QTPP and risk assessment

Based on FDA (2008) guidelines for the characteristics of prepared ODT, the QTPP of ODTs has been defined as disintegration times <30 s, tablet weight <500 mg [8], tablet friability <1%, highly robust to withstand packaging, and maximum drug release in exact time [25].

A risk assessment of the formulation variables was performed to evaluate the influence of each variable on drug product CQAs. The result of the risk assessment and the justification were provided as a summary table, as shown in Tables S1 and S2. The high risk required further investigation; the risk was unacceptable.

The medium risk can be needed further investigation to reduce the risk. The low risk required no further investigation; the risk was acceptable.

2.2. Characterization of granules

2.2.1. Granule Morphology and Loss on Drying

Low concentration Kollicoat® MAE 30DP granules were viewed under a digital microscope, as shown in Figure 1. The granules tend to be spherical-like in shape with a rough surface. In addition, the moisture content of dried granules was below 2.5% w/w.

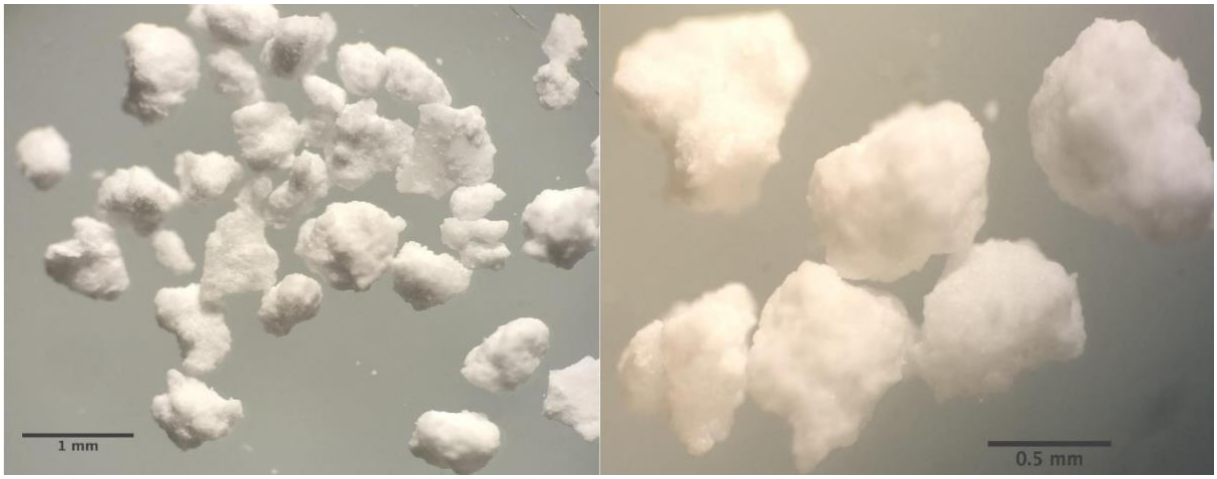


Figure 1. An optical microscope image of low concentration Kollicoat MAE 30DP granules at different magnifications (left: (ImageJ-calibrated scale bar = 1 mm; right: ImageJ-calibrated scale bar = 0.5 mm).

2.2. Characterization of Taste Masked DEX ODTs

2.2.1. Tablet Friability

The weight loss percentage should be less than 1% in order to comply with the USP friability test method principles [26]. The friability test confirmed the robustness of the prepared tablets, which showed no cracking or splitting after tumbling [27]. In addition, all formulations lie within the accepted range (less than 1%), except for one formulation (5.17% for F13), as shown in Figure 2.

The excellent mechanical resistance is consistent with the findings of previous studies on co-processed excipients. For instance, Tranova et al. [28] reported that formulations containing Prosolv® ODT G2 exhibit superior tablet robustness and significantly lower friability than simple physical mixtures, due to enhanced inter-particulate bonding.

2.2.2. Tablet Breaking Strength

A critical attribute of a well-formulated of tablet batch is the capacity to exhibit sufficient mechanical strength, thus ensuring resistance to abrasion, cracking, and fracture during the manufacturing, packaging, transportation, and storage processes. Meanwhile, the batch should also possess the ability to disintegrate within the predetermined time period [29]. Figure S4 illustrates the average measurements of breaking strength measurements. The breaking strength values obtained are consistent with those in the literature, which states that the addition of microcrystalline cellulose (MCC)-based excipients (Prosolv® ODT G2) and dextrates (Emdex®) provides DC matrices with optimal compressibility [30].

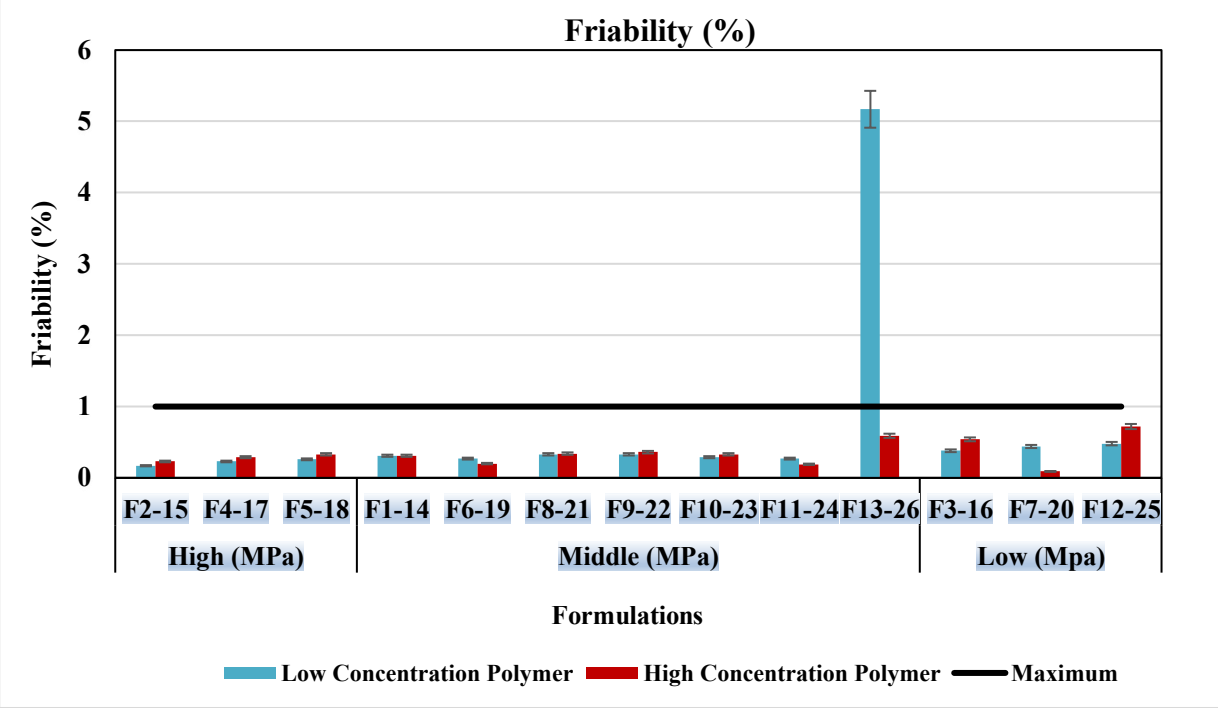


Figure 2. Friability (%) of the granulated DEX ODT formulations (mean ± SD, n=20).

2.2.3. Tablet Disintegration Time

Figure 3 illustrates the disintegration time for all investigated taste-masked ODT formulations. Formulations compressed at lower pressures (Low MPa group) exhibited rapid disintegration, predominantly well within the pharmacopeial limits (< 180 s), regardless of the Kollicoat MAE 30DP concentration. Conversely, elevated compression pressures (High MPa group) resulted in drastically prolonged disintegration times, peaking at nearly 800 seconds (e.g., formulation F4). Moreover, the effects of two different concentrations of the granulation agent (Kollicoat® MAE 30DP at 15.16 and 17.34%), as well as Prosolv® ODT G2, Emdex®, and tablet compression pressure, on tablet disintegration time can be observed. Tablets subjected to a moderate compression force (3.44 MPa) generally exhibited prolonged *in vitro* disintegration times, particularly those containing higher polymer concentrations. Mechanistically, this phenomenon can be attributed to the formation of dense, hydrophobic polymethacrylate-based polymer networks that act as a physical barrier, significantly delaying liquid penetration into the tablet core [31]. However, further analysis of the disintegration profiles reveals a complex interaction regarding this polymer concentration. While elevated polymer levels notably delayed disintegration in specific middle-pressure formulations (e.g., F21, F22, and F23), the magnitude of this barrier effect was highly variable and strongly dependent on the specific combination of surrounding excipients."

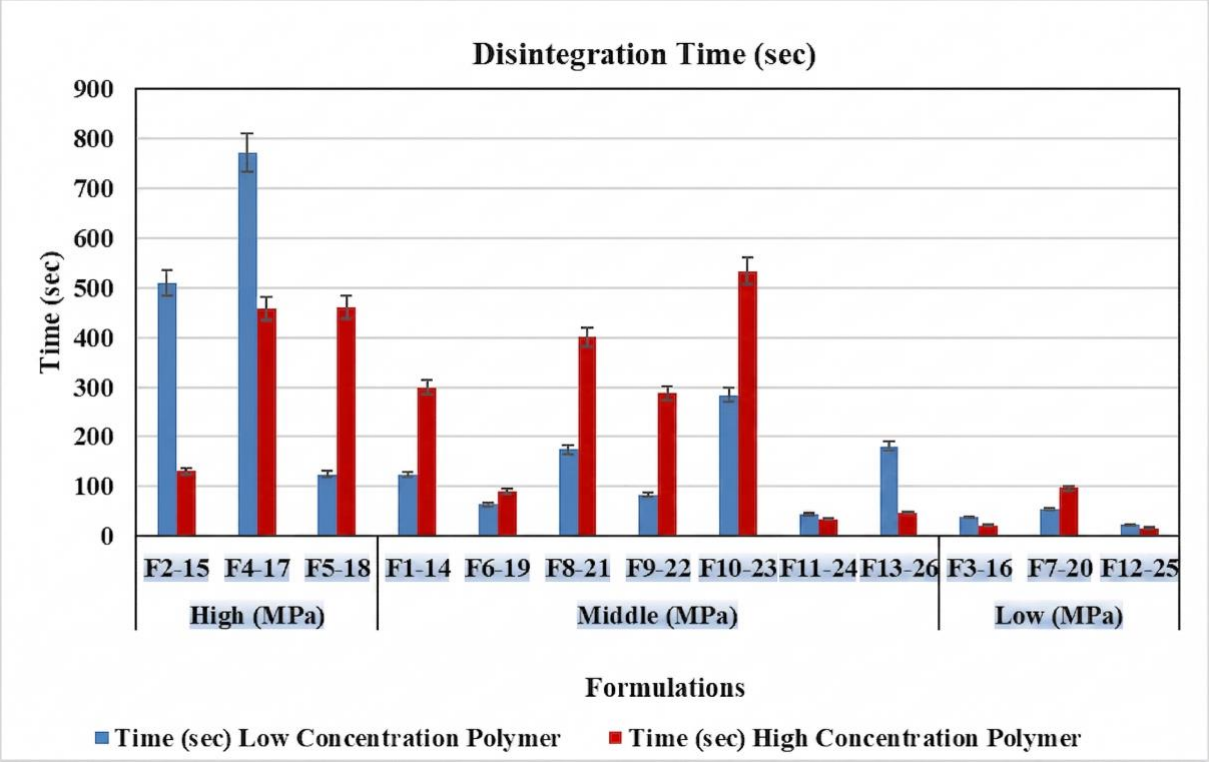


Figure 3. *In vitro* disintegration times (seconds) for granulated DEX ODTs (mean ±SD, n=3).

2.2.4. Dissolution Studies

Figure 4 (a and b) presents the dissolution profiles of the ODT formulations containing both low and high concentrations of taste-masking polymer, respectively. After 30 minutes, formulations F5 and F18 formulations achieved the highest cumulative drug release (101.49 and 99.70%), respectively. For F5, this rapid drug release can largely be attributed to the low concentration of Kollicoat MAE 30DP combined with an optimal ratio of excipients. Interestingly, F18 achieved a similarly extensive release despite its high polymer concentration (17.34%), demonstrating that an optimized superdisintegrant matrix can successfully overcome the retarding effect of a thicker hydrophobic coating [32]. However, formulations F13 and F16 formulations exhibited the lowest dissolution rate (47.04 and 73.41%, respectively). Formulation F13 contained the lowest amount of the superdisintegrant-rich matrix (Prosolv® ODT G2, = 150 mg) and the highest amount of the binder/diluent (Emdex®, = 200 mg), leading to inadequate water penetration. In a similar manner, F16 had the highest amount of Emdex® within the high-concentration polymer group (17.34%). These observations comply with the existing literature, which highlights those elevated concentrations of taste-masking polymers, in conjunction with a decreased superdisintegrant-to-binder ratio, may establish a more substantial physical barrier. This, in turn, may lead to a reduction in the dissolution rate [32, 33].

The validation parameters of the spectroscopy method presented an excellent linearity with a coefficient of determination (R^2) > 0.9997 as in the concentration range of 2.8 µg.mL^{-1} and 33.6 µg.mL^{-1}. In addition, limit of detection and limit of quantification values were 0.386 µg.mL^{-1} and 1.171 µg.mL^{-1}, respectively.

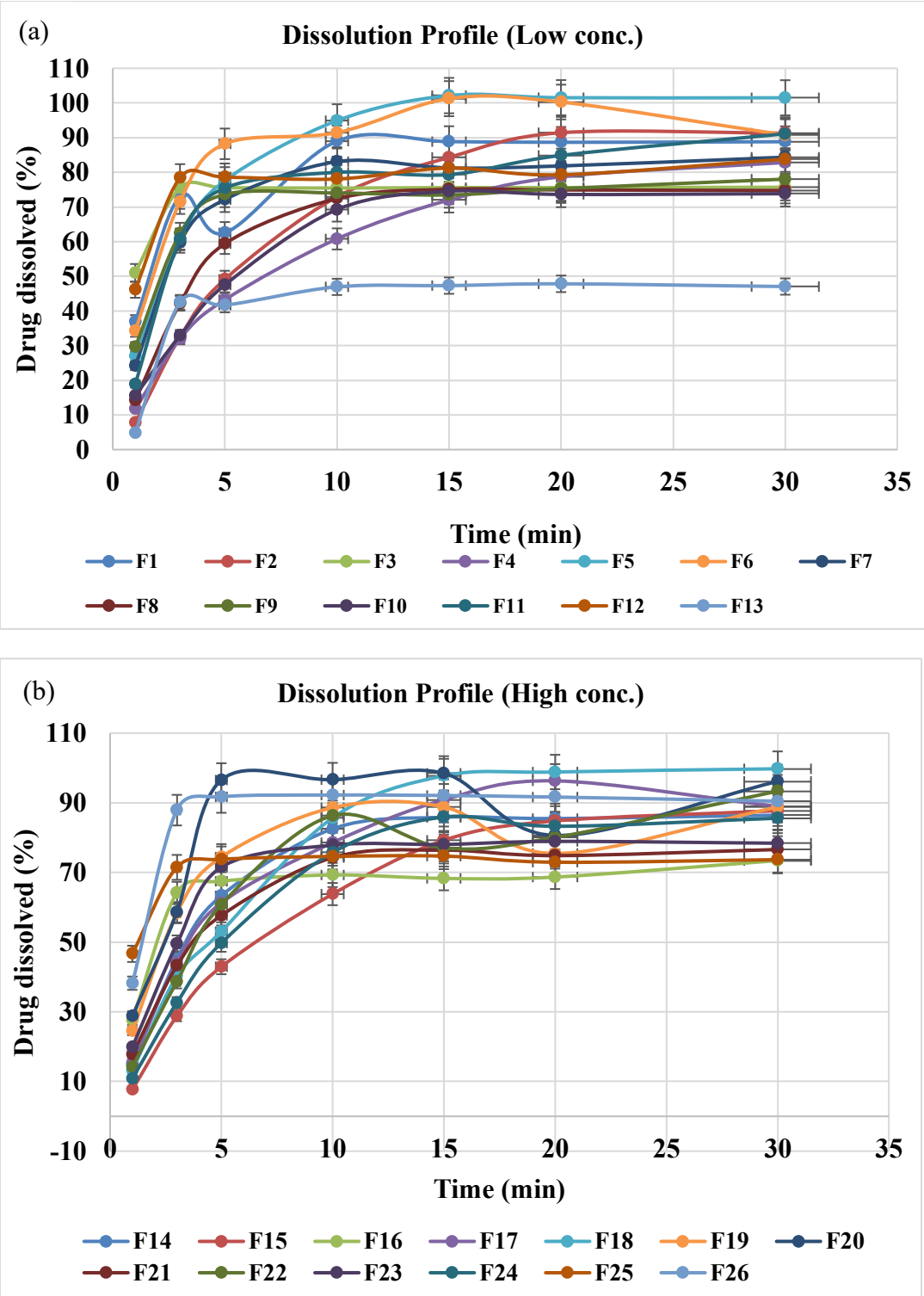


Figure 4. The dissolution profiles of ODT formulations (a) low concentration polymer; (b) high concentration polymer (mean ± SD, n=3).

3. DISCUSSION

3.1. Preparations of DEX ODTs

Prosolv® ODT G2 and Emdex® were specifically chosen for DC to prepare DEX ODTs. Excipients that possess desired physicochemical properties can generally present good flowability and compressibility in DC. These excipients also offer high stability and low friability, thus enabling the formulation to rapidly and

completely release the active pharmaceutical ingredient [34]. The multifunctionality excipient Prosolv® ODT G2 consists of MCC, colloidal silicon dioxide, mannitol, fructose, and crospovidone. Prosolv® ODT G2 has been demonstrated to offer a number of advantages and is employed in the development of ODTs [35]. Emdex® is composed of 95% glucose monohydrate and dextrates, provides several functions (binder and filler), and enhances several properties (flowability, compaction, and tablet strength) in DC applications [36]. The presence of both excipients contributes to the attainment of a pleasant, sweet taste and a cool mouth feel [37].

The high solubility of mannitol is critical for ensuring a palatable mouth feel for ODTs. Furthermore, the presence of polyol groups contributes to the mouth feel characterised by a creamy texture, sweet taste, and a cooling effect. These measures have been demonstrated to enhance patient compliance with regard to ODTs [34]. Moreover, it has an essential feature of lower hygroscopicity than other sugars and sugar alcohols [38].

MCC is one of the best binders, which offers high compressibility at a low tablet compression pressure in the DC method; furthermore, it undergoes plastic deformation under the employed compression pressure [29].

Crospovidone exhibits certain behaviors during the disintegration of tablets, such as swelling, wicking action and secondary swelling. Consequently, swelling without gelling is useful for developing ODTs as gelling can retard tablet dissolution of the tablets. Crospovidone absorbs water through capillary action, restoring its natural structure, and releasing energy, which has the potential to disintegrate the tablet [39, 40]. Magnesium stearate (Parteck® LUB MST) was added for direct compression to reduce tablet-die wall friction, prevent punch sticking during tableting and acquire further flowability [41,42].

3.2. Characterization of granules

3.2.1. Granule Morphology and Loss on Drying

The spherical-like morphology with a rough surface suggests that the drug granulated with Kollicoat MAE 30DP polymer. Previous studies have reported that being a spherical particle shape can enhance flowability [40] and improve mixing performance [43]. Moreover, no issues such as sticking or poor flowability were observed during tablet compression, indicating that the moisture content was within an acceptable range [44].

The selection of Kollicoat MAE 30DP as the coating polymer was also driven by its functional properties. As an enteric polymer with a pH-dependent solubility profile, it dissolves at pH ≥ 6.8, while remaining intact under oral cavity conditions (pH 6.7–7.4). This characteristic limits drug–taste receptor interaction during the brief residence time in the mouth, thereby providing effective taste masking for the bitter drug, as evidenced by its registered patent [45]. To the best of our knowledge, this polymer has not been previously employed in ODT formulations; however, the use of pH-dependent polymers as taste-masking agents in ODTs is well documented in the literature, with Eudragit® E-based coatings being the most widely studied examples [46, 47, 48].

3.3. Characterization of Taste Masked DEX ODTs

Within the framework of QbD, a systematic experimental design was applied to identify the critical formulation and process parameters influencing the quality attributes of the ODTs. In this study, a Box–Behnken response surface design was employed because it allows the evaluation of main effects, interaction effects, and quadratic relationships between variables with a reduced number of experimental runs compared with full factorial designs [49]. The independent variables included the amount of Prosolv® ODT G2 (X_1), Emdex® (X_2), and tablet compression pressure (X_3), while the responses evaluated were friability, breaking strength, disintegration time, and dissolution performance, which represent CQAs of ODTs.

To interpret the statistical significance of the investigated factors, pareto charts were generated for each response variable. Pareto analysis ranks the magnitude of standardized effects and highlights statistically significant parameters influencing tablet performance. Factors crossing the significance threshold line are considered critical parameters affecting the response. This approach enables identification of the most influential formulation variables and supports optimization of ODT formulations according to QbD principles.

3.3.1. Tablet Friability

The Pareto chart analysis demonstrated that none of the investigated variables – Prosolv® ODT G2, Emdex®, or tablet compression pressure – significantly influenced tablet friability in formulations containing a low concentration of Kollicoat MAE 30DP. In contrast, for formulations containing a high concentration of Kollicoat MAE 30DP, several factors showed measurable effects on friability as presented in Figure 5. Specifically, the main effect of Prosolv® ODT G2 (A) and the two-way interaction between Emdex® and compression pressure (referred to as BC) exhibited a negative influence on the response, indicating a desirable reduction in tablet friability. Conversely, the main effect of Emdex® (B) and the two-way interaction between Prosolv® ODT G2 and compression pressure (AC) showed a positive influence, suggesting an increase in friability under certain conditions.

As illustrated in Figure S1, increasing the quantity of Prosolv® ODT G2 from 150 mg to 250 mg resulted in a notable reduction in tablet friability. These results are in strong agreement with the findings of Tranova et al. [28], who demonstrated that formulations incorporating Prosolv® ODT G2 exhibited the lowest friability and the highest tensile strength. However, the percentage of friability was increased within the range of 160 – 200 mg of Emdex®, which can be explained by its porous and physical structure. Thus, a high amount of porous particles has the capacity to increase the porosity of the ODT matrix, thereby increasing the friability value. Pabari and Ramtoola have elucidated that the friability value is associated with the tablet porosity. The tablets with high porosity showed high levels of friability, while those with low porosit exhibited low friability [50].

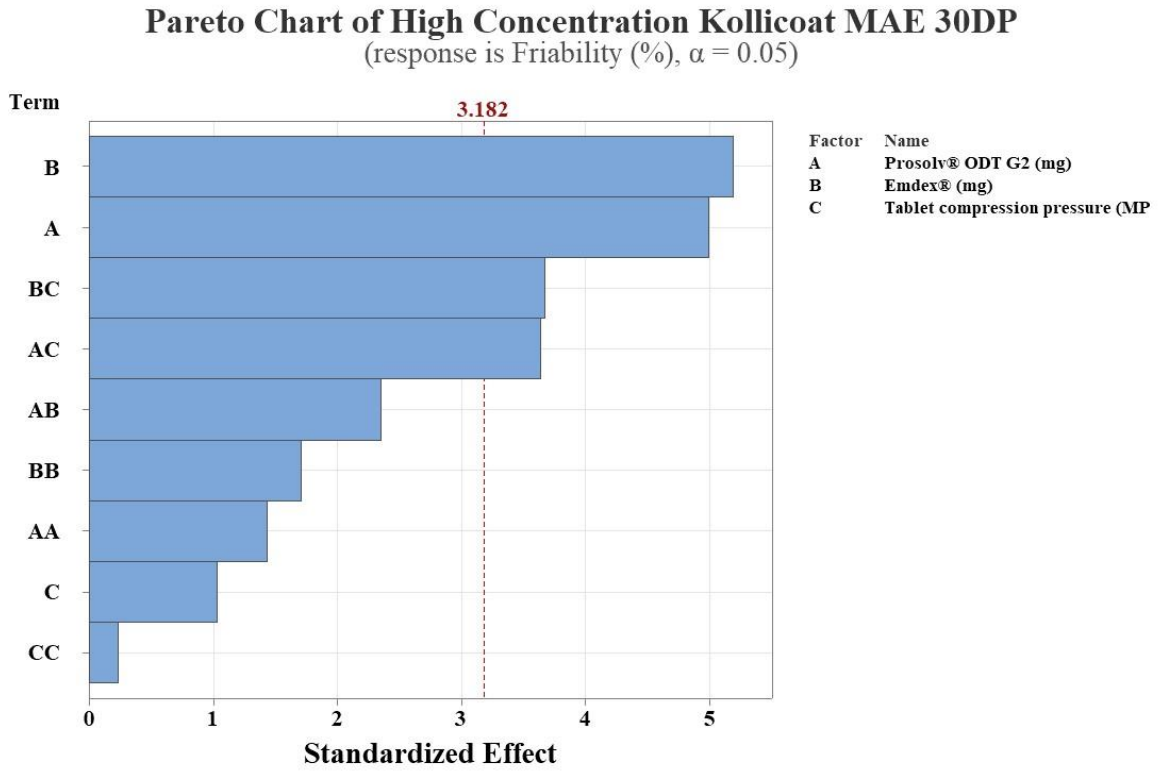


Figure 5. Pareto chart of friability for formulations with high concentration Kollicoat MAE 30DP.

3.3.2. Tablet Breaking Strength

As demonstrated in Figure S2, the breaking strength values of the formulations with low concentration Kollicoat MAE 30DP ranged from 45 to 178 N, whereas the high concentration Kollicoat MAE 30DP formulations ranged from 48 to 187 N. It has been observed that an increase in tablet compression pressure resulted in an increase in the breaking strength value in all the formulations.

Furthermore, as illustrated in Figure 6 (a), tablet compression pressure exerted a positive impact on tablet breaking strength with low concentration Kollicoat MAE 30DP formulations. With regard to the high concentration Kollicoat MAE 30DP formulations, breaking strength was positively impacted by tablet compression pressure, Prosolv® ODT G2, as illustrated in Figure 6 (b) and Figure S3. The production of tablets with high breaking strength is facilitated by the incorporation of MCC [28], which contributes to optimal tabletability through its plastic deformation behaviour [51]. The obtained breaking strength values are consistent with those reported in the literature, which demonstrates that the incorporation of microcrystalline cellulose-based excipients (Prosolv® ODT G2) and dextrates (Emdex®) optimises the compressibility of direct compression matrices [52].

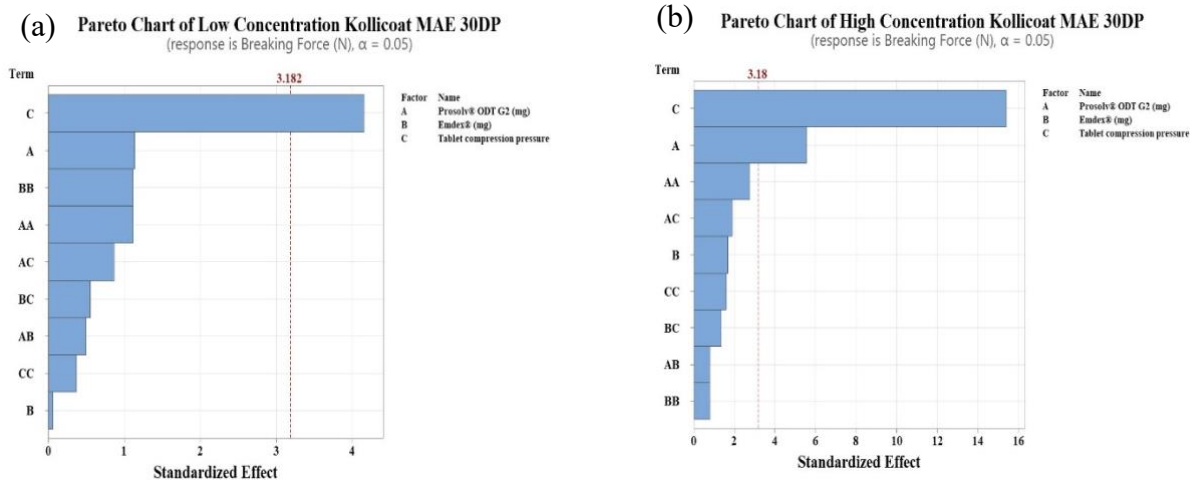


Figure 6. Pareto charts of breaking strength for formulations containing (a) low concentration Kollicoat MAE 30DP; (b) high concentration Kollicoat MAE 30DP.

3.3.3. Tablet Disintegration Time

Figure 3 illustrates the comparative disintegration times of formulations containing low and high concentrations of Kollicoat MAE 30DP across varying compression pressures (see Table 1 and Table 2).-The data clearly demonstrates that compression pressure is the dominant variable; formulations in the 'Low (MPa)' group consistently achieved rapid disintegration (generally < 100 s), while those in the 'High (MPa)' group experienced significant delays, extending up to approximately 800 seconds. The increase in tablet compression pressure led to a decrease in tablet porosity. Hence, the absorption of water into the tablet core is restricted, and the wetting time is extended [7, 53]. The influence of the polymer concentration itself proved to be formulation-dependent. This non-linear behaviour strongly highlights the importance of optimizing the superdisintegrant-to-binder ratio via the QbD approach to counteract the retardation effect of the taste-masking polymer.

Table 1. The quantitative composition and compression pressure of DEX ODT formulations.

Formulations	Granulated DEX (mg)	Prosolv® ODT G2 (mg, X_1)	Emdex® (mg, X_2)	Parteck® LUB (mg)	Magnasweet® MM100 (%)	Tablet Compression Pressure (MPa, X_3)
The formulations with low concentration (15.16% Kollicoat MAE 30DP) taste masking polymer.						
F1	29.5	200	150	2.5	0.24	3.44
F2	29.5	200	100	2.5	0.02	5.17
F3	29.5	200	200	2.5	0.02	1.72
F4	29.5	200	200	2.5	0.13	5.17
F5	29.5	150	150	2.5	0.13	5.17
F6	29.5	250	200	2.5	0.13	3.44
F7	29.5	200	100	2.5	0.13	1.72
F8	29.5	200	150	2.5	0.13	3.44
F9	29.5	200	150	2.5	0.13	3.44
F10	29.5	150	100	2.5	0.13	3.44
F11	29.5	250	100	2.5	0.24	3.44

F12	29.5	150	150	2.5	0.24	1.72
F13	29.5	150	200	2.5	0.02	3.44

Table 2. The quantitative composition and compression pressure of DEX ODT formulations.

Formulations	Granulated DEX (mg)	Prosolv® ODT G2 (mg, X1)	Emdex® (mg, X2)	Parteck® LUB (mg)	Magnasweet ® MM100 (%)	Tablet Compression Pressure (MPa, X3)
The formulations with high concentration (17.34% Kollicoat MAE 30DP) taste masking polymer.						
F14	30.0	200	150	2.5	0.24	3.44
F15	30.0	200	100	2.5	0.13	5.17
F16	30.0	200	200	2.5	0.13	1.72
F17	30.0	200	200	2.5	0.13	5.17
F18	30.0	150	150	2.5	0.24	5.17
F19	30.0	250	200	2.5	0.13	3.44
F20	30.0	200	100	2.5	0.24	1.72
F21	30.0	200	150	2.5	0.02	3.44
F22	30.0	200	150	2.5	0.13	3.44
F23	30.0	150	100	2.5	0.13	3.44
F24	30.0	250	100	2.5	0.13	3.44
F25	30.0	150	150	2.5	0.02	1.72
F26	30.0	150	200	2.5	0.24	3.44

In addition, coefficient results (Figure 7) indicated that, in formulation with low concentration Kollicoat MAE 30DP, disintegration time was positively affected by tablet compression pressure,the squared term of Emdex (BB) and the two-way interaction between Prosolv® ODT G2 and tablet compression pressure (AC). In contrast, the squared term of Prosolv® ODT G2 (AA) showed a negative effect on disintegration time. The research study by Martino et al. also reported that disintegration time increased mainly with increasing tablet compression pressure [54].

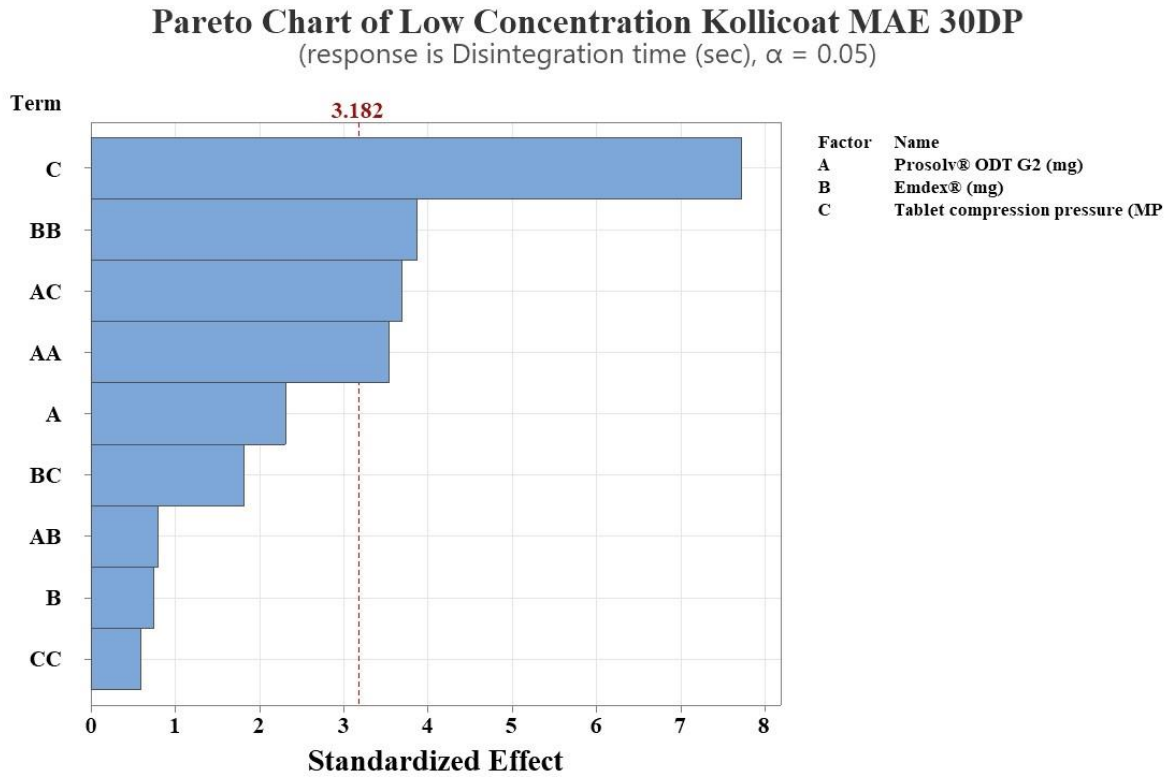
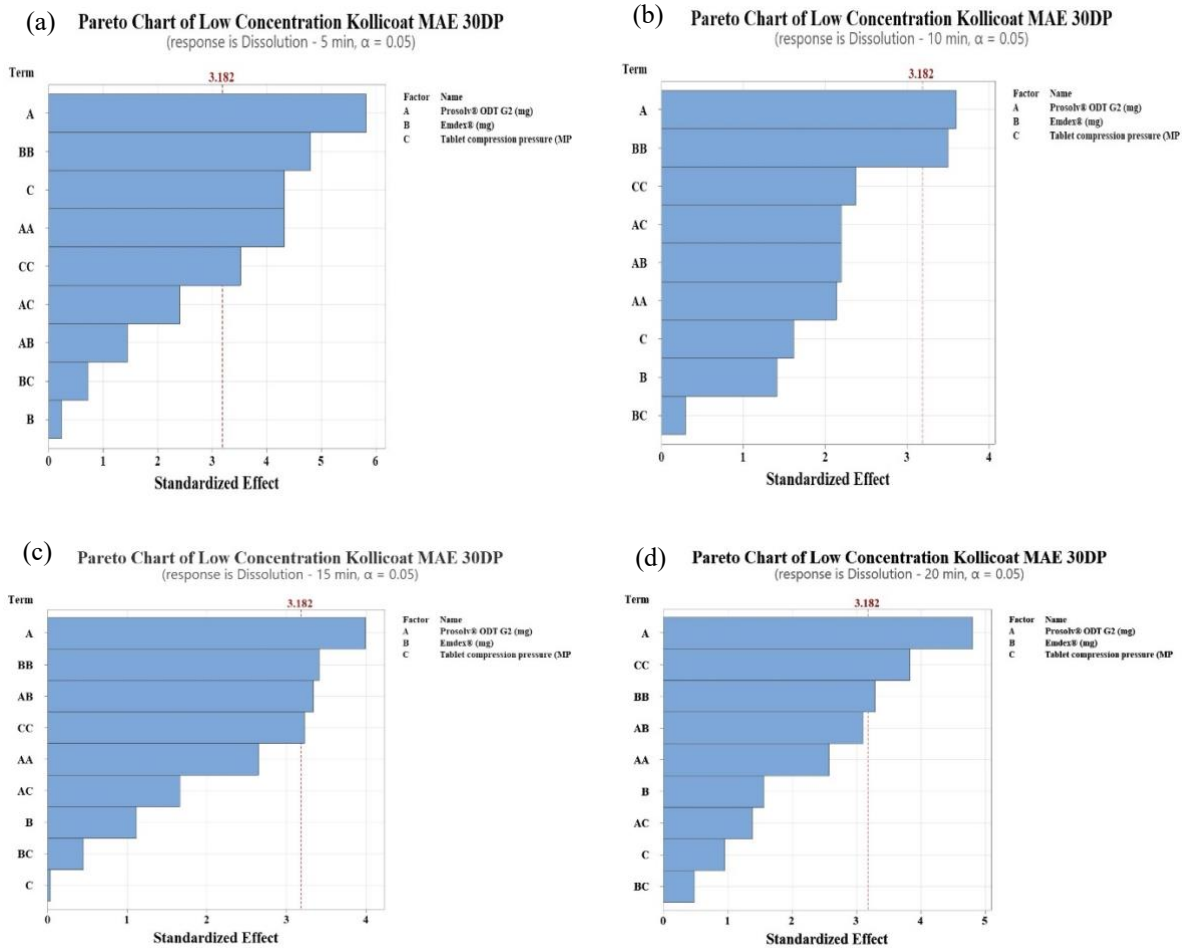


Figure 7. Pareto chart of disintegration time for formulations containing low concentration Kollicoat MAE 30DP.

3.3.4. Dissolution Studies

As depicted in the dissolution profiles (Figure 4), the cumulative drug release for most formulations containing a high concentration of Kollicoat MAE 30DP was greater than 85%. This finding indicates that a prolonged disintegration time may not inherently restrict the total amount of the dissolved drug; a formulation may disintegrate more slowly while still achieving a substantial extent of drug release. Although the thickness of the taste-masking polymer layer exerted a significant influence on the initial dissolution kinetics (as demonstrated in Figure 4), it clearly did not impede a high cumulative release. Many researchers have argued that faster disintegration strictly correlates with a more rapid dissolution rate, and quicker onset of action [54]. In order to evaluate this relationship between the disintegration time and dissolution rate in the formulation with high concentration polymer, the Pearson correlation coefficient (R) was used. The analysis yielded correlation coefficients (R) of -0.500, -0.446, and -0.301 at 1, 3, and 5 minutes, respectively. These results indicated that disintegration time did not have any significant correlation ($p > 0.05$) with dissolution rate and dissolution behaviour. This finding is consistent with the observations reported by Mishra and Rohera, who also reported that tablet disintegration time did not significantly correlate with dissolution rate at any time point, as indicated by the low negative Pearson correlation coefficient [55].

According to the Pareto chart analysis for the low concentration Kollicoat MAE 30DP formulations (Figure 8a-e), none of the parameters significantly influenced the dissolution profile during the initial time points (1 and 3 minutes). However, as the dissolution progressed (5, 10, 15, 20, and 30 minutes), Prosolv® ODT G2 exerted a significant positive linear effect on the dissolution profile, whereas tablet compression pressure had a negative impact specifically at the 5-minute mark. Regarding the quadratic effects (squared terms), Emdex® (BB) negatively influenced the release across a number of time points (5, 10, 15, 20, and 30 minutes), as well as tablet compression pressure (CC) at 5, 15, 20, and 30 minutes. In contrast, the quadratic term for Prosolv® ODT G2 (AA) exhibited a favourable impact at the 5-minute mark. Furthermore, the two-way interaction between Prosolv® ODT G2 and Emdex® (AB) had a positive effect on the dissolution profile at 15 minute.



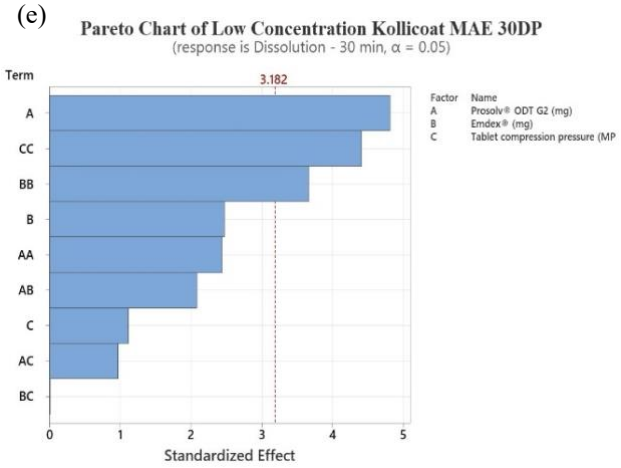


Figure 8. The Pareto chart of the dissolution test for formulations with low concentration Kollicoat MAE 30DP at (a) 5 minutes; (b) 10 minutes; (c) 15 minutes; (d) 20 minutes and (e) 30 minutes.

As illustrated in Figure 9 (a and b) for high concentration Kollicoat MAE 30DP formulations, Emdex® positively influenced the dissolution profile at 3 minutes. Conversely, tablet compression pressure negatively affected the dissolution process at the 20 minute time point.

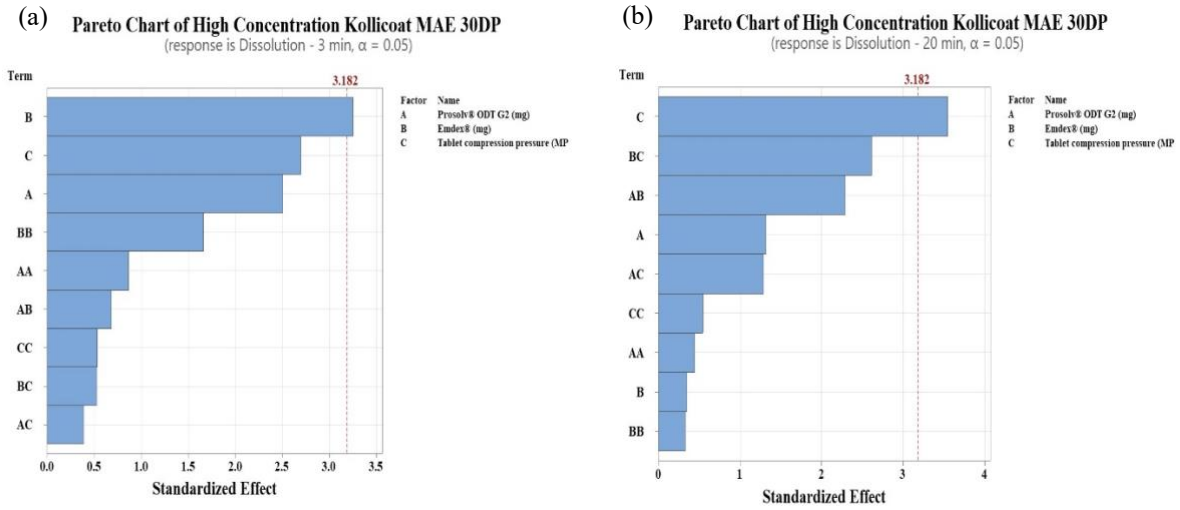


Fig. 9. The Pareto charts of the dissolution test for formulations with high concentration Kollicoat MAE 30DP at time points of (a) 3 minutes and (b) 20 minutes.

3.4. Optimization of taste masked ODTs by using QbD approach

The main challenge in developing ODTs is to achieve a disintegration time ranging from less than 30 seconds to a maximum of 180 seconds, in accordance with USP and the Ph. Eu standards, while ensuring sufficient mechanical strength. Therefore, the optimization step aimed to determine the optimal level of the formulation and processing factors necessary to fulfil the predefined CQAs of the final product. Minitab® software (version 20.2) was used to optimize the independent variables. During this process, specific CQAs were targeted for minimisation (disintegration time and friability) or maximisation (breaking strength and dissolution rate).

For the low-concentration Kollicoat® MAE 30DP group, the optimized formulation consisted of Prosolv® ODT G2 (240 mg), Emdex® (200 mg), and a tablet compression pressure of 3 MPa. This formulation yielded a friability of 0.05%, a breaking strength of 104 N, a disintegration time of 30 seconds, and a dissolution rate of 86% at 30 minutes. Conversely, the optimised formulation for the high-concentration Kollicoat® MAE 30DP group contained Prosolv® ODT G2 (248 mg), Emdex® (110 mg), and a compression pressure of 2.9 MPa,

resulting in a friability of 0.10%, a breaking strength of 97 N, a disintegration time of 12 seconds, and a dissolution rate of 94% at 30 minutes.

The study demonstrated that the employment of a taste-masking polymer at elevated concentrations is imperative for the attainment of the desired CQAs. The predicted values obtained from the optimization model exhibited a strong correlation with experimental values of responses. Moreover, the desirability value of 0.9 confirmed the robustness and suitability of the optimized formulation.

4. CONCLUSION

In the present study, a QbD approach was successfully implemented for the development and optimisation of taste-masked ODTs containing DEX. The application of a Box-Behnken design proved highly effective in evaluating the complex interactions between the taste-masking polymer (Kollicoat® MAE 30DP), the superdisintegrant matrix (Prosolv® ODT G2), the binder (Emdex®), and tablet compression pressure.

A pivotal finding of this research was the statistical decoupling of disintegration time and dissolution behaviour. Contrary to the conventional assumption that rapid disintegration strictly dictates rapid drug release, our Pearson correlation analysis demonstrated no significant correlation between the two parameters ($p > 0.05$). The findings revealed that while higher concentrations of the taste-masking polymer create a denser physical barrier, an optimised superdisintegrant-to-binder ratio can successfully overcome this retardation, achieving extensive cumulative drug release (exceeding 85%). Furthermore, Pareto chart analyses confirmed that Prosolv® ODT G2 significantly enhanced the dissolution profile, whereas elevated compression pressures and excessive Emdex® concentrations negatively impacted the release.

Ultimately, the statistical optimisation process identified a highly desirable formulation (desirability = 0.9) within the high-concentration polymer group. This formulation exhibited excellent CQAs, including friability of 0.10%, robust breaking strength of 97 N, rapid disintegration in 12 seconds and 94% dissolution in 30 minutes. This study shows that balancing high concentrations of Kollicoat MAE 30DP with a finely tuned excipient matrix creates an effective and robust process for making palatable, mechanically resilient ODTs. This significantly improves patient-centric drug delivery systems.

5. MATERIALS AND METHODS

5.1. Materials

Dexketoprofen trometamol and Kollicoat MAE 30DP® were kindly gifted from Menarini Pharmaceutical Company (Istanbul, Turkey) and BASF (Germany), respectively. Ready-to-use matrix excipient for DC method (Prosolv® ODT G2, JRS Pharma, USA), dextrates (Emdex®, JRS Pharma, USA), magnesium stearate (Parteck® LUB MST, Merck, Germany), Magnasweet® MM100 (chewing gum aroma) (Magnasweet®, Mafco Worldwide LLC, Dubai) were kindly gifted.

5.2. Methods

5.2.1. Experimental Design

The amounts of Prosolv® ODT G2 (X_1), Emdex® (X_2), and tablet compression pressure (X_3) were selected as independent variables, taking critical material attributes and critical process parameter into consideration. Independent variables were evaluated at three levels (Low (-1), Middle (0), and High (1)). Dissolution rate (Y_1), disintegration time (Y_2), tablet breaking strength (Y_3), and friability (Y_4) were chosen as dependent variables, as demonstrated in Table 3. The formulation design was constituted with a four-factor, three-level Box-Behnken method. As mentioned previously, Kollicoat MAE 30DP was used to obtain taste masked DEX. Low (15.16%) and high (17.34%) concentrations were applied to understand the effect of the polymer agent on tablet properties. These concentrations were determined according to the granulating efficiency of Kollicoat MAE 30DP. Thus, formulations were applied to the Box-Behnken design with a biserial concentration of the polymer agent.

Table 3. Variables of the Box-Behnken design to optimize the formulation.

Independent Variables, Factors	Levels		
	Low (-1)	Middle (0)	High (1)
X_1: Prosolv® ODT G2 (mg)	150	200	250
X_2: Emdex® (mg)	100	150	200
X_3: Tablet compression pressure (MPa)	1.72	3.44	5.17
Dependent Variables, Responses			
Y_1: Dissolution Rate (%)			
Y_2: Disintegration Time (sec)			
Y_3: Tablet Breaking Strength (N)			
Y_4: Friability (%)			

5.2.2. Preparation of DEX ODTs

To obtain granular drug, firstly DEX was granulated manually with Kollicoat MAE 30DP. Due to Kollicoat MAE 30DP being in liquid form, a solvent was not necessary to obtain wet granules. The concentrations of Kollicoat MAE 30DP were determined according to their granulating ability. The lowest and the highest concentrations of obtaining wet granulation were 15.16 % and 17.34 %, respectively. Following, the wet granules were dried within a few minutes at room temperature until the granulation liquid evaporated. Dried granules were passed through a 1.25 mm sieve for each concentration to standardize the particle size.

The composition of DEX ODTs is displayed in Tables 1 and 2. Tableting mixtures containing granulated DEX, Prosolv® ODT G2, Emdex®, and Magnasweet® MM100 were blended for 10 minutes at 80 rpm in a small cubic mixer (Yener Kalip, Turkiye). Finally, Parteck® LUB MST as a lubricant was added and blended for a further three minutes. Powder mixtures were directly compressed with a 9.525 mm diameter punch of a manual tablet press machine (Yener Kalip, Turkiye); tablet compression pressure is also shown in Tables 1 and 2.

5.2.3. Characterization of Granules

Granule Morphology: The morphology of granules was investigated by a digital microscope with a standard resolution of 3 Megapixels (Leica DFC295, Germany). ImageJ program (National Institutes of Health, USA) was used to analyze the images of granules.

Loss on Drying: The residual moisture content of the dried granules (2 g, n=2) was determined by loss on drying (LoD) using a Mettler Toledo HR73 Halogen Moisture Analyzer (Mettler Toledo, Switzerland). A sample was dried at 105 °C for 2 minutes, then the percentage of LoD was recorded.

5.2.4. Characterization of Taste Masked DEX ODTs

a. Tablet Friability: Tablet friability was determined using a friabilator (Aymes Company, Turkiye) according to USP <*1216 Tablet Friability*> [26]. For each formulation, twenty tablets were selected, accurately weighed, and placed into the friabilator at 25 rpm for four minutes. The tablets were then accurately reweighted after removing any loose dust. Lastly, tablet friability was evaluated as a loss in tablet weight (%).

b. Tablet Breaking Strength: The strength of tablets was determined using a hardness tester (Sotax HT1, Switzerland) according to tablet breaking strength test [56]. Randomly, ten tablets of each formulation were investigated by the breaking strength test, and then the mean was measured.

c. Tablet Disintegration Time: USP disintegration test apparatus (Sotax DT2, Switzerland) was employed for determining the disintegration time. Three tablets of each formulation were separately placed into the basket-rack of the disintegration equipment, filled with 900 mL of distilled water presented at 37 ± 0.5 °C. The disintegration time was recorded when all the tablets disintegrated completely and no remaining observed as specified in the disintegration test method [57].

d. Dissolution Studies: Dissolution studies were performed for all prepared ODTs, implementing the USP apparatus II method (Sotax AT2, Switzerland). The study was conducted in 900 ml of phosphate buffer, pH

6.8, as a dissolution medium with a paddle speed of 50 rpm at a temperature of 37±0.5 °C [58, 59]. Aliquots of three ml were withdrawn manually at specific time points (1, 3, 5, 10, 15, 20, and 30 minutes) without replacing the medium, considering the loss during the calculation.

The concentrations of released DEX were determined using an ultraviolet-visible spectrophotometer at 260 nm (Schimadzu UV-1600, Japan), according to a modified method from Martinez et al. study [60]. The obtained samples from dissolution studies were filtered through a 0.45 µm cellulose acetate filter (Alwsci, China). In brief, 10 mg of DEX was placed in a 100 ml volumetric flask, and then dissolved and completed the volume with phosphate buffer (pH 6.8±0.05) solution. Standard solutions were prepared via withdrawing different amounts from the previous solution to obtain several levels or concentrations (10%, 30%, 50%, 80%, 100%, and 120%) of standard solutions for linearity study. For instance, 2.8 mL was withdrawn from a 10 ml volumetric flask to obtain a level of 100% of the standard solution (0.028 $mg.mL^{-1}$). The volume was completed with the phosphate buffer solution (pH 6.8±0.05).

5.2.2. Statistical Evaluation

The Minitab® (version 20.2) (Minitab Inc., USA) statistical software was used to evaluate the data and establish design space. The charts and tables were prepared in Microsoft Office Excel 2010 (Microsoft, USA), Minitab®. Statistical significance was considered by p-value < 0.05. Unless otherwise stated, all experiments were performed in triplicate (n = 3), and the results are expressed as mean ± standard deviation (SD). The specific sample sizes (n) for the loss on drying, tablet friability, and tablet breaking strength tests are detailed in their respective methodology sections. The overall desirability (D) can be interpreted as geometric mean of desirability of each response and has a range from 0 (not desired) to 1 (maximum desirability) [55,61].

Author contributions: Concept – Y.P.T., B.D.; Design – Y.P.T., B.D.; Supervision – B.D., Y.O.; Resources – B.D. Y.O.; Materials – B.D., Y.O.; Data Collection and/or Processing – Y.P.T., M.A.M.; Analysis and/or Interpretation –Y.P.T., M.A.M.; Literature Search – Y.P.T., M.A.M.; Writing – Y.P.T., M.A.M., B.D; Critical Reviews – B.D., Y.O.

Conflict of interest statement: "The authors declared no conflict of interest" in the manuscript.

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