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Abstract

The delivery of antihistaminic agents via the oral route is problematic, especially for elderly patients. This study aimed to develop a sublingual formulation of promethazine hydrochloride by direct compression, and to mask its intensely bitter taste. Promethazine hydrochloride (PMZ) sublingual tablets prepared by direct compression were optimized using Box-Behnken full factorial design. The effect of a taste-masking agent (Eudragit E 100, X1), superdisintegrant (crospovidone; CPV, X2) and lubricant (sodium stearyl fumarate; SSF, X3) on sublingual tablets' attributes (responses, Y) was optimized. The prepared sublingual tablets were characterized for hardness (Y1), disintegration time (Y2), initial dissolution rate (IDR; Y3) and dissolution efficiency after 30 min (Dissolution Efficiency (DE); Y4). The obtained results showed a significant positive effect of the three independent factors on tablet hardness ($P < 0.05$), and the interactive effect of Eudragit E 100 and CPV on tablet hardness was significant. Disintegration time was mainly affected by Eudragit E 100 and CPV concentrations. Moreover, IDR was employed to assess the taste masking effect, lower values were obtained at higher Eudragit E 100 concentration despite it was statistically insignificant ($p>0.05$). Optimized formulation that was suggested by the software was composed of: Eudragit E 100 (X1)= 2.5% w/w, CPV (X2)= 4.13 % w/w, and SSF (X3)= 1.0 % w/w. The observed values of the optimized formula were found to be close to the predicted optimized values. The Differential Scanning Calorimetric (DSC) studies indicated no interaction between PMZ and tablet excipients.

1. Introduction

Promethazine hydrochloride (PMZ), a first-generation antihistaminic agent which is derived from phenothiazine, inhibits the action of natural histamine by blocking histamine H_1 receptors (Suzuki et al., 2003; Kolhe, 2013). It is widely used to control dizziness, motion sickness, nausea and vomiting (Mallappa and Samritha Bhat, 2020). Further, it is prescribed to treat several allergy symptoms, such as itching and runny nose (Kolahian et al., 2012; Zur, 2013; Fahler, 2012). Additionally, it can help patients to fall asleep or get relaxed before and after surgery. Promethazine is currently available in three oral dosage forms: syrup, tablet, or elixir. Usually, 25 mg of promethazine is administered orally every 4 to 6 hours when used to treat nausea and vomiting. Nevertheless, the delivery of oral antihistaminic agents can be problematic, especially for those undergoing chemotherapy and anaesthesia for surgery due to nausea and emesis. Additionally, drinking water is required for swallowing orally taken medications. This could be an additional challenge, as difficulty in swallowing tablets is widespread in all age groups, particularly paediatrics and the elderly, due to physiological changes (Kavitha et al., 2011). Administration of conventional tablets requires water, particularly in the case of motion sickness and coughing during the common cold, allergic conditions and bronchitis. Hence, it is common for nauseous patients to take promethazine via direct intravenous injection or suppository (Deshmukh, Jadhav and Sakarkar, 2015). Besides oral administration of promethazine hydrochloride requires time for the onset of action, which may in some cases give rise to therapy failure due to the delay in the release of the active pharmaceutical ingredient. Patient compliance and rapid onset of action are important for improved therapy; this can be achieved through developing sublingual tablets which can rapidly disintegrate and dissolve in the oral cavity (Rachid et al., 2012).

The latest technologies in drug delivery systems present many pharmaceutical and patient characteristics, ranging from enhanced life-cycle management to convenient dosing for paediatric and geriatric patients, and patients with dysphagia. Sublingual drug delivery is considered to be an effective route of delivery which provides rapid and direct drug absorption into systemic circulation compared to conventional tablets (Laffleur and Keckeis, 202; Mostafa et al., 2013). In the buccal cavity, the sublingual area is most permeable for drug absorption. When the drug molecules are absorbed through the sublingual blood vessels, this helps the avoidance of hepatic first-pass metabolism, which shows greater bioavailability with better patient compliance (Nayak and Sourajit, 2017; Vishakha et al., 2019). A small volume of saliva is usually sufficient for such formulations, which requires these tablets to disintegrate immediately in the oral cavity. Sublingual absorption is mostly rapid in action, but also short-acting in duration (Laffleur and Keckeis, 2020). The absorption of the drug from this route of administration can be 3 to 10 times greater than the oral route (Garg and Sani, 2015). To date, there is no commercially available promethazine sublingual formulation, although such an orodispersible formulation could be an ideal option for paediatric or geriatric patients as well as anyone who has difficulties swallowing.

Therefore, the purpose of the present study is to develop a sublingual formulation for the promethazine hydrochloride by direct compression, and to mask the intensely bitter taste of the drug using the pH-sensitive polymer Eudragit E 100. Such tablets can disintegrate rapidly in the saliva without the need for water ('Traveller-Friendly Drug Delivery System'), releasing the drug instantly for immediate therapeutic effect (Chinwala, 2020; Dhar, Sarma and Sharma, 2020).

2. Methods

2.1. Experimental Materials

Promethazine hydrochloride (PMT) was purchased from Carbosynth Limited (Compton, UK). Sodium stearyl fumarate (SSF, Pruv®) was kindly supplied by JRS (Aalen, Germany). Spray-dried mannitol, Mannogem™ EZ, was kindly supplied by SPI (Grand Haven, USA). Spray-dried lactose monohydrate (Flowlac®100) was kindly supplied by Meggle (Wasserburg, Germany). Crospovidone (CPV) was kindly supplied by Riyadh Pharma (Riyadh, KSA). Eudragit E100 was obtained from Evonik Rohm GmbH (Germany).

2.2. Experimental design

Three-factor, three-level (3^3) Box-Behnken factorial design was used to optimise the effect of the taste-masking agent; Eudragit E 100, (X_1), superdisintegrant (Crospovidone) (X2) and sodium stearyl fumarate (X3) on sublingual tablet attributes using a statistical package (Statgraphics Plus, version 5). Statistical models with interaction terms were derived to evaluate the effect of these independent factors on sublingual tablet hardness (Y_1), disintegration time (Y_2), initial dissolution rate (IDR) (Y3) and dissolution efficiency (DE) (Y4) . The selected ranges were based on initial screening studies. Spray dried lactose and mannitol were employed as filler diluents and were not included as independent variables in the study. These two excipients are commonly used in rapidly disintegrating dosage forms owing to their favourable properties including, cooling effect of mannitol safety profile and affordability (Shu et al., 2002; Ohrem, 2013).

The selected three factors, their levels and the analysed targeted responses are presented in **Table 1**. In addition, the composition of PMZ tablets is illustrated in **Table 2**. This design provided an empirical second-order polynomial model. In this mathematical approach each experimental response Y can be represented by a quadratic equation of the response surface:

$$Y_n = B_0 + B_1X_1 + B_2X_2 + B_3X_3 + B_{12}X_1X_2 + B_{13}X_1X_3 + B_{23}X_2X_3 + B_{11}{X_1}^2 + B_{22}{X_2}^2 + B_{33}{X_3}^2 + B_{123}X_1X_2X_3$$

Where Y_n is the modelled response, B_0 is arithmetic mean response of the run. B_1, B_2 and B_3 are the coefficients of the factors X_1, X_2 and X_3 respectively. X_1X_2, X_1X_3, X_2X_3 and $X_1X_2X_3$ represent the interaction terms while ${X_1}^2$, ${X_2}^2$ and ${X_3}^2$ represent the quadratic terms (non-linear effect of factors).

2.3. Tablet manufacturing

Tablets were manufactured by direct compression method. According to the composition of PMZ sublingual tablet formulations, the corresponding amounts of the drug, filler (mannitol 1: 1 lactose), Eudragit E 100 and superdisintegrant (CPV) were accurately weighed. The weighed powder excipients were transferred into a turbula mixer and mixed for 10 minutes. The formula weight of the lubricant (SSF) was then mixed with the powder in the turbula mixer for 2 minutes. Finally, the powder was compressed into tablets using a Korsh single punch machine (Erweka, EKO, Germany) with 7 mm shallow concave punches. The employed compression force was maintained at 2 tons for all the formulations.

Weight variation

Twenty tablets from each batch were individually weighed using an analytical balance (Shimadzu, EB-3200D, Kyoto, Japan) and the average weight and standard deviation were reported.

Thickness

The thickness of ten pre-weighed tablets of each batch was tested using a micrometer caliper (Starrett, Athol MA, USA) and the average thickness and standard deviation were reported.

Hardness

Tablet hardness was determined using a hardness tester (Pharma test GmbH, Hainburg, Germany) for ten tablets of each batch with known weight and thickness. The average hardness, standard deviation and relative standard variation were reported.

Friability

Tablet friability was determined according to USP35 ⟨1216⟩ monograph of tablet friability. In brief, 20 tablets were weighed (W_1) and placed into the friabilator (Erweka, TA3R, Heusenstamm, Germany), which was rotated at 25 rpm for 4 min. The tablets were then reweighed after removal of fines (W_2), and the friability was calculated using the following formula (USP 35_:

$$\% \, Friability = \frac{W1 - W2}{W1} \times 100 \quad (1)$$

Uniformity of Dosage Unit

The uniformity of dosage unit was assessed according to USP 34 harmonized monograph for content uniformity. The batch meets the USP requirements if content uniformity acceptance value (AV) was not more than 15 of the first 10 tested tablets (stage 1-AV). If the AV exceeded the criterion (AV >15), 20 additional tablets were tested (stage 2-AV). If the Stage-2 AV and the extreme of the 30 units are compliant with the criteria, the test passes.

PMT content in the sublingual tablets was examined using UV Spectrophotometer (Labomed, Inc, USA) at a wavelength of 224 nm. Ten individual tablets were placed in a 100 ml volumetric flask and 70 ml of phosphate buffer pH 6.8 was added, the dispersion was sonicated to dissolve the tablets and then the volume was completed to 100 ml with the buffer. The dispersion was then filtered and the drug concentration was measured using the constructed standard calibration curve. AV was calculated as follows:

General Formula:

$$\mathrm{AV} = |M - X - | + ks \quad (2)$$

where *AV* is the acceptance value, X^{-} is the mean value of drug content, *s* is the standard deviation and *k* is a constant value either equal to 2.4 for 10 dosage units or equal to 2 for 30 dosage units. For *M* in the above expression there are three cases. If 98.5% ≤ X^{-} ≤ 101.5%, $M = X^{-}$ and $AV = ks$, if X^{-} < 98.5%, *M* = 98.5% and if X^{-} > 101.5%, *M* = 101.5%.

***In vitro* disintegration test**

In vitro disintegration test was assessed according to the USP30-NF25 requirements for immediate release tablets. One dosage unit was put in each of the six tubes of the basket. The apparatus (Electrolab, ED-21, Mumbai, India) was operated, using distilled water as the immersion fluid, maintained at 37° C ± 2° C. The time for complete disintegration of each tablet, standard deviation and relative standard deviation were calculated.

***In vitro* dissolution studies**

Despite the lack of specific compendial method for dissolution testing of sublingual dosage forms which possess specific requirements pertinent to low physiological agitation, and a small volume of saliva to support disintegration and dissolution (Rachid et al., 2011), the dissolution methods of tablets is still in use and was employed in this study.

A minimum of six tablets of each product was tested. The dissolution of oral disintegrating tablets was monitored using an automated dissolution tester (LOGAN Instrument Corp, Somerset, NJ, USA) coupled to an automated sample collector (SP-100 peristaltic pump, Somerset, NJ, USA). The USP 30 (apparatus 2) paddle method was used. Dissolution was carried out in 900 ml phosphate buffer, pH 6.8 ± 0.05. The paddle was rotated at 50 rpm at 37 ± 0.5 ºC. Samples were withdrawn and analysed automatically at wavelength 224 nm at specified time intervals (2, 5, 10, 15, 20 and 30 min). Despite the value of taste masking techniques such as electronic tongue as described by Rachid et al. (2010), this was not available for this project. Therefore, the immediate dissolution rate (IDR) was employed as an indirect indication of taste covering by slowing the initial release of the drug. IDR was calculated from the amount dissolved of PMZ after 2 minutes, whereas the dissolution efficiency (DE) was based on the total amount of dissolved PMZ after 30 minutes (Mostafa et al., 2013).

Differential scanning Calorimetric Studies (DSC)

Thermal analysis was carried out using the DSC technique. A DSC 25 system (TA Instruments' Discovery, USA) was employed to determine the melting point temperatures of the API, excipients and physical mixture in their powder forms to assess the compatibility between sublingual tablet excipients and API. About 2 mg of the sample was weighed and loaded into aluminium pans and heated to 200-300°C at 10°C/min with a nitrogen gas purge. An empty aluminium pan was used as a reference for all measurements. The resulting graphs were analysed by TRIOS manager software. Melting point values were determined from the intersection of relative tangents to the baseline.

3. Results and discussion

3.1 Content uniformity of PMZ tablets (uniformity of dosage unit)

Content uniformity data of PMZ sublingual tablets prepared by direct compression are presented in **Table 3**. The results were expressed as a percentage of drug content and standard deviation as well as acceptance value (AV). The results were analysed according to USP pharmacopoeia (USP 34) on 10 individual units in the first stage and to meet the criteria of AV less than 15 (1.06-14.7) and standard deviation less than or equal to 6%. The obtained data of AV indicated the compliance of the prepared PMZ to the dosage unit uniformity pharmacopoeial guidelines.

3.2. Effect of independent formulation parameters on PMZ tablets properties

Effect on tablet hardness

The results of the ANOVA test for the effects of independent factors on PMZ tablet hardness (Y1) values are depicted in **Table 4**. The three individual independent factors exhibited a significant synergistic effect on tablet hardness. The effects of these parameters exhibited very small P; 0.0014, 0.0012 and 0.0030, respectively, as can be seen in the Pareto chart (**Figure 1A**). Moreover, the interaction between Eudragit E 100 and CPV (X1X2) and the quadratic effect of SSF (X3) showed significant synergism on tablet hardness ($P < 0.05$). Response surface plot for the effect of Eudragit E100 and CPV on PMZ sublingual tablets at constant medium SSF level (**Figure 2A**) revealed also the synergistic effects of these excipients on tablet hardness, especially at higher concentrations.

The highest hardness values (5.8, 5.6, and 5.1 kp) were recorded in PMZ sublingual tablet formulations F8, F4and F9 respectively, **Table 5**. These formulas were prepared using the medium to highest levels of the Eudragit E 100, CPV and SSF. In contrast, low hardness values were observed for formulations with the lowest quantity of Eudragit E 100 (F5 and F12) and low to medium disintegrant content.

Our results are in accordance with previously reported results. Obeidat et al. (2015) showed that the higher crushing strengths of paracetamol matrix tablets were associated also with lower tablet porosities caused by Eudragit E 100. Chaulang et al. (2008) revealed that at a higher concentration of superdisintegrant, CPV, the crushing strength of directly compressed frusemide tablets was increased.

In the present study, SSF exhibited a significant synergistic effect on PMZ tablet hardness. However, Mahrous et al. (2019) showed that lubricant (SSF) concentration did not show any significant influence on tablet hardness on dextromethorphan hydrobromide orally disintegrating tablets. The significant synergistic effect of SSF on PMZ tablet hardness ($P = 0.0030$) in the present study might be due to its combined agonistic effects with the taste-masking agent, superdisintegrant and lubricant (SSF). A study by Paul and Sun (2018) revealed that SSF effect on tablet hardness when lactose is used as filler binder is less prominent on tablet hardness. Lactose particles fragment upon compression therefore, provide lubricant free surfaces which produce strong inter-particular bonding that is unaffected by the lubricant. Further, the results in our study showed that the lubricant concentration showed quadratic effect with $p<0.05$, indicating that the effect is not positive on tablet hardness at all concentrations.

Effect on tablet disintegration

Figure 1B and **Table 4** display the analysis of variance for the effect of the independent factors on the disintegration time (Y2) of PMZ sublingual tablets. Individual effects of both Eudragit E 100 and CPV as well as the quadratic effect of CPV exhibited a synergistic impact on Y2 ($P < 0.05$, along with a high sum of square values (SS). In contrast, the interaction between Eudragit E 100 and CPV exerted a significant increase in the tablets' disintegration time. The response surface plot for the effects of Eudragit E 100 and CPV (at a constant medium level of SSF) on disintegration time of PMZ tablets is displayed in **Figure 2B**. The results revealed that at low CPV concentration (up to 4-5%), the tablets exhibited a shorter disintegration time, after which the disintegration time became prolonged. This might explain why the interactive effect of Eudragit E 100-CPV showed reduction of tablet disintegration time. Eudragit E 100 showed an agonistic effect on tablet disintegration time at all tested levels.

The prolonged disintegration times of PMZ tablets (42 s, 41 s and 38 s) were recorded in the case of formulations F7, F8 and F11, respectively (**Table 5**). These formulations were prepared by using the highest and medium levels of the Eudragit E100. F7 contained the highest Eudragit amount and the lowest amount of CPV and hence the low disintegration time.

A direct relationship was reported between tablet disintegration time and tablet hardness (Okuda et al., 2009). In this study, formulations with hardness above 4.0 kp demonstrated longer disintegration time and formulations with low hardness (2 kp or lower) shwoed shorter disintegration time despite low CPV level (e.g., F5) due to low Eudragit E 100 concentration. The higher percentage of Eudragit E100 reduces the permeation of water inside the tablet and thus produces slower disintegration (Saravanan et al., 2002). A study by Kanugo and Mathur (2013) revealed SSF containing tablets showed less impact on hardness which is following the findings of this study. However, results of a study done by Kuno et al. (2008) reported that the disintegration time of the ODTs containing SSF increased with an increase in tablet hardness (Okuda et al., 2009).

Effect on Initial dissolution rate; IDR (Y3)

The initial dissolution rate (IDR) of PMZ from its sublingual tablet formulations is an important parameter that should be optimised, because IDR describes the % of drug dissolved within the first 2 min from tablet formulation. Eudragit E 100 is commonly used in taste-masking as it requires a low pH for dissolution. It is expected that it contributes to the reduction of IDR of PMZ.

The tested independent factors (Eudragit E 100, CPV and SSF) did not exert any significant effect on the IDR of PMZ from its sublingual tablet formulations at the individual, interactive or quadratic levels ($P > 0.05$), Table 4. However, there are some noticeable (but insignificant) retarding effects of Eudragit E 100 and SSF on IDR at their individual or quadratic levels as seen from high SS values and the Pareto chart (**Figure 1C**). The response surface plot in **Figure 2C** showed a minor retarding effect of Eudragit E 100 on PMZ IDR from tablets, and CPV exhibited an agonistic (but insignificant) effect on the response.

The highest IDR (about 28% of PMZ) from its sublingual tablets was found in the case of formulations F2, F6 and F11, as seen in **Figure 3** and **Table 5**. The disintegration and dissolution retarding effects exerted by Eudragit E 100 and SSF are counteracted by the tablet disintegration enhancing effect of the superdisintegrant, CPV (Mahrous et al., 2019; Kuno et al., 2008; Li and Wu, 2014).

Effect on dissolution efficiency; DE (Y4)

Dissolution efficiency was evaluated from the total amount of PMZ dissolved after 30 minutes. The ANOVA results for the effects of independent factors on PMZ DE from its sublingual tablets are listed in Table 4 and the standardised Pareto chart in **Figure 1**. Both Eudragit E 100 and SSF showed significant reduction of DE as seen from the high SS values (28.56 and 61.29) for the effects of the taste-masking agent and lubricant, respectively, along with $P < 0.05$. Similar to IDR data, the effect of CPV on PMZ DE from sublingual tablets was insignificant. The response surface plot for the effect of Eudragit E 100 and SSF (at constant medium CPV level) on the DE of PMZ from tablets is illustrated in **Figure 2**. The drug dissolution rate was found to be retarded by the presence of both the taste-masking agent and the lubricant, especially at high concentrations of these excipients. **Table 5** and **Figure 3** showed the DE % values of PMZ from tablet formulas. The highest DE% values (42.14%, 41.21%, 41.67%, 41.38% and 44.31%) were exhibited from tablet formula F2, F5, F6, F11 and F12, respectively.

The retarding effect of both the taste-masking agent (Eudragit E 100) and lubricant (SSF) on PMZ dissolution from its tablets might be attributed to the increased tablet hardness along with prolonged tablet disintegration time caused by high levels of both. These findings are supported by the data obtained by Kuno et al. (2008). Also, Ibrahim and Abou el Ela (2017) showed that Eudragit E 100 showed a reduction on the dissolution rate of furosemide from oral disintegrating tablets after 5 and 30 min.

Optimisation of promethazine hydrochloride sublingual tablets

The following desirability parameters were selected for testing the independent factors affecting PMZ sublingual tablets: minimum tablet hardness, tablet minimum disintegration time, maximum drug IDR and maximum drug DE (**Table 6**). Based on the modelling using software statistical program (Statgraphics Centurion, version 17), with a desirability factor equal to 95%, the following levels of the independent factors were suggested for the preparation of the optimised PMZ tablet formulation: Eudragit E 100 (X1) = 2.5% w/w, CPV (X2)= 4.13% w/w, and SSF (X3)= 1.0 % w/w. The observed values were found to be close to the predicted optimised values for the tablet formula. The observed hardness was 1.95±0.12 kp (predicted value was 1.82 kp). The disintegration time observed value was 16.5±1.8 s, which is comparable to the predicted disintegration time, 18.52 s. In addition, the observed value for IDR was 25.64±1.74% (the predicted value was 27.45%), and the observed value for DE was 45.73±2.41% (the predicted value was 45.53). When the results are compared to F12 (the closest to optimal formulations), the results demonstrate closeness to the optimised formulation with hardness value of 2.1 kp, disintegration time of 21 s, IDR was 23.97% and DE was 44.31%.

The *in vitro* dissolution profile of PMZ from the optimised sublingual tablet formulation is displayed in **Figure 4**. In the optimised formula, the dissolution retarding effect of Eudragit E 100 and SSF was counteracted and minimised by the effect of the superdisintegrant, CPV.

Compatibility studies (DSC)

The DSC scans of the individual ingredients of the optimised PMZ sublingual tablet formula compared to the physical mixes of these ingredients at equivalent weights are displayed in **Figure 5**. The drug exhibited an endothermic peak at 234.9^{o}C indicating the drug melting point. Lactose showed two melting points: at 142.69^{o}C referring to water evaporation, and at 218.77^{o}C referring to lactose melting. In addition, mannitol showed a highly intense endothermic melting peak at 168.68^{o}C. Moreover, the superdisintegrant (CPV) exhibited a shallow and broad endotherm at 98.38 due to water loss, while Eudragit E 100 did not show melting at the tested temperature range. Furthermore, a melting endothermic peak was found at 200.75234.9^{o}C for the lubricant; SSF, melting, and broad peak was observed at the range of 115-138^{o}C due to water evaporation from the sample. The DSC scan of the excipient's physical mixtures indicated the disappearance of the endothermic peak of PMZ, lactose and SSF, and only the endothermic peak of mannitol was detected. The disappearance of the drug endothermic peak in the case of physical mixtures might be due to the melting of the drug crystals in the molten polymeric matrix during DSC scans and the difference in the melting points of PMZ and mannitol, in addition to suggesting an interaction between the drug and tablet excipients (Mahrous et al., 2016.).

4. Conclusion

The objective of this study was to develop and validate taste-masked PMZ sublingual tablets that target individuals with swallowing difficulty. High drug solubility stands as an obstacle because of the intensity of the drug's bitter taste, which might lead to patient rejection of the medication. Therefore, Eudragit E100 was added to improve drug taste, in addition to SSF as a lubricant and taste-masking agent. Box-Behnken factorial design of experiment applied in this study enabled an understanding of the effect of independent variables (superdisintegrant concentration, taste-masking polymer concentration, and lubricant concentration) on four responses. The analysis of variance revealed that all the independent variables (individual, interactive or quadratic) had a significant effect on the hardness, disintegration time, and dissolution efficiency, but not the immediate dissolution rate. Novel PMZ-loaded sublingual tablets with very good properties were successfully produced. Optimal properties in terms of disintegration time (less than 20 seconds), hardness (around 2 kp), IDR of less than 30% were obtained. This work has been able to produce a formulation of water-soluble drugs (as PMZ) in sublingual or orally dissolving tablets with optimal properties.

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Declaration of Competing Interest

The authors declare no conflict of interest.

References

Suzuki A, Yasui-Furukori N, Mihara K, Kondo T, Furukori H, Inoue Y, Kaneko S, Otani K. Histamine H1-receptor antagonists, promethazine and homochlorcyclizine, increase the steady-state plasma concentrations of haloperidol and reduced haloperidol. *Ther Drug Monit.* 2003 Apr; 25(2):192-6. doi: 10.1097/00007691-200304000-00008. PMID: 12657913.

Kolahian S, Jarolmasjed SH. Antiemetic efficacy of promethazine on xylazine-induced emesis in cats. *Can Vet J*. 2012;53(2):193-5.

Zur E. Nausea and vomiting in pregnancy: a review of the pathology and compounding opportunities. *Int J Pharm Compd*. 2013;17(2):113-23.

Fahler J, Wall GC, Leman BI. Gastroparesis-associated refractory nausea treated with aprepitant. *Ann Pharmacother*. 2012;46(12):e38.

Chinwala, M. (2020) 'Recent Formulation Advances and Therapeutic Usefulness of Orally Disintegrating Tablets (ODTs)', *Pharmacy*, 8(4), p. 186. doi: 10.3390/pharmacy8040186.

Deshmukh, V. N., Jadhav, J. K. and Sakarkar, D. M. (2015) 'Formulation and in vitro evaluation of in situ gelling liquid suppository of promethazine HCl', *World Journal of Pharmaceutical Research*, 4(11), pp. 273–286.

Dhar, P., Sarma, H. and Sharma, H. K. (2020) 'Fixed Dose Oral Dispersible Tablet of Bitter Drug Using Okra Mucilage: Formulation and Evaluation', *Journal of Drug Delivery and Therapeutics*, 10(5), pp. 149–158. doi: 10.22270/jddt.v10i5.4393.

Kavitha, K. *et al.* (2011) 'Formulation and evaluation of oral fast dissolving tablets of promethazine HCL by sublimation method', *International Journal of PharmTech Research*, 3(2), pp. 660–663.

Kolhe, S. (2013) 'Formulation and Evaluation of Taste Masked Fast Disintegrating Tablet of Promethazine Hydrochloride', *IOSR Journal of Pharmacy (IOSRPHR)*, 03(11), pp. 01–11. doi: 10.9790/3013-031101-11.

Laffleur, F. and Keckeis, V. (2020) 'Advances in drug delivery systems: Work in progress still needed?', *International Journal of Pharmaceutics: X*, 2(June). doi: 10.1016/j.ijpx.2020.100050.

Mallappa, D. P. and Samritha Bhat, U. (2020) 'Formulation Development and Evaluation of Promethazine As A Lozenge', *American Journal of Pharmacy And Health Research*, 8(8), pp. 18–30. doi: 10.46624/ajphr.2020.v8.i8.002.

Nayak, B. S. and Sourajit, S. (2017) 'Sublingual Drug Delivery System : a novel approach', *International Journal Of Pharmaceutics and Drug Analysis*, 10(5), pp. 399–405.

Vishakha, C. *et al.* (2019) 'Formulation and evaluation of sublingual tablet of Venlafaxine hydrochloride for the treatment of depression', *Journal of Drug Delivery and Therapeutics*, 9(2-A), pp. 56–58. Available at: http://jddtonline.info/index.php/jddt/article/view/2779.

Obeidat, WM, Nokhodchi, A, Alkhatib, H. Evaluation of Matrix Tablets Based on Eudragit®E100/Carbopol®971P Combinations for Controlled Release and Improved Compaction Properties of Water Soluble Model Drug Paracetamol. *AAPS PharmSciTech.* 2015, 2, 1-11.

Chaulang, GM, Patil, KS, Ghodke, DS, Yeole, PG, Bhosale, Av, Hardikar, SR. Effect of some physical parameters and crospovidone on directly compressed frusemide tablets. *Asian J Pharmaceut.* 2008 (10-12), 235-240.

Mahrous, GM, Ibrahima, MA, Mostafa, HF, Elzayat, EM. Application of a quality-by-design approach for utilizing sodium stearyl fumarate as a taste-masking agent in dextromethorphan hydrobromide orally disintegrating tablets. *Pharm. Dev. Technol*, 1, 2019, 1-9.

Saravanan, M, Nataraj, KS, Ganesh, KS. The Effect of Tablet Formulation and Hardness on in Vitro Release of Cephalexin from Eudragit L100 Based Extended Release Tablets. *Biol. Pharm. Bull*. 25(4) 541—545 (2002).

Kanugo, AK, Mathur VB. 2013. Evaluation and comparison of highly soluble sodium stearyl fumarate with other lubricants in-vitro. *Indo Am J Pharm Res*. 5:4042–4049.

Kuno Y, Kojima M, Nakagami H, Yonemochi E, Terada K. 2008. Effect of the type of lubricant on the characteristics of orally disintegrating tablets manufactured using the phase transition of sugar alcohol. *Eur J Pharm Biopharm*. 69:986–992.

Li J, Wu Y. 2014. Lubricants in pharmaceutical solid dosage forms. Lubricants. 2:21–43.

Ibrahim, MA, Abou El Ela, AESF. Optimized furosemide taste masked orally disintegrating tablets. *Saudi Pharm J*. 2017 (25)1055-1062.

Mahrous, GM, Kassem, MG, Ibrahim, MA, Auda, SA. 2016. Formulation and evaluation of orally disintegrating clopidogrel tablets. *Brazil. J. Pharm. Sci.* 2; 309-317.

United States Pharmacopiea, USP 35, ⟨1216⟩ monograph of tablet friability.

United States Pharmacopoeia; USP 34 harmonized monograph.

Rachid, O., Simons, F. E. R., Rawas-Qalaji, M., Simons, K. J. 2010. An electronic tongue: evaluation of the masking efficacy of sweetening and/or flavoring agents on the bitter taste of epinephrine. AAPS PharmSciTech, 11(2), 550-557.

Rachid, O., Rawas-Qalaji, M., Simons, F.E., Simons, K.J. 2011. Dissolution testing of sublingual tablets: a novel in vitro method. AAPS PharmSciTech.. 12(2), 544–552.

Rachid, O., Rawas-Qalaji, M., Simons, F.E., Simons, K.J. 2012. Rapidly-disintegrating sublingual tablets of epinephrine: role of non-medicinal ingredients in formulation development. Eur. J. Pharm. Biopharm. (3), 598-604.

Mostafa, H.F., Ibrahim, M.A., Sakr, A. 2012. Development and optimization of dextromethorphan hydrobromide oral disintegrating tablets: effect of formulation and process variables. Pharm. Dev. Technol. 18(2), 454-63.

Garg, R., Saini, S. 2015. Sublingual Route During Perioperative and Chronic Pain Management. J. Anesth. Crit. Care. 3(1), 1-2.

Shu, T., Suzuki, H., Hironaka, K., Ito, K. 2002. Studies of Rapidly Disintegrating tablets in the oral cavity using co-ground mixtures of mannitol with crospovidone. ChemPharma Bull. 50(2), 193-198.

Ohrem, H.L., Schornick, E., Kalivoda, A., Ognibene, R. 2013. Why is mannitol becoming more and more popular as a pharmaceutical excipient in solid dosage forms? Pharm DevTechnol 19(3), 257-262. Paul, S. Sun, C.C. 2018. Systematic evaluation of common lubricants for optimal use in tablet formulation. Eur J Pharm Sci. 117, 118-127.

Okuda, Y., Irisawa, Y., Okimoto, K., Osawa, T., Yamashita, S., 2009. A new formulation for orally disintegrating tablets using a suspension spray-coating method. Int J Pharm. 382(1-2), 80-87.

Tables:

Table 1 Variables in Box-Behnken factorial design for PMZ sublingual tablet formulations.

Independent Variables (Factors)	**Low (-1)**	**Middle (0)**	**High (+1)**
X1: Eudragit E100 (%)	2.5	6.25	10.0
X2: CPV* (%)	2.0	5.0	8.0
X3: SSF* (%)	1.0	5.0	9.0
Dependent Variable (Response)			
Y1: Hardness		kp	
Y2: Disintegration Time		seconds	
Y3: Initial Dissolution Rate (IDR)		%	
Y4: Dissolution Efficiency (DE)		%	
*CPV: Crospovidone; SSF: Sodium stearyl fumarate			

Table 2 Composition of PMZ sublingual tablet formulations based on Box-Behnken factorial design (Total tablet weight was 100 mg).

	Amount of Ingredients (mg):				
Formulation	**Eudragit E100**	**CPV***	**SSF***	**PMZ***	**Lactose: Mannitol (1: 1)**
F1	10	5	1	12.5	71.5
F2	2.5	8	5	12.5	72
F3	6.25	5	5	12.5	71.25
F4	10	8	5	12.5	64.5
F5	2.5	2	5	12.5	78
F6	6.25	2	1	12.5	78.25
F7	10	2	5	12.5	70.5
F8	6.25	8	9	12.5	64.25
F9	10	5	9	12.5	63.5
F10	2.5	5	9	12.5	71
F11	6.25	8	1	12.5	72.25

F12	2.5	5	1	12.5	79
F13	6.25	2	9	12.5	70.25
*CPV: Crospovidone; SSF: Sodium stearyl fumarate; PMZ: Promethazine					

Table 3 Content uniformity data of PMZ sublingual tablet formulations.

Formula	X⁻	SD	Max	Min	K	M	AV
F1	101.66	0.37	102.19	101.16	2.4	101.5	1.06
F2	102.53	5.64	111.7	93.28	2.4	101.5	14.57
F3	100.31	4.65	108.75	95.16	2.4	100.31	11.16
F4	96.56	5.32	106.88	85.78	2.4	98.5	14.7
F5	99.72	6.08	110.64	92.9	2.4	99.72	14.58
F6	107.53	1.59	110.16	104.53	2.4	101.5	9.84
F7	99.34	5.06	108.65	88.59	2.4	99.34	12.16
F8	100.5	5.12	11.56	91.41	2.4	100.5	12.29
F9	93.5	3.12	11.56	91.41	2.4	98.5	12.49
F10	95.18	1.71	11.56	91.41	2.4	98.5	7.41
F11	102.39	2	110.16	104.53	2.4	101.5	5.7
F12	105	2.71	11.56	91.41	2.4	101.5	10
F13	103.98	1.9	11.56	91.41	2.4	101.5	7.04
X⁻: mean, SD: standard deviation, Max: maximum value, Min: minimum value, K: constant, M:, AV: acceptance level.							

Table 4 Analysis of variance for immediate release rate (IDR), dissolution efficiency (%DE), disintegration time and hardness of PMZ tablets SS (sum of squares).

Source	Hardness (kp)		Disintegration (sec)		IDR (%)		DE (%)	
	SS	P	SS	P	SS	P	SS	P
X1: Eudragit E100	6.30	0.0014	88.78	0.0191	19.22	0.3710	28.56	0.0340
X2: CPV	6.84	0.0012	48.90	0.0417	3.19	0.6979	0.833	0.5713
X3: SSF	3.78	0.0030	0.08	0.9662	17.61	0.3891	61.29	0.0122
$X1^2$	0.023	0.5407	0.57	0.7357	14.55	0.4284	16.31	0.0676
X1X2	0.64	0.0350	49.00	0.0416	0.01	0.9806	0.72	0.6027
X1X3	0.123	0.2066	1.00	0.6578	1.96	0.7596	2.50	0.3528
$X2^2$	0.413	0.0601	302.29	0.0034	21.42	0.3487	0.40	0.6917

X2X3	0.283	0.094	9.00	0.2380	8.27	0.5408	1.90	0.4086
X3²	0.516	0.046	0.57	0.7357	52.35	0.3126	3.56	0.2812

Table 5 Properties of PMZ sublingual tablet formulations.

Formulation	**DE* (%)**		**IDR* (%)**		**Hardness (kp)**		**Friability (%)**	**Disintegration time (s)**	
	Mean	SD	Mean	SD	Mean	SD	Mean	Mean	SD
F1	40.60	1.00	26.36	1.74	4.5	*0.31*	0.21	29	1.2
F2	42.14	0.66	28.41	1.42	3.8	0.21	0.41	37	1.8
F3	36.47	1.49	19.24	0.94	3.1	0.12	0.51	24	0.9
F4	37.07	0.62	21.11	0.88	5.6	0.18	0.2	37	2.4
F5	41.21	0.11	18.73	1.40	2.1	0.31	0.74	28	1.7
F6	41.67	0.64	28.32	1.50	2.4	0.21	0.65	34	1.1
F7	37.81	3.31	18.73	0.83	4.1	0.41	0.35	42	2.1
F8	35.98	1.41	20.10	1.46	5.8	0.41	0.18	41	2.8
F9	38.05	0.87	24.85	4.25	5.1	0.31	0.21	28	1.5
F10	38.60	0.94	25.26	0.13	4.3	0.21	0.31	22	0.8
F11	41.38	0.20	28.80	0.33	4.1	0.42	0.29	38	2.6
F12	44.31	1.03	23.97	2.37	2.1	0.11	0.84	21	0.8
F13	33.51	1.27	25.37	1.21	3.4	0.24	0.28	31	1.7

*DE: Dissolution efficiency; IDR: Immediate dissolution rate

Table 6 The composition, predicted and observed responses of PMZ sublingual tablets optimised formula. Initially, 25.64±1.74% of the incorporated drug was dissolved within 2 min, and a complete drug dissolution was observed after 5 min.

Optimised Independent factors	**Response (Y)**			
		Desirability	**Predicted**	**Observed**
	Hardness (Y1); kp	Minimum	1.82	1.95±0.12
Eudragit E 100 (X1): 2.5% w/w	Disintegration time (Y2); s	Minimum	18.52	16.5±1.8

CPV (X2): 4.13 % w/w	IDR (Y3); %	Maximum	27.45	25.64±1.74
SSF (X3): 1.0 % w/w	DE (Y4); %	Maximum	45.53	45.73±2.41

Figures:

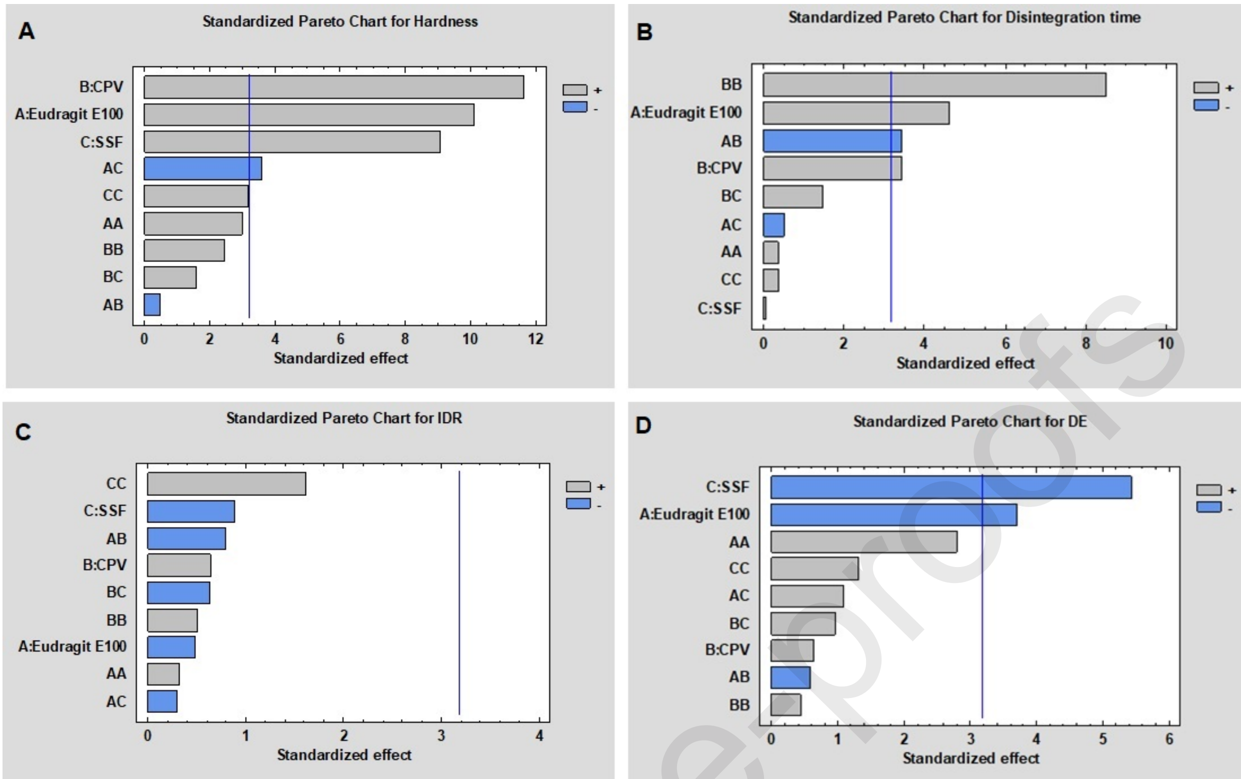

Figure 1 Standardized Pareto chart for the effect of independent variables on promethazine (PMZ) sublingual tablet hardness (A), disintegration time (B), Immediate dissolution rate (IDR) (C) and dissolution efficiency (DE) (D).

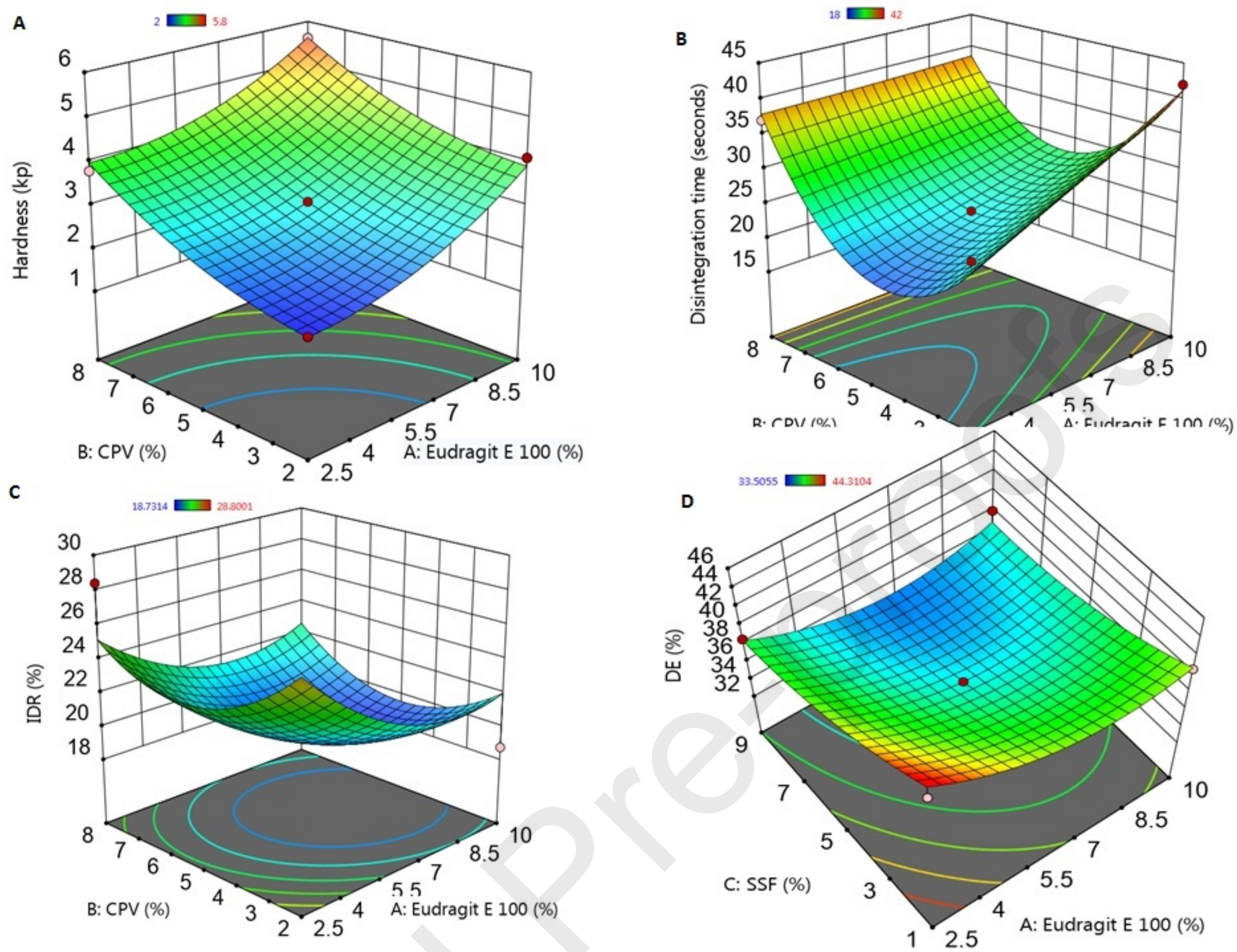

Figure 2 Response surface plots for the effect of independent variables on promethazine (PMZ) tablet hardness (A), disintegration time (B), Immediate dissolution rate (IDR) (c) and dissolution efficiency (DE) (D). The plot highlights the interactive effect of two factors on the response when the third factor is maintained at its middle range.

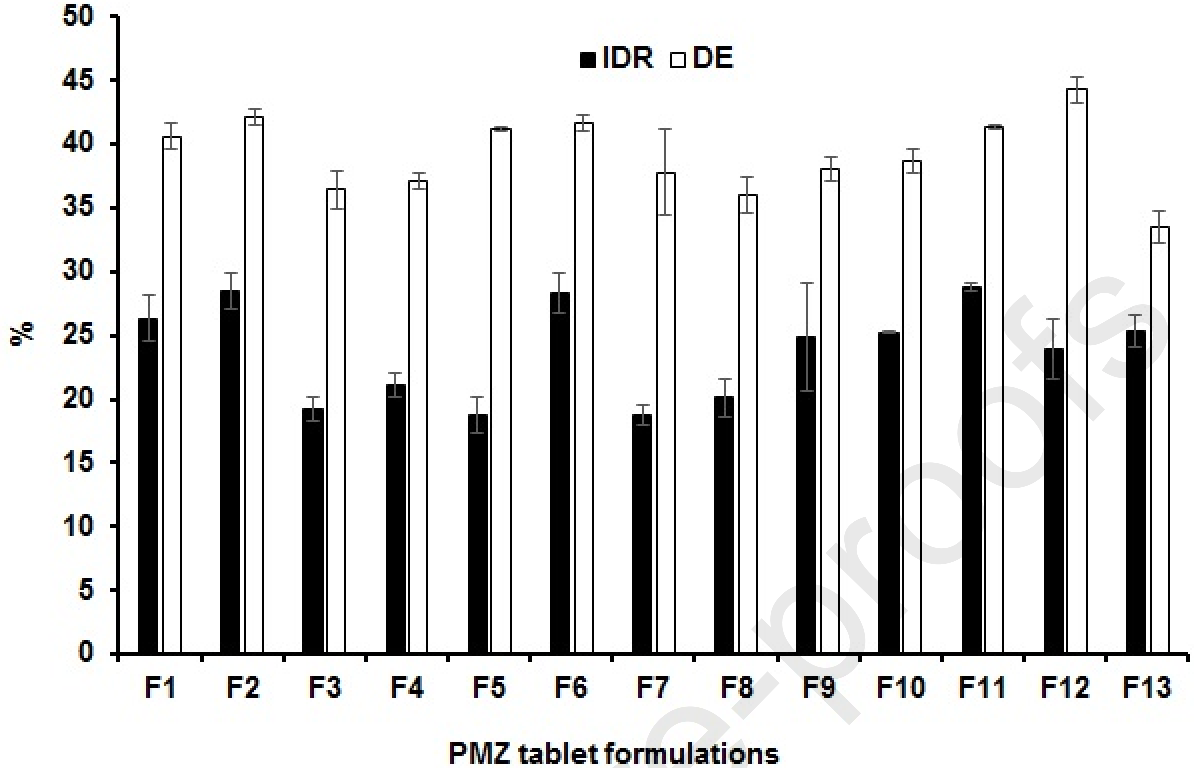

Figure 3 Immediate dissolution rate (IDR) and dissolution efficiency (DE) of promethazine (PMZ) from sublingual tablet formulations (mean± SD, n=6).

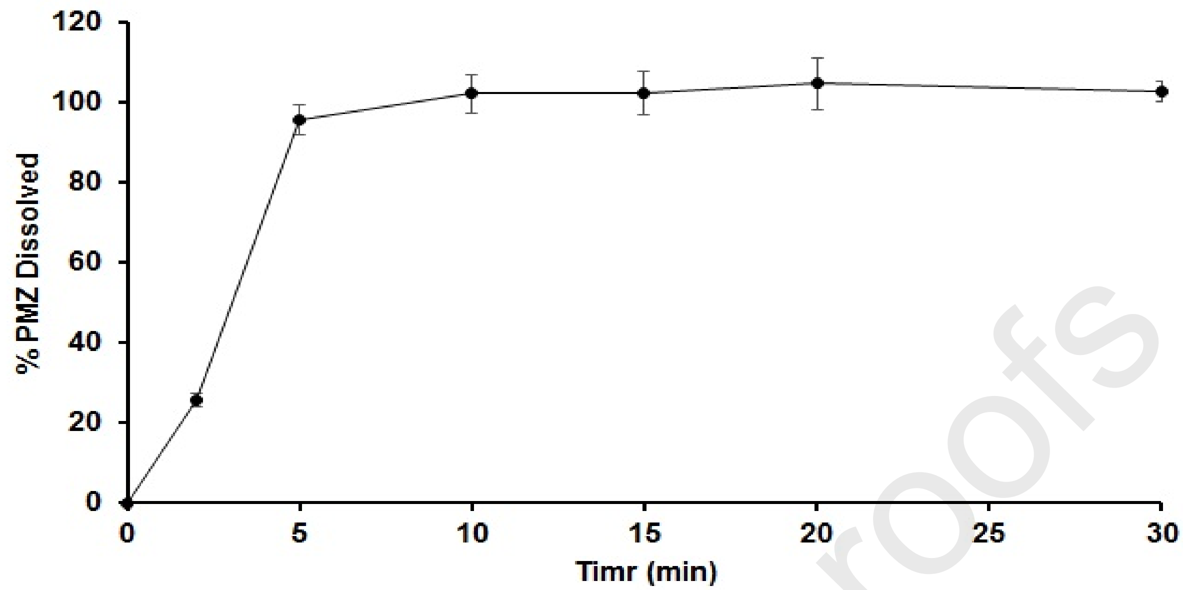

Figure 4 ***In vitro*** **dissolution profile of PMZ from the optimized sublingual tablet formulation at 37°C.**

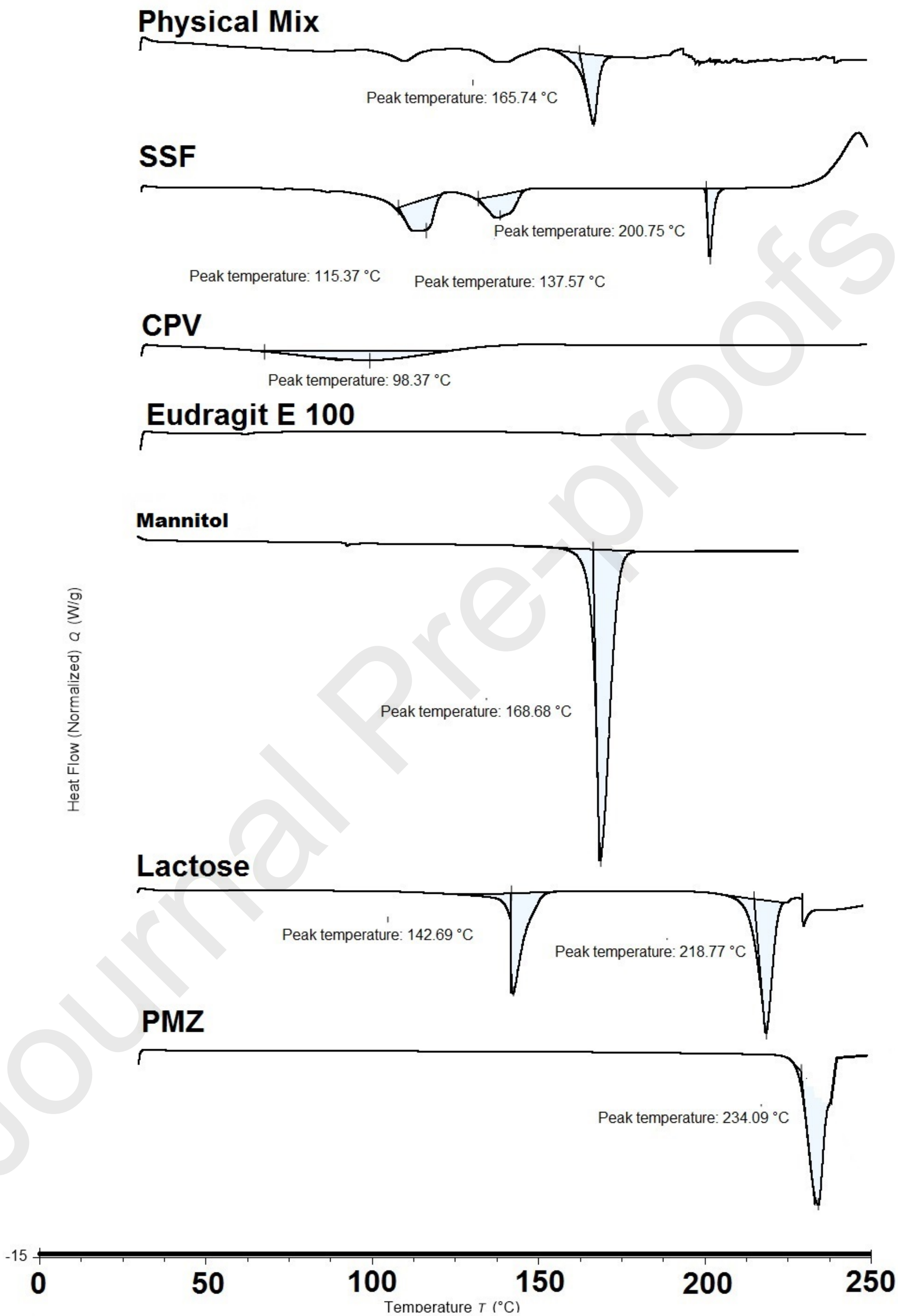
Physical Mix
Peak temperature: 165.74 °C
SSF
Peak temperature: 200.75 °C
Peak temperature: 115.37 °C
Peak temperature: 137.57 °C
CPV
Peak temperature: 98.37 °C
Eudragit E 100
Mannitol
Peak temperature: 168.68 °C
Lactose
Peak temperature: 142.69 °C
Peak temperature: 218.77 °C
PMZ
Peak temperature: 234.09 °C
Heat Flow (Normalized) Q (W/g)
-15
0
50
100
150
200
250
Temperature T (°C)

Figure 5 Differential scanning calorimetric scans of untreated promethazine (PMZ), lactose, mannitol, Eudragit E 100, crospovidone (CPV), sodium stearyl fumarate (SSF) and their physical mixture.