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RESEARCH ARTICLE

Development and optimization of lyophilized orally disintegrating tablets using factorial design

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Abstract

The aim of this study was to evaluate the use of maltodextrin as a sugar-matrix former along with several cellulosic binders in the preparation of freeze—dried orally disintegrating tablets (ODT). The ODT was prepared by freeze—drying an aqueous dispersion of nimesulide (NM) containing maltodextrin and a cellulosic binder. The influence of formulation parameters on the *in vitro/in vivo* disintegration time and *in vitro* dissolution of NM from ODTs along with other tablet characteristics was investigated using full factorial design. The optimized ODT contained 5% w/v maltodextrin DE 29, 2% w/v Methocel®E15, and 5% w/v NM, disintegrated in less than 10 s and showed more than 70% of NM in ODTs dissolved within 2 min, compared to only 1.52% of NM plain drug and 7.25% of NM in immediate release commercial tablet. Crystalline state evaluation of NM in the optimized ODT was conducted through differential scanning calorimetry, and X-ray powder diffraction. The study suggests that the optimized ODT formulation developed in this work may be an alternative to conventional formulations of NM inconvenient to the patients such as intramuscular or rectal administration.

Keywords: Maltodextrin, freeze drying, factorial design

Introduction

Oral fast-disintegrating dosage forms, also known as fast-melt, fast-disintegrating or fast-dissolving, are a relatively novel dosage technology that involves the rapid disintegration or dissolution of the dosage form, be it a tablet (the most common form) or a capsule, into a solution or suspension in the mouth without the need for water. The dosage form starts to disintegrate immediately after coming into contact with saliva, with complete disintegration normally occurring within 30–50 sec after administration.[1,2] The solution containing the active ingredients is swallowed, and the active ingredients are then absorbed through the gastrointestinal epithelium to reach the target and produce the desired effect.

Tablets are the most favorable and popular among the currently used dosage forms, and efficacy of this type of tablets have been clinically evaluated.[3,4,5] However, to make rapidly disintegrating tablets with sufficient mechanical integrity and good stability necessitate careful selection of the excipients used in tablet formulation. Products of orally disintegrating tablet (ODT) technologies entered the market in the 1980s, have grown steadily in demand, and their product pipelines are rapidly expanding. Many patented technologies like Durasolv, Flash Dose, Flashtab, Oraquick, Orasolv, Wowtab, and Zydis have also gained importance in the international market. Several lyophilized tablet preparations are available now in the market, such as: Claritin® RediTabs® (loratidine, Schering plough Corp., USA), Zyprexia® (Olanzapine, Eli lilly, Indianapolis), and Felden® Flash (piroxicam, Pfiser Inc., NY).

Maltodextrin is a mixture of purified nutritive saccharides obtained from hydrolysis of starch. It has been widely used in food industry. It is important as moisture conditioner, food plasticizer, crystallization inhibitor, stabilizer, carrier, and bulking agent. Maltodextrins

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are used in tablet formulation as a binder and filler in both direct compression and wet granulation process.[6] Maltodextrin grades with a high dextrose equivalent (DE) value are particularly useful in chewable tablet formulations, as they can mask the bitter taste of drugs. Corveleyn and Remon[7] studied the influence of different formulation and process parameters on the preparation of lyophilized tablets, using hydrochlorothiazide as a model poorly water soluble drug. They proved that maltodextrins are useful matrix forming agents for the formulation of lyophilized tablets as freeze drying of a maltodextrin solution results in an amorphous porous network which dissolves in water in less than 1 min, but the final product was reported to be fragile and difficult to handle. Further work proved that maltodextrins can be used as an amorphous cryo-protectant and solid support for the formulation of lyophilized dry emulsion tablets.[8] In a formulation study using lactose as filler, Vennat et al.[9] reported that the best results in disintegration time of lyophilized tablets were obtained when using cellulose derivatives as binders. In a previous study, gelatin was evaluated as a non-sugar matrix former in the preparation of NM ODT and only a tablet formulation containing a disintegration accelerator was found to have good tablet properties.[10]

In this study, the feasibility of using different cellulosic binders along with maltodextrin DE 29 as a matrix former for the preparation of ODT using the freeze drying technique will be evaluated. Nimesulide (NM) was selected as a model drug. NM shows high anti-inflammatory, antipyretic and analgesic activity with moderate incidence of gastric side effects. NM belongs, according to the biopharmaceutic classification system (BCS), to Class II drugs with poor solubility and high permeability. It is virtually insoluble in aqueous systems (solubility 0.01 mg/ml).[10] The mean terminal half life varied between 1.8 and 4.73 h. The effect of different formulation variables were evaluated using experimental full factorial design.

Material and methods

Materials

Nimesulide (NM) was kindly supplied from Alkan Pharma, Egypt. Maltodextrin DE 29 was donated by Roquette Pharma, France. Methocel® E5, Methocel® E15, and Methocel® A15 (Colorcon, UK). All water used was distilled deionized water. All other chemicals were reagent grade and used as received. Sulide® 100 mg immediate release tablet (batch no. 319, Alkan Company, Egypt) was used as a reference tablet.

Methods

Preparation of ODTs

NM ODTs were prepared using maltodextrin (MD) DE 29 as a matrix former along with different cellulosic binders. Three cellulosic binders were used; namely: Methocel® E5 (Hdroxy propyl methyl cellulose E5: HPMC E5), Methocel® E15 (HPMC E15) and Methocel® A15 (methylcellulose A15), each in two concentrations (2% and 3% w/v).[7] The cellulosic binder concentrations (2%, 3%) were selected based on preliminary trials as suitable binder concentrations for the preparation of lyophilized tablets. MD-DE 29 and the cellulosic binder were first dissolved in distilled water using a magnetic stirrer to obtain the required concentration, and then an accurately weighed amount of NM powder was dispersed in the prepared aqueous solution using a magnetic stirrer to result in a dose of 50 mg NM per 1 ml. One milliliter of the suspension was then poured in each pocket of a poly vinyl chloride (PVC) blister pack having a diameter of 13 mm and a depth of 3 mm. The tablet blister packs were frozen at–22˚C for 24 h, then placed in a lyophilizer (Novalyphe-NL 500 Freeze Dryer) with a condenser temperature of–45˚C and a pressure of 7×10^{-2} mbar for 24 h.

Characterization of ODTs

Uniformity of weight

The test was carried out according to the European pharmacopoeia (EP, 4th edition) specifications.[11] Twenty tablets, from each formula, were individually weighed and the mean of tablet weights was calculated. Results are presented as the percent relative standard deviation (% RSD) of the tablet mass.

Tablet friability

The tablet friability test was done according to EP (4th edition) specifications.[11] Twenty tablets, from each formulation, were accurately weighed and placed in the drum of friabilator (Erweka type, GmbH, Germany). The tablets were rotated at 25 rpm for a period of 4 min and then removed, dedusted and accurately reweighed. The percentage loss in weight was calculated and taken as a measure of friability.

In vitro disintegration time

Disintegration times of the prepared ODTs were determined with six tablets in distilled water kept at 37 ± 0.5˚C using a DST-3 disintegration tester (Logan Instruments Corp., NJ) according to EP (4th edition) specifications.[11] The disintegration time was defined as the time necessary for the ODT to completely disintegrate until no solid residue remains or only a trace amount of soft residue remains on the screen. A digital stopwatch was used to measure the disintegration time to the nearest second. Only one ODT was analyzed at a time in order to ensure maximum accuracy. All results are presented as mean value ± SD ($n = 6$).

In vivo disintegration time

The *in vivo* disintegration time of each of the prepared ODTs was evaluated in six human volunteers after giving informed written consent. The volunteers had no history of hypersensitivity to NSAIDs. Prior to the test, all volunteers were asked to rinse their mouth with distilled water. Each of the six subjects was given a coded tablet. Tablets were placed on the tongue and immediately the time was

recorded. They were allowed to move the tablet against the upper palate of the mouth with their tongue and to cause a gentle tumbling action on the tablet without biting on it or tumbling it from side to side. Immediately after the last noticeable mass had disintegrated, the time was recorded. The subjects were asked to spit out the content of the oral cavity after tablet disintegration and rinse their mouth with distilled water. The swallowing of saliva was prohibited during the test, and also saliva was rinsed from the mouth after each measurement. The test results are presented as mean value ± SD ($n = 6$).[12]

Moisture analysis

The residual moisture content after lyophilization was determined in the tablets using Karl-Fischer titrator (Veego Matic-MD, Veego Instruments Corporation, India). Each tablet was pulverized, inserted in the titration vessel containing dried methanol (Karl-Fischer grade) and titrated with Hydranal Composite 5 reagent (Riedel-de-Haën, Seelze, Germany) after a stirring time of 3 min. Results are presented as mean value ± SD ($n = 3$).

In vitro dissolution studies

Dissolution studies were carried out following the USP XXII paddle method at 37°C and 50 rpm using a dissolution tester (Pharma Test Dissolution Tester, Germany). The dissolution medium was 900 ml simulated saliva fluid without enzymes (SSF) at pH = 6.8. Dissolution profiles of NM in ODTs were compared with the plain drug and to the market product, Sulide®. The amount of drug used was equivalent to 50 mg. At specified time intervals (1, 2, 3, 5, 7, 10, and 15 min.), samples were withdrawn, filtered through 0.45 µm millipore filter and assayed for drug content spectrophotometrically at 393 nm after appropriate dilution. Cumulative amount of drug dissolved in the preparations was calculated using calibration equation. Dissolution tests were performed in three vessels per formulation ($n = 3$). The market product, Sulide® was tested using simulated intestinal fluid without enzymes at pH 7.4.

Experimental design

A $3^1 \cdot 2^2$ full factorial design was employed to evaluate the individual and combined effects of the formulation variables. In this design, three factors were evaluated; two of them at two levels, and the third at three levels. The experimental trials were performed at all twelve possible combinations with replication. The independent variables studied were type of cellulosic binder (X_1), concentration of cellulosic binder (X_2), and concentration of MD-DE 29 (X_3). The chosen dependent variables or responses were the tablet friability (Y_1), *in vitro* disintegration time (Y_2), *in vivo* disintegration time (Y_3), residual moisture content (Y_4), and the percentage NM dissolved after 2 min (Y_5). All analyses were performed using the Design-Expert ® 8 Software.

The detailed composition of the prepared ODTs is presented in Table 1. The prepared ODTs were kept in tightly

Table 1. Experimental runs, independent variables, and measured responses of the $3^1 \cdot 2^2$ full factorial experimental design.

	Independent variables			Responses				
Run	X_1:Type of cellulosic binder	X_2:Concentration of cellulosic binder	X_3:Concentration of MD-DE 29	Y_1:Friability (%)	Y_2:*in vitro* disintegration time (sec)	Y_3:*in vivo* disintegration time(sec)	Y_4:Residual moisture content %	Y_5:% NM dissolved after 2 min
M1	Methocel® A15	2%	5%	0.97	171.0	152.0	0.33	5.13
M2	Methocel® A15	2%	10%	1.77	198.5	178.0	0.68	3.40
M3	Methocel® A15	3%	5%	0.05	722.0	605.0	0.45	4.20
M4	Methocel® A15	3%	10%	0.23	813.3	675.0	0.65	3.30
M5	Methocel® E5	2%	5%	8.00	4.0	2.0	2.30	60.00
M6	Methocel® E5	2%	10%	6.36	8.5	8.5	2.45	65.30
M7	Methocel® E5	3%	5%	0.26	32.5	3.6	4.68	43.00
M8	Methocel® E5	3%	10%	0.29	43.5	14.5	3.95	61.80
M9	Methocel® E15	2%	5%	0.18	10.5	8.5	2.51	72.60
M10	Methocel® E15	2%	10%	2.85	16.5	14.0	2.78	70.55
M11	Methocel® E15	3%	5%	0.26	21.0	16.5	3.00	49.20
M12	Methocel® E15	3%	10%	0.14	68.6	37.0	1.54	63.60

*5% NM was used, to obtain a dose of 50 mg NM per tablet.

closed containers in desiccators over calcium chloride at room temperature until further use.

Differential scanning calorimetry (DSC) studies

Thermograms for NM plain powder and NM in a selected tablet formulation and its corresponding physical mixture were obtained. The samples were sealed in aluminum pans and analyzed using a Shimadzu DSC-60 (Kyoto, Japan). The samples were heated in an atmosphere of nitrogen and thermograms were obtained by heating at a constant heating rate of 10˚C/minute in the range of 20–350˚C.

Powder X-Ray Diffraction (XRD)

Diffraction patterns of NM plain powder and NM in a selected tablet formulation and its corresponding physical mixtures were determined in a Scintag X-ray diffractometer (USA) using Cu K α radiation with a nickel filter, a voltage of 45 kV, and a current of 40 mA.

Results and discussion

Characterization of NM ODTs

The tablets were successfully dried and withstood manual handling. A 2% binder solution shows a viscosity of 5 cp, 15 cp and 15 cp for Methocel®E5, Methocel®E15 and Methocel®A15, respectively. No collapse protectant, such as mannitol, was required in the formulation of the tablets, as maltodextrins are known to also have anti-collapse properties, i.e., prevent shrinkage upon lyophilization.[13] Previous work showed that when gelatin was used as a matrix former, only tablets containing mannitol showed good tablet properties.[10] All the prepared tablets were located within the acceptable weight variation range; the relative standard deviation (RSD) of the tablet mass ranged from less than 1% to less than 4% for all formulations and the mean % NM content in ODTs was found to be more than 90% from all formulations. Friability studies showed that tablets formulated with 2% cellulosic binder and 10% MD as matrix former did not comply with compendial limit for friability, namely ODTs M2, M5, M6, and M10, where the percentage weight loss was 1.77%, 8.00%, 6.36%, and 2.85%, respectively. The decreased mechanical properties of these formulations could be attributed to the low concentration of binder which was not enough to bind the large solid content present in these tablets as they all contained 10% MD-DE 29.

Analysis of the experimental design

In order to investigate the effect of the used excipients, and their interaction on the properties of the prepared ODTs, a $3^1.2^2$ full factorial design with 12 test runs was carried out. ANOVA test was applied for estimating the significance of the model, at 5% significance level. A model is considered significant if the p value ≤ 0.05. In addition, graphical analysis of responses was carried out. This analysis allowed the important factors for the considered responses to be pointed out and the optimum factor level to be selected.[14,15]

Results from the friability testing show that only the concentration of cellulosic binder had a significant effect on the friability of tablets ($p = 0.0393$). Increasing the concentration of the cellulosic binder from 2% to 3% resulted in a significant decrease in the friability of tablets. This could be attributed to the high binding capacity at the higher binder concentration. On the other hand, the type of cellulosic binder and the concentration of MD-DE 29 had no significant effect on the friability of tablets ($p = 0.0984$, and $p = 0.668$, respectively).

Results showed that the longest disintegration times were taken by tablets prepared using Methocel® A15 as a binder. On the other hand, tablet formulations containing Methocel® E5, and Methocel® E15 disintegrated in less than 70 sec. Statistical analysis revealed that the type of cellulosic binder had a significant effect on the *in vitro,* and *in vivo* disintegration time of tablets ($p = 0.0008$, and $p = 0.0005$, respectively). Statistical analysis also revealed that increasing the concentration of cellulosic binder resulted in a significant increase in the *in vitro,* and *in vivo* disintegration time of tablets ($p = 0.0015$, and $p = 0.0013$, respectively). These results comply with the results of friability testing of tablets, where increasing the concentration of cellulosic binder resulted in decreasing the friability of tablets. Again this could be attributed to the high binding capacity at the higher binder concentration. Figure 1 shows the effect of the type and concentration of cellulosic binder on the *in vitro* disintegration time of tablets (similar results were observed for the *in vivo* disintegration time). It is noticeable that the effect of increasing the concentration of cellulosic binder on prolonging the *in vitro,* and *in vivo* disintegration time of tablets was more pronounced when Methocel® A15 was used as a binder. This may be attributed to the higher hydrophilic nature of Methocel® E5 and Methocel® E15 compared to Methocel® A15, owing to the presence of more polar groups (hydroxyl group).

On the other hand, the concentration of the matrix former, MD-DE 29, had no significant effect on the *in vitro,* and *in vivo* disintegration studies ($p = 0.0642$, and $p = 0.0592$). These results are not in accordance with the results obtained by Corveleyn and Remon[7,8] in a study on formulating rapidly disintegrating tablets of hydrochlorothiazide by lyophilization. They reported that increasing the maltodextrin concentration in the tablets resulted in a significant decrease in tablet porosity and an increase in tablet disintegration time. On the other hand, Mollan and Celik[16,17] stated that the slow disintegration of maltodextrin containing tablets was not controlled by the porosity of the tablet, but by a gel layer which is formed around the tablet on immersion in water. This layer limited water penetration and was the controlling factor in disintegration behavior in maltodextrin containing tablets.

From Table 1, it is noticeable that *in vivo* disintegration times were shorter when compared to corresponding *in vitro* disintegration times for all formulations. In a previous study,[10] ODTs made using gelatin as matrix former also showed the same pattern, i.e. shorter *in vivo*

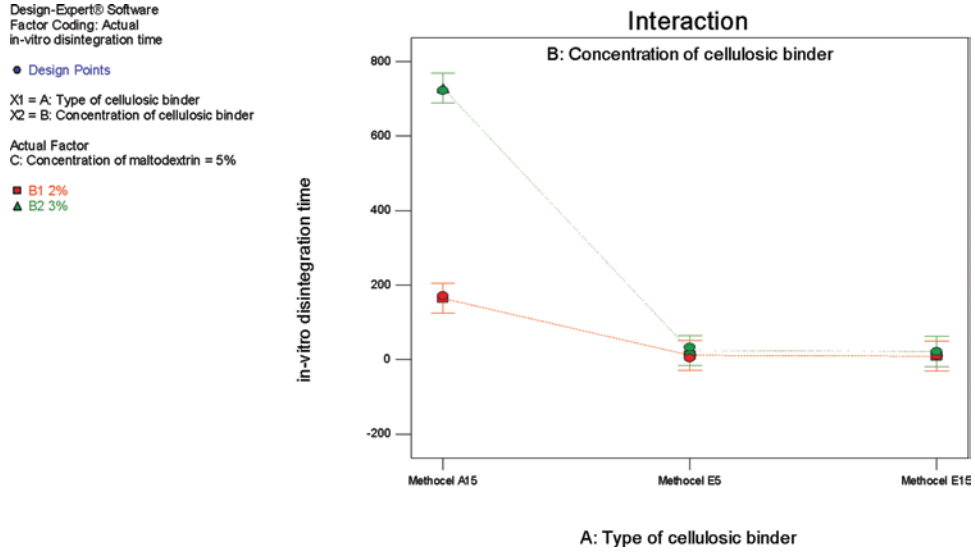

Figure 1. Interaction plot showing the effect of type and concentration of cellulosic binder on the *in vitro* disintegration time of ODTs.

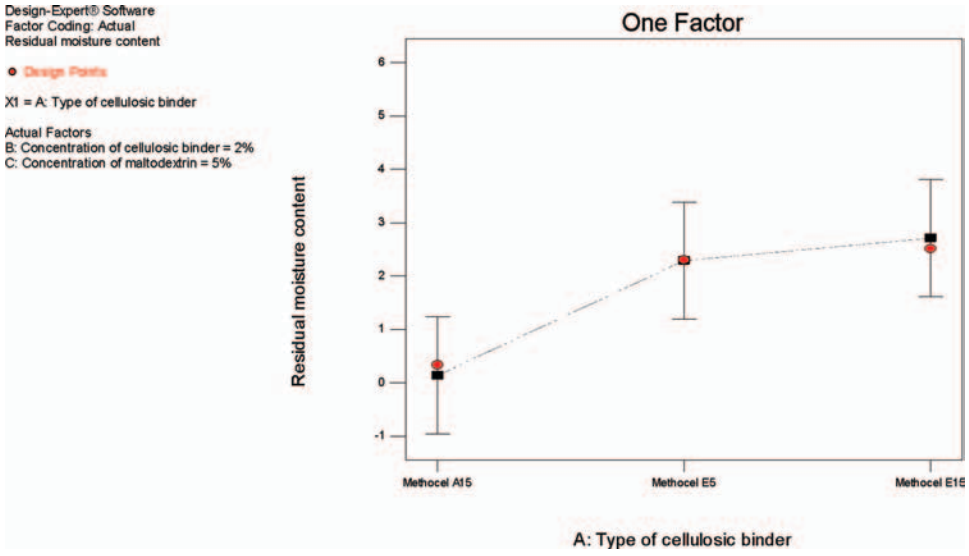

Figure 2. Effect of the type of cellulosic binder on the residual moisture content of ODTs.

disintegration times compared to *in vitro* disintegration times. However, published work showed that *in vitro* disintegration time can be significantly longer or shorter than disintegration time *in vivo*.[18]

The residual moisture content in all tablets was no more than 4% indicating that the lyophilization process was efficient in removing water from the tablets. ANOVA results revealed that the type of cellulosic binder had a significant effect on the residual moisture content of the prepared tablets ($p = 0.0185$). Figure 2 shows that tablets prepared using Methocel® A15 as a binder had a significantly lower residual moisture content compared to those containing Methocel® E5 and Methocel® E15 as a binder. This may be attributed to the higher hydrophilic nature of Methocel® E5 and Methocel® E15 compared to Methocel® A15, which resulted in more retention of moisture, owing to the presence of more polar groups (hydroxyl group).

In vitro dissolution studies

Dissolution results from ODTs compared to NM plain powder and the market product Sulide® are illustrated in Figures 3–5. The rate and extent of drug dissolution were greatly enhanced from the prepared ODT formulations compared to the plain drug and the commercial tablet. Results show rapid dissolution of drug from tablets containing Methocel® E5 and Methocel® E15. Statistical analysis revealed that only the type of cellulosic binder had a significant effect on the percentage drug dissolved after 2 min. Tablets containing Methocel®A15 showed significantly smaller percentage drug dissolved after 2 min compared to those containing Methocel®E5 or Methocel®E15 ($p = 0.004$) (Figure 6). These results are in accordance with the *in vitro, and in vitro* disintegration time results and again could be attributed to the high hydrophobic nature of the Methocel® A15 grade.

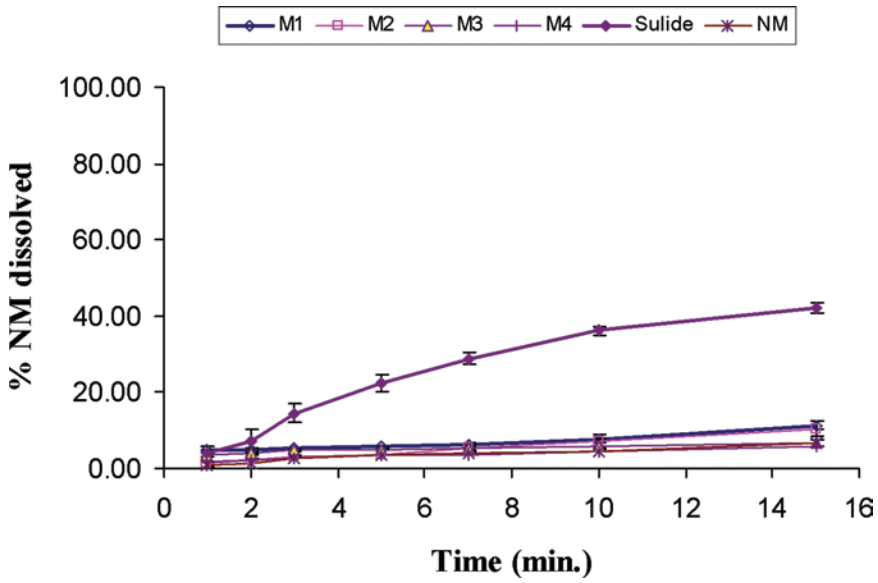

Figure 3. Dissolution profiles of NM plain powder and NM in ODTs containing Methocel® A15 as a binder in SSF (pH = 6.8) and NM in commercial tablets in SIF (pH = 7.4) at 37°C ($n = 3$)

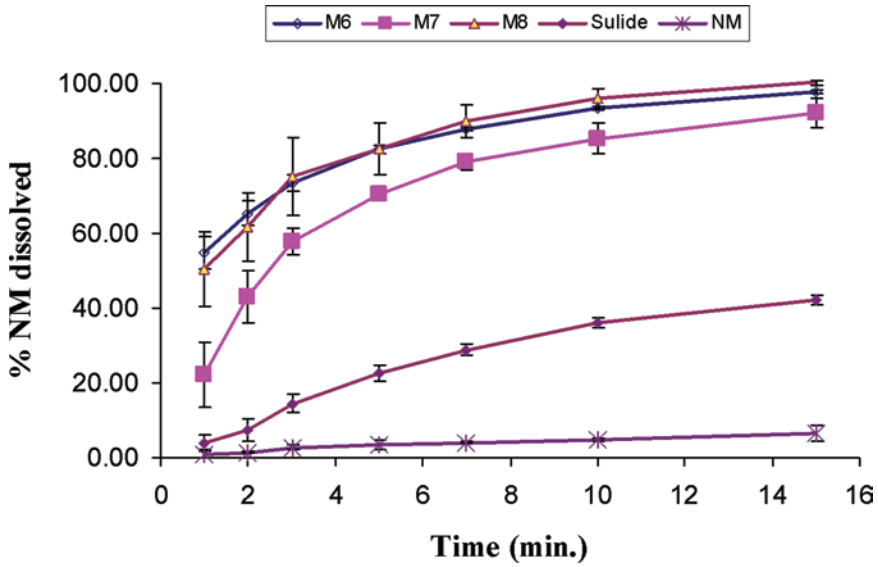

Figure 4. Dissolution profiles of NM plain powder and NM in ODTs containing Methocel® E5 as a binder in SSF (pH = 6.8) and NM in commercial tablets in SIF (pH = 7.4) at 37°C ($n = 3$).

Although the concentration of cellulosic binder had a profound effect on the disintegration time of tablets, ANOVA results revealed that it had no significant effect on the percentage drug dissolved after 2 min ($p = 0.0689$). ANOVA results also revealed that the concentration of the matrix former, MD-DE 29, had no significant effect on the percentage drug dissolved after 2 min ($p = 0.1429$).

Optimization

The aim of the optimization of pharmaceutical dosage formulations is generally to determine the levels of variables from which a robust product with high quality characteristics may be produced. Most of the developed ODTs show a disintegration time of around one minute depending on tablet formulation, however, it is preferable to have a short disintegration time of 30 sec or less especially if the drug is to be mainly absorbed from the buccal mucosa such as in case to bypass the liver.[19] Since NM is a drug that is largely eliminated via metabolic transformation it is necessary that the tablet disintegrates within few seconds and rapidly dissolve so that most of drug absorption takes place in the mouth cavity before being swallowed.

The ODT formulation was optimized for the responses Y1–Y5. The desirable range of these responses was restricted to $0\% \le Y1 \le 1\%$, $0 \le Y2 \le 180$ sec., $0 \le Y3 \le 60$ sec., $0 \le Y4 \le 3\%$, and $60\% \le Y5 \le 75\%$, respectively. The target ranges of these responses were selected based on the required properties for successful ODTs having sufficient mechanical strength and yet maintaining fast disintegration and dissolution of the drug; friability ≤ 1%, *in vitro*

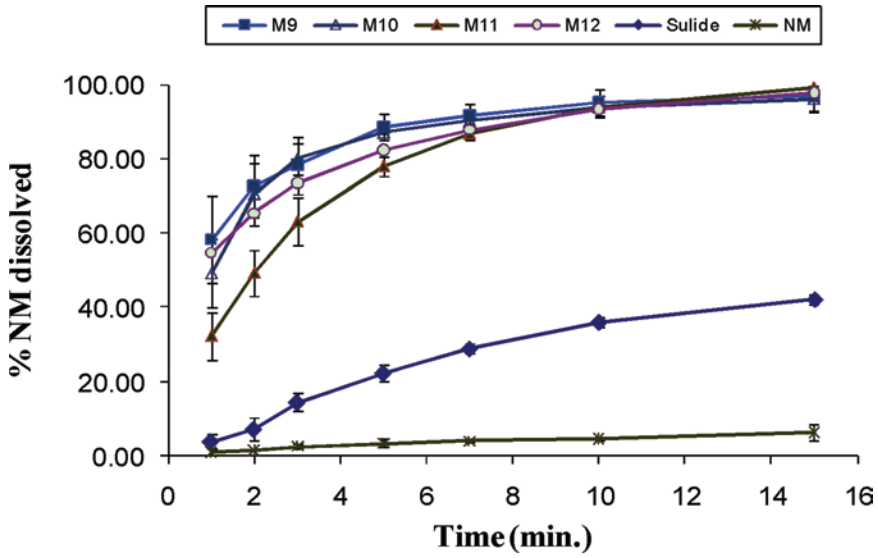

Figure 5. Dissolution profiles of NM plain powder and NM in ODTs containing Methocel® E15 as a binder in SSF (pH = 6.8) and NM in commercial tablets in SIF (pH = 7.4) at 37°C (n = 3).

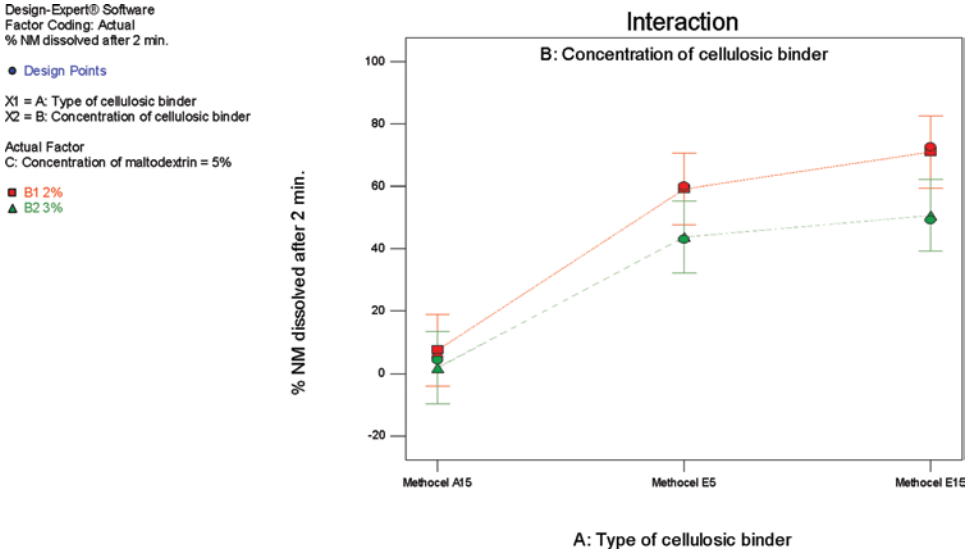

Figure 6. Interaction plot showing the effect of type and concentration of cellulosic binder on the percentage NM dissolved after 2 min from different ODTs.

disintegration time ≤ 180 sec., *in vivo* disintegration time ≤ 60 sec., residual moisture content ≤ 3%, and high percentage NM released between 60% and 75%. The optimum values of the variables were obtained by graphical and numerical analyses using the Design-Expert® software and based on the criterion of desirability.

The composition and predicted and observed responses of the optimized ODT formulation are presented in Table 2. The optimized ODT contained 5% w/v MD, 2% w/v Methocel®E15, and 5% w/v NM. Results showed that the observed values of the optimized formulation were highly similar to the predicted values. Based on these results, it can be concluded that optimized NM ODT provides a promising manufacturing procedure directly resulting in orodispersable tablets without any other mixing or formulation steps, therefore, it was selected for further investigations.

Table 2. Composition and predicted and observed responses of the optimized ODT formulation.

Variables	Values	Response	Predicted values	Observed values
X_1	Methocel® E15	Y_1	0.73%	0.45%
X_2	2%	Y_2	9.42 sec	12.34 sec
X_3	5%	Y_3	10.03 sec	11.54 sec
		Y_4	2.71%	2.94%
		Y_5	71.05%	70.43%

Differential scanning calorimetry (DSC) studies

Figure 7 shows the DSC thermogram of NM plain powder, the optimized ODT, and its physical mixture. DSC studies were done to evaluate the crystalline state of NM in NM plain powder, the optimized ODT, and its corresponding physical mixture. DSC of other excipients in

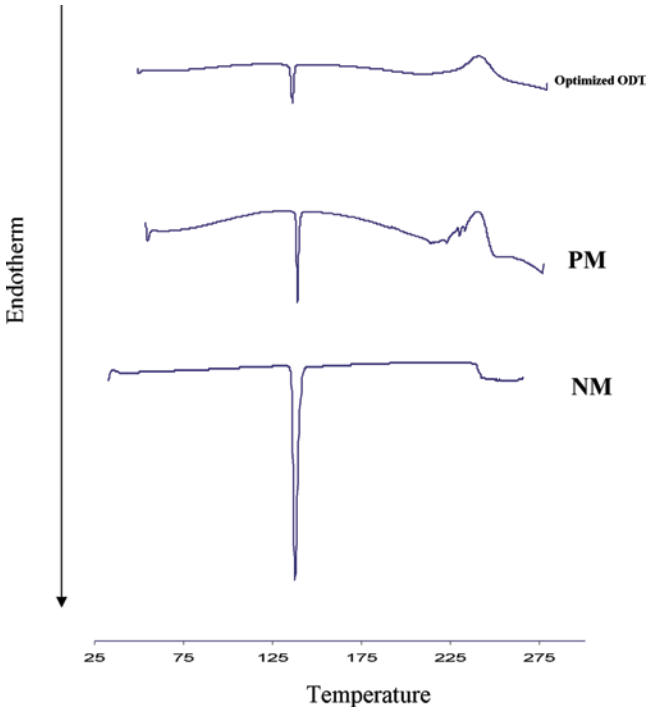

Figure 7. DSC thermograms of NM plain powder (NM), NM in physical mixture (PM) and NM in the optimized ODT.

the formulations such as MD-DE 29 was also performed. The DSC thermogram of NM showed a sharp endothermic peak at nearly 147°C corresponding to its melting transition point. The thermogram of the optimized ODT showed a small endotherm of the drug suggesting significant reduction in the crystallinity of the drug. The thermogram of the corresponding physical mixture showed larger endothermic peak of NM indicating that the crystallinity is retained in the physical mixture. The reduced crystallinity of the drug in the optimized ODT suggests that mostly an amorphous form existed in the ODT which might explain the faster dissolution of the drug from the lyophilized tablet compared to the physical mixture, and the plain powder.

Powder X-ray diffraction (XRD)

Figure 8 shows the powder XRD pattern of NM plain powder, the optimized ODT and its corresponding physical mixture. The crystalline nature of NM powder is exhibited by a strong and characteristic XRD pattern. NM shows intense scattering peaks located at 12.03°, 19.34°, and 21.6° 2θ. The diffraction pattern of the physical mixture of the drug and excipients showed the peaks corresponding to the crystalline drug molecules present in the mixture. The diffraction pattern in optimized ODT

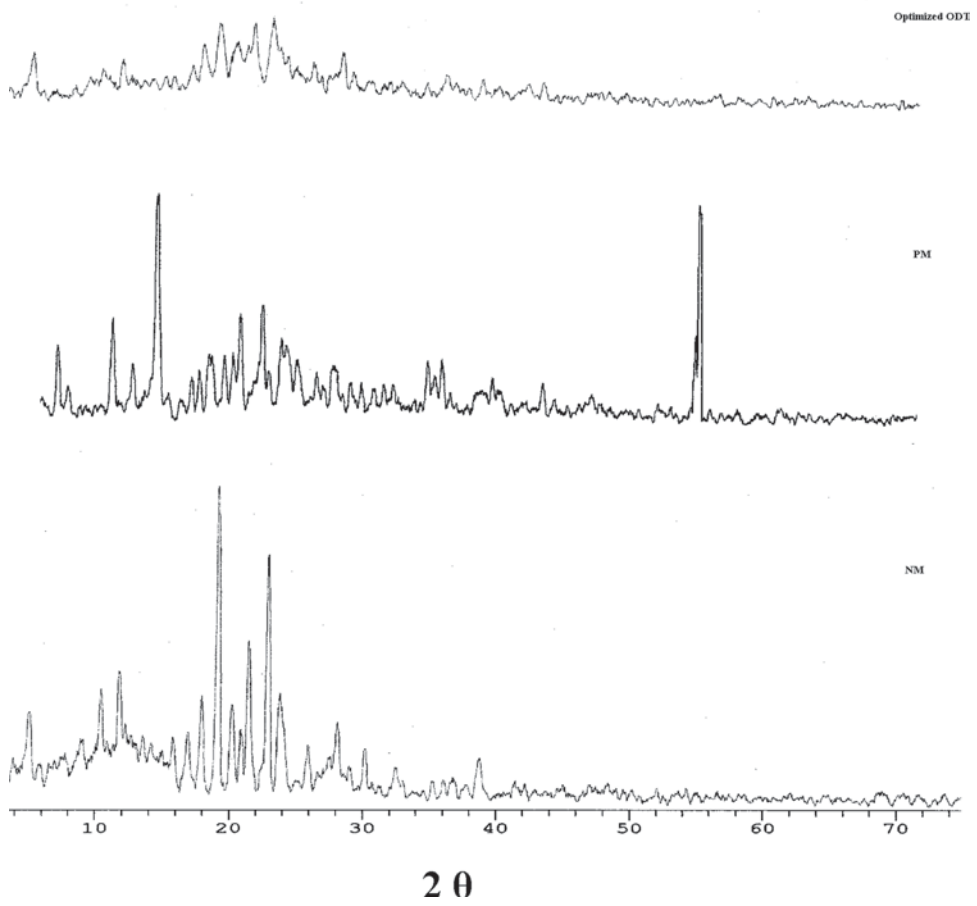

Figure 8. Powder X-ray diffraction spectra of NM plain powder (NM), NM in physical mixture (PM) and NM in the optimized ODT.

showed absence, broadening and reduction of major NM diffraction peaks indicating that mostly an amorphous form (disordered state) existed in the ODT. The relative degree of crystallinity (*RDC*) was calculated using the following relationship:

$$\mathrm{RDC} = I_{\mathrm{sam}} \cdot / I_{\mathrm{drug}}$$

where I_{sam}. = the peak height of the sample (ODT) under investigation, and I_{drug} = the peak height at the same angle for the drug.[20] Pure drug peak at 19.34° 2θ was used for calculating the *RDC*. The calculated *RDC* value for the optimized ODT was 0.22. These results are in agreement with DSC results and again explain the faster dissolution obtained from optimized ODT compared to its physical mixture, and the plain drug. The amorphous state of the drug is often preferred in solid dispersions, since it shows improved solubility and dissolution rate.

Conclusion

A promising formulation of a lyophilized tablet of NM made only of maltodextrin and a cellulosic binder is successfully prepared. The study suggests that the optimized formulation developed in this work may be an alternative to conventional formulations of NM inconvenient to the patients such as intramuscular or rectal administration.

Declaration of interest

The authors report no declaration of interest.

References

1. Ciper M, Bodmeier R. Modified conventional hard gelatin capsules as fast disintegrating dosage form in the oral cavity. Eur J Pharm Biopharm 2006;62:178–184.
2. Mizumoto T, Masuda Y, Yamamoto T, Yonemochi E, Terada K. Formulation design of a novel fast-disintegrating tablet. Int J Pharm 2005;306:83–90.
3. Maya MT, Goncalves NJ, Silva NE, Filipe AE, Morais JA, Caturla MC et al. Comparative bioavailability of two immediate release tablets of enalapril/hydrochlorothiazide in healthy volunteers. Eur J Drug Metab Pharmacokinet 2002;27:91–99.
4. Lohitnavy M, Lohitnavy O, Wittaya-areekul S, Sareekan K, Polnok S, Chaiyaput W. Average bioequivalence of clarithromycin immediate released tablet formulations in healthy male volunteers. Drug Dev Ind Pharm 2003;29:653–659.
5. Carpay J, Schoenen J, Ahmad F, Kinrade F, Boswell D. Efficacy and tolerability of sumatriptan tablets in a fast-disintegrating, rapid-release formulation for the acute treatment of migraine: results of a multicenter, randomized, placebo-controlled study. Clin Ther 2004;26:214–223.
6. Papadimitriou E, Efantakis M, Choulis NH. Evaluation of maltodextrins as excipients for direct compression tablets and their influence on the rate of dissolution. Int J Pharm 1992;86:131–136.
7. Corveleyn S, Remon JP. Formulation and production of rapidly disintegrating tablets by lyophilization using hydrochlorothiazide as a model drug. Int J Pharm 1997;152:215–225.
8. Corveleyn S, Remon JP. Formulation of a lyophilized dry emulsion tablet for the delivery of poorly soluble drugs. Int J Pharm 1998;166:65–74.
9. Vennat B, Gross D, Pourrat A, Legret P. [Oral freeze-dried forms of procyanidins]. J Pharm Belg 1993;48:430–436.
10. Shoukri RA, Ahmed IS, Shamma RN. *In vitro* and *in vivo* evaluation of nimesulide lyophilized orally disintegrating tablets. Eur J Pharm Biopharm 2009;73:162–171.
11. European Pharmacopoeia fourth ed., Suppl. 4.1. Published by the directorate for the quality of medicines of the council of Europe 9EDQM, Strasbourg, France, 2002b.
12. Abdelbary G, Eouani C, Prinderre P, Joachim J, Reynier J, Piccerelle P. Determination of the *in vitro* disintegration profile of rapidly disintegrating tablets and correlation with oral disintegration. Int J Pharm 2005;292:29–41.
13. Furlanetto S, Maestrelli F, Orlandini S, Pinzauti S, Mura P. Optimization of dissolution test precision for a ketoprofen oral extended-release product. J Pharm Biomed Anal 2003;32:159–165.
14. Furlanetto S, Cirri M, Maestrelli F, Corti G, Mura P. Study of formulation variables influencing the drug release rate from matrix tablets by experimental design. Eur J Pharm Biopharm 2006;62:77–84.
15. `Dekeyser PM, Corveleyn S, Demeester J, Remon JP. Stabilization of fully active chymopapain by lyophilization. Int J Pharm 1997;159:19–25.
16. Mollan MJ, Celik M. Characterization of directly compressible maltodextrins manufactured by three different processes. Drug Dev Ind Pharm 1993;19:2335–2358.
17. Mollan MJ, Celik M. Tabletability of maltodextrin and acetaminophen mixtures. Drug Dev Ind Pharm 1994;20:3131–3149.
18. Dobetti L. Fast-Melting Tablets: Developments and Technologies. Pharm Technol 2001;25:44–50.
19. Kuno Y, Kojima M, Ando S, Nakagami H. Evaluation of rapidly disintegrating tablets manufactured by phase transition of sugar alcohols. J Control Release 2005;105:16–22.
20. Buchi Nalluri N, Chowdary KPR, Murthy KVR, Becket G, Peter Crooks A. Tablet formulation studies on nimesulide and meloxicam – cyclodextrin binary systems. AAPS Pharm Sci Tech 2007;8, Article 36.