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Research paper

In vitro and in vivo evaluation of nimesulide lyophilized orally disintegrating tablets

Raguia Ali Shoukri [a], Iman Saad Ahmed [b,*], Rehab N. Shamma [a]

[a] Department of Pharmaceutics and Industrial Pharmacy, Cairo University, Cairo, Egypt
[b] Department of Pharmacology and Pharmaceutics, College of Pharmacy, University of Sharjah, Sharjah 27271, United Arab Emirates

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ABSTRACT

Development of a lyophilized orally disintegrating tablet (ODT) that enhanced the in vitro dissolution and in vivo absorption of nimesulide (NM), a drug with poor solubility and poor bioavailability, is presented. The ODTs were prepared by freeze-drying an aqueous dispersion of NM containing a matrix former, a sugar alcohol, and a collapse protectant. In addition, different disintegration accelerators were tested. The influence of formulation parameters on the disintegration time and in vitro dissolution of NM from ODTs along with other tablet characteristics was investigated. Results obtained from disintegration and dissolution studies showed that lyophilized ODTs disintegrated within few seconds and showed significantly faster dissolution rate of NM compared to the plain powder drug and NM in commercially available immediate release tablet Sulide®. The ODTs were also examined using differential scanning calorimetry, X-ray diffraction, and scanning electron microscope. Stability results, after 12-month storage of selected ODTs at 25 °C and 60% relative humidity, were satisfactory. The extent of absorption of NM from a selected ODT when compared to an conventional immediate release tablet as a reference after administration of 100 mg oral dose of NM was determined in healthy subjects using a randomized cross-over design. In this study, the rate of absorption of NM from ODT was faster than that from the reference tablet, had a significantly higher ($p = 0.012$) peak plasma concentration, and shortened time to C_{max} by 1 h ($p = 0.029$). The extent of absorption expressed by AUC was 62% larger when compared to the commercially available tablet.

1. Introduction

Clinically, non-steroidal anti-inflammatory drugs (NSAIDs) are the most frequently prescribed preparations. Nimesulide (NM), a preferential COX-2 inhibitor, shows high anti-inflammatory, antipyretic and analgesic activity with moderate incidence of gastric side effects and a high therapeutic index [1]. NM belongs, according to the biopharmaceutic classification system (BCS), to Class II drugs with poor solubility and high permeability [2,3]. Class II drugs suffer from low bioavailability following oral administration of traditional dosage forms. NM is virtually insoluble in aqueous systems (solubility 0.01 mg/ml) [4]. The very poor aqueous solubility and wettability of NM gives rise to difficulties in the pharmaceutical formulation of oral or injectable solutions and leads to a variable bioavailability. Several studies have been carried out to increase the aqueous solubility of NM such as by complexing NM with β-cyclodextrin [5,6] or by incorporating it within a NM-L-lysine–β-cyclodextrin complex [4]. An enhanced dissolution of NM from crystals prepared by solvent change (ethanol to water, 1:1) in the presence of Tween 80 (1%) has also been reported [7]. In all these studies, in vivo testing in human volunteers was not reported.

In this study, ODTs containing NM were prepared by a freeze-drying technique in order to improve the dissolution rate and oral bioavailability of NM. NM is largely eliminated via metabolic transformation [8]; therefore, an ODT of NM that is partially absorbed through the oral mucosa directly enters the systemic circulation, bypassing the gastrointestinal tract and first-pass metabolism of the liver, which may result in an increase in the fraction of drug reaching the systemic circulation and also result in a rapid onset of action via a more comfortable and convenient delivery route than the intravenous route.

2. Materials and methods

2.1. Materials

Nimesulide was kindly supplied by Alkan Pharma, Egypt. Sorbitol and mannitol were kindly supplied by Roquette Pharma, France. Gelatin, glycine, Tween 20, Tween 80, sodium chloride and potassium chloride were received from Adwic, El-Nasr Pharmaceutical Chemicals Co., Egypt. Polyethylene glycol (PEG 400, PEG 4000 and PEG 6000) and polyvinyl pyrrolidine (PVP K25, PVP K30 and PVP K 90) were purchased from Fluka AG (Buchs, Switzerland). The water used was distilled de-ionized water. All other chemicals were reagent grade and used as received. Sulide® 100 mg (Alkan, Egypt) was used as a reference tablet in in vivo studies.

* Corresponding author. Department of Pharmacology and Pharmaceutics, College of Pharmacy, University of Sharjah, UAE. Tel.: +971503794374.
E-mail address: Iman.Saad@Lycos.com (I.S. Ahmed).

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2.2. Preparation of ODTs

Nimesulide ODTs were prepared using gelatin as a matrix former, a sugar alcohol (sorbitol or mannitol) and a collapse protectant (glycine). Gelatin was used in three different concentrations (1%, 2% and 3% w/v), while the two sugar alcohols and glycine were used at a concentration of 0.886% w/v. The percentage of sugar alcohol and glycine used was optimized during the formulation process to result in a strong and elegant tablet that could be handled with ease. Gelatin was first dissolved in distilled water at about 40 °C to obtain the required concentration. Sorbitol (or mannitol) and glycine were then added to the gelatin solution in the predetermined concentration. 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 PVC blister pack with a diameter of 13 mm and a depth of 3 mm resulting in a dose of 50 mg per tablet. The tablet blister packs were then transferred to a freezer at −22 °C and kept in the freezer for 24 h. The frozen tablets were placed in a lyophilizer for 24 h using a Novalyphe-NL 500 Freeze Dryer with a condenser temperature of −45 °C and a pressure of 7×10^{-2} mbar. The best of these formulations (based on tablet properties) was taken forward to the next stage which involved the addition of a water-soluble surface active agent or polymer in order to improve disintegration time and/or friability. These disintegration accelerators were sodium lauryl sulphate (SLS); three grades of PEG, namely PEG 400, PEG 4000 and PEG 6000; three grades of PVP, namely PVP K25, PVP K30 and PVP K90; and two grades of Tweens, namely Tween 20 and Tween 80. All of these were added at a concentration of 1% w/v except SLS, which was added at 0.05% w/v. The detailed composition of the prepared ODTs is presented in Table 1. The prepared ODTs were kept in tightly closed containers in desiccators over calcium chloride (0% relative humidity) at room temperature until further use.

2.3. Characterization of ODTs

2.3.1. Uniformity of weight

The test was carried out according to the European pharmacopoeia [9]. Twenty tablets, from each formula, were individually weighed and the mean of tablet weights was calculated. Results are presented as mean value ± standard deviation (SD).

2.3.2. Tablet friability

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 re-weighed (EP 2000). The percentage loss in weight was calculated and taken as a measure of friability.

Table 1
Composition of NM ODT formulations.

Formulation	Gelatin (%w/v)	Sorbitol (%w/v)	Mannitol (%w/v)	Glycine (%w/v)	Disintegration accelerators (%w/v)	NM (%w/v)
G1	1	0.886		0.886		5
G2	1		0.886	0.886		5
G3	2	0.886		0.886		5
G4	2		0.886	0.886		5
G5	3	0.886		0.886		5
G6	3		0.886	0.886		5
G7	2		0.886	0.886	0.05% SLS	5
G8	2		0.886	0.886	1% PEG 400	5
G9	2		0.886	0.886	1% PEG 4000	5
G10	2		0.886	0.886	1% PEG 6000	5
G11	2		0.886	0.886	1% PVP K25	5
G12	2		0.886	0.886	1% PVP K30	5
G13	2		0.886	0.886	1% PVP K90	5
G14	2		0.886	0.886	1% Tween 20	5
G15	2		0.886	0.886	1% Tween 80	5

2.3.3. 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, USA) according to EP (2002) specifications. 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 utmost accuracy. All results are presented as mean value ± SD ($n = 6$).

2.3.4. 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 [10].

2.3.5. Wetting time

Ten milliliters of distilled water containing eosin, a water-soluble dye was placed in a Petri dish of 10 cm diameter. Tablets were carefully placed in the centre of the Petri dish and the time required for water to reach the upper surface of the tablet was noted as the wetting time. The test results are presented as mean value of three determinations ± SD [11].

2.3.6. Moisture analysis

The tablets were analyzed for their residual moisture content after lyophilization 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 ($n = 3$).

2.3.7. In vitro dissolution studies

The dissolution profiles of NM in ODTs compared with the plain drug were determined in a dissolution tester (Pharma Test Dissolution Tester, Germany) following the USP paddle method. All tests were conducted in 900 ml simulated saliva fluid without enzymes (SSF) at pH = 6.8. The dissolution medium was maintained at a temperature of 37 ± 0.5 °C with a paddle rotation speed at 50 rpm. The amount of drug used was equivalent to 50 mg. At specified time intervals (1, 2, 3, 5, 7, 10, and 15 min), 3 ml of dissolution medium was withdrawn and replaced with an equal volume of fresh medium to maintain a constant total volume. Samples were 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 cal-

culated using calibration equation. Dissolution tests were performed in three vessels per formulation ($n = 3$). The market product, Sulide®, was also tested in the same way for comparison purposes using simulated intestinal fluid without enzymes at pH 7.4.

2.3.8. Differential scanning calorimetry (DSC) studies

Samples weighing approximately 5 mg were obtained by cutting small pieces from the tablets using a blade. 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/min in the range of 20–350 °C. Thermograms for NM plain powder and NM in selected tablet formulations and their corresponding physical mixtures were obtained.

2.3.9. Powder X-ray diffraction (XRD)

X-ray diffraction experiments were performed 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. Diffraction patterns of NM plain powder and NM in selected tablet formulations and their corresponding physical mixtures were obtained.

2.3.10. Scanning electron microscopic (SEM) analysis

Surface morphology and cross-sections of selected tablet formulations were examined using Jeol JSM-6400 scanning electron microscope (Tokyo, Japan). Cross-section samples were prepared by cutting a thin slice of the tablet using a scalpel.

2.4. Storage of ODTs

Selected tablet formulations were stored in PVC blisters covered with aluminum foil at room temperature and 60% relative humidity during a period of 12 months [12]. The relative humidity was maintained using ammonium nitrate (NH_4NO_3)- saturated salt solution. Stability was assessed by comparing the results from in vitro disintegration, dissolution studies, and residual moisture content analysis experiments at 0-, 3-, 6-, and 12-month storage. To evaluate the crystalline state of NM in selected stored ODTs, DSC and XRD studies were also performed. The results were checked for statistical significance using the one-way analysis of variance (ANOVA) *F*-test for testing the equality of several means. A p-value > 0.05 was considered statistically insignificant.

2.5. In vivo absorption studies

2.5.1. Study design

The study was carried out to compare the pharmacokinetics of NM from a selected ODT formulation (G13) to a conventional commercially available immediate release (IR) tablet (Sulide®, Alkan) following the administration of single doses equivalent to 100 mg each using a non-blind, two-treatment, two-period, randomized crossover design. Four healthy male volunteers participated in the study after giving informed written consent and were randomly assigned to one of two groups of equal size. The subjects ranged in age from 20 to 45 years (mean 34), in height from 165 to 178 cm (mean 171 cm) and in weight from 68 to 79 kg (mean 73 kg). The study was approved by the University Protection of Human Subjects Committee and the protocol complies with Helsinki and Tokyo declarations for humans. Health status of the volunteers was confirmed by complete medical history, physical examination and laboratory analysis for complete hematological and biochemical examination. The subjects were instructed to take no medicines for 1 week prior to and during the course of the study. The subjects were received in the facility at 7.00 a.m. of the study day after an overnight fast as instructed before the study. All subjects fasted for at least 10 h before the study day [13]. From this time on, they remained at the study site under controlled dietary and liquid intake until the end of the study day. No food was allowed for 4 h after dosing. The washout time was 1 week. The ODT was administered orally without water (two tablets per dose, each 50 mg), and each subject was asked to keep the ODT in the mouth until it was completely dissolved in the saliva (Treatment A). Water was allowed after 30 min. The IR tablet (one tablet, 100 mg), Sulide®, was ingested with 200 ml of water (treatment B). Venous blood samples (10 ml) were collected in heparinized glass tubes at the following time points: 0 (predose), 15, 30 min and 1, 2, 3, 4, 6, 8, 12 and 24 h after administration of a treatment. Plasma was immediately separated from the blood cells by centrifugation at 2000*g* for 10 min and stored frozen at −20 °C until ready to be analyzed.

2.5.2. Chromatographic conditions

Plasma concentrations of NM were determined following the HPLC procedure described by Ptáček et al. [14]. The mobile phase consisted of acetonitrile–methanol–15 mM potassium dihydrogen phosphate buffer, pH 7.3 (30:5:65 v/v) and was delivered to the system at a flow rate of 1 ml/min. The column was a reversed-phase column (Nucleosil C_{18}, particle size 10 μm, 250 mm × 4.6 mm, Germany). The detector was ultraviolet variable wavelength detector (Model SPD-10 A, Shimadzu, Japan). The detection wavelength was 404 nm. Peak areas were determined with C-R6A chromatopac integrator (Shimadzu, Japan). All assays were performed at ambient conditions.

2.5.3. Standard solutions

Blank plasma samples were spiked with NM methanolic stock solution (100 mg/l) to contain 0.0625, 0.125, 0.25, 0.5, 1, 2, 4, and 6 μg/ml of NM. The analytical method consists of single-step extraction of NM from plasma with 1 ml methanol. The samples were vortexed for 30 s and centrifuged for 5 min at 3500*g*. A 500 μl aliquot of the supernatant was added to 500 μl of the buffer (15 mM KH_2PO_4, pH adjusted to 7.3 using 1 M KOH) and the vial was briefly shaken. A sample of 25 μl was injected onto the HPLC column. Retention time of NM was 5.3 min. A standard curve was constructed by plotting the peak area of NM against NM concentrations in plasma. The lower limit of quantification was 0.025 μg/ml and linear response across the full range of concentrations from 0.0625 to 6 μg/ml ($r^2 = 0.999$) was obtained.

2.5.4. Plasma analysis

The plasma obtained from the four subjects after receiving treatment A and treatment B was assayed as described above without the addition of NM.

2.5.5. Pharmacokinetic analysis

Pharmacokinetic characteristics from plasma data following administration of the two treatments were estimated for each subject by using a computer program, WinNonlin® (version 1.5, Scientific consulting, Inc., NC). Non-compartmental analysis was used. C_{max} (μg/ml) and t_{max} (h) were the observed maximal drug concentration and its time, respectively. The area under the curve, AUC_{0-24}, (μg h/ml) was determined as the area under the plasma concentration–time curve up to the last measured sampling time point calculated by the linear trapezoidal rule. The area under the curve from zero to infinity, $AUC_{0-\infty}$ (μg h/ml), was calculated as $AUC_{0-\infty} = AUC_{0-24} + C_t/k$ where C_t is the last measured concentration at the time t, and k is the terminal elimination rate constant estimated by log-linear regression analysis on data visually assessed to be a terminal log-linear phase. Apparent terminal elimination half-life ($t_{1/2}$) was calculated as $t_{1/2} = 0.693/k$. Mean residence time (MRT) was calculated from AUMC/AUC. The relative bioavailability (f_{rel}) was calculated as $(AUC_{ODT}/AUC_{IR}) \times 100$.

2.5.6. Statistical analysis

Descriptive statistics were provided for all pharmacokinetic parameters for all subjects. An ANOVA was performed on untransformed and log-transformed data for the pharmacokinetic parameters, C_{max}, AUC_{0-24}, $AUC_{0-\infty}$ and untransformed data for $t_{1/2}$ using the software SPSS 11.0 (SPSS Inc., Chicago, USA). Statistical inference were based on both untransformed and log-transformed values for the C_{max}, AUC parameters and observed values for $t_{1/2}$. The non-parametric Signed Rank Test (Mann–Whitney's test) was used to compare the t_{max} for test and reference. The level of significance was $\alpha = 0.05$. A p-value of $\leqslant 0.05$ was considered statistically significant. The sample size ($n = 4$) was selected not based on statistical consideration but rather on economic consideration.

3. Results and discussion

3.1. Characterization of NM ODTs

All formulations resulted in successfully dried and elegant tablets that withstood manual handling. All the prepared tablets were located within the acceptable weight variation range; the relative standard deviation of the tablet mass ranged from 1% to 5% for the different formulations and the mean% NM content in ODTs was found to be more than 95% from all formulations. All tablets showed residual moisture content of no more than 5%, indicating that the lyophilization process was efficient in removing water from the tablets. According to compendial standards, the tablets comply with the friability test if the weight loss during the friability test was less than 1%; in addition, the tablets should not break or show any capping or cracking during the test. Friability studies showed that tablets formulated with 2% and 3% gelatin showed no cracked or broken tablets in the tablet sample after tumbling and the calculated percentage weight loss was found to lie within the acceptable range for tablets (less than 1%) indicating that the tablets were non-fragile and could be handled easily. On the other hand, tablets formulated with 1% gelatin were friable and showed percentage weight loss that exceeded pharmacopoeial limits, namely G1 and G2, and showed percentage weight loss of 1.28%, and 2.22%, respectively. These formulations were excluded from further testing. The decreased mechanical properties of ODTs formulated with 1% gelatin could be attributed to the fewer number of crosslinks formed between the gelatin strands as the concentration decreases. It has been reported that increasing the gelatin concentration usually results in a more extensive and rigid 3D network after freeze-drying due to increase in the number of gelatin fibers forming crosslinks and interchain H-bonds, thereby resulting in an increase in the overall hardness of the tablets [15]. The percentage of relative standard deviation of the tablet mass, the mean% drug content, percentage of weight loss from friability studies, and residual moisture content for the prepared ODTs are listed in Table 2. It was also observed that tablets formulated with sorbitol (G1, G3, G5) showed significantly lower weight losses compared to tablets formulated with mannitol (G2, G4, G6) ($p < 0.05$). This is in accordance with previously reported results in which saccharides like mannitol, lactose and sucrose were described as poorly compressible or mouldable saccharides resulting in poor tablet hardness as they possess a lower surface free energy of the polar component of the saccharides compared to the surface free energy of highly compressible saccharides like sorbitol and trehalose, which usually result in the formation of harder tablets [16,17].

In vitro disintegration studies showed that ODTs containing sorbitol (G3, G5) showed longer disintegration times compared to ODTs containing mannitol (G4, G6). ODTs prepared using 3% gelatin (G5, G6) showed statistically significantly longer disintegration times compared to ODTs prepared using 2% gelatin ($p < 0.01$). ODTs G5 and G6 containing 3% gelatin showed average disintegration times of 93 s and 83.7 s, respectively, while ODTs G3 and G4 containing 2% gelatin showed average disintegration times of 26.7 and 19.0 s, respectively. These results indicate that increasing the gelatin concentration in the tablets results in the formation of more cohesive and stable gels that are less likely to break up or dissolve easily in water. These results are further confirmed by wetting time experiments in which tablets containing 3% gelatin show significantly higher wetting times compared to tablets containing 2% gelatin ($p < 0.01$). Short wetting time is indicative of the highly porous nature of the tablet matrix. In vitro disintegration results are also in accordance with friability results in which harder tablets (containing 3% gelatin and sorbitol) showed longer disintegration times. The average in vitro disintegration time, in vivo disintegration time and wetting time for the prepared ODTs are listed in Table 3.

Neither the EUP nor the USP has described disintegration tests specifically for fast disintegrating tablets, and the disintegration tests currently used are those described to test dispersible and effervescent tablets. Moreover, in vitro disintegration tests only approximate the true disintegration time in vivo. It has been reported that in vitro disintegration time may be significantly higher or lower than the disintegration time in vivo [18]. For this reason, disintegration of the prepared ODTs was tested in the mouth of human volunteers. Results show that in vivo disintegration times were shorter when compared to corresponding in vitro disintegration times for all formulations. All tablets disintegrated in less than 60 s, however, similar to in vitro results; ODTs prepared with 3% gelatin showed longer in vivo disintegration times compared to those prepared with 2% gelatin ($p < 0.05$).

Table 2
Influence of formulation parameters on weight variation, mean percentage of drug content, friability, and residual moisture content.

Formulation	Weight variation (%RSD)	Drug content (%)	Friability (%)	Residual moisture (%)
G1	2.10	96.80 ± 1.40	1.28	1.64 ± 0.41
G2	2.52	98.33 ± 0.76	2.22	1.74 ± 0.34
G3	0.88	95.03 ± 2.76	0.23	2.58 ± 1.59
G4	1.12	95.07 ± 1.96	0.7	2.01 ± 0.35
G5	1.15	97.80 ± 1.27	0.03	4.26 ± 2.34
G6	2.09	102.00 ± 1.98	0.42	5.06 ± 1.56

Data are mean values ± SD.

3.2. In vitro dissolution studies

The cumulative NM dissolved as a function of time from ODTs compared to NM plain powder and the market product Sulide® are illustrated in Fig. 1. Remarkable differences in the shape of the dissolution profiles of the prepared ODTs and those of the plain drug and commercial tablet are observed. The percentages of drug dissolved from ODTs G3, G4, G5 and G6 after 2 minutes were 62.5%, 71.9%, 21.5% and 40.9%, respectively, compared to only 1.52% and 7.25% for the plain drug and Sulide®, respectively. These results indicate

Table 3
Influence of formulation parameters on in vitro disintegration time, in vivo disintegration time and wetting time.

Formulation	In vitro disintegration time (s)	In vivo disintegration time (s)	Wetting time (s)
G3	26.7 ± 3.3	15.88 ± 1.30	44.21 ± 4.46
G4	19.0 ± 2.2	14.38 ± 1.44	33.80 ± 6.90
G5	93.0 ± 7.3	54.10 ± 12.86	145.46 ± 16.77
G6	83.7 ± 15.2	45.84 ± 9.11	125.00 ± 22.20

Data are mean values ± SD.

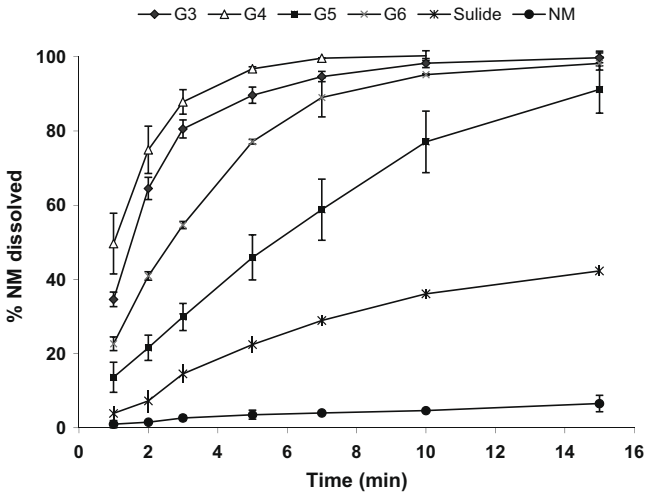

Fig. 1. Dissolution profiles of NM plain powder and NM in ODTs in SSF (pH = 6.8) and NM in commercial tablets in SIF (pH = 7.4) at 37 °C.

that the process used to prepare the ODTs greatly enhanced the extent and rate of dissolution of NM from the prepared tablets. ODTs containing 2% gelatin (G3 and G4) showed faster dissolution rates when compared to ODTs containing 3% gelatin (G5 and G6). These results correlate well with disintegration and wetting time testing results, where increasing the gelatin concentration resulted in longer disintegration and wetting times. Also tablet formulations containing mannitol (G4 and G6) showed faster drug release than the corresponding formulations containing sorbitol (G3 and G5). Similar results were obtained in a study on improving the dissolution rates of hydrocortisone and prednisone utilizing solid sugar dispersion systems [19]. The study revealed that the mannitol system had the fastest dissolution rate followed by the sorbitol–mannitol system, the sucrose–mannitol system, and then finally the sorbitol dispersion system. The percentage of drug dissolved from all ODT formulations was almost 100% after 15 min compared to only 6.56% and 42.3% for the plain powder drug and Sulide® tablets.

Although the European Pharmacopoeia describes orodispersible tablets as tablets which should disintegrate within 3 min, many critics find that a maximum disintegration time of 3 min for any tablet is too long and that the presence of a gritty tablet in the patient's mouth for 3 min would be unpleasant and uncomfortable. According to the literature, the oral disintegration time of mouth-dissolved tablets is one minute or less, preferably about 30 s or less [20]. Also because NM ODT was designed to be mainly absorbed from the buccal mucosa to bypass the liver, 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. Therefore, the best of the abovementioned formulations (judged based on tablet properties) was taken forward to the next stage, which involved the addition of water-soluble excipient, mainly a surface active agent or polymer, in order to improve disintegration time and/or friability.

Orally disintegrating tablet G4 showed the highest and the fastest drug dissolution during the first two minutes (71.9%), in addition to fast disintegration and fast wetting. Although G4 tablet showed slightly higher friability compared to other formulations (still within acceptable limit), it was thought that increasing the solid content of the tablet by the addition of water-soluble excipient might further improve tablet hardness. For this reason, the formula G4 was taken to the next stage to be tested with different disintegration accelerators. ODT G4 is formed of 2% w/v gelatin, 0.886% w/v mannitol, and 0.886% w/v glycine.

All of the prepared tablets, obtained by adding a disintegration accelerator to G4 tablet, were also successfully dried showing acceptable weight variation range; the relative standard deviation of the tablet mass ranged from less than 1% to 3%, the mean% NM content was more than 95% and residual moisture content was no more than 4%. The percentage weight loss, calculated from friability studies, was less among all the second-stage tablets compared to G4 tablet, indicating that increasing the solid content of the tablet improved the tablet hardness. Addition of disintegration accelerators in most formulations resulted in faster in vitro and in vivo disintegration when compared to G4 tablet. The percentage of weight loss from friability studies, the in vitro disintegration time, the in vivo disintegration time and wetting time results for the prepared ODTs in the second stage are listed in Table 4. Statistical analysis revealed that ODTs G8 (containing 1% PEG 400) and G13 (containing 1% PVP K90) showed significantly shorter in vitro and in vivo disintegration times compared to ODT G4 ($p < 0.05$). The wetting of all tablets was also improved except those containing SLS which showed longer wetting time compared to G4 tablet. This effect is probably attributable to the reduction in electrostatic charges, which tend to keep drug particles united together, owing to the presence of the hydrophilic polymer or non-ionic surfactant like Tweens [21]. SLS, which is an anionic surfactant, might have hindered the penetration of water instead. ODT G13 also showed the shortest wetting time (5.53 s) when compared to G4 tablet (33.80 s).

Fig. 2 shows dissolution results from NM ODTs containing different disintegration accelerators compared to G4 tablet and NM

Table 4
Influence of different disintegration accelerators on the friability, in vitro disintegration time, in vivo disintegration time and wetting time of ODT G4.

Formulation	Friability (%)	In vitro disintegration time (s)	In vivo disintegration time (s)	Wetting time (s)
G4	0.7	19.0 ± 2.2	14.38 ± 1.44	33.80 ± 6.90
G7	0.02	16.0 ± 1.6	14.36 ± 1.07	35.69 ± 17.82
G8	0.47	8.0 ± 0.8	8.20 ± 4.61	11.06 ± 2.61
G9	0.39	16.3 ± 1.5	11.66 ± 2.97	9.96 ± 4.74
G10	0.38	9.0 ± 1.6	10.38 ± 5.25	12.58 ± 1.17
G11	0.3	9.3 ± 4.2	16.77 ± 6.52	14.58 ± 1.05
G12	0.37	17.5 ± 2.1	10.58 ± 5.55	10.10 ± 0.57
G13	0.26	7.3 ± 2.5	8.41 ± 3.22	5.53 ± 3.27
G14	0.40	7.3 ± 2.1	14.93 ± 0.90	13.90 ± 1.11
G15	0.06	8.7 ± 3.1	10.57 ± 1.20	6.46 ± 2.59

Data are mean values ± SD.

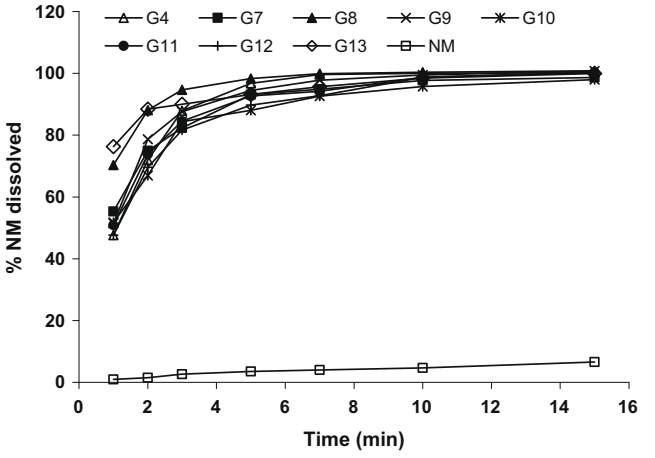

Fig. 2. Dissolution profiles of NM in ODTs containing different disintegration accelerators and NM powder alone in SSF (pH = 6.8) at 37 °C.

plain powder. During the first two minutes, the percentage of drug dissolved from ODT G7 (SLS), G8 (PEG 400), G9 (PEG 4000), G10 (PEG 6000), G11 (PVP K25), G12 (PVP K30), G13 (PVP K 90), G14 (Tween 20), and G15 (Tween 80) were 74.31%, 88.07%, 78.6%, 66.9%, 73.8%, 69.5%, 88.4%, 62.67% and 68.65%, respectively, compared to 72% and 1.5% for ODT G4 and NM powder, respectively. Results showed that addition of a disintegration accelerator to G4 tablet either increased or decreased initial dissolution rate depending on the type and grade of the polymer added. SLS did not have a significant effect on the percentage of drug dissolved within the first two minutes compared to G4 tablet. The percentage of NM dissolved from ODTs containing PEGs was inversely proportional to the chain length of PEG. This may be attributed to the fact that the water solubility of PEGs decreases with increase in the molecular weight of the polymer. Similar results were reported on the dissolution properties of PEGs and PEG–drug systems [22,23]. Statistical analysis showed that addition of PEGs 4000 and 6000 had no significant effect on the percentage of drug dissolved within the first two minutes compared to ODT G4, while the addition of PEG 400 showed a significant difference in the percentage of drug dissolved compared to G4 tablet. Dissolution results from tablets containing PVP showed that the initial dissolution rate depended on the type of PVP used. Addition of PVP K25 and K30 to ODT G4 showed no significant difference in the percentage of drug dissolved within the first two minutes, while the addition of the higher molecular weight PVP (K90) showed a significant difference in the percentage of drug initially dissolved compared to G4 tablet ($p = 0.003$) after 2 min. Addition of Tweens did not result in any significant difference in the percentage of drug initially dissolved compared to G4 tablet. Dissolution studies revealed that only ODT G8 and G13 showed significant increase in the percentage of drug initially (after 2 min) dissolved compared to G4 tablet. Based on friability, in vitro disintegration, in vivo disintegration and dissolution studies, ODTs G4, G8 and G13 were selected for further physico-pharmaceutical evaluation and stability testing.

3.3. Differential scanning calorimetry (DSC) studies

To evaluate the crystalline state of NM in selected ODTs, DSC studies were carried out on NM plain powder, ODTs G4, G8 and G13 and their corresponding physical mixtures. DSC of other excipients in the formulations such as mannitol 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 ODT G4 showed a small endotherm corresponding to the melting point of the drug, indicating the presence of crystalline drug. The endothermic peak of mannitol was no longer present indicating the formation of amorphous form of mannitol by the process of lyophilization (data not shown). The thermogram of ODTs G8 and G13 showed a small endotherm of the drug suggesting significant reduction in the crystallinity of the drug. These results are shown in Fig. 3. The thermograms of the corresponding physical mixtures showed larger endothermic peak of NM (data not shown).

3.4. Powder X-ray diffraction (XRD)

Nimesulide exhibits a strong and characteristic XRD pattern, showing the crystalline nature of the powder. Although the powder pattern contains a number of scattering lines, the pattern is dominated by intense scattering peaks located at 12.03°, 19.34°, and 21.6° 2θ. The diffraction patterns of NM in the ODTs showed absence of, broadening of and reduction in major NM diffraction peaks indicating that mostly an amorphous form (disordered state) existed in the ODTs (Fig. 4). Crystallinity was determined by comparing some representative peak heights in the diffraction patterns of the ODTs with those of a NM powder. The relationship used to calculate the relative degree of crystallinity (RDC) was:

$$RDC = I_{\text{sam.}}/I_{\text{drug}}$$

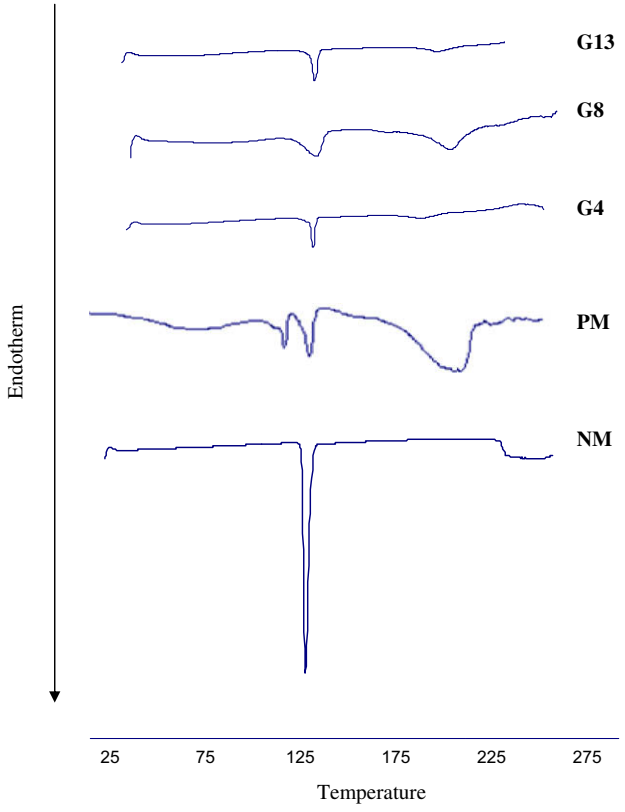

Fig. 3. DSC thermograms of NM plain powder (NM), NM in physical mixture (PM) and NM in ODTs (G4, G8, G13).

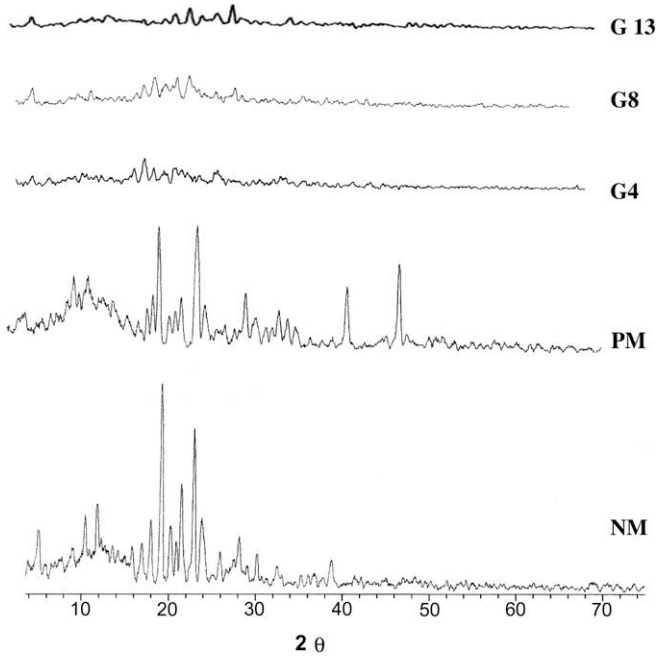

Fig. 4. Powder X-ray diffraction spectra of NM plain powder (NM), NM in physical mixture (PM) and NM in ODTs (G4, G8, G13).

where I_{sam} is the peak height of the sample (ODT) under investigation and I_{drug} is the peak height at the same angle for the drug [24]. Pure drug peak at 19.34° 2θ was used for calculating the RDC. The calculated RDC values were 0.3, 0.25 and 0.219 for ODTs G4, G8 and G13, respectively.

Nimesulide has a high melting point (147 °C), which is indicative of strong crystal lattice energy. This high melting point is one of the factors responsible for poor aqueous solubility [25]. Therefore, any approach which disrupts the crystalline nature and/or results in lower crystal lattice energy would improve the aqueous solubility of the drug. The crystalline nature of the drug can be disrupted by solid-state dispersion of the drug into water-soluble carrier molecules which replace the drug molecule in the crystal lattice. This results in a total or partial loss of crystallinity, resulting in a significant increase in solubility and dissolution rate. RDC results show that ODT G13 (containing PVP K90) has the least degree of drug crystallinity. As a water-soluble polymer, PVP has been demonstrated to retard and inhibit the crystallization of drugs, giving amorphous solid dispersions with increased drug dissolution rate and supersaturated solubility. The inhibitory effect of PVP on crystallization may be due to a change in the molecular mobility of the drug, ultimately leading to an amorphous form of the drug [26,27], and also pointed out that PVP might inhibit the association of the drug molecules to form the crystal nucleus and inhibit the crystal growth. It has also been reported that this inhibitory effect is associated with molecular weight; hence, a suitable molecular length of PVP may be required to form the polymer net upon the crystal surface or among the drug molecule [28]. The diffraction patterns of the corresponding physical mixtures showed full peaks corresponding to crystalline drug (data not shown).

3.5. Scanning electron microscopic (SEM) analysis

Scanning electron micrographs of the surface and cross-section views of ODTs G4, G8 and G13 are shown in Fig. 5. The micrographs show the highly porous nature of the prepared lyophilized tablets, which appears in both the surface and the inner structure. The highly porous nature of the tablets explains the rapid penetration of water, which results in rapid wetting, disintegration, and dissolution in the oral cavity. Micrographs show that ODT G13 contains larger and more diffuse pores (especially from the cross-section view) compared to G4 and G8 tablets which might explain the very fast in vitro and in vivo disintegration as well as short wetting time obtained from G13 tablet. The surface view and the cross-section of G8 tablets also show a more porous structure compared to G4 tablet which might explain the faster wetting and disintegration obtained from G8 tablet compared to G4 tablet. These results indicate that the addition of water-soluble polymer greatly affected the inner structure of the tablet with subsequent impact on wetting, disintegration and dissolution of the final tablet.

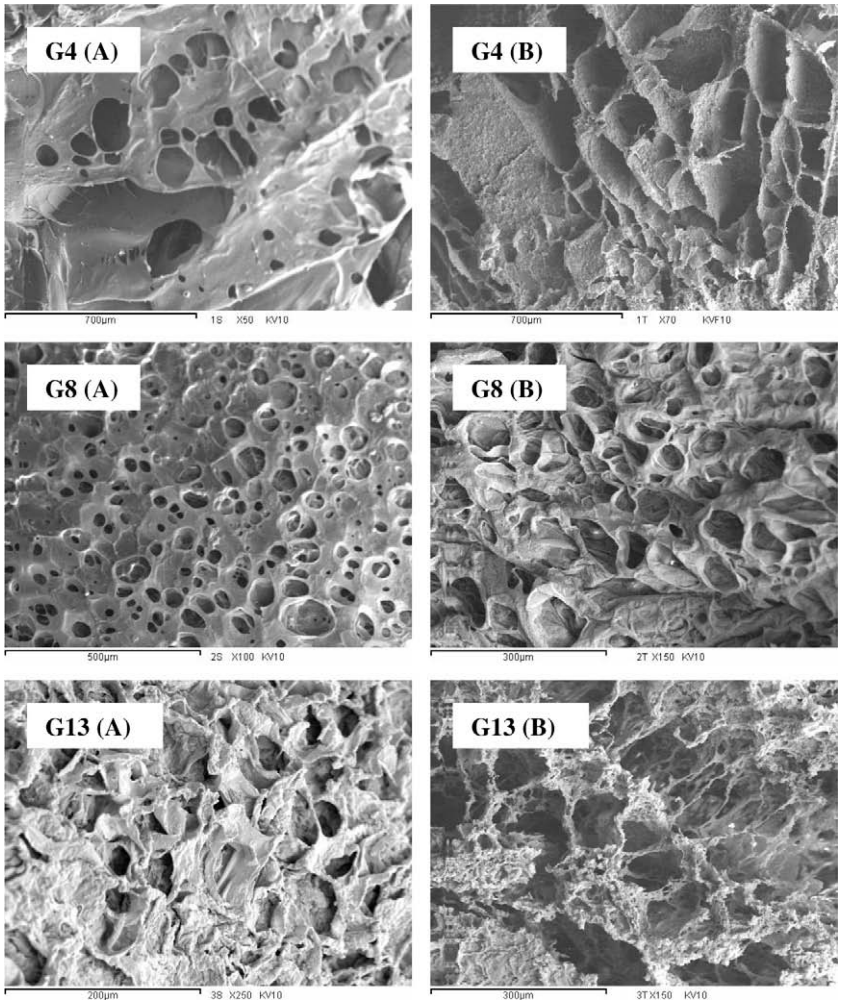

Fig. 5. Scanning electron micrographs of ODTs in surface views (A) and cross-section views (B).

3.6. Storage of ODTs

Stability studies showed that there is no significant difference in the in vitro disintegration times of the three formulations during storage for 12 months ($p > 0.05$) compared to as before storage. Results also showed no significant difference in the residual moisture content of ODTs G4 and G13 during 12-month storage ($p > 0.05$). On the other hand, ODT G8 showed significant increase in the residual moisture content after storage ($p < 0.05$) compared to as before storage. This could be due to the highly hygroscopic nature of PEG. Results from dissolution studies showed no significant difference in the percentage of NM dissolved after 1, 2, and 5 min for ODTs G4 and G13, while ODT G8 showed significantly slower initial release compared to as before storage. This appears to be in accordance with the results from moisture content analysis for G8 tablet and could be due to the formation of a less porous matrix usually promoted by the plasticizing effect of the absorbed water and/or the transformation of amorphous drug to a crystalline form usually encountered with moisture uptake [29]. Results from stability studies after 0-, 6- and 12-month storage of ODTs are presented in Table 5. DSC thermogram and XRD spectrum of NM in ODT G13 after 12-month storage were no different compared to as before storage suggesting the maintenance of amorphous state of the drug upon storage in ODT G13 (Fig. 6).

Based on results obtained from physico-pharmaceutical evaluation and stability testing, ODT G13 was selected for further in vivo testing in human volunteers. ODT G13 theoretical composition after lyophilization is as follows: 20 mg gelatin, 8.86 mg mannitol, 8.86 mg glycine, 10 mg PVP K90 and 50 mg NM with a total tablet weight of 97.72 mg.

3.7. In vivo absorption studies

The mean plasma concentration–time courses for NM following the administration of ODT G13 and Sulide® tablet in four healthy volunteers are shown in Fig. 7. The rate and extent of absorption of NM were found to be different following the two treatments, expressed by higher C_{max} (by about 60%) and earlier t_{max} (by 1 h) values for the ODT.

Nimesulide was detected in plasma as soon as the 15 min sampling time in the four subjects following the administration of the ODT, indicating very rapid absorption by this route of administration. On the contrary, NM did not appear in plasma until the 30 min sampling time in the four subjects following administration of the IR tablet. The mean C_{max} estimated from the IR tablet and the ODT were 2.52 ± 0.89 μg/ml and 4.10 ± 0.98 μg/ml, respectively, reached after times (t_{max}) 3 h and 2 h, respectively. The differences between the two treatments for C_{max} and t_{max} were statistically significantly different ($p < 0.05$). The higher C_{max} and faster t_{max} observed after ODT administration could be due to rapid disintegration and dissolution of the drug in the saliva even with the absence of water, resulting in very fast absorption from the buccal cavity. The mean AUC_{0-24} estimate from ODT (29.03 μg h/ml), which reflects the total amount of drug absorbed over the 24 h time period, was determined to be about 62% larger and statistically significantly different ($p = 0.002$) relative to the mean from Sulide® tablet (17.93 μg h/ml). The improved bioavailability of NM from ODT suggests that rapid absorption from the buccal mucosa resulted in the reduction of hepatic first-pass effect of NM. The relative bioavailability (f_{rel}) of ODT G13 compared to Sulide® tablet was estimated to be on average 162%. The mean NM half-life estimate from ODT (5.40 ± 1.83 h) was determined to be larger but not statistically significantly different relative to the mean half-life estimate from the IR tablet (2.31 ± 1.39 h). Although the increase in NM half-life from ODT is inconsistent with the pharmacokinetic theory, in which an increase in absorption should not affect elimination, this result could be attributed to the small number of subjects and/or the high variability associated with the mean half-life parameter from the ODT. It has been reported that drugs that show low extraction ratio and eliminated primarily by metabolism (such as NM) demonstrate marked variation in the overall elimination half-lives within a population. This variation in half-life is thought to be mainly due to genetic differences in intrinsic hepatic enzyme activity along with some other factors such as age and nutrition [30]. Statistical comparison of MRT parameter indicated an insignificant difference between the ODT (6.24 ± 1.29) and Sulide® tablet (5.03 ± 2.10). The statistical analysis comparing the pharmacokinetic parameters between the two treatments is summarized in Table 6 with p values.

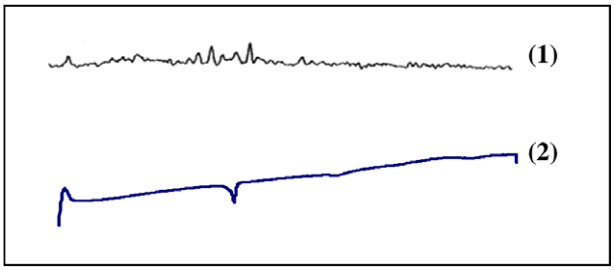

Fig. 6. XRD spectrum (1) and DSC thermogram (2) of NM in ODT G13 after 12-month storage showing maintenance of amorphous state of NM.

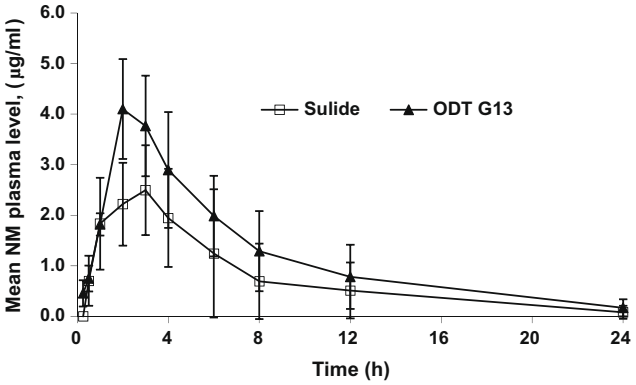

Fig. 7. Mean (±SD) plasma NM concentrations following administration of 100 mg NM in ODT G13 or Sulide® tablets in four subjects.

Table 5
Results from stability studies of ODTs after 0-, 6- and 12-month storage at room temperature and 60% relative humidity.

Attribute	0-month	6-month	12-month
G4			
Residual moisture (%)	2.67 ± 0.03	3.36 ± 0.02	2.85 ± 0.08
Disintegration time (s)	19.0 ± 2.2	20.0 ± 0.2	17.3 ± 2.1
Drug dissolved after 1 min (%)	47.6 ± 1.6	50.1 ± 7.1	49.3 ± 3.9
G8			
Residual moisture (%)	2.11 ± 0.05	3.62 ± 0.05	4.96 ± 0.03
Disintegration time (s)	8.0 ± 0.8	12.7 ± 0.8	15.6 ± 0.4
Drug dissolved after 1 min (%)	70.3 ± 4.0	55.1 ± 4.1	48.1 ± 9.4
G13			
Residual moisture (%)	2.78 ± 0.09	2.24 ± 0.01	3.06 ± 0.02
Disintegration time (s)	7.3 ± 2.5	8.4 ± 0.7	9.0 ± 1.1
Drug dissolved after 1 min (%)	76.8 ± 5.4	77.2 ± 1.2	70.1 ± 9.2

Data are mean values ± SD.

Table 6
The mean pharmacokinetic parameters of NM after administration of 100 mg in ODT G13 and Sulide® tablet to four volunteers.

Parameter	ODT G13	Sulide®	Statistical tests (p)
C_{max} (μg/ml)	4.102 ± 0.98	2.521 ± 0.89	0.012
t_{max} (h)	2	3	0.029
$AUC_{(0-t)}$ (μg h/ml)	29.03 ± 12.63	17.93 ± 12.68	0.002
$AUC_{(0-\infty)}$ (μg h/ml)	30.48 ± 13.70	18.13 ± 12.76	0.002
$t_{1/2}$ (h)	5.40 ± 1.83	2.31 ± 1.39	0.051
MRT (h)	6.24 ± 1.29	5.03 ± 2.10	0.095

Data are mean values ($n - 4$) ± SD ∗ medians.

With regard to the extent parameters for NM from the two treatments, the ANOVA model for log-transformed data indicated significant treatment effects for C_{max} and AUC_{0-24} with $p = 0.012$ and $p = 0.002$, respectively. The mean C_{max} estimate from the ODT was determined to be 163% of that obtained from the IR treatment. The bioavailability of NM from ODT determined from log-transformed data was about 162% relative to the IR tablet. The estimates of the geometric mean of C_{max} and $AUC_{(0-24)}$ parameters along with the 90% confidence interval for the ratio of the C_{max} and AUC of ODT/IR are presented in Table 7.

Based on these results, it can be concluded that the greater bioavailability obtained from ODT G13, which was about 62% larger than that measured after administration of the IR tablet, with higher $C_{max,}$ and shortened t_{max}, may be attributed to rapid and efficient absorption of NM from the buccal mucosa, resulting in decreased presystemic biotransformation due to either first-pass hepatic extraction or metabolism in the epithelium and/or lumen of gastrointestinal (GI) tract. Since the oral administration of conventional dosage forms of NM is reported to cause serious local and systemic side effects, mainly gastric disturbances and hepatotoxicity, NM ODT as a drug delivery system ensures less irritation of the GI tract and probably reduced hepatic side effects that may result either from the reduction of the required dose due to increased bioavailability or from the reduction of the dose reaching the liver due to bypassing the liver especially with increased exposure. Because ODT need not be swallowed, it could be convenient of pediatric and geriatric patients and may replace intramuscular and rectal administration.

However, because of the nature of the study design and the small number of subjects recruited in the study, the results can only be considered preliminary and further studies with a larger number of subjects under different conditions such as varying conditions of ingesting ODTs with water and food intake should be conducted.

4. Conclusions

We demonstrated that an orally rapidly disintegrating tablet of NM is a promising formulation resulting in NM being rapidly dissolved and effectively absorbed into the blood stream with significantly higher bioavailability when compared to standard IR oral dosage form. The study suggests that ODT G13 formulation developed in this work may be an alternative to conventional formulations of NM, such as oral tablets, that are reported to suffer from GI side effects or that are not convenient to the patients such as intramuscular or rectal administration.

Table 7
Geometric mean (±SD) and 90% confidence intervals (in parentheses) for log-transformed pharmacokinetic parameters of NM after the administration of 100 mg in ODT G13 and Sulide® tablet to four volunteers.

Parameter	ODT G13	Sulide®	Statistical tests (p)
C_{max} (μg/ml)	1.39 ± 0.24	0.86 ± 0.43	$p = 0.033$
	(119.4 – 240.6%)[a]		
$AUC_{(0-t)}$ (μg h/ml)	3.28 ± 0.47	2.64 ± 0.87	$p = 0.030$
	(126 – 292.3%)[a]		

[a] 90% CI for ODT/IR.

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