International Journal of Drug Delivery 3 (2011) 712-733

http://www.arjournals.org/index.php/ijdd/index

Original Research Article

ISSN: 0975-0215

Formulation, evaluation and optimization of miconazole nitrate tablet prepared by foam granulation technique

Tarek A. Ahmed*[1], Maged F. Mahmoud[1], Ahmed M. Samy[1], Alia A. Badawi[2], Khairy E. Gabr[3]

*Corresponding author:

Tarek A. Ahmed

[1]Department of Pharmaceutics and Industrial Pharmacy, Faculty of Pharmacy, Al-Azhar university, Cairo, Egypt

[2]Department of pharmaceutics and industrial Pharmacy, Faculty of pharmacy, Cairo University, Cairo, Egypt

[3] Department of pharmaceutics and industrial Pharmacy, Faculty of pharmacy, Mansoura University, Mansoura, Egypt

Abstract

The aim of our study was to utilize novel foam granulation technique in formulation of miconazole nitrate; a model hydrophobic drug as oral disintegrating tablets "ODT" particularly to enhance its bioavailability. Foam granulation technique has additional advantages over the other traditional granulation technique since; it enhances the granulation process and produce acceptable tablets. Fractional factorial design was used to investigate the effect of formulation and processing variables on the prepared miconazole ODT. The prepared granules were evaluated by measuring their density, flowability, granules size and shape, and granules wetting time. The quality attributes of the prepared tablets; drug content, tablet thickness, uniformity of weight, tablet tensile strength, friability, disintegration, and dissolution were also evaluated. The results indicated that, the prepared granules showed acceptable characteristics and is significantly affected by the disintegrant type, urea concentration, and the lubricant type. The quality attributes of the tablets were not affected by the processing parameters. From the prepared formulas; F20, F19, F12, and F20 displayed 18, 35, 35, and 40 seconds disintegration time respectively and the percent of dissolution after 15 minutes ranged from 94.4-100%. These results ascertained that foam granulation technique fulfill the requirement in preparation of miconazole ODT.

Keywords: miconazole nitrate, foam granulation, oral disintegrating tablet.

Introduction

Foam granulation is a relatively new technique developed by Dow Chemical Company in early 2000s [1]. The technique involves incorporation of air into conventional water-soluble polymeric excipients in which the binder solution is supplied in the form of foam rather than solution or spray resulting in foam has a consistency like shaving cream. In a small-scale laboratory setting or in a full-scale production setting, the foam generator can be connected directly to high-shear, low-shear, or fluid bed granulation equipment [2]. Adding the binder solution as foam rather than a spray eliminates the problem related to conventional techniques such as overwetting that can cause the powder to cake in the equipment, inconsistent and unpredictable binder distribution that can affect tablet hardness and drug release, and finally clogged spray nozzles that may exacerbate the situation. The technique offers additional benefits such as improves distribution of the binder, reduces the amount of binder required, adds less water to the powder mass, allows for higher rates of binder addition, and makes mixing of binder and powder more efficient [1].

Dysphagia; the symptom of difficulty in swallowing is reported in about 35% of the general population, as well as up to 60% of the elderly institutionalized population and 18-22% of all patients in long-term care facilities [3]. So, oral disintegrating tablets (ODT) were developed to be more convenient to use and to address potential issues of patient compliance. ODT are designed to disintegrate or dissolve rapidly on contact with saliva, thus eliminating the need to chew the tablet, swallow an intact tablet, or take the tablet with liquids. ODT could be used as drug delivery system for immediate release products as well as sustained release products [4].

Miconazole is an antifungal drug that inhibit the enzyme cytochrome P450 CYP51 14α-demethylase; the enzyme necessary to convert lanosterol to ergosterol. Depletion of ergosterol in fungal membrane disrupts the structure and many functions of fungal membrane leading to inhibition of fungal growth [5]. The limited solubility of miconazole nitrate and the

drug intensive hepatic transformation that results in poor oral drug bioavailability (25-30%) hinders its use for systemic treatment via gastro intestinal tract. Miconazole peak plasma concentrations of about 1 mcg/ml have been achieved 4 hours after a dose of 1 g [6].

The purpose of this work was to develop an oral dispersible tablet of miconazole nitrate as a model water-insoluble drug by relatively new foam granulation technique. This formulation might give a lead to an alternative route of administration of the drug through much easier granulation process.

Materials and Methods

Materials

Miconazole nitrate USP32 was obtained from Sharon Biomedicine Ltd (Mumbai, India). Mannitol USP32 direct compression grade was purchased from Roquette (Lestrem, France). Microcrystalline cellulose (Avicel PH101) and Croscarmellose sodium (Ac-Di-sol) from FMC International (Wallingstown, Little Island Co. Cork, Ireland). Hydroxypropyl Methylcellulose from BASF Company (Ulm, Germany). Urea analytical grade; Sodium Starch glycolate (Explotab low pH & high pH) from JRS (Rosenberg, Germany). Crospovidone (Plasdone XL10) from ISP (Baar, Switzerland). Colloidal silicon dioxide (Aerosil 200, 300, 380 and R972), from Evonik (Frankfurt, Germany). Sodium Lauryl sulfate, from Fisher Scientific (Pittsburg, PA, USA). Magnesium stearate from Kirsch pharma company (Salzgitter, Germany). F D Green No. 3 (Fast green color) from Univar (Cheshire, UK). Methanol HPLC far UV and Acetonitrile HPLC far UV from Merck Chemicals Co. (Darmstadt, Germany) and Ammonium acetate from Panreac Quimica SA (Barcelona, Spain).

All the above materials were in analytical grade and were used without further purification.

Methods

Estimation of possible interaction between miconazole nitrate and added excipients

Miconazole nitrate was mixed with the fillers, super-disintegrants, sublimable agent, glidant, lubricant and binder in which the compatibility of miconazole nitrate with these tablet excipients have been proven by the following:

Differential scanning calorimetry (DSC)

Samples of miconazole nitrate and binary blends of the drug with the studied excipients were scanned using DSC, ambient type apparatus (Perkin Elmer Corp., USA). The blending ratio was determined based on the common drug: excipients ratio (1:1 in case of fillers, binder and subliming agent, 1:0.5 in case of disintegrant, and 10:1 was used for drug/ lubricant and glidant).

Fourier transform infrared spectroscopy (FTIR)

All the materials used in the DSC study were tested in this section. The scanning was performed within the range 4000–500 cm-1 using Nicolet is 10, IR spectrometer (Thermo Scientific, USA). The samples were kept in closed vials under stress conditions (14 days at 50º C).

Design of the optimization program

Taguchi optimization program was used to identify the critical and key factors that affect the performance of ODT. A mixed-level, L_{32} Orthogonal array had been chosen. The design characteristics (responses) were determined. Development of optimization program involves; identification of the product formulation, determination of the formulation quality characteristics (responses) and selection of variables and their levels.

Identification of the product formulation

The preliminary trials revealed that miconazole nitrate can be formulated using foam granulation process. Mannitol/MCC was used as fillers, HPMC as a foamy binder, urea as sublimable agent, aerosil as glidant and magnesium stearate or sodium lauryl sulfate as lubricant. The superdisintegrant was chosen to be one of the following; croscarmelose sodium, sodium starch glycolate type A or type B and plasdone XL.

Determination of the Quality characteristics (responses)

Foam quality characteristics, Un-lubricated granules characteristics (densities, granule size & shape), Lubricated granules characteristics (flowability and wetting time), and routine quality control (QC) tests for tablet (drug content, surface scanning, thickness, uniformity of weight, tablet tensile strength , friability, disintegration time, and dissolution rate) were selected to be studied. In addition; *in-vivo* disintegration time, tablet wetting time, water absorption ratio, and SEM micrographs of the tablet surface were also studied.

Selection of variables and their levels

Nine design variables were considered the most critical variables that are needed to be optimized; six variables related to the formula and three variables related to the process; the urea concentration, type and concentration of disintegrant, intra-

granular disintegrant concentration, mannitol/ microcrystalline cellulose ratio, lubricant type, aerosil grade, impeller speed, milling conditions and tablet hardness.

According to the previously stated factors for the development of the optimization program, 32 formulas were proposed as illustrated in table (1).

Foam quality characterization

Foam quality "FQ" is defined as the fraction of air contained in the foam and could be calculated according to the following equation [7]:

$FQ = [V_g / (V_g + V_l)] \times 100$

Where V_g is the volume of gas and V_l is the volume of the liquid binder.

Increasing the air fraction result in increasing the foam quality and the resultant foam are considered relatively stable. The foam quality was measured by using modified Tan and Hapgood method, 10 ml foam was pumped in a 10 ml measuring cylinder at room temperature, and the collapse of foam was measured after 10 minutes [7].

Granulation process

Mixing and granulation processes were carried out using Laboratory scale high shear double jacketed granulator (Chitra, India), which is equipped with three bladed impeller of plough like shape fixed in the bottom of the pot; the impeller operates at variable speed and is equipped with chopper that is fixed in the lid. The impeller speed and milling parameters were adjusted according to the pre-determined factors illustrated in table (1). The granulating liquid (HPMC/Urea in water) quantity was fixed (35% w/w of the total dry mass). After 5 minutes of starting the granulation process, the granulating liquid was pumped through the foam generating pump and the chopper was operated at fixed speed of 800 rpm. The obtained wet granules were dried using vacuum oven, (Binder, Germany) at 70-80 ºC, - 800 mbar till the loss on drying reach less than 2%, measured by moisture analyzer apparatus (Mettler Toledo, Switzerland). The dried agglomerates were weighed to calculate the product yield, milled and characterized.

Characterization of granules

Measurement of granules densities

The different types of densities were measured to assess the granules flow properties. Bulk density is the mass of the granules divided by the packing volume. The bulk (D_B) and tapped (D_T) densities was determined using measuring cylinder tapping procedure. A sample of 100 ml of the granules was poured in a measuring cylinder and the weight of the poured volume was recorded after taping a measuring cylinder 500 times from a height of ~ 1.5 inch [8].

Flowability parameters

The flowability of the granules was evaluated by the following methods:

Carr's index

Many factors affect the powder flowability including powder cohesiveness, particle size and size distribution. Carr described the flow rate by indirect method via the following equation:

$$C_i = 100 \times (D_T - D_B) / D_T$$

Where C_i is the Carr's index, D_T is the tapped density and D_B is the bulk density [9].

Flow rate

Granules flow rate was assessed using a flowmeter consisting of a funnel (12 cm diameter at top and 0.9 cm diameter at the efflux tube) that is fixed at pre-determined height to a Fritsch shaker to get precise vibration. 50 g sample of the granules was poured into the funnel and the powder flow rate through the funnel was determined as g/sec [10].

Angle of repose

Fixed height cone was utilized as a technique for measuring the angle of repose [10]. The flow rate, the diameter (D) and the height (h) of the formed heap were measured and utilized in calculation of the angle of repose according to the following equation: $\text{Tan } \theta = 2h/D$

Granules size and shape

Volume surface mean diameter "D43"

The granules volume surface mean diameter "D_{43} was determined using Malvern mastersizer 2000 with dry cell (Malvern instrument, UK) and was calculated using Edmundson equation [11]:

$$D = [(\sum nd^{p+f}) / (\sum nd^{f})]^{1/p}$$

Where n is the number of particles in a size range, d is the average diameter of the particles in that range, p is an index related to the size of an individual particle, and f is a frequency index.

Granules sample of 5-10 g were placed into the vibratory hopper of the Scirocco dry dispersion unit. The mass flow was adjusted until a stable and correct particle concentration was achieved at 2-bar disperser pressure.

Geometric standard deviation

Samples of 50 g granules were placed in the top of a series of standard stainless steel sieve (Fritsch, Germany) of 710, 500, 355, 250, 125, 75 and 45 micron. The vibration rate was adjusted to 40 and the process time was 10 minutes. The geometric mean diameter was calculated graphically from a log-probability plot of particle size versus percent cumulative weight undersize.

Geometric mean standard deviation was calculated from geometric mean diameter data [11].

Elongation ratio

The elongation ratio (ER) is a useful tool to assess the deviation from the spherical shape to an elongated form. Agglomerates shape was examined using an optical microscope connected to digital camera 1.3 megapixel, with magnification ratio 10-230 X and adjustable 8 LED fine tuned white light, connected to software that enables particle measurement (Chronos, Taiwan). Micrographs of these granules were captured and the length and breadth of the 20 particles were measured. The averages were calculated. The elongation ratio was calculated using the following formula:

ER = b / L

Where "b" is the length of major axis and "L" is the length of minor axis [12].

Granules wetting time

Granules wetting time was assessed using the method previously described by Yadav et al [13]. Sample of 2 g granules were put in sintered glass funnel partially plunged (1 mm) into water. The time required for water capillary to rise up to the powder bed was measured. Few milligrams of fast green dye were put at the top of powder bed to help in accurate measure the granule wetting time.

Compression of miconazole oral disintegrating tablets

The glidant (Aerosil) and lubricant were added to the granules and mixed for 2 minutes using 5 liters capacity blender (Hualian, China). The lubricated granules were compressed to the pre-specified tablet hardness using rotary press with variable speed (Karnavati Engineering Ltd, India) equipped with 8 mm diameter tools in which the tablet weight was adjusted to 200 mg. The rotary tablet press was run at low speed 5 rpm to guarantee accurate filling of the die. The compressed tablets were subjected to characterization.

Characterization of tablets

Visual inspection

Upper and lower punches were inspected by naked eye for presence of sticking or picking.

Drug content

Ten tablets were weighed, ground and mixed in a mortar then this powder was sieved. Accurately weighed portion of the ground tablets equivalent to about 50 mg miconazole nitrate was dispersed in 25 ml of 50% methanol; the samples were filtered using syringe filter before subjecting to HPLC analysis using HPLC apparatus (Waters, USA). The mobile phase was prepared by dissolving 6 g Ammonium acetate in 1 liter of a mixture of acetonitrile, methanol and water in ratio 45:35:20 respectively, and filtered using nylon membrane filter 0.45 µm. Kromasil 100 C18, 5 µm, (150 mm ˣ 4.6 mm) column was used. The flow rate was adjusted to 1.5 ml/minute; the UV detector was adjusted to 235 nm wave length. The injection volume was 20 µl. Different miconazole nitrate concentrations were prepared to construct drug standard curve by dissolving 50 mg of Miconazole nitrate in 25 ml methanol. The method described in the USP for determination of the drug content was followed except for slight modification in the chromatographic conditions [14].

Tablet thickness

Tablet thickness was measured using dial thickness gauge (Mitutoya, Japan). Thickness measurement was performed directly after compression process.

Uniformity of weight

Uniformity of weight test was performed according to the method described in the USP [14].

Tablet tensile strength

Hardness was determined according to standard method described in BP 2010 using tablet hardness tester (Pharmatest, Germany). The tablet tensile strength was calculated by using the following equation [15]:

$$\sigma_t = 2P / [\pi Dt]$$

Where σ_t is tablet tensile strength, P is fracture load in Newton, D is tablet diameter in cm and t is tablet thickness in cm [15].

Tablet friability

Friability was determined according to standard method described in the USP using Friability tester (Pharmatest, Germany).

In-vitro dissolution

The dissolution of the prepared miconazole nitrate ODT was carried out using USP type I apparatus that has autosampler system based on peristaltic pump (Pharmatest, Germany) contain 900 ml 0.45% w/w sodium lauryl sulfate and rotating at 75 rpm. Samples were withdrawn every 15 minutes and filtered. These were immediately replaced by equivalent volumes of freshly prepared 0.45% sodium lauryl sulfate. The amount of the drug released was measured spectrophotometrically using UV Spectrophotometer, 1650 PC (Schimadzu, Japan) at 230 nm. These conditions were selected to be in agreement with the dissolution of miconazole nitrate vaginal suppositories stated in the USFDA except for slight modification to make the process more discriminating [16].

Disintegration time

Disintegration was determined according to standard method described in USP34 using tablet disintegration test apparatus (Pharmatest, Germany).

In-vivo disintegration time

The *in-vivo* disintegration time of the tablets in the oral cavity was measured in healthy volunteers using the method described by Okuda, in which the tablet disintegration end point is the time for the tablet previously placed on the tongue had disintegrated until no lumps remained. The volunteer rinsed out their mouth with water before the test [17].

Tablet wetting time and water absorption ratio

A piece of double folded tissue paper was placed in a petri dish containing 6 ml of water. One tablet was placed on this paper and the time for complete wetting of tablet was recorded. The wetted tablet was weighed and the water absorption ratio, R, was determined according to the following equation:

$$R = 100 (Wa - Wb) / Wb$$

Where Wb and Wa are the weights of tablet before and after water absorption, respectively [18].

Tablet surface scanning with SEM

The morphological examination of the tablet surface was performed using scanning electron microscopy (SEM) (JOEl Ltd, Japan). Before microscopy, the tablets were mounted at carbon tape and were sputter-coated using gold. The photomicrography was taken at an acceleration voltage of 10 Kv at different magnification powers; 100X, 500X and 1000X [19].

Analysis and ranking

The results were analyzed using Minitab 16th edition statistical software using analysis of Taguchi design function. The interpreting of the results was based on calculating the Delta statistics. The relative rank was based on the corresponding delta-value. The ranks indicate the relative importance of each factor to the response. Analysis of variance (ANOVA) was used to analyze the significance of the various variables on the responses. The variables were scored according to the effect on each response.

Results and Discussions

Estimation of possible interaction between miconazole nitrate and added excipients

DSC chromatograms

According to Figure (1), the DSC thermogram of plain miconazole nitrate showed characteristic endothermic peak at 183.9 °C represents the melting. Mixing the drug with the studied additives doesn't significantly affect the drug endothermic peak as indicated in the thermograms of the drug-additives physical blend.

IR Spectroscopy

The IR spectrum of miconazole nitrate showed a characteristic peaks at 1589, 1475 and 827 cm^{-1} which is in a good agreement with the work done by Barillaro et al who explained that the characteristic peak at 1589cm^{-1} is related to stretching of C-C bond of dichloro-substituted benzene ring, while the peak at 1470 cm^{-1} is related to CH bending of the two dichlorobenzene groups and to the CH bending of the C6 and C17 [20, 21]. The peak at 827 cm^{-1} may represent the C-H group of the Meta di-substituted benzene ring. The IR spectra of miconazole nitrate binary mixture with sodium lauryl sulfate showed the same characteristic peaks of the drug at 1589 and 827 cm^{-1} while the drug peak at 1475 cm^{-1} was slightly shifted, whereas the IR spectrum of miconazole nitrate and mannitol showed the drug characteristic peaks at 1588 and 1475 cm^{-1}, while the peak at 827 cm^{-1} was also slightly shifted as illustrated in figure (2). The IR spectra for the other used additives (magnesium stearate, colloidal silicon dioxide, HPMC, plasdone XL, croscarmelose sodium, sodium starch glycolate type A and B, microcrystalline cellulose, and urea) don't show any shift or interference between the drug and studied substances.

Characterization of foam quality

The foam quality for the binder solution composed of HPMC and different percent of urea showed that, the binder solution with low urea content results in fine foam while the high urea content result in coarse foam. The foam quality percent was 84, 83, 82, and 59 % respectively for 3, 6, 9, and 12 % urea. It is previously stated that, the foam quality for proper foam granulation should be around 90% and the higher the foam quality the narrow the nuclei size distribution [7]. Other reports mentioned also that, urea increases the surface tension of the aqueous solution [22]. The higher the foam quality, the longer the contact time between the foam and the powder to be granulated. This may result in better granulation process which results in more spherical granules. The statistical results for the significance of foam quality of different HPMC/urea solutions on the different properties of miconazole granules indicated that, the foam quality is significantly affecting the elongation ratio and granule wetting time.

Characterization of granules

Flowability parameters of granules:

The bulk and tapped densities of the granules of different formulae were evaluated and the results were used in the calculation of Carr's index as displayed in table (2). The results of Carr's index were used as indicator of the flowability of the granules. It is obvious from the calculated Carr's index for the different formulae that the granules have moderate to poor flowability (Carr's index range 18 to 37 %) which could be improved by addition of glidant. The results of statistical analysis

for the effect of different variables (urea concentration, disintegrant type and concentration, intragranular disintegrant concentration, Mannitol / MCC, impeller speed and milling parameters) on Carr's index of miconazole un-lubricated granules indicated that, the disintegrant type affect the Carr's index significantly. Utilization of Plasdone XL10 produce larger granule size and hence increase the percent of fines in the powder which result in high Carr's index, this may be due to the large particle size of plasdone XL (58 micron) compared with the particle size of croscarmelose sodium (51 micron) or sodium starch glycolate (29 micron) [23]. The results showed also that, the granule densities and the Carr's index were not affected by the processing parameters. This indicates the ruggedness of the formula and process.

Granules size and shape

Volume surface mean diameter "D43"

Statistical analysis of volume mean diameter D_{43} data shows that, the disintegrant type is the most important parameter that affects the volume surface mean diameter. The large particle size was produced by utilization of insoluble disintegrant "plasdone XL" while the other soluble disintegrants result in small particle size. This may be due to the large particle size of plasdone XL (58 micron) compared to the particle size of croscarmellose sodium (51 micron) or sodium starch glycolate (29 micron). It is previously described that, initial particle size distribution has a strong effect upon granule growth rate and the mechanism by which wet granulation occurs [24]. The large particle size produced when plasdone were used may be also related to the difference in water uptake by the disintegrants. The total water added to each batch was constant at 35% regardless of the formulation. Plasdone adsorbs less water and hence allowing large granules to be formed. Croscarmellose adsorbs a lot of water, and so effectively there is less free liquid for granule formation.

Geometric mean standard deviation

Statistical analysis for the effect of different variables on geometric mean standard deviation of un-lubricated miconazole granules revealed that, the disintegrant concentration is the main factor that affects geometric mean standard deviation.

Elongation ratio

Specific software was used to calculate the length and width for each particle after microscopic imaging of the prepared granules in order to determine the elongation ratio. Formulae F1, F3 and F4 showed the highest elongation ratio (1.46, 1.48 and 1.48 respectively). These formulae contain low urea content (3%). Figure (3) represents the microscopic graph of miconazole nitrate F19. The statistical analysis for the effect of different variables on elongation ratio of un-lubricated miconazole granules showed that, urea concentration affects the particle shape significantly, increasing the urea concentration results in more spherical granules and the effect of urea concentration reach a plateau level at 9 – 12%. The obtained results are in a good agreement with previous work emphasized that, the addition of urea increases the critical micelle concentration values of the surfactant [25]. The obtained results are also in a good agreement with previous work showed that, narrowest nuclei size distribution is obtained by granulating with high-quality foam [26]. It is reported that, elongation ratio of explotab is smaller than that of plasdone XL due to the spherical shape of explotab particles, while the plasdone XL particles are irregular in shape whereas, croscarmellose sodium particles have cylindrical shape which affects the resultant elongation ratio [23].

Flow rate of lubricated granules

Table (3) summarizes the results of flow rate, angle of repose and wetting time of the lubricated granules. The flow rate was affected by lubricant type and glidant. Miconazole nitrate granules are hygroscopic since they contain high percentage of hygroscopic ingredients (urea and disintegrants). The presence of high percentage of hygroscopic materials in the granules may result in adsorption of moisture on the granules surfaces and increase of cohesion. Plasdone XL10 is less hygroscopic than croscarmellose sodium and sodium starch glycolate. Hydrophobic lubricant as well as hydrophobic glidant were more effective than hydrophilic ones in decreasing the powder cohesiveness. This may be explained by the presence of hydrophobic barrier on the granules surfaces that hinder the water bridging between granules. The obtained results consistent with previous results demonstrated that, hygroscopicity of formulation composition may increase the cohesive forces that result in poor powder flow in which the granule cohesiveness could be overcome by using hydrophobic stearate [27]. The presence of hydrophobic aerosil R972 in F5 results in its good flow, while the presence of stearate in F24 results in its good flow. The presence of 6% urea results in more spherical granules which enhance the flowability as previously mentioned. F1 did not contain hydrophobic glidant nor lubricant, but it contains low concentration of hygroscopic urea as well as relative low concentration of mannitol. Mannitol may exhibit crystal change during granulation process to needle shaped. The needle shaped crystals had poor flowability. It is hypothesized that, polymorphic transition of crystalline mannitol occurred during wet granulation process and the resultant filament-like mannitol crystals had good compressability properties as previously reported [28]. The poor flowability of F3 and F 11 may be due to absence of any hydrophobic ingredients in the formulae while, the poor flowability of F20 may be contributed to presence of high hygroscopic materials (3% urea and 12% croscarmellose sodium) and aerosil 380 (which surface area is almost twice than that of aerosil 200) and the poor flowability of F27 may be contributed to presence of high hygroscopic materials (9% urea and 12% plasdone) and high mannitol content.

Angle of repose

Angle of repose was affected significantly by lubricant type. The results of angle of repose were in a good agreement with the

results of flow rate and Carr's index. Hydrophobic aerosil and hydrophobic lubricant gave better flow than hydrophilic ones. The statistical analysis shows significant direct relationship between angle of repose and geometric standard deviation of the granules. The increase in geometric mean standard deviation results in particles interlocking and stacking which affect the angle of repose. This relationship is in agreement with previous work revealed that, the presence of fines in polydisperse powders increases the angle of repose and this may be due to interlocking of particles [29].

Granule wetting time

Granule wettability was significantly affected by the lubricant type. The use of hydrophilic lubricant results in enhancing the granule wetting time. Sodium lauryl sulfate (SLS) facilitates uptake of water into the granules more rapidly than hydrophobic stearate which was previous stated in a study for the effect of various surfactants on the granules wettability [30]. These findings consistent also with previous results that indicated, SLS was more effective than other surfactants in promoting the wetting of hydrophobic drugs [31].

Characterization of the compressed tablets

Visual inspection

The compressed tablets show neither sticking nor picking. The punches were clean and the tablets logos were clear.

Drug content

The results of the drug content in the prepared compressed tablets is represented in table (4) which were within the range 90.0 – 110 % which met the common pharmacopeias limit [14].

Tablet thickness

Table (4) shows also the thickness of the compressed tablets which was used to calculate the tensile strength, the true density and the theoretical total tablet porosity.

Uniformity of weight

Table (4) shows the results of the weight variation. Statistical analysis for the effect of various parameters on tablet weight variation revealed that, variation in tablet weight is significantly affected by mannitol/MCC ratio. The increase in mannitol resulted in more weight variation which could be related to the moisture that induces polymorphic transition of crystalline mannitol [28]. The SEM micrographs of the tablets surfaces show that mannitol exhibited crystal change into needle shaped.

Tensile strength

Tablet tensile strength was significantly affected by urea concentration, aerosil type and lubricant type but these effects were not significant according to the statistical results obtained for the effect of various parameters on the tensile strength. The increase in urea concentration results in higher tensile strength of the produced tablets which may be explained by the ability of urea molecules to form hydrogen bonding between the molecules. One urea molecule is able to make 8 hydrogen bonding [32]. The results showed that the tensile strength was rugged enough so that it did not affected by change in the processing parameters (impeller speed and the milling parameters).

Friability

Tablets friability was significantly affected by tablet hardness. Increasing tablet hardness is a result of increasing the compression force which result in increasing the bonding of the granules and hence decreasing the tablet friability.

Tablet wetting time and water absorption ratio

Wetting time was significantly affected by disintegrant type and lubricant. Formulae F16, F24 and F32 showed the shortest tablet wetting time (26, 25 and 24 seconds respectively) while F7 showed the longest tablet wetting time (165 seconds). F16, F24 and F32 contain croscarmellose sodium as disintegrant, while F7 contains plasdone XL as disintegrant. Croscarmellose sodium shows the shortest wetting time, followed by explotab low pH, explotab high pH while plasdone XL shows the longest wetting time. The filament structure of croscarmellose sodium aid in rapid uptake of water by tablets and hence enhancing the tablet wetting time. The plasdone XL is insoluble disintegrant. Zhao et al stated that significant reductions in the rate and extent of water uptake and swelling were observed for both sodium starch glycolate and croscarmellose sodium in an acidic medium (0.1N HCl), but not for plasdone XL [33]. The pH 20% miconazole nitrate aqueous solution was measured and the pH was 3.8 which indicate the acidity of the miconazole nitrate. Although croscarmellose sodium swelling capacity may decrease in the miconazole tablet microenvironment but still this swelling is more than that of plasdone XL (51 vs 33% respectively) [33].

The water absorption ratio is highly affected by urea concentration and tablet hardness. Urea is highly soluble that compete with the disintegrants on the adsorption of water. Formulae F20 and F2 showed the highest water absorption ratio (143.1 and 85.5 respectively) while F13 and F16 showed the smallest water absorption ratio (10.7 and 11.3 respectively) as illustrated in table (5). Although F2 is more hydrophilic than F20 due to lubricant nature, F20 showed superior water absorption ratio than F2, which may be explained by the presence of aerosil of larger surface area (aerosil 380 vs aerosil 300), presence of higher concentration of MCC (mannitol/MCC ratio 1:1 vs 2:1) and although explotab normally swells by 251% while croscarmellose swells only by 104% [33], the acidic microenvironment of miconazole nitrate tablets affect the swelling capacity of these disintegrants dramatically so that, explotab swells only by 43% and croscarmellose sodium swells by 51%. Previous work utilized

PEG/ urea to enhance the dissolution of miconazole nitrate using solid dispersion technique [34].

Calculated tablet total porosity

Table (5) also shows the calculated true density and the calculated total porosity. In general, decreasing the tablet hardness increases the tablet porosity and hence gives the opportunity to the water to penetrate through the tablet surface pores and hence enhance the disintegration. The achieved tablet total porosity was in the range 16-36%. The high porosity of F1 may be explained by its low content of mannitol. Mannitol is compressed by plastic deformation and fragmentation [19]. The concentration of mannitol is adversely affecting the porosity of tablets. It is previously stated that, 30% porosity of ODT is desirable to get proper disintegration in the mouth [35].

Disintegration time

The disintegration time for all the studied formulas was below 180 seconds as shown in table (5) which is the limit in the European pharmacopeia, while the disintegration of F12 tablets were below 60 seconds which is the common limit in the USP. Rapid disintegration (≤ 35 seconds) was noticed in trial F13, F19 and F20. These formulae contain not less than 9% superdisintegrant and 50% of this concentration was added as intragranular disintegrant. All these formulae were compressed to get hardness 35N or less. Formula 20 showed the fastest disintegration (18 seconds) followed by F13 and F19 which showed 35 seconds. F 20 contains: 12% croscarmelose sodium, Relative high content of MCC, and Hydrophilic aerosil 380. These ingredients may attribute to accelerating the disintegration of the tablets. The porous structure of the tablets (porosity was 30%) may also explain the high water absorption ratio and the short disintegration time. F13 and F19 have the same disintegration time (35 seconds), the same tablet hardness and same disintegrant concentration. F13 has more hydrophilic surface than F19. This hydrophilicity is a result of presence hydrophilic glidant, hydrophilic lubricant and high concentration of urea. On the other hand F19 was characterized by higher total porosity (30% more than that of F13) and higher MCC content. MCC has disintegrating properties which may add positive effect to enhance the tablet wetting time and disintegration time. Tablet wetting time of F19 was 4 times faster than that of F13. Disintegration time is significantly affected by tablet hardness. The tablet hardness is directly proportional to the disintegration time, in the same time it was concluded that the calculated tablet total porosity does not have any significant effect on the disintegration time.

In-vitro dissolution

The dissolution results were satisfactory for most of the studied formulae as shown in table (5). The enhanced dissolution is related to the use of hydrophilic excipients which ensure wettability as well as rapid uptake of water. Formulae 7, 12, 13, 19 and 20 showed higher dissolution rate (>90%) among all the studied formulas. Dissolution was highly affected by hardness. Tablet hardness is inversely proportional to the dissolution rate. The main advantage of using water as granulating liquid is enhancing the hydrophilization of the miconazole nitrate and hence enhancing the dissolution. Lerk et al demonstrated that, the release of hydrophobic drugs can be improved by hydrophilization process. The hydrophilization was done by creation of hydrophilic surface on the drug [36]. Previous work demonstrated that, the solubility of miconazole nitrate could be enhanced by water soluble excipients [34].

Tablet surface scanning with SEM

Figure (4) shows surface scan of various miconazole ODT, where there existed many
empty spaces between the granules throughout the tablet in which water could be absorbed by capillary forces. It is these pores that increase the absorption of water by capillary forces which may explain the fast disintegration time noticed for F12. F12 contains croscarmelose sodium as super disintegrant which characterized by rapid swelling and wicking. The low hardness of the tablets (25N) result in relatively high total porosity (34.6%) and this is confirmed by SEM micrograph. The pore size may be characterized according to the opening size; macropores (pores with openings exceeding 500A^{o}), micropore (pores with openings not exceeding 20A^{o}) and mesopores (pores with intermediate size openings) [37]. The Pore size in F12 was measured from SEM micrograph, the pore diameter was around 30 micron which is considered as mesopores. The pores on the tablet surface were characterized by being inter-connected. The porous structure of the tablets was the result of the low mannitol content and low hardness of the tablets, the pore size measurement is matched with the calculated total porosity (relatively high porosity value). The pores F13 was shown to be less distributed and smaller in size (< 10 micron) and this was confirmed by the calculated total porosity (25%). The decreased in porosity in F13 may be explained by the increased in the mannitol content in the tablets, the mannitol is compressed by the fragmentation compression profile, which may result in less porous structure. Compression of mannitol granules using low compression force results in decrease pore volume and porosity percentage [38]. Tablets of the F19 were compressed to low hardness (25 N), the pores have size ranged 20 – 30 micron, and these pores are well distributed on the tablet surface. The calculated total porosity is lower than that of the F12 but is more than that of F13; these results are matching with SEM micrographs analysis. Tablets of the F20 showed more cracked surface indicates highly porous structure, this graph confirm the relatively high calculated total porosity. The total porosity of these tablets is maintained although it was compressed with relatively high hardness (35 N), but the low mannitol content seems to be the predominant factor in the high porosity. The disintegration time of this formula was the lowest among all the studied formulae (18 seconds) which may be explained by the tablet total porosity and its content of MCC, as it acts as disintegrant. It was expected that the relatively high hardness of the tablets and the used lubricant may have retarding

effect on the disintegration time, but the effect of MCC and tablet total porosity were more predominant.

In vivo disintegration time

The results for the *in vivo* disintegration time graphically illustrated in figure (5). It was noted that, most of the *in-vivo* disintegration time results are longer than that of the *in-vitro* which could be explained by the low saliva volume (7 ml) compared to the high volume *in-vitro* testing (700 ml). All the results are complying with the European pharmacopeia standard for oral dispersible tablets (NMT 3 minutes).

Analysis and ranking

Rank order for the effect of various parameters on miconazole nitrate granules is shown in table (6). The ranking was done based on the relative rank for each variable "based on delta value" that was calculated for each parameter during the study. The ranking showed that the preparation of miconazole nitrate granules by foam granulation was affected by mannitol/MCC ratio, disintegrant type and milling parameters. These results indicate that, foam granulation process is rugged enough and did not affect by impeller speed. The ruggedness of the foam granulation process makes it superior to routine wet granulation process. This conclusion indicates that, the foam granulation is easily scaled up taking in account few scaling issues. Sheskey et al mentioned, the binder rate of addition and nozzle placement is among that issues [39]. Rank order for the effect of various parameters on compression of miconazole nitrate ODT is shown in table (7) in which the compression of miconazole nitrate ODT was affected by tablet hardness and the urea concentration.

Conclusion

It can be concluded that, miconazole nitrate can be formulated as oral disintegrating tablet by foam granulation technique. Testing of the prepared miconazole nitrate granules and compressed tablet prepared by foam granulation results in a formulation with acceptable quality control characters.

Authors' contributions

TAA is the corresponding author who has been involved in interpretation and analysis of the data, drafting, organizing, and revising the manuscript. MFM was responsible totally for the practical work of this study and performed the statistical analysis. AMS, AAB, KEG have an outstanding contribution to the conception and design of the study; they also contribute to the analysis and interpretation of the results.

References

[1]. Sheskey P, Keary C, Inbasekaran P, Deyarmond V, Balwinski K. Foam Technology: The Development of a Novel Technique for the Delivery of Aqueous Binder Systems in High-Shear and Fluid-Bed Wet-Granulation Applications, American Association of Pharmaceutical Scientists, 2003.

[2]. Himanshu KS, Tarashankar B, Jalaram HT, Chirag A.P. Recent Advances in Granulation Technology (Review article). International Journal of Pharmaceutical Sciences Review and Research, 2010; 5 (3); Article-008.

[3]. Pfister WR, Ghosh T. K. Orally disintegrating tablets, products, technologies and development issues, Pharmaceutical technology, [online] ; available from: pharmatech.com, (accessed on 28.08.2010), 2005; P.1-4.

[4]. Abbaspour MR, Sadeghi F, Garekani HA. Design and study of ibuprofen disintegrating sustained-release tablets comprising coated pellets, European Journal of Pharmaceutics and Biopharmaceutics, 2008; 68; P.747–759.

[5]. Sheehan DJ, Hitchcock CA., Sibley CM. Current and emerging azole antifungal agents, Clinical microbiology review, 1999; 12(1); P.40–79.

[6]. Sweetman SC. Martindale the extra pharmacopeia. Antifungals, Pharma Press, China, 2009; P541-542.

[7]. Tan MXL, Hapgood KP. Foam granulation: Binder dispersion and nucleation in mixer-granulators, Chemical engineering research and design, 2011; 89; P.526–536.

[8]. Harshal AP Priscilla MD. Development and Evaluation of Herbal Laxative Granules. J. Chem. Pharm. Res., 2011; 3(3); 646-650.

[9]. Aulton ME. Pharmaceutics: The science of dosage form design, 2nd

edition. New York: Churchill Livingstone, 2002; pp154-155.

[10]. Wells J. Pharmaceutical preformulation, Pharmaceutics the science of dosage form design, second edition, Aulton M. E., Churchill Livingstone, UK, 2003; P.133-134.

[11]. Sinko PJ. Martin's Physical Pharmacy and Pharmaceutical Sciences. Philadelphia: Lippincott Williams & Wilkins; Micromeritics, 2007; P. 533-60.

[12]. Bouwman AM, Bosmaa JC, Vonk P, Wesselingh J, (Hans) A, Frijlink HW. Which shape factor(s) best describe granules?, Powder Technology, 2004; 146; P. 66– 72, Elsevier.

[13]. Yadav VB, Yadav AV. Enhancement of solubility and dissolution rate of Fenofibrate by melt granulation technique, International Journal of PharmTech Research, 2009; 1(2); P.256-263.

[14]. USP, the united States Pharmacopoeia, 34th Ed., Rockville, MD: Pharmacopoeial Convention, Inc, 2011.

[15]. Haririan I, Newton JM. Tensile strength of circular flat and convex-faced avicel PH102 tablets, Daru, 1999; 7 (3); P.36-39.

[16]. USFDA, dissolution methods database[online]; available from: accessdata.fda.gov/scripts/cder/dissolution,(accessed on 15.06.2010), 2010.

[17]. Okuda Y, Irisawa Y, Okimoto K, Osawa T, Yamashita SA. new formulation for orally disintegrating tablets using a suspension spray-coating method, International Journal of Pharmaceutics, 2009; 382, P.80–87.

[18]. Bhardwaj S, Jain V, Jat RC, Mangal A, Jain S. Formulation and evaluation of fast dissolving tablet of aceclofenac, International Journal of Drug Delivery, 2010; P.93-97.

[19]. Westermarck S, Juppo AM, Kervinen L, Yliruusi J. Pore structure and surface area of mannitol powder, granules and tablets determined with mercury porosimetry and nitrogen adsorption, European Journal of Pharmaceutics and Biopharmaceutics, 1998; 46; P. 61–68.

[20]. Barillaro V, Bertholet P, Sandrine HH. Effect of acidic ternary compounds on the formation of miconazole/cyclodextrin inclusion complexes by means of supercritical carbon dioxide, Journal of Pharmaceutical Science, 2004; 7(3); P.378-388.

[21]. Barillaro V, Dive G, Bertholet P, Evrard B, Delattre L, Frederich M, Ziemons E, Piel G. Theoretical and experimental investigations of organic acids/ cyclodextrin complexes and their consequences upon the formation of miconazole/ previous termcyclodextrin/ acid ternary inclusion complexes, Int. J. Pharm, 2007; 342; P.152–160.

[22]. Kumar S, Khan ZA, Parveen N, Kabir-ud-Din. Influence of different ureas on aggregational properties of aqueous surfactant systems, Colloids and Surfaces, Physicochem. Eng. Aspects, 2005; 268; P.45–51.

[23]. Prasad KPP, Wan LSC. Measurement of the particle size of tablet excipients with the aid of video recording, Pharmaceutical Research, 1987; 4(6); P.504-508.

[24]. Realpe A, Velázquez C. Growth kinetics and mechanism of wet granulation in a laboratory-scale high shear mixer: Effect of initial polydispersity of particle size. Chemical Engineering Science, 2008; 63(6); P.1602-1611.

[25]. Hao J, Wang T, Shi S, Lu R, Wang H. Electron spin resonance study of effect of urea on micro-environmental Properties of Alkyl benzenesulfonate micellar solutions, Langmuir, 1997; 13 (7); P.1897–1900.

[26]. Tan MXL, Hapgood KP. A comparison of foam and spray granulation technology, American Association of Pharmacist Scientists, Annual Meeting and Exposition, 2009.

[27]. Faqih AN, Mehrotra A, Hammond SV, Muzzio FJ. Effect of moisture and magnesium stearate concentration on flow properties of cohesive granular materials, International Journal of Pharmaceutics, 2007; 336; P.338–345.

[28]. Yoshinari T, Forbes RT, York P, Kawashima Y. The improved compaction properties of mannitol after a moisture-induced polymorphic transition, International Journal of Pharmaceutics, 2003; 258; P.121–131.

[29]. Carstensen JT, Chan PC. Relation between particle size and repose angles of powders, Powder Technology, 1976; 15; P.129-131

[30]. Varadaraj R, Bock J, Brons N, Zushma S. Influence of surfactant structure on wettability modification of hydrophobic granular surfaces, Journal of Colloid and Interface Science, 1994; 167(1); P.207-210.

[31]. He X, Barone MR, Marsac PJ, Sperry DC. Development of a rapidly dispersing tablet of a poorly wettable compound formulation DOE and mechanistic study of effect of formulation excipients on wetting of celecoxib, International Journal of Pharmaceutics, 2008; 353; P.176–186.

[32]. Nie X. Heat and moisture migration within a porous urea particle bed, PhD thesis, University of Saskatchewan, 2010; P.8-9.

[33]. Zhao N, Augsburger LL. The Influence of swelling capacity of super disintegrants in different pH media on the dissolution of

hydrochlorothiazide from directly compressed tablets, American Association of Pharmaceutical Scientists PharmSciTech, 2005.

[34]. Jafari MR, Danti AG. Ahmed I. Comparison of polyethylene glycol, polyvinylpyrrolidone and urea as excipients for solid dispersion systems of miconazole nitrate, International Journal of Pharmaceutics, 1988; 48; P.207-215.

[35]. Sugimoto M, Maejima T, Narisawa S, Matsubara K, Yoshino H. Factors affecting the characteristics of rapidly disintegrating tablets in the mouth prepared by the crystalline transition of amorphous sucrose, International Journal of Pharmaceutics, 2005; 296; P. 64–72.

[36]. Lerk CF, LM, Fell JT, Nauta P. Effect of hydrophilization of hydrophobic drugs on release rate from capsules, Journal of Pharmaceutical Sciences, 1978; 67(7); P. 935–939.

[37]. Nova user manual. High speed gas sorption analyzer, Quantachrome, 2000.

[38]. Juppo AM. Change in porosity parameters of lactose glucose and mannitol granules caused by low compression force, International Journal of Pharmaceutics, 1996; 130; P.149–157,

[39]. Sheskey P, Keary C, Clark D, Balwinski K. Scale up formulae of foam granulation technology- high shear, Pharmaceutical technology, 2007; 31(4); P94-99.

Table 1: Orthogonal array for miconazole nitrate 50 mg ODT optimization program

FC	LT [a]	UC %	D [b]	TD Conc.%	ID %	M/MCC ratio	IS "rpm"	MP [c]	GT	TH "N"
1	1	3	1	12	30	1	40	2	200	25
2	1	3	2	9	40	2	60	1	300	35
3	1	3	3	6	50	3	80	4	380	45
4	1	3	4	3	60	4	100	3	R972	55
5	1	6	1	12	40	2	80	4	R972	55
6	1	6	2	9	30	1	100	3	380	45
7	1	6	3	6	60	4	40	2	300	35
8	1	6	4	3	50	3	60	1	200	25
9	1	9	1	9	50	4	40	1	380	55
10	1	9	2	12	60	3	60	2	R972	45
11	1	9	3	3	30	2	80	3	200	35
12	1	9	4	6	40	1	100	4	300	25
13	1	12	1	9	60	3	80	3	300	25
14	1	12	2	12	50	4	100	4	200	35
15	1	12	3	3	40	1	40	1	R972	45
16	1	12	4	6	30	2	60	2	380	55
17	2	3	1	3	30	4	60	4	300	45
18	2	3	2	6	40	3	40	3	200	55
19	2	3	3	9	50	2	100	2	R972	25
20	2	3	4	12	60	1	80	1	380	35
21	2	6	1	3	40	3	100	2	380	35
22	2	6	2	6	30	4	80	1	R972	25
23	2	6	3	9	60	1	60	4	200	55
24	2	6	4	12	50	2	40	3	300	45
25	2	9	1	6	50	1	60	3	R972	35
26	2	9	2	3	60	2	40	4	380	25
27	2	9	3	12	30	3	100	1	300	55
28	2	9	4	9	40	4	80	2	200	45
29	2	12	1	6	60	2	100	1	200	45
30	2	12	2	3	50	1	80	2	300	55
31	2	12	3	12	40	4	60	3	380	25
32	2	12	4	9	30	3	40	4	R972	35

FC: Formula code, **LT:** lubricant type, **UC:** Urea Concentration, **D:** Disintegrant, **TD:** total disintegrant, **I.D:** Intragranular disintegrant, **M:** Mannitol, **MCC:** Microcrystalline cellulose, **IS:** Impeller Speed, **MP:** Milling Parameters, **GT:** glidant type (Aerosil), and **TH:** tablet hardness. **a:** Lubricant: (1) Sodium lauryl sulfate (Hydrophilic) vs (2) Magnesium Stearate (Hydrophobic). **b:** Disintegrant :(1) Explotab low pH, (2) Explotab High pH, (3) Plasdone XL10, (4) Croscarmelose sodium. **c:** Milling parameters: (1) Sieve 500 micron speed 2000 rpm, (2) Sieve 500 micron speed 1000 rpm, (3) Sieve 1000 micron speed 2000 rpm and (4) Sieve 1000 micron speed 1000 rpm.

Table 2: Different properties of un-lubricated miconazole nitrate granules prepared by foam granulation

Formula Code	Bulk Density gm/cc	Tapped Density gm/cc	Carr's Index (%)	Volume surface mean diameter D[4,3]	Geometric mean Standard deviation	Elongation Ratio
F1	0.41	0.52	22	262.9	1.69	1.46
F2	0.34	0.46	26	223.3	1.69	1.35
F3	0.43	0.59	28	460.4	1.68	1.48
F4	0.37	0.49	26	216.4	1.69	1.48
F5	0.42	0.51	18	241.0	1.62	1.22
F6	0.41	0.53	22	209.2	1.70	1.37
F7	0.33	0.52	37	386.6	1.67	1.33
F8	0.38	0.56	33	547.3	1.69	1.34
F9	0.41	0.57	29	257.2	1.70	1.30
F10	0.38	0.51	26	248.2	1.69	1.36
F11	0.39	0.57	31	437.4	1.68	1.38
F12	0.36	0.49	26	390.4	1.68	1.31
F13	0.40	0.52	24	358.4	1.69	1.27
F14	0.45	0.55	19	285.6	1.69	1.36
F15	0.37	0.52	30	409.6	1.69	1.28
F16	0.38	0.53	29	048.6	1.68	1.30
F17	0.35	0.48	28	078.0	1.68	1.34
F18	0.37	0.48	24	263.0	1.69	1.29
F19	0.38	0.50	24	544.0	1.69	1.43
F20	0.40	0.52	23	273.8	1.69	1.38
F21	0.38	0.52	26	304.3	1.70	1.42
F22	0.35	0.51	31	270.7	1.69	1.36
F23	0.37	0.49	24	283.2	1.69	1.43
F24	0.39	0.52	24	254.0	1.68	1.36
F25	0.38	0.50	24	213.6	1.69	1.27
F26	0.37	0.50	25	263.2	1.68	1.34
F27	0.36	0.55	34	553.0	1.68	1.25
F28	0.43	0.54	21	317.6	1.69	1.37
F29	0.45	0.56	20	327.4	1.69	1.35
F30	0.41	0.56	27	221.4	1.69	1.32
F31	0.50	0.69	27	451.2	1.67	1.35
F32	0.42	0.55	24	308.6	1.69	1.37

Table 3: Different properties of lubricated miconazole nitrate granules prepared by foam granulation

Formula code	Flow Rate "gm/sec"	Angle of Repose "degree"	Wetting Time "seconds"
F1	1.9	30.4	110
F2	1.2	34.6	200
F3	0.6	37.8	70
F4	1.7	31.5	85
F5	1.9	26.9	100
F6	1.7	28.8	50
F7	0.7	41.2	80
F8	0.7	38.4	50
F9	1.3	35.3	40
F10	1.7	30.2	55
F11	0.6	37.6	75
F12	1.7	31.3	75
F13	1.0	30.9	60
F14	1.4	31.6	65
F15	1.2	31.4	125
F16	1.2	37.8	75
F17	0.7	35.7	115
F18	1.0	29.5	75
F19	0.8	28.1	180
F20	0.6	26.6	80
F21	0.7	33.7	90
F22	0.9	32.5	115
F23	0.9	29.5	70
F24	1.9	26.6	100
F25	1.3	28.1	140
F26	0.8	30.6	150
F27	0.6	38.2	210
F28	1.2	29.1	130
F29	1.3	26.4	60
F30	1.2	30.1	85
F31	1.1	36.5	55
F32	1.4	27.3	140

Table 4: Drug content, tablet thickness, weight variation, tablet tensile strength and friability of prepared miconazole ODT

Formula No.	Drug content %	Tablet Thickness "mm"	Weight variation "%"	Tablet Tensile Strength N/cm^2	Friability "%"
1	100.9	3.82	0.73	52.1	0.37
2	98.0	3.5	0.70	79.6	0.00
3	109.7	3.17	2.56	113.0	0.02
4	98.7	2.96	0.88	147.9	0.11
5	95.5	2.95	0.55	148.4	0.04
6	98.3	3.06	0.85	117.1	0.03
7	101.0	3.2	0.92	87.1	0.43
8	108.7	3.47	2.10	57.4	1.47
9	96.4	2.88	1.34	152.0	0.00
10	93.0	3.03	1.51	118.2	0.13
11	102.9	3.23	1.79	86.3	0.21
12	100.8	3.53	0.62	56.4	0.45
13	101.5	3.02	2.10	65.9	0.67
14	96.4	2.99	1.09	93.2	0.39
15	100.2	2.85	1.12	125.7	0.00
16	103.8	2.75	0.97	159.2	0.03
17	102.0	3.4	1.24	105.4	1.04
18	95.5	3.05	0.71	143.6	0.00
19	97.9	3.76	0.95	52.9	0.44
20	96.6	3.52	1.70	79.2	0.18
21	100.1	3.55	0.90	78.5	0.44
22	105.9	3.61	1.11	55.1	0.39
23	91.3	3.05	0.92	143.6	0.05
24	104.5	3.14	1.09	114.1	0.34
25	94.5	3.25	0.55	85.7	0.15
26	97.6	3.45	1.11	57.7	0.22
27	101.9	3.07	1.39	142.6	0.10
28	99.4	3.05	0.99	117.5	0.15
29	99.5	2.96	1.47	121.0	0.18
30	93.1	2.8	0.49	156.4	0.00
31	100.4	3.4	0.77	58.5	0.00
32	95.6	2.82	1.15	98.8	0.16

Table 5: Tablet wetting time, water absorption ratio, calculated true density, calculated total porosity of miconazole ODT, dissolution value and disintegration time for miconazole ODT

Formula code	Tablet Wetting time "seconds"	Water Absorption Ratio	Calculated True Density gm/cm^3	Calculated total Porosity"%"	Dissolution value after 15 minutes "%"	Disintegration time "seconds"
F1	65	53.6	1.567	36	44.8	60
F2	100	85.5	1.555	29	50.6	55
F3	120	29.3	1.529	20	76.8	45
F4	60	69.2	1.544	16	55.7	92
F5	44	21.8	1.554	18	77.3	125
F6	110	53.8	1.568	22	72.3	80
F7	130	22.4	1.525	23	92.0	165
F8	130	41.6	1.548	30	82.1	51
F9	60	13.9	1.544	19	80.2	145
F10	45	37.7	1.548	23	82.3	100
F11	40	51.7	1.546	27	47.1	105
F12	35	59.5	1.568	35	94.4	40
F13	30	10.7	1.548	25	98.5	35
F14	50	36.1	1.544	24	51.9	95
F15	130	28.7	1.559	21	42.3	93
F16	26	11.3	1.554	18	53.7	105
F17	45	12.5	1.544	26	57.2	50
F18	130	17.5	1.548	18	75.2	125
F19	130	45.0	1.526	33	100.0	35
F20	60	143.1	1.567	30	100.0	18
F21	120	39.7	1.548	32	55.1	45
F22	200	66.5	1.544	33	83.5	50
F23	180	30.2	1.539	20	59.4	85
F24	25	18.9	1.554	23	78.3	50
F25	65	50.1	1.568	29	62.8	54
F26	150	36.4	1.555	33	62.1	60
F27	200	19.7	1.509	22	38.1	130
F28	60	20.9	1.544	23	46.6	85
F29	120	22.9	1.555	24	52.3	120
F30	190	27.8	1.569	20	48.5	100
F31	200	17.8	1.505	32	74.7	40
F32	24	16.0	1.548	20	45.2	97

Table 6: Ranking of the variables affecting the formulation and processing of miconazole nitrate granules prepared by foam granulation

	VMD	GMSD	ER	CI	AOR	FR	WT	sum	Rank
Urea conc.	6	7	1	7	7	2	2	32	4
D. type	1	6	4	1	1	4	8	25	3
D. conc.	7	1	6	3	3	6	7	33	5
Intragranular D conc.	4	5	3	4	8	7	4	35	6
Mannitol/MCC ratio	2	2.5	7	5	2	1	3	22.5	1
Impeller speed	3	4	5	6	6	5	9	38	7
Milling parameters	5	2.5	2	2	5	3	5	24.5	2

VMD = volume mean diameter, GMSD = geometric mean standard deviation, ER =elongation ratio, CI = Carr's index, AOR = angle of repose, FR = flow rate, WT=wetting time, D=disintegrant

Table 7: Ranking of the variables affecting the quality control parameters of miconazole nitrate ODT prepared by foam granulation

Variable	WV	TS	F	DIS	DT	WTT	WAR	TP	sum	Rank
Urea conc.	7	1	4	4	2	5	1	2	26	2
D type	4	4	6	6	5	1	5	7	38	5
D. conc.	8	5	3	2	8	7	7	4	44	7
Mannitol/MCC ratio	1	7	5	7	3	6	2	3	34	4
Milling parameters	3	6	7	5	7	3	4	5	40	6
Lubricant	6	3	8	8	6	2	8	5	46	8
Aerosil type	-	2	2	3	4	8	6	8	33	3
Hardness	2	-	1	1	1	4	3	1	13	1

WV=Weight variation, TS=Tensile strength, F=Friability, DIS=Dissolution, TP=Tablet porosity, DT=Disintegration time, WTT=Wetting time tablets, WAR=Water absorption ratio, D=disintegrant

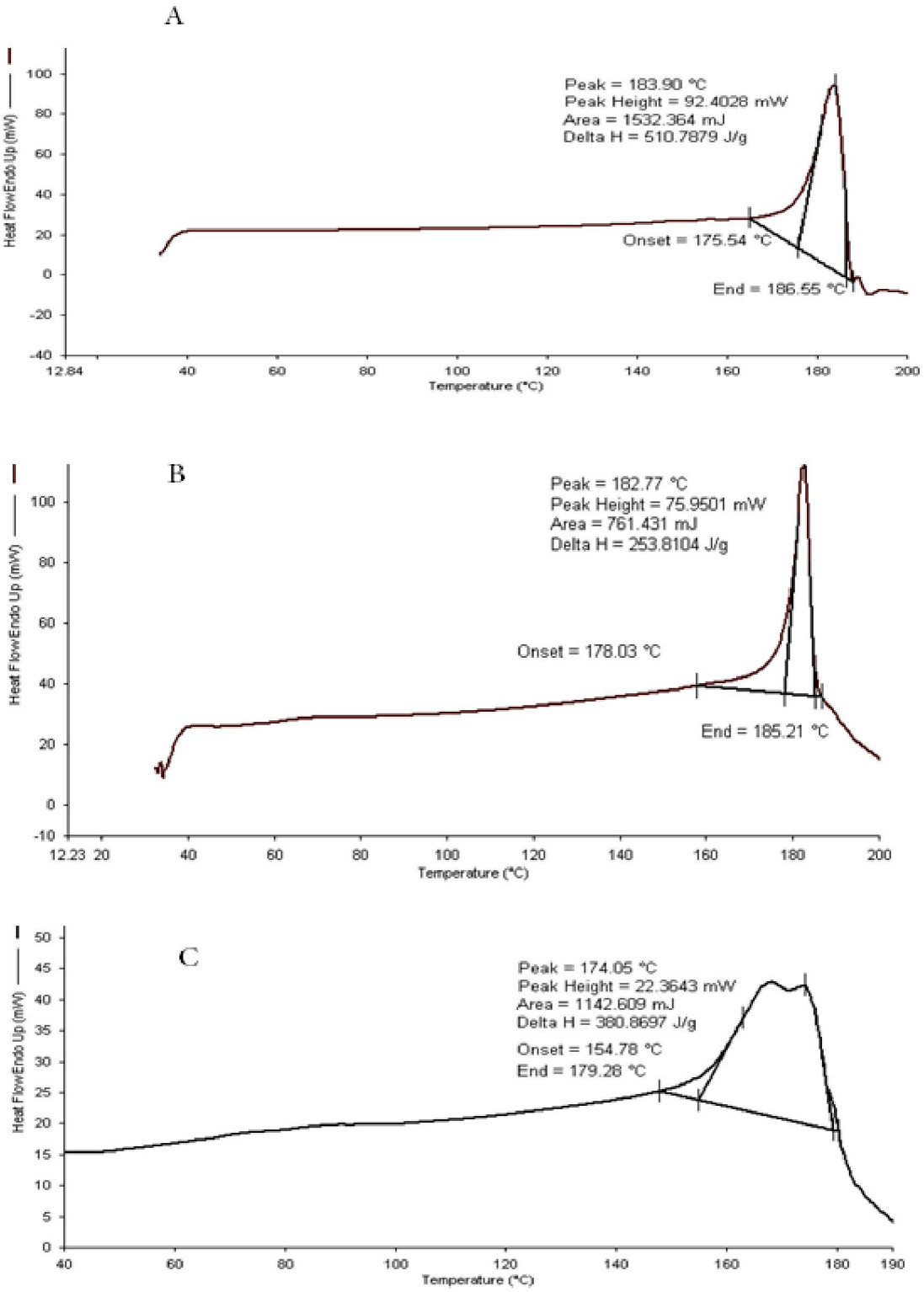

Figure 1: DSC chromatogram of pure miconazole nitrate (A), physical blend of miconazole nitrate and hydroxy propyl methylcellulose at ratio 10:1 (B), and physical blend of miconazole nitrate and magnesium stearate at ratio 10:1(C)

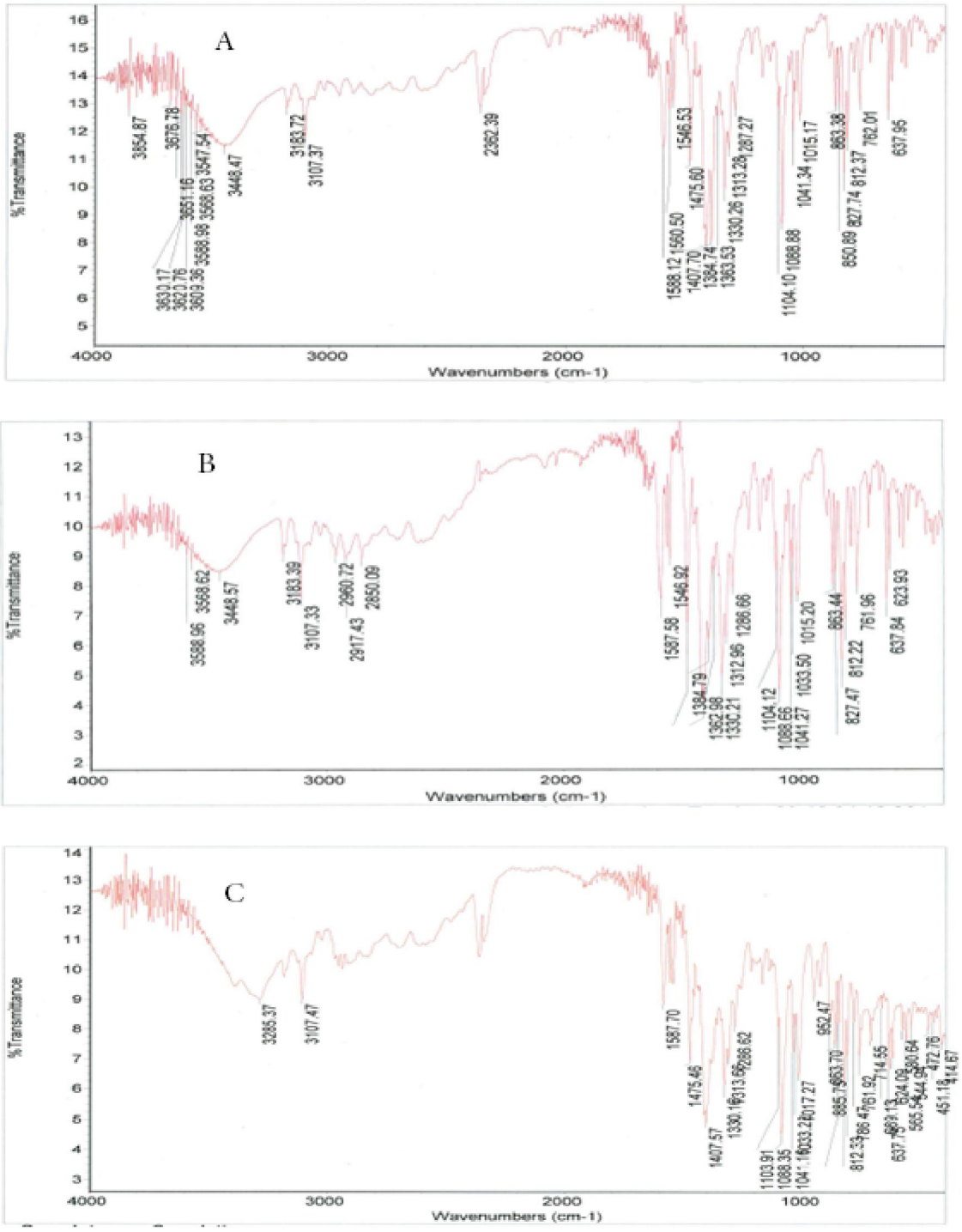

Figure 2: The IR spectrum of miconazole nitrate (A), IR spectrum of miconazole nitrate : Sodium lauryl sulfate at ratio 1 : 0.1 (B), IR spectrum of miconazole nitrate : mannitol at ratio 1: 1 (C)

Figure 3: Microscopic graph of miconazole granules F19 prepared by foam granulation.

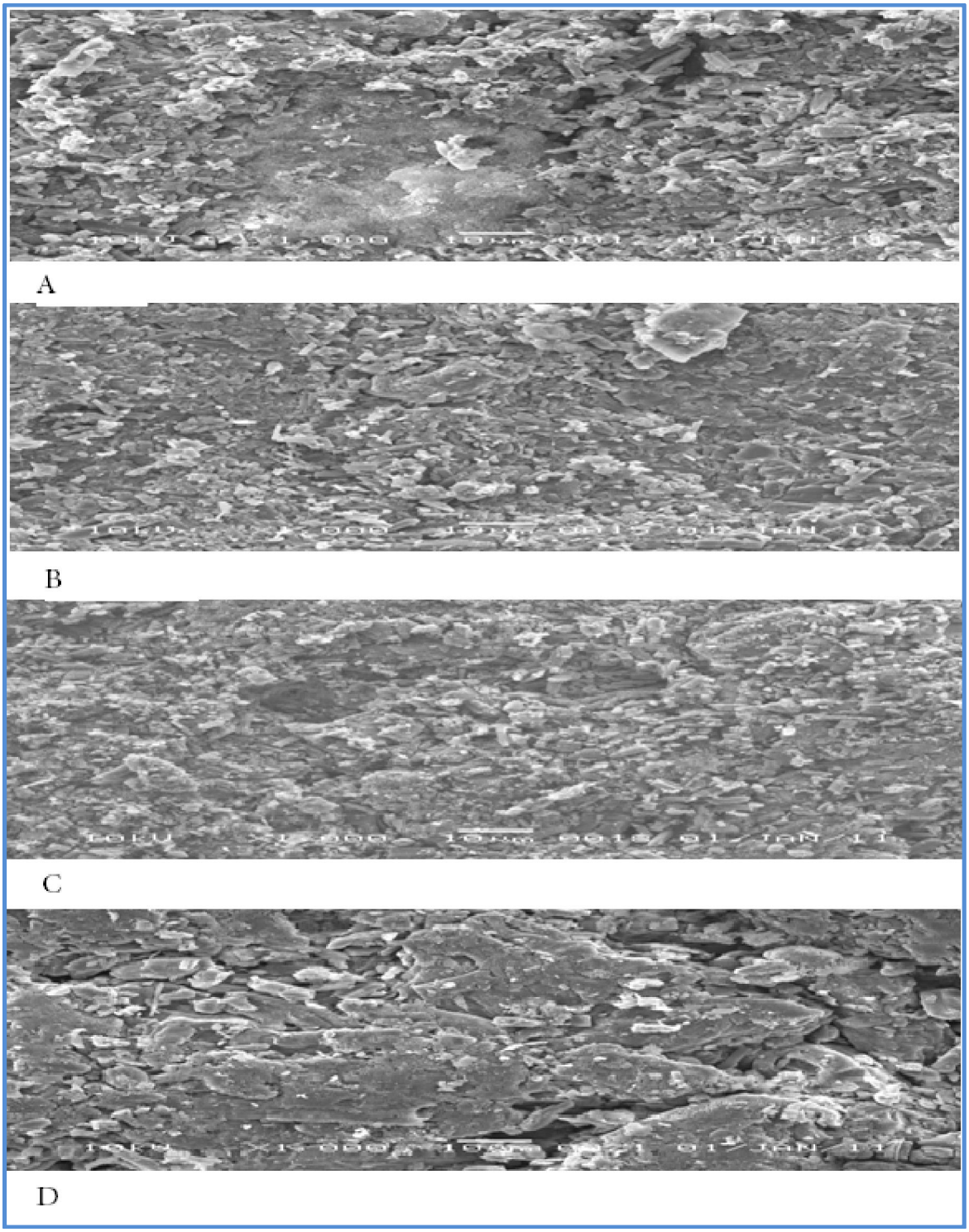

Figure (4): SEM micrograph of tablet surface of miconazole ODT F12 (A), F13 (B), F19 (C), and F20 (D)

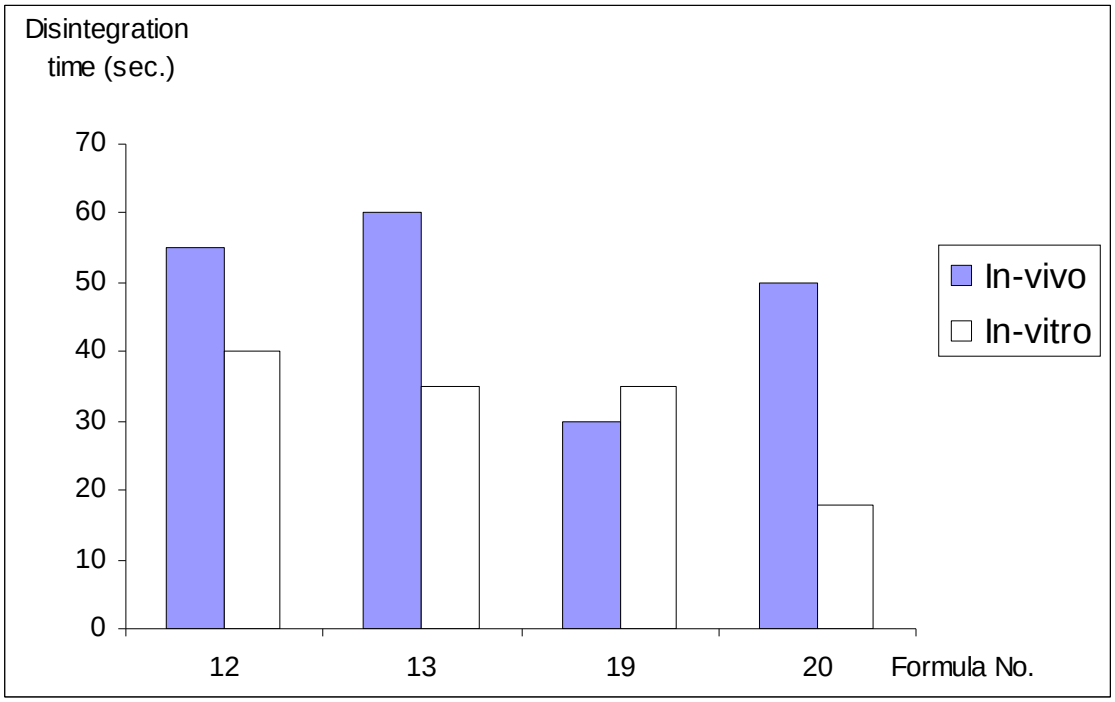

Figure 5: In vivo and in vitro disintegration time of miconazole ODT prepared by foam granulation