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Design and characterization of taste masked metronidazole microcapsules and its utilization in the formulation of orodispersible tablets

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Abstract

Orodispersible tablet (ODT) containing microcapsules is an advanced and convenient drug delivery system that offers advantages of easy administration, and increased bioavailability. Metronidazole is an antiprotozoal, with a bitter and metallic taste as its major drawback. A taste masking is required since the tablet will disintegrate in the oral cavity releasing the drug into close proximity to the taste buds. The purpose of the study is to design and evaluate metronidazole microcapsules for formulation of taste masked orally ODT metronidazole tablets. Taste masked metronidazole microcapsules were prepared by emulsion polymerization method with sodium alginate as polymer using different drug to polymer ratio. The microcapsules were evaluated for drug loading, entrapment efficiency, drug-polymer interaction by FTIR spectrometry, DTA, and flow properties. Batches B4 and B5 were formulated into orally disintegrating tablet by direct compression method. The results of FTIR spectrometry and DTA characterization of microcapsules revealed absence of drug-polymer interaction. Evaluation of the microcapsules showed fairly good flow properties and increase in entrapment efficiency as the polymer concentration increased. Evaluation of the directly compressed ODTs showed acceptable weight variation, and average disintegration time less than 60 sec. The average tablet crushing strength range from 18 to 19 N, and the drug release profiles showed greater than 80% release of metronidazole within 10 min. The successful microencapsulation of metronidazole, fast disintegration, rapid drug release profile, and evidence of compatibility between metronidazole and the process polymer demonstrates the suitability of the microcapsules for formulation of orally disintegrating tablet for convenient delivery of metronidazole.

Keywords: Orally disintegrating tablets, microencapsulation, taste masking.

INTRODUCTION

Oral medications is the safest and more acceptable route of drug administration, but swallowing oral medications in form of pills, tablets, or capsules present a challenge for patients in different age groups [1]. A survey revealed that more than 40% of adults in general community experience problems swallowing pills out of which fourteen percent disclosed that they had delayed taking a dose of their medication, and 8% had skipped a dose completely [2]. Thus, adults who have difficulty swallowing the conventional tablets and capsules may not comply with prescribed regimens [3]. Thus, it is necessary to improve methods to effectively deliver oral medications to patients. Oral disintegrating (orodispersible)

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tablet technologies offers a means by which drugs are delivered through fast disintegration of the tablet within the oral cavity facilitating absorption through the upper aero-digestive system without the need of water or chewing to aid swallowing [3]. The disintegration time for a good orodispersible tablet varies from several seconds to a minute [1]. ODTs provide many advantages such as easy administration, rapid drug therapy intervention due to rapid disintegration and absorption in the buccal, pharyngeal and gastric regions; and increased bioavailability due to ability to bypass first-pass metabolism [2]. The primary patients for ODTs are pediatric, bedridden or disabled patients; patients with persistent nausea; geriatric, patients who have little or no access to water (e.g. travelling persons) [4].

Taste is very important parameter governing patient compliance in oral medication [5]. Taste is the ability of the tongue to respond to dissolved molecules and ions- "gatekeeper to the body". Taste receptor cells in humans are clustered into onion-shaped organs called taste buds [5]. Orally disintegrating drugs disintegrate in the oral cavity, thus releasing the active ingredients that dissolve in close proximity to the taste buds. Hence, palatability of the drug in the mouth is critical to patient compliance [6]. Taste masking techniques are applied to overcome the bitter or unpleasant taste of active pharmaceutical ingredient to achieve patient acceptability and adherence [7]. There are various techniques used in taste masking. They include the addition of flavoring and sweetening agents, coating, micro encapsulation, solid dispersion system, granulation, ion-exchange resin, inclusion complexes, adsorption, pro-drug approach, multiple emulsion technique, pH modifier, viscosity enhancer, liposomes, effervescent agent, salt formation [8,9].

Metronidazole [1-(beta-hydroxyethyl)-2-methyl-5-nitroimidazole] is used for treatment of *Trichomonas vaginalis* infection (Bowman & Rand, 1980) [10]. It is a 5-nitroimidazole antimicrobial. It has been successfully used in the treatment of vaginal infections, antibiotic-associated pseudo-membranous colitis, trichomoniasis and symptomatic amebiasis, drug of first choice in the infections of Helicobacter pylori and also reported to be of value in Crohn's disease [11]. It is usually absorbed well (80-90%) by oral route [12]. The principal route of elimination is hepatic oxidation and glucuronidation. Metronidazole has common adverse effects like nausea, diarrhea, anorexia, vomiting and urticaria [13].

EXPERIMENTAL

Chemicals and reagents. Metronidazole (Liaoyuama Pharm, China), Sodium Alginate, Coconut Oil, Sodium Lauryl Sulphate, Formaldehyde, n-Hexane (BDH Chemicals, China), Sodium Starch Glycolate (Lobachemie Mumbai, India), Cellatose (Meggle, Germany), Mannitol (Harris Chemical, England), Talc, Magnesium Stearate, Aerosil, Potassium dihydrogen phosphate (BDH Chemicals, China), Sodium Hydroxide pellets (Trust Chemical Laboratories, India).

Preparation of metronidazole calibration curve. Hundred milligram (100 mg) of metronidazole was accurately weighed using an analytical balance(AWS, USA), transferred to a 100 ml volumetric flask containing 10 ml of phosphate buffer pH 7.4. The powder was dispersed and made up to volume with the phosphate buffer to give the stock solution. From the stock solution, final concentrations of 0.010, 0.015, 0.020, 0.025, 0.030, 0.035 and 0.040 mg/ml were prepared in 100 ml volumetric flask. Then the absorbance of the resulting solutions were measured spectrophotometrically at λ max of 340 nm using the phosphate buffer as blank using GS-UV 61PC double beam Spectrophotometer (General Scientific, India).

Then, the absorbance versus concentration of solutions were plotted to obtain the calibration curve.

Preparation of polymeric-metronidazole microcapsules. Phase separation emulsion polymerization method was employed for the preparation of metronidazole microspheres [14]. In a mortar, 1 g of metronidazole was added to 10 mL of 10% solution of sodium alginate and triturated continuously until uniform dispersion was obtained. In a separate beaker, to 86 mL of coconut oil in the organic phase, 1 mL of 0.5% sodium lauryl sulphate was added and stirred adequately to give a uniform dispersion. The drug-polymer mixture was added dropwise using a 21-gauge needle (Anhui Kangda medical products, India) into the organic phase and stirred continuously to form uniform dispersion. The temperature of the solution was gradually increased to 65^{o}C on the water bath (Fisher Scientific Company, USA) and stirred at this temperature for 1 hour. The solution was cooled to room temperature with continuous stirring. After the room temperature was attained, 1 mL of formaldehyde and 20 mL of n-hexane was added to separate the microspheres from the organic phase, which were filtered and separated. The obtained microspheres were washed thrice with n-hexane then followed by distilled water, dried and stored in airtight containers. The same procedure was carried for polymer concentration of 15%, 20%, 25% and 30% as shown in Table 1 [14].

Characterization

Spectral analysis by FT-IR. The prepared microcapsules were characterized by Fourier Transformed Infrared Spectroscopic (FT-IR) analysis. The FT-IR spectra measurements were recorded at ambient temperature using a Shimadzu, Model 8033 (USA). Potassium disks were prepared by mixing few milligram of sample with potassium bromide by compacting in a hydrostatic press under vacuum at 6-8 tons (6000 -8000 kg/cm^3) pressure. The resultant disc was mounted in a suitable holder in IR spectrophotometer and the IR spectrum was recorded from 4000 cm^{-1} to 500 cm^{-1} in a scan time of 12 minutes. The resultant spectrum for the microcapsules was compared with spectrum of metronidazole, sodium alginate and direct physical mixture of metronidazole and sodium alginate for any spectral changes. They were observed for the presence of characteristic peaks for respective functional group in the compound.

Differential Thermal Analysis (DTA). The DTA is a thermoanalytic technique that is similar to differential scanning calorimetry. DTA of the microcapsules, metronidazole was performed using Differential scanning calorimeter 60 Shimadzu to obtain suitable thermograms. Few milligrams of the sample was weighed and placed in an aluminium pan, and an empty aluminium pan was used as reference. The experiment was performed under nitrogen flow, at a scanning rate of 30^{o}C / min. over a temperature range of 50-350^{o}C. The differential temperature is then plotted against temperature (thermogram). Changes in the sample, either exothermic or endothermic, can be detected relative to the reference. Thus, a DTA thermogram (curve) provides data on the transformations that have occurred, such as glass transitions, crystallization, melting and sublimation. The area under the DTA peak is the enthalpy change.

Evaluation of the microcapsules

Percentage yield. The prepared micro spheres/microcapsules were dried and stored in a desiccator at room temperature for 24 hours. The percentage yield of microspheres was calculated according to the following equation:

$$\text{Percentage yield} = \frac{\text{Weight of microspheres/microcapsules}}{\text{Total weight of solid material}} \times 100 \quad \ldots(1)$$

Drug loading. The various batches of the microcapsules were subjected to drug content

analysis. One hundred milligram (100mg) of microsphere samples were weighed and mechanically powdered in a mortar. The powdered microspheres were dispersed in 100 ml of phosphate buffer (pH 7.4), stirred and then filtered. Then, 2 ml of the solution was analyzed spectrophotometrically at a wavelength of 340 nm using a GS-UV 61PC double beam Spectrophotometer (General Scientific, India)[15]Thedrugconcentration in each batch of the microspheres was derived from a Beer's plot previously determined for metronidazole. An average of five determinations was taken as the mean drug content for each batch of microspheres.

Drug Loading =

$$\frac{Weight\ of\ drug\ in\ microspheres/\text{microcapsules}}{Total\ weight\ of\ microspheres\ weighed} \times 100 \quad ...(2)$$

A single point method of determination of content of microspheres/microcapsules was also employed to confirm weight of drug in various batches as follows: One hundred milligram (100 mg) of microsphere/microcapsules samples were weighed and mechanically powdered in a mortar. The powdered microspheres/microcapsules were dispersed in 100 ml of phosphate buffer (pH 7.4) in a conical flask, vigorously shaken and filtered. Then 1 ml of theabove solution was further diluted to 100 ml given unknown concentration (C_u) and was analyzed spectrophotometrically at a wavelength of 340 nm using a GS-UV 61PC double beam Spectrophotometer (General Scientific, India). A standard solution of metronidazole also prepared by weighing 100 mg of metronidazole and dispersed in 100 ml of phosphate buffer (pH 7.4) with vigorous shaken in a conical flask given a standard solution (1 mg/ml). One milliliter (1 ml) of this solution was further transferred to a 100 ml conical flask, and volume adjusted to the mark with the buffer solution to yield a solution with concentration of 0.01 mg/ml. The absorbance of this standard solution was recorded spectrophotometrically. Knowing the absorbance of the standard solution and absorbance of the unknown concentration, then the unknown concentration of the microspheres were determined.

Entrapment efficiency. The loading efficiency of the drug in the microcapsules was determined using a spectrophotometer as described above. Percentage encapsulation / entrapment efficiency was determined using the formula:

Percentage entrapment efficiency =

$$\frac{Actual\ weight\ of\ drug\ in\ sample}{Theoretical\ weight\ of\ drug} \times 100 \quad \ldots(3)$$

Morphological examination of microcapsules. All the microcapsules were evaluated with respect to their morphology using a specialized LCD Micro (Bresser) microscope.

Preparation of orodispersible tablet. Tablets containing equivalent of 100 mg metronidazole were prepared by direct compression method. An equivalent weight of microcapsules containing 100 mg metronidazole (≃ 455 mg, microcapsules) was weighed and blended with other excipients (table 3). The powder blend was compressed on a single punch (Erweka, Germany) tableting machine at 2 kN using die size 12.5 mm.

Evaluation of the Orodispersible Tablets.

Diameter and thickness. The thickness and diameter of the matrix tablets was determined using a digital caliper (Aerospace) and the results were expressed as a mean value of five determinations.

Weight Variation. Twenty tablets were selected randomly from the lot, weight of individual tablet and average weight for all the determined and the weight variation limit was computed.

Hardness. The hardness of the tablets was determined using a Monsanto hardness tester

and the results were expressed as a mean value of five determinations.

Wetting time. A piece of double folded tissue paper was placed on a Petri dish containing 10 mL of water. The tablet was placed on the paper and the time for complete wetting of the tablet was measured.

Water absorption ratio. Water absorption ratio was measured by keeping a tablet on a piece of tissue paper folded twice in a petri dish containing 10 mL of water. The value was calculated using the following equation:

$$\text{Water absorption ratio} = \frac{W_A - W_B}{W_B} \times 100 \quad (4)$$

W_A – Weight of tablet after water absorption

W_B – Weight of tablet before water absorption

Disintegration test. A tablet was placed in each tube in the disintegration apparatus (Copley Scientific, England) and the basket rack was positioned in a 1 L capacity beaker filled with distilled water to 600 ml mark at 37ºC. The time for the tablet to completely disintegrate and pass through the mesh at the lower end of each tube was recorded as the disintegration time. The results were expressed as mean of five determinations.

***In vitro* drug release.** *In vitro* drug release studies of all the formulations were carried out using tablet dissolution test apparatus. Phosphate buffer pH 7.4 was used as the dissolution media with temperature maintained at 37 ± 0.5°C and 10 mL sample was withdrawn at different intervals (0, 2, 5, 10, 15, 20, 25, 30 and 60 minutes), filtered and analyzed spectrophotometrically at a wavelength of 340 nm using a GS-UV 61PC double beam Spectrophotometer (General Scientific, India) [15].

Statistical analysis. All data obtained were expressed as Mean ± Standard Deviation.The data obtained from the dissolution test was evaluated using one- way analysis of variance (ANOVA). The level of significance was set at $p < 0.05$.

RESULTS AND DISCUSSION

Morphological images of formulated microparticles (Mag. x400) revealed irregular shaped microcapsules and not microspheres (Figure 1). The particle morphology of the prepared orodispersible microcapsules were as shown in figure 1.

Evaluation of microcapsules. The microcapsules prepared were brown in color (possible due to the brown color of sodium alginate) and irregular in shape when observed visually in figure 1. The percentage yields of all batches were determined and the results were shown in the figure 2. The results showed that formulations B4 and B5 have the greatest recovery rates of 85.86% and 97.00% respectively. Data analysis was performed using One-way ANOVA $p \leq 0.05$. A $p \leq 0.05$ was considered statistically significant.

Entrapment efficacy and percentage drug content. The percentage drug loading and percentage entrapment efficacy were derived from equations 2 and 3 stated earlier. These two parameters: the entrapment efficiency and drug content (figure 3) were carried out to determine the actual amount of metronidazole that was encapsulated into the polymer. Batches B4 and B5 had the highest entrapment efficiency, that is the microspheres had the highest percentage of drug encapsulated into the coating material.

Data analysis was performed using One-way ANOVA $p \leq 0.05$A $p \leq 0.05$ was considered statistically significant.

Flow characteristics of the microcapsules. The granular characteristics of the microcapsules prepared was determined as flow rates, angle of repose, bulk and tapped densities, Carr's index and Hausner's ratio.

The table 3 summarizes the flow properties of the formulated microcapsules. Flow rate

increases with the increase in concentration of polymer in each batch of the microcapsules. More so, both bulk and tapped density followed the same trend with little deviation noticed in tapped density values for B3 and B5. This is due to the irregular shaped granules i.e., microcapsules which due to their nature resisted free densification with the low force applied during tapping.

Excipient interaction. IR spectroscopy was used to characterize the complex microcapsules. FTIR spectra of the pure drug, polymer, Batch B4 and Batch B5 are shown in the figures 5, 6, 7, 8 and 9 below.

The chemical structure of analyte sample gives characteristic vibrational peak (stretching, bending etc.) on FT-IR spectra of the functional groups present, which is unique for that particular functional group [16]. These vibrational peaks can be used for the interpretation and structural characterization of test compounds. The FTIR spectral features of Metronidazole (Fig.4), was characterized by υ(OH) alcoholic band at 3207 cm^{-1}, and the ring torsion band at 826 cm^{-1}. The sample also showed characteristic vibrational peak for C-H stretching at 2991 cm^{-1}. Vibrational absorption peaks at 1535 cm^{-1} was assigned to C=N stretching. The N=O asymmetric stretching was assigned to peak at 1479 cm^{-1}, and C-C stretching peak was assigned to peak at 1425 cm^{-1}. The absorption peaks at 1367 and 1354 cm^{-1} were assigned to CH_3 bending and N=O asymmetric stretching, respectively. Absorption peaks at 1073 and 3099 cm^{-1} were assigned to C-N and aromatic C-H stretching respectively while 1265 and 1185 cm^{-1} were assigned to C-O stretching. FT-IR data of control metronidazole was well supported by the literature data [16].

From figure 4 (sodium alginate spectra), it can be observed that the absorption bands around 1589.7, 1405, and 1313 cm^{-1} are attributed to stretching vibrations of asymmetric and symmetric bands of carboxylate anions, respectively while 2933 $cm^{-1}$is attributed to CH_2 stretching. The broad peak that appeared at 3237 cm^{-1} corresponds to stretching vibrations of hydroxyl groups.

The physical mixture of metronidazole and sodium alginate (Fig. 4), showed characteristic vibrational peak for C-H stretching at 2991 cm^{-1}, 1533 cm^{-1} for C=N stretching, 1586 cm^{-1} for C=C stretching. The N=O asymmetric stretching peak at 1474 cm^{-1}, and C-C stretching peak was assigned to peak at 1425 cm^{-1}. The absorption peaks at 1367 and 1354 cm^{-1} were assigned to CH_3 bending and N=O asymmetric stretching, respectively. Absorption peaks at 1073 and 3099 cm^{-1} were assigned to C-N and aromatic C-H stretching respectively while 1265 and 1185 cm^{-1} were assigned to C-O stretching. 1586 cm^{-1} attributed to stretching vibrations of asymmetric bands of carboxylate anions. The sharp peak appeared at 3211 cm^{-1} corresponds to stretching vibrations of hydroxyl groups with little hydrogen bonding. FTIR Spectra of both Batch B4 and B5 microcapsules (Fig. 4) showed Absorption peaks at 1597 and 1410 cm^{-1} attributed to stretching vibrations of asymmetric and symmetric bands of carboxylate anions respectively while 2855 and 2933 cm^{-1} were from sodium alginate attributed to CH_2 stretching. The 1023 cm^{-1} attributed to C-O stretching. The broad peak that appeared at 3231 cm^{-1} corresponds to stretching vibrations of hydroxyl groups as shown in figure 3.

Differential Thermal Analysis (DTA). Technical improvements of DTA over time have resulted in it being a very relevant tool for investigating the thermodynamic properties of various pharmaceutical products [17,18]. With the abilities to test both drug and excipient for purity, stability or pharmacological properties, DTA is becoming increasingly popular in the pharmaceutical industry [19]. DTA is a technique used to determine the energetics of phase transitions and conformational changes and also allows quantification of their temperature

dependence [18]. The physiochemical properties of different pharmaceutical products can be determined effectively using DTA thus facilitating improvement in modifications of the existing compounds or designing of new drugs [19].

The DTA results of metronidazole (Fig. 5) shows exothermic recrystalisation at 167.2^{o}C (range 156.4 to 163.6^{o}C) and an endothermic melting at 273.6^{o}C (which range 266.5 – 270.2^{o}C). For the microsphere 1:3, the recrystalisation took place at 119.5^{o}C lower than that of metronidazole with onset at 101.5^{o}C and end at 120^{o}C while it melts at 236.7^{o}C with onset at 230.3^{o}C and ends at 235.9^{o}C after which it recrystallises and again melts at 352.5^{o}C (range 351.0 - 363.3^{o}C). This result shows no interaction of the drug with excipient. The increase in melting point of microcapsules after recrystallization, and the FT-IR stretching vibration shift of C-O from 1096cm^{-1} to 1023 cm^{-1}could be due to the presence of larger amount of sodium alginate forming a protective coating around metronidazole (22 mg of metronidazole in 100 mg microcapsules) requiring higher temperature to achieve melting. From the FT-IR and DTA analysis there is no clear interaction between metronidazole and sodium alginate.

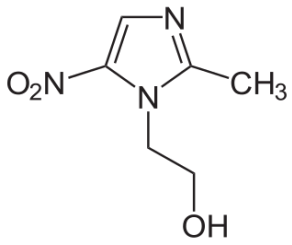
Evaluation of orally disintegrating tablets. Batches B4 and B5 were chosen (due to their high entrapment efficiency, high percentage yield and adequately taste masked drug) to be formulated into orally disintegrating tablets.
All the formulations were evaluated for weight variation, diameter, thickness, hardness, water absorption, wetting time and disintegration time and their results are shown in Table 4. From the parameters, it was observed that weight, diameter and thickness of all batches complied with the desired specification for orally disintegrating tablets.

Tablet hardness test. Hardness of all formulations fall within the range of 18 and 19N, this is satisfactory for mouth disintegrating tablets as shown in Table 6.

Wetting time and water absorption test. The results of wetting time and water absorption test for microspheres B4 and B5 were 52.00 $\pm$ 2.0 and 51.33 $\pm$ 3.21 respectively. There is a linear relationship between drug release and wetting time and water absorption. The faster the wetting and water absorption of a tablet, the more rapid the release of the active ingredient. The outcome of this experiment explains the rapid release of more than 80 % of metronidazole from the orodispersible tablet within a short time of 8 minutes.

***In vitro* disintegration study.** The *in vitro* disintegration time for all the compressed orodispersible tablets was determined and shown in Table 4. The disintegration time for orally disintegrating tablets is generally less than 1 minute [20]. The disintegration time of the two best formulations were in the range of 50 and 58 seconds and this was found to be in accordance with the required specification, (< 3min) for fast release and absorption of API. Orally disintegrating tablets (ODT) are designed to rapidly disintegrate in the oral cavity. The December 2008 FDA Guidance for Industry recommends a disintegration time of no more than 30 s and a tablet weight of less than 500 mg. The European Pharmacopeia calls these products orodispersible tablets and defines them as having a disintegration time within 3 min. No other features was specified [20]. The administration of ODTs may not inherently result in a faster therapeutic onset, but can circumvent problems such as difficulty in swallowing traditional solid oral dosage forms like tablets and capsules, and can improve ease of use of a product by providing a means of drug delivery without water or liquids. ODTs can have buccal and/or GI absorption, so both dissolution testing and disintegration testing are important.

***In vitro* drug release study.** The time points were selected based on the FDA recommendation for most orally disintegrating tablets. *In vitro* release study (Fig. 6) showed that greater than 50 % of the drug was released from the two best formulations (drug to polymer ratio 1:2.5 and drug to polymer ratio 1:3) after 2 minutes and over 80% within 10 minutes.



Metronidazole ($C_6H_9N_3O_3$, mol. wt. 171.154 $gmol^{-1}$)

Table 1: Composition of all batches of Metronidazole Microcapsules

BATCHES	D:P RATIO	CONSTITUENTS
B1	1:1	Metronidazole 1g; Sodium alginate 10 mL of 10%
B2	1:1.5	Metronidazole 1g; Sodium alginate 10 mL of 15%
B3	1:2	Metronidazole 1g; Sodium alginate 10 mL of 20%
B4	1:2.5	Metronidazole 1g; Sodium alginate 10 mL of 25%
B5	1:3	Metronidazole 1g; Sodium alginate 10 mL of 30%

D = Drug P = Polymer

Table 2: Composition of orodispersible tablets of metronidazole

Formulation	D: ratio	Composition of Ingredients (%W/W)				
		Metronidazole loaded microcapsules	Sodium Starch Glycolate	Cellactose	Mannitol	Aerosi
B5	1:3	45	10	25	13	5

Table 3: Flow characteristics of the microcapsules

Batch	Angle of Repose	Flow Rate (g/s)	Bulk density	Tapped Density	Hausner's ratio	Carr's index	Flow property
B1	21.50 ±0.55	1.91	0.320 ±0	0.453 ±0.04	1.433 ±0.13	29.047 ±6.02	Good
B2	17.66 ±0.16	2.04	0.337 ±0.34	0.490 ±0.05	1.437 ±0.10	30.960 ±4.68	Excellent
B3	17.85 ±0.20	3.02	0.350 ±0	0.450 ±0.02	1.277 ±0.06	22.140 ±3.07	Excellent
B4	18.01 ±0.17	3.12	0.460 ±0	0.550 ±0	1.180 ±0	16.36 ±0	Excellent
B5	15.71 ±1.36	3.14	0.460 ±0	0.517 ±0.03	1.113 ±0.06	10.787 ±4.83	Excellent

n = 3 ±SD; B1 – Drug to Polymer Ratio 1:1; B2 – Drug to Polymer Ratio 1:1.5; B3 – Drug to Polymer Ratio 1:2; B4 – Drug to Polymer Ratio 1:2.5; B5 – Drug to Polymer Ratio 1:3

Table 4: Evaluation of tablet for hardness, dimension, disintegration time, wetting time and weight variation.

Formulations	Tablet weight***(g)	Diameter ** (mm)	Thickness ** (mm)	Hardness * (N)	Wetting time * (s)	Water absorption ratio * (%)	Disintegration test* (s)
B4	1.011±0.01	12.86±0.02	4.66 ±0.06	18.33±0.29	52.00 ±2.0	85.61 ±3.92	51.67 ±2.89
B5	1.014 ±0.01	12.88±0.01	4.70±0.06	19.00 ±0.17	51.33±3.21	80.64 ±4.60	57.67 ±2.52

F1 – Drug to Polymer ratio 1:2.5; F2 – Drug to Polymer ratio 1:3; *** - n=10±SD; ** - n=5 ±SD * - n=3±SD

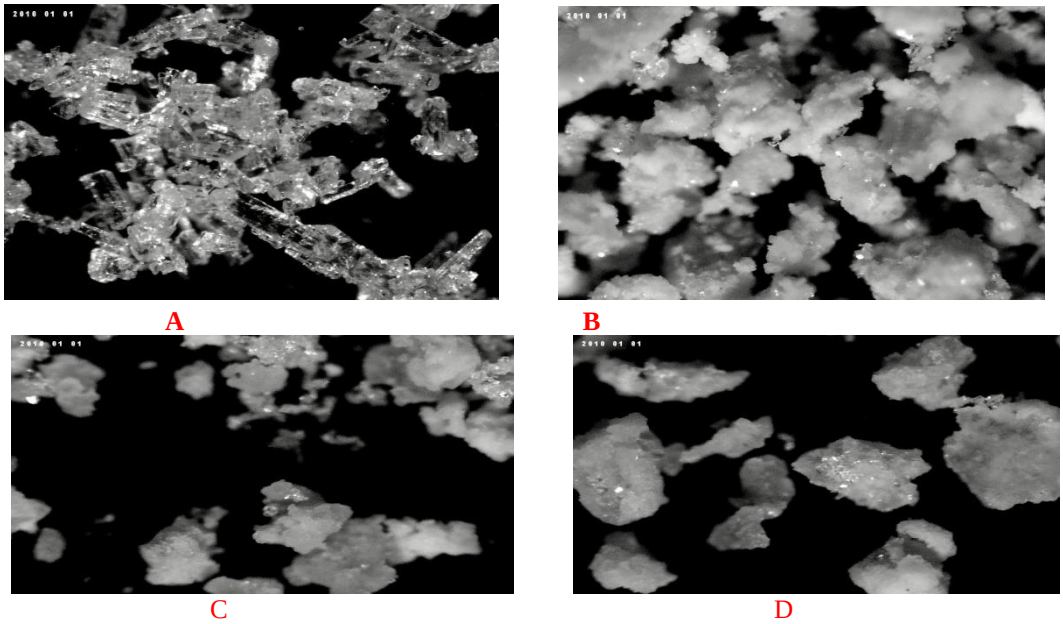


Figure 1: LSD microscopic images. (A) Metronidazole; (B) Orodispersible microcapsules, 1:2.5; (C) &(D) Orodispersible microcapsules, 1:3

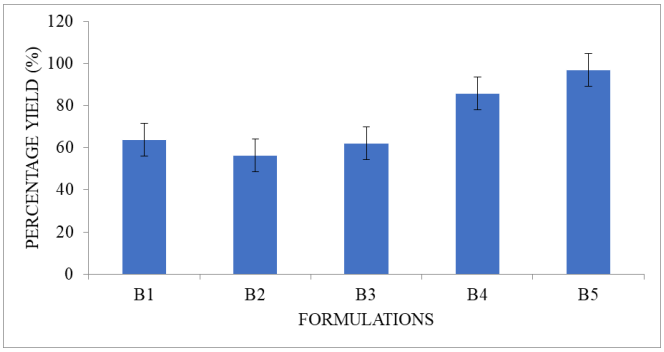


Figure 2: Percentage yield of various batches of the microspheres.

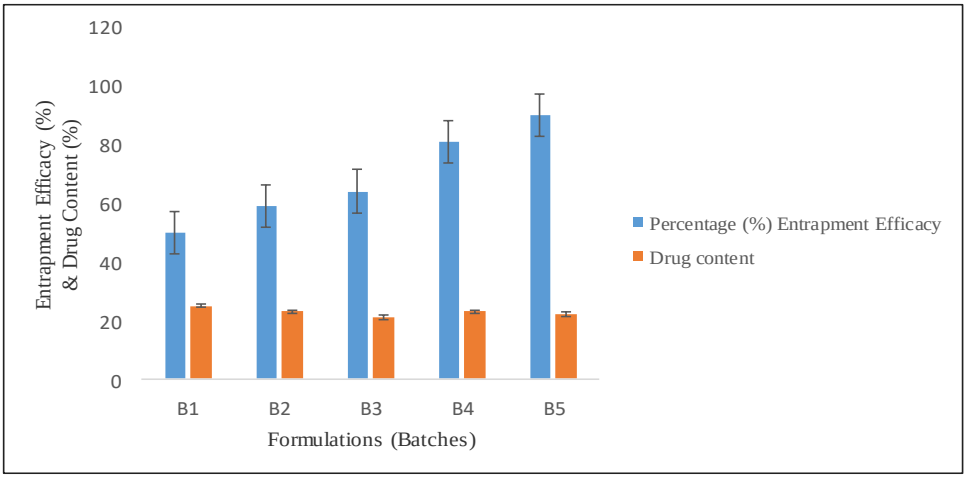


Figure 3: Drug content and Entrapment efficiency on various batches of the microcapsules.

FTIR Spectroscopic Investigations of the Studied Microcapsules

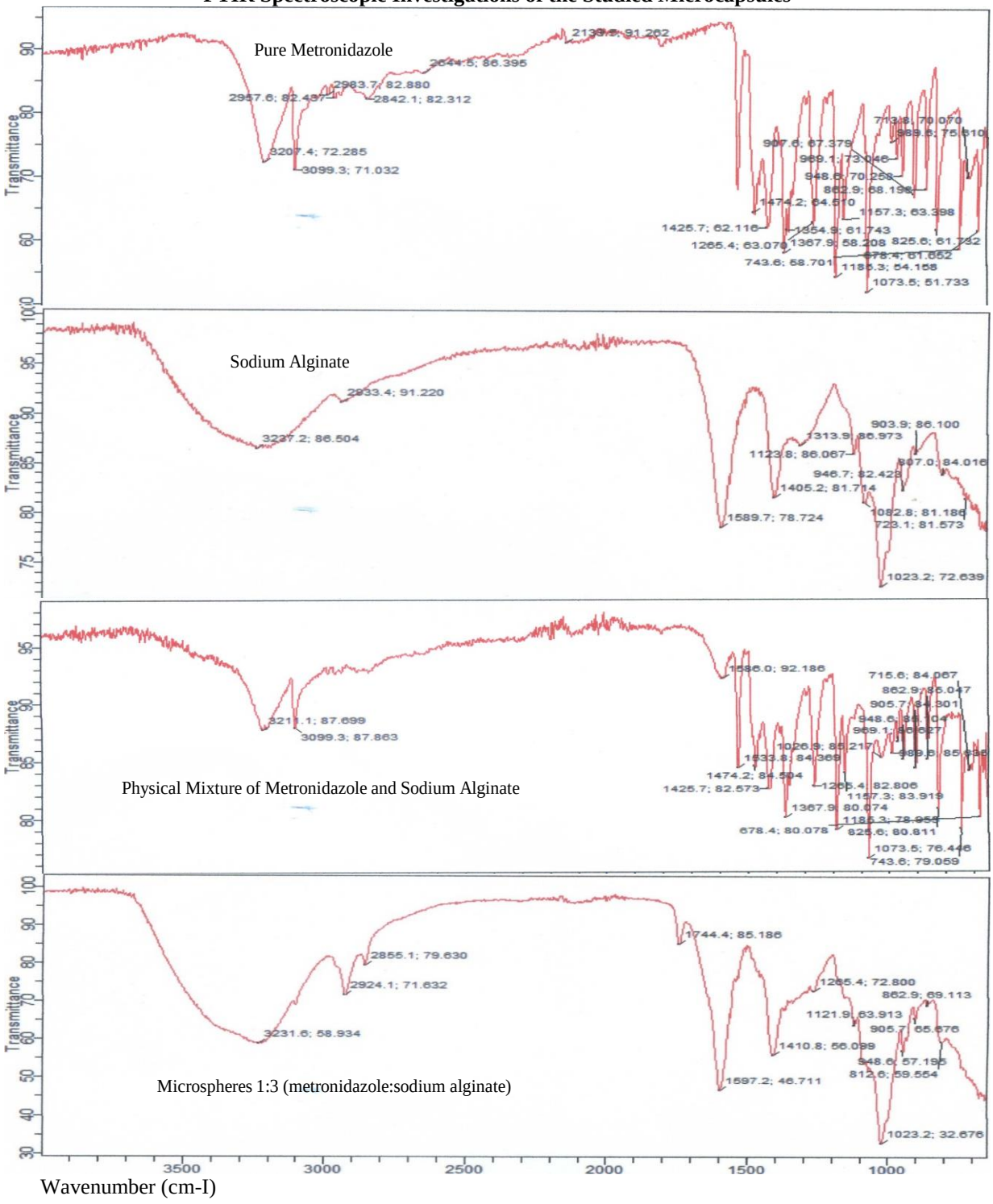


Figure 4: FTIR Spectra of pure metronidazole, sodium alginate, physical mixture of metronidazole and sodium alginate, Batch B4 microcapsules and Batch B5 microcapsules

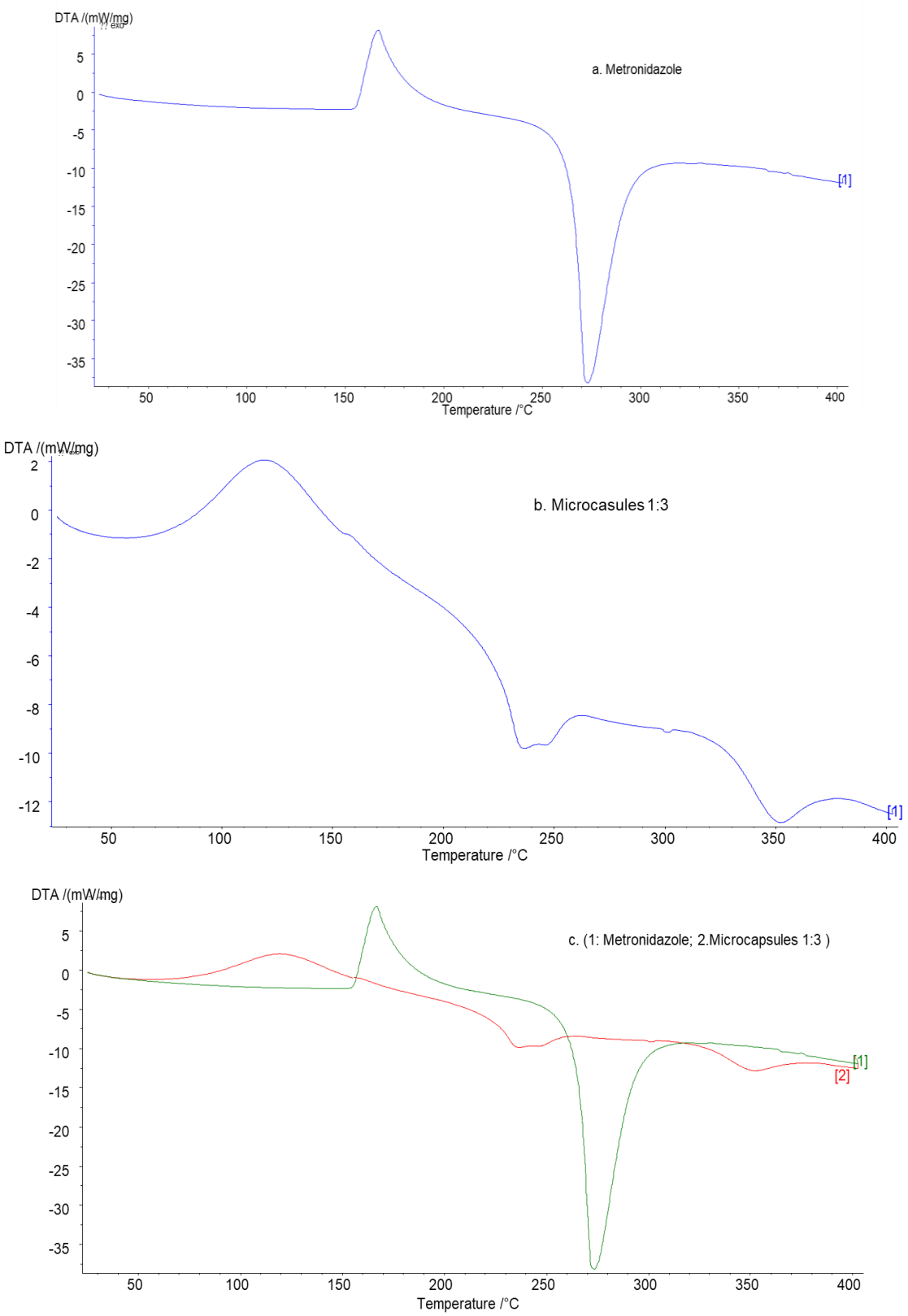


Fig.5: DTA analysis: (a) Metronidazole; (b) Microcapsules 1:3; (c) Metronidazole microcapsules.

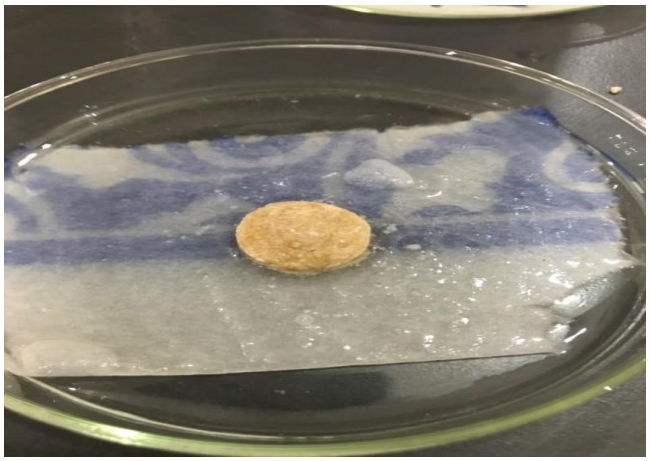


Plate 1: Wetting time and water absorption test.

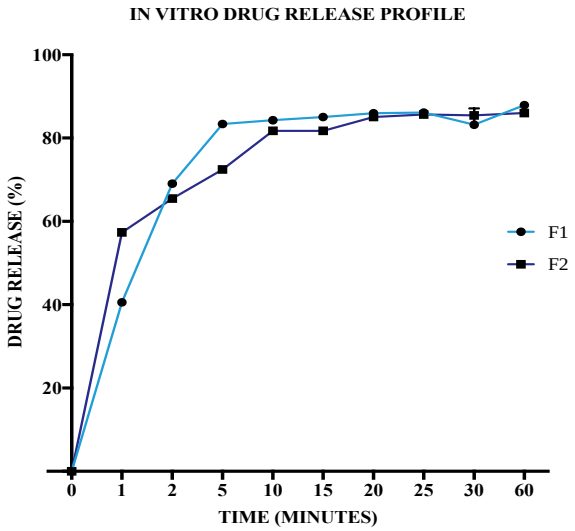


Figure 6: In- vitro release profile of the ODTs
F1 (B4) – Drug to Polymer ratio 1:2.5, F2 (B5) – Drug to Polymer ratio 1:3

Conclusion. The results from this work suggests that the preparation of metronidazole microcapsules and its utilization in the formulation of orodispersible tablets could be a promising approach to improve drug release and absorption thereby solving the problem of poor oral bioavailability associated with most drug by bypassing hepatic metabolism. Thus, adults who have difficulty swallowing the conventional oral medications, patients with dysphagia who fail to comply with prescribed medication dosing thereby likely to encounter increased morbidity and mortality due to poor compliance and geriatric patients and traveling patients who may not have ready access to water are most likely to benefit from there ODT of metronidazole.

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