African Journal of Pharmaceutical Research & Development

Vol. 12 No.2; pp. 172-180 (2020)

FORMULATION AND CHARACTERIZATION OF PALM OLEIN/CAPRYLIC TRIGLYCERIDES ESTER BASED EMULGEL FOR TOPICAL USE

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ABSTRACT

A major limitation of hydrogels is in the delivery of hydrophobic drugs. This study aims at designing and optimizing a metronidazole emulgel by utilizing a blend of palm olein and caprylic triglycerides esters as the oil base. The emulgel was prepared by fusion method. The gel phase in the formulations was prepared by dispersing carbopol 940 in Milli-Q water, this was mixed at with the emulsion in a 1:1 ratio with gentle stirring to obtain the emulgel. The prepared emulgel formulations were inspected visually for their microscopic studies, colour, appearance, phase separation and consistency. *In vitro* release studies of metronidazole were carried using Franz diffusion cell and kinetics of drug released evaluated using different kinetic models. The pH values of all prepared formulation ranged from 6.17 to 6.75, which were considered acceptable to avoid the risk of irritation upon application to the skin. The percentage of the drug diffused for 12 h was highest for E8 and E6 at 12 h 88.72% ± 1.33 and 86.11% ± 1.72 respectively. The emulgels were efficacious for the delivery of lipophilic and poorly soluble drug metronidazole. Release of the drug followed zero order kinetics via drug reservoir consitution within the emugel matrix.This facilitated sustained release and can be applied to other active pharmaceutical ingredients for sustained drug delivery.

KEYWORDS: **Emulgel, Metronidazole, Palm olein, Caprylic triglycerides.**

INTRODUCTION

Gel dosage forms are used as drug delivery systems to control drug release and protect the medications from a hostile environment [1]. A major limitation of gels is in the delivery of hydrophobic drugs, hence the formulation of emulgels which allows hydrophobic drugs enjoy the unique properties of gels [2-4]. Microemulsion based gels or emulgels are combination of a gel and an emulsion. The presence of a gelling agent in the water phase converts a classical emulsion into an emulgel. Emulgels for dermatological use have several properties such as being thixotropic, greaseless, easily spreadable, easily removable, emollient, non-staining, water-soluble, longer shelf life, bio friendly and pleasing appearance [4]. Utilization of *Zingiber officinale* essential oil in the clotrimazole emulgel formulation at 3% w/w gave an enhanced release of clotrimazole *in vivo* and *ex vivo* with flux 131.21±0.19 mg/cm^2/h and 22.01±0.66mg/cm^2/h respectively. These results were better than the marketed cream formulations due to the dual phase system of emulsion and gel as well as the presence of the essential oil which enhanced skin permeation of the active pharmaceutical ingredient [4].

Palm olein is the liquid fraction obtained during fractionation of palm oil, which involves crystallization under controlled temperature and removal of crystals by filtration. Palm olein contains higher amounts of oleic (39–45%) and linoleic acids (10–13%) compared to palm oil [5-6]. It has a melting point of 18–20°C and therefore is a liquid at room temperature (25°C) [5-6]. Palm olein is

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utilized as cooking oil, being an important source of fats and oil for nutritional purposes. It is also utilized in soap and oleo chemical manufacturing [5, 6]. It contains a high amount of the antioxidants, β-carotene, and vitamin E. Palm olein contains a high proportion of palmitic acid as well as considerable quantities of oleic and linoleic acids hence its use in the cosmetics industry[7].The enhancement of the permeation capacities of the essential oilshave been proven to be significantly increase with increasing terpene composition. Niaouli oil and its main terpene components (1,8-cineole, α-pinene, α-terpineol and D-limonene) promoted permeation of oestradiol through skin. *Citrus sinensis* oil is extracted from the orange peel by cold-pressing and yields 0.3-0.5%. Orange oil possesses antiseptic, anti-depressant, antispasmodic and anti-inflammatory properties [8-10]. The main chemical components of orange oil are a-pinene, sabinene, myrcene, limonene, linalool, citronellal, and geranial. Essential oils of *Citrus sinensis* have been utilized in optimization of clotrimazole emulgel to aid permeation when applied topically [4].

Caprylic triglyceride ester is usually made from combining coconut oil with glycerine [6] and has been widely used as an antioxidant. It also functions as a binder for ingredients in semi solid dosage forms and can work as a preservative of sorts to make the active ingredients in cosmetics last longer [6-8].

Various anti-infective topical preparations used for management of bacterial and fungal infections are marketed as creams, ointments and pastes. Metronidazole which has antibacterial properties and is used for the treatment of acne vulgaris, skin lesions, wound drainage, and wound odour. Metronidazole is a member of the imidazole class of antibacterial agents and is classified therapeutically as an antiprotozoal and antibacterial agent. Chemically, metronidazole is a 2-methyl-5-nitroimidazole-1-ethanol. It has a chemical formula of $C_6H_9N_3O_3$, a molecular weight of 171.16 [5]. Metronidazole is poorly water soluble and hydrophobic thus solubilization in an emulgel is a good approach for delivery of the drug topically.

The rationale for this study is to increase and improve the absorption of a model drug metronidazole using an oil base blend of palm olein and caprylic triglycerides esters with *Citrus sinensis* oil as a permeation enhancer. The proposed emulgel formulation will enhance delivery at the target site to enable sustained release of the metronidazole when applied topically.

METERIALS AND METHODS

Materials

The materials used in the study include: metronidazole powder BP (≥ 98% purity) (Sigma Aldrich St. Louis, MO USA), (Batch No M3761-5G), Tween 20 (BDH Chemicals, England), Ethanol 95% (Surfachem, UK), Propylene glycol (Niram chemicals, India), Carbopol® 940 (Shree organics, India), Caprylic triglycerides ester (Gattefosse, Cedex, France), methyl paraben and propyl paraben (Sigma–Aldrich St. Louis, USA), Triethanolamine (TEA) (DBS Chemicals, India), Palm oil (Raffles Oil LFTZ Enterprise, Ibeju Lekki-Lagos), *Citrus sinensis* oil (Neroli® essential oils USA), Milli-Q water (Millipore, USA). All other chemical reagents and solvents were of analytical grade and was used for this research without further purification.

Formulation of Emulgels

Different formulations were prepared using varying amount of gelling agent. The preparation of gel and emulsion were the same in all the formulations. The gel phase in the formulations was prepared by dispersing Carbopol 940 in Milli-Q water with constant stirring at a moderate speed using a mechanical shaker, and then the pH was adjusted to 6.17-6.75 using triethanolamine. The oil phase of the emulsion was prepared by adding caprylic triglycerides ester, *Citrus sinensis* oil and dissolving metronidazole in palm olein while aqueous phase was prepared by adding Tween 20, ethanol and dissolving methyl and propyl parabens in propylene glycol.

Both the oily and aqueous phases were separately heated to 65ºC for 5 minutes, then the oily phase was added to the aqueous phase with continuous stirring until it got cooled to room temperature. The obtained emulsion was mixed with the gel in 1:1 ratio with gentle stirring to obtain the emulgel [11]. The composition of different formulation is shown in Table 1.

Physicochemical evaluation of the emulgels microscopic studies

These were carried out on the formulations, which were also inspected visually for their colour, appearance, phase separation and consistency [12]. Physicochemical evaluation of all the emulgel formulations were repeated after 90 days after being exposed to accelerated stability testing at 60-70% relative humidity and 37°C ± 1°C.

Emulgel viscosity

The viscosity of the formulations was determined using a digital viscometer with spindle 4. The assembly was connected to a thermometer which ensured that the temperature was at 25ºC. The formulation whose viscosity was to be determined was added to a beaker covered with thermostatic jacket. The viscometer was set at different revolution per minute, 10, 20, 30, 40 and 60 and viscosity readings taken in triplicate [12].

Spreading coefficient

Predetermined amount of sample (0.5 g) was placed in between two glass plates of equal weight and area. Varying weights of 10, 20, 50 and 100 g were placed over the upper glass plate. The initial spreading diameter before placing the weight was noted. The final diameter was noted over a period of 60 s. The spreadability of the formulations were reported as percentage (%) spreadability [13].

$$\% Spreadability = \frac{D2-D1}{D1} X\ 100 \quad \text{.....Equation 1}$$

Chemical characterization of emulgel formulations

The chemical interaction was analyzed using BOMEM MB 104Fourier Transform infra-red (FTIR) spectroscopy using the method of Ghodekar*et al.,* [12]. The thermal properties of the emulgels were determined using differential scanning calorimeter (DSC)while the crystallinity was assessed using X-ray diffraction by method of Satapathy *et al.,* [13].

In vitro release studies

Metronidazole content in emulgel was measured by dissolving 500 mg of emulgel formulation in 100 mL of 0.1 N HCl by sonication. Absorbance was measured after suitable dilution at 277nm using UV-Vis spectrophotometer (UV-Vis 2600 Shimadzu Analytical and measuring instruments) [14]. Modified Franz diffusion cells (PermeGear Inc. PA USA) with diffusion area of 3.71cm^2 were used for the drug release studies. 1 g of emulgel was evenly applied onto the surface of dialysis membrane. *In vitro* release studies were carried out with 10µm diameter ciprophan cellulose membrane (Medicell London, UK) with a pore size of 0.45µm. The membranes were mounted on modified Franz diffusion cells with diffusion area of 3.71cm. The receptor compartment contained 30mL phosphate buffer (pH of 7.4 at 37.1 $^oC \pm 0.2\ ^oC$). The receptor chamber was filled with freshly prepared phosphate buffer (pH 7.4). The receptor chamber was stirred by magnetic stirrer. The aliquots (1 ml) were collected at time intervals of 0.25 h up to 12 h. Samples were analyzed for drug content by using UV-Vis spectrophotometer after appropriate dilutions [14].To examine the drug release kinetics and mechanism, the cumulative release data were fitted to various kinetic using method of Rao *et al.,*[14].

Statistical analysis

The data were expressed as the mean ± standard deviation of more than three experimental values for individual variables and analyzed by one-way ANOVA using DATAPLOT® version 1.4.14. Significant difference was set at P value < 0.05.

RESULTS

Physicochemical evaluation of the emulgels

All the emulgels formulated were white viscous creamy preparations with smooth homogeneous appearance. The pH values of all prepared formulation ranged from 6.17 to 6.75, which were considered acceptable to avoid the risk of irritation upon application to the skin. Drug content for all the formulations fall within the USP specifications [14] (Table 2).

Batches E2, E3, E6 and E8 exhibited lower viscosity and % spreadability than E1, E4, E5, and E7 (Table 2). The increase in polymer concentration from 1% to 2% was the major factor behind this phenomenon. Increasing the shear rate via increasing the revolutions per minute led to a decrease in the viscosity of the all the formulations (Figure 1B). The homogeneity of the formulations was not altered after the 90-day accelerated stability testing at 60-70% relative humidity and 37°C ± 1°C (Table 2) hence all the formulations were stable after accelerated stability testing. The formulations were coded G (good homogeneity), W (white emulgel), and NCC (no colour change) in deference to their homogeneity and appearance before and after storage (Table 2). It was observed that all the formulations exhibited granular and rough surface texture except E2 (Figure 1A) which exhibited a smooth surface texture.

Chemical characterization of emulgel formulations

The FTIR results were presented on Figure 2A. Metronidazole emulgel formulations showed characteristic broad vibrational peak at wavelength of 3383.13cm^{-1} which shows the presence of –OH functional group with hydrogen bonding characteristic of the polymer. The IR peaks at 3099.78 cm^{-1}, 2982.70 cm^{-1} and 1523.31 cm^{-1}

denotes =C-H, -C-H, and N=O stretching respectively characteristic of metronidazole.

The heat flow for metronidazole emulgel formulations first showed endothermic peaks before exothermic peaks. Pure metronidazole had sharp and strong spike for the endothermic peaks at 155ºC, 163.5ºC and 170ºC respectively [14]. The difference between end set endothermic peaks and on set endothermic peaks was narrow showing purity. All the emulgel formulations had broad and strong spikes at different onset, peak and end set endothermic peaks. All the peak temperatures of the formulations were below that of the pure metronidazole. The difference between end set and onset endothermic peaks were wide Figure 2B. The different formulations were stable but had lower melting point when compared with pure metronidazole [14].

The XRD profile of the emulgel formulations are shown in Figure 3A. The emulgels showed peak at 20º. The intensity of the peaks and the profile for the diffractogram were considerably alike except for formulations E3, E4 and E5 which were slightly different. The presence of sharp peaks indicates the crystalline nature of metronidazole which may be attributed to the highly ordered molecular structure. The presence of the peaks at the same position indicated that the composition of the emulgels is same.

In vitro release studies

The percentage of the drug diffused for 12 h is shown in Figure 3B. Formulations E8 and E6 exhibited the highest drug release from the formulation at 12 h 88.72% ± 1.33 and 86.11% ± 1.72 respectively. Percentage drug release across all formulation exhibited a graded release with increasing time interval. At 2 h, an average of 60.75% ± 1.33 was released from all formulations with formulation E8 exhibiting the highest release. The sustained release of metronidazole from the emulgel extended till 12 h, thus ensuring that when applied topically drug release will be optimized if applied once or twice daily [5].

DISCUSSION

Due to the barrier properties of the *stratum corneum*, it is important that the formulations can penetrate the skin and reach the site of action. The human skin contains various lipids, such as phospholipids and ceramides, and different transporters which impart hydrophobic character to skin [15]. The inclusion of *Citrus sinensis* oil in the metronidazole emulgel formulations is to optimize and increase permeability of the drug incorporated in the emulgel when applied to the skin. This effect is due to the increase skin-vehicle partitioning by the oil. The pH of the emulgel formulations ranged from 6.1 to 6.7, this is ideal to ensure the partitioning of metronidazole through the lipid layer [16]. The pH of normal skin is 5.5 to 5.9 how ever in the presence of infection this equilibrium is altered. Topical antimicrobial gel of pH 6.0 to 6.9 are usually useful in normalizing skin pH whilst also facilitating microbial clearance. It increases skin permeability by interfering with the composition of the stratum corneum lipid bilayer coating to increase their permeation into the skin [4]. Metronidazole an antibacterial agent was formulated in an emulgel form for topical application. Its mechanism of action in acne vulgaris is thought to be associated with its anti-inflammatory, immunosuppressive, and/or antimicrobial properties [5, 15]. The high efficacy of 1- 2% metronidazole gel is widely documented even though Propionibacterium acnes have traditionally been considered a metronidazole-resistant microorganism [16]. So, mechanisms other than microbicidal action may underlie the therapeutic effect of metronidazole, such as anti-inflammatory, immunosuppressive, and anti-itching actions, as well as the inhibition of free radical generation by human neutrophils [16]. The nature of the carrier system developed to deliver metronidazole topical must be such that takes into consideration the hydrophobicity of the API as well as the need for the formulation to be retained topically to release metronidazole over a period of time at constant concentration.

Diffusion studies were carried out using a modified ciprophan membrane for all formulations in pH 7.4 phosphate buffer saline solution. Release from the emulgel was controlled by the interactions between drug and surfactant mixture and/or partitioning of drug between oil and water phase [16]. Increase in the alkyl acrylate polymer concentration resulted in a corresponding increase in viscosity of the system. Drug entrapment in this emulgel system was further stabilized with the increase in polymer concentration, hence leading to decreased drug release in formulation E1. Retardation of release was however time dependent and the process took place at a constant rate independent of metronidazole initial concentration.

The emugels act as reserviour systems developed to release metronidazole at zero-order kinetics. The drug reservoir was constituted by thepalm olein and caprylic triglycerides esters oil base incorporated with emulsion system. Utilization of a dual oil base composing of palm olein and caprylic triglycerides esters

Table 1: Composition of various emulgel formulations

Ingredient	E1	E2	E3	E4	E5	E6	E7	E8
Metronidazole (mg)	1	1	1	1	1	1	1	1
Palm olein (mL)	30	10	10	10	10	30	30	30
Caprylictriglycerides esters (mL)	6.67	16.67	6.67	16.67	6.67	6.67	16.67	16.67
Tween 20 (mL)	4.33	14.33	4.33	14.33	4.33	4.33	14.33	14.33
Propylene glycol (mL)	25	25	25	25	25	25	25	25
Methyl paraben (mg)	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2
Propyl paraben (mg)	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01
Carbopol 940 (%)	2	1	1	2	2	1	2	1
Citrus oil (mL)	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Triethanolamine	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
Ethanol (mL)	10	10	10	10	10	10	10	10
Water to (mL)	100	100	100	100	100	100	100	100

Table 2: Physicochemical evaluation of the emulgels at day 0 and at day 90 after accelerated stability testing

Time in days	Formulation	pH	Drug content (%)	Spreadability (%)	Homogeneity and Appearance
DAY 0	E1	6.17 ± 0.02	99.70 ±1.20	64.71 ±2.30	G/W
	E2	6.75 ± 0.04	98.90 ±1.90	95.21± 1.76	G/W
	E3	6.51 ± 0.04	100.10 ±1.30	87.63 ±3.88	G/W
	E4	6.38 ±0.03	99.20 ± 1.00	69.44 ±1.97	G/W
	E5	6.42 ± 0.03	99.10 ±1.30	65.22 ±2.39	G/W
	E6	6.63 ± 0.1	99.50 ±1.80	80.02 ±1.01	G/W
	E7	6.25 ± 0.03	101.31 ±1.20	62.01 ±1.03	G/W
	E8	6.69 ± 0.07	98.92 ±1.90	90.01 ±1.20	G/W
DAY 90	E1	6.18 ± 0.02	99.70 ±1.20	64.71 ±2.30	G/NCC
	E2	6.74 ± 0.1	98.90 ±1.90	95.21± 1.76	G/NCC
	E3	6.51 ± 0.04	100.10 ±1.30	87.63 ±3.88	G/NCC
	E4	6.38 ± 0.11	99.20 ± 1.00	69.44 ±1.97	G/NCC
	E5	6.42 ± 0.08	99.10 ±1.30	65.22 ±2.39	G/NCC
	E6	6.60 ± 0.11	99.50 ±1.80	80.02 ±1.01	G/NCC
	E7	6.22 ± 0.09	101.31 ±1.20	62.01 ±1.03	G/NCC
	E8	6.65 ± 0.08	98.92 ±1.90	90.01 ±1.20	G/NCC

($p \leq 0.05$ is significant)

provided a suitable vehicle for development of sustained release vehicle for hydrophobic drugs. The oil based was able to entrap metronidazole and facilitate a reservoir system for drug release.

CONCLUSIONS

This study reports successful development of emulgels using palm olein and caprylic triglycerides ester as the base. The emulgels were efficacious for the delivery of lipophilic and poorly soluble drug metronidazole. Release of the metronidazole followed zero order kinetics via drug reservoir consitution within the emugel matrix, which facilitated sustained release.Therefore, providing a topical product that can be effectively utlized in the management of acne vulgaris.

ACKNOWLEDGEMENT

Gattefosse (Cedex, France) for providing Caprylic triglycerides ester (Labrafac®) as a gift, the authors acknowledge Dr Kunal Pal Department of Biotechnology & Medical Engineering, National Institute of Technology, Rourkela- 769008 India for carrying out the XRD analysis on all formulations.

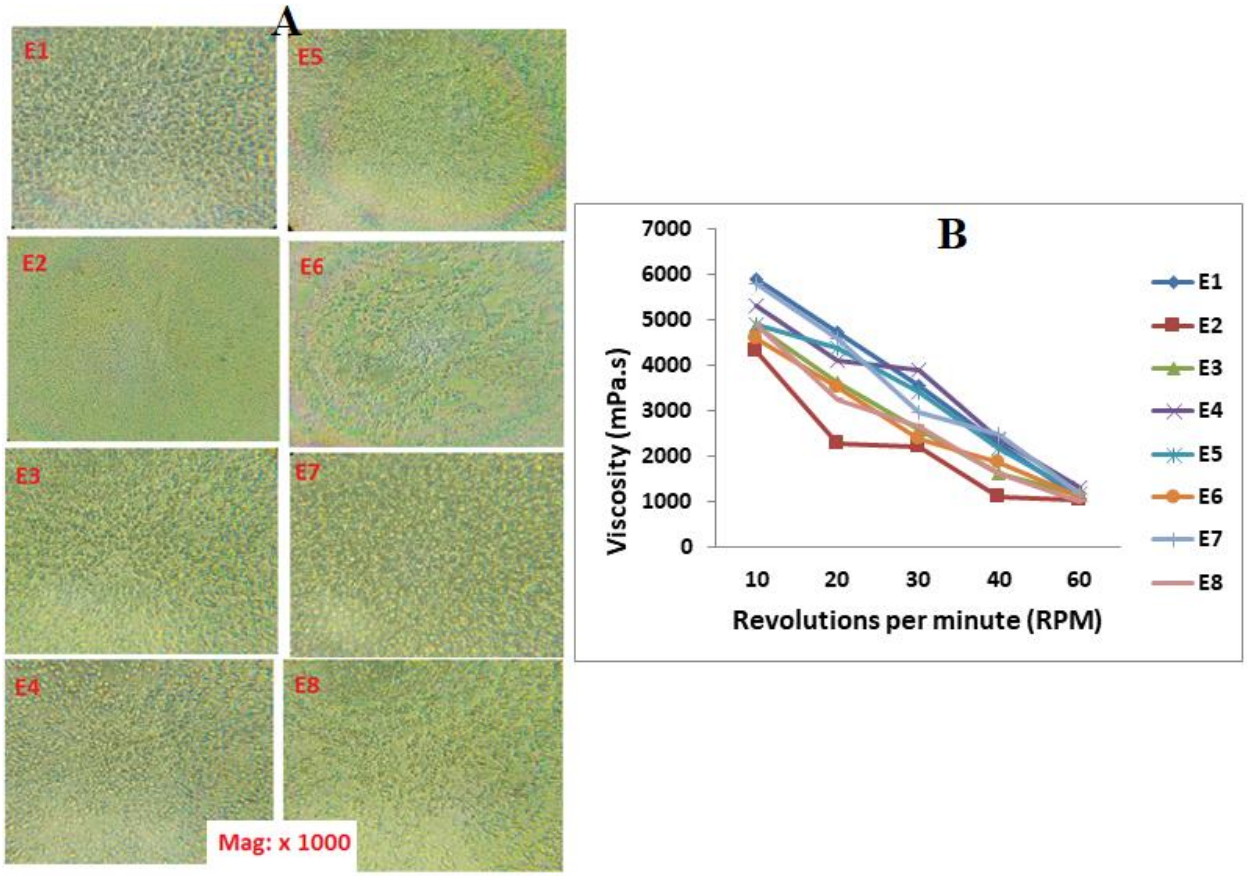

Figure 1: (A) Micrographs of the emulgels E1 to E8 (B) Effect of increased shearing on viscosity of the emulgels E1 to E8.

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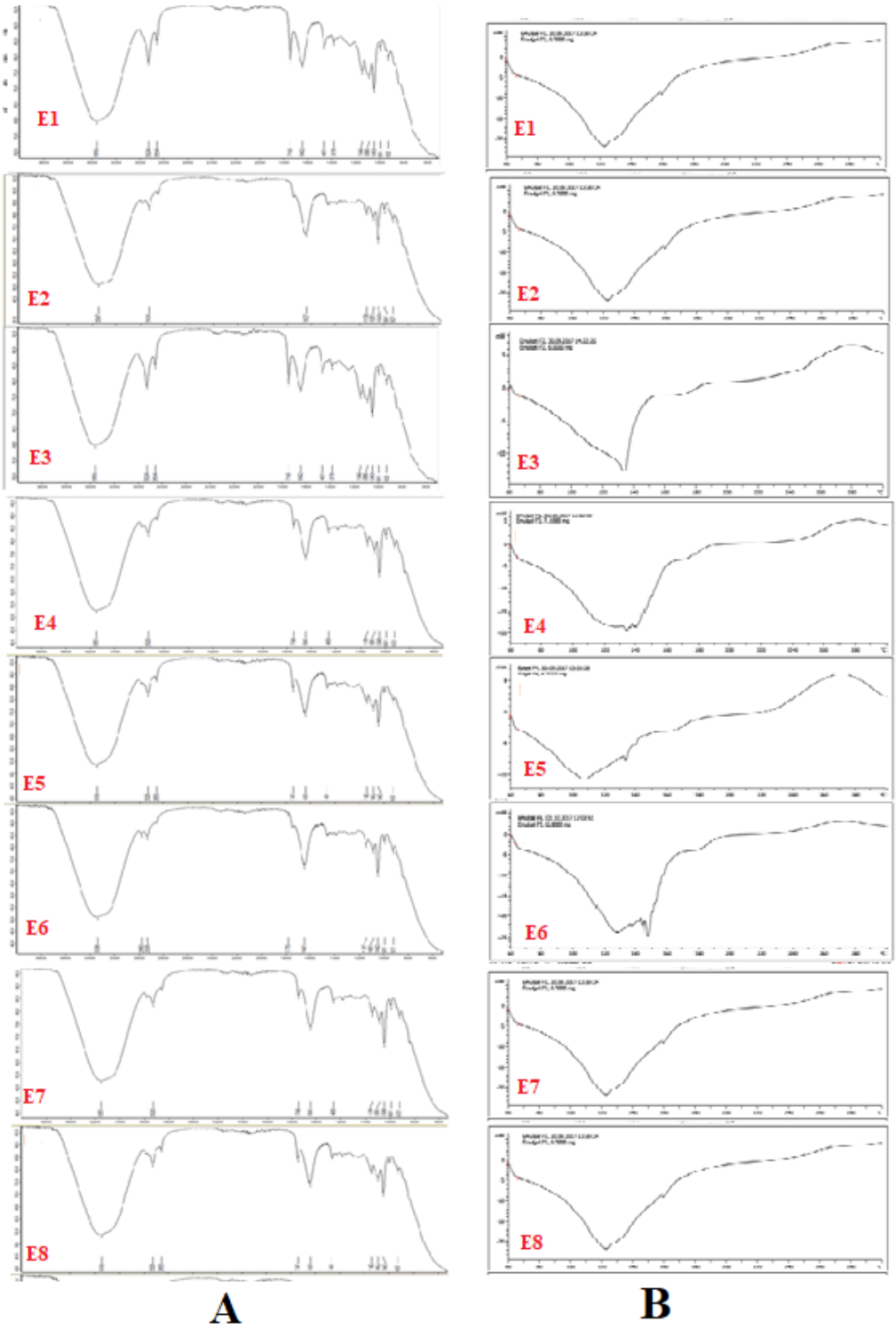

Figure 2: (A)FT-IR spectra and (B) DSC thermograms of the metronidazole emulgels E1 to E8.

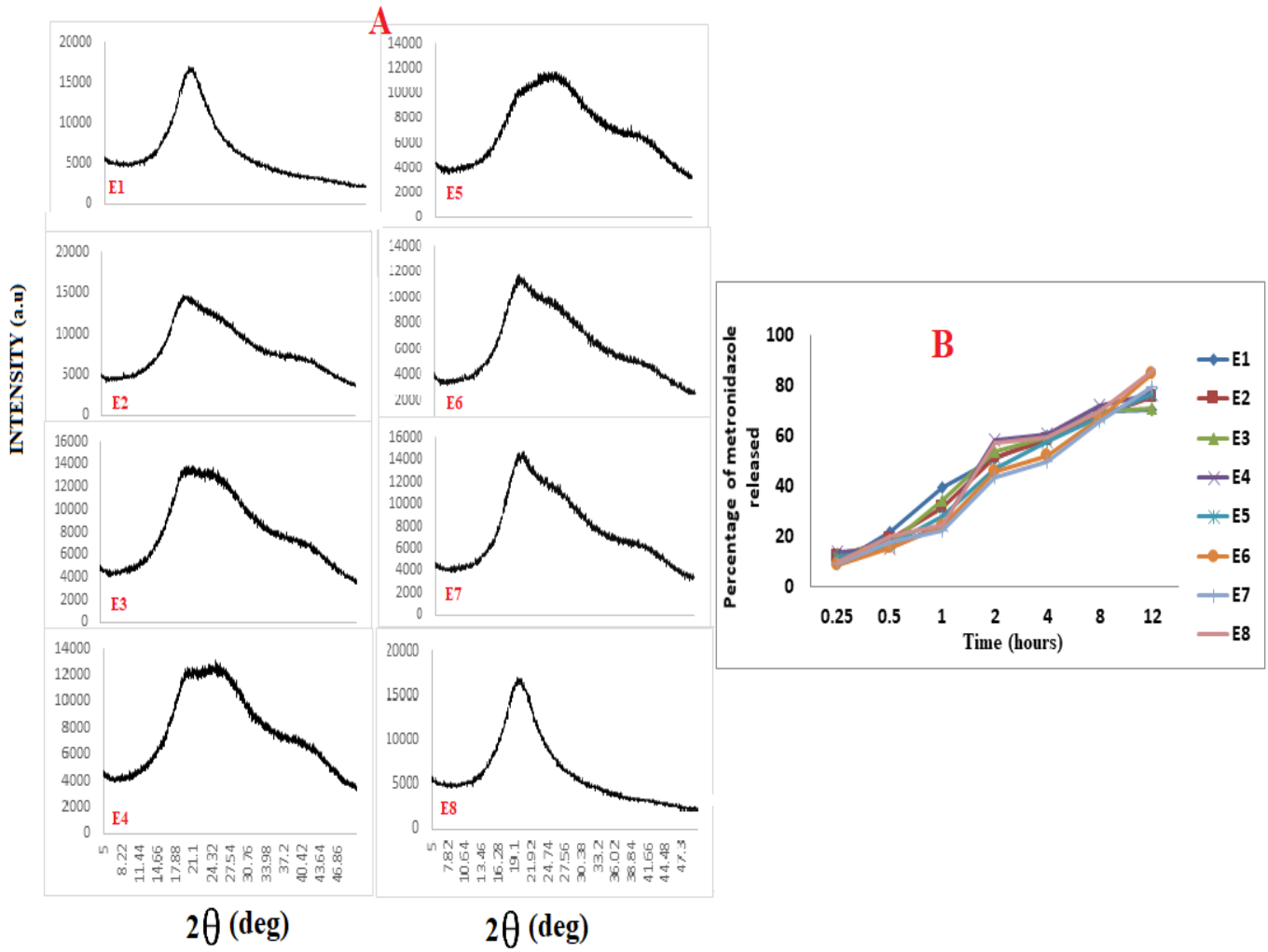

Figure 3: (A) X-RD diffraction profiles of emulgels E1 to E8 (B) Percentage of metronidazole released from emulgels E1 to E8 against time in hours

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