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Research paper

Release and diffusional modeling of metronidazole lipid matrices

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Abstract

In this study, the first aim was to investigate the swelling and relaxation properties of lipid matrix on diffusional exponent (n). The second aim was to determine the desired release profile of metronidazole lipid matrix tablets. We prepared metronidazole lipid matrix granules using Carnauba wax, Beeswax, Stearic acid, Cutina HR, Precirol® ATO 5, and Compritol® ATO 888 by hot fusion method and pressed the tablets of these granules. In vitro release test was performed using a standard USP dissolution apparatus I (basket method) with a stirring rate of 100 rpm at 37 °C in 900 ml of 0.1 N hydrochloric acid, adjusted to pH 1.2, as medium for the formulations' screening. Hardness, diameter–height ratio, friability, and swelling ratio were determined. Target release profile of metronidazole was also drawn. Stearic acid showed the highest and Carnauba wax showed the lowest release rates in all formulations used. Swelling ratios were calculated after the dissolution of tablets as 9.24%, 6.03%, 1.74%, and 1.07% for Cutina HR, Beeswax, Precirol® ATO 5, and Compritol® ATO 888, respectively. There was erosion in Stearic acid, but neither erosion nor swelling in Carnauba wax, was detected. According to the power law analysis, the diffusion mechanism was expressed as pure Fickian for Stearic acid and Carnauba wax and the coupling of Fickian and relaxation contributions for other Cutina HR, Beeswax, Compritol® ATO 888, and Precirol® ATO 5 tablets. It was found that Beeswax ($k_d = 2.13$) has a very close drug release rate with the target profile ($k_t = 1.95$). Our results suggested that swelling and relaxation properties of lipid matrices should be examined together for a correct evaluation on drug diffusion mechanism of insoluble matrices.

Keywords: Metronidazole; Controlled release; Lipid matrix; Swelling; Diffusion mechanism

1. Introduction

Metronidazole, 2-methyl-5-nitroimidazole-1-ethanol, is a nitroimidazole derivative with activity against anaerobic protozoa, aerobic and microaerophilic bacteria. Common adverse effects of metronidazole involve the gastrointestinal tract and the neurological system with high doses. Therefore, reduction of side effects of metronidazole (plasma peak levels) while prolonging its action by using controlled oral dosage forms is highly desirable [1].

Controlled release is usually accomplished employing a membrane or matrix. Matrix type formulations are prepared from either swellable hydrophilic polymers or non-swellable lipophilic excipients, like waxes and lipids [2]. Lipophilic matrix agents were frequently used in the preparation of sustained release tablets [3]. Wax matrix dosage forms are utilized to incorporate drugs into inert water-insoluble matrix materials. Many types of matrix forms, including granules and tablets, have been tried in order to obtain effective sustained release [4].

Waxy materials have major applications in sustained-release systems and the use of wax matrix appears to have several advantages such as being a multiple-unit system, chemical inertness against other materials, and ease of manufacturing with high reproducibility that can be obtained without special instrumentation, as well as low production cost [5,6]. Moreover, as the matrix delivery system passes through the gastrointestinal tract, the active ingredient is slowly released and absorbed [7]. Therefore,

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resistance to gastrointestinal motility has to be confirmed to maintain the expected-release profiles of lipid matrices [8].

Drug release properties of insoluble polymer matrices were investigated and the Fickian diffusional release was explained by Higuchi [9]. The release profiles of this type of drug diffusion also obeyed Higuchi square root of time kinetic [10]. The purpose of Cobby et al. [11] was to explain the relation between the drug release and the wax matrix shape. Then diffusional exponents have first been expressed for insoluble matrix shape such as 0.43 for sphere, 0.45 for the cylinder, and 0.5 for slap, which shows the pure Fickian diffusional release. Beyond these values, two mechanisms as a Fickian diffusional release and a Case II relaxational release are incorporated into a single function [12]. There were some attempts related with the effects of swelling in the medium on the drug release from insoluble matrices [13–15]. It was reported that the release rate of potassium dichromate from silicone matrices was directly proportional to the degree of swelling of the matrix [13]. Another study suggested that the swelling property of the insoluble rate-controlling agent had more significant contribution to make to the dissolution of diclofenac sodium than dissolution property [14]. Although the effect of swelling kinetics of unsaturated monoglycerides on chlorpheniramine maleate, propranolol hydrochloride, and pseudoephedrine hydrochloride release was investigated [15], the effect of swelling of insoluble materials on diffusion mechanism has not been fully characterized.

The first aim of this study was to produce lipid matrix granules and tablets of metronidazole using Carnauba wax, Cutina® HR (hydrogenated castor oil), Beeswax, Stearic acid, Compritol® ATO 888 (glyceryl behenate), and Precirol® ATO 5 (glycerol palmitostearate) as insoluble lipid matrices and to explain the relationship between the swelling behavior and power law (n exponent) of these matrices. The second aim was to determine the lipid attaining the desired release profile.

2. Materials and methods

2.1. Materials

Metronidazole was supplied from I.E. Ulagay Ilaç Sanayi Türk A. Ş., Carnauba wax and Beeswax were both supplied from Fako Ilaç Sanayii, Turkey. Stearic acid and Cutina® HR (Cutina) were obtained by E. Merck and Henkel (Germany), respectively. Precirol® ATO 5 (Precirol) and Compritol® ATO 888 (Compritol) were kindly donated from Gattefossé, France. All other agents were of analytical grade.

2.2. Methods

2.2.1. Preparation of lipid matrix granules

The matrices were prepared by hot fusion method where the lipids were melted with continuous stirring in a porcelain dish placed on a water bath maintained at approximately 80 °C [7]. Metronidazole was added to the fused lipids with continuous stirring. The weight ratio of the drug to the lipophilic excipient was 2:1 (w/w). The molten mass of each formulation was allowed to cool down and screened through a 1 mm sieve, when the temperature was at around the congealing point. The prepared lipid matrix granules were sieved through a combined sieve set (Retsch). Two different particle size fractions (>1000 and 500–1000 μm) were collected. The samples were stored in a desiccator.

2.2.2. Recovery of metronidazole lipid matrix granules

Ten milligrams of well-powdered lipid matrix granules was weighed, put into the tubes, and placed in a shaker (B. Braun). The content was shaken for 1.5 h upon addition of 10 ml of 0.1 N hydrochloric acid adjusted to pH 1.2. The filtrate was taken and its metronidazole content determined spectrophotometrically. The weight ratio of the drug to the lipophilic excipient was 2:1 (w/w). The % metronidazole recovery obtained from the extraction of the granules was calculated according to the weight of drug in the polymer.

2.2.3. Preparation of lipid matrix tablets by direct compression

Tablets (500 mg) were prepared from 500 to 1000 μm size fraction of granules by compressing them for 10 s using a hydraulic hand press tablet machine (Perkin-Elmer) fitted with a pressure to 2.0 tons. Stainless steel, flat-faced molds were used to produce lipid matrix tablets. Magnesium stearate (1%) was added as lubricant and mixed with the granules 2 min before compression. The punches were also lubricated with magnesium stearate before the process.

2.2.4. Physical tests of lipid matrix tablets

Tablets were physically analyzed for hardness, diameter–height ratio, and friability [16]. The friability was determined as the percent weight loss of 10 tablets. Ten tablets were weighed (W_1) and rotated for 100 revolutions in 4 min in a Roche friabilitor. The tablets were then weighed (W_2) again and percentage friability (%F) calculated with the following equation:

$$\%F = \frac{(W_1 - W_2)}{W_1}. \quad (1)$$

Three tablets from each formulation were randomly selected and tested for their hardness using Monsanto apparatus. Diameter–height ratio was determined using a micrometer.

2.2.5. Dissolution studies

A standard USP 24 dissolution apparatus I (basket method) was employed in the release studies with a stirring rate of 100 rpm at 37 ± 0.5 °C [17]. The dissolution medium was 900 ml of 0.1 N hydrochloric acid adjusted to pH 1.2. Aliquots were withdrawn with a syringe through a

membrane filter (0.8 μm) and diluted to 10 ml with dissolution medium at predetermined time intervals. The resultant loss in volume was compensated with the same volume of fresh dissolution medium. The samples were measured at 277 nm for metronidazole content using an ultraviolet spectrophotometer (UV–vis Shimadzu model 1208). None of the matrix agents interfered with the assay. The results were expressed as the percentage of the released drug as a function of time according to the drug content gained from extraction studies. All samples were run in triplicate, from which the mean was calculated.

2.2.6. Measurement of swelling ratio

Measurement and calculation of swelling ratios of prepared tablets were carried out according to studies of Sato et al. [6]. The thickness and diameter of the tablets were measured using a calliper (Callipergauge, direct reading, 0.1 mm) before and after the dissolution procedure. Swelling ratio as an index of swelling ability was calculated by the following equation:

$$\text{swelling ratio} = \frac{V_a - V_i}{V_i} \times 100, \quad (2)$$

where V_i and V_a are volumes of tablet before and after dissolution, respectively.

2.2.7. Release kinetics

Four kinetic models were chosen to describe the release profiles of the bases from the known physical geometry of the particles and tablets with the fact that the matrices are not disintegrating systems. Thus, the following kinetic models represented in Eqs. (3)–(6) were investigated using a computer program developed in our laboratory for empirical analysis [18]. First-order model

$$\ln(100 - W) = \ln 100 - k_f t, \quad (3)$$

Higuchi square root of time model

$$W = k_H t^{1/2}, \quad (4)$$

Hixson and Crowell cube-root model

$$(100 - W)^{1/3} = 100^{1/3} - k_{HC} t, \quad (5)$$

Zero-order model

$$m = 100 - k_0 t, \quad (6)$$

where W the percent drug release rate at time t, and k_f, k_H, k_{HC}, and k_0 are release rate constants.

2.2.8. Plotting of target profile

Target profile with initial dose for metronidazole was drawn using the following Eqs. (7)–(11) [19,20]:

$$W_t = D_I + D_m, \quad (7)$$

$$D_m = k_r^0 \times h,$$

$$k_r^0 = k_d \times C_p \times V_d, \quad (8)$$

$$T_p = 2.3/k_a - k_d(\log k_a/k_d), \quad (9)$$

$$D_b = C_p \times V_d, \quad (10)$$

$$D_i = D_b - (k_r^0 \times T_p), \quad (11)$$

where, W_t the total dose, D_I the initial dose, D_m the maintenance dose, k_r^0 the zero-order rate of release constant, h is the total desired time for sustained action in hours, k_d the drug elimination rate constant, C_p the peak concentration of drug release, V_d the apparent volume of distribution, T_p the peak height time, and D_b the dose required to give the desired blood level, when given in an immediately available form.

2.2.9. Differential scanning calorimetry

Accurately weighed metronidazole, lipid matrix, and lipid matrix granules (12 mg) were scanned (DSC-60 Differential Scanning Calorimeter, Shimadzu) from 40 to 180 °C and to 40 °C again at 10 °C min^{-1}, in nitrogen with 50 ml min^{-1} flow rate in aluminum pans. The phase transition range of the prepared matrix was determined.

3. Results and discussion

Metronidazole lipid matrix granules were prepared with the fusion method because this method does not require solvent or water, since the molten polymer acts like a binder. The intense mixing and agitation during fusion also deaggregates particles and improves the content uniformity for the extrudates. It was also reported that the fusion method provided slower release profiles compared to the direct compression or wet granulation method [4]. This method generally requires relatively high processing temperatures (>80 °C). The excipients and the active ingredients need to be stable under these conditions. Generally waxes are inert and have lower melting points than those of polymers [4]. In this study, we used different kinds of lipophilic waxes as thermal binders for the process due to their stability and inertness.

Particle size is one of the important factors that affect the release profiles of granules [4]. Therefore, extraction studies were carried out with two different size fractions. According to the extraction results, the drug recovery of particles between 500 and 1000 μm was found to be higher than that of particles above 1000 μm. The drug recovery was calculated with the results obtained from the extraction of the granules. The recovery values are given in Table 1.

Table 1
Metronidazole recovery obtained from the extraction of different particle sizes of lipid matrix granules prepared from Carnauba wax (CW), Cutina HR (CHR), Beeswax (BW), Stearic acid (SA), Compritol (C), and Precirol (P), and % yield of lipid matrix granule production by fusion method

Particle sizes (μm)	CW	CHR	BW	SA	C	P
% metronidazole recovery of lipid matrix granules						
>1000	68	66	64	90	60	61
500–1000	75	82.5	75	90	75	75
% yield of lipid matrix granule production						
>1000	80.1	59.4	75.4	89.7	73.2	72.6
500–1000	89.5	88.7	89.6	97.1	97.0	96.4

The production yield of metronidazole lipid matrix granules between 500 and 1000 μm was also higher than that of granules >1000 μm (Table 1). Since the highest drug recovery and production yield were gained from 500 to 1000 μm particle size fraction, we compressed the lipid matrix tablets from these granules.

The weight of the tablets was uniform because the granules (500 mg) were first weighed and then compressed 10 s using a hydraulic hand press tablet machine (Perkin-Elmer) fitted with a pressure to 2.0 tons. One percentage of magnesium stearate was added and mixed with the granules 2 min before compression. Although some of the matrices studied were lubricants themselves, sticky characteristics of the waxes appeared when high amounts were used. In order to avoid punch sticking and capping problems, magnesium stearate had to be applied to lubricate the upper and lower punch faces.

The performance of sustained-release dosage forms is considerably influenced by anatomical and physiological constraints. The sustained dosage forms should attain a certain mechanical strength to prevent the unexpected burst effect caused by gastrointestinal motility [8,14]. Therefore, the hardness tests were performed. The hardest tablets were obtained from Carnauba wax (5.5 kg/monsanto). The hardness values of the other formulations evaluated as 1 and 2 kg/monsanto for Stearic acid and Cutina, respectively. Beeswax, Compritol, and Precirol tablets showed a value of 1.5 kg/monsanto. None of the formulations disintegrated during the dissolution studies; cracks were observed, but they kept their original shape. There was erosion on the edges of Stearic acid tablets. Diameter–height (mm/mm) ratio was 4.063 ± 0.0 for all tablets except Cutina. The ratio was detected as 4.194 ± 0.0 for Cutina formulation.

Friability (%F) of the tablets can be arranged in order as: Beeswax$_{(0.060\pm0.010)}$ < Carnauba wax$_{(0.639\pm0.763)}$ < Cutina$_{(0.974\pm0.020)}$ < Stearic acid$_{(0.981\pm0.020)}$ < Compritol$_{(1.124\pm0.050)}$ < Precirol$_{(1.221\pm0.080)}$.

Different release profiles gained from dissolution studies could be caused by the matrix material, since the only difference between the formulations was the lipophilic matrix agent used. The classification of the matrices, their melting points, and chemical structures are given in Table 2.

Table 2
Classification and the chemical structures of the lipophilic matrix forming agents

Category	Lipid	Chemical structure	Melting point (°C)	Description	Acid value
Fatty acid ester of glycerol	Compritol	$CH_2OOC(CH_2)_{20}CH_3$ | $CHOOC(CH_2)_{20}CH_3$ | $CH_2OOC(CH_2)_{20}CH_3$	~70	Glyceryl behenate	4>
Fatty acid	Stearic acid	$CH_3(CH_2)_{16}COOH$	~55	C18 acid	200–210
Fatty acid ester	Precirol	$CH_3(CH_2)_{16}COOH$ $CH_3(CH_2)_{14}COOH$ $OHCH_2$ CH CH_2OH | OH	~57	Glyceryl palmitostearate	–
Hydrogenated fatty acid ester	Cutina HR	$O(C_2H_4O)H$ | $H_2CO(C_2H_4O)CO(CH_2)_{10}CH(CH_2)_5CH_3$ | $O(C_2H_4O)H$ | $HCO(C_2H_4O)CO(CH_2)_{10}CH(CH_2)_5CH_3$ | $O(C_2H_4O)H$ | $H_2CO(C_2H_4O)CO(CH_2)_{10}CH(CH_2)_5CH_3$	~85	Hydrogenated castor wax	5>
Polar wax	Carnauba wax	$C_{25}H_{51}$ $COOC_{30}H_{61}$	~80	A complex mixture; esters of acids and hydroxyacids	2–7
Polar wax	Beeswax	$CH_3(CH_2)_{18}CH_2COO(CH_2)_{18}CH_3$	~65	A complex mixture; esters of acids, free wax alcohols, and fatty acids	17–24

Savolainen et al. [2] reported that drug release was expected to be slower from more lipophilic matrices. As seen from Figs. 1–4, the release from Carnauba wax was very slow; 49–54% after 6.5 and 12 h. Carnauba wax is a more lipophilic matrix that hardly allows any water to penetrate into the pores of the matrix structure. Besides, the tablets prepared with Carnauba wax are also the hardest tablets. Carnauba wax contains lower percentage of free fatty acids and hydroxyl number but contains higher percentage of fatty esters (ester value of 75–85) [21,22]. In addition, Carnauba wax contains 5% of resins [23]. These factors may account for the observed low dissolution behavior of this matrix in acidic medium. In previous studies, drug release from this matrix has been found to be gradually lower than those from other materials, as expected [6,14,24,25]. However, Savolainen et al. [2] observed a relatively fast release with the Carnauba wax due to the easy disintegration of the tablets in the dissolution medium.

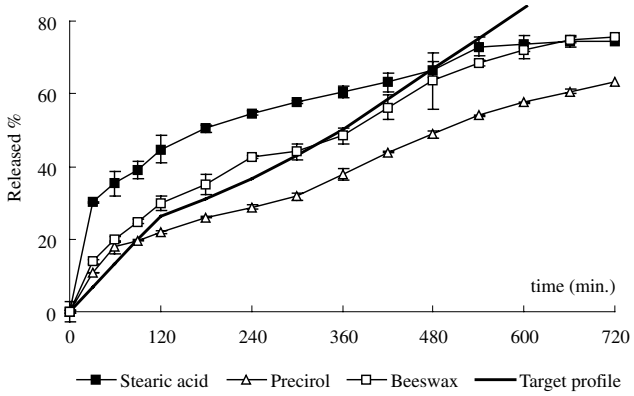

Fig. 3. The dissolution profiles of metronidazole released from the Stearic acid, Precirol and Beeswax lipid matrix tablets using USP 24 basket method at 900 ml, 0.1 N hydrochloric acid (pH 1.2) at 37 ± 0.5 °C as dissolution medium. The rotation speed is 100 rpm. All samples were run in triplicate. The error bars show standard deviation. Sometimes the error bars are smaller than the symbols.

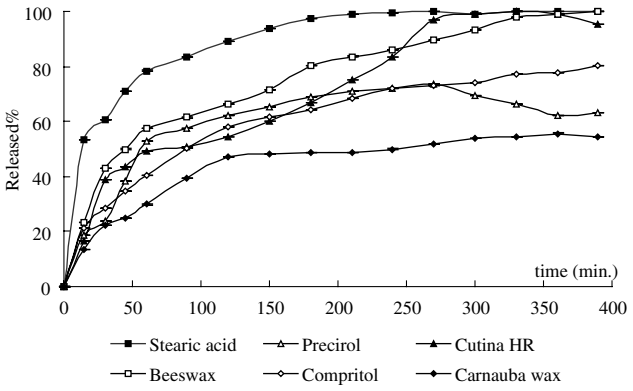

Fig. 1. The dissolution profiles of metronidazole released from the lipid matrix granules 500–1000 μm using USP 24 basket method at 900 ml, 0.1 N hydrochloric acid (pH 1.2) at 37 ± 0.5 °C as dissolution medium. The rotation speed is 100 rpm. All samples were run in triplicate. The error bars show standard deviation. Sometimes the error bars are smaller than the symbols.

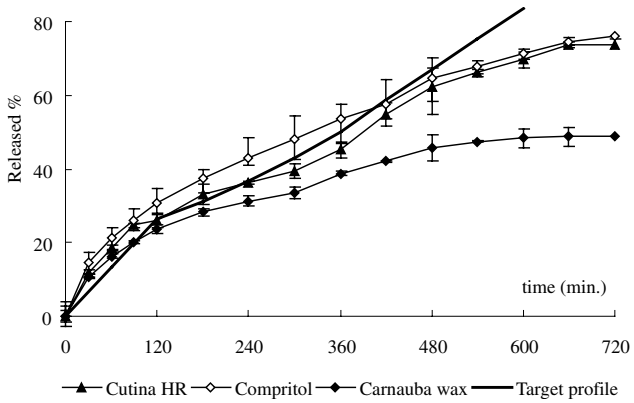

Fig. 4. The dissolution profiles of metronidazole released from the Compritol, Carnauba wax, and Cutina lipid matrix tablets using USP 24 basket method at 900 ml, 0.1 N hydrochloric acid (pH 1.2) at 37 ± 0.5 °C as dissolution medium. The rotation speed is 100 rpm. All samples were run in triplicate. The error bars show standard deviation. Sometimes the error bars are smaller than the symbols.

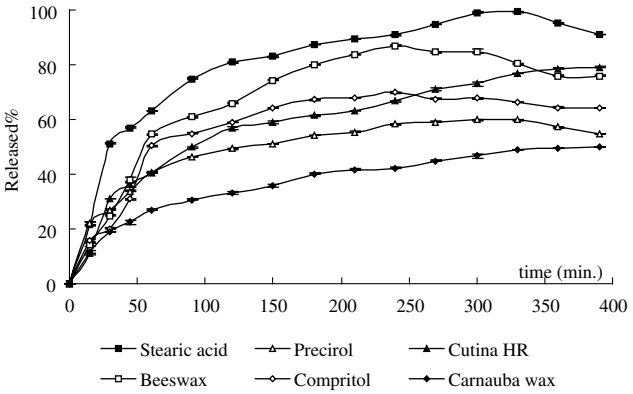

Fig. 2. The dissolution profiles of metronidazole released from the lipid matrix granules >1000 μm using USP 24 basket method at 900 ml, 0.1 N hydrochloric acid (pH 1.2) at 37 ± 0.5 °C as dissolution medium. The rotation speed is 100 rpm. All samples were run in triplicate. The error bars show standard deviation. Sometimes the error bars are smaller than the symbols.

Although the lipids used in this study are insoluble in water, it is known that Stearic acid is somewhat hydrophilic with the tendency of being hydrated in aqueous medium [23]. In addition, Stearic acid shows a well-known erodibility [25]. Therefore, this matrix showed the highest release in dissolution studies, approximately 75–100% in 6.5–12 h. These data fit well with those of other studies [24,25] with the exception of Savolainen et al. [2]. They reported more drug release with the Carnauba wax than the Stearic acid. This fact has been explained with degradation of the tablets and using pH 7.4 buffer as dissolution medium in which Stearic acid ionizes and stearat anion decreases the surface tension of the medium and increases the wettability of the dissolving particles [25].

The other four materials, which are Beeswax, Cutina, Compritol, and Precirol have release rates between that

of Stearic acid and Carnauba wax. The release rates and dissolution coefficients are seen in Figs. 1–4 and Tables 3–5, respectively.

Although Beeswax and Carnauba wax had similar structure, they showed greatly different release rates. They are both natural, complex lipid materials [23], consisting of different amounts of primarily acid esters, free acids, fatty alcohols, and hydrocarbons. Carnauba wax contains a lower percentage of free fatty acids (acid value of 2–7) than Beeswax (acid value of 17–24) but it contains a higher percentage of fatty esters (ester value of 75–85) than Beeswax (ester value of 72–79) [26]. In addition, Carnauba wax contains 5% of resins [23]. Beeswax is added into the water-absorbing ointments as emulsion stabilizers in the range of 10% [26]. It was thought that Beeswax released more drug than Carnauba wax in the acidic dissolution medium because of the difference in chemical characteristics mentioned.

Table 3
Drug release parameters for lipid matrix granules (500–1000 μm) obtained from Peppas equation

	Lipid matrix granules (500–1000 μm)		
	n	r^2	k
Stearic acid	0.1977	0.9425	33.0590
Carnauba wax	0.4136	0.9327	5.2960
Cutina HR	0.4766	0.9867	6.0930
Beeswax	0.3985	0.9608	9.7990
Compritol	0.4129	0.9835	6.8540
Precirol	0.3752	0.7830	8.7030

Table 4
Drug release parameters for lipid matrix granules (>1000 μm) obtained from Peppas equation

	Lipid matrix granules (>1000 μm)		
	n	r^2	k
Stearic acid	0.3671	0.8433	12.3760
Carnauba wax	0.4941	0.9649	2.7580
Cutina HR	0.4952	0.8912	4.6250
Beeswax	0.4934	0.8581	5.3410
Compritol	0.4361	0.8399	6.0380
Precirol	0.3046	0.9257	10.5240

Table 5
Drug release parameters for lipid matrix tablets obtained from Peppas equation

	Lipid matrix tablets		
	n	r^2	k
Stearic acid	0.3056	0.9885	10.1760
Carnauba wax	0.4774	0.9921	1.7310
Cutina HR	0.5705	0.9867	2.2882
Beeswax	0.5438	0.9948	2.1335
Compritol	0.5267	0.9887	4.5877
Precirol	0.5414	0.9759	1.6838

Cutina HR (hydrogenated castor oil) is made of primarily partially hydrogenated glyceryl triricinoleate. It contains very few free acids. A relatively large proportion of its fatty ester content is in the form of triglycerides of unsaturated fatty acids (iodine values of 38). It is known that the presence of a significant amount of hydroxyl groups (hydroxyl value of 154–162) in matrix gives a partial hydrophilic character [21]. This would also account for the relatively high dissolution rates in our dissolution medium.

The esterification of glycerol by long-chain fatty acids and the absence of polyethyleneglycol esters give Compritol (glyceryl behenate) and Precirol (glycerol palmitostearate) a hydrophobic character [27]. The hydroxyl number of Compritol and Precirol were given as 102.6 and 106.4, respectively [22]. Compritol is a nonionic surfactant [28]. The high release rate of Compritol if compared with that of Precirol may be the result of it being a nonionic surfactant, because it was assumed that the presence of a surfactant increases the wettability of the particles in an aqueous dissolution system [21]. In the present study, it was detected that Precirol matrices released less metronidazole in the dissolution medium. Some authors also determined low drug release from Precirol [2,29,30].

One of the aims of this study was to characterize metronidazole release mechanism from the prepared lipid matrices. Mathematical models and different equations have been used to describe the relationship between drug release behavior and time for swelling, unswelling, and erodible matrices [9,31–33]. Siepmann and Peppas [12] introduced an exponential model to analyze drug release from polymeric devices with various geometrical shapes, given below

$$\frac{M_t}{M_\infty} = kt^n, \tag{12}$$

where M_t/M_∞, is the fractional amount of the drug released at time t (release time), k is a characteristic constant of the system, and n is the diffusional exponent characteristic of the release mechanism. It is shown that this equation can adequately describe the release of drugs or other solutes from slabs, spheres, cylinders, and discs (tablets). In the case of pure Fickian release, the exponent n has the limiting values of 0.50, 0.45, and 0.43 for release from slabs, cylinders, and spheres, respectively. Table 6 shows the exponent n of the power law and drug release mechanism from polymeric controlled delivery systems of different geometry.

Table 6
Exponent n of the power law and drug release mechanism from controlled delivery systems of different geometry

Exponent, n			Drug release mechanism
Thin film	Cylinder	Sphere	
0.5	0.45	0.43	Fickian diffusion
$0.5 < n < 1.0$	$0.45 < n < 0.89$	$0.43 < n < 0.85$	Anomalous transport
1.0	0.89	0.85	Case-II transport

The values of diffusional exponent (n), correlation coefficient (r^2), and release rate coefficients (k) obtained from lipid matrix granules and tablets of metronidazole are shown in Table 3–5, which clearly shows that metronidazole release from 500 to 1000 μm granules could be described as pure Fickian release according to exponent n values. As previously mentioned, Stearic acid shows the highest ($k_d = 33.059$) and Carnauba wax the lowest ($k_d = 5.296$) release rates. This property is also valid for the granules greater than 1000 μm. There is a gradual increase in the exponent n values, most notably for Carnauba wax, Cutina and Beeswax, with the use of bigger granules (>1000 μm) in dissolution. n exponents show an increase as 0.5705, 0.5438, 0.5414, and 0.5267 for Cutina, Beeswax, and Precirol and Compritol, respectively (Table 5), when dissolution was performed for tablets. This phenomenon, representing an anomalous drug transport, which has the Fickian and relaxation mechanisms together (Table 7) and Eq. (13) related with this kind of drug transport, was represented by Peppas and Sahlin [34]

$$\frac{M_t}{M_\infty} = k_1 t^m + k_2 t^{2m}, \tag{13}$$

where the first term of the right-hand is the Fickian contribution and the second term the Case II relaxational contribution. The coefficient m is the purely Fickian diffusion exponent and k_1 and k_2 are the kinetic constants. Fickian release fraction is calculated with Eq. (14), according to the results of Eq. (13)

$$F = \frac{1}{1 + (k_2/k_1)t^m}. \tag{14}$$

The Fickian and relaxation behaviors of the lipid tablets are given in Figs. 5 and 6, respectively. Stearic acid and Carnauba wax show pure Fickian and Cutina, Beeswax, and Precirol show a gradual relaxation. The relaxation of Compritol is limited. Shellammer et al. [23] reported that Beeswax exhibited a larger degree of stress relaxation than Carnauba wax and this result is in agreement with those of our findings. In this section, swelling studies were carried out to elucidate the origin of this relaxation behavior. The results of the swelling studies are in accordance with that of relaxation of the lipid tablets (Table 7). The erosion (negative swelling ratio in Table 7) but not swelling was observed with Stearic acid. However, there was neither erosion nor swelling in the Carnauba wax tablets, indicating a pure Fickian release. Since Carnauba wax shows no relaxation and swelling, it gave gradually higher n values bigger than 0.45 [12] for granules and tablets (Tables 3–5), but the drug release rate should be higher than 60% for a reliable determination according to Peppas and Sahlin [34]. As mentioned previously, the release rate for Carnauba wax was found to be a maximum of 54%. This could be attributed to the n value as it is bigger than 0.45. The swelling ratios are 9.24, 6.03, 1.74, and 1.07 for Cutina, Beeswax, Precirol, and Compritol, respectively.

As for the kinetic evaluation, it was found that the square root of time relationship indicating a pure Fickian diffusion-controlled mechanism was operative for tablets prepared with Stearic acid and Carnauba wax (Table 8).

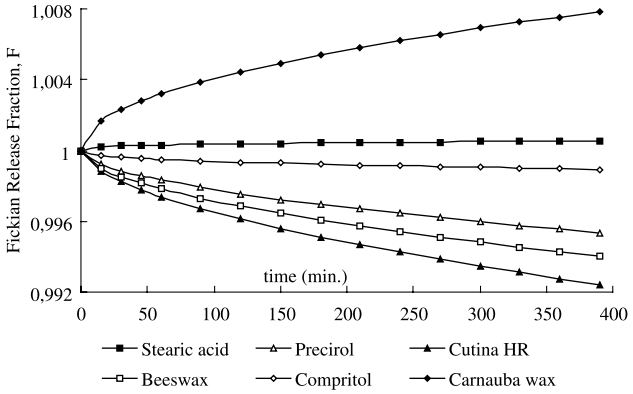

Fig. 5. The Fickian release fractions obtained from metronidazole lipid matrix tablets.

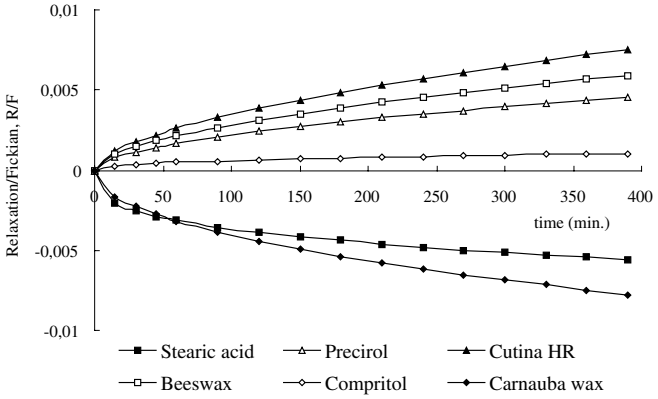

Fig. 6. The values of Relaxation/Fickian (R/F) ratio versus released fraction for metronidazole lipid matrix tablets.

Table 7
Swelling ratios and drug release parameters for lipid matrix tablets obtained from Peppas 2nd equation

	n	Dissolution k	Fickian k_1	Relaxation k_2	Swelling ratio % ±SD
Stearic acid	0.3056	10.176	10.1776	−0.00089	−1.540 ± 0.002
Carnauba wax	0.4774	1.7310	1.7308	0.00044	0.000 ± 0.000
Cutina HR	0.5705	2.2882	2.2889	−0.00078	9.240 ± 2.536
Beeswax	0.5438	2.1355	2.1350	0.0005	6.030 ± 0.142
Compritol	0.5267	4.5877	4.5865	0.00042	1.070 ± 0.085
Precirol	0.5414	1.6838	1.6828	0.00031	1.740 ± 0.074

Table 8
The determination coefficient (r^2) of release kinetics for lipid matrix tablet formulations

	First order	Zero order	Higuchi	Hixon-Crowell
Stearic acid	0.9752	0.9365	0.9861	0.9666
Carnauba wax	0.9574	0.9314	0.9857	0.9498
Cutina HR	0.9764	0.9230	0.9695	0.9645
Beeswax	0.9880	0.9776	0.9894	0.9902
Compritol	0.9764	0.9230	0.9795	0.9645
Precirol	0.9752	0.9365	0.9861	0.9666

A Fickian diffusion-controlled mechanism was also dominant for Precirol and Compritol tablets due to limited swelling. First-order kinetic was predominantly valid for Cutina tablets. The kinetic coefficients of the first order and the square root of time are nearly equal for the Beeswax. It is clear from Table 8 that first-order kinetic constants increase with the swelling of the lipid tablets. This is also evidence for the relaxation of the lipid tablets because, as reported in previous studies, swelling causes the kinetic to turn from the square root of time to first order [29,35]. Golomb and Fisher [13] have used a millimeter ruled paper to measure the swelled slabs. Our clipper measure method for swelling is more sensitive (0.1 mm) and therefore more reliable than this millimeter ruled paper method (0.25 mm) proposed by Golomb and Fisher [13].

In general, lots of release profiles are obtained from the studies and it is difficult to make a decision on the one desired. For this reason, target profile is very functional. The target profile graphics are plotted according to the in vivo data and ideal performance of the drug [19,20].

The release rate coefficients of the lipid matrix tablets and target profile (Table 7) can be arranged in order as: $\text{Precirol}_{(1.6838)} < \text{Carnauba wax}_{(1.7310)} < \text{Target profile}_{(1.95)} < \text{Beeswax}_{(2.1355)} < \text{Cutina HR}_{(2.2882)} < \text{Compritol}_{(4.5877)} < \text{Stearic acid}_{(10.176)}$.

A target profile with initial dose was plotted for detected desired release profile and it was seen that Beeswax tablet ($k_d = 2.13$) has a very close drug release rate with the target profile ($k_t = 1.95$) (Figs. 3 and 4).

In drug formulation studies, it is essential to evaluate the possible interactions between the active substance and the excipients, as the choice of the excipients should be performed in relation to the drug delivery, to their compatibility with the same drug, and to the stability of the final product [36]. Differential scanning calorimetry (DSC) has been a standard method for the characterization of solid drugs for many years, in particular for preformulation studies [37]. The technique is used in preformulation studies because the interactions between drug and excipients often result in appearance or disappearance of endothermic or exothermic peaks and on the change of other enthalpic values on thermal curves obtained with DSC method.

In DSC conditions used in this study, the results are reproducible, the peaks appearing well defined.

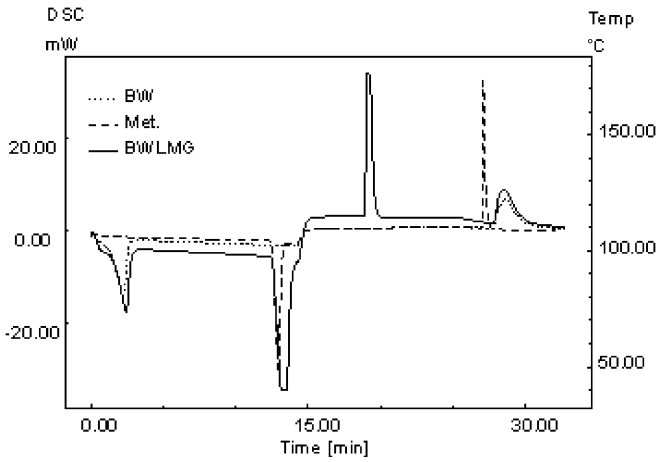

Fig. 7. DSC thermogram of metronidazole and Beeswax alone and the lipid matrix form. Met, metronidazole; BW, Beeswax; BWLMG, metronidazole lipid matrix granule with Beeswax.

The DSC profile in Fig. 7 demonstrated that the locations of the peak for Beeswax (ideal polymer) and metronidazole in the granule remained essentially the same. In addition, it was very sharp and tight. From these results, it appears that an interaction between the components of the granule did not occur. Other enthalpic phenomena were not observed; therefore, no degradation occurs in these conditions. Metronidazole was in crystalline form and no decomposition product was formed at 180 °C.

As a result, it is known that some hydrophobic materials also swell like hydrophilic materials in the dissolution medium [38], but this restricted swelling does not produce gel with water. Therefore, the relaxation of this kind of material is limited. The reason for increment in n values, according to Peppas' norms for the matrix shapes, could be due to swelling of insoluble hydrophobic dosage forms in the dissolution medium. Meshali et al. [39] found the n values of Compritol matrix tablets containing varying percentages of potassium chloride to be 0.474–0.516, not confirming pure Fickian kinetic according to Peppas' norms. The reason for the partial deviation of the Fickian kinetic could be due to the restricted swelling of the Compritol in the dissolution medium. The present study suggests that swelling and relaxation ability of insoluble dosage forms should be examined before making a decision regarding the diffusion mechanism.

4. Conclusion

In conclusion, an ideal sustained release dosage form of metronidazole can be prepared with Beeswax. Diffusion mechanism can change from pure Fickian to anomalous transport due to swelling of the lipid matrix in the dissolution medium. The model of the drug release can approach the first order from Higuchi kinetic one due to the same reason. Obviously, a reliable development requires more in vitro and in vivo experiments.

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