



GELUCIRE 39/01 AS EXCIPIENT FOR GASTRORETENTIVE METRONIDAZOLE SUSTAINED DELIVERY

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ABSTRACT

Gelucires (54/02, 43/01) have been used in preparation of floating sustained release formulations to prolong gastric residence time and increase its bioavailability. In this type of formulations Methocel K100M CR has been used as a swelling as well as a release-retarding polymer. The objective of this study was to explore the application of Gelucire 39/01 for the design of sustained release multi-unit and single-unit floating systems of metronidazole. Metronidazole-Gelucire 39/01 granules were prepared by melt granulation technique, alone and after addition of hydroxypropylmethylcellulose K15M (HPMC) or sodium cross-linked carboxymethylcellulose (Carmacel). The formulations were evaluated in vitro for their floating ability and drug release. Increasing proportions of Gelucire decrease the initial fast release of the drug that stabilizes and practically come to an end thereafter. The granules floating times were greater than 6 hours. The addition of HPMC and Carmacel increase the drug release that stabilizes after 2 hours. The use of single-unit systems (tablets) allowed a more gradual drug release. Carmacel formulations showed a span of drug dissolved after 3 hours ranging from 20 mg to 495 mg, with a trend to stabilize after 3 hours while HPMC formulations showed a range from 16 mg to 156 mg and a trend to increase the drug release. HPMC tablets floated more than 3 hours while Carmacel tablets showed no floatability. Gelucire 39/01, can be considered as a carrier for design of floating drug delivery systems only when mixed with dissolution enhancers that increase the permeability of the almost impermeable wax matrix.

Keywords: Gelucire; sustained release; floating behaviour; Carmacel; HPMC K15M.

INTRODUCTION

Sustained release dosage forms prolong the effect of drug therapy, reduce side-effects and increase safety and patient compliance by reducing the frequency of dosing. An alternative to obtain a sustained release dosage form is offered by the development of matrix formulations. Several studies have shown the possibility to formulate matrix formulations using different types of manufacturing techniques such as extrusion-spheronization, melt suspension, solvent evaporation, coarservation, hot-melt extrusion and melt granulation technique ¹.

Oral sustained release formulations with drugs that are not well absorbed throughout the GIT would be troublesome. From this point of view, some drugs are not amendable to conventional sustained release formulations if they cannot be retained in a certain part of the gastrointestinal tract favouring an efficient absorption, for instance, the stomach. Intra-gastric floating systems have been used pharmaceutically to deliver active substances for sustained release and targeting. Among other, one of the systems that can be used to maintain floating a dosage form in the stomach is that based on a reduction of the matrices density ².

Floating drug delivery systems were first described by Davis in 1968. These systems were used to prolong the gastric residence time. They remain buoyant in the stomach for prolonged period of time without affecting the gastric emptying rate of other contents. A floating dosage form is useful for those drugs that act locally in the proximal gastrointestinal tract (GIT), are unstable in lower parts of GIT, or are poorly absorbed in the intestine. This type of formulation has been also used for drugs absorbed only in the initial part of the small intestine. These systems help in continuously releasing the drug before it reaches the absorption window, thus ensuring optimal bioavailability ³.

Higher bioavailability from floating dosage forms has been attributed to the fact that the upper gastrointestinal tract is the primary site of absorption for the drug. Gastroretentive delivery systems, however, are not suitable for drugs unstable in the environment of the stomach ⁴.

Peroral floating dosage forms made in 1970s were hydrodynamically balanced systems such as non-disintegrating hydrophilic matrix capsules or tablets that have a bulk density lower

than that of the gastric fluids. It was claimed these floating forms to remain in a buoyant state upon the stomach contents for a prolonged period of time and recommended their use when aiming to enhance the gastrointestinal transit time of an orally taken medication or to obtain a sustained local action of the later inside of the stomach ⁵.

Buoyancy in peroral floating dosage forms can also be attained by incorporating various types of low density hydrophobic materials such as fats, waxes and oils, for instance, sunflower oil. Besides aiding in flotation, the hydrophobic material (i.e. sunflower oil) provides advantages of prolonging the floating duration (≥ 24 hours), decreasing lag time as well as increasing entrapment efficiency and modifying drug release. In the case of buoyant alginate beads of furosemide, a higher level of oil increased drug entrapment efficiency but retarded drug release rate as compared to a lower level of oil containing beads ⁶.

Diltiazem HCl has been also used to prepare a single unit floating delivery system. Floating matrix tablets of the drug were developed to prolong gastric residence time and increase its bioavailability. The tablets were prepared by direct compression technique, using polymers such as hydroxypropylmethylcellulose (HPMC, Methocel K100M CR) and Compritol 888 ATO, alone or in combination and other standard excipients. Sodium bicarbonate was incorporated as a gas-generating agent. The results showed that an increase in the concentration of Methocel K100M CR or Compritol 888 ATO decreases the rate of release of Diltiazem HCl from matrix. In this formulation, Methocel K100M CR retards the release by diffusion mechanism, and Compritol 888 ATO decreases the hydration of matrix and retards the release by erosion mechanism owing to its hydrophobic property ⁷.

Stearic acid has been used for the controlled release as a dispersion medium of drugs in the form of microspheres made of fats and waxes. The microspheres are obtained by the spray and congealing method. Mixtures of diclofenac with greasy materials such as glyceryl monostearate decrease their dissolution rate as the proportion of the greasy material in the formulation increases ⁸. In a similar experimental design, stearic acid has been used with hydrophilic excipients to obtain felodipine microparticles by the spray and congealing method. In this particular case, the effect of the hydrophilic excipients was considered of no consequence. The

felodipine dissolution from matrices containing 50% or more stearic acid attained 20% after 7 hours⁹.

Gelucires are a group of inert semisolid waxy amphiphilic excipients, which are surface active in nature and disperse or solubilise in aqueous media forming micelles, microscopic globules or vesicles. They have been studied as controlled release matrices as well as for improvement of physicochemical properties of drugs. They are identified with respect to their melting point and HLB value. The wide varieties of gelucires are characterized by a wide range of melting points from about 33°C to about 64°C and most commonly from about 35°C to about 55°C, and by a variety of HLB values from about 1 to about 14, most commonly from about 7 to about 14. In the designation of gelucire names, for example, Gelucire 54/02, 54 indicates melting point and 02 indicates its HLB value. Low HLB gelucire can be used to reduce the dissolution rate of drugs. High HLB gelucire can be used for faster release of drugs¹⁰.

Gelucires are vehicles derived from mixtures of mono-, di-, and triglycerides with polyethylene glycol (PEG) esters of fatty acids. Gelucires containing only glycerides or a mixture of glycerides and PEG esters (Gelucire 54/02, 50/13, 43/01) are used in preparation of sustained release formulations. It has been reported sustained release single unit matrices using Gelucire 43/01, where only 1.7% theophylline was released over a period of 20 hours. Gelucire 43/01 has been also used for the design of multi-unit floating systems of a highly water-soluble drug, diltiazem HCl. The granules were retained in stomach at least for 6 hours. Approximately 65% to 80% drug was released over 6 hours with initial fast release from the surface¹¹.

The hydrophobic Gelucire 43/01 (GEL) has been used as a coat to extend the release of Felodipine. Caprol PGE-860 was added to this coat as a release enhancer. Caprol PGE-860, by virtue of channel formation in Gelucire coat favoured the Felodipine release. The Felodipine preparation encased within the Gelucire coat was considered to be useful as an extended release composition for lipophilic drugs. The drug release was primarily controlled by diffusion in case of hydrophobic variants of Gelucire (Gelucire 43/01 and 54/02)¹².

Gelucire 43/01 has been used for floating delivery of metformin hydrochloride (MH). Photomicrographs showed that the beads surface was porous in nature. The beads demonstrated favourable in vitro floating ability. It was found that there was no significant effect on floating ability of aged beads since it remain floats up to 8 h study period. Thus, it considered that beads of Gelucire 43/01 could be used as an effective carrier for highly water-soluble drugs like metformin for the controlled delivery. It is considered that the obtained release patterns provide an idea about the effect of concentration of Gelucire 43/01 on drug release from beads, i.e., the higher the Gelucire 43/01 content, better the controlled drug release¹³.

A controlled-release multiunit floating system of a highly water soluble drug, ranitidine HCl, has been made using Compritol, Gelucire 50/13, and Gelucire 43/01 as lipid carriers. Ranitidine HCl-lipid granules were prepared by the melt granulation technique and evaluated for in vitro floating and drug release. The results revealed that the moderate amount of Gelucire 43/01 and ethyl cellulose provides desired release of ranitidine hydrochloride from a floating system. The temperature sensitivity studies for the prepared formulations at 40°C/75% relative humidity for 3 months showed no significant change in in vitro drug release pattern. These studies indicate that the hydrophobic lipid Gelucire 43/01 can be considered an effective carrier for design of a multiunit floating drug delivery system for highly water soluble drugs such as ranitidine HCl¹⁴.

In some cases, the addition of greasy materials to a pharmaceutical formulation has been observed to produce an increased dissolution rate. These results are attributed to decreasing matrices coherence, for instance, by increasing the quantity of stearic acid and reducing the polymer proportion².

MATERIALS AND METHODS

The drug Metronidazole batch 1001934001 was obtained from Química Alkano. The excipients Gelucire® 39/01 (waxy solid,

melting point=39°C,HLB=01) , batch 5E0907-2 and GE2007-2 was obtained from Lubrizol Mexico; Carmacel P-(CC) (Sodium cross linked carboxymethylcellulose) batch 02 was obtained from Reliance Cellulose Products Limited; Methocel K15M CR premium USP (hydroxypropyl methylcellulose - HPMC), batch MC28912N01 was obtained from Dow Chemical. All of them were used as received.

Preparation of floating granules and tablets

Floating granules containing metronidazole were prepared using the melt granulation technique. The drug:lipid ratios used to prepare the different formulations were 1:1, 1:0.8, 1:0.6, 1:0.4 and 1:0.2. To study the effect of agents such as HPMC and Carmacel were added separately to the formulations. The proportion of additives was 3%, 5%, 7%, 10%, 15%, 20%, 30% and 40% for both HPMC and Carmacel. Lipid was melted at 50°C, and the drug or drug and additives mixture was added, mixed well, and cooled to room temperature. The mass was passed through a number 16 sieve to obtain uniform-sized granules. The tablets were obtained from the granules after compaction at a minimal compaction pressure, using flat faced punch and die with diameter of 12.7 mm.

In vitro evaluation of floating ability

The floating time was determined by direct observation during the dissolution test. The floating times were measured by visual observation as an average of 3 repetitions. Floating was determined in the interval of 3 and 5 hours.

In vitro drug release

In vitro drug release studies (in triplicates) were carried out using USP 24 type II dissolution test apparatus (SRII 6, Hanson Research Corporation, Chatsworth, California, USA), commonly known as the paddle method. A tablet or the equivalent quantity of granules containing 500 mg metronidazole was added to 900 ml HCl 0.1 N. Dissolution media was thermostated at 37±0.5°C and stirred at 50 rpm. Aliquots were collected periodically and replaced with fresh and prewarmed dissolution medium. The aliquots, after filtration, were analyzed using spectrophotometer at 278 nm for metronidazole content. Dissolution was determined in the interval of 3 and 5 hours.

RESULTS AND DISCUSSION

Metronidazole:gelucire granules

Lipidic materials like Gelucire are considered as an alternative to polymers used in the sustained release formulations because some advantages such as low melt viscosity, absence of toxic impurities, potential biocompatibility and biodegradability and prevention of gastric irritation by forming a coat around the gastric irritant¹⁰.

Together with some other, the objective of a dosage form development is to ensure the delivery of specific and reproducible amounts of pharmacologically active compounds to the body. Particularly, by sustained release products, one of the goals is to maintain a steady state level of drug concentration in the blood. In doing so a balance can be achieved between the amount absorbed and that being excreted. This is attained by releasing constant quantities of the drug per unit of time, equivalent to the drug quantities being eliminated from the body; in theoretical zero order release kinetics.

Metronidazole:Gelucire granules dissolving in 0.1 N HCl showed that drug release was retarded notably with an increasing amount of Gelucire (Fig. 1). As can be seen, the release profiles do not show a zero order release and Gelucire can not be recommended, by itself, as a sustained release excipient. All 5 drug:lipid ratios showed burst release in the initial stage and a particularly slow drug release thereafter.

The increase of the lipid ratio above 1:0.8 caused a retardation that can be considered as unsuitable for gastroretentive release. The granules containing a drug to lipid ratio of 1:0.8 parts by weight showed significant release retardation, as less than 25% of the drug was released after 5 hours. This level of lipid was taken as a reference in the study for further evaluation of release modifying excipients. All the formulations floated for more than 5 hours.

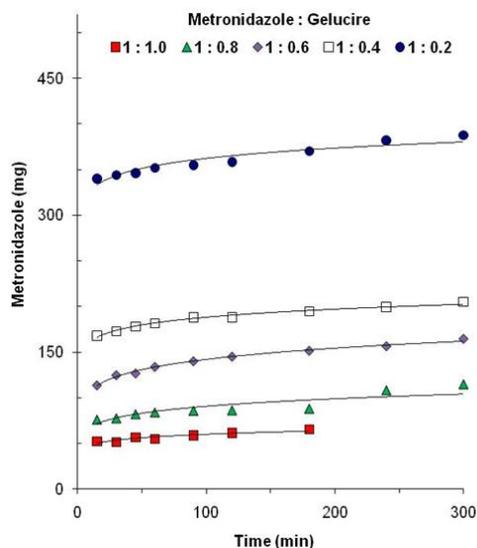


Fig. 1: Release profile of metronidazole from granules containing different proportions of Gelucire 39/01, in HCl 0.1 N.

The drug released after 3 hours from granules containing different proportions of Gelucire 39/01, in 0.1 N HCl, is shown in Fig. 2. It is observed that an increasing amount of the lipid in the granules decreases logarithmically the drug released, ranging in a quantity of metronidazole between 60 mg and 370 mg. It seems that the drug released is that not covered by the lipid and that found in channels formed by dissolution of particles percolating the granules. After this part of the drug has been released the lipid covering the drug particles allows only a quite small part of the drug to be released. This slow drug release can be seen in Fig. 2 expressed as the slopes (n) of release profiles expressed as the logarithmic form of a potential model (eq. 1). These slopes lie in a range between 0.044 and 0.095.

$$= Mt = kt^n \text{ or } \ln(Mt) = n \ln t + \ln k \quad (1)$$

Where: Mt is the drug released at a time t and k is the release constant or the quantity of drug released after 1 minute. The metronidazole released after 1 minute (k) could be considered as representative of the drug released without the control of the release restricting matrix.

Although Gelucires are recommended as such a sustained release agent, the above mentioned burst release and subsequent exceedingly slow drug release have been observed before. E.g. the in vitro drug release profiles of floating beads of metformin hydrochloride/Gelucire 43/01 (1:10) showed that approximately 42% drug was released after 9 hours while 26% was already dissolved after 15 min. It means 16% of the drug was released in 9 h¹³. In the same way, after an initial fast release of about 40% diltiazem, only another 35% was released after 6 hours from granules containing diltiazem/Gelucire 43/01 (1:1.3)¹¹.

A similar effect has been observed by application of hot-melt coating for controlled release of propranolol hydrochloride pellets. The coat was a mixture of Gelucire 50/02 and glycerol palmitostearate (Precirol AT05). The initial fast release occurred within a period of 3 hours, attaining an area of stability thereafter. The plateau of drug released was between 50% and 80% by lipid coats from 35% to 45% and with Precirol:Gelucire proportions of 9.5:0.5 and 7:3. The findings indicated that the thicker the wax coat, the larger was the decrease in drug release¹⁵.

The potential use of this burst effect could be the modulation of the short-term release, because many controlled release systems are characterized by an exceedingly slow initial release that can result in ineffective doses.

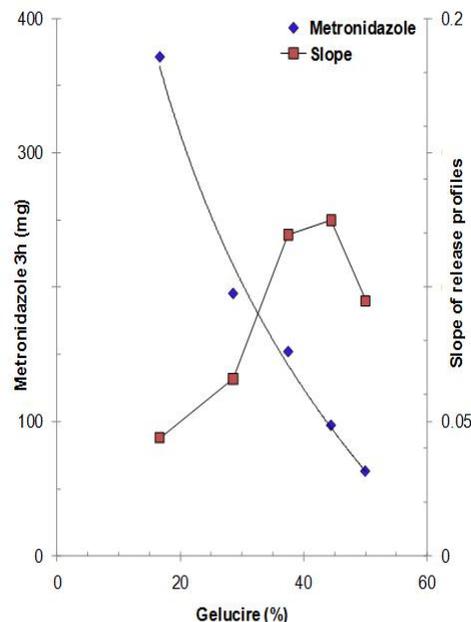


Fig. 2: Effect of Gelucire 39/01 proportion on the release profile of metronidazole from granules, considering the drug released after 3 hours and the slope of the release profile.

Metronidazole:Gelucire granules containing a release enhancer

Gelucire can be used as extended delivery excipient, however, it is necessary to add a release modifying agent to improve the drug release kinetics. This has been made to design an extended release felodipine self-nanoemulsifying system, using Gelucire 43/01 as release retarding agent and Caprol PGE-860 as a release enhancer. In this case, leaching of Caprol during the release resulted in formation of aqueous channels which eventually got enlarged at the later time points, thus promoting drug diffusion through the hydrophobic barrier¹².

Polymers such as Methocel K100M CR have been used as a swelling as well as a release-retarding polymer in the development of an oral floating matrix tablet of diltiazem. In this formulation, Methocel K100M CR (25-35%) retards the release by diffusion mechanism, and a relative similar proportion of the lipid (15-25%), Compritol 888 ATO, decreases the hydration of the matrix and retards the release by an erosion mechanism owing to its hydrophobic property. Together, these polymers retarded the release of the drug using different mechanisms⁷.

The addition of HPMC (Methocel K15M) to granules of metronidazole:Gelucire 39/01 (1:0.8), as a release enhancer, showed an increase in drug release compared to plain drug:lipid granules (Fig. 3). Although HPMC is used commonly as a controlled release carrier, it can function as a swelling as well as a release-retarding polymer. In this case, it seems that the combination of HPMC and Gelucire 39/01 do not display a shared effect, at least no one clearly observed at all HPMC:Gelucire proportions. All the formulations floated throughout the dissolution study, 3 hours.

The immiscibility between the hydrophobic Gelucire and the hydrophilic polymer may obstruct the performance of each material to function as a release retardant. It seems that swelling of HPMC breaks off the continuity of the hydrophobic domain of Gelucire, leading to faster drug release from the granules. In the same manner, Gelucire can obstruct the interaction between the particles of the swelling polymer to form a gelled matrix. The final result seems to depend on the relative proportions of the hydrophilic and the hydrophobic polymers as well as on the total proportion of the polymers in the formulation.

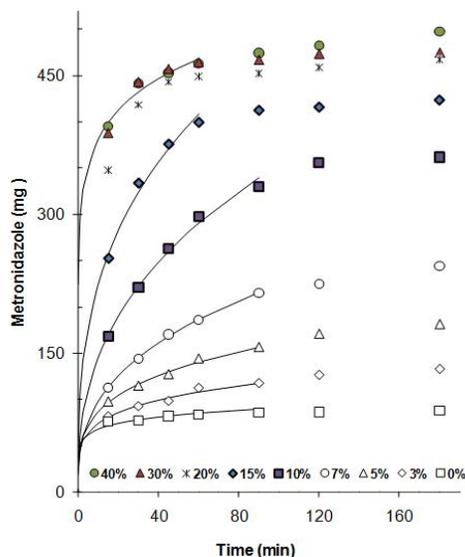


Fig. 3: Release profile of granules of metronidazole:Gelucire 39/01 (1:0.8) added of different proportions of hydroxypropyl methylcellulose (HPMC K15M).

The above mentioned effect has been observed before by granules of Gelucire 43/01 added of HPMC K4M, using a relative low HPMC proportion of 0.5 parts (14%) with 1 part of the drug (28%) and 2 parts of Gelucire (57%)¹⁶.

The drug release rate from metronidazole:Gelucire 39/01 (1:0.8) granules increases as the quantity of added HPMC increases from 3% to 40% (Figure 3). The drug dissolved after 3 hours, of the release profiles shown in Figure 3, increases as the added HPMC proportion increases, ranging from 133 mg (26.6%) to 497 mg (99.4%). At the beginning, the increase in release rate and in the attained drug released after 3 hours is high. However, at HPMC proportions of 20-40% the release rate and the attained plateau of drug released show practically no differences. At HPMC proportions of 20% and higher the granules show similar fast release rates of the drug, producing a drug release of about 90% after 45 min; most probably because the release rate is too fast to discriminate any difference.

Fig. 4 shows the release profiles of the same formulations showed before, in Fig. 3, but now as tablets obtained from the granules. The tablets display a slower release rate than the granules, reaching after 3 hours dissolution metronidazole quantities ranging between 16 mg (3%) and 156 mg (31%). This is attributed to a smaller surface area available for dissolution and to a more coherent matrix. In the same manner as the granules, increasing amounts of HPMC increase the drug released. Tablets containing 30% and 40% HPMC floated throughout the dissolution test, 3 hours. These tablets showed the formation of a gelled matrix that increased its volume with time. However, tablets containing 3% to 20% HPMC do not float although showed some up and down movement in the dissolution medium.

Although at lower HPMC proportions the slopes of the release profiles are similar for both tablets and granules, at HPMC proportions of 7% and higher the slopes of the tablets release profiles (Slope-7%=0.611) attain much higher values than that of the granules (Slope-7%=0.360). The fact that the slope of the release profiles increases constantly can be ascribed to the swelling effect of the hydrophilic polymer.

The regression parameters for the initial part of release profiles, calculated according to a potential model (eq. 1) and corresponding to granules and tablets of formulations containing HPMC, are summarized in Table 1.

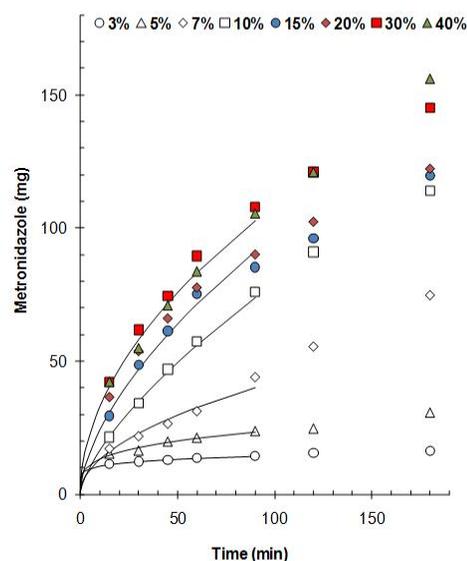


Fig. 4: Release profile of tablets obtained from granules of metronidazole:Gelucire 39/01 (1:0.8) added of different proportions of hydroxypropylmethylcellulose (HPMC K15M).

Table 1: Regression parameters for the initial part of release profiles of formulations of granules and tablets of metronidazole:Gelucire 39/01 (1:0.8) containing different proportions of HPMC K15M. According to equation 1: $Mt = kt^n$.

| HPMC (%) | Granules | | | Tablets | | |
|----------|----------|-------|----------------|---------|-------|----------------|
| | k | n | r ² | k | n | r ² |
| 3 | 45.5 | 0.212 | 0.967 | 7.79 | 0.136 | 0.993 |
| 5 | 46.7 | 0.269 | 0.989 | 7.28 | 0.26 | 0.952 |
| 7 | 42.7 | 0.360 | 0.999 | 3.98 | 0.512 | 0.956 |
| 10 | 59.5 | 0.387 | 0.994 | 3.42 | 0.683 | 0.998 |
| 15 | 123 | 0.282 | 0.940 | 5.94 | 0.607 | 0.984 |
| 20 | 242 | 0.149 | 0.859 | 9.25 | 0.513 | 0.995 |
| 29 | 301 | 0.104 | 0.863 | 10.1 | 0.526 | 0.998 |
| 40 | 305 | 0.101 | 0.944 | 9.92 | 0.519 | 0.989 |

The hydrophilic polymer (HPMC) plays two different roles in a Gelucire 39/01 sustained release matrix, that of a swelling polymer breaking off the domain of a Gelucire matrix, and that of a release retarding polymer due to formation of a gelled matrix that can be obstructed by the presence of a hydrophobic material such as Gelucire. At low HPMC (3-10%) proportions the swelling effect leads to an importantly increasing drug release rate while at higher HPMC proportions (10-40%) the release retarding effect of a gelled matrix slow down the increase of release rate, leading to less important increases in the drug released after 3 h. The end effect of the hydrophilic polymer particles in a hydrophobic matrix seems to depend on the possibility that these particles have to percolate the matrix. At low HPMC proportions the particles are isolated or form small particle clusters and the observed effect is that of swelling. When the hydrophilic polymer can form a chain of particles percolating the waxy matrix the release retarding effect begins.

The above mentioned concepts can explain why a hydrophilic polymer (a HPMC K100M proportion of 25-35% against a Compritol proportion of 15-25%) can produce a release retarding effect while an equally hydrophilic polymer (HPMC K4M proportion of 14% against a Gelucire proportion of 57%) produce not a release retarding effect but a swelling effect.

Fig. 5 shows the release profiles of metronidazole:Gelucire (1:0.8) granules added of Carmacel (sodium cross linked carboxymethylcellulose) as a release enhancing agent. As observed

before by granules containing HPMC, the drug release rate from metronidazole:Gelucire 39/01 (1:0.8) granules increases as the quantity of added Carmacel increases from 3% to 40%. The drug dissolved after 3 hours attains values ranging from 95 mg (19%) to 496 mg (99.2%). The results can be described in a similar way than those observed by granules added of HPMC, although Carmacel is not a release retarding agent it is a water wicking and swelling agent. Carmacel swelling properties facilitate a faster metronidazole release rate, compared to the plain metronidazole:Gelucire granules.

Granules containing Carmacel showed disintegration after 15 min, disintegration that allowed more sudden or less gradual drug dissolution, compared to granules containing HPMC. The disintegration of granules was faster as the Carmacel content increased. The dissolution medium became turbid. The turbidity was greater at lower parts of the dissolution vessel presumable due to partial sedimentation of the not dissolving portions of the granules.

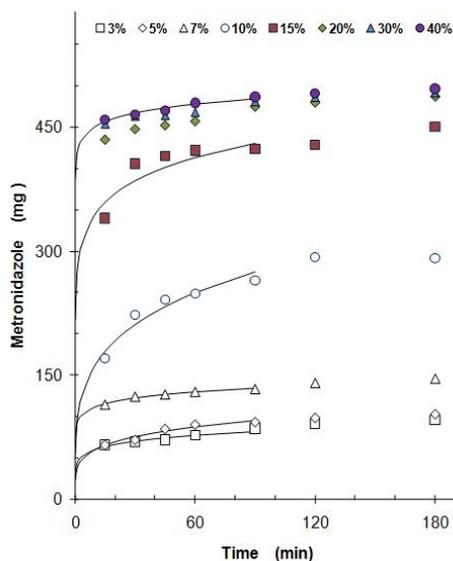


Fig. 5: Release profile of granules of metronidazole:Gelucire 39/01 (1:0.8) added of different proportions of sodium cross linked carboxymethylcellulose (Carmacel).

Fig. 6 shows the release profiles of tablets made with granules of Metronidazole:Gelucire (1:0.8) added of Carmacel. As by tablets of granules added of HPMC, tablets of granules added of Carmacel increase the metronidazole release rate with increasing proportions of Carmacel. The metronidazole released after 3 hours dissolution lie between 16 mg (3%) and 496 mg (99.2%). The release rate of metronidazole from the tablets containing Carmacel is similar to that observed by tablets containing HPMC, at lower proportions of Carmacel (3-10%). However, at Carmacel proportions higher than 10% the release rate of the tablets is much higher than that of the corresponding tablets containing HPMC. The metronidazole released after 3 hours dissolution attains values between 16 mg and 496 mg (99.2%) while tablets containing HPMC attain only quantities of metronidazole dissolved up to 156 mg (31%).

Carmacel containing tablets show different floating behaviour depending on the release enhancer content. Tablets containing 3-5% Carmacel do not float at all while tablets containing 7-10% Carmacel showed some floating after 15 min, adhering to the paddles of the dissolution equipment. Tablets containing 15-40% Carmacel showed only some movement, beginning to split after 30 min to break in two or 3 parts. Particularly, tablets containing 30-40% Carmacel showed some turbidity during the dissolution test and after 90 min disintegrated completely.

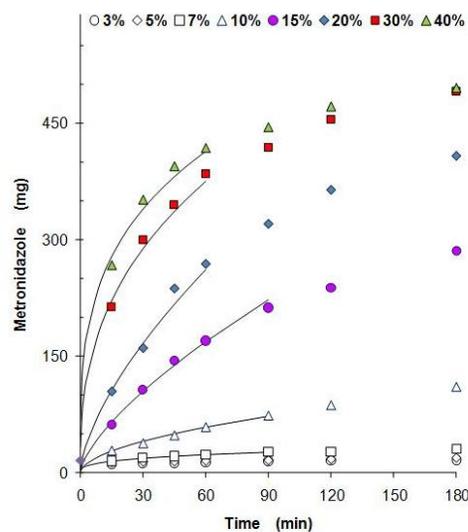


Fig. 6: Release profile of tablets obtained with the granules of metronidazole:Gelucire 39/01 (1:0.8) added of different proportions of sodium cross linked carboxymethylcellulose (Carmacel).

The regression parameters of release profiles, according to a potential model and corresponding to granules and tablets of formulations containing Carmacel, are summarized in Table 2.

Table 2: Regression parameters calculated for the initial part of release profiles of formulations of granules and tablets containing different proportions of Carmacel. According to equation 1: $Mt = kt^n$.

| Carmacel (%) | Granules | | | Tablets | | |
|--------------|----------|--------|----------------|---------|--------|----------------|
| | k | n | r ² | k | n | r ² |
| 3 | 43.67 | 0.1404 | 0.91 | 5.953 | 0.1987 | 0.892 |
| 5 | 36.82 | 0.2107 | 0.945 | 10.29 | 0.0972 | 0.971 |
| 7 | 91.66 | 0.0845 | 0.977 | 6.512 | 0.3118 | 0.995 |
| 10 | 92.18 | 0.2435 | 0.934 | 6.68 | 0.5286 | 0.989 |
| 15 | 255.4 | 0.1212 | 0.801 | 9.941 | 0.6907 | 0.993 |
| 20 | 383.5 | 0.0451 | 0.938 | 15.14 | 0.7071 | 0.989 |
| 30 | 417.9 | 0.0291 | 0.894 | 69.17 | 0.4223 | 0.994 |
| 40 | 418.4 | 0.0327 | 0.942 | 112.1 | 0.3277 | 0.984 |

Fig. 7 displays the comparative changes in release rate, expressed as the drug released after 3 hours, of granules and tablets of different metronidazole formulations containing a release enhancing agent. It is clear that both release enhancers, HPMC and Carmacel, produce an increasing release rate as the proportion of the enhancer increases.

Although the granules containing HPMC show greater release rates at low proportions of the enhancer, after addition of enhancer proportions higher than 15% the opposite occurs. Even so, the release enhancing effect of both enhancers is similar. On the other hand, the release rate of formulations containing the same enhancers in the form of tablets is different. Tablets containing Carmacel show a continuous and important increase of the metronidazole released as the Carmacel proportion increases. Tablets containing HPMC show this effect only at low HPMC proportions, up to 10%, showing thereafter only discrete increases of the drug released after 3 h.

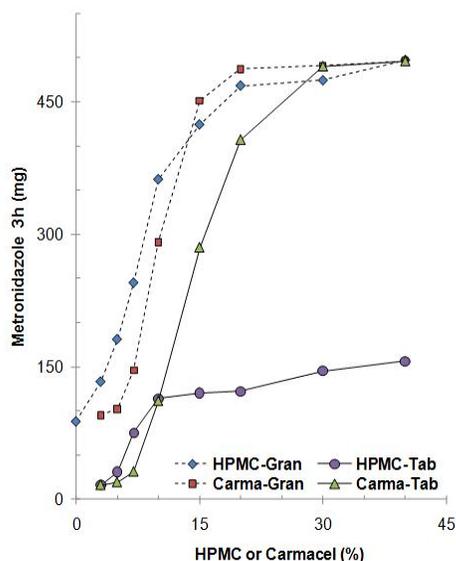


Fig. 7: Effect of addition of a release enhancer (HPMC or Carmacel) on the drug released after 3 hours from metronidazole:Gelucire 39/01 (1:0.8) formulations, granules and the tablets.

The results depicted in Fig. 7 are attributed to a non limited action of Carmacel as a disintegrant while HPMC displays only a limited swelling effect due to its counteracting gelling effect that allows the formation of a gelled matrix, slowing the release rate of the drug. The cross-linking of sodium carboxymethylcellulose reduces its water solubility while still allowing the material to swell and absorb many times its weight in water.

CONCLUSION

Gelucire 39/01 can not be used as itself as an extended release agent, when prepared by the melt granulation process. The use of Gelucire produces matrices with a burst effect and a subsequent very low drug release rate. Addition of release enhancers such as HPMC and Carmacel to Gelucire matrices allow a more gradual drug release. There is a more gradual dissolution when HPMC is used as release enhancing agent because of its dual functioning as a swelling and as a dissolution retarding agent.

The effect of the release enhancers seems to be related to the Gelucire matrix consistency. A more coherent matrix like that of a tablet allows the deployment of the superior disintegrant activity of Carmacel over that of HPMC, to break off the continuity of the waxy matrix. A smaller volume for a given metronidazole dose and a greater particle density of the tablets increase the probability to find HPMC particles close enough to be united and to form a gelled matrix. As the granules are smaller and less coherent require lesser disintegrant activity to break off the continuity of the waxy matrix. The smaller size and the lesser coherence of the granules reduce the

probability to find HPMC particles that are close enough to form a gelled matrix, avoiding the release retarding effect of HPMC.

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