IJPPR
INTERNATIONAL JOURNAL OF PHARMACY & PHARMACEUTICAL RESEARCH
An official Publication of Human Journals
ISSN 2349-7203
HUMAN

Human Journals
Research Article
July 2020 Vol.:18, Issue:4

Effect on Drug Release Characteristics of the Inclusion of Hydrophobic Excipients in the Formulation of Metronidazole Tablet by Melt Granulation

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ISSN 2349-7203
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Submission: 26 June 2020
Accepted: 02 July 2020
Published: 30 July 2020

Keywords: Metronidazole, Hydrophobic excipient, Carnauba wax, Melt granulation, Controlled release

ABSTRACT

Melt granulation is the process whereby the drug powder is mixed with melted wax, and it has been used to modify the dissolution characteristics of the drug particles. This study investigated the effect of the inclusion of hydrophobic excipients (magnesium stearate or talc powder) in the formulation of metronidazole tablets and to see their effects on the release patterns of the drug. The hydrophobic excipient powder was mixed with the drug (metronidazole) powder and melt granulated with Carnauba wax. The content of the wax was constant, while the hydrophobic excipient was varied from 0, 6.25, 12.5, 31.25, and 43.75 to 50% w/w respectively. The conventional granules of metronidazole were formed by wet granulation using 20% w/v starch mucilage, screened and dried. The granules of the different formulations were then compressed in a Single Punch Tableting Machine (Manesty, England) at 4kg and tablet weight of 320 mg to obtain 250 mg metronidazole. The tablets were subjected to disintegration time and dissolution tests respectively. The results showed that melt granulation prolonged the disintegration time of the tablets (conventional tablet (8.5min) and melt (25.4 min). These were further prolonged by the inclusion of hydrophobic excipients. The increase was however concentration-dependent ranging from 18.4 – 65.3 min for magnesium stearate, and 18.4 – 63.5 min for talc respectively. A comparison of the dissolution profiles of the conventional metronidazole tablets and the melt granulated tablets (without a hydrophobic agent) showed retardation of the drug release with the melt formulation. There was further retardation of the dissolution of the drug particles with the inclusion of the hydrophobic excipients (magnesium stearate and talc) which were concentration-dependent. The study reveals that the inclusion of intragranular hydrophobic excipient in the melt formulation can be utilized to achieve extra control of drug release from metronidazole tablet formulation and other solid dosage drug formulations.

INTRODUCTION:

The physicochemical properties of a dosage form such as drug release, bioavailability, and stability are greatly affected by pharmaceutical excipients. Hence, the study of excipients has become very essential for a formulation scientist. Excipients are the additives used to convert pharmacologically active ingredients (API) into pharmaceutical dosage forms suitable for the administration. The International Pharmaceutical Excipients Council (IPEC) defines excipient as "substances other than the API in a finished dosage form which has been appropriately evaluated for safety and is included in a drug delivery system to either aid the processing or to aid manufacture, protect, support, enhance stability, bioavailability or patient acceptability, assist in product identification, or enhance any other attribute of the overall safety and effectiveness of the drug delivery system during storage or use[1]. Controlled release solid dosage forms are either formulated as a single unit or as multiple unit forms[2,3]. Multiunit dosage form consists of particles of differing release patterns concerning onset, rate, and the maximum release, etc. These products are formulated to decrease dosing frequency and improve patient compliance. For some time now, sustained-release dosage forms have made profound progress in clinical efficacy and patient compliance. Hydrophobic excipients such as talc, magnesium stearate, sodium stearate, have the potential to repel water influx into the core of granules – which can be compressed directly into tablets or filled into empty hard gelatin shells; thus influencing the release pattern of the drug in dosage form[4]. Talc is mostly used as a glidant and magnesium stearate as a lubricant in tablet formulations. These materials are hydrophobic with the potential to repel water influx into tablets. This effect will retard drug release from such tablets. Previous studies[4, 5], have shown that melt granulation (whereby the drug powder is triturated with a melted wax to form granules) is an effective means of retarding drug from drug particles. This technique has also been used to retard the release of Ibuprofen and Paracetamol from their melt granules using goat wax, carnauba wax, and glyceryl monosterate in the melt granulation[6,7]. Carnauba wax is a hydrophobic meltable binder and is preferred for prolonged-release formulations. It is obtained from the leaves of *Copernicia prunifera* palm by collecting and beating the leaves to loosen the wax; then refining and bleaching the wax. Carnauba wax contains mainly esters of fatty acids (80 -85%), fatty alcohols (10 – 16%), acids (3 – 6%), and hydrocarbons (1 – 3%)[8].

Metronidazole is a semi-synthetic 5-nitroimidazole compound. It is antiamoebic, antiprotozoal and antibacterial; antiparasitic and antitrichomonal agent. Metronidazole when

used as a bactericidal agent, works at low concentration. Its range of activities includes almost all anaerobic bacteria such as Gram +ve and Gram –ve[9]. It is readily absorbed after oral administration from the gastrointestinal tract and extensively distributed into all body tissues and fluids. It is metabolized by the liver through conjugation and oxidation. It is reported to have a half-life of seven (7) to eight (8) hours necessitating the drug (in tablet form) to be administered up to 3 times daily[9]. This creates compliance problems with most patients, resulting in abandonment of their medication. To optimize therapy and improve the bioavailability of metronidazole, several attempts have been made to design hydrogel-based metronidazole bioadhesive tablets to achieve the controlled release of drugs for a prolonged period of time[10]. The purpose of this study is to investigate how the incorporation of hydrophobic excipients (talc and magnesium stearate) will influence the release characteristics of the metronidazole granules formulated by melt granulation. The melt granules produced could ultimately be encapsulated or compressed into a tablet for multiunit dose administration.

MATERIALS AND METHODS:

MATERIALS:

Metronidazole pure power (Rovet Chemicals Ltd, Benin City, Nigeria)

Magnesium stearate powder (BDH, Poole, UK)

Talc (Rovet Chemicals Ltd, Benin City, Nigeria)

Carnauba wax (Rovet Chemicals Ltd, Benin City, Nigeria)

Carnauba wax used in the melt granulation is a fine waxy solid and has a melting point range of 82 – 88ºC, and yellowish. The choice for carnauba wax as the coating material is because it is not sticky and thus produces free-flowing granules. Metronidazole is a drug with short biologic half-life and it is readily available, hence their choices to demonstrate the fundamental essence of controlled-release by melt granulation.

METHODS:

Melt granulation technique:

Carnauba wax (20g) was melted in a crucible container in a water bath at a temperature higher than the melting point of the wax material (95^{o}C). Metronidazole powder and the hydrophobic excipient (talc and magnesium stearate powder) were blended separately in different proportions of 0, 5, 10, 25, 35, and 40g each; accounting for 0, 6.25, 12.5, 31.25, 43.75 and 50% respectively of a sample of metronidazole alone or the powder mixture (80g). The varying samples of metronidazole (alone) or the mixture were in turn mixed with the melted carnauba wax in a Kenwood mixer. The wet mass was pressed through a stainless steel sieve of 710µm size and dried in a vacuum oven (Gallenkamp, England) at 30^{o}C for 1hr. Convectional granules of metronidazole powder (50g) were produced by wet granulation using 20% w/v starch mucilage (35ml). The wet mass was sieved and dried in a vacuum oven at 30^{o}C for 1hr to obtain granules of moisture content (2.10% w/w) for conventional wet granulation and (2.0% w/w) for melt granulation with carnauba wax.

Compression of granules into tablets

A sample of each batch of granules (320 mg) was weighed and carefully hand-filled into the die space of a single punch tableting machine (Manesty, England) and compressed at a force of 4kg to obtain metronidazole tablets of 250 mg each.

Evaluation of physicochemical parameters:

Disintegration time test

The test was carried out with a Manesty disintegration test apparatus (Model MK4, Liverpool). Five (5) tablets were randomly selected from each batch and placed each into each tube of the apparatus, and lowered into the assemblage containing 800ml distilled water as the disintegration medium. The temperature of the medium and the water bath was maintained at 37 $\pm$ 0.5^{o}c with the aid of a thermostat. The time for each tablet to break into small fragments and passed through the stainless steel mesh was recorded. The mean disintegration time of 5 tablets from each batch was calculated and carefully recorded in (min).

Preparation of standard calibration curve for metronidazole

Pure metronidazole powder (10 mg) was dissolved in 50ml distilled water and the volume made up to 100 ml with the same solvent to obtain the stock solution containing 100 µg/ml. Serial dilution was made by pipetting 0.5, 1, 1.5, 2, 2.5, 3.0, 3.5 and 4ml respectively from the stock solution into series of pre-labeled flasks which were then made up to mark with the solvent to get 5, 15, 20, 25, 30, 35 and 40 µg/ml respectively. The absorbance of each of the solutions was spectrophotometrically determined at a maximum wavelength of 340 nm.

Dissolution Test

The United States Pharmacopoeia tablet dissolution apparatus 11 (paddle) was adapted to determine the dissolution rate of the tablets of the different formulation batches. A tablet each was placed in the round bottom dissolution vessel which contained 800ml of the dissolution medium (distilled water) maintained at 37 $\pm$ 0.5^{o}c. The fluid was stirred with the paddle set to rotate at 100 rpm. Aliquots of 5ml sample were withdrawn at different time intervals of 15, 30, 45, 60, 75, 90, 105 and 120 min with a pipette fitted with cotton wool plug into pre-labeled test tubes, and assayed using UV spectrophotometer at λ_{max} 340nm. The 5ml withdrawal was replaced with an equal volume of drug-free dissolution fluid. The procedure was repeated with two additional tablets of each batch and their mean calculated and recorded. The amounts released were expressed as a percentage of the initial amount of metronidazole in the tablet samples. Plots of amounts released (%) versus time (min) were made.

RESULTS AND DISCUSSION:

RESULTS:

Disintegration test. Effect of melt granulation and inclusion of hydrophobic excipient on the disintegration time of the metronidazole tablets:

Table No. 1: Disintegration time (min) of the different batches of metronidazole tablets

Hydrophobic Excipient content (% w/w)	Disintegration Time (min)			
	Melt granulation with Magnesium stearate	Melt granulation with Talc	Conventional tablet (20% w/v) CS	Melt granulation Tab (without HE)
0	18.4	18.4	8.5	25.4
6.25	22.4	21.5		
12.50	27.8	26.7		
31.25	35.5	34.8		
43.75	50.4	49.0		
50	65.3	63.5		

Note: CS = Corn Starch mucilage; HE = Hydrophobic excipient

The disintegration time of the different formulations of metronidazole tablets is shown in Table 1. These formulations were those of

(i) Conventional metronidazole tablets formulated using 20% w/v corn starch mucilage.

(ii) Metronidazole tablets formulated with melt granulation using carnauba wax without hydrophobic excipients;

(iii)Metronidazole tablets formulated with melt granulation using carnauba wax and different concentrations (0, 6.25, 12.50, 31.25, 43.75, and 50% w/w) of magnesium stearate and talc respectively.

Dissolution test profiles. The results of the dissolution profiles of the different batches of metronidazole tablets are shown in Figures 1, 2, and 3 respectively.

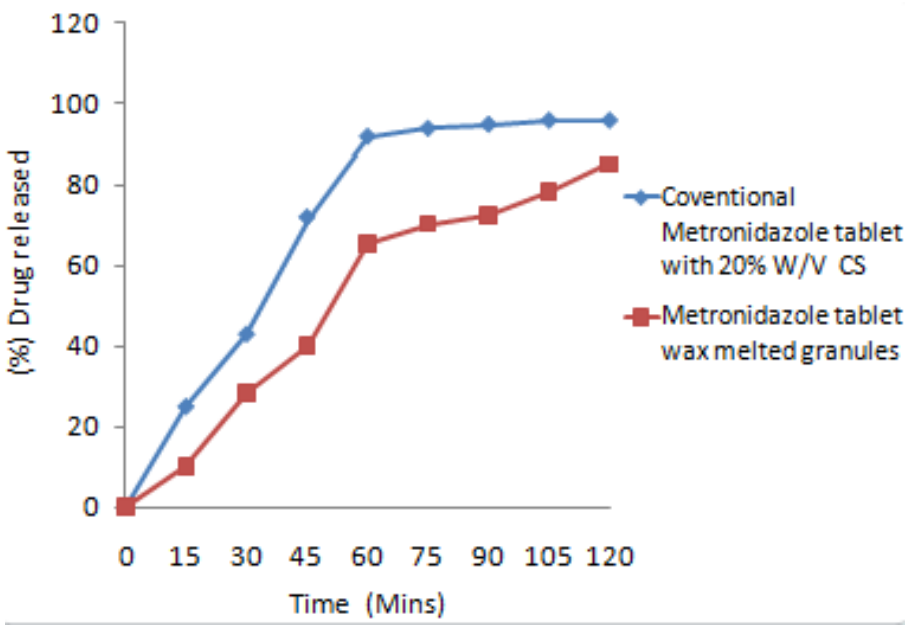

Figure No. 1: Dissolution profile of conventional and wax melted (without HE) metronidazole tablets

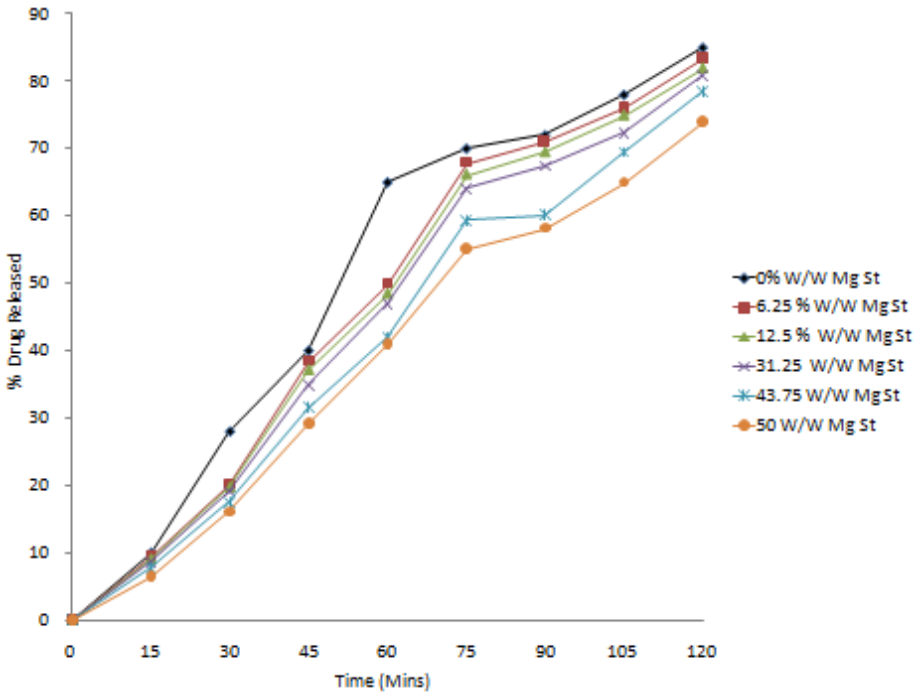

Figure No. 2: Dissolution profiles of melt granulated metronidazole tablets with magnesium stearate

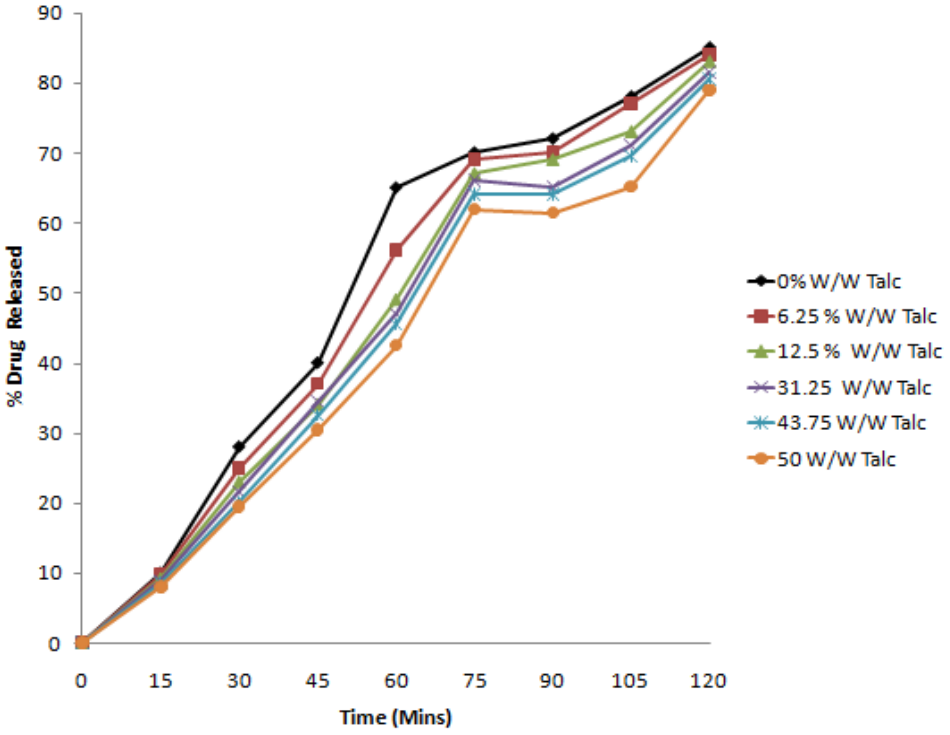

Figure No. 3: Dissolution profiles of melt granulated metronidazole tablets with talc

DISCUSSION:

The effect of melt granulation on the disintegration time (min) of metronidazole tablets is shown in Table 1. The melt granulated formulation showed a prolonged disintegration time of the tablet. While conventional tablets disintegrated within the mean of 8.5 min, that of melt granulated tablets without hydrophobic excipient disintegrated within the mean of 18.4 min. However, with the inclusion of magnesium stearate and talc; there was a proportional increase of the disintegration time with an increase in the concentration of the hydrophobic excipients (Table 1). From the release profiles, the conventional metronidazole tablet attained its maximum release of 96% in 105min and the release rate was 0.91% min^{-1}. After melt granulation with carnauba wax (without HE), it took 120 min to release 85% of its drug, at an average release rate of 0.71% min^{-1}.

Effect of inclusion of hydrophobic excipients (magnesium stearate and talc) on the drug release profiles of metronidazole tablets. The results on the effect of inclusion of hydrophobic excipients on the drug release profiles of the melt granulated tablet formulations are presented in Figures 2 and 3 respectively. The results revealed that there is progressive retardation in the release patterns and hence the rates, following the inclusion of a

hydrophobic excipient. This exhibited an inverse proportion to the concentration of the hydrophobic excipient. However, the inclusion of a hydrophobic excipient in the formulation of metronidazole tablets beyond a concentration range of between 1.25 – 43.75% w/w may not be able to release enough of the drug necessary to elicit the pharmacological effect at the target site(s) within the expected time. The dissolution pattern in Figures 2 and 3 showed that magnesium stearate and talc were equivalent in delaying drug release from metronidazole tablets. It has been reported by previous authors[6,7], that the melt granules are more suitable for prolonged-release formulations. A major attribute of the hydrophobic excipients in the further retardation of the release of drugs is due to the water-repellent characteristic of the excipients. This prolongs the disintegration time of the tablet compact into its constituent particles before dissolving and going into solution in the body fluids[11,12].

CONCLUSION:

This study has revealed that drug release from melt granulations could be essentially modified by the intragranular inclusion of hydrophobic excipients (magnesium stearate or talc) to accomplish retardation of drug release. This formulation approach then provides a way of further controlling drug release from melt granulations. This formulation approach can find application in the design of multi-unit dosage forms where the prompt release will come from the conventional granules and then a sustained release from the melt granulated particles. Metronidazole is a drug with short, biologic half-life; hence this formulation approach has been found suitable as demonstrated from the results of this study. Thus metronidazole tablets could then be given twice daily instead of the conventional thrice daily administration. This will enhance patient compliance and acceptability.

CONFLICT OF INTEREST:

We the authors of this research article hereby declare that there is no conflict of interest whatsoever in this research work, whether financial or commercial.

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