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DEXTROMETHORPHAN HYDROBROMIDE EXTENDED-RELEASE TABLETS PREPARED BY HIGH SHEAR WET GRANULATION

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ABSTRACT

The present study aimed to investigate the effect of wet granulation using a high shear mixer on dextromethorphan (DM) produced granules properties. The effect of Carbopol 71G-NF, HPMC K15M and CMC on DM release from the prepared granules after tableting was also studied. DSC showed that the drug endothermic peak was seen in its melting range with the corresponding physical mixtures indicating no interaction between DM and the tested excipients. This was also confirmed by FTIR results. The angle of repose for all granule mesh cuts ranged from 31.6° to 33.5° indicating good flowability, which was confirmed by the results of Carr's index and Hausner ratio. The average content for all granule sizes ranged between 98.5 to 108% of the theoretical content implying good content uniformity. DM release from tablet formulations in phosphate buffer pH 6.8 revealed that formula F1, which is compressed granules with no polymer added, showed immediate release. The addition of 20 % Carbopol resulted in extended release tablets that approaches nearly zero order release kinetics. Using a combination of Carbopol 10% and CMC 10% showed anomalous non-fickian release pattern with more extended release. However, a combination of Carbopol with HPMC lead to more sustained release that is controlled with Higuhci diffusion model. Repeating the release experiments in biphasic media (pH 1.2 for 2 h then in pH 6.8 for up to

24 h) showed extended release behavior with an increase in the release rate constant for all formulations.

1. INTRODUCTION

Pharmaceutical tablets represent the most popular drug delivery system. They have numerous advantages like relatively easy to manufacture, convenience of dosing and stability. Moreover, high patient compliance is expected due to their appealing appearance and the ease of use.[1] In the pharmaceutical industry, the preferred tablet production method is direct compression technique. However, it is often necessary to improve the material's compaction and flow properties to obtain uniform die filling and to produce tablets of adequate quality. These properties are commonly enhanced by converting fine powders into large agglomerate by the process of wet or dry granulation.[2] Wet granulation is traditionally used and performed by spraying a liquid binder onto the particles while they are agitated in a tumbling drum, a fluidized bed, a high shear mixer or similar devices.[3] High shear wet granulation is one of the most commonly used techniques. The main objectives of this process are to improve the flow and compressibility characteristics of the particles as well as final product homogeneity.[4] Among the different methods, high shear mixers are classically used for wet granulation because they provide granules with a high density and a high strength in a short granulation time.[5,6] Classically, the high shear wet granulation process is divided into three distinct stages: (i) wetting and nucleation where granulating liquid contacts the powder to form nuclei; (ii) granules grow from nuclei primarily due to intergranular collisions and consolidation; and (iii) attrition and breakage of granules due to impact, wear, or compaction.[7,8] These mechanisms control the obtained granule properties and are influenced by a combination of formulation design and process design.[9] However, one of the most important necessities for granulation is to ensure homogeneity of the formulation ingredients, especially in case of low dosage products. The wet massing of the ingredients should result in granules that are homogeneous in content. They are expected to contain the active pharmaceutical ingredient (API) and the excipients in the same proportion as the original bulk mixture. Thus, despite the ability of some formulations to be directly compacted (due to good compaction characteristics and flow properties), they are granulated to improve confidence in content uniformity.

The most important process variables studied using high shear mixers for granulation were the main impeller speed and the wet massing time[10,11] Additionally, in a previous study,

Mahrous et al., studied the effect of dry mixing time of the powder blend prior to granulation with fixation of the main impeller speed and the wet massing time in an attempt to clarify the importance of this process factor and its impact on the content uniformity of chlorpheniramine maleate.[12] Another important factor of wet granulation is the selection of the binder and its concentration where the effect of various binders on wet granulation has been studied.[13] An example is polyvinyl pyrrolidone (PVP) that was found to produce granules and subsequent tablets exhibiting good physical properties.[14]

It is worth noting that technological advancements in the area of matrix formulation have made controlled release product development much easier than before and have improved the feasibility of delivering a wide variety of drugs with different physicochemical and biopharmaceutical properties.[15] Drug release usually occurs by diffusion and/or erosion of the matrix system[16] and both hydrophilic and hydrophobic polymeric matrix systems are widely used to provide sustained delivery of drug substances. Hydrophilic polymers that are well known and widely used as excipients for extended-release formulations include hydroxypropyl methylcellulose (HPMC), alginate and xanthan gum.[17] When a matrix containing swellable glassy polymer comes in contact with an aqueous medium, there is an abrupt change from a glassy to a rubbery state, which is associated with the swelling process.[18,19] Carbopol® resins are crosslinked polyacrylic acids that hydrate in the presence of water and the carboxylic acid groups in the molecules can dissociate in aqueous systems.[20] The negative charges on the polymer backbone repel each other to cause marked polymer expansion.[20] Although Carbopol has many advantages as a candidate for an extended-release matrix tablet, there are only few reports on its application in such dosage forms. Khan and Zhu[21] reported that Carbopol 974P can enhance the controlled-release properties of slightly water-soluble drugs such as ibuprofen, and it can form strong matrices because of its inherent crosslinked structure.

Dextromethorphan hydrobromide (DM) is a nonnarcotic antitussive agent generally used as an ingredient in cough and cold remedies. The dosage of the drug is usually three to four times a day because of its short half-life (2.7 h). Therefore, DM sustained release dosage forms were developed to avoid repeated administration and increase patient compliance.[22] Sakr and coworkers[23] reported that extended-release DM matrix tablets were developed using HPMC K100LV/ methacrylic acid copolymer (Eudragit® L100-55) combination and polyvinyl acetate–povidone (PVAP). Both selected extended-release DM matrix tablets

followed the square root of time-dependent kinetics for drug release, indicating a diffusion-controlled release mechanism. In another study, Sakr and coworkers[24] reported that the selected extended-release HPMC/Eudragit and PVAP DM tablets were not bioequivalent to the marketed capsule product, Tuss Hustenstiller Retardkapslen®. However, the tablets had higher bioavailability as shown by the area under the curve (0 - ∞).

The present study aimed to investigate the effect of wet granulation using a high shear mixer on the produced granules properties. Furthermore, the effect of Carbopol 71G-NF, HPMC K15M and CMC on the release of DM from the prepared granules after tableting was studied.

MATERIALS

Dextromethorphan hydrobromide (DM) was kindly supplied by RIYADH PHARMA (Riyadh, Saudi Arabia). Carbopol® 71G-NF (MW, 2,376,000 Da) was kindly donated from Lubrizol Advanced Materials, Inc. (Cleveland, OH). Methocel® K 15M (MW, 10,000 Da) Premium CR Grade (HPMC) was obtained from Colorcon (England), Avicel PH 101 (FMC biopolymer, Ireland), Povidone (PVP K90) (GAF chemicals Corp., USA). Carboxymethyl cellulose (CMC) and Sodium stearyl fumarate (SSF) was purchased from Riedel-de Haën (Seelze, Germany).

Methods

Compatibility studies

Differential scanning calorimetry (DSC)

DSC scans of DM, the individual solid components and their corresponding physical mixtures were performed. In an aluminum pan, the samples (3-5 mg) were hermetically sealed and heated at a steady rate of 10 °C/min, over a temperature range of 25 °C to 160 °C. Test thermograms were collected using calorimetric differential scanning (DSC-60, Shimadzu, Japan). The thermal analytics data were collected using a TA 50I PC device with software programs from Shimadzu. The DSC temperature and enthalpy scale is measured using an indium standard. N_2 was used as purging gas at a rate of 40 ml/min.

Fourier transform infrared (FTIR) spectroscopy

FTIR spectra were registered on the Perkin Elmer FTIR (Perkin Elmer FT-IR, USA) instrument. Samples were primed as KBr pellets and screened against a blank backdrop of KBr pellets at a wave number of 4000 - 650 cm^{-1} with a resolution of 1.0 cm^{-1}. The data were evaluated using the Perkin Elmer (Spectrum V5.3.1) program.

Preparation of granules

The procedure was based on previously published data.[25] The wet granulation of DM powder was performed using povidone as a binder and water as a granulating agent. Granulation of DM and excipients was done through the following procedure: The high shear mixer with the Gentelwing mechanism (Mycromix, Oyster Huttlen, Germany) was charged with 250 g of the powder blend (15 g DM, 5 g PVP and 230 g avecil pH101). The powder was mixed at the main impeller speed of 200 rpm and a chopper speed of 2500 rpm for dry mixing time of five minutes prior to the addition of the granulating solution (Distilled water, 250 ml at 50 ml/min). The powder was then granulated with the granulating solution for a fixed time of 4 min. The wet mass was then transferred and screened through a 2 mm screen. The resulted granules were dried in the oven overnight at 50 °C. The moisture content of the granules was determined using moisture balance (Mettler PM 480 Deltarange, model LP 16) and was kept around 1% for all formulations. The dried granules were then removed, sized and stored for subsequent evaluation and tablet compression.

Tablet preparation

For each formula, part of the produced granules (mesh cut 0.8/0.3 mm) was compressed into tablets after mixing with polymer as shown in table 1 using an Ereweka tablet press; model EKO with concave 11 mm punches. The compression force was kept constant and the tablet was adjusted to the specified weight.

Granule evaluation

1. **Sizing:** The produced granules were sized by passing through a 2 mm screen opening sieve and received on 1.7, 1.2, 0.8 and 0.3 mm screen opening sieves.
2. **Granule flowability:** The flow properties of the granules were determined by measuring the angle of repose.

   $\theta = tan^{-1} h / r$
3. **Granulation bulk / tapped density:** Bulk and tap densities were determined using a 100 ml graduated cylinder. The bulk density was measured by carefully pouring the material into a pre-weighed 100 ml graduated cylinder and was calculated by dividing the weight of the material (g) by the volume (ml) occupied in the cylinder. The filled cylinder was then placed on the Vankle tap density tester and tapped to a constant volume. Both bulk and tapped densities were measured. In addition, the flow properties were evaluated using Carr's index and Hausner ratio measurements.

$$Hausner\ ratio = \frac{Tapped\ density}{Bulk\ density}$$

$$Carr's\ Index = \frac{Tapped\ density - Bulk\ density}{Tapped\ density} \times 100$$

Tablet evaluation

1. Tablet hardness

Tablet hardness was measured using a hardness tester (Erweka TBH-28, Germany). The crushing strength of 10 tablets with known weight and thickness of each was recorded in Kp. The average hardness, standard deviation (SD), and relative standard deviation (RSD) were reported.

2. Tablet friability

Twenty tablets were selected from each batch, dedusted and weighed. Each group of tablets was rotated at 25 rpm for 4 min in the friabilator (Eletrolab EF-2 USP, India). The tablets were then dedusted and reweighed to determine the loss in weight. Friability had been calculated as percent loss in weight.

3. Content uniformity

Content uniformity test for each batch was conducted using the USP procedure as follows:

Each of ten tablets was accurately weighed, finely powdered, and transferred into a volumetric flask. About 40 ml of 0.1 N HCl was added, sonicated for 10 min, then shaken by mechanical means for 30 min. The volume was then completed to 50 ml with the same solvent, sonicated and filtrated using Millipore filters. The drug content was determined spectrophotometrically at 278 nm. The test was repeated on individual ten tablets and the average content ± SD as well as the acceptance value (AV) was presented.

In vitro drug release

In vitro drug release was performed over a 12-h period using an automated dissolution tester (LOGAN Instrument Corp., Somerset, NJ) coupled to an automated sample collector (SP-100 peristaltic pump, Somerset, NJ). The USP 24 (apparatus 2) paddle method was used at 100 rpm. The dissolution medium was 0.1 N HCl (pH 1.2) with a volume of 750 ml for the first 2 h, after which, 250 ml of 0.2 M tribasic sodium phosphate was added to give a final pH of 6.8

and maintained at 37 ± 0.5°C. A minimum of six tablets per batch were tested and the mean value of the % DM release was plotted against the time interval.

Analysis of the release data

The release data were kinetically analyzed using different kinetic models (Zero order, first order and Higuchi diffusion model) to determine the mechanism of drug release from the different formulations. To determine the release model which best describes the pattern of drug release, the in-vitro release data were fitted to zero order, first order and diffusion controlled release mechanisms according to the simplified Higuchi model.[14]

a. Zero-order Kinetic model

$C = C_o - K_o t.$

b. First Order Kinetic model

$\text{Log } C = \log C_o - Kt/2.303$

c. Higuchi diffusion model

$Q = 2 C_o (Dt/\pi)^{½}$

Where

C_o = initial drug concentration

C = drug concentration (released) at time t.

T = time of release

Q = amount of drug released/unit area

K_o = zero order rate constant, K = first order rate constant and D = diffusion Coefficient and it was calculated according to the following equation.

$D = (\text{Slope}/2C_o)^2 \pi$

Table 1: Tablet formulations.

Formula	DM granules mgs (0.8/0.3)(Contains 6% DM)	Carbopol(mg)	CMC (mg)	HPMC (mg)	SSF %	Tablet weight (mg)
F1	500				10	510
F2	500	128			12	640
F3	500	64	64		12	640
F4	500	64		64	12	640
F5	400 + 100 (bilayer)	128			12	640

RESULTS AND DISCUSSION

Spectrophotometric assay of DM

DM was determined spectrophotometrically at λ_{max} of 278 nm where the calibration curve was constructed. A linear relationship between the absorbance and the concentration of DM in phosphate buffer pH 6.8 at 278 nm was obtained in a concentration range of 25 - 200 ug/ml. The regression equation is y = 0.0057 x and r value is 0. 9939.

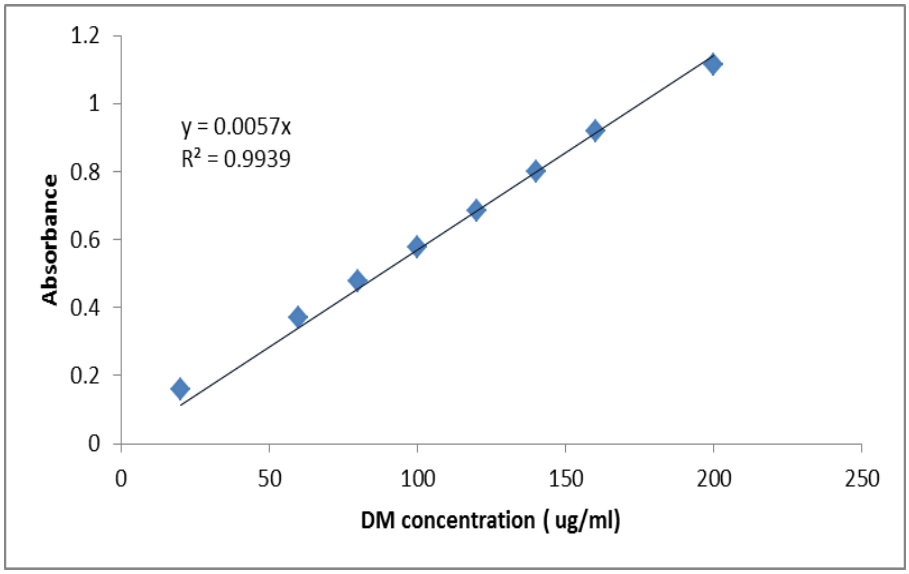

Figure 1: Calibration curve of DM in phosphate buffer pH 6.8.

Differential scanning calorimetry

Differential scanning calorimetry (DSC) was used by studying the thermal activity of the preparations to measure the melting point, crystallinity, decomposition and drug-excipient interactions.[28] DSC scan on the DM, the excipients and their related specific physical mixtures were performed. The Untreated DM DSC scan displayed a typical endothermic peak at 123 ^{o}C (Figure 2 & 3), referring to its melting point. None of the evaluated additives had characteristic peaks inside the observed temperature range (Figure 3 A-E). The drug endothermic peak was shown in its melting range (Figure 2) with the corresponding physical mixtures. This means that there is no interaction between DM and the tested excipients.

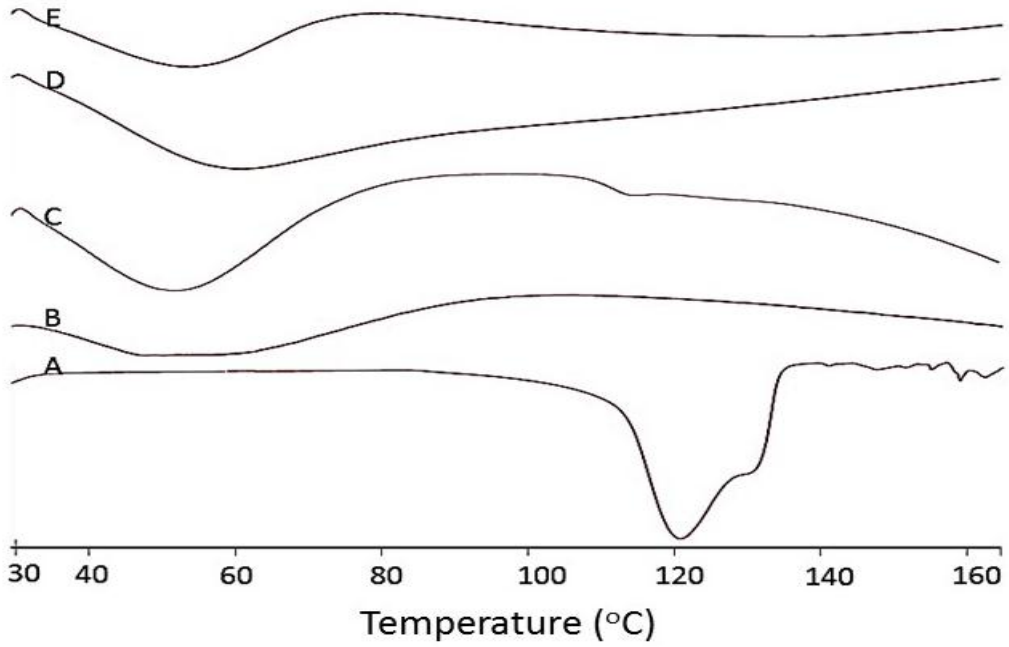

Figure 2: DSC thermograms of the drug and the tested excipients: (A) DM; (B) Microcrystalline cellulose (MCC); (C) Carbopol; (D) Sodium carboxy methylcellulose (Na CMC); (E) Hydroxyprobyl methyl cellulose (HPMC).

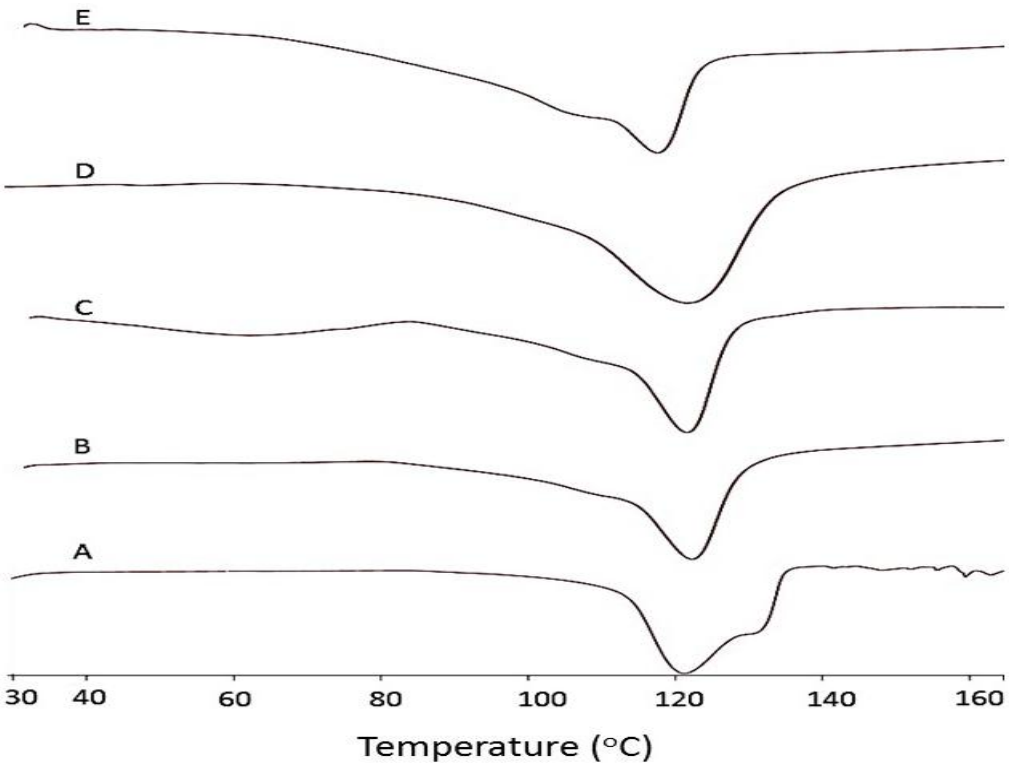

Figure 3: DSC thermograms of DM and its physical mixtures with the tested excipients: (A) DM; (B) DM: MCC; (C) DM:Carbopol; (D) DM:NaCMC; (E) DM:HHPMC.

Fourier transforms infrared spectroscopy (FTIR)

FTIR spectra of DM, the tested excipients and their physical mixtures were recorded to determine whether there were any chemical interactions between them. Figure 4 displays the FTIR spectra of DM and the tested excipients in the solid single form. DM spectrum shows prominent absorption bands at 2165 and 2590 cm^{-1}, corresponding to the NH^{+} stretching vibration in the tertiary amine group of the drug.[29] Figure 5 shows the FTIR spectra of DM and its physical mixtures with different excepients. All of the principal absorption beaks of DM appeared in the physical mixture at the same positions. No additional peaks were observed in case of the physical mixtures. These results indicate that there is no interaction between DM and the tested excipients.

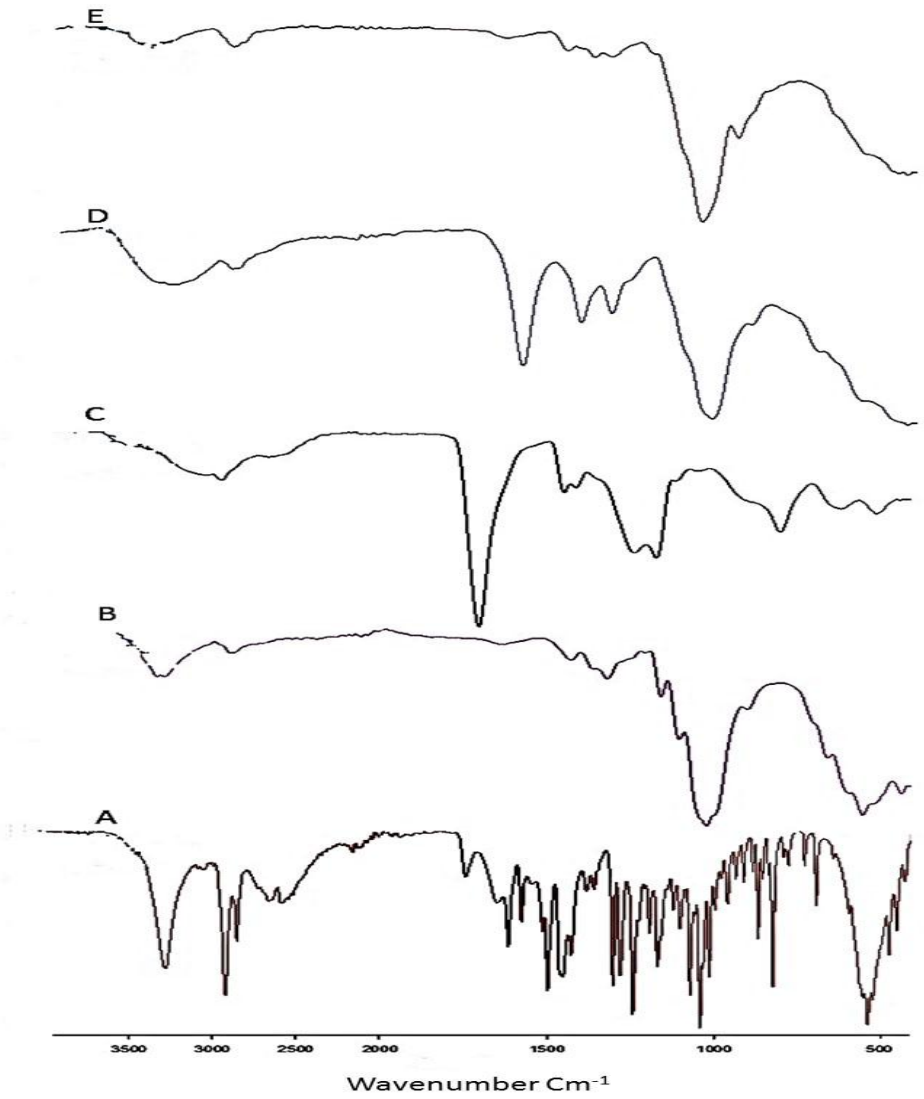

Figure 4: FTIR spectra of the drug and the tested excipients: (A) DM; (B) MCC; (C) Carbopol; (D) Na CMC; (E) HPMC.

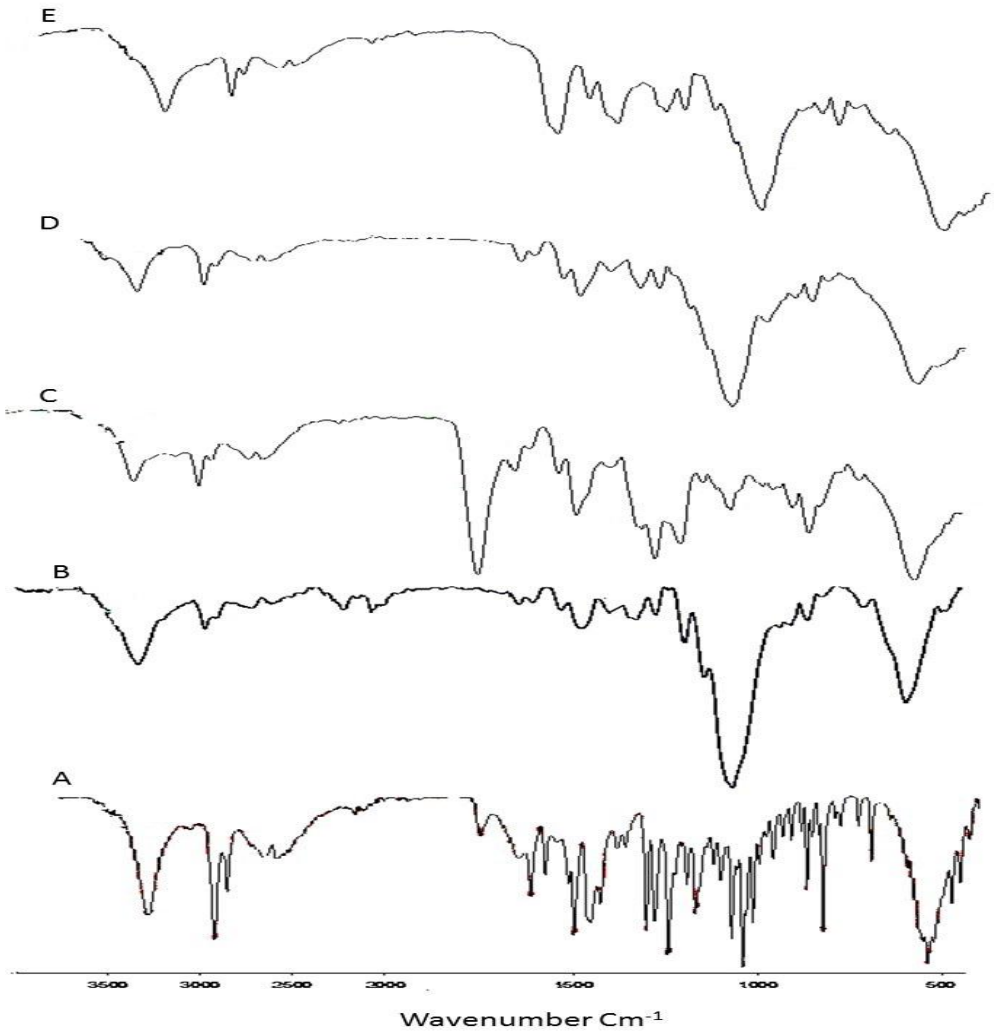

Figure 5: DM and its physical mixtures with the tested excipients: (A) DM; (B) DM: MCC; (C) DM: Carbopol; (D) DM Na CMC; (E) DM:HHPMC.

Granule size distribution (GSD)

GSD of the un milled dried granules was characterized by sieving. Gentle-wing granulator is a new vertical high-shear granulator which is available in laboratory and production scale sizes, as either a bottom-driven or a top-driven unit.[26] The gentle-wing technology applies the principle of a positive displacement impeller for blending a non-Newtonian medium. The impeller configuration matches the contour of the mixing container, and its angled impeller plate ensures a forced mixing of the product and reduced wall caking. Rather than using the impulse of an impeller for mixing, the Gentle-wing's uniform distributes the mixing energy throughout the product container at lower speeds and higher torque, evenly throughout the

product. Thus, this will reduce segregation issues typically caused by high dynamic forces of traditional high-shear granulators.[26,27]

Granule evaluation

Angle of repose

The angle of repose is one of the most common techniques to assess powder flowability. The angle of repose for all granule mesh cuts ranged from 31.6° to 33.5° indicating good flow. This good flowability was confirmed by the results of Carr's index and Hausner ratio (Table 2).

Table 2: Granule characterization.

Granule's size (mm)	Carr's Index (%)	Hausner Ratio	Angle of repose (degree)	Average content (%)	d(0.9) (um)
0.3/0.8	6.49	1.07	31.61	98.5	720
0.8/1.2	10.13	1.11	32.83	104.2	1100
1.2/1.7	15.07	1.18	33.69	107	1580
1.7/2	14	1.14	33.5	108	1800

The average content for all granule sizes was ranged from 98.5 to 108% of the theoretical content implying good content uniformity.

Figure 6 shows the dissolution of different granule mesh cuts. It is clear that all particle sizes exhibited complete DM release in less than 1 h.

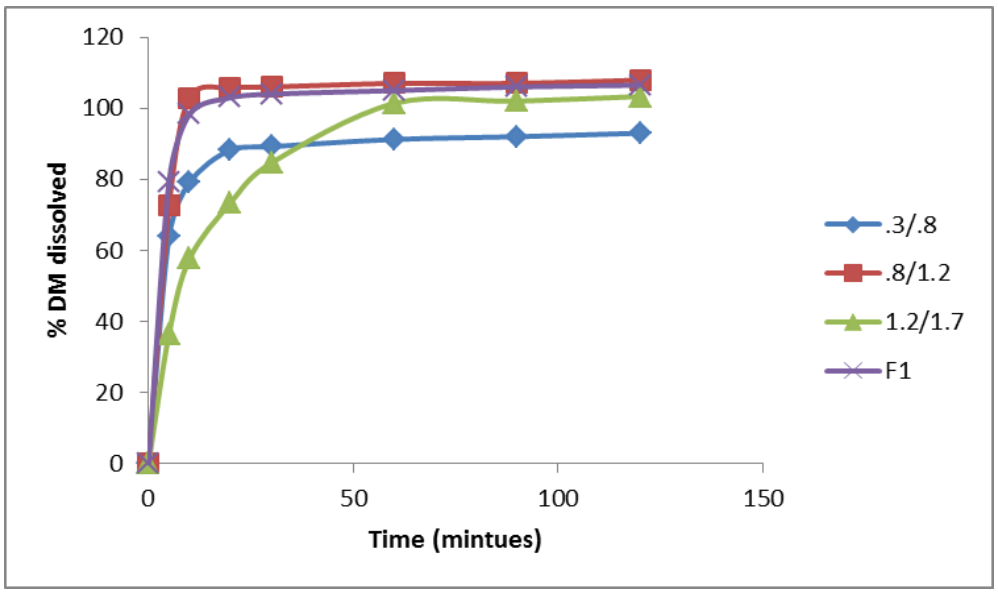

Figure 6: Dissolution of DM from different granules and from F1 tablets.

Tablet evaluation

Table 3 shows the physical characteristics of the tablet formulas. All formulations showed acceptable hardness (4.7 - 6.5 kp), acceptable friability (less than 1%) and good content uniformity with acceptance value (AV) less than 15.

Table 3: Tablets characterization.

Formula	Hardness (Kp)	Friability (%)	Average content (%)	SD	AV
F1	6.5	0.4	100.5	2.1	5.04
F2	6.2	0.4	103.1	2.5	7.4
F3	5.5	0.6	104.4	2.4	5.76
F4	4.8	0.8	105.2	2.3	9.32
F5	4.7	0.9	104.5	2.5	9.0

Drug release studies

DM release from tablet formulations (F1-F4) in phosphate buffer pH 6.8 is presented in figure 7. From this igure and Table 4 it could be concluded that F1, which is composed of compressed granules with no polymer added, showed immediate release. The addition of 20 % Carbopol resulted in extended release tablets that approaches nearly zero order release kinetics.

Using combinations of Carbopol 10% and CMC 10% showed anomalous non-fickian release pattern with more extended release, however, combination of Carbopol with HPMC lead to more sustained release controlled with Highchi diffusion model.

Repeating the release experiments in biphasic media (pH 1.2 for 2 h then in pH 6.8 for up to 24 h) showed extended release behavior with an increase in the release rate constant for all formulations (Table 4 and Figure 8). This could be attributed to the fact that the gel layer formed around the tablet became stronger with less region of microviscosity in the swollen tablets as a result of the anionic character of Carbopol. It is worth mentioning that drug release from Carbopol matrices is medium dependent. At low pH (the first 2 h.), the release of the drug was fast because the polymer was not fully swollen and there were larger regions of microviscosity. At pH 6.8 (after pH change of the dissolution medium), the carboxylic groups were ionized and repelled each other causing maximum swelling, resulting in a fewer and smaller region of microviscosity. The rapid gel formation acted as a barrier for the drug diffusion, thus prolonging its release. In addition, the swelling of the tablets could occur as a

result of the hydration of the polymer, which results in a rapid decrease in its glass transition temperature (*T*g = 105°C) to the temperature of the dissolution medium.[30] Increasing the amount of Carbopol in the formulation resulted in sustaining the drug release. This may be due to a reduction in regions of low microviscosity and the closing of micropores in the swollen tablets.[31] Based on the above results, it was found that Carbopol polymers are more effective than cellulosic materials in sustaining the DM release when used at the same levels. Carbopol is a lightly crosslinked polymer, unlike the cellulosic materials, which are linear. In matrix tablets prepared with linear hydrophilic polymers (such as HPMC, which do not have a covalently crosslinked structure), a gelatinous layer is formed on the surface of the tablets on hydration. On the other hand, the crosslinked network of Carbopol enables the entrapment of the drug in the hydrogel domains. These hydrogels erode in a manner slower than that occurs in case of linear polymers.[32] Interestingly, the combination of Carbopol and HPMC significantly ($P < 0.05$) retarded the release of DM. These data showed that a combination of anionic polymer (Carbopol 71G-NF) and nonionic HPMC produced a synergistic effect. This is in accordance with a previously published data.[25] To enhance the release from F2 in the first hour, bi layer tablets were prepared (F5) that contains components of F2 in first compression then a second layer of granules was compressed on the formed tablet. The release of DM from F5 was comparable with F3 as shown in Figure 8.

Table 4: Kinetic modeling of DM Release.

Release model		Formula no:-						
		Buffer			pH change			
		F2	F3	F4	F2	F3	F4	F5
Zero order	R	0.996	0.980	0.9690	0.9910	0.860	0.866	0.91
	K_o (mg/h)	11.9	9.35	6.08	6.733	6.32	6.22	8.68
First order	R	0.991	0.9890	0.984	0.997	0.935	0.933	0.982
	K1(h^{-1})	0.085	0.064	0.034	0.044	0.05	0.046	0.09
Highchi diffusion model	R	0.956	0.9760	0.9966	0.985	0.958	0.972	0.985
	($mg/h^{½}$)	30.926	24.8	16.66	20.4	21.4	21.3	28.61
Log M/mas Vis log t	R	0.995	0.946	0.9787	0.996	0.932	0.996	0.978
	n	1.01	0.818	0.536	0.678	0.234	0.293	0.32
Selected model		Approaches Zero order	anamoulas non-fickian release pattern	Highchi diffusion model	anamoulas non-fickian release pattern			

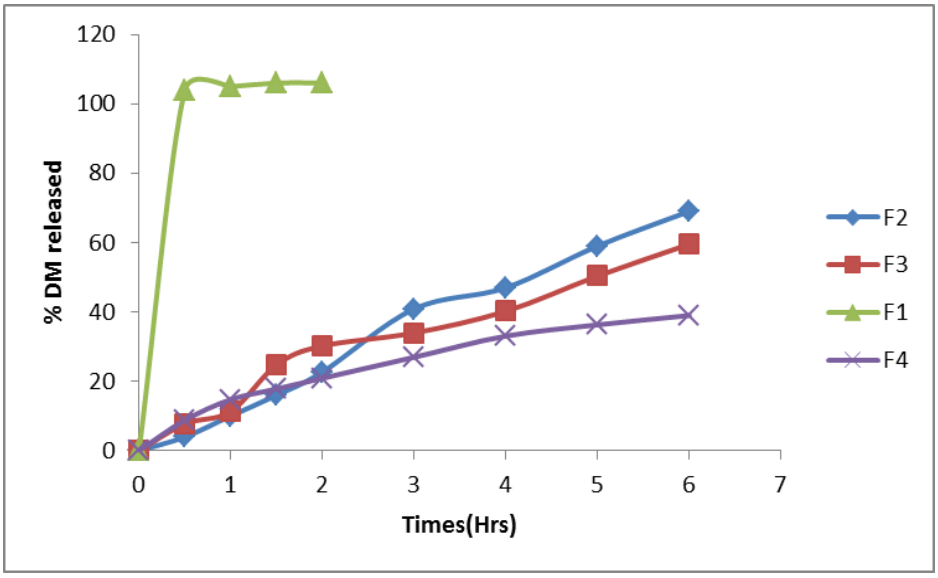

Figure 7: Drug release of DM From tablet formulations (F1-F4 in phosphate buffer pH 6.8.

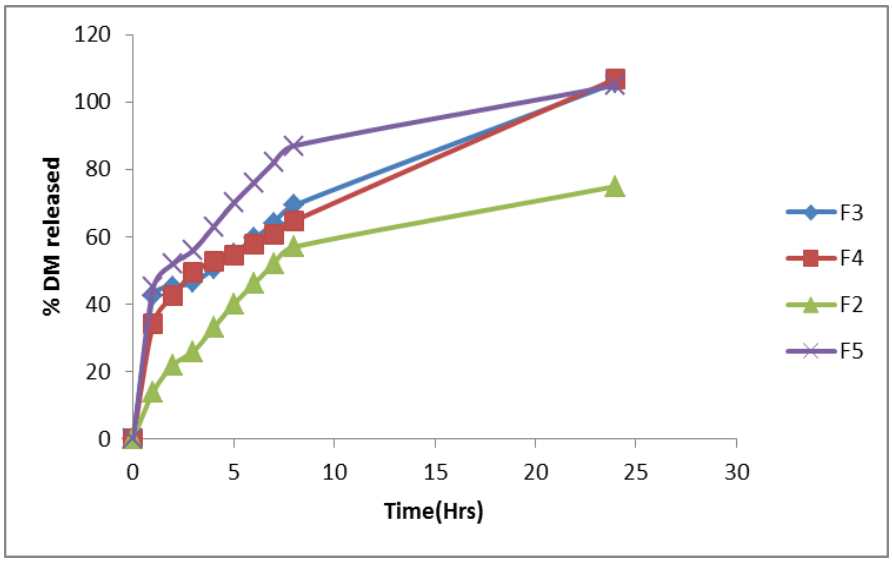

Figure 8: Drug release of DM from tablet formulations (F2-F5) in pH 1.2 and phosphate buffer pH 6.8.

CONCLUSION

The present study investigated the effect of wet granulation using a high shear mixer on the produced granules properties. Furthermore, the effect of Carbopol 71G-NF, HPMC K15M and CMC on the release of DM from the prepared granules after tableting was studied. DSC showed that the drug endothermic peak was shown in its melting range with the corresponding physical mixtures. Indicating no interactions between DM and the tested excipients. FTIR results confirmed that there is no interaction between DM and the tested

excipients. The produced granules showed good flow properties. The average content for all granule sizes ranged between 98.5 to 108% of the theoretical content implying good content uniformity. Drug release of DM from tablet formulations in phosphate buffer pH 6.8 revealed that F1, which is a compressed granules with no polymers, showed immediate release. The addition of 20 % Carbopol resulted in extended release tablets that approaches nearly zero order release kinetics. Using combinations of Carbopol 10% and CMC 10% showed anomalous non-fickian release pattern with more extended release, however, combination of Carbopol with HPMC lead to more sustain release controlled with Higuhci diffusion model. Repeating the release experiments in biphasic media (pH 1.2 for 2 h then in pH 6.8 up to 24 h) showed extended release behavior with an increase in the release rate constant for all formulations.

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