Psyllium as a promising polymer for sustained release formulations in combination with HPMC polymers

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Abstract

Psyllium has a mucilaginous property that makes it a good candidate to be utilized as an excipient in the preparation of controlled release systems. Various formulations were prepared using theophylline as a model drug and investigated with view to achieve an ideal slow drug release profile. The addition of HPMC to psyllium significantly reduced burst release however the percentage of drug release within a 12 h period was too slow and thereby inadequate. This was overcome by the addition of lactose as hydrophilic filler which enabled a slow release with roughly 80% drug release in 12 h. The inclusion of HPMC within psyllium formulations changed the drug release kinetics from Fickian diffusion to anomalous transport. Granulated formulations demonstrated slower drug release than ungranulated or physical mixture and caused a change in dissolution kinetics from Fickian diffusion to anomalous transport. Milled granules showed more efficient controlled drug release with no burst release. Milling of the granules also changed the drug release kinetics to anomalous transport. Although, psyllium was proved to be a promising polymer to control the drug release, a combination of psyllium-HPMC and formulation processes should be considered in an attempt to achieve a zero-order release.

Keywords: Psyllium, Theophylline, HPMC K4M, sustained release, dissolution, hydration, release mechanism and granulation**.**

Introduction

Several oral sustained release formulations have been developed including film coated preparations, osmotic devices, floating systems, bioadhesive systems and matrix systems. These oral preparations can be subdivided into two groups: single (manufactured by coating tablets with release controlling films or soluble polymers) and multiunit (consist of particles or granules of different release profiles that could also be coated with water soluble polymers) preparations. Such formulations have several advantages including being useful for once daily dosing (or a less frequent dosing regimen), beneficial for drugs that can cause local irritations, reduce the incidence of dose related side effects, increase in patient compliance and prolonging the effect of the drug by maintaining a steady concentration in the bloodstream. Polymeric materials are widely used for controlling the release of drugs. Matrix tablets are polymer based delivery systems which enable a slow controlled release of drugs into the body. The swelling of the polymeric networks depends on the composition of the polymer and the pH of the surrounding medium. [1, 2] Drugs that are covalently bound to polymers or dispersed within the polymer matrix are released via diffusion and erosion mechanisms. [3] Researchers have demonstrated that the gel layer formed around hydrophilic matrices, upon its contact with gastro-intestinal (GI) fluids, is eroded allowing drug release. This erosion is the dominant release mechanism for poorly soluble drugs. The other mechanistic approach is that the soluble portion of drug is released through the process of diffusion through the gel layer. [4-7] An increase in the polymer hydrogel concentration increases the viscosity of the gel layer around the tablets, thereby limiting the penetration and release of active ingredient which results in a slower drug release. However, formulations with low levels of polymer concentrations could cause an inconstant release and initial burst of the drug. [8]

Hydroxypropyl methyl cellulose (HPMC) is a synthetic derivative of cellulose and a widely used polymer in the production of sustained release matrix tablets due to its rapid hydration, good compression, gelling characteristics and very low toxicity. [9] There has been a link established between the retarding effects of HPMC to the gelatinous layer formed when the polymer is hydrated by water.[10]

Psyllium could be an effective and cheap therapy for chronic diarrhoea [11], promoting healthy bowel function[12-15] as a bulking agent or laxative[16]. It also acts as a substrate for microbial growth that increases stool mass[17]. Psyllium decreases post-prandial glucose concentrations in men with type II diabetes [18-21]. Recently, psyllium was used for the controlled delivery of peptides such as insulin[22]. It has been shown that psyllium could reduce the concentration of low-density lipoprotein (LDL) and cholesterol in the plasma,[23] and can be used in the treatment of irritable bowel syndrome (IBS),[24-27] maintaining remission in ulcerative colitis,[28,29] and inhibiting carcinogenic processes.[30,31]

Psyllium not only has pharmacological importance but it also can be used to develop drug delivery devices such as sustained release matrix tablets and hydrogels. Psyllium has a characteristic of forming a viscous gel almost immediately when in contact with water and so the drug release rate is controlled quicker.[32] The hydrogel matrix formed by psyllium resists hydrolysis; therefore psyllium can resist colonic bacterial degradation. Therefore, the double potential of the psyllium hydrogel can be used to prepare novel drug delivery systems.[33] Psyllium is also relatively safe with low toxicity [34] cost effective, [35-38] and has global consumer acceptance having been used for hundreds of years in traditional medicines and products and it has been approved by the FDA.[39] Several researchers have modified psyllium husk powder to improve its application in drug delivery systems. Gohel *et al.* [40] modified psyllium husk powder

with tartaric and succinic acid to develop a suitable sustained release tablet for diltiazem HCl via direct compression. The treated psyllium husk powder showed better gelling and swelling characteristics. Kaith and Kumar[41] modified psyllium with acrylic acids using potassium persulphate and hexa- methylene tetramine (KPS-HMTA) to optimize the polymer gel. They found the gel produced to be pH and temperature sensitive and selective towards water absorption from oil-water emulsions. Singh *et al.* [33] modified psyllium hydrogels by using acrylic acid and radiation. They showed the psyllium hydrogels developed to have the capability to be used as double potential drug delivery devices in the colon and to provide drug release in a controlled and sustained manner. Siahi-Shadbad *et al.* [42] evaluated the release behaviour of propranolol HCl from psyllium matrices in the presence of HPMC K4M, sodium alginate, sodium carboxy methylcellulose (NaCMC) in different concentrations on the drug release from psyllium matrices. They found that binary mixtures of psyllium and HPMC, psyllium and sodium alginate and NaCMC and psyllium in various ratios caused a significant decrease in the release rate of propranolol HCl. As the type of filler can change the drug release profile, in the present study the authors focused on the effect of the type of filler on the drug release from tablet matrices containing psyllium. The present research work further investigated the effect of granulation and milling on the performance of psyllium in controlling the drug release in tablet matrices.

Theophylline (1,3-dimethyl xanthine) is a potent methylxanthine bronchodilator widely used in the treatment of asthma, chronic obstructive airways disease (COAD) and bronchospasm in adults. For drugs such as theophylline, it is beneficial to have a steady plasma concentration over night to reduce symptoms experienced early in the morning, hence preparation a sustained release formulation for theophylline is highly beneficial. [43-46]

In the present study, theophylline was chosen as the model drug for evaluating the polymer psyllium for sustained release. Lactose and Emcompress^{R} (dicalcium phosphate dehydrate) were used as two examples of hydrophilic and hydrophobic fillers respectively. The key aim of this project is to show promising release behaviour of drug in the presence of psyllium under different processing conditions.

Materials and methods

Materials

Theophylline anhydrous, potassium phosphate monobasic and calcium phosphate dibasic dihydrate (Emcompress) were purchased from Acros Organics, USA. Sodium hydroxide and Magnesium stearate were obtained from Fisher Scientific, UK. HPMC K4M Premium and psyllium (>99% purity) were supplied by Colorcon, UK and Shiv Psyllium Industry, India respectively. Micronized lactose was generously supplied by DMV International, Netherland. Phosphate buffer (pH 6.8) was prepared according to the USP method.

Psyllium husk milling

The psyllium husk was milled for 15 min using a Ball mill (Pulverisette, RS232, Fritsch) at 400 rpm to reduce the particle size. The Ball mill rotates around a horizontal axis and thereby the stainless steel balls cause an internal cascading effect which reduces the husk into a fine powder.

Preparation of powder mixtures

The preparation of physical mixture formulations was studied as listed in Table 1. The weight and composition of the powder mixture ratios for the granulation process are listed in Table 2. The powders for each formulation were mixed in a Turbula® (Type T2 C, Switzerland) blender

for 10 min, after which the equivalent weight of the 1% Magnesium stearate as listed in Tables 1 and 2, was added as a lubricant. The contents were then mixed for a further 5 min.

Wet granulation

Following theophylline-polymers mixing, 7 mL of distilled water was added using a pipette (10 ml borosilicate pipette was used). Using a pestle and mortar, this was ground into a paste. The paste was then sieved using a 1 mm sieve to produce granules which were then transferred into the drying oven set at 65 ºC for 1 h. The second method used for granulation was similar to the first method; however, the active drug theophylline was not added to the initial mixture. The polymers were first granulated and dried in the oven, then theophylline was added, and the contents were mixed for 10 min in the Turbula mixer. Only 4 mL of distilled water was used for the granulation of the polymers with Emcompress® and lactose. In the final method, the granulation steps stated above were repeated; however, the granules produced were milled for 10 min in the ball mill. The milling and granulation processes bears relevance in industry, as such, the authors believe the employed methodology has application in industry on a large scale.

Tablet Preparation

Tablets, 10 mm round concave, with target weights as detailed in (Tables 1 and 2) were weighed and were compressed using a single punch tableting machine (Model MTCM-1, Globe Pharma, US) at 2000 psi (7.65 kN). The die wall was lubricated each time after tablet compression with a 1% w/v suspension of magnesium stearate in acetone to enable easy ejection of the tablets from the die. The mean tablet weight was 405.2 ±1.0 mg.

Dissolution Testing

The *in-vitro* dissolution tests were performed on the USP dissolution apparatus 1 (basket method) (Varian Auto Sampler, VK 7010), using 900 mL phosphate buffer (pH 6.8) with a rotation speed of 100 rpm. The temperature of the dissolution medium was maintained at 37.2±0.1 ºC. Agitation was stopped after a 12 h period. Theophylline released was measured at 271 nm using a UV/Visible spectrophotometer (Varian, Cary 50). Each dissolution data point represents the mean of minimum three dissolution runs.

Release Kinetics

The kinetics of drug release was analyzed using Peppas equation (the equation below) [47] as detailed previously. [48]

$$\mathbf{Q=kt^n}$$

Where Q is the fraction of drug release in time t, k is the rate constant incorporating characteristics of the macromolecular network system and the drug, and n is the diffusional exponent (for more details refer to discussion section).

Differential Scanning Calorimetry (DSC)

This was performed as detailed previously.[49] In this study the flat faced 4 mm mini tablets with a target weight of 20 mg were compacted at 2000 psi (7.65 kN). Due to the poor compactability of psyllium's mini tablets, a mixture of 50 % psyllium and 50 % HPMC was utilised. The discs were hydrated for 10 minutes using 25 mg of phosphate buffer (pH 6.8) in a standard aluminium pan sealed with a lid. The aluminium pans were firstly cooled down from ambient temperature (25^{o}C) to -30^{o}C at 55^{o}C/min in order to freeze any unbound (free) water; then kept at -30^{o}C for 5

minutes for equilibration to occur and heated up again from -30^{o}C up to 50^{o}C at 10^{o}C/min under nitrogen gas to determine the amount of free and bound water using endotherm scanning of the melted free water. The reference standard using phosphate buffer (pH 6.8) was prepared using 25 mg of phosphate buffer (pH 6.8) in standard aluminium pan sealed with a lid and allowing it to go through the same process as the hydrated disks. The integration of the endotherm represented 100% free water. From this deduction, bound and free water were determined. All these experiments were performed in triplicate.

Scanning Electron Microscopy (SEM)

The psyllium husk and the ground psyllium were coated with gold using an ion sputter coater. The coated samples' morphologies were then viewed using a SEM (Stereoscan 360 – Edward sputter coater-gold coater, S150B, Cambridge instruments UK LTD) operating at 10 kV. Micrographs were taken at different magnifications.

Results and discussion

Dissolution

Release profiles of theophylline from physical mixtures composed of psyllium:theophylline or psyllium:HPMC:theophylline are depicted in Figures 1-a and 1-b respectively. There was a reduction in theophylline release with an increase in psyllium concentration (Figure 1-a). The increase in psyllium content also was able to supress the initial burst release observed (Figure 1-a). For example, the burst release of theophylline decreased from 58% when the polymer content was at 33.3% to 23% drug released when the polymer level increased to 50% (Figure 1-a). Interestingly, the inclusion of HPMC to the physical mixture of theophylline and psyllium improved the quality of the tablets and drug release profiles with the burst release of the drug

being significantly reduced **($p<0.05$)** (Figure 1-b). For example, the incorporation of 12.5 % HPMC reduced the burst effect seen for the 50% psyllium from 28% (Figure 1-a, 50% psyllium-50% drug) to 7% (Figure 1-b) and further additions of HPMC reduced it further to 3% (Figure 1-b).

The tablets made of granulated psyllium had a very similar drug release profile to the one where psyllium and theophylline were granulated together (Figure 1-c). This suggests that there is a change in the polymer and perhaps better uniformity that leads to better dissolution profiles. Figure 1-c implies that the effect of the addition of HPMC to the psyllium formulation and using granulation techniques at the various ratios also demonstrated a release profile similar to zero-order (n values for these formulations varied between 0.719-0.790 indicating erosion is the main mechanism of drug release); however, there was still only about 40% of drug release within 12 h. The granulated samples showed relatively similar release profiles in all the formulations under study (e.g. Figure 1-c). By comparing the granulated vs. un-granulated dissolution profiles (Figures 1-b, -c), it was clear that the granulated psyllium formulations have a slower drug release in comparison with the un-granulated formulations.

Figures 2-a, -b show the dissolution profiles of theophylline from granulated psyllium or HPMC and Emcompress formulation *versus* the milled granules. The combination of using wet granulation followed by milling of the granules exhibited interesting results for all the Emcompress and psyllium formulations. Hydrophobic fillers like Emcompress do not dissolve in water. Therefore the drug can only diffuse out of the limited gaps within the polymer and the majority of the drug release will depend on the disintegration or erosion of the polymeric matrix leading to a slower drug release rate as demonstrated in Figures 2-a, -b. This could be due to several factors. First, milled granules have increased surface area for hydration, decreased

porosity and water penetration and thereby the drug release is controlled in a more efficient manner after the polymer swelling. Secondly, the formulations consisting of the granules have higher porosity and therefore the drug diffuses out of the matrix much faster.

Figure 3 shows a graph of 2 formulations with the same ratios, however different excipients, namely, psyllium and lactose *versus* psyllium and Emompress both after granulation and milling. Both formulations demonstrated very similar release profiles with more than 70% of drug release after 10 h, however the formulation containing Emcompress being slightly slower but not significant statistically ($p > 0.05$) (Figure 3). Such result reinforces the beneficial effects of psyllium in forming a variation of robust formulations.

Figures 4-a, -b show the dissolution profiles of theophylline from granulated psyllium or HPMC and lactose formulation *versus* the milled granules. The presence of a hydrophilic filler such as lactose leads to a faster dissolution rate. This is because lactose dissolves in contact with water. Once the lactose has dissolved, gaps are left within the polymer which allows the drug to diffuse out of the system. The drug release profiles for the milled samples in formulations containing psyllium and HPMC (Figure 4-a) exhibit release profiles similar to zero order release. The 12.5% and 25% psyllium or HPMC content of formulations that were milled showed a slow release pattern with over 70% drug release within 12 h. In the case of milled formulations containing either psyllium or HPMC, no remarkable burst release was observed (Figures 4-a, -b). In contrary, theophylline formulated with both HPMC and lactose granules showed undesirable initial burst release (Figures 4-b) which could be due to the presence of drug particles on the surface of the matrix.[42] This indicates that the milling had a remarkable influence on the drug dissolution profiles from the matrix. Indeed, the hydration of the polymer is believed to be at faster rate in the case of milled formulations due to reduced particle size, as proved later. This

suppressed the burst release and had the drug profiles exhibiting profiles similar to zero order release pattern.

Figure 5 compares two formulations: 25 psyllium + 25 Lactose: 50 drug and 25 HPMC + 25 Lactose: 50 drug. Both formulations demonstrated very similar release profiles with an adequate amount of drug being released within 12 h; however, the formulation containing psyllium had a slightly slower ($p<0.05$) release rate in comparison to the formulation containing HPMC.

The release of the drug from a swellable hydrophilic matrix initiates with the penetration of water into the matrix. In matrix systems, the drug is homogenously dispersed throughout a rate controlling medium. Next, the drug is dissolved and the penetrated water hydrates the polymer and causes swelling to form a gel like structure, thereby bringing about a relaxation of the polymer chains and consequently the polymer mesh size increases. This enables the drug to diffuse through the swollen network of the matrix out to the external environment. Therefore, the release of the drug is very closely related to the swelling characteristic of the psyllium hydrogel. In erodible systems, the mechanism of drug release occurs by bulk erosion or surface erosion. If bulk erosion occurs, the polymer degradation occurs through bulk hydrolysis; however, if surface erosion occurs, only the surface of the polymer degrades resulting in a release rate that is proportional to the surface area of the delivery system. In this study, theophylline is considered to have medium water solubility [50] and psyllium forms gel matrix thus both erosion and diffusion could occur. Mathematical models were used to evaluate the kinetics and mechanisms of drug release from the tablets. For matrix (cylindrical) tablets, an n value equal to or less than 0.45 indicates Fickian diffusion (or case-I) mainly controlled by diffusion. For $n \geq 0.89$ (i.e. $0.89 < n < 1.00$), a super case-II transport takes place, when dissolution process is controlled mainly by erosion and the release rate is independent of time (‘zero-order’ kinetics). Intermediate values

(i.e. $0.45 \leq n \leq 0.89$) represent a non-Fickian or anomalous transport and suggest that erosion (polymer matrix relaxation) and drug diffusion both contribute to the overall drug release mechanisms. [51]

The physical mixture of the pysllium and drug as in Figure 1 had Fickian diffusion as its sole kinetics of drug release with *n* values ranging from 0.102–0.233 (Table 3). The *n* values however seemed to increase with increasing psyllium content. The inclusion of HPMC changed the drug release kinetics from Fickian diffusion to anomalous transport indicating that a combination of erosion and diffusion taking place with *n* values ranging from 0.482–0.745 (Table 3). Granulation also had a remarkable effect on the drug release kinetics. A look at the *n* values of the pysllium and drug physical mixture formulation ($n = 0.102$) and the pysllium and drug granulated formulation ($n = 0.719$) in the ratio of 1:1 suggest that there is a change from Fickian diffusion to anomalous transport (Table 3) caused by granulation during formulation preparation. Figure 6 shows the appearance of tablets made from 50% theophylline + 50 % psyllium physical mixture (ungranulated) and from granulated psyllium-theophylline after 12 h dissolution period. The tablets made from granulated powders maintained their integrity after the dissolution compared to ungranulated formulations. The nature of the tablet after the dissolution process which could be a contributory factor to why there was such a remarkable change in the drug release kinetics. All granulated formulations of psyllium, HPMC and drug were dominated by anomalous transport whereas all granulated formulation of HPMC or psyllium with lactose or Emcompress had Fickian diffusion dominating their kinetics of drug release. Milling after the granulation process however changed their drug release kinetics to anomalous transport (Table 3).

Scanning Electron Microscopy

To investigate the effect of milling on the psyllium husk particles, SEM photographs of the milled and un-milled husk was taken at different magnifications as shown in Figure 7. SEM image of un-ground psyllium husk showed large particles with irregular-elongated shape (Figure 7). Such elongated shape could be a possible reason for the poor compactability and compressibility observed of the psyllium husk.[42] Following milling, psyllium husk particles demonstrated reduced size and irregular-flat shape (Figure 7), both could contribute to the poor compressibility of the psyllium powder. Also, this could lead to an increased surface area for hydration and gelling for the psyllium.

Differential Scanning Calorimetry

DSC was conducted to investigate the hydration of the polymers (Figure 8). From basic observations, the mini tablets containing psyllium swelled immediately and faster than the HPMC samples, even before the cap closing of the aluminium crucible. However, it is worth noting that psyllium had poor compactibility and the mini tablets crumbled despite the efforts to decrease/increase the weight of the mini- tablet and increasing the tablet compaction force. Therefore HPMC was added and the effect of psyllium on the hydration of HPMC was observed. Each sample was allowed 10 min for the phosphate buffer (pH 6.8) to penetrate the polymer.

The first exothermic curves indicate the freezing process. The endothermic transitions correspond to the melting of the free water in each sample **(**Figure 8**)**. Melting enthalpy and all transition temperatures for all samples are listed in Table 4. The values of the percentage bound water shows HPMC improves the hydration of psyllium (Table 4). HPMC granules demonstrated a slightly slower rate of hydration compared to psyllium granules which could be due to a decrease of the surface area of the particles. In matrix systems, the drug is dispersed as fine solid

powder particles within a porous matrix. Initially, the drug particles on the surface of the release unit are dissolved and the drug is released rapidly. Table 4 also shows psyllium to bind less to water than HPMC, meaning more water being available for the hydration process and for the movement of drug particles. This is evident in Figure 1a and b where drug release is quicker for psyllium as compared to HPMC only. The diffusion of the active ingredient out of the matrix system greatly depends on the water content of the tablet. This could be due to the fact that mobility of the polymer chains is dependent on water content. At a higher water concentration, polymer chain relaxation occurs leading to volume expansion which in turn moves the diffusion boundaries.[47]Aoki and co workers[52] explained that during the initial stages of dissolution, water penetrates into the matrix and usually acts as non-freezing (bound) water. In the next stage consists of the water content of the matrix increasing and freezable water being detected at levels related to drug release. They also reported that the transport of solutes mainly occurs through the free water and that only little transport occurs through bound water.[52] Asare-Addo and co workers[49] also hydrated K chemistry HPMC polymers with theophylline as a model drug and found the hydration at the 10 min time point to correlate with drug release from their dissolution studies.

Conclusion

This study proved that psyllium is a potential polymer which is capable to generate a wide variation of robust formulations. Reduced theophylline release with restrained initial burst release was proved with increasing psyllium concentration. Improved tablet quality and drug release profiles with lower initial burst release were obtained when HPMC was incorporated with formulations consisting of theophylline-psyllium physical mixtures. Also, a release profile comparable to zero-order was obtained when HPMC was granulated with psyllium. All

granulated formulations demonstrated relatively similar release profiles; however, granulated formulations generated slower drug release than un-granulated formulations. A change in drug release kinetics from Fickian diffusion to anomalous transport was observed when HMPC was included with the theophylline formulations.

Psyllium and lactose or Emcompress formulations could be utilized to achieve an ideal drug release profile close to zero order release. Psyllium could also be used in conjunction with HPMC to achieve a variety of drug release profiles that could be beneficial for certain drugs. Both milling and granulation had a significant effect of drug release. Milling was proved useful in obtaining controlled dissolution profiles similar to that of zero-order. This could be due to an increase in uniformity; however, it could have also been due to a further reduction in the polymer particle size which increases the surface area for hydration and exhibits a slower dissolution rate. Milling following granulation process altered drug release kinetics to anomalous transport.

The use of psyllium in the production of sustained release oral formulations is a very fruitful area for research. The wide range of therapeutic and physiological benefits and the economical/cost effectiveness that psyllium has makes it a superb candidate for a novel double potential drug delivery device.

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Declaration of interest

The authors report no declarations of interest.

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Table 1. Required weight of excipients for preparing physical mixture formulations with different ratios

Drug ratio	Psyllium ratio	HPMC ratio	Theophylline (mg)	Psyllium (mg)	HPMC K4M (mg)	Mg Stearate (mg)	Tablet (mg)
66.6	33.3	…	1000	500	…	15	303
60.0	40.0	…	1000	666.65	…	16.66	336.66
55.0	45.0	…	1000	818.18	…	18.18	367.27
52.5	47.5	…	1000	904.76	…	19.04	384.76
50.0	50.0	…	1000	1000	…	20	404
50.0	…	50.0	1000	…	1000	20	404
50.0	12.5	37.5	1000	250	750	20	404
50.0	37.5	12.5	1000	750	250	20	404
50.0	25.0	25.0	1000	500	500	20	404

Table 2. The composition of each formulation for granulated formulations

Ratio (%)				**Weight (mg)**				
Psyllium	**HPMC**	**Lactose**	**EM**	**Psyllium**	**HPMC-K4M**	**Lactose**	**EMC**	**Tablet**
50	…	…	…	1000	…	…	…	404
…	50	…	…	…	1000	…	…	404
12.5	37.5	…	…	250	750	…	…	404
25	25	…	…	500	500	…	…	404
37.5	12.5	…	…	750	250	…	…	404
25	…	25	…	500	…	500	…	404
37.5	…	12.5	…	750	…	250	…	404
12.5		37.5	…	250	…	750	…	404
…	25	25	…	…	500	500	…	404
…	37.5	12.5	…	…	750	250	…	404
…	12.5	37.5	…	…	250	750	…	404
25	…	…	25	500	…	…	500	404
37.5	…	…	12.5	750	…	…	250	404
12.5	…	…	37.5	250	…	…	750	404
…	25	…	25	…	500	…	500	404
…	12.5	…	12.5	…	750	…	250	404
…	37.5	…	37.5	…	250	…	750	404

[a] the ratio of theopylline was 50% or 1000 mg

[b] the amount of magnesium stearate was 20 mg

Table 3. Kinetics of drug release for different formulations under investigation

Drug	Psyllium	HPMC	Lactose	EM Compress	Formulation type*	n value
66.6	33.3	…	…	…	Physical mix	0.102
60	40	…	…	…	Physical mix	0.146
55	45	…	…	…	Physical mix	0.216
52.5	47.5	…	…	…	Physical mix	0.215
50	50	…	…	…	Physical mix	0.233
50	…	50	…	…	Physical mix	0.745
50	12.5	37.5	…	…	Physical mix	0.760
50	25	25	…	…	Physical mix	0.668
50	37.5	12.5	…	…	Physical mix	0.482
50	50	…	…	…	Granulated (polymer)	0.701
50	…	50	…	…	Granulated	0.772
50	12.5	37.5	…	…	Granulated	0.790
50	25	25	…	…	Granulated	0.721
50	37.5	12.5	…	…	Granulated	0.730
50	50	…	…	…	Granulated	0.719
50	25	…	25	…	Milled	0.722
50	25	…	25	…	Granules	0.310
50	37.5	…	12.5	…	Milled	0.722
50	37.5	…	12.5	…	Granules	0.336
50	12.5	…	37.5	…	Milled	0.836
50	12.5	…	37.5	…	Granules	0.429
50	…	25	25	…	Milled	0.798
50	…	25	25	…	Granules	0.118
50	…	37.5	12.5	…	Milled	0.772
50	…	37.5	12.5	…	Granules	0.224
50	…	12.5	37.5	…	Milled	0.732
50	…	12.5	37.5	…	Granules	0.131
50	25	…	…	25	Milled	0.638
50	25	…	…	25	Granules	0.345
50	37.5	…	…	12.5	Milled	0.693
50	37.5	…	…	12.5	Granules	0.397
50	12.5	…	…	37.5	Milled	0.695
50	12.5	…	…	37.5	Granules	0.387
50	…	25	…	25	Milled	0.818
50	…	25	…	25	Granules	0.379
50	…	37.5	…	12.5	Milled	0.619
50	…	37.5	…	12.5	Granules	0.472
50	…	12.5	…	37.5	Milled	0.648
50	…	12.5	…	37.5	Granules	0.145

***milling was took place after granulation**

Table 4. Melting enthalpy (J/g), peak (ºC), % free water, and % bound water for phosphate buffer (control), HPMC K4M, psyllium, HPMC K4M granules, and 50 HPMC K4M + 50 Psyllium (mean ± SD, *n*=3).

	Enthalpy (J/g)	**Peak (ºC)**	**% free water**	**% bound water**
Phosphate buffer (pH 6.8)	260.4±22.1	5.5±2.6	100	0
HPMC K4M	186.0±15.9	1.9±0.8	71.4±6.1	28.5±6.1
Psyllium	197.9±4.4	2.3±0.5	76.0±1.7	24.0±1.7
HPMC K4M granules	193.8±7.2	2.5±0.3	74.4±2.8	25.6±2.8
50% HPMC K4M + 50% psyllium	156.5±2.7	3.1±1.2	60.1±1.0	39.9±1.0

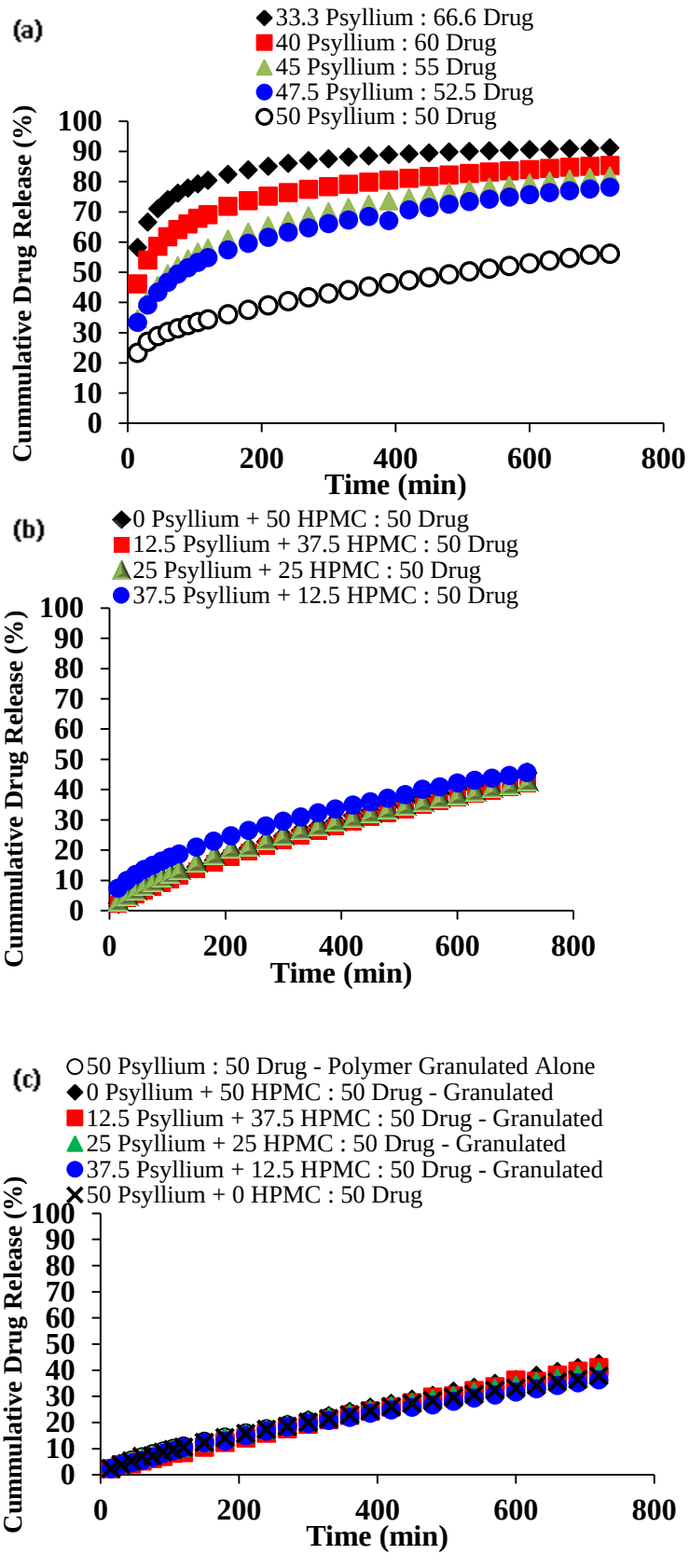
(a)
33.3 Psyllium : 66.6 Drug
40 Psyllium : 60 Drug
45 Psyllium : 55 Drug
47.5 Psyllium : 52.5 Drug
50 Psyllium : 50 Drug
Cummulative Drug Release (%)
Time (min)
(b)
0 Psyllium + 50 HPMC : 50 Drug
12.5 Psyllium + 37.5 HPMC : 50 Drug
25 Psyllium + 25 HPMC : 50 Drug
37.5 Psyllium + 12.5 HPMC : 50 Drug
Cummulative Drug Release (%)
Time (min)
(c)
50 Psyllium : 50 Drug - Polymer Granulated Alone
0 Psyllium + 50 HPMC : 50 Drug - Granulated
12.5 Psyllium + 37.5 HPMC : 50 Drug - Granulated
25 Psyllium + 25 HPMC : 50 Drug - Granulated
37.5 Psyllium + 12.5 HPMC : 50 Drug - Granulated
50 Psyllium + 0 HPMC : 50 Drug
Cummulative Drug Release (%)
Time (min)

Figure 1. Release rates of Theophylline from **(a)** tablets consist of physical mixtures of either Psyllium and Theophylline; **(b)** Psyllium:HPMC:Theophylline **(c)** formulations; and release rates of Theophylline from granulated mixtures of Psyllium, HPMC and Theophylline tablets

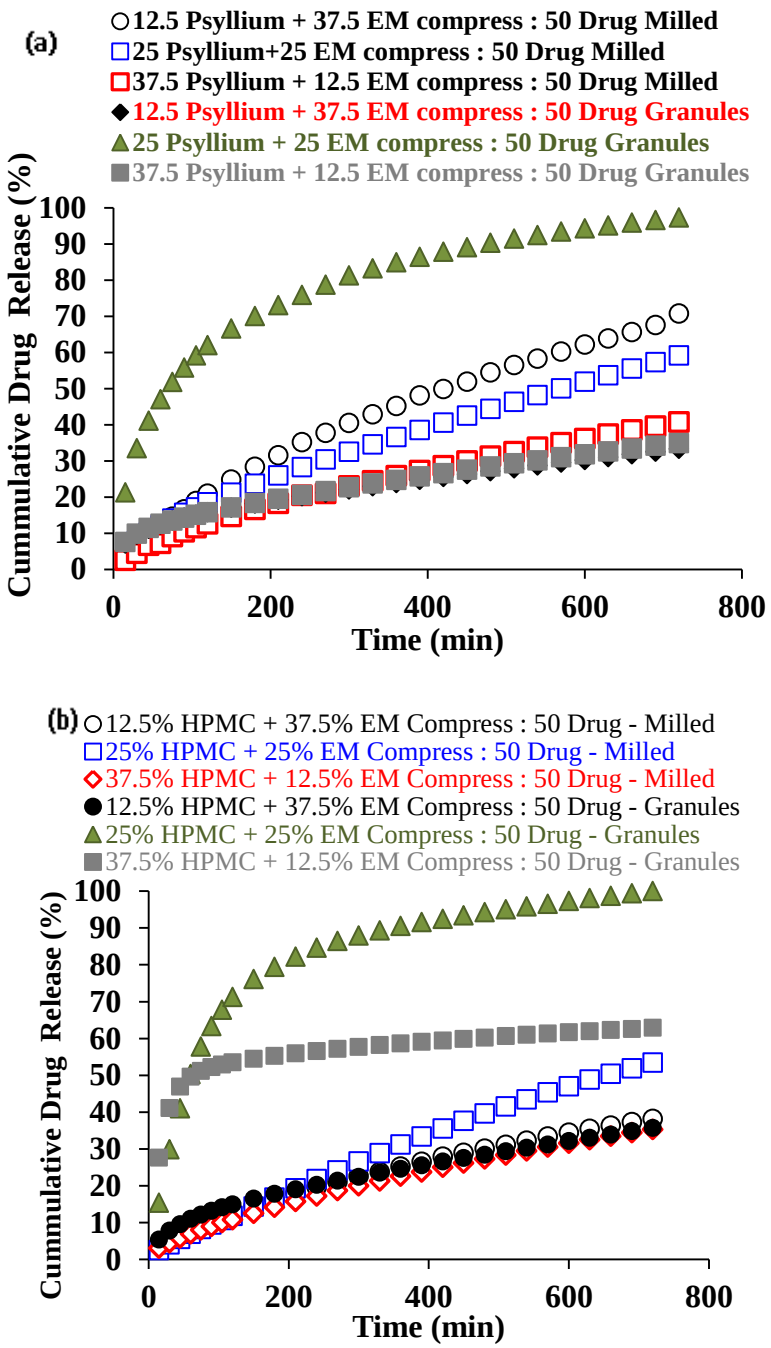

Figure 2: Release profiles of Theophylline from granulated psyllium, EM Compress and Theophylline tablets **(a)**; and release profiles of Theophylline from granulated HPMC, EM Compress and Theophylline tablets **(b)**.

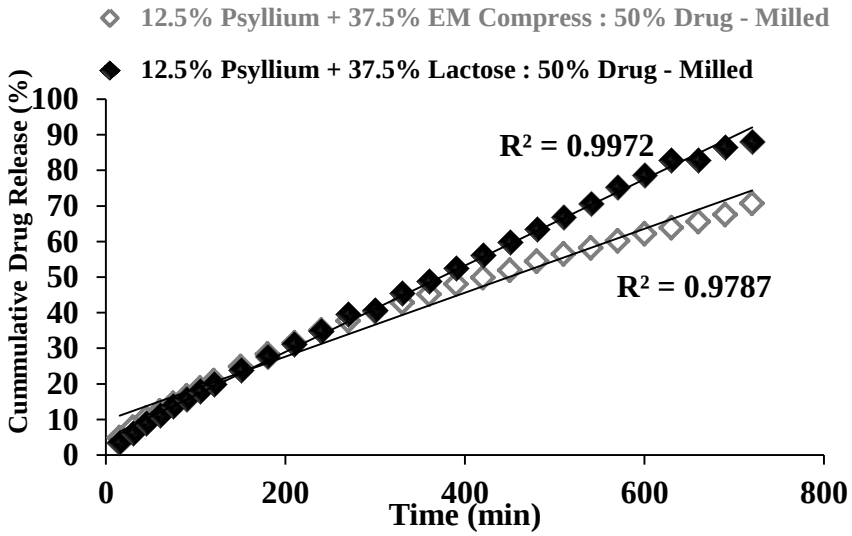

Figure 3: Release profiles of Theophylline from granulated 12.5% Psyllium, 37.5% EM Compress, 37.5% lactose and 50% Theophylline tablets

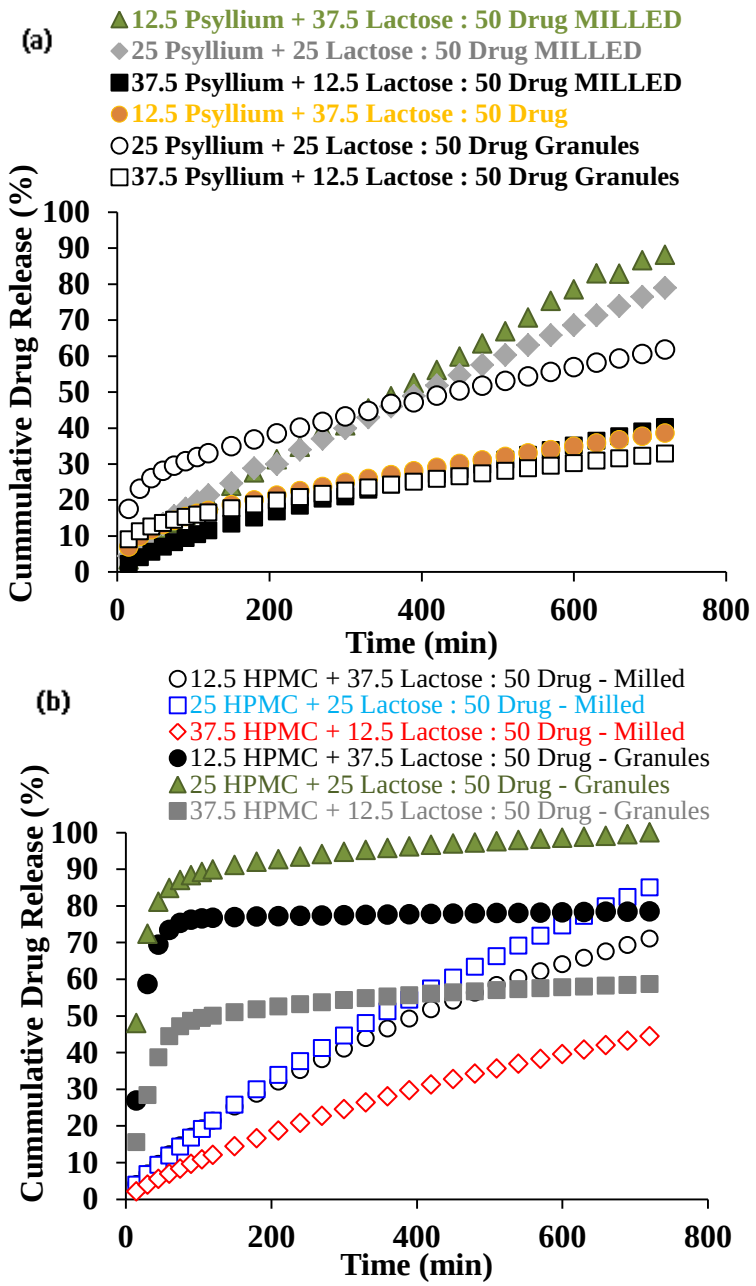

Figure 4: Release profiles of theophylline from granulated psyllium, Lactose and Theophylline tablets **(a)**; and release profiles of theophylline from granulated HPMC, Lactose and Theophylline tablets **(b)**.

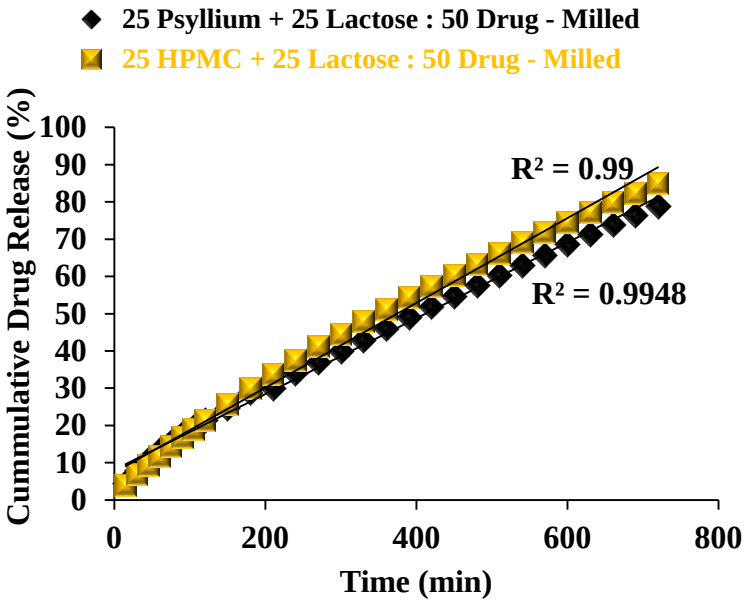

Figure 5: Release profiles of Theophylline from granulated 25% Psyllium, 25% HPMC, 25% lactose and 50% Theophylline tablets.

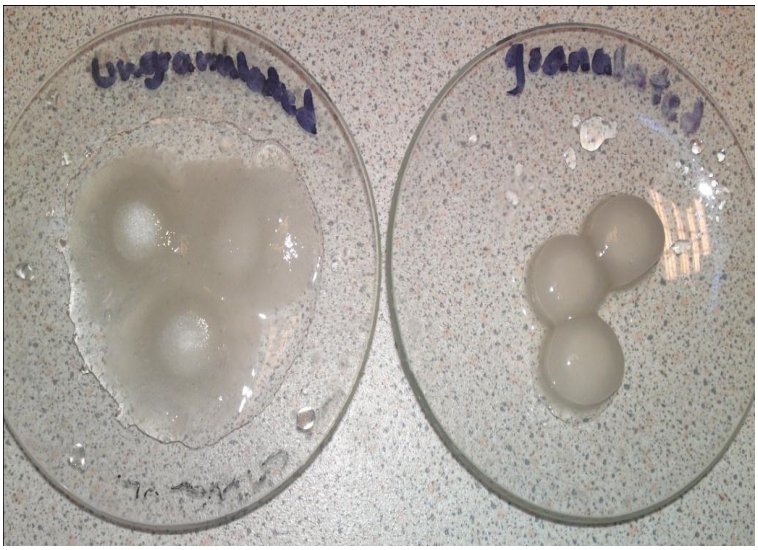

Figure 6: Comparison between 50 % Theophylline + 50 % Psyllium physical mix (ungranulated) and granulated tablets after the 12hr dissolution period. The tablets made from granulated powders maintained their integrity after the dissolution compared to the un-granulated formulations

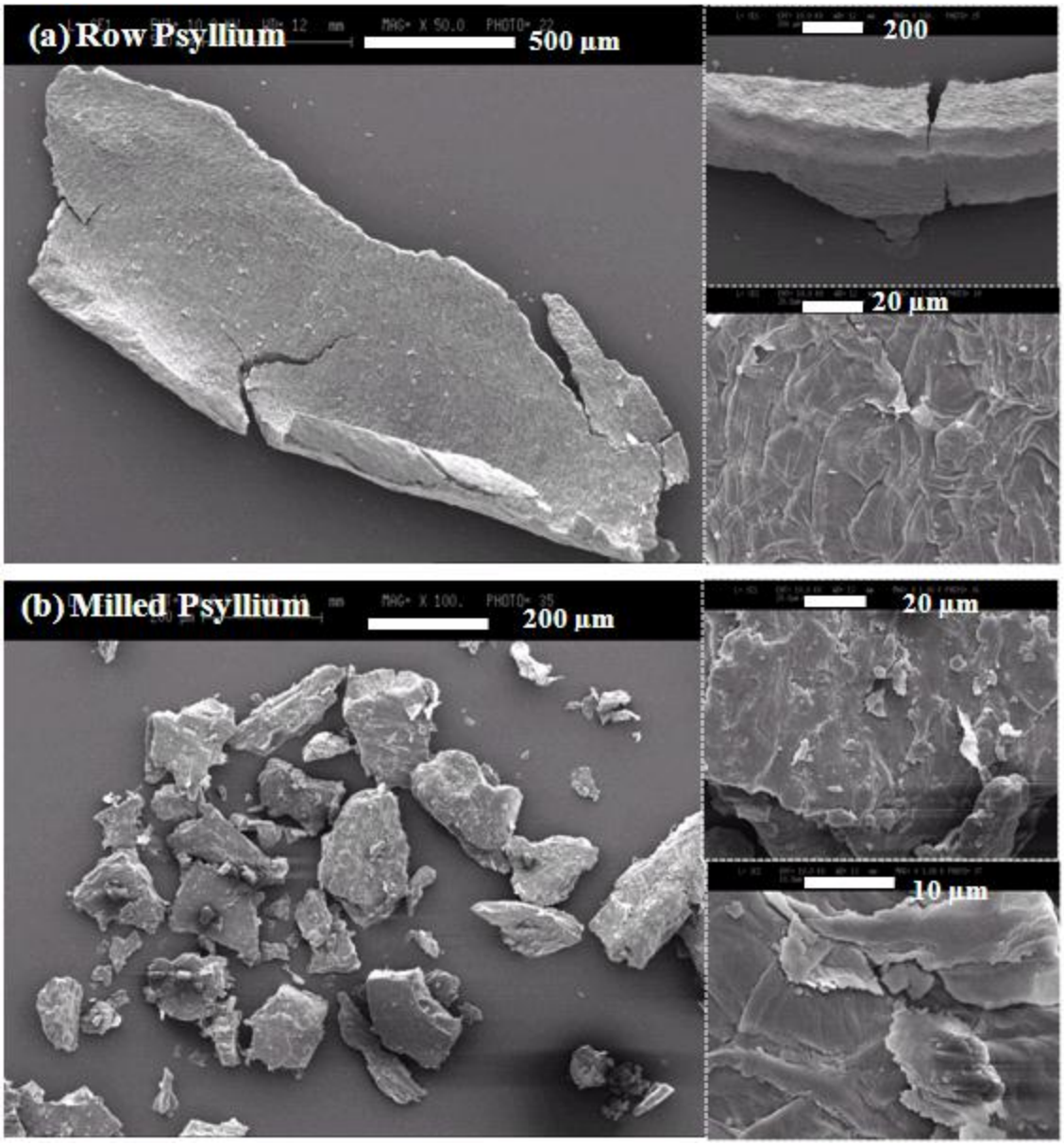

Figure 7: SEM images of raw psyllium husk **(a)** and psyllium husk after being milled for 15 min **(b)**.

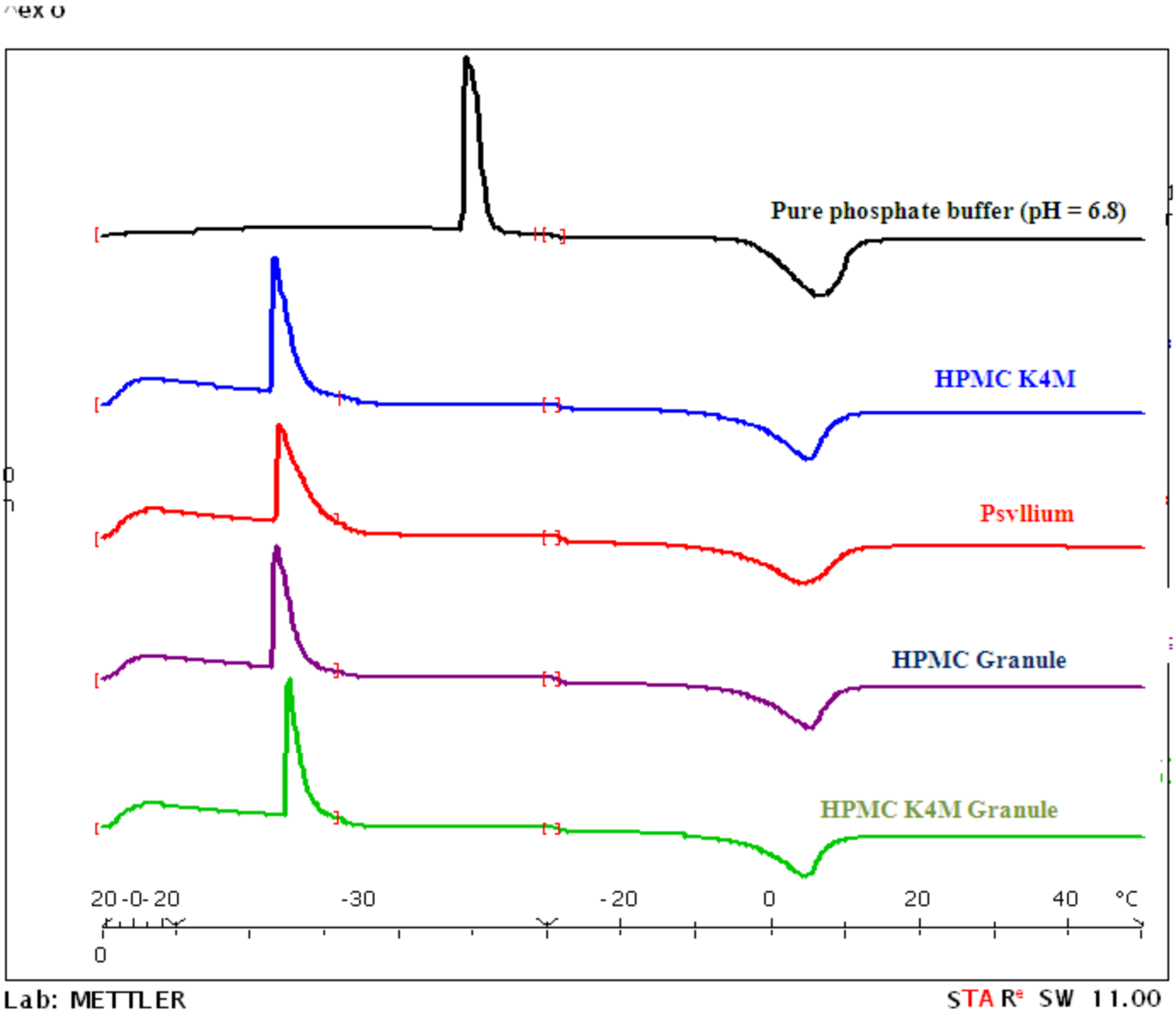

Figure 8. DSC traces for pure phosphate buffer (pH=6.8), HPMC K4M, Psyllium, HPMC granule, and HPMC K4M granule.