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Research paper

The use of Agar as a novel filler for monolithic matrices produced using hot melt extrusion

John G. Lyons [1], Declan M. Devine [2], James E. Kennedy [3], Luke M. Geever [3], Patrick O'Sullivan [1], Clement L. Higginbotham *

Centre for Biopolymer and Biomolecular Research, Athlone Institute of Technology, Westmeath, Ireland

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Abstract

The use of filler materials in an extended release monolithic polymer matrix can lead to a vastly altered release profile for the active pharmaceutical ingredient. A range of excipients for use in monolithic matrices have been discussed in the literature. The body of work described in this research paper outlines the use of agar as a novel filler material in a hot melt extruded polymer matrix. Several batches of matrix material were prepared with Diclofenac sodium used as the active pharmaceutical ingredient (API). Agar and microcrystalline cellulose were used as the filler materials in varying ratios, to examine the effect of % filler content as well as filler type on the properties of the hot melt extruded matrix. The resultant extrudates were characterised using steady state parallel plate rheometry, differential scanning calorimetry (DSC) and dissolution testing. The rheometry analysis concluded that the fillers used resulted in an increase in the matrix viscosity. The DSC scans obtained showed negligible effects on the melting behavior of the matrix as a result of the filler inclusion. Dissolution analysis showed that the presence of the fillers resulted in a slower release rate of API than for the matrix alone. The results detailed within this paper indicate that agar is a viable filler for extended release hot melt produced dosage forms.

Keywords: Agar; Polyethylene oxide; Eudragit; Matrix; Hot melt extrusion; Controlled drug delivery devices

1. Introduction

Controlled release of therapeutic agents remains one of the biggest challenges in drug delivery. Repeated administration of a drug so as to maintain drug concentration within the therapeutic window may cause serious side effects, which in many cases necessitates the patient to stop taking medication [1]. With conventional dosage forms, high peak blood concentrations may be reached soon after administration with possible adverse effects related to the transiently high concentration. An example is hypotension in patients taking rapid-release nifedipine products. Recently, the development of tablets which can be swallowed and thereafter slowly release the drug in the gastrointestinal tract has garnered great interest. There are currently many different nomenclatures available for the aforementioned dosage forms, such as slow release, prolonged release, sustained release and extended release. The term extended release has been adopted by the European Pharmacopeia as the denominator for this type of device. The release pattern from such a device may vary from continuous to two or more pulses [2]. Over the past decade the use of biodegradable polymers for the administration of pharmaceuticals and biomedical devices has increased dramatically. The most important biomedical applications of biodegradable polymers are in the areas

* Corresponding author. Centre for Biopolymer and Biomolecular Research, Athlone Institute of Technology, Dublin Rd, Athlone, Co. Westmeath, Ireland. Tel.: +353 90 6424463; fax: +353 90 6424493.
E-mail addresses: slyons@ait.ie (J.G. Lyons), ddevine@ait.ie (D.M. Devine), jkennedy@ait.ie (J.E. Kennedy), lgeever@ait.ie (L.M. Geever), chigginbotham@ait.ie (C.L. Higginbotham).
[1] Tel.: +353 90 6422549; fax: +353 90 6424493.
[2] Tel.: +353 90 6424553; fax: +353 90 6424493.
[3] Tel.: +353 90 6424408; fax: +353 90 6424493.

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of controlled drug delivery systems [3], in the forms of implants and devices for bone and dental repairs [4,5].

Hot melt extrusion of biodegradable polymers for extended release applications has received increased attention in the pharmaceutical literature recently. Hot melt extrusion is the process of converting a raw material into a product of uniform shape and density by forcing it through a die under controlled conditions [6]. Extrusion process technology can be divided into two categories; ram extrusion and screw extrusion. Ram extrusion consists of a positive displacement ram capable of generating high pressures forcing material through a shaping die while screw extrusion consists of a rotating screw or set of screws inside a barrel. In a pharmaceutical environment hot melt extrusion offers many advantages over more traditional tablet preparation methods; all the processing steps (mixing, melting and homogenising) are carried out on a single machine and neither water or solvents are involved in the process, thus due to the anhydrous nature of the process any potential drug degradation from hydrolysis can be avoided. The intensive mixing provided by a twin screw extruder causes suspended drug particles to de-aggregate in the polymer melt resulting in a more uniform distribution of fine particles. Hot melt extrusion offers a high throughput and a low material loss while preparing extrudates that possess excellent homogeneity.

In 1989 and 1990 Mank et al. reported extrusion of a number of thermoplastic polymers to produce sustained-release pellets [7,8]. Follonier and co-workers investigated the feasibility of using melt extrusion to produce sustained-release pellets in 1994 [9]. The goal of their research was to create a dosage form using a simple and continuous process. In a later study by Follonier et al., the authors examined different parameters influencing the release rate of diltiazem hydrochloride from hot melt extruded pellets incorporated into hard gelatine capsules [10]. Results of this study indicated that release rate of drug was dependent on several critical factors including polymer type, drug/polymer ratio, addition of pore forming additives or hydrophilic polymers and pellet size. Zhang and McGinity investigated the properties of polyethylene oxide (PEO) as a drug carrier in 1999 [11] by studying the release rate of chloropheniramine maleate (CPM) from matrix tablets produced by hot melt extrusion. Polyethylene glycol (PEG) 3350 was utilised as a processing aid and as a plasticiser. The loading of the drug as well as the molecular weight of the PEO and the inclusion of PEG were all found to contribute greatly to the processing conditions and the rate of release of the drug. In addition, the researchers showed that additional mixing of the components occurred in the barrel of the extruder, since the content uniformity of the extruded tablets was within 99.0–101.0% of the theoretical content.

In this work the use of agar as a novel filler material in hot melt extruded dosage forms was investigated. Two hot melt prepared matrices were used to test the release rate of an active pharmaceutical ingredient when agar was incorporated as a filler material. These matrices were compared with matrices incorporating the common pharmaceutical excipient microcrystalline cellulose.

2. Experimental

2.1. Hot melt extrusion

All the melt compounding detailed herein was carried out on a bench-top Prism™ twin screw extruder with 16 mm diameter screws and a 25/1 length to diameter ratio. Prism™ co-rotating extruder screw configurations are designed and manufactured in a modular construction, the screws are made up of individual sections that slide onto a keyed or splined shaft. Therefore different screw configurations using narrow disk bi-lobal kneading elements can be arranged at any location along the shaft to generate controlled shear or mixing effects. For the compounding detailed in this work, the screws were assembled in the co-rotating intermeshing mode with a long continuous mixing section made up of 30°, 60° and 90° bi-lobal kneading elements which ensured that the transition from conveying to high shear mixing was very gradual. The mixing section was positioned towards the die end of the extruder. The required compounding temperature profile was established on the Prism™ extruder by means of four temperature controllers placed along the length of the barrel. A fifth temperature controller was used to regulate the temperature at the die. Extrudate was cooled via two cool air fans and was subsequently granulated using a Prism™ granulator. The extrusion conditions used are outlined in Table 1. The positions of the heating zones and mixing sections are visible on the schematic diagram of the barrel of the Prism™ twin screw extruder in Fig. 1.

Batches of polymer extrudates were prepared using the extrusion profile outlined in Table 1. The active agent incorporated in this work was Diclofenac Sodium obtained from Pharmaplaz Ltd. Polyethylene oxide (M_w 1 million and M_w 200,000) was obtained from Polysciences Ltd as was the agar utilised in this study. Microcrystalline Cellulose (Avicel PH101) was purchased from FMC, Ireland. The Eudragit L100 incorporated in batches 9–16 was obtained from Degussa Ltd. The full list of batch compositions can be seen in Table 2.

2.2. Modulated differential scanning calorimetry

The DSC method was among the techniques used for examination of the extruded pellets. The analyses were performed using a DSC 2920 Modulated DSC (TA Instru-

Table 1
Extrusion conditions

Screw Speed (RPM)	Temperature (°C)				
	Zone 1	Zone 2	Zone 3	Zone 4	Die
30	70	130	130	130	140

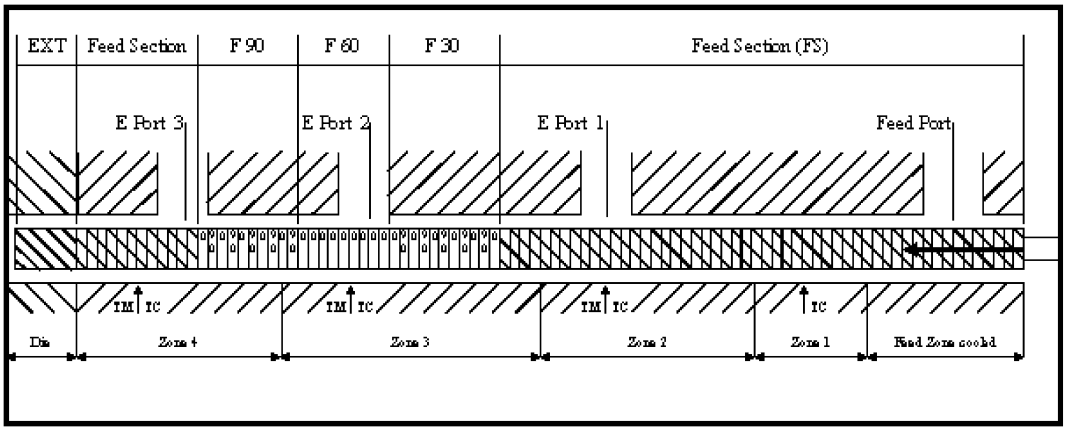

Fig. 1. Schematic representation of Prism™ twin screw extruder barrel.

Table 2
Batch compositions (all values are in grams)

Batch name	PEO (M_w 1 million)	PEO (M_w 200,000)	Eudragit L 100	API	Agar	MCC
1	20	20	0	0	0	0
2	32.5	32.5	0	15	0	0
3	27.5	27.5	0	15	10	0
4	22.5	22.5	0	15	20	0
5	17.5	17.5	0	15	30	0
6	27.5	27.5	0	15	0	10
7	22.5	22.5	0	15	0	20
8	17.5	17.5	0	15	0	30
9	0	20	20	0	0	0
10	0	32.5	32.5	15	0	0
11	0	27.5	27.5	15	10	0
12	0	22.5	22.5	15	20	0
13	0	17.5	17.5	15	30	0
14	0	27.5	27.5	15	0	10
15	0	22.5	22.5	15	0	20
16	0	17.5	17.5	15	0	30

ments) coupled with a refrigerated cooling system. Samples of between 9.0 and 9.8 mg were weighed out using a Sartorius scale having a resolution of 0.00001 g. Samples were then placed in non-perforated aluminum pans which were crimped before testing, with an empty crimped aluminum pan being used as the reference cell. Calorimetry scans were carried out from 20 to 190 °C for each extruded pellet. All DSC measurements were carried out at a scanning rate of 1 °C/min. Volatiles were removed from the purging head with nitrogen at a rate of 30 ml/min. Calibration of the instrument was performed using indium as standard. After each scan was completed the melting points were analysed to determine heats of fusion and T_m of each batch.

2.3. Steady state parallel plate rheometry

The method used to study the rheological properties of the samples detailed in this study was a steady state parallel plate viscometer, the AR1000™ rheometer from TA instruments©. It is a versatile research-grade rheometer designed for rapid characterisation of mobile and viscous liquids. It is fitted with an environmental test chamber (ETC), for use as the temperature control environment in the analysis of polymer melts using parallel plate or cone/plate measurement geometries with provision for nitrogen purging.

The following is the procedure used in all of the rheological studies detailed herein. The air and nitrogen supplies were turned on and the air bearing guard was removed. The instrument was calibrated for inertia and the geometry was set for the 25 mm steel parallel plates being used. The instrument was mapped and with the ETC closed the rheometer was brought to test temperature of 140 °C. The gap between the plates was zeroed. The doors were opened and with the plates returned to the default back off distance, the sample was loaded. The amount of sample loaded has an effect, and so extreme care was taken during sample loading to ensure the correct fill. The apparatus was set to take 10 points per decade with 5% tolerance. After each test a bronze scraper was used to remove the sample from the plates, before the machine was brought back to temperature for the next sample.

2.4. Dissolution testing

Dissolution testing was carried out using a Sotax AT7 smart dissolution system from Carl Stuart Ltd. The standard was prepared by transferring 60 mg of USP Diclofenac Sodium RS, accurately weighed, to a 100 ml volumetric flask, 80 ml of methanol was added, dissolved using an ultrasonic bath and when at room temperature brought to 100 ml with methanol and mixed well. This was further diluted 2/100 with 0.1 N HCl, and mixed. This standard solution contained 12 μg of USP Diclofenac Sodium RS per ml. The strand of extrudate produced by each of the batches in Table 2 was of constant diameter 0.1 cm. In order to produce granules of constant size and surface geometry for dissolution testing, the extrudate strands were cut manually to give granules of constant length 0.5 cm. The resulting extrudate granules were tested in an acidic dissolution medium (0.1 N hydrochloric acid,

pH 1.2). The test was carried out at 37 °C. The stir rate was set to 50 rpm with 900 ml of dissolution media being used per vessel. Samples were automatically taken every 15 min and analysed by ultraviolet (UV) at 276 nm using a 1 cm quartz cuvette on a Perkin-Elmer lambda 2 spectrometer. The dissolution profile was observed from a plot of time versus absorbance.

3. Results and discussion

3.1. Hot melt extrusion

During the hot melt extrusion processing of the batches outlined in Table 2, the values for the die head pressure and the extruder torque were recorded. The trends observed showed increases in the die head pressure and the torque values obtained for batches containing filler materials. The increase in the torque and die head pressure observed was more pronounced for the batches containing agar filler than for the batches containing MCC filler, indicating that the blends containing the agar filler were more viscous than those containing the MCC filler. The values obtained also indicated that the incorporation of the active agent led to a plasticising effect in the hot melt extrusion process as the values for torque and die head pressure observed were lower than for batches containing matrix material alone. The values for the torque and die head pressure observed during the hot melt processing step can be seen in Figs. 2 and 3.

3.2. Differential scanning calorimetry (DSC)

Differential scanning calorimetry was used to ascertain if the inclusion of the Diclofenac sodium or the filler materials had any effect on the thermal characteristics of the matrix material. Fig. 4 shows a DSC scan of batch 1 which was typical of the DSC scans obtained in this work. When the API was incorporated, the DSC scans obtained showed

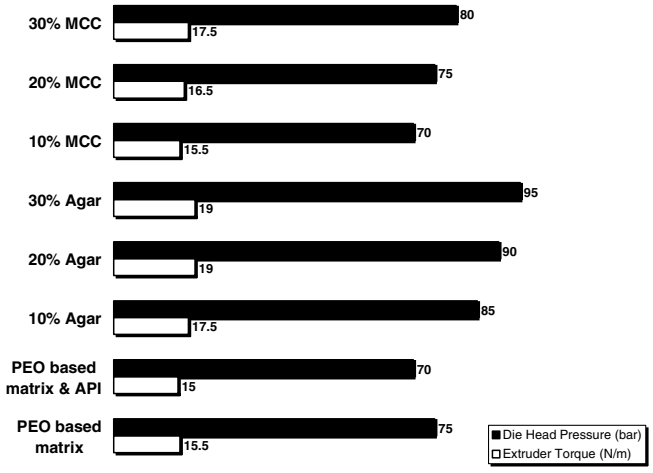

Fig. 2. Extruder torque and die head pressure values observed during hot melt processing of PEO based matrices.

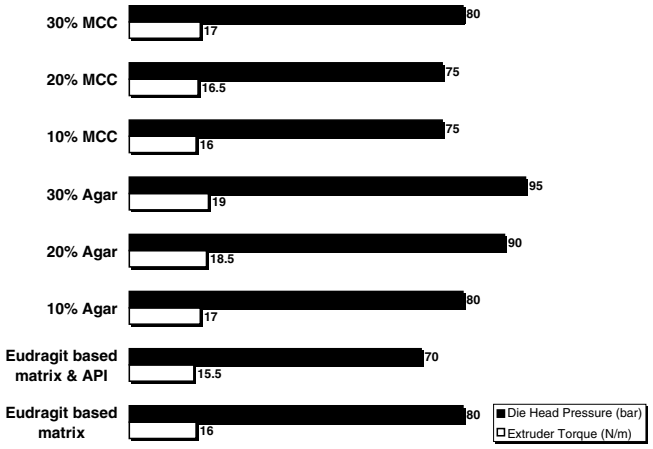

Fig. 3. Extruder torque and die head pressure values observed during hot melt processing of Eudragit based matrices.

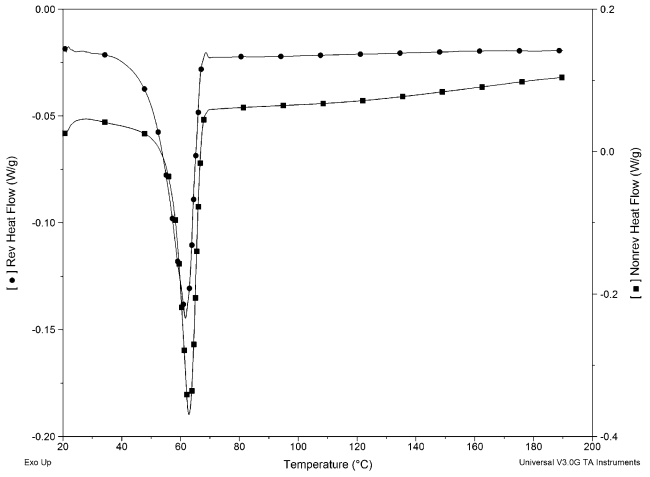

Fig. 4. Modulated differential calorimetry scan of the PEO based matrix, batch 1, showing both the reversing heat flow and non-reversing heat flow signals.

a drop in approximately 3 °C of the T_m of both the PEO based and Eudragit based matrices, with the melting point of the PEO based matrix dropping from 57.23 to 54.43 °C and the melting point of the Eudragit based matrix dropping from 62.76 to 59.96 °C. These results indicate that the Diclofenac sodium is acting as a plasticiser in the polymer matrix, confirming the observations made during the hot melt processing of the samples. This behavior was also noted by Ozeki et al. [11].

Endotherms associated with hydration of the Diclofenac sodium are visible in the vicinity of 100 °C. These endotherms disappear when the matrix containing the active agent has been heated to above 100 °C and reappear slowly when the dried active agent containing matrix has been stored in a humid environment. This effect was previously reported in the literature [12] and would not prove to be an obstacle to the use of Diclofenac sodium in hot melt prepared dosage forms as long as the Diclofenac sodium was sufficiently dried prior to the extrusion process, and the resultant extrudates were stored in a dry environment prior

to packaging. The inclusion of both the filler materials had a negligible effect on the melting behavior of the matrix indicating that the agar would be a viable alternative excipient for hot melt processing.

3.3. Steady state rheometry

The calculations of applied stresses and resulting deformations are based on the geometry details with the assumption that the correct amount of sample is present. Too little sample and the sample will experience a higher stress than actually applied resulting in a lower viscosity, as the stress applied is calculated for the geometry surface area and it is assumed that this is the same for the sample. Too much sample and edge effects can be sensed where the excess sample experiences little or no shearing forces and so cause viscous drag effects and so a higher viscosity is measured. Sample geometry was constant for all the samples used.

The effect of filler on both matrices is to increase the viscosity of the matrix. The increase of viscosity of the matrix becomes more pronounced as the percentage of filler is increased. A more substantial increase in viscosity is obtained with the inclusion of agar as a filler material when compared to the inclusion of microcrystalline cellulose. This can be explained by the fibrous nature of the microcrystalline cellulose compared to the stronger gel forming capabilities of agar. Figs. 5 and 6 shows steady state rheometry results for both matrices, with viscosity displayed as a function of shear rate.

3.4. Dissolution studies

It has been reported in the literature [13] that Eudragit L100 and different molecular weight blends of PEO have proved useful for modulating the release of active agents in monolithic devices for drug release. The dissolution profile shown in Fig. 7 is that of the Eudragit L100 and PEO based matrices without fillers other than the API. It can be clearly seen from this plot that the PEO based matrix releases the active agent quicker than Eudragit based matrix.

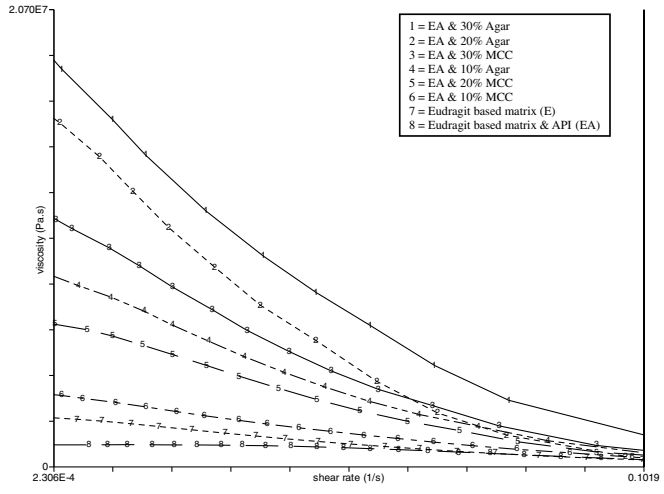

Fig. 5. Viscosity curves for Eudragit based matrix and filled Eudragit based matrices.

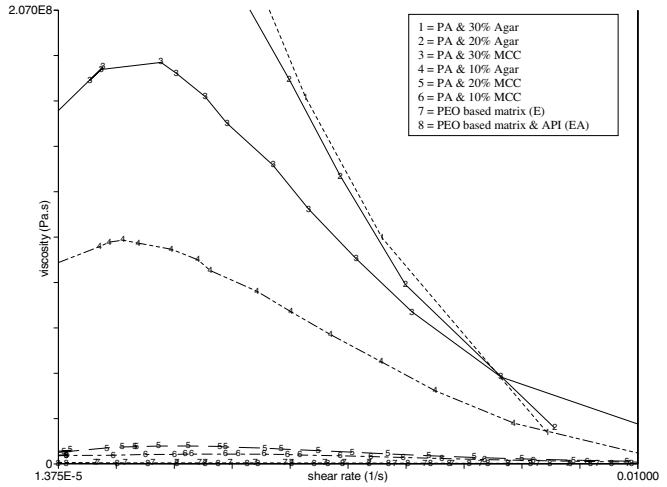

Fig. 6. Viscosity curves for PEO based matrix and filled PEO based matrices.

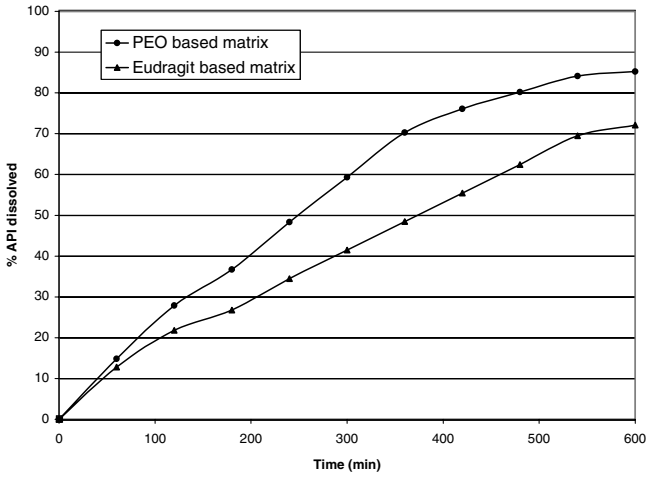

Fig. 7. Drug release from PEO based matrix and Eudragit based matrix.

The addition of the microcrystalline cellulose filler to both matrices has a marked effect on the dissolution rate. As can be seen from both Figs. 8 and 9 in both cases the microcrystalline cellulose is seen to decrease the release rate. This effect becomes more pronounced as the percentage of microcrystalline cellulose in the matrix increases, correlating with findings in the literature by Thommes and Kleinebudde [14]. The main characteristic of the use of microcrystalline cellulose as a filler material is the lack of disintegration [15] which results in a prolonged matrix type drug release [16]. For drugs with low solubility the time for complete release might be slower than the gastrointestinal passage time resulting in decreased bioavailability and excretion of active pharmaceutical ingredient. However, the use of microcrystalline cellulose as a filler material in extended release devices has a major disadvantage in the reported adsorption of some drugs to MCC

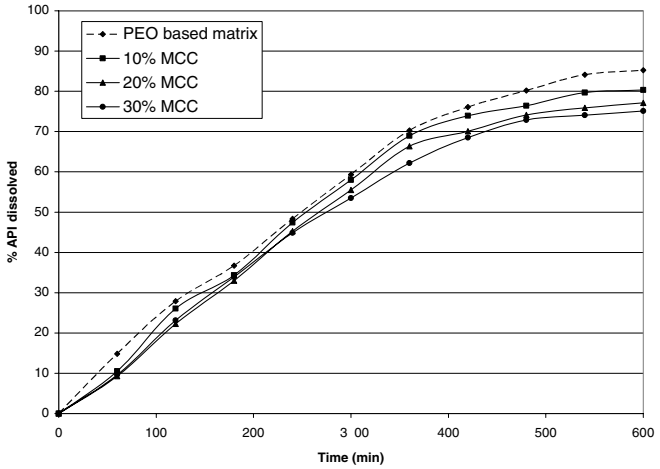

Fig. 8. Drug release from PEO based matrix and MCC filled PEO based matrices.

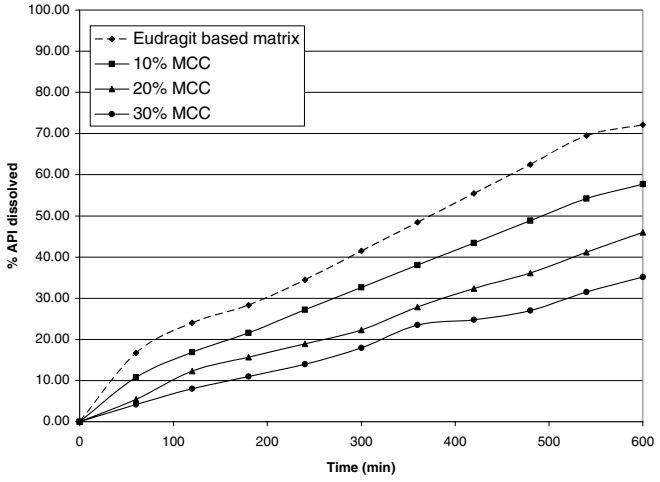

Fig. 9. Drug release from Eudragit based matrix and MCC filled Eudragit based matrices.

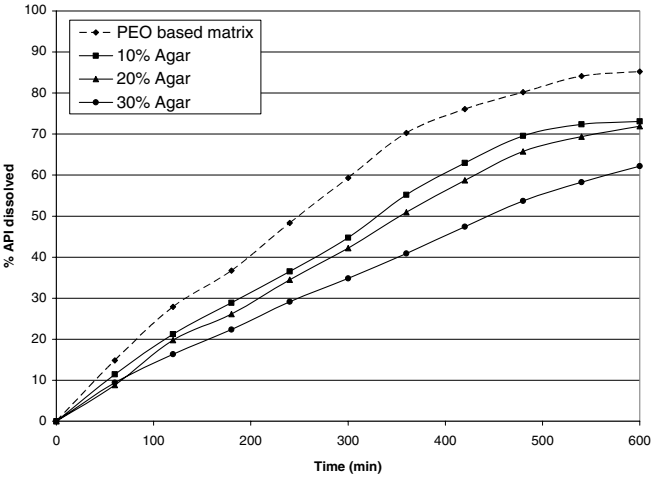

Fig. 10. Drug release from PEO based matrix and Agar filled PEO based matrices.

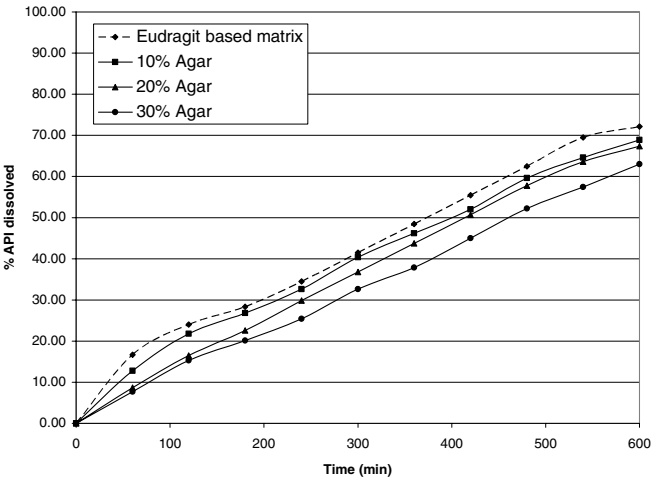

Fig. 11. Drug release from Eudragit based matrix and Agar filled Eudragit based matrices.

[17–19] that can affect the drug release. Also, a decomposition of some drugs in the presence of MCC could be observed [20].

Hydrogels from agar (polysaccharide) have received particular attention, due to their natural origin, low cost and good biocompatibility [21–23]. Furthermore, their resemblance to human tissues is of value for these polymers to be used to study or mimic solute transport through biological media [24]. They have been widely used in drug delivery systems [25,26]. However studies on the use of agar as a filler material in hot melt prepared dosage forms have thus far not been carried out. As a result, agar was chosen as an alternative filler to microcrystalline cellulose in this study. As can be seen in Figs. 10 and 11 the matrix blends containing agar show a similar trend as those containing microcrystalline cellulose. The incorporation of the agar into the polymer matrix leads to a reduction in the release rate of the active pharmaceutical ingredient, prolonging the release time of the matrix.

4. Conclusions

The use of agar as a novel filler substance for hot melt extruded dosage forms was investigated and compared to the commonly used pharmaceutical excipient microcrystalline cellulose. It was found that the presence of the agar filler in the matrix material led to an increase in the viscosity of the matrix material, thus affecting the hot melt extrusion process. This effect was confirmed by steady state rheometry analysis. The rheometry analysis also confirmed that the increase in matrix viscosity was a direct result of percentage inclusion of filler. However, the increase in viscosity was not so substantial as to rule out the use of agar as a filler material in hot melt produced dosage forms. It would, however, limit the amount of agar filler that could be used in the dosage form. Dissolution studies carried out on the dosage forms produced showed that the agar filler slowed down the release of the pharmaceutical agent in an acidic environment. The extent of the increase in dissolution time

increased in proportion to the amount of filler present in the matrix. This effect could be of use for extended release dosage forms. The agar filler system explored in this study proved to be a viable alternative to microcrystalline cellulose as a filler system in hot melt extruded dosage forms.

Acknowledgements

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