INTRODUCTION

An ideal drug delivery system aims to deliver the drug selectively and effectively, to the site of action in the body. Such system should be capable to prevent and retard the drug release until reaching the target site; thus improving the drug availability and therapeutic efficacy and reducing potential side effects. The poor bioavailability represents a major issue for new drug entities as around 60% of these new drugs are reported to have bioavailability issue due to solubility problems. This has increased the attention towards the continuous development and improvement of drug delivery systems, capable to enhance the solubility of poorly soluble drugs; thus enhancing the drug bioavailability and therapeutic efficacy [1]. Various methods and technologies have been reported to improve the bioavailability of poorly soluble drugs, such as mesoporous silica based systems, solid dispersion technology, nanocrystals, liposomes, supercritical fluid technology, self-emulsifying systems and melt extrusion [2-8]. The crystalline drug form might be converted to the more soluble amorphous form (no energy is required to break the intermolecular forces of the crystal lattice) in these approaches. Capmul® MCM products have been widely employed in skin care products and food industries such as; ice creams, bakery, beverages, chewing gums and confectionery. They are obtained via direct esterification of glycerin with vegetable sourced octanoic and decanoic acids. They can enhance the solubility and or absorption of poorly soluble/absorbed drugs [9-11]. Shalendrakumar et al. [12] incorporated Capmul® MCM in the development of a promising controlled delivery system to enhance the oral bioavailability of pentoxifylline. In another study, Meola et al. [13] used Capmul® MCM in the preparation of silica-lipid hybrid microparticles to improve the dissolution and oral delivery of simvastatin. 2-Hydroxyethyl methacrylate (HEMA) represents one of the most commonly used synthetic monomers for the preparation of crosslinked polymers and it has been widely used in many pharmaceutical applications such as soft contact lenses [14] and drug carriers [15]. The easiness of preparation, the flexibility in modifying the polymer structure, the ability to control the drug release and protect it from degradation as well as the polymer swelling behaviour are all features encouraged its use in many biomedical and drug delivery applications. The chemical and thermal stability as well as biodegradability and biocompatibility of poly (2-hydroxyethyl methacrylate) based polymers have also made them attractive for many pharmaceutical and biomedical applications [16-20]. Mangiuc et al. [21] used HEMA in the development of polymeric mucoadhesive nanoparticles, as a potential ophthalmic drug delivery system. Rashid et al. [22] have also used HEMA in the synthesis of polymeric microgels designed for the controlled delivery of acid labile therapeutic agents. The synthesized carrier was loaded with esomeprazole as a model drug. The in vitro and in vivo studies had shown that the carrier was able to retard the drug release in the stomach; while trigger the release in the intestinal environment. The main objective of this study was to develop a drug delivery system, based on poly (2-hydroxyethyl methacrylate) polymer with different concentrations of Capmul® MCM C8, prepared using a free radical polymerization method as a promising system to control and enhance the release of poorly water soluble drugs. Felodipine was selected as a model drug to be loaded in the prepared carriers and in vitro release studies were also performed to study the effect of changing the concentration of Capmul® MCM C8 on the release profiles of the model drug.

MATERIALS AND METHODS

Materials

2-Hydroxyethyl methacrylate, ethylene glycol dimethacrylate, 2,2'-Azobis(2-methylpropionitrile), sodium chloride, sodium phosphate dibasic decahydrate, sodium dodecyl sulphate (SDS), potassium chloride and felodipine were supplied by Sigma-Aldrich, USA. Sodium hydride and potassium phosphate monobasic were supplied by Scharlau Chemie, Spain. Capmul® MCM C8 was supplied by ABITEC, UK. Hydrochloric acid (37%) was supplied by Biosolve Chimie, France. Water used in all experiments was HPLC grade water. All chemicals were used as supplied without any modification.

Methods

Preparation of polymeric films with different concentrations of Capmul® MCM C8

A free radical polymerization method was used to prepare Six polymeric films (P1-P3 and F1-F3) using the quantities described in table 1 by
dissolving the ingredients of each formula together at room temperature with stirring. After that medical syringes (10 ml) with needles were used to pour the prepared solutions into designed molds. A release liner was placed over two glass plates and a medical grade silicone tubing was placed in a hemispherical shape over one of the plates to draw the borders of the mold. The two plate were held together vertically using foldback clips. After pouring the solutions, the molds were placed in the oven allow polymerization at 60 °C for 18 h. After polymerization, the films were then taken out the molds and placed in HPLC grade water and replaced daily to remove any unreacted species, which was confirmed using a UV/VIS spectrophotometer (Spectroscan 80 D, Biotech Engineering Ltd., UK). A cork borer no. 2 (6.25 mm in diameter) was used to cut the swollen polymers into small discs. Finally, these discs were dried until a constant weight was reached.

### Swelling studies

The effect of Capmul® MCM C8 concentration on the swelling ration of the produced discs was investigated in Phosphate Buffered Saline (PBS) at 37 °C. The dried polymeric were weighed and then placed in a McCartney bottle containing 5 ml PBS. The discs were removed from the swelling media at predetermined time points. The removed samples were weighed after being dried superficially using a medical tissue paper and then returned back to the swelling medium. The swelling behavior of the prepared discs was studied via calculating the swelling ratio, using Equation 1, at each time point. The obtained data were analyzed statistically (GraphPad Prism 8 software) using a two-way analysis of variance, followed by Tukey's multiple comparisons test (n=3, p<0.05).

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\text{Swelling ratio (\%)} = \left(\frac{\text{Weight of the swollen disc}}{\text{Weight of the dried disc}}\right) \times 100\%
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#### In vitro drug release studies

The in vitro release of the model drug was investigated in PBS (pH 7.4), containing 1% w/v SDS, using a modified method of Heelan and Corrigan [26-28]. The prepared formulations were immersed in 20 ml PBS (previously maintained at 37 °C) inside a sealed McCartney bottle. The bottle was stirred in a shaking water bath at 37 °C and 100 cycles/min. At predetermined time points, 0.5 ml samples were removed from the bottles and replaced with the same volume of fresh PBS (previously maintained at 37 °C). The withdrawn samples were filtered and analyzed spectrophotometrically (Spectroscan 80 D, Biotech Engineering Ltd., UK) at 364 nm. A calibration curve was constructed at 364 nm and the method was fully validated. The obtained data were analyzed statistically (GraphPad Prism 8 software) using a two-way analysis of variance, followed by Tukey's multiple comparisons test (n=5, p<0.05).

### Table 1: The Prepared polymeric films

| Formula | 2-Hydroxyethyl methacrylate (grams) | Capmul® MCM C8 (grams) | Ethylene glycol dimethacrylate (grams) | 2, 2′-Azobis(2-methylpropionitrile) (grams) | Felodipine (grams) |
|---------|-----------------------------------|-----------------------|---------------------------------------|-------------------------------------------|------------------|
| P1      | 9.8                               | -                     | 0.1                                   | 0.1                                       | -                |
| P2      | 8.8                               | 1.0                   | 0.1                                   | 0.1                                       | -                |
| P3      | 7.8                               | 2.0                   | 0.1                                   | 0.1                                       | -                |
| F1      | 9.3                               | -                     | 0.1                                   | 0.1                                       | 0.5              |
| F2      | 8.3                               | 1.0                   | 0.1                                   | 0.1                                       | 0.5              |
| F3      | 7.3                               | 2.0                   | 0.1                                   | 0.1                                       | 0.5              |

### RESULTS AND DISCUSSION

#### Preparation of polymeric films with different concentrations of Capmul® MCM C8

Six polymeric films loaded with different concentrations (0, 10 and 20% w/w) of the bioavailability enhancer (Capmul® MCM C8), based on 2-Hydroxyethyl methacrylate as a monomer and ethylene glycol dimethacrylate as a crosslinker, were synthesised successfully using a thermal bulk polymerization method. Theses formulations were developed as promising controlled delivery systems and loaded with Capmul® MCM C8 for the potential enhancement of release and bioavailability of poorly water soluble drug. Patel et al. have employed Capmul® MCM C8 as a bioavailability enhancer in pellets designed for improved oral drug delivery of gliclazide [29]. The prepared formulations were loaded with 5% w/w of the antihypertensive agent, felodipine, as a model drug.

#### Swelling studies

A quantitative method was used to evaluate the swelling behaviour of the prepared non-drug loaded formulations (P1-P3) in PBS [30]. The swelling ratio of a polymer in aqueous medium is mainly controlled by the polymer-polymer and polymer-medium interactions and the equilibrium swelling ratio is obtained when a balance occurs between these two interactions [31]. Fig. 1-2 shows the effect of Capmul® MCM C8 concentration on the polymer’s swelling behaviour. The three formulations showed statistically similar profiles with an equilibrium swelling ratio of 35% obtained within 24 h. This indicates the non-significant effect of the used Capmul® MCM C8 concentrations on the polymer’s swelling profile.

![Fig. 1: Time-dependent swelling ratio (mean±SD, n=5) of P1, P2 and P3 in PBS](image-url)
In vitro drug release studies

The release profiles and release rate constants ($K_m$) of felodipine from the prepared formulations (F1-F3) are presented in fig. 3 and table 2. It can be observed that all profiles exhibited a delayed-controlled release for the model drug. The effect of Capmul® MCM C8 on the swelling behavior of the polymer as the three formulations showed statistically similar swelling profiles. All formulations showed a delayed drug release. The formulation with the highest concentration of Capmul® MCM C8 (20 % w/w) exhibited a significant higher drug release compared with the other formulations, which makes a promising system to control and enhance drug release of poorly water soluble drugs.

Table 2: $R^2$, n and $K_m$ after data fitting to the korsmeyer peppas model

| Formulation | $R^2$   | n    | $K_m$   |
|-------------|---------|------|---------|
| F1          | 0.945   | 0.619| 0.082   |
| F2          | 0.962   | 0.610| 0.088   |
| F3          | 0.989   | 0.702| 0.100   |

CONCLUSION

Polymeric drug carriers with different concentrations of Capmul® MCM C8 were prepared successfully using a free radical polymerization method. The formulations were loaded felodipine as a model drug. The effect of added Capmul® MCM C8 on the swelling degree of the polymer was investigated in PBS. There was no significant effect for increasing the concentration of Capmul® MCM C8 on the swelling behavior of the polymer as the three formulations showed statistically similar swelling profiles. All formulations showed a delayed drug release. The formulation with the highest concentration of Capmul® MCM C8 (20 % w/w), exhibited a significant higher drug release compared with the other formulations, which makes a promising system to control and enhance drug release of poorly water soluble drugs.

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ABBREVIATION

HEMA: 2-hydroxyethyl methacrylate; BCS: Biopharmaceutics Classification System; SDS: Sodium Dodecyl Sulphate; PBS: Phosphate Buffered Saline.

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AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

CONFLICT OF INTERESTS

No conflicts of interest to disclose.

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