Hydrophilic Matrices for Oral Control Drug Delivery

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Abstract: Oral controlled drug delivery has gathered tremendous attention over the years due to its many advantages over conventional dosage forms. Polymer-based matrices have become an integral part of the pharmaceutical industry. Hydrophilic matrices are capable of controlling the release of drug over an extended period of time. Hydrophilic polymers, especially the hydrophilic derivatives of cellulose ethers, are frequently used for these applications. Therefore, the objective of this review is to discuss the scientific and physicochemical aspects of these polymeric systems that can affect the drug release from such formulations.

Keywords: Hydrophilic matrices; Hyromellose; Methylcellulose; Matrix swelling; Matrix erosion

1. Introduction

The goal of any drug delivery system is to provide a therapeutic amount of drug to its intended site in the body, so that a desired drug concentration at the site of action is achieved promptly and then maintained over a specified period of time. Thus, an ideal drug delivery system should have the capacity to deliver drugs at a particular rate as required by the patient. However, most traditional oral dosage forms require frequent and repeated doses to achieve these objectives [1,2]. Thus, it is far from an ideal therapeutic environment as fluctuation of plasma drug concentrations over successive administrations may lead to overdosing or underdosing of the patient. Moreover, drugs with short biological half-lives require frequent doses to maintain therapeutic concentrations in the body. Additionally, the lack of compliance due to a forgotten dose or overnight troughs can significantly deteriorate the treatment plan [3].

Owing to these problems, controlled drug release approaches have become popular over the years. The use of hydrophilic polymers to develop hydrophilic matrices became eminent as they enable the drugs to be released continuously over long periods of time, which ultimately improves patient compliance and decreases patient-to -patient variations in drug administration patterns. Furthermore, it reduces the total amount of administered drug and possible side-effects related to high peak plasma drug levels [4].

2. Hydrophilic matrices

Hydrophilic matrix tablets are the most frequently used controlled release oral dosage forms intended for oral administration [5,6]. Commonly, hydrophilic matrices are compressed matrix tablets and can easily be prepared by direct compression of a powder mixture of drug with a release retardant, swellable polymer and other additives to aid processing. Such matrices are commonly employed because of the advantages associated with their manufacturing, including simple formulation, the use of existing tableting technologies and the low cost of polymers, which are generally regarded as safe excipients [7]. These hydrophilic matrices have the ability to release the drug over a defined period of time, as they do not undergo disintegration when delivered to patients, as the drug is entrapped in the polymeric network at the particulate level (Figure 1).

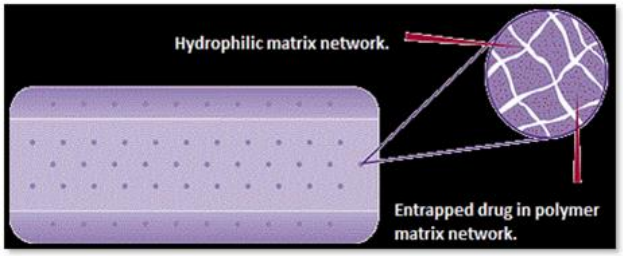

Figure 1, Cross-sectional view of typical hydrophilic matrix tablet

Numerous swellable, carbohydrate-based polymers are available, allowing flexibility for the needs of an individual formulation to achieve specific goals in drug therapy [8].

3. Cellulose ether-based hydrophilic matrices

Among the swellable polymers usually used to develop these hydrophilic matrices, cellulose ethers, specifically methylcellulose (MC) and hypromellose (hydroxypropyl methylcellulose, HPMC), have provoked extensive interest [6]. Their widespread acceptance can be attributed to good compression properties, adequate swelling characteristics which allow the matrix tablet to develop an

external gel layer on the surface of matrix tablet, non-toxic nature, availability in different grades, ability to give pH independent drug release profiles, anti-static properties and amenability to high levels of drug loading [7,8].

4. Mechanism of swelling, erosion and drug release

Polymer swelling, drug dissolution and matrix erosion are the phenomena that determine the mechanism of drug release from hydrophilic matrix tablets, either on a macroscopic or molecular level [11]. When drug loaded swellable cellulose ethers based hydrophilic matrices are exposed to dissolution fluid, steep water concentration gradients are formed between the dissolution fluid and the outermost surface of matrix tablet. This results in water imbibition into the polymer matrix network. To describe this process adequately, it is important to consider the exact geometry of the matrix tablet, as in the case of cylinders, both axial and radial directions of mass transport can be manifested which have a significant dependence of the water diffusion coefficient and the matrix swelling [12,13].When dry matrix tablets are introduced into the liquid system, the diffusion coefficient tends to be very low, whereas in highly swollen gels, it is of the same magnitude as pure water. So, the liquid acts as a plasticizer and the glass transition temperature (T_g) reduces from somewhere between 154 – 184 ºC to around the system temperature, 37 ºC [14]. Once the T_g equals the temperature of the system, the polymer chains start to relax and eventually disentangle increasing the molecular surface area [6]. This phenomenon of polymer chain relaxation is termed 'swelling' and the continuous inward ingression of liquid breaks the hydrogen bonds formed during tablet compaction and can lead to the development of new hydrogen bonds accommodating water molecules [15]. Therefore, the reduction in T_g and formation of new hydrogen bonds results in the swelling of polymer chains. As a consequence, a thick gelatinous layer appears on the surface of matrix tablets, commonly known as a gel layer, as MC/HPMC pass from the amorphous glassy state to the rubbery state ([8, 16-19]

The development of the gel layer actually divides the matrix tablet into three different distinguishable regions. The highly swollen outer region (erosion front) has the highest amount of water molecules but it is mechanically weak. However, it acts as a diffusion barrier preventing water penetration into the other two regions. The middle region (dissolution front) is moderately swollen and is relatively stronger than the outer one. The core of the matrix tablet which actually forms the innermost region (swelling front), remains essentially dry and holds its glassy state for a longer period of time [6,20]. Moreover, there is evidence that a fourth front (penetration front) is also present, between the swelling and dissolution fronts, adding further complexity to the system [21]. A schematic illustration of the different fronts which develop due to liquid penetration is shown in Figure 2.

The gel layer grows over time as more water penetrates into the matrix tablet. The polymer chains present on the surface of matrix tablet hydrate quickly compared to those located inside the core and contact with the liquid causes chain relaxation (swelling) which initiates erosion of the matrix. Instantaneously, the outermost layer becomes fully hydrated and starts to relax, leading to the disentanglement of polymeric chains [22]. Consequently, matrices start to dissolve from their surface, as water continuously permeates towards the core [23]. The relative rates of liquid uptake and erosion of a polymer matrix play a critical role in controlling the rate of drug release. The swelling, matrix erosion, drug release mechanism and rate are dependent on the concentration, degree of substitution and polymer chain length of HPMC being used in the hydrophilic matrices [24,25]. HPMC has the potential to hydrate quickly enough to form a gel layer before the drug entrapped in the tablet matrix can dissolve.

There are two processes involved during the dissolution of hydrophilic matrix tablets, by which polymer erosion from the hydrophilic matrices takes place. Firstly, the disentanglement of individual polymer chains at the surface of matrix tablets and secondly their subsequent transport to the surrounding bulk solution. The physical

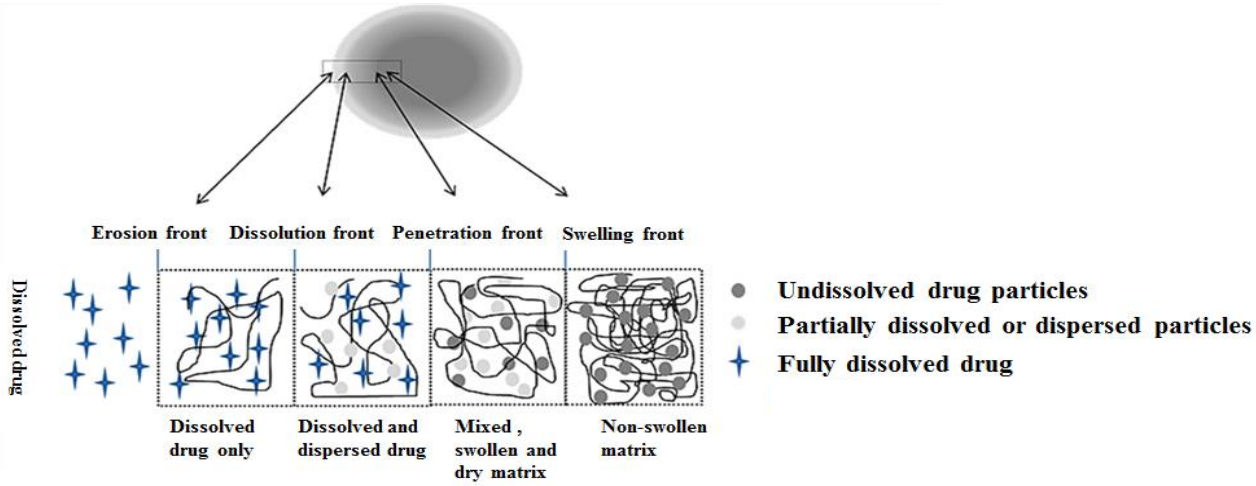

Figure 2, Mechanism of drug release from hydrophilic matrix tablet

entanglement of the polymer chains precludes polymer dissolution, but polymer present at the outermost surface is diluted by the bulk dissolution medium over time to a point when the polymeric network no longer has structural integrity. This eventually leads to polymer disentanglement and the matrix tablet starts to disappear [4,6,13,17,26]. Both MC and HPMC are water soluble and, as the water penetrates into the hydrophilic matrix, the polymer chains become hydrated and these eventually start to disentangle from the matrix because MC and HPMC contain linear hydrophilic polymeric chains which do not chemically cross-link but instead form a gelatinous layer on the surface of the tablets that is vulnerable to matrix erosion. At high polymer concentrations, the linear polymer chains entangle to form what may be considered a physically cross-linked structure, which eventually erodes, resulting in the liberation of polymer and drug molecules [24]. However, the rate of polymer erosion is dependent on the viscosity of the MC/HPMC grade being used in the formulation. Tablets fabricated using a high molecular weight and viscosity grade MC/HPMC show more resistance to polymer erosion than the low molecular weight and low viscosity grades [4,27].

Figure 3 illustrates a general drug release mechanism on the basis of solubility of incorporated drugs. Release is controlled by diffusion through, and erosion of, the gel layer and any drug present on the surface of the matrix tablet is quickly released. This is followed by expansion of the gel layer as water permeates into the tablet, increasing the thickness of the gel layer [28,29]. If a well-defined gel layer is formed, the rate of drug release is reduced and becomes dependent on the rate at which the drug molecules diffuse through the gel, as well as the rate at which the barrier layer is mechanically removed by attrition and disentanglement of the matrix. In most cases, both diffusion and erosion occur simultaneously [30-34] Highly water soluble drugs diffuse through the gel layer before the matrix erodes, but it is suggested that the presence of poorly soluble drugs can increase matrix erosion by imperilling the integrity of the gel layer [33,34]. So, the solubility of entrapped drugs is another key factor in determining the drug release behaviour from hydrophilic matrices. Mechanistically, both diffusion and erosion will be contributing factors in controlling drug release from a hydrophilic matrix tablet. In practical terms, however, one process will often play a dominant role over the other depending on the HPMC level and solubility of other matrix tablet contents [35].

5. Factors affecting drug release

Although the fabrication of compressed hydrophilic matrices may be simple, it becomes very complex and challenging when it comes to explaining the mechanism of drug release from these polymeric devices. The physicochemical properties of MC/HPMC and incorporated drug significantly impact the swelling, erosion and drug release. In this section, the principal factors that can affect swelling, erosion and drug release will be discussed; however, a summary of all the major contributing factors is presented in Table 4.1.

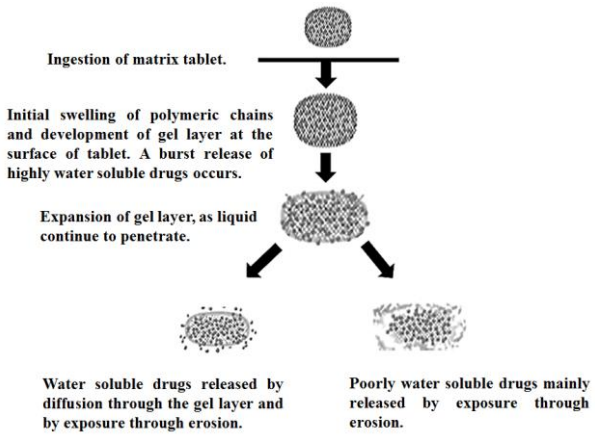

Figure 3, Release mechanism of water soluble and poorly water soluble drugs from hydrophilic matrix tablet

5.1. Effect of concentration

Commonly, it is noticed that regardless of the physicochemical properties of hydrophilic polymer, the drug release rate decreases with an increase in the levels of polymer in a hydrophilic matrix tablet. Reza et al. (2003) [36] reported that higher levels of polymer correspond to a lower porosity of the matrix tablet and slower drug release rates can be achieved. Moreover, Ebube et al. (2004) [37] investigated the effect of polymer levels on the release of acetaminophen and found an increase in the percentage of polymer (3.5% to 19.2%) in the matrix tablet led to a decrease in the drug release rate. The results of these experiments are in complete agreement with the findings of Mitchell et al. (1993) [24], who concluded that a greater degree of physical cross-linking of polymer chains is evident when the amount of HPMC has been increased. This in turn increases the tortuosity of release pathway from the matrix tablets and essentially corresponds to slower drug release. The first 5 min contact between the matrix tablet and aqueous fluids is a very important time for the development of the gel layer on the surface of matrix tablet [38,39]. After such times, if the structure has not formed, the matrix may erode too quickly and lead to premature drug release. Higher polymer content in a matrix tablet results in the formation of a stronger gel; at low polymer levels the gel does not form quickly. As hypromellose content is increased, the resulting gelatinous diffusion layer becomes stronger and more resistant to diffusion and erosion [40]. Recently, Jain et al. (2014) [41] concluded that the higher levels of HPMC in a matrix tablet exhibit slower erosion and drug release rate. These conclusions are in complete accordance with the findings of Ghori et al. (2014) [34], who reported that the increase in the HPMC concentration (20% to 80 %) in a matrix tablet tends to decrease the rate drug release, regardless of drug solubility.

However, there is a difference of opinion, as some authors do not agree with this notion, as in the case of [23]. In their studies, these authors prepared the hydrophilic matrices incorporating a highly water soluble drug, tramadol, and failed to observe significant changes in the release profile with changes in the polymer concentration. In formulations of drugs that are highly

soluble in water, it is usual to find that, above a certain percentage of polymer, the release rate does not decrease.

It was reported that once a particular polymer level is reached, the effects from characteristics such as viscosity, burst effect and particle size are less evident. A polymer content of 30% – 40% appears to be the level at which similar drug-release profiles are obtained from differing grades of hypromellose (2208, 2906, and 2910) [39]. However, Campos-Aldrete and Villafuerte-Robles (1997) [38] reported that the HPMC concentrations higher than 20% can become the overriding factor and the effect of viscosity and particle size do not cause any significant changes in the drug release profiles. Moreover, the conclusions of Heng et al. (2001) [42] are in complete accordance with aforementioned studies, and that the increase in HPMC concentration can significantly suppress the impact of particle size.

5.2. Effect of particle size

Over the years, the effect of the particle size of the polymer on drug release has been studied in depth by different authors [38, 43-46]. A general observation can be drawn from these studies that the particle size of the polymer is not as decisive as expected. However, narrower particle size distribution of polymer in a matrix system initiates the prompt development of the gel layer on the surface of matrix tablet. Hydrophilic matrices formulated with polymer particles sizes larger than 200 µm disintegrate before the development of the so-called surface gel layer, while those formulated with particle sizes smaller than 150 µm can form the gel layer rapidly, preventing the disintegration of the system and lead to prolonged drug release profiles [47]. Mitchell et al. (1993) [24] reported that the polymer particles tend to dissolve slowly and failed to provide adequate controlled drug release. The use of larger sized hypromellose K15M particles (> 355 µm) left much larger pores on the surface of matrices that essentially make the gel layer structure unstable and lead to rapid drug release. Some authors have proposed that the effect of MC/HPMC particle size can be minimised with high concentrations of polymers, as described in the earlier section, 4.5.1. Heng et al. (2001) [42] carried out experiments to elucidate the impact of particle size on drug release profiles. It was revealed that the HPMC K15M matrices, with a mean particle size smaller than 113 µm, release drug through a combination of erosion and diffusion mechanisms. However, for matrix tablets having a HPMC particle size of greater than 113 µm there was rapid drug release behaviour and the release mechanism was considered to be more erosion-based. Furthermore, Miranda et al. (2007) [48] reported on the relationship between particle size of matrix components and their percolation threshold. It was concluded that the larger polymer particle sizes were less effective in the formation of a homogeneous gel layer.

5.3. Effect of substitution

Different polymer properties have been reported to be responsible for the rate of polymer hydration, including substitution type. It was initially proposed that cellulose ethers of different substitution levels hydrate at different rates and this factor may be used to optimise the formulation of sustained release matrices (Alderman, 1984). However, using a combination of differential scanning calorimetry (DSC) and dissolution studies showed that the differences in release rates for HPMCs [24] with different substitution levels are not due to differences in hydration rate. Further studies using thermo-mechanical analysis [49] indicated that the gel layer thickness (which will affect the diffusional path length) is similar in HPMCs of different substitution type. The type of the substituent determines the hydration rate of the polymer and can significantly affect the hydration rate and drug release. The drug release is dependent on the substitution type if the polymer level is kept low, so that the polymer concentration is not the overriding factor in controlling the swelling, erosion and drug release behaviour of hydrophilic matrices [18,50]. The change in the substitution levels impacts the polymer relaxation in tablet matrices; it was confirmed that different substitution levels gave rise to different water mobility, leading to differing drug-release characteristics [51]. Furthermore, McCrystal et al. (1999) [52] confirmed that the amount of water that attaches to the polymer and the amount of tightly bound water significantly depend on the degree of substitution. The substituents of a polymer side chain alter its polarity and melting point. For example, substitutions of the side-chain groups by more polar groups result in a reduction in the crystallinity of the polymer, which is reflected in a decrease in its melting point. This affects the solubility of the polymer in water. In general, the aqueous solubility of a polymer can be said to be related to its ability to establish hydrogen bridges between the hydrogen atoms of the water and those of the oxygen present in the side chain and the substituents of the polymer [53]. In the particular case of matrix systems, the type of substitution not only influences the solubility of the polymer in water, but also the gel strength, and the swelling and erosion of the polymer. In the case of HPMC, the rate of swelling depends on the side-chain substituents, such that the higher the number of hydroxyl groups, the faster the hydration [54-57]. Moreover, Escudero et al. (2010) [57] studied the influence of replacement of the HPMC chain on the release of theophylline contained in mixtures of a swelling polymer with an inert one. Three different types of substitution based on methoxyl and hydroxyl groups were tested; E4M, K4M and F4M, and the HPMC F4M resulted in slower drug release rates because it had the largest number of hydrophobic substituents (methoxyl). For the ratio, inert polymer/swelling polymer 75:25, where the characteristics of viscosity and substitution of the HPMC were less important than the properties of the inert polymer, the mixtures made with HPMC F4M and E4M allowed a more homogeneous gel structure and easier modulation of drug release rate.

5.4. Effect of viscosity (molecular size/chain length)

The viscosity of MC/ HPMC is considered to be another important parameter that controls and determines the mechanism of release. The viscosity of a polymer in solution very much depends on the chemical structure of the polymer, its molecular weight and its interaction with the solvent. Various authors have studied the impact of MC/HPMC viscosity on drug release from hydrophilic matrices. It can be concluded from these studies that the higher the viscosity of a polymer, the faster the swelling of its side chains, forming a very strong gel, which decreases the drug release rate. Moreover, various studies have reported a decline in the rate of drug release with increase in the polymer viscosity [58-60].

A study carried out by Wan et al. (1991) [61] proposed that an increase in viscosity of HPMC tends to increase

the swelling and drug release rates. It can be attributed to the fact that the pores of high-viscosity hypromellose block up quickly and inhibit further liquid uptake. This in turn leads to the formation of a turbid gel, which resists dilution and erosion, subsequently resulting in slower drug diffusion and release rates [62].

Furthermore, it has been demonstrated by Campos-Aldrete and Villafuerte-Robles (1997) [38] that in the case of HPMC, increases in the viscosity of the polymer lead to slower drug release rates as long as the percentages of polymer do not surpass 20%. Studies addressing swelling and erosion carried out by Ravi et al. (2008) [63] have shown that the percentages of swelling and erosion are completely dependent on the viscosity of the polymer and the percentage of swelling increases as the viscosity of HPMC increases, however, the percentage of erosion decreases when the viscosity of the polymer increases.

5.5. Effect of drug solubility

Drug solubility is a very important factor as high or low solubility can significantly affect the gel characteristics and drug release [62, 64, 65]. Ford et al. (1985) [66] studied the release of both water soluble (promethazine hydrochloride, aminophylline and propranolol hydrochloride) and poorly soluble (indomethacin) drugs from HPMC matrix systems. For indomethacin, both the viscosity grade of HPMC and the particle size of the drug were reported to contribute more to controlling the drug release than was the case for water soluble drugs. This was primarily due to the dominant erosion mechanism of drug release in the case of poorly soluble drugs. High concentrations of insoluble drugs and excipients may cause non-uniform swelling of the hydrophilic matrix tablet. However, careful tailoring of the concentrations of insoluble drug and polymer in a system can be used to slow the dissolution rate of the insoluble drug [67]. It has been suggested that highly-soluble drugs can be released by diffusing through the gel matrices and this is considered to be the main pathway for their release. However, drug release also occurs through erosion of the gel matrix. It is said that highly soluble drugs can also act as pore formers with the formation of micro-cavities, rendering the gel structure more porous and weaker, hence leading to increased drug release rates. Poorly soluble drugs, however, are released predominantly by erosion of the gel matrix, as the drug particles translocate and their presence compromises the structural integrity of the gel layer present on the surface of the matrix tablet, leading to drug release through matrix erosion [33,68]. Several authors have studied whether the incorporation of highly water-soluble drugs into matrix systems with hydrophilic or hydrophobic polymers affects the drug release rate. Tramadol was formulated with HPMC or hydrogenated castor oil (HCO) and it was easier to modulate the release rate of the highly water-soluble drug from HMPC matrices than in those made of HCO [23]. Recently, Ghori et al. (2014) [34] reported similar findings, i.e., that the poorly soluble drug was released predominately through erosion while the water soluble drug was released via a diffusion mechanism. Furthermore, Ghori et al. (2014) [34] demonstrated that the values of the drug diffusion co-efficient (for a poorly soluble model drug) of the Korsmeyer and Peppas model (n) are linearly related to the erosion rate of matrices, endorsing the view that poorly water soluble drugs are released mainly through an erosion mechanism.

6. Conclusions

Hydrophilic matrices have distinct advantages which make them interesting candidate for oral controlled drug delivery. This review has elaborated the factors related to drug release mechanism from hydrophilic matrices. Moreover, various physicochemical attributes associated with polymers have significant impact on the performance and functionalities of hydrophilic matrices. This critical information can be used in the development of hydrophilic matrices.

Acknowledgements

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References

[1] WISE, D. L. 2000. Handbook of Pharmaceutical Controlled Release Technology, Taylor & Francis.

[2] YIHONG, Q. 2009. Development of modified release oral solid dosage forms. In: Q. YIHONG, C. Y., G. Z. ZHANG (ed.) Developing solid oral dosage forms: pharmaceutical theory and practice Elsevier.

[3] REMINGTON, J. P. & ALLEN, L. V. 2013. Remington: The Science and Practice of Pharmacy, Pharmaceutical Press.

[4] WEN, H. & PARK, K. 2011. Oral Controlled Release Formulation Design and Drug Delivery: Theory to Practice, Wiley.

[5] ALDERMAN, D. A. 1984. A review of cellulose ethers in hydrophilic matrices for oral controlled-release dosage forms. International Journal of Pharmaceutical Technology and Product Manufacture, 5, 1-9.

[6] MADERUELO, C., ZARZUELO, A. & LANAO, J. M. 2011. Critical factors in the release of drugs from sustained release hydrophilic matrices. Journal of Controlled Release, 154, 2-19.

[7] WEN, X., ALI, N. & ALI, R.-S. 2010. Oral extended release hydrophilic matrices: formulation and design. In: WEN, H. & PARK, K. (eds.) Oral Controlled Release Formulation Design and Drug Delivery: Theory to Practice. John Wiley & Sons.

[8] SIEPMANN, J., SIEGEL, R. A. & RATHBONE, M. J. 2011. Fundamentals and Applications of Controlled Release Drug Delivery, Springer.

[9] GHORI, M. U., ŠUPUK, E., & CONWAY, B. R. 2014. Tribo-electric charging and adhesion of cellulose ethers and their mixtures with flurbiprofen. European Journal of Pharmaceutical Sciences, 65, 1-8.

[10] GHORI, M. U., ŠUPUK, E., & CONWAY, B. R. 2015. Tribo-electrification and powder adhesion studies in the development of polymeric hydrophilic drug matrices. Materials, 8(4), 1482-1498.

[11] CHAIBVA, F. A., KHAMANGA, S. M. M. & WALKER, R. B. 2010. Swelling, erosion and drug release characteristics of salbutamol sulfate from hydroxypropyl methylcellulose-based matrix tablets. Drug Development and Industrial Pharmacy, 36, 1497-1510.

[12] FORD, J. L., RUBINSTEIN, M. H., MCCAUL, F., HOGAN, J. E. & EDGAR, P. J. 1987. Importance of drug type, tablet shape and added diluents on drug release kinetics from hydroxypropylmethylcellulose matrix tablets. International Journal of Pharmaceutics, 40, 223-234.

[13] SIEPMANN, J. & PEPPAS, N. A. 2001. Modeling of drug release from delivery systems based on hydroxypropyl methylcellulose (HPMC). Advanced Drug Delivery Reviews, 48, 139-157.

[14] CONTI, S., MAGGI, L., SEGALE, L., OCHOA MACHISTE, E., CONTE, U., GRENIER, P. & VERGNAULT, G. 2007. Matrices containing NaCMC and HPMC. 2. Swelling and release mechanism study. International Journal of Pharmaceutics, 333, 143-151.

[15] LI, C. L., MARTINI, L. G., FORD, J. L. & ROBERTS, M. 2005. The use of hypromellose in oral drug delivery. Journal of Pharmacy and Pharmacology, 57, 533-546.

[16] COLOMBO. P., BETTINI, R., PEPPAS. N. A., Observation of swelling process and diffusion front position during swelling in hydroxypropyl methyl cellulose (HPMC) matrices containing a soluble drug. Journal of Controlled Release 61 (1999) 83-91.

[17] COLOMBO. P., BETTINI, R., SANTI. P., PEPPAS. N. A., Swellable matrices for controlled drug delivery: gel-layer behaviour, mechanisms and optimal performance. Pharmaceutical Science and Technology Today, 3 (2000) 198-204.

[18] GHORI, M. U. 2014. Release kinetics, compaction and electrostatic properties of hydrophilic matrices. PhD thesis, University of Huddersfield, UK.

[19] GHORI, M. U., SMITH, A. M., & CONWAY, B. R. 2014. Hydration and erosion properties of cellulose ethers. In-Proceedings of The AAPS Annual meeting and Exposition.

[20] OMIDIAN, H. P., Swelling agents and devices in oral drug delivery. Journal of Drug Delivery Science and Technology, 18 (2008) 83-93.

[21] FERRERO, C., MASSUELLE, D. & DOELKER, E. 2010. Towards elucidation of the drug release mechanism from compressed hydrophilic matrices made of cellulose ethers. II. Evaluation of a possible swelling-controlled drug release mechanism using dimensionless analysis. Journal of Controlled Release, 141, 223-233.

[22] VUEBA, M. L., BATISTA DE CARVALHO, L. A. E., VEIGA, F., SOUSA, J. J. & PINA, M. E. 2005. Role of cellulose ether polymers on ibuprofen release from matrix tablets. Drug Development and Industrial Pharmacy, 31, 653-665.

[23] TIWARI, S. B., MURTHY, T. K., PAI, M. R., MEHTA, P. R. & CHOWDARY, P. B. 2003. Controlled release formulation of tramadol hydrochloride using hydrophilic and hydrophobic matrix system. AAPS PharmSciTech, 4, 18-23.

[24] MITCHELL, K., FORD, J. L., ARMSTRONG, D. J., ELLIOTT, P. N. C., ROSTRON, C. & HOGAN, J. E. 1993. The influence of concentration on the release of drugs from gels and matrices containing Cellulose ethers . International Journal of Pharmaceutics, 100, 155-163.

[25] WAN, L. S. C., HENG, P. W. S. & WONG, L. F. 1991. The effect of hydroxypropylmethylcellulose on water penetration into a matrix system. International Journal of Pharmaceutics, 73, 111-116.

[26] MILLER-CHOU, B. A. & KOENIG, J. L. 2003. A review of polymer dissolution. Progress in Polymer Science, 28, 1223-1270.

[27] GHORI, M. U., & CONWAY, B. R. 2015. Effect of viscosity on swelling, dissolution and compaction properties of hypromellose matrices . In-Proceedings of CRS Annual meeting & Exposition.

[28] FORD, J. L., RUBINSTEIN, M. H., CHANGELA, A. & HOGAN, J. E. 1985a. Influence of pH on the dissolution of promethazine hydrochloride from hydroxypropylmethylcellulose controlled release tablets. Journal of Pharmacy and Pharmacology, 37, 115P-115P.

[29] TALUKDAR, M. M., MICHOEL, A., ROMBAUT, P. & KINGET, R. 1996. Comparative study on xanthan gum and hydroxypropylmethyl cellulose as matrices for controlled-release drug delivery I. Compaction and *in vitro* drug release behaviour. International journal of pharmaceutics, 129, 233-241.

[30] GAO, P., SKOUG, J. W., NIXON, P. R., ROBERT JU, T., STEMM, N. L. & SUNG, K.-C. 1996. Swelling of hydroxypropyl methylcellulose matrix tablets. 2. Mechanistic study of the influence of formulation variables on matrix performance and drug release. Journal of Pharmaceutical Sciences, 85, 732-740.

[31] KIM, C.-J. 1999. Release kinetics of coated, donut-shaped tablets for water soluble drugs. European Journal of Pharmaceutical Sciences, 7, 237-242.

[32] KIM, H. & FASSIHI, R. 1997. Application of a binary polymer system in drug release rate modulation. 1. Characterization of release mechanism. Journal of Pharmaceutical Sciences, 86, 316-322.

[33] BETTINI, R., CATELLANI, P. L., SANTI, P., MASSIMO, G., PEPPAS, N. A. & COLOMBO, P. 2001. Translocation of drug particles in HPMC matrix gel layer: Effect of drug solubility and influence on release rate. Journal of Controlled Release, 70, 383-391.

[34] GHORI, M. U., GINTING, G., SMITH, A. M. & CONWAY, B. R. 2014. Simultaneous quantification of drug release and erosion from hypromellose hydrophilic matrices. International Journal of Pharmaceutics, 465, 406-412.

[35] SINHA ROY, D. & ROHERA, B. D. 2002. Comparative evaluation of rate of hydration and matrix erosion of HEC and HPC and study of drug release from their matrices. European Journal of Pharmaceutical Sciences, 16, 193-199.

[36] REZA, M. S., QUADIR, M. A. & HAIDER, S. S. 2003. Comparative evaluation of plastic, hydrophobic and hydrophilic polymers as matrices for controlled-release drug delivery. Journal of Pharmacy and Pharmaceutical Sciences, 6, 282-291.

[37] EBUBE, N. K & JONES, A. B. 2004. Sustained release of acetaminophen from heterogeneous mixture of two hydrophilic non-ionic cellulose ether polymers International Journal of Pharmaceutics, 272, 19-27.

[38] CAMPOS-ALDRETE, M. E. & VILLAFUERTE-ROBLES, L. 1997. Influence of the viscosity grade and the particle size of HPMC on metronidazole release from matrix tablets. European Journal of Pharmaceutics and Biopharmaceutics, 43, 173-178.

[39] NELLORE, R. V., SINGH REKHI, G., HUSSAIN, A. S., TILLMAN, L. G. & AUGSBURGER, L. L. 1998. Development of metoprolol tartrate extended-release matrix tablet formulations for regulatory policy consideration. Journal of Controlled Release, 50, 247-256.

[40] KLANČAR, U., BAUMGARTNER, S., LEGEN, I., SMRDEL, P., KAMPUŠ, N. J., KRAJCAR, D., ... & KOČEVAR, K. (2015). Determining the Polymer Threshold Amount for Achieving Robust Drug Release from HPMC and HPC Matrix Tablets Containing a High-Dose BCS Class I Model Drug: In Vitro and In Vivo Studies. AAPS PharmSciTech, 16(2), 398-406.

[41] JAIN, A. K., SÖDERLIND, E., VIRIDÉN, A., SCHUG, B., ABRAHAMSSON, B., KNOPKE, C., TAJAROBI, F., BLUME, H., ANSCHÜTZ, M. & WELINDER, A. 2014. The influence of hydroxypropyl methylcellulose (HPMC) molecular weight, concentration and effect of food on in vivo erosion behavior of HPMC matrix tablets. Journal of Controlled Release. 187 50-58.

[42] HENG, P. W. S., CHAN, L. W., EASTERBROOK, M. G. & LI, X. 2001. Investigation of the influence of mean HPMC particle size and number of polymer particles on the release of aspirin from swellable hydrophilic matrix tablets. Journal of Controlled Release, 76, 39-49.

[43] CARABALLO, I. 2010. Factors affecting drug release from hydroxypropyl methylcellulose matrix systems in the light of classical and percolation theories. Expert Opinion on Drug Delivery, 7, 1291-1301.

[44] DABBAGH, M. A., FORD, J. L., RUBINSTEIN, M. H. & HOGAN, J. E. 1996. Effects of polymer particle size, compaction pressure and hydrophilic polymers on drug release from matrices containing ethylcellulose. International Journal of Pharmaceutics, 140, 85-95.

[45] VELASCO, M., FORD, J. L., ROWE, P. & RAJABI-SIAHBOOMI, A. R. 1999. Influence of drug: hydroxypropylmethylcellulose ratio, drug and polymer particle size and compression force on the release of diclofenac sodium from HPMC tablets. Journal of Controlled Release, 57, 75-85.

[46] ZULEGER, S. & LIPPOLD, B. C. 2001. Polymer particle erosion controlling drug release. I. Factors influencing drug release and characterization of the release mechanism. International Journal of Pharmaceutics, 217, 139-152.

[47] DOW 2006. The dow chemical company, Using Dow Excipients for Controlled Release of Drugs in Hydrophilic Matrix Systems, 2006.

[48] MIRANDA, A., , MILLAN, M., & CARABALLO, I., 2007. Investigation of the influence of particle size on the excipient percolation thresholds of HPMC hydrophilic matrix tablets. Journal of Pharmaceutical Sciences 96.10 : 2746-2756.

[49] MALAMATARIS, S. & KARIDAS, T. 1994. Effect of particle size and sorbed moisture on the tensile strength of some tableted hydroxypropyl methylcellulose (HPMC) polymers. International Journal of Pharmaceutics, 104, 115-123.

[50] GHORI, M. U., SUPUK, E., CONWAY., B.R. 2012. Impact of hypromellose substitution levels on tribo-electrification, swelling and dissolution rate of flurbiprofen matrices. In-Proceedings of UKPharmSci.

[51] RAJABI-SIAHBOOMI, A. R., BOWTELL, R. W., MANSFIELD, P., DAVIES, M. C. & MELIA, C. D. 1996. Structure and behavior in hydrophilic matrix sustained release dosage forms: 4. Studies of water mobility and diffusion coefficients in the gel layer of HPMC tablets using NMR imaging. Pharmaceutical Research, 13, 376-380.

[52] MCCRYSTAL, C. B., FORD, J. L. & RAJABI SIAHBOOMI, A. R. 1999. Water distribution studies within cellulose ethers using differential scanning calorimetry. 2. Effect of polymer substitution type and drug addition. Journal of Pharmaceutical Sciences, 88, 797-801.

[53] SARKAR, N. & WALKER, L. 1995. Hydration—dehydration properties of methylcellulose and hydroxypropylmethylcellulose. Carbohydrate Polymers, 27, 177-185.

[54] ASARE-ADDO, K., KAIALY, W., LEVINA, M., RAJABI-SIAHBOOMI, A., GHORI, M. U., SUPUK, E., LAITY, P. R., CONWAY, B. R. & NOKHODCHI, A. 2013. The influence of

agitation sequence and ionic strength on *in vitro* drug release from hypromellose (E4M and K4M) ER matrices-The use of the USP III apparatus. Colloids and Surfaces B: Biointerfaces, 104, 54-60.

[55] VIRIDÉN, A., LARSSON, A. & WITTGREN, B. 2010. The effect of substitution pattern of HPMC on polymer release from matrix tablets. International Journal of Pharmaceutics, 389, 147-156.

[56] VIRIDÉN, A., WITTGREN, B., ANDERSSON, T. & LARSSON, A. 2009. The effect of chemical heterogeneity of HPMC on polymer release from matrix tablets. European Journal of Pharmaceutical Sciences, 36, 392-400.

[57] ESCUDERO, J., FERRERO, C. & JIMÉNEZ-CASTELLANOS, M. 2010. Compaction properties, drug release kinetics and fronts movement studies from matrices combining mixtures of swellable and inert polymers. II. Effect of HPMC with different degrees of methoxy/hydroxypropyl substitution. International Journal of Pharmaceutics, 387, 56-64.

[58] DALY, P., DAVIS, S. & KEIMERLEY, J. 1984. The effect of anionic surfactants on the release of chlorpheniramine from a polymer matrix tablet. International Journal of Pharmaceutics, 18, 201-205.

[59] NAKANO, M., OHMORI, N., OGATA, A., SUGIMOTO, K., TOBINO, Y., IWAOKU, R. & JUNI, K. 1983. Sustained release of theophylline from hydroxypropylcellulose tablets. Journal of Pharmaceutical Sciences, 72, 378-380.

[60] SALAMONE, J. C. 1996. Polymeric Materials Encyclopedia, Twelve Volume Set, Taylor & Francis.

[61] WAN, L. S. C., HENG, P. W. S. & WONG, L. F. 1991. The effect of hydroxypropylmethylcellulose on water penetration into a matrix system. International Journal of Pharmaceutics, 73, 111-116.

[62] GAO, P., SKOUG, J. W., NIXON, P. R., ROBERT JU, T., STEMM, N. L. & SUNG, K.-C. 1996. Swelling of hydroxypropyl methylcellulose matrix tablets. 2. Mechanistic study of the influence of formulation variables on matrix performance and drug release. Journal of Pharmaceutical Sciences, 85, 732-740.

[63] RAVI, P. R., KOTREKA, U. K., & SAHA, R. N. 2008. Controlled release matrix tablets of zidovudine: effect of formulation variables on the in vitro drug release kinetics. AAPS PharmsciTech, 9(1), 302-313.

[64] CONTE, U. & MAGGI, L. 1996. Modulation of the dissolution profiles from Geomatrix sup® multi-layer matrix tablets containing drugs of different solubility. Biomaterials, 17, 889-896.

[65] REYNOLDS, T. D., MITCHELL, S. A. & BALWINSKI, K. M. 2002. Investigation of the effect of tablet surface area/volume on drug release from hydroxypropylmethylcellulose controlled-release matrix tablets. Drug Development and Industrial Pharmacy, 28, 457-466.

[66] FORD, J. L., RUBINSTEIN, M. H. & HOGAN, J. E. 1985b. Formulation of sustained release promethazine hydrochloride tablets using hydroxypropyl-methylcellulose matrices. International Journal of Pharmaceutics, 24, 327-338.

[67] FORD, J. L., RUBINSTEIN, M. H., MCCAUL, F., HOGAN, J. E. & EDGAR, P. J. 1987. Importance of drug type, tablet shape and added diluents on drug release kinetics from hydroxypropylmethylcellulose matrix tablets. International Journal of Pharmaceutics, 40, 223-234.

[68] GHORI, M. U., ALBA, K., SMITH, A. M., CONWAY, B. R., & KONTOGIORGOS, V. 2014. Okra extracts in pharmaceutical and food applications. Food Hydrocolloids, 42, 342-347.