EVALUATION OF THE POTENTIAL OF HYDROXYPROPYLCELULOSE ON PRODUCING EXTRUDATES BY WET EXTRUSION.

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SUMMARY

Hydrophilic polymers are often used as controlled release systems for water-soluble or insoluble drugs in tablets, matrices or pellets, due to their high swelling capacity and water absorption capability. In this study, hydroxypropylcellulose was used as rate-controlling polymer and evaluated in the extrusion process. This polymer was mixed with paracetamol as model drug and calcium phosphate dibasic as filler, water was added to aid formation of a wet mass which was subjected to extrusion.

In order to determine the limits of the ratio polymer/filler in which extrusion is enabled, a range of these ratios was created. In addition, the properties of polymers with different viscosity grades were compared. The extrusion was carried out by a ram extruder and the extrudability of all formulations was evaluated.

All formulations were characterized by testing properties such as water loss, density, porosity, mechanical strength, swelling behaviour. It can be stated that a larger concentration and higher degree of viscosity of a polymer has a bigger water retention capacity, resulting in a more expressed swelling mechanism. It has been observed that there was no clear relationship between the porosity and the mechanical strength.

Finally, the drug release was investigated from extrudates by a dissolution test carried out in a water medium. The drug release of HPC was controlled by diffusion through the channels and pores and also by erosion of the polymer swelling. This study confirmed that a higher degree of viscosity and concentration of the polymer was accompanied by a stronger polymer entanglement and thus a slower drug release.

Future research should focus on HPC polymers with an even higher viscosity, in which a more desired delayed drug release would be obtained which is desired due to the numerous benefits for the patient. In addition, good quality extrudates could give rise to pellets which can be integrated into tablets or capsules, characterized by a sustained release of the drug. Further, a different shape of extrudates such as laminar extrudates could be developed with the aim to generate bio adhesive patches.
SAMENVATTING

Hydrofiele polymeren worden vaak aangewend als vertraagde vrijstelling systemen in tabletten, matrixen of pellets dankzij hun grote zwellingscapaciteit en waterabsorptievermogen. In deze studie werd het polymer hydroxypropylcellulose aangewend en geëvalueerd in het extrusieproces. Dit polymer werd gemengd met paracetamol als het modelgeneesmiddel, dibasisch calcium fosfaat als vulstof en tenslotte water werd toegevoegd om tot de vorming van een natte massa te komen die onderworpen werd aan extrusie.

Opdat de uiterste grenzen van de verhouding polymer/vulstof die extrusie mogelijk maken, bepaald zou kunnen worden, werd een range van deze verhoudingen gemaakt. Daarnaast werden de eigenschappen van polymeren met een verschillende viscositeit vergeleken. Het extrusieproces werd uitgevoerd gebruikmakend van een ram extruder en de extrusiemogelijkheid werd geëvalueerd.

Alle formulaties werden gekarakteriseerd door de eigenschappen zoals waterverlies, densiteit, porositeit, mechanische sterkte en zwellingseigenschappen te testen. Aangenomen wordt dat, hoe groter de viscositeit en concentratie van een polymer, hoe meer waterhoudingscapaciteit de formulatie bezit, wat duidelijk wordt in een meer uitgesproken zwelling. Geen duidelijke verband tussen de porositeit en de mechanische sterkte van de extrudaten werd geobserveerd.

Als laatste werd de geneesmiddelvrijstelling uit extrudaten onderzocht met behulp van een dissolutietest die uitgevoerd werd in een waterig medium. De geneesmiddelvrijstelling van HPC werd gecontroleerd door diffusie doorheen de kanalen en poriën en daarnaast ook door de erosie van de gezwollen polymer. Deze studie bevestigt dat een hogere viscositeitsgraad en concentratie van een polymer gepaard gaat met een sterkere polymer verstrengeling en daardoor ook met een tragere geneesmiddelvrijstelling.

Toekomstig onderzoek zou zich kunnen toespitsen op HPC polymeren met een nog hogere viscositeit, waarbij een nog meer vertraagde geneesmiddelvrijstelling zou kunnen worden verkregen. Daarnaast zouden sommige succesvolle extrudaten kunnen aanleiding geven tot pellets, dewelke daarna in tablets of capsules met vertraagde vrijstelling eigenschappen, kunnen geïntegreerd worden.
Verder kan een andere vorm van extrudaten worden gecreeërd zoals laminaire extrudaten, met als doel transdermale patches te produceren.
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LIST OF ABBREVIATIONS

API : Active pharmaceutical ingredient
DS : Degree of substitution
HME : Hot melt extrusion
HPMC : Hydroxypropylmethylcellulose
HPC : Hydroxypropylcellulose
MCC : Microcrystalline cellulose
MS : Moles of substitution
1. INTRODUCTION

1.1. EXTRUSION

Extrusion is a widespread technology process which is used in the pharmaceutical, plastic, food and ceramic industries (1) for the production of pellets, plastic bottles, pasta or bricks. In the pharmaceutical industry, extrusion is an important operation which usually leads to the production of pellets, beads, tablets, matrices and multiparticulates usually as oral controlled drug delivery systems (2). The formation of pellets is preceded by 5 steps: blending, wet massing, extrusion, spheronization and drying (3, 4).

In the first step, the different constituents are mixed to achieve a homogeneous blend which is moistened with a liquid, resulting in a plastic wet mass. This mass is filled into a barrel, pressed through a well-defined die which provides a shape with a specific density similar to the die. In the spheronization step, the rounding of the obtained extruded rod particles into spherical particles occurs in a spheronizer. In order to obtain the correct moisture content, the last step involves the drying of the particles (5).

Distinction is made between masses which are solid or molten formulations, applied respectively in wet extrusion and in hot melt extrusion (HME) (4). The focus of this research is on the third step of the process: extrusion, in which the wet mass is formed into rod extrudates.

Extrusion is performed in an extruder. The extruder consists of an upper section which conveys the materials into the die and a lower section where the appropriate shape is provided to these materials. The various extruders are discussed more detail in sections 1.1.1 and 1.1.2.
The process of extrusion is recorded as a force – ram displacement profile. Three stages can be distinguished; the first stage (Fig. 1.1, A) is the compression stage when the ram penetrates into the barrel requiring a large force, for a small displacement. The force increases until it is high enough for the material to flow out of the die.

After the compression stage, a steady state flow (Fig. 1.1, B) can be observed for an increasing displacement. This steady state corresponds to the extrusion of the materials at a constant rate and force.

The graph will peak at the end of the process of extrusion and is due to the forced flow (i.e., laminar flow was replaced by a turbulent flow inside the barrel) of materials (Fig. 1.1, C). In addition, the slip stick phenomenon, described more in detail in chapter 1.4, is responsible for this forced flow and is characterized by the alternating slipping and sticking behaviour of the extrudate at the die wall surfaces which results in a sudden jump of velocity (i.e., turbulent flow) (6). Moreover, Harrisson et al. declared this last stadium by the inability of the system to retain a convergent angle of entry into the die (7).

![Figure 1.1: Example of a profile of extrusion](image)

Force (kN) versus distance (mm) with the compression stage (A), the steady state (B) and forced flow (C) (6).
1.1.1. Wet extrusion

Solid systems are created by adding a liquid binder to a homogeneous powder mixture of drug and excipients, resulting in a dense cohesive wet mass. The liquid phase can be the water or aqueous solutions combined with other solvents such as ethanol or isopropanol (8). The amount of added fluid determines the cohesiveness and plasticity of the wet mass which contributes to the final quality of the extrudate, if not to the pellet.

First, the wet plastic mass is fed into the barrel. Afterwards, the ram or piston, which fits into the barrel, pushes the moistened mass through the die due to an applied force. The resulting extrudates have a shape corresponding to the used die: for example a rod, tubular or co-tubular shape.

Extruders can be divided into 3 different groups according to the feed mechanism accomplished by the screws, by the gravity of the feed or by the piston. The first group consists of the screw-fed extruders, which are equipped with 1 (single) or 2 (twin) screws, responsible for the transport and compression of the wet mass through the barrel towards the extrusion zone. Various types of screw-fed extruders are distinguished based on the differences in the extrusion zone, such as the orientation of the plane, the thickness of the plate, the L/R ratio or the number of holes in the die. A more detailed description and comparison between single and twin screw extruder can be found in chapter 1.1.2.

The second class comprises the gravity extruder and can be divided into 2 types. The first type is the roll extruder, including the cylinder and gear extruders. The wet mass is fed into the extruder due to gravity and is compressed through the holes to form the extrudate. The second type is the radial extruder in which the wet mass is stirred by rotating arms, followed by the wiping of the wet mass into the nips by the rotational blades (5).

Screw and gravity extruders are used for manufacturing and development (2, 9). A piston-fed ram extruder is generally used in the research (Fig. 1.2).
The process performed by the ram extruder, is less expensive since it requires only a small quantity of material. In addition, it correlates to the performance of the commercial long die gravity extruder, in which the quality of the extrudate is much better in comparison with thin screen extruders. As final advantage, the extrusion profile, obtained by a ram extruder, provides information about the consistency of the wet mass (3).

Figure 1.2: Diagram of a ram-extruder (a) and dies for a rod (1), tubular (2) and laminar (3) extrudates (b).

Wet extrusion does not show temperature stress because the temperature is maintained ambient, which makes it feasible for heat sensitive active pharmaceutical ingredients (API’s). Although, wet extrusion is not suitable for drugs which are unstable or have compatibility problems in presence of solvents (2, 10).
1.1.1.1. Rod extrusion

Extrudates produced by wet mass extrusion usually obtain a simple cylindrical shape (Fig 1.3, a), by feeding the barrel of a ram-extruder with a specific die (Fig. 1.2, b 1) (11).

Figure 1.3: Illustration of a rod extrudate (a), a tubular extrudate (b) and a co-extrudate (c) (11).

Two variants of the rod extrusion, in which different shapes are obtained, are described below. The first type is the laminar extrusion in which the dies present a rectangular cross-section (Fig. 1.2, b 3). In the plastic industry, the production of sheets and films (Fig. 1.4) is one of the largest volume processes. Products needed in sheet form are for the production of roll roofing, filtration membranes, printing plates, kitchen countertops, photographic and x-ray films (6). For pharmaceutical applications, the laminar extrusion is found in transdermal drug delivery, usually in case of specific dose needs with geriatrics and psychiatrics.

Fig 1.4: Illustration of a laminar extrudate (4).

Present work is involved in research on design of oral drug formulations using the laminar extrusion process (4).
The second recent type of rod extrusion is originated in order to improve the low drug solution of the rod extrudates. The shape of the extrudate might be influenced acquiring a larger surface area available for the medium. Helical extrudates are produced by hot-stage processes (Fig. 1.5). It is also more convenient since it fits well into a hard gelatin capsule (12).

![Fig. 1.5: Illustration of a helical extrudate with 4 blades(12).]

1.1.1.2. Tubular extrusion

Tubular shaped extrudates, which are hollow in the middle (Fig. 1.3, b), are obtained by feeding the external chamber of a co-extruder (Fig. 1.2, b 2).

1.1.1.3. Co-extrusion

A co-extrudate is a multilayered extrudate due to the presence of 2 or more different materials (Fig. 1.3, c). By filling both the internal and external chambers of the co-extruder with the wet mass (Fig. 1.2), a co-extrudate is obtained (13). The presence of these different layers provides advantages over the simple rod ones. The outer layer can protect the API in the inner layer or it might act as a coat that modifies the drug release of the active ingredient. Moreover, by loading the layers with different drugs or the incorporation of drugs in different matrices, the release of the drug can be modified (11).

Due the double shear stress, both in the outer and inner part of the barrel, between the extrudates and the barrel, the load needed for extrusion is higher than for rod extrudates. For the latter, shear only appears at the external part of the tube (11).
1.1.2. Hot melt extrusion (HME)

HME is a technique in which a polymer is melted in order to obtain an extrudate that might be transformed into a good matrix pellet. It was developed to overcome the disadvantages of wet extrusion (2). This technique is often used in the plastic, food and rubber industry for the production of bags, pipes, hoses, cables, pasta products and sheets (14). HME also finds applications in the pharmaceutical industry where the polymeric extrudates are used for the preparation of drug delivery devices and dosage forms, sustained released tablets, granules and pellets, transdermal and mucosal drug delivery systems (4, 15).

HME includes a lot of advantages in comparison to traditional extrusion processes. As there is no addition of solvents involved, the probability of drug degradation due to a solvent is minimized. In addition, it is characterized by a reduced number of processing steps, a short production time, continuous processing (because the drying stage is not required) and the closed process prevents cross contamination (2, 16). Other benefits are the improvement of the bioavailability and solubility of water insoluble drugs, no requirements on the compressibility of the active ingredients are needed and a more uniform content of the extrudates is obtained.

A screw extruder is commonly used in HME and wet extrusion. A distinction is made between the single and twin screw extruder, which have either one or two augers to transport the wet mass from the feed region to the metering zone and differs in terms of mixing abilities and transport mechanism (6). Single screw extruders are less efficient which results in a longer equipment length. Although, the single screw extruder is characterized by its mechanical simplicity and his high production-to-cost ratio. Advantages of the twin screw extruder over the single screw extruder are the shorter residence time, the stability of the melting process, the shorter equipment length and the better mixing ability. It provides more shear stress and intense mixing which create a more homogeneous mixture in comparison with the poor mixing ability of the single screw extruder (14, 17).
In fact, the twin screw-extruder has a higher throughput, because a number of separate batch operations can be performed by a single unit operation. However, the high temperatures, present in the hot melt extruder, can cause disintegration of heat-sensitive API's. In addition, a high energy input is required and the materials have to be thermally stable at the processing temperature, so some actives are not appropriate for this technique (18). Also polymers and excipients, which need high flow properties to allow the processing, might be not suitable for these high temperatures (17, 19).

![Schematic representation of a screw extruder](image)

**Figure 1.6: Schematic representation of a screw extruder (14).**

A blend of fillers, plasticizers, bulking agents and other excipients is added to the hopper and enters consistently the first zone or the feed zone (Fig 1.6). Thus, the active substance is embedded in a meltable carrier, such as a polymer, that acts as a thermal binder or drug depot. While passing through the barrel to the transition or compression section, the blend is mixed, compressed, melted and plasticized by rotary movements of the barrel around the stationary screw.

The temperature of the different zones of the extruder is controlled by electrical heating, depending on the formulation being considered, and is monitored by thermocouples. The material inside the barrel melts due to the heat that is generated by frictional forces as the mass passes between the screws and the wall of the barrel and due to the screw turnings (6, 20). In addition, the pressure in the extruder is controlled by the screw design and the conditions for processing (6).
The plastic melt suitable for extrusion, achieves the last region, the metering zone that provides a uniform delivery rate and passes the die which is attached to the end of the extruder. The molten mass cools down by the chill rolls, which influence also the thickness of the films and the mechanical properties. Barrel cooling occurs to maintain the desired melt viscosity, to prevent material degradation and to absorb the energy which was lost due to the vaporization of the liquid (6). The films are extruded and can be cut in the required size.

1.1.3. Other types of extrusion

Other types of extrusion are the blow molding and food extrusion process, found in a different area than the pharmaceutical extrusion process. Blow molding extrusion, for example, is one of the most common manufacturing processes in the plastic industry which results in the production of hoses, pipes and bottles of shampoo (Fig. 1.7) (21). Thermoplastic material is heated to a molten state, conveyed by a piston and extruded in a hollow tube or parison (step A), followed by closing the parison with a mold (step B). A parison is a tube-like plastic substance with a hole in one end. Compressed air is pumped through the hole of the parison (step C), so that the plastic material expands and takes the desired shape. After adequate cooling, the material hardens and the mold can be removed resulting in the final product (step D) (22).

Fig 1.7: The process of a molten tube of plastic which is extruded into a molten cavity and is blown with compressed air (23).
Recently, the (injection) blow molding is also used in the pharmaceutical industry for the production of oral time controlled drug delivery preparations, in particular to manufacture a swellable/erodible device composed of hydrophilic cellulose ethers, polyethylene glycol, xanthan gum or sodium alginate (24). This device (Fig 1.8) consists of a cap and an associated body, which is filled with the desired active ingredients, powders, granules, pellets or fluids and are an advantageous alternative for a coated dosage form.

The production of this extrudate is similar to the process described above. After ingestion of the extrudate, the polymer starts to dissolve due to the thinning of the walls until they break which results in the release of the powder (25).

![Figure 1.8: Picture of an extrudate composed of hydropropylcellulose (24).](image)

A shell containing the swellable polymer hydroxypropylcellulose (HPC), responsible for the controlled release action, in combination with the plasticizer polyethyleneglycol has been investigated and prepared successfully by Gazzaniga et al (24). Due to the satisfactory prospects in process stability, drug release, stability characteristics, inherent versatility, scalability, and patentability prospects, more depth investigation and manufacturing of these devices are worth it (24).

In the food industry, extrusion cooking has a significant impact on the development of low cost, protein-rich and more digestible food (26). This process of extrusion allows the manufacturing of cereals, pasta, croutons, pet food and baby food. Food ingredients are brought together, plasticised, cooked and pushed through an opening in a perforated plate which results in food products with a typical shape and size (Fig. 1.9) (27).
Both single and twin screw extruders are used in the production of food. Depending on the desired products, different process parameters such as time, temperature, shear stress and moisture content should be monitored. This technique is characterized by some positive features such as the denaturation of undesirable enzymes and proteins, the inactivation of inhibitors, fat globules modification and the retention of typical colours and flavours (29).
1.2. CELLULOSES AS EXCIPIENTS

In the development of release dosage forms, in which the release of the drug is controlled, the use of polymers plays a key role (30). Cellulose ethers, which are examples of the water soluble natural polymers, can be divided into different groups with respect to the type of substituents, the substitution level, the molecular weight and the particle size. Due to properties such as pseudoplastic behaviour, film formation and water retention capacity, cellulose derivatives find applications as binders, thickeners, stabilizing, emulsifying and coating agents and tablet disintegrants in the pharmaceutical industry (31, 32). Also, a lot of applications with celluloses in pharmaceutical, food and cosmetic products is provided since they are well-tolerated by the mucous membranes and skin (31).

1.2.1. Microcrystalline cellulose (MCC)

MCC is the most important and commonly used standard aid in the extrusion process. It has a 2-fold property: it will distribute the fluid throughout the powder bed and it affects the rheological properties of the other ingredients, so that the mixture becomes more plastic which improves the extrusion process.

The unique role of MCC is explained by the crystallite gel model (33). Small subunits, which are a result of the shear stress during extrusion or granulation on the MCC particles, form a gel network while separating the liquid. Due to the insolubility in water, the gel is not sticky and contains a high proportion of polymer compared to gels prepared with other cellulose derivatives (33).

MCC in wet formulations provides good breaking properties, controls the uniformity of the water soluble drug and is able to absorb and retain a large amount of water due to its large surface area which facilitates wetting and accelerate drying (8).

Due to the high water retention ability, the water movement can be controlled which prevents phase separation and water migration through the barrel. This can cause a leakage of water droplets at the end of the barrel.
However, MCC has various disadvantages such as the lack of pellet disintegration, the possibility of drug adsorption at MCC, a prolonged drug release of poorly soluble drugs and the chemical incompatibility with specific drugs (8).

So far, all MCC products and brands were manufactured from the polymorph MCC I, which is one of the four crystal modifications of MCC. To overcome previously described disadvantages of the MCC I polymer with focus on the slow dissolution of poorly soluble drugs and the lack in disintegration, the investigation of the polymer MCC II was carried out by Krueger et al (34).

They can be distinguished based on their chemical structure. MCC I contains only hydrogen bonds between chains of the same sheet, while in MCC II hydrogen bonds exists between different sheets, resulting in a 3D structure. Transition from MCC I to II can occur during ball milling, mainly in the presence of 30 wt % of water in the cellulose (35). It is reported that the transition from polymorph II to I is not favourable because of the high stability of MCC I. However, there is a lack of knowledge about the conversion of these polymorphs (34).

The properties of MCC II pellets are characterized by a shorter disintegration time which results in a more rapid drug release, a higher porosity and a shorter drying time due to a lower required water content in the extrudates. The use of 20 or 50% MCC II in a formulation results in sufficient pellets (34).

For a general description of the cellulose excipient MCC the reader is referred to annex I.
1.2.2. Hydroxypropylmethyl cellulose (HPMC)

HPMC finds application as spheronisation aid in formulations with water-sensitive drugs, in formulations in which an organic liquid is needed or in which a complete water solubility of the formulation is required (36). HPMC is a water-soluble polymer and therefore water cannot be used as granulation liquid.

In the presence of the dissolution medium, HPMC absorbs water and forms a viscous gel layer around the pharmaceutical formulation. This facilitates the sustained release behaviour by the slow dissolution (36, 37). During this swelling process of the HPMC polymer in water, three regions can be distinguished.

The swelling front is identified by the contact between the dry central core with drug particles and the hydrated gel region with the dissolved drug. The dissolution front is the region where the drug concentration is the highest. The third and outer boundary, which is called the erosion front, separates the matrix from the dissolution medium (38).

The extent of swelling increases with a higher molecular weight of the polymer because higher molecular weight chains can occupy a larger hydrodynamic volume, dilute and reach the critical polymer concentration. Below this concentration the polymer chains unravel and detach from a gelled matrix and starts to swell, dissolve and diffuse into the bulk medium (8, 39).

The following conclusions were reported in the literature: the lower the HPMC content, the higher the release rate of the drug in the HPMC matrix (40) and an increase in water content of a formulation containing HPMC is associated with a decrease in yield of pellets. Due to the adhesive nature of the HPMC polymer and the increase of the water, the adherence to the inner wall is more pronounced, resulting in a lower yield (41).

For a general description of the cellulose excipient HPMC the reader is referred to annex II.
1.2.3. **Hydroxypropylcellulose (HPC)**

HPC possess a range of properties such as thermoplasticity, surface activity, organic solvent solubility and thickening properties (42). These properties provide efficient tablet binding, adhesive tablet coating and extrusion possibility (43). This polymer is used as a tablet binder, film coating agent and an extended release-matrix former.

A wide range of different viscosity types of HPC are available which creates different solubility’s in water and ethanol and which affects the modified release of the drug (43). It has been observed, the higher the concentration of polymer included in a formulation, the less amount of drug is dissolved and the slower the drug release rate (44).

For a general description of the cellulose excipient HPC the reader is referred to annex III.

1.2.4. **Other water-soluble celluloses excipients**

Besides the most common cellulose excipients MCC, HPMC and HPC used in the process of extrusion-spheronization, a wide range of other cellulose derivatives exists. However, none of these alternatives can surpass the flexibility of the common used MCC, although realizing that not all information of these alternatives relating to their properties is available. Other derivatives are hydroxyethylcellulose (HEC), sodium carboxymethyl cellulose (NaCMC), methylcellulose (MC) (32).
1.3. PARACETAMOL

In this research, paracetamol (Fig. 1.10) was selected as model drug. It is well tolerated, offers an advantageous safety profile, is stable at room temperature and should be stored under dry conditions. Generally paracetamol is orally administered, characterized by a rapid absorption from the gastrointestinal tract, a bioavailability of 70 – 90%, duration of action of 2 to 5 hours and onset of action within 30 minutes after ingestion (45).

In therapeutic doses, paracetamol has analgesic and antipyretic properties used in the treatment for musculoskeletal pain and pain full disorders such as headaches, dysmenorrhea and other minor aches and it is used as a fever reducer. It does not provide anti-inflammatory effects. In over dosage it can cause hepatic necrosis (23).

![Fig 1.10 Structure of N-(4-hydroxyphenyl)acetamide or paracetamol or C8H9NO2 (46).](image)

The physicochemical properties of paracetamol are characterized by a slight solubility in water and ether and a good solubility in organic solvents such as ethanol and methanol, a melting point between 168 °C and 172 °C and a pH range between 5.5 and 6.5 (46).
1.4. FLOW PROPERTIES OF THE WET MIXTURE

The flow properties and the rheological, particularly the viscoelastic behaviour of the cellulose derivatives can be influenced by its molecular mass and its distribution, particle size and its chemical structure including the degree of substitution (DS) and the molar substitution (MS). The higher the molecular mass, the more formation of entanglements of polymer coils, the more pronounced intermolecular interaction so the lower the critical shear rate. Above this critical value, a shear-rate dependent viscosity occurs. In addition, the influence of the DS and the MS on the fluid properties is less important.

The shear-rate dependent viscosity in polymers is characterized by shear thinning. During this stage, a decrease of viscosity occurs with an increase of shear rate caused by disentanglements of the polymer in solution or by the increased orientation of the polymer coils in the direction of the flow. This behaviour is called non-Newtonian, in particular pseudoplastic (31).

Polymers, known as viscoelastic materials, are characterized by viscous and elastic properties. The energy expended in deformation is dissipated immediately in pure viscous solutions, while it is recoverable in pure elastic materials so that the deformation is reversible (47). This viscoelastic behaviour becomes clear in several phenomena that arise during the extrusion process.

The first phenomenon occurs at the die and is called extrudate swell, which is influenced by the rate of the flow stream. The flow rate of the extruding material is constant before entering the die, once the mass is in the die the flow rate increases, resulting in physical entanglements of the polymer (48). Leaving the die, the polymer tends to recoil and regain its conformation associated with an increased extent of the extrudate after exiting the die (49). The internal energy, stored during extrusion, is re-equilibrated in the form of elastic recovery which explains the bigger diameter of the extrudate than that of the die hole, which is caused by the swelling (50). A low shear rate and high die length and temperature reduces the extrudate swelling process.
A low shear rate and large L/R eliminate the effect of the entrance flow, responsible for the big molecular orientation, by providing a longer time period which enables the polymer to disentangle (48). A high temperature causes a faster relaxation of the polymer in which the return to their initial configuration is facilitated (50).

A second common elastic effect is flow instability which includes the melt fracture, the shark skin and the slip phenomena (50). It is claimed that the surface of an extrudate shows more irregularities and undulations with increasing flow rates at which it exits the barrel (Fig. 1.11) (51, 52). The undulations can be so intense that it causes the breakage of an extrudate, known as melt fracture. This phenomenon is dedicated to both the stress relief at the die wall or entrance and the different flow induced molecular orientation (50).

Figure 1.11 Illustration of molten polymers in which the flow rate increased (from the left to the right). The surface of A and B exhibits good and smooth surface properties. C, D and E exhibit more irregularities due to an increased flow rate (51).

Shark skin is known as the appearance of distortions and irregularities at the surface of the extrudate (Fig. 1.12).

Figure 1.12: Illustration of an extrudate with a shark skin surface.
The stick slip phenomenon occurs due to variations in flow rate and pressure. As the shear stress at the die wall reaches a critical value, the adhesion of the polymer fails resulting in the slip behaviour, if the shear stress falls down under another critical value the stick behaviour arises (53).

The requirements for a suitable formulation for the wet extrusion/spheronization process were summarized by Fielden and Newton (54). The moistened powder mixture must remain homogeneous during extrusion, possess fluidity and self-lubricating properties allowing to flow through the die (8). As the extruded products exit the die, the proposed shape (usually cylindrical) must be retained, the strands should not stick to each other and the appearance of surface irregularities should be absent.

In addition to obtain good quality extrudates, the force-displacement profile must be characterized by predominating long steady-state flow (Fig. 1.1, B) and short compression and forced flow states (11, 55). It has been reported that forced flow profiles would give rise to difficulties in spheronizing, resulting in pellets with a wide size distribution (11).

A critical parameter in the process of extrusion-spheronization that affects the surface characteristics, plasticity and cohesiveness of the extrudate is the moisture content of the formulation. The quantity of liquid can range between an upper and lower limit. Overwetted mixtures tend to form large agglomerates due the presence of an excess of water at the surface of the pellets. Unlikely too dry mixtures are brittle and tend to produce a large quantity of dust resulting in the production of fines. In addition, they lose plasticity so that the flow through the barrel is not satisfactory anymore (9, 11, 56). Basically, a wet mass with self-lubricating, plastic and any brittle but not friable properties should be suitable for wet extrusion(4).
1.5. PROPERTIES OF THE EXTRUDATES

1.5.1. Process parameters

The process variables in the process of extrusion, in which the properties of the end product might be dependent on, are the equipment type of the extruder, the ratio die length to diameter or L/R and the extrusion force.

The extrusion force gives a significant estimation of the probability of success of the extrusion process (3). Too wet masses are characterized by a small force, whereas mixtures which require a too large force to allow extrusion are too dry. An extrudate of good quality exhibits a long period of steady-state in the extrusion profile (11).

Parameters more typical for the HME process are the screw speed, the space between the screw turnings and the space between the end of the screws and the beginning of the die, the feed rate and the temperature along the barrel. Varying this parameters result in a different density and lubricant ability of the wet mix. Another important parameter of the HME process during the feed step is the flow ability of the powder when it is added to the hopper of the screw extruder. The flow ability influences the homogeneity of the blend. Uneven powder flow might cause a variation in weight of the different extrudates and this poor flow ability leads to difficulties to deliver the powder to the compression and metering zone (57).
1.5.2. Characterization

1.5.2.1. Diameter

The diameter, a measurement of the cross section of the extrudate, is a property that allows describing the expansion of the extrudate. By comparing the diameters of different extrudates, they can be distinguished by the degree of swelling and by the expression of extrudate swell. In addition is the diameter ratio (DR), the ratio of the diameter of the extrudate to the diameter of the die opening, a measurement which can be applied (58). The square of the preceding equation is referred to as the expansion ratio (ER). It has been reported that the ER is most influenced by the feed rate, moisture content en product temperature (59). Both equations are illustrated in equation 1.1.

\[
\begin{align*}
DR &= \frac{D_e}{D_d} \\
ER &= \frac{D_e^2}{D_d^2}
\end{align*}
\]

Equation 1.1

DR: diameter ratio; \(D_e\): diameter of the extrudate; \(D_d\): diameter of the die opening

1.5.2.2. Surface roughness

A characteristic of the extrudate, that can cause problems when it is converted into a pellet, is the presence of irregularities on the surface. Due to stresses exerted by the outer wall of the barrel on the extrudate when exiting the die, defects on the surface appear. A good choice of output velocity, moisture content of the formulation and die length can improve the quality of the surface. The parameter, expressed as surface roughness, can be measured on a dry extrudate by using a non-contact profilometer (60).

1.5.2.3. Loss on drying (LOD)

The different materials present in the formulation have different solubilities and capacity to retain water, which is observed during the measurement of the water content (3).
1.5.2.4. Density and porosity

The density should be taken into consideration because this characteristic might influence the release of the drug, the porosity, the mechanical properties and the powder fluidization (3, 57). Variations of porosity properties can explain different performance in disintegration, dissolution and tensile strength results.

1.5.2.5. Rheological characterization

The rheological behaviour includes the melt flow and the viscoelastic properties such as storage shear modulus and loss shear modulus. This property can be determined by a torque or capillary rheometer in case of hot melted extrudates and by a dynamic rheometer in case of wet mass extrudates.

A torque rheometer measures the torque on the mixing screws which reflects the relative viscosity. A capillary rheometer pushes the mass through a heated barrel with a piston and measures changes of viscoelastic properties in function of temperature and pressure by the construction of flow and viscosity curves (50, 61). An increase in food moisture content and a decrease in screw speed, results in a higher torque value (52).

1.5.2.6. Mechanical characterization

Measurements of the maximum strength at failure, the tensile strength and Young’s modulus, a measurement for the stiffness of the material are included in the mechanical characterization.

It is assumed that extrudates with a low porosity are stronger, in that way that they can resist a larger force, than extrudates with a high porosity (3, 11), so that the strength decreases with the increasing porosity (62). Although, if the strength of the bonds between the different particles is high, a material might withstand high forces independently of its porosity in which a previous relationship no longer applies.
This is confirmed by Tekmann et al., in which is assumed that the existence of large pores is more effective than the average porosity, when measuring the tensile strength (63). The amount of polymer plays also a role, the greater the amount of MCC/polymer, the larger the mechanical strength (3).

In case of HME, by varying the extrusion temperature, moisture content and feed rate, the effects on the mechanical properties can be determined. The breaking stress from extruded food samples increases with a higher feed rate and moisture content and a lower extrusion temperature and residence time (64). The plasticization by the moisture makes the food behave as a semisolid mass, resulting in a high strain resistance during compression.

1.5.2.7. Swelling and water uptake

Gel strength, water uptake and gel layer thickness are typical characteristics for the swelling behaviour. These swelling characteristics can be determined by the porosity and polymer content and can affect the drug release of the formulation. A high porosity leads to a high rate of weight gain and a large extent of swelling (65). A high amount of polymer in a mixture is able to absorb more water, which is associated with a big swelling and gel strength (4). The swelling of a polymer strongly depends on the rate at which the liquid penetrates. The effect of the penetrant-polymer interaction is a parameter to evaluate the rate of the release of the drug (4).

1.5.2.8. Bioadhesion properties

Bioadhesive experiments are performed on extrudate films which are used in the transdermal drug delivery and produced via HME. Bioadhesion is the capacity of a synthetic material to stick to the skin or to the mucous membranes. The samples of this synthetic material are tested by the measurement of the adhesive force, the force required to remove the film and the adhesive failure (18).
1.5.2.9. Release of a drug

Drug release rate is dependent on many factors such as the solubility and distribution of the drug, the ratio drug/polymer, the extent of swelling, the mechanical strength of the matrix, the disintegration characteristics. Further, in terms of polymer, the type, the percentage, the degree of viscosity and the polymer particle size might influence the release (30). Blanque et al. reported that the higher the concentration and the viscosity of the polymer, the larger the cross-linking between the polymer chains, decreasing the porosity and increasing the tortuosity and the concentration of the gel which results in a delay of drug release (66).

The dissolution test provides information about the dissolution rate of the active ingredients under controlled conditions from the dissolution assay such as the temperature, the volume and the composition of the dissolution medium, the rotation speed of the paddles.

A mathematical model, based on the different possible chemical and physical phenomena that occur during drug release, is practically impossible. The models, which approach the drug exemption in polymers the most, are discussed below (67).

The time dependent drug release in a swelling-controlled release polymeric system may be simply described by the Korsmeyer-Peppas model (Eq. 1.2) (68).

\[
\frac{M_t}{M_\infty} = k t^n
\]

Equation 1.2

\(M_t/M_\infty\): the fraction of drug release at time t, \(k\): release rate constant incorporating diffusivity, porosity and amount of liquid transferred over an infinite time of the device, \(n\): a diffusional exponent representing the mechanism of drug release.

This equation is valid for a drug cumulative release of \(M_t/M_\infty < 0.6\). A high value for \(k\) suggests burst drug release from the matrices.
A value ≤ 0.45 for the exponent n corresponds to Fickian diffusion mechanism, 0.45 ≤ n ≤ 0.89 to non Fickian transport mechanism, n = 0.89 to case II transport or zero-order transport and n ≥ 0.89 to super case II transport (69).

The Fickian mechanism refers to a drug release based on the diffusion mechanism through the outside layers of the matrix. A non Fickian mechanism or an anomalous behaviour refers to a drug which release is controlled by the diffusion mechanism and the swelling. This indicates that the drug diffuses through the swollen polymer matrix and also partly through the gradually expanding hydrated matrix (30). A case II transport mechanism refers to drug release based on erosion and relaxation of the polymeric chain. A super case II transport is characterized by a completely hydrated layer at the surface of the matrix, subjected to continuous erosion (66).

In case of transdermal systems and semi solid or solid matrixes containing water-soluble drugs and low soluble drugs, the simplified Higuchi model can be used. Although, this model should not be applied to controlled drug release systems because they do not meet the requirements of this equation (70). In general, this equation is applied to analyze the experimental drug release data and to get an idea about the release mechanism. Equation 1.3 is used to describe the drug dissolution (67).

\[
Q_t = K_h \cdot t^{(1/2)} \quad \text{Equation 1.3}
\]

\(Q_t\): amount of drug released at time \(t\), \(K_h\): Higuchi dissolution constant

A model-independent method is the measurement of the mean dissolution time, given by the equation 1.4 (67). This method can be used to compare different drug release profiles.

\[
MDT = \frac{\sum_{j=1}^{n} t_j^\ast \Delta M_j}{\sum_{j=1}^{n} \Delta M_j} \quad \text{Equation 1.4}
\]

\(j\): dissolution sample, \(n\): number of dissolution sample times, \(t_j^\ast\): time at midpoint between \(t_j\) and \(t_{j-1}\) and \(M_j\): additional amount of drug dissolved between \(t_j\) and \(t_{j-1}\).
Blanque et al. reported that the drug release of matrix pellets containing polymers, was dependent on the solubility of the drug and filler, the proportion of the drug and a little on the molecular weight of the polymer (71). The drug release was prolonged with a decreasing solubility of filler and drug, a higher proportion of the drug and the increasing molecular weight of the polymer (60, 64).
2. OBJECTIVES

This thesis focuses on the behaviour of the polymer hydroxypropylcellulose and in addition, this study wants to improve the knowledge about the properties and characteristics during the wet extrusion process, which are so far little examined in the pharmaceutical industry.

Thus, the main objectives of this thesis are:

- The evaluation of the ability of HPC on manufacturing extrudates by wet mass extrusion.
- The study of the effect of different water fractions in a wet mass on the extrudability.
- The study of the effect of varying viscosities of this polymer on the quality and properties of the extrudates and on the drug release.

To achieve these objectives the thesis was organized as follows:

A first section of this research involves the creation of an optimal formulation, consisting of a binder, a polymer and an API that permit the extrusion, performed by a ram extruder (See section 3.2.1). An optimal formulation is defined as a formulation with the highest possible fraction of HPC, in which a better sustained release profile is expected, allowing extrusion. In order to achieve this optimal formulation, initially a range of mixtures with a different ratio polymer/diluent was prepared by trial and error and the extrudability of these wet masses was examined.

In addition, the viscosity of the polymer hydroxypropylcellulose, which was first focussed on the most viscous polymer MF HPC, was varied (HPC LF and GF). An important concern is the water content, which was changed in different mixtures. The water content present in the formulation determines the possibility of extrusion. In addition, the type of diluent was varied in one single formulation; calcium phosphate dibasic was replaced by lactose. This approach is not further discussed.
The second part consists of the characterization of the extruded samples. These samples were tested for several properties such as the physical characterization, including the density, porosity and the water absorption. In addition, the mechanical characterization was determined, which reveals the pseudoplastic properties of the extrudate. The swelling test was carried out which gives a visual impression of the swelling behaviour of the extrudate.

In the last part, dissolution tests were performed. The release of the drug in extrudates with different concentrations and viscosities of HPC was compared. A sustained release profile is expected due to the use of the extended release polymer and is desired due to advantages as reduction in frequency of intakes, less adverse effects, the improve of the patient compliance and an uniform release of drug over time.
3. MATERIALS AND METHODS

3.1. MATERIALS

The mixture consists of a certain content of HPC (Ashland Klucel, Wilmington, USA), dibasic calcium phosphate (Sigma Aldrich, Spruces, USA) or lactose (Granulac 200, Meggle, Germany) as diluent and demineralized water. In addition the active substance paracetamol (Lusifar, Lisboa, Portugal) was present.

3.2. METHODS

3.2.1. Extrusion process

Extrusion was performed using a ram extruder attached to a mechanical press (Lloyd instrument, LR 50K, UK) equipped with 50 kN load cell, allowing the collection of the data for the extrusion profiles. The extrusion rate was set to 100 mm/min. The distance through which the piston moved was 150 mm and the maximum applied force was 20 000 N.

All wet mixes of different formulations were prepared according to the following procedure. The powders, as mentioned above, were mixed with the aid of a mixer (Kenwood Chef, UK) for 10 min. After slowly adding the liquid, the mass was re-mixed for another 10 min. The wet mass was collected in a well-sealed polyethylene bag and stored for 24h.

The wet mass was fed manually into the barrel, followed by the descent of the piston which pushes the mixture through the die with dimensions of 1 mm in diameter and 4 mm in length. The gathered extrudates were cut into samples of 4 cm and dried in an oven (Memmert, Germany) for 24 hours.

First, a range of HPC fractions was created by considering different mixtures in which the concentration of HPC was varied between a maximum of 70% and a minimum of 10% HPC (Table 3.1).
Table 3.1: Summary of the different formulations (%).

<table>
<thead>
<tr>
<th>Formulation</th>
<th>HPC*</th>
<th>Dibasic Calcium phosphate</th>
<th>Paracetamol</th>
<th>Water**</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>70</td>
<td>10</td>
<td>20</td>
<td>20/25/35</td>
</tr>
<tr>
<td>2</td>
<td>60</td>
<td>20</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>50</td>
<td>30</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>40</td>
<td>40</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>30</td>
<td>50</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>20</td>
<td>60</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>10</td>
<td>70</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* HPC was either LF, GF or MF.
** The water content was maintained constant at 20%, 25% and 35% for HPC LF, GF and MF respectively.

In the next step, the water content in formulation 5 was varied, in response to the good results obtained in the previous section. Formulation with 25%, 30%, 35% and 40% of water were assayed. Mixtures, containing LF or GF HPC, were also prepared with 15% and 20% of water. In addition to the effect of varying the amount of water and polymer, the type of the diluent may also play a role. Lactose monohydrate was compared to dibasic calcium phosphate in formulation 5 containing MF HPC (Table 3.2).

Table 3.2: Formulation 5 (%) with a varying amount of water.

<table>
<thead>
<tr>
<th>Formulation</th>
<th>HPC*</th>
<th>Dibasic calcium phosphate</th>
<th>Paracetamol</th>
<th>Water</th>
</tr>
</thead>
<tbody>
<tr>
<td>5a**</td>
<td>30</td>
<td>50</td>
<td>20</td>
<td>15</td>
</tr>
<tr>
<td>5b**</td>
<td></td>
<td></td>
<td></td>
<td>20</td>
</tr>
<tr>
<td>5c</td>
<td></td>
<td></td>
<td></td>
<td>25</td>
</tr>
<tr>
<td>5d***</td>
<td></td>
<td></td>
<td></td>
<td>30</td>
</tr>
<tr>
<td>5e***</td>
<td></td>
<td></td>
<td></td>
<td>35</td>
</tr>
<tr>
<td>5f</td>
<td></td>
<td></td>
<td></td>
<td>40</td>
</tr>
</tbody>
</table>

* HPC was either LF, GF or MF.
** Mixtures 5a and 5b, containing 15% and 20% water respectively, were assayed with HPC LF and GF.
*** Mixtures 5d and 5f, containing 30% and 35% water respectively, were assayed with calcium phosphate dibasic and lactose.
3.2.2. Physical characterization of the extrudates

3.2.2.1. Water loss on drying (LOD)

Using the LOD method, the capacity of the polymer to retain the water is compared in the different formulations. A sample of extrudate (n=5) was weighed right after the extrusion, dried in an oven for a period of 24 hours and reweighed. The water uptake or moisture content is calculated as a percentage increase in the wet weight, according to the equation 3.1(4).

\[ W = \frac{\text{wet mass (g) - dry mass (g)}}{\text{wet mass (g)}} \times 100 \]  \hspace{0.5cm} \text{Equation 3.1}

\( W \): moisture content (%), \( \text{wet mass} \): weight of wet mass (g) and \( \text{dry mass} \): weight of dry mass (g).

3.2.2.2. Density and porosity

True density is defined as the solid material density, excluding volume of open and closed pores. The true density of the extrudates and the raw materials was determined by a helium pycnometer (Accupyc 1330, Micrometrics, USA). The volume occupied by a known mass of the extrudates is equivalent to the volume of gas displaced by the extrudates. Various measurements (n=5) for each formulation were performed and for each sample, 3 measurements were recorded. The average and the standard deviation values were calculated. The porosity is calculated according to the following relationship by equation 3.2.

\[ \varepsilon = 1 - \frac{\rho_{\text{bulk}}}{\rho_{\text{particle}}} \]  \hspace{0.5cm} \text{Equation 3.2}

\( \varepsilon \): porosity (%), \( \rho_{\text{bulk}} \): density measured by the pycnometer (g/cm³) and \( \rho_{\text{particle}} \): density of the individual materials in the extrudates (g/cm³).
3.2.3. Mechanical characterization

The ends of the ductile extrudates were held as a loop and attached by a wooden cord, while the ends of the brittle extrudates were kept straight without forming a loop. The extrudates were strained \( n=5 \), until fracture occurred. By pulling the extrudate, the force necessary to fracture the extrudate could be measured by a texture analyser (TA XT plus, stable Microsystems, Godalming, UK).

3.2.4. Swelling and water uptake

Water uptake and swelling properties of the different formulations were defined by placing 3 samples in 3 different Petri dishes \( n=3 \), filled with the same amount of distilled water. At time intervals 0, 20, 40, 60, 80, 100, 120, 150 and 180 min, the length and width of the extrudates was measured and compared.

3.2.5. Release of paracetamol

Drug release experiments were carried out with a dissolution apparatus (AT 7, Sotax, Switzerland) using the paddle method with the paddles rotating at 50 rpm. Dissolution vessels were filled with 1000 mL of distilled water and maintained at a temperature of 37°C ± 0.5 °C. The extrudates were embedded in a metal spiral and added to the dissolution vessels. Each time, 3 samples of 2 different formulations were tested \( n=3 \). Aliquots of 4 mL of dissolution medium were withdrawn at 20, 40, 60, 120, 180, 240, 360, 480, 720, 960 and 1440 min and replaced with an equal volume of fresh dissolution medium. The samples were analysed for the drug concentration at 243 nm for paracetamol, in a spectrophotometer (Hitachi U-2000, Japan). The paracetamol concentrations were calculated from a calibration curve between 0 and 0,014 mg/mL.
4. RESULTS AND DISCUSSION

4.1. EVALUATION OF THE FORMULATION

4.1.1. Extrusion profiles

By considering different mixtures in which the concentration of HPC was varied between 10 and 70% (Table 3.1), longer and more stable steady state profiles have been obtained with a lower fraction of HPC. The higher the HPC content, the more waving around the plateau of the steady state was observed due to more expressed extrudate swell and stick slip phenomena described in section 1.4. The elastic recovery of the polymer after leaving the cylinder, due to the release of the internal stored energy, was much more pronounced at higher polymer fractions. In addition the mass might be faced with a larger shear stress, due to the larger expanding properties and viscosity of the polymer inside the barrel, which negatively influences the quality of the extrusion profiles (72).

However, it should be noticed that the extrusion profile of formulation 7 with HPC LF was unstable and was characterized by a high extrusion force. This might be due to a low water uptake of the little present and less viscous HPC. At too low water fractions the high shear forces predominated and the extrusion failed. The role of the amount of water is discussed below. A summary of the results is illustrated in Figure 4.1.
Figure 4.1: Extrusion profiles of formulations with a different ratio HPC / dibasic calcium phosphate with 70:10, 60:20, 50:30, 40:40, 30:50, 20:60, 10:70 with LF (a), GF (b) and MF (c).
Relying on the steady state profiles, formulation 5 gave the best results with respect to the fraction of HPC. In the next step, the fraction of water was varied between 15 to 40% for HPC LF and GF and between 25 to 40% for MF formulations (Table 3.2).

The water content in the formulation was negative correlated with the extrusion force and positive correlated with the duration of the steady state stage, which were in good agreement with the findings of E. Jerwanska et al. (7) (Figure 4.2). As explained in the literature, water works as a lubricant at the die wall and decreases the shear stress, so that the mixture passes more easily out of the barrel (4) and in addition it increases the plasticity of the wet mass (73). As previously reported, the wetter the mass the less force is required to push the mass through the die due to its soft appearance, which leads to an extrusion profile with a low extrusion force (7). This relationship has to be assumed when the water fraction is varied within the same formulation. According to the previous statement, it has been reported that a higher fraction of polymer MCC absorbs more water and thus the water was not free to lubricate the wall of the cylinder (4). This resulted in a higher required extrusion force, even though the water fraction was higher than compared to the other formulation.

J erwanska et al. confirmed the positive relationship between water content and porosity and contributes to the previous stated relationship between the water content and extrusion force. During the compression stage of the extrusion process, the porosity was reduced until no gas was contained in the extrudate. Once the extrusion was started, a higher liquid content could provide a more complete filling of the pore spaces in the matrix which resulted in a reduction of particle-particle attraction. These lower binding forces, enhanced the possibility of particle movement and rearrangement during extrusion, which explains the lower extrusion force (7).
Figure 4.2: Extrusion profiles of formulation 5 (Table 3.1) with different water contents(%) with LF (a), GF (b) and MF (c).
All formulations with HPC MF and water fractions varying from 25 % to 40 % were extrudable. The extrusion of HPC GF mixtures with 15% of water and HPC MF mixtures with 25% of water failed, which can be considered as the lower water limit for these types of polymer. The mixtures were too dry, blocked the extruder and required too much force to leave the barrel represented as a sudden increase in load, known as the forced flow. The same phenomenon was reported when powdered cellulose, which was studied as alternative excipient for MCC in extrusion-spheronization, was used. Due to its low water holding ability and thus higher water requirement, difficulties during extrusion were present (8).

Another study, which was carried out with cotubular extrudates containing MCC as polymer, concluded that once 35 kN extrusion force was exceeded, the wet mass turned out too dry. In this research, too dry products gave extrusion forces much lower than previous reported 35 kN. This higher limit found in cotubular extrudates can be explained by the double shear stress occurring at both internal and external walls of the cotubular barrel, described in section 1.1.1.3.

The upper limit of the water level for the extrusion ability of mixtures containing HPC LF, GF and MF was 25%, 30% and 40% respectively. These extrudates were characterized by enormous stickiness and adhesiveness, due to the over wetting of the mass. It is assumed that a too high water level exceeded the ability of the polymer to hold and incorporate the water into the matrix (4). This can result in an emerge of water droplets during the compression stage due to an excessive water movement through the barrel, as previously reported (73). In this research, no water migration was observed so it can be supposed that ram speed and range of water fraction was chosen properly. A wet mass giving an extrusion force smaller than 10 kN was considered as overwet (11), in which the value was again much higher compared to the value found in this research.

Studies where 22,5 to 32,5 % MCC was incorporated for the production of laminar extrudates (4) and 43% MCC for rod extrudates (11), defined a range of adequate water level between 35 % and 45% and a ideal fraction of 43% respectively. In this research, the range of the most viscous HPC polymer (MF) can be considered between 30% and 40%.
Through optimization of various parameters the ideal amount of water can be determined. It has been observed that faster extrusion speeds, give more uniform water content in the formulation compared to slower speeds. In the last case, the water has more time to move into the voids between the particles in which the water distribution was not evenly, which has to be avoided (11, 73).

Based on the collectability and satisfactory appearance of the extrudate and the steady state profile, optimal water fraction of 20% in LF HPC, 25% in GF HPC and 30 to 35 % in MF HPC was suggested.

Finally, the effect of the use of various diluents as dibasic calcium phosphate and lactose in formulation 5 is illustrated in figure 4.3. The extrusion profiles obtained in the formulation with dibasic calcium phosphate surpassed the results of those with lactose, because a better steady state stage and less waving in the extrusion profile was observed.

![Figure 4.3: Extrusion profiles of formulation 5 including dibasic calcium phosphate with a water content of [30], [35] or including lactose with a water content [30], [35].](image)

However, Baert et al. demonstrated that the extrusion force of the low soluble dibasic calcium phosphate was higher compared to the force of the soluble lactose, which is not in agreement with our findings (74). Probably, this is caused by the high lactose content (50%) incorporated in this formulation. The remaining lactose of this high content was not soluble due to the saturation of the liquid by the initial solubilised lactose.
4.1.2. Quality of the extrudates

Formulations with a high HPC fraction were characterized by surface irregularities and a larger diameter than expected, taking into account the dimensions of the die. When the wet mass is moving through the barrel, the rate of flow is larger along the central axis than along the wall so that the central mass flows ahead and starts to expand when exiting the die due to its plastic properties. This flow arrangement at the exit of the die is known as the extrudate swell, previously described in section 1.4. The sharkskin was another manifestation of this stress release at the exit of the die (75).

On the other hand, formulations with a low HPC fraction had a smaller diameter although they were subjected to the same die with the same diameter. The formulation was able to resist the extra force exerted by the central mass of the mixture when it flowed through the barrel. The shark-like surface was less expressed.
4.2. CHARACTERIZATION OF THE EXTRUDATES

4.2.1. Summary of the results

Table 4.1: Overview of the results from the LOD, density, porosity and tension test with LF HPC (a), GF HPC (b), MF HPC (c) (mean ± SD, n = 5).

<table>
<thead>
<tr>
<th>Formulation</th>
<th>LOD (%)</th>
<th>Density (g/cm³)</th>
<th>Porosity (%)</th>
<th>Force (N)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HPC LF</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1b</td>
<td>15,2± 0,5</td>
<td>1,2266± 0,06</td>
<td>11,8</td>
<td>11,1± 0,5</td>
</tr>
<tr>
<td>2b</td>
<td>14,6± 0,5</td>
<td>1,3208± 0,01</td>
<td>14,9</td>
<td>10,0± 2,4</td>
</tr>
<tr>
<td>3b</td>
<td>12,4± 0,2</td>
<td>1,4261± 0,01</td>
<td>16,8</td>
<td>8,6± 1,1</td>
</tr>
<tr>
<td>4b</td>
<td>12,3± 0,7</td>
<td>1,5333± 0,02</td>
<td>18,2</td>
<td>4,9± 1,1</td>
</tr>
<tr>
<td>5b</td>
<td>12,2± 1,1</td>
<td>1,7511± 0,01</td>
<td>14,0</td>
<td>2,2± 0,7</td>
</tr>
<tr>
<td>6b</td>
<td>9,3± 0,6</td>
<td>1,8145± 0,00</td>
<td>17,4</td>
<td>1</td>
</tr>
<tr>
<td>7b</td>
<td>9,2± 0,4</td>
<td>2,5578± 0,01</td>
<td>8,4</td>
<td>1</td>
</tr>
<tr>
<td><strong>HPC GF</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1c</td>
<td>17,1± 0,5</td>
<td>1,0831± 0,01</td>
<td>21,8</td>
<td>15,8± 0,1</td>
</tr>
<tr>
<td>2c</td>
<td>16,9± 0,9</td>
<td>1,1540± 0,01</td>
<td>25,4</td>
<td>10,2± 1,8</td>
</tr>
<tr>
<td>3c</td>
<td>16,6± 0,1</td>
<td>1,3732± 0,01</td>
<td>19,7</td>
<td>9,1± 1,8</td>
</tr>
<tr>
<td>4c</td>
<td>16,6± 0,4</td>
<td>1,4512± 0,02</td>
<td>22,5</td>
<td>14,6± 1,8</td>
</tr>
<tr>
<td>5c</td>
<td>12,2± 0,4</td>
<td>1,5795± 0,02</td>
<td>22,3</td>
<td>8,1± 0,8</td>
</tr>
<tr>
<td>6c</td>
<td>11,2± 0,3</td>
<td>1,7266± 0,02</td>
<td>21,4</td>
<td>1</td>
</tr>
<tr>
<td>7c</td>
<td>11,1± 0,4</td>
<td>2,0987± 0,04</td>
<td>11,0</td>
<td>1</td>
</tr>
<tr>
<td><strong>HPC MF</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1e</td>
<td>20,9± 0,2</td>
<td>1,1026± 0,01</td>
<td>20,1</td>
<td>4,9± 0,7</td>
</tr>
<tr>
<td>2e</td>
<td>19,5± 0,4</td>
<td>1,1648± 0,01</td>
<td>24,5</td>
<td>6,7± 1,6</td>
</tr>
<tr>
<td>3e</td>
<td>19,4± 0,3</td>
<td>1,2093± 0,01</td>
<td>29,1</td>
<td>9,0± 2,5</td>
</tr>
<tr>
<td>4e</td>
<td>18,0± 0,7</td>
<td>1,3080± 0,01</td>
<td>30,0</td>
<td>9,7± 2,4</td>
</tr>
<tr>
<td>5e</td>
<td>18,0± 0,2</td>
<td>1,5565± 0,02</td>
<td>23,4</td>
<td>11,8± 1,1</td>
</tr>
<tr>
<td>6e</td>
<td>17,3± 0,3</td>
<td>1,5737± 0,01</td>
<td>28,3</td>
<td>3,1± 0,5</td>
</tr>
<tr>
<td>7e</td>
<td>11,9± 0,3</td>
<td>2,2234± 0,04</td>
<td>5,7</td>
<td>1</td>
</tr>
</tbody>
</table>

1 Impossible measurement because the extrudate was too brittle to be attached to the cord.

Table 4.2: Overview densities (g/cm³) of the raw materials.

<table>
<thead>
<tr>
<th>Paracetamol</th>
<th>Dibasic calcium phosphate</th>
<th>HPC LF</th>
<th>HPC GF</th>
<th>HPC MF</th>
</tr>
</thead>
<tbody>
<tr>
<td>1,3150</td>
<td>2,8215</td>
<td>1,2084</td>
<td>1,2002</td>
<td>1,1937</td>
</tr>
</tbody>
</table>
4.2.2. Water loss on drying (LOD)

![Graph showing the relationship between LOD (%) and formulations with a different ratio of HPC: dibasic calcium phosphate with HPC LF, HPC GF and HPC MF.](image)

It can be noticed (Fig. 4.4) that the higher the concentration and the viscosity of the polymer, the larger the ability to absorb and capture the water in the matrix. This larger absorption ability of water was detected and measured after drying (76). This was certified by Maderuelo et al. (66).

Although, it should be noted that the detected water fraction was lower than the initially amount of water added. A water loss around 10, 15 and 20% was detected, while in HPC LF, GF and MF formulations originally 20, 25 and 35% water respectively was added. First, this is due to the evaporation and escape of water during the preparation of the wet mix, secondly due to water migration in the wet mass through the barrel during the extrusion process and finally, due to an incomplete detection of water loss by this drying procedure.

Beside, unexpected small differences in water loss between some formulations (for instance formulations 4 versus 5) can be explained by the collection of the extrudates at different moments during extrusion. It has been shown that extrudates collected at the start of the extrusion are wetter than these ones in the end (73, 77).

A large water absorption and retention capacity improves the plasticity of the wet mass and facilitates the extrusion. It was defined as one of the required properties of an extrudate to allow extrusion (8).
4.2.3. Density and porosity

Figure 4.5: Relationship between density (g/cm³) and formulations with a different ratio of HPC: dibasic calcium phosphate with LF HPC, GF HPC and MF HPC.

Concluding from figure 4.5, the fraction of the diluent, dibasic calcium phosphate, determined the density of the formulation. The higher the dibasic calcium phosphate content in the formulation, the higher the density of the extrudate.

In addition, a high polymer content is associated with a low density value which can be explained by the ability to retain water. This was reported by Kleinebudde et al., in which it is assumed that a large water uptake during wet extrusion, resulted in a greater contraction during drying and thus a lower density value (78).

The density of the extrudate was lower than compared to the density of the raw materials in the powder mixture. First, this can be explained by the migration of the water through the matrix towards the surface, where the water was replaced by the air. The presence of the air reduced the total density of the mixture.

Second, this difference of density was confirmed by JJ Soussa et al. (3) and was certified by the lack of dissolution and recrystallisation of the water insoluble fillers, in which dibasic calcium phosphate is part of. Basically, the low filler solubility affect negatively the degree of solute migration through the matrix which results in a density lower than expected (79). In addition, the values of both densities are more spread the higher the density of the fillers (3).
Beside the filler solubility, also the drug solubility might affect the variability of the densities between pellets or extrudates and raw materials. An increase of drug solubility increases the pellet density, explained by the dissolution of the drugs in the water and its recrystallisation in the pores while drying (3). The impact of the drug solubility was not relevant in this research.

The density of the formulations, containing the HPC LF polymer, was the highest compared to formulations which included the HPC GF and MF polymer. This was due to the higher density of the raw polymer LF HPC.

![Figure 4.6: Relationship between the porosity (%) and formulations with a different ratio of HPC: dibasic calcium phosphate with HPC LF, HPC GF and HPC MF.](image)

No anticipating pattern (Fig 4.6) of the porosity was achieved. The tendency of this curve is discussed below.

In the first part of the graph, in formulations 1 to 4 (Fig. 4.6), with HPC MF and LF, and in formulations 1 and 2 with GF the percentage of the polymer occurred. The higher the polymer concentration, the stronger the degree of cross-linking between the polymer side chains and the lower the degree of porosity, which was confirmed by Maderuelo et al (66).

This relationship can be linked to the ability of water absorption (LOD test). A higher polymer content in the formulation is able to absorb more water.
The higher the water absorption, the more water that was retained in the matrix and thus the more pores are filled with water, resulting in a lower porosity.

Another variable which influences the porosity was the drug load. A higher drug load results in an increase of mean pore diameter and a decrease of number of pores and it delays the drug release (80). The impact of the drug load is not relevant in this research.

In addition the increase of porosity in formulation 1 to 4 might be confirmed by the behaviour of the extrudates noticed during the swelling test (Section 4.2.5). The expansion of the extrudate was more evident in formulation 4, in which more air spaces appeared, resulting in a larger porosity.

In the second part of the graph, the porosity tends to decrease, in particular once there was less than 40% of HPC MF and LF and less than 60% GF present in the formulation. This sudden decrease might be due to behaviour of the polymer as binder instead of an extended release matrix former or gel forming agent. Binders are used to hold the ingredients and active drug together in a cohesive mass to give volume to low dose active drugs, which explains the lower porosity.

In the production of laminar extrudates (4), HPMC was included as a binder and tend to increase the elasticity properties of the wet mass resulting in surface defects. These surface defects and brittle characteristics are also typical for the extrudates containing a low fraction of HPC (Section 4.2.4).

In the last part of the graph, the porosity of formulation 7 is inverse related with the density, which is a known relationship especially in crystalline rocks (81).
4.2.4. Mechanical characterization

![Graph showing force vs. HPC content](image)

Figure 4.7: Maximum force needed to fracture the extrudate as a function of the different ratio of HPC: dibasic calcium phosphate with HPC LF, HPC GF and HPC MF.

It was assumed that a high porosity was accompanied by a high brittleness, resulting in a small tensile strength (79). This inverse relationship between porosity and the tensile strength was reported in various literature studies, explained by the loss of isolated close interconnected pores the higher the porosity (79, 82). Although, the tensile strength of the extrudates, examined in this study, was not so closely related to the porosity (Fig. 4.7). This was probably due to the extremes of polymer content contained in the different formulations.

A higher fraction of polymer is characterized by a higher tensile strength. At first, due to their higher elasticity and viscosity, stronger bonding forces between the particles in the matrix were formed which resulted in a high resistance to deformation by tensile strength (83). These conclusions were in agreement with findings in MCC extrudates, including HPMC as binder. When increasing the HPMC content, an increase of bend strength due to the increase of deformability before breakage was observed (4). Although, the force needed to break this elastic extrudate was not that high. By pulling the extrudate, the sample started to stretch with at the end the disruption of the extrudate. During the stretching stage, the profile of the curve exhibits a plateau which explains the low value.

On the other hand, the lower the fraction of polymer contained in the formulation, the higher the brittleness and the smaller the tensile strength.
It should be noticed that the results of this test were not reproducible, due to the difficult performance. When the test was performed on different samples of the same formulation, the values of tensile strength were distributed. This can be explained by the different degree of surface irregularities and water content between samples of the same formulation.

At first, the exerted shear stress on the extrudate determines the expression of the distortions on the surface of the extrudate.

In the second case, a higher water content can allow particles to slip more easily in shear by each other resulting in a lower tensile strength (33). However initially in each formulation the same amount of water was added, still one of the previous mentioned processes of water loss (section 4.2.2) can be more pronounced between the samples. In addition, it has been reported that collected extrudates at the start of the extrusion are wetter than in the end (73), thus the difference in tensile strength can be due to the sampling at different moments during extrusion.

4.2.5. Swelling and water uptake

Water diffuses into the matrix of the extrudate, as soon it had contact with the aqueous medium, which resulted in polymer swelling and drug dissolution. This swelling mechanism can be described by the rate of diffusion of the liquid into the matrix. The swelling kinetics for HPC were described in the literature as anomalous or complex, in which the rate of penetrant entry and that of the macromolecular relaxation of the polymer are almost of the same magnitude (30). The swelling behaviour of the different formulations is discussed below (Table 4.3).
Table 4.3: Length or diameter (x 10^2) (%) for the different formulations, containing MF HPC, during several time intervals (min).

<table>
<thead>
<tr>
<th>Formulation</th>
<th>0</th>
<th>20</th>
<th>40</th>
<th>60</th>
<th>80</th>
<th>100</th>
<th>120</th>
<th>150</th>
<th>180</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>1/1</td>
<td>0.96/1.5</td>
<td>0.96/2.0</td>
<td>0.96/2.0</td>
<td>0.95/2.0</td>
<td>0.95/2.0</td>
<td>0.95/2.0</td>
<td>0.95/2.0</td>
<td>0.95/2.0</td>
</tr>
<tr>
<td>F2</td>
<td>1/1</td>
<td>0.98/1.5</td>
<td>0.96/1.5</td>
<td>0.96/1.5</td>
<td>0.96/2.0</td>
<td>0.93/2.0</td>
<td>0.85/2.0</td>
<td>0.80/2.5</td>
<td>0.76/3.0</td>
</tr>
<tr>
<td>F3</td>
<td>1/1</td>
<td>0.95/1.0</td>
<td>0.86/1.5</td>
<td>0.79/2.0</td>
<td>0.70/2.5</td>
<td>0.69/2.5</td>
<td>0.60/2.5</td>
<td>0.51/2.5</td>
<td>0.44/3.0</td>
</tr>
<tr>
<td>F4</td>
<td>1/1</td>
<td>0.98/1.0</td>
<td>0.91/1.0</td>
<td>0.79/1.5</td>
<td>0.70/2.0</td>
<td>0.61/2.5</td>
<td>0.57/2.5</td>
<td>0.5/3.0</td>
<td>0.48/3.0</td>
</tr>
<tr>
<td>F5</td>
<td>1/1</td>
<td>1.0/2.0</td>
<td>1.0/2.0</td>
<td>0.975/2.0</td>
<td>0.95/2.0</td>
<td>0.93/2.0</td>
<td>0.88/3.0</td>
<td>0.88/3.0</td>
<td></td>
</tr>
<tr>
<td>F6</td>
<td>1/1</td>
<td>1.0/2.0</td>
<td>1.0/2.0</td>
<td>1.0/2.0</td>
<td>0.97/2.0</td>
<td>0.97/3.0</td>
<td>0.95/3.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>F7</td>
<td>1/1</td>
<td>1.0/2.0</td>
<td>1.0/2.0</td>
<td>1.0/2.0</td>
<td>1.0/2.0</td>
<td>0.98/2.0</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1 Impossible to measure, due to the appearance as a curly extrudate.

Formulations 3 and 4 with HPC MF (Table 4.3, Annex IV) and formulations 1 and 2 with HPC GF (Annex V) exhibit most shrinking and densification, which was characterized by a shortening of the length and an expanding of the diameter due to the swelling. This swelling behaviour was also confirmed in other polymer extrudates, containing MCC as diluent and HPMC as binder (4). This was in agreement with findings of Kleinebudde, who reported that the extent of shrinking increased with the fraction of MCC and reduced with the fraction of filler (33).

Although in spite of the high HPC MF fraction, less expression of swelling is noticed in formulations 1 and 2, which might be due to their lower porosity, in which the water penetration into the pores of the mixture was more complex.

In all formulations with HPC LF, in formulations starting from 3 with HPC GF and starting from 5 with HPC MF no clear water uptake, gel formation and swelling mechanism was observed. The lower concentration of the polymer (4), the degree of viscosity and the higher density might declare this observation.

The impact of the degree of viscosity was explained as follow: the higher the degree of viscosity, the faster the swelling of the polymer side chains and the stronger the gel network (66).
Finally, the higher density of the extrudate, due to the higher amount of filler dibasic calcium phosphate, the particle-particle attraction is increased, so that the water penetration into this extrudate matrix was harder (73). In addition, in formulations with a high filler content, a curling mechanism and clear loss of load was more expressed. The first mechanism can be considered as the disintegration of the extrudate. The second mechanism was responsible for the sinkage of the extrudate. Although, at the start all formulations were floating, the higher the density the faster the sinkage process occurred.

It has been demonstrated that the duration of the increase of swelling observed in HPC matrices (30) and MCC extrudates (4) last for the first 5h, followed by a plateau of water uptake in the next hours. In this research the swelling behaviour was investigated for only 3 hours.

During the exposure of the extrudate at the water, the shark-like surface of the extrudates became clear, especially in formulations with a higher HPC content.

It has been reported that the swelling energy of HPC was higher than that of HPMC (84), which makes HPC a more important drug retardant release polymer.

In order to gain insight into the swelling process of the different formulations of the extrudates, the reader is referred to annex IV, where different images are exhibited.
4.2.6. Release of paracetamol

Concluding from figure 4.8, 100 % release of paracetamol was achieved in all formulations including different degrees of polymer viscosity. Generally, after 6 hours (360 min) a maximum release of paracetamol was reached. Although, the t_{50%} of HPC matrix tablets, using chlopheniramine maleate as model drug and including 40% of polymer, was 6.5h (30). Compared to this research, in which extrudates included the same fraction of HPC LF, GF and MF the t_{50%} was 20, 30 and 60 minutes respectively. The drug release of this matrix tablet was much lower than the observed release of these HPC extrudates which implicates that the drug release was more sustained.

Both the effect of ratio HPC/dibasic calcium phosphate and different viscosity of the polymers on the drug release are discussed.

First, the ratio of excipients is considered, in which it should be noticed that the drug release rate increases with a lower HPC content. For example, formulation 1 takes about 100 minutes to release 50 % of the drug, while formulation 7 only takes 40 minutes. The first formulation contains a high amount of HPC, characterized by a high viscosity and thus a bigger resistance to the dilution and erosion mechanism (30) in which slower drug release rates are achieved (66).

Secondly the effect of the degree of polymer viscosity on the drug release was examined and the same inverse relationship was found. It was observed that the drug release was faster over all formulations when the less viscous polymer HPC LF was used. Formulation 1, including HPC LF, GF and MF, reaches 70%, 40 % and 20% of drug release respectively after 40 minutes. The same conclusions were found in the literature, a higher degree of viscosity grade of HPMC corresponds with a stronger polymer entanglement, which results in a slower polymer erosion and thus a slower dissolution rate (76).

In addition, it is assumed that the drug release can be influenced by the porosity (84). Water penetration in a matrix of a formulation with a higher porosity is easier, so that the drug release is achieved more quickly (80). A large percentage of polymer corresponds with a low porosity and thus decreases the drug release rate (66).
Figure 4.8: Release of paracetamol (%) versus time (min) in formulations with a different ratio of HPC: dibasic calcium phosphate 70:10, 60:20, 50:30, 40:40, 30:50, 20:60, 10:70 with HPC LF (a), HPC GF (b), HPC MF (c).
In figure 4.9, in which the mass release was plotted against the time, the release rate can be determined. The release rate was related to the drug release and was in line with the preceding conclusions. The lower the concentration and viscosity of the polymer, the faster the drug release rate. This release rate was related to the porosity, except for formulation 7. The lower the amount of polymer, the higher the porosity, the easier the drug escape from the matrix. In addition an inverse relationship occurred between the swelling or polymer ratio and the drug release rate. The higher the fraction of polymer, the more swelling and the faster a gel formation occurred, making it harder for the paracetamol to escape from the matrix.

Better results are expected for the more viscous MF HPC, confirmed by the literature as: the higher the viscosity, the slower the release of the drug allowing us to obtain better controlled-release profiles (42).
Figure 4.9: Mass release of paracetamol (mg) versus time (min) in formulations with a different ratio of HPC: dibasic calcium phosphate - 70:10, 60:20, 50:30, 40:40, 30:50, 20:60, 10:70 with HPC LF (a), HPC GF (b), HPC MF (c).
The time dependent drug release in a polymeric system may be simply described by the Korsmeyer-Peppas model (Eq. 1.2, Fig. 4.10) (68). As showed in table 4.4, the value of the n exponent was nearly in each formulation located between 0.45 and 0.89, which corresponds with a non-Fickian transport mechanism, as mentioned in equation 1.4. The drug release was based on both erosion caused by polymer swelling and a diffusion mechanism of the drug.

The study of the drug release with a matrix containing polymer HPC and the model drug Chlorpheniramine maleate was investigated by Sinha et al. and was described as Fickian released (30), which was in contrary to our conclusion. Colombo et al. reported that matrices containing HPMC polymer and a water soluble drug, were characterized by an anomalous drug release (86).

It should be noted that the Korsmeyer Peppas equation was not applied on formulations containing the polymer HPC LF and GF. Considering the very fast drug release, these formulations do not satisfy the requirement of sustained release that is provided in this equation.

| Table 4.4: Korsmeyer Peppas constant n and R² for the different formulations (Table 3.1) |
|---|---|---|---|---|---|---|---|
|   | F1 | F2 | F3 | F4 | F5 | F6 | F7 |
| N | 0,81 | 0,92 | 0,81 | 0,72 | 0,86 | 0,89 | 0,91 |
| R² | 0,979 | 0,967 | 0,937 | 0,957 | 0,936 | 0,999 | 0,999 |

.Figure 4.10: Graph according to the Korsmeyer Peppas equation with \( \frac{M_t}{M_{\infty}} \) in function of \( t^n \) with a different ratio of HPC: dibasic calcium phosphate 70:10, 60:20, 50:30, 40:40, 30:50, 20:60, 10:70 with HPC LF (a), HPC GF (b), HPC MF (c).
5. CONCLUSIONS

The potential use of HPC for the production of extrudates in the wet extrusion is confirmed in this research. Previous studies have focused particularly on the use of MCC and HPMC as rate-controlling polymer in the extrusion-spheronization process.

First, we can conclude that a different need in moisture content for different degree of polymer viscosities was required for a successful extrusion. The ideal water fractions for polymers HPC LF, GF and MF are 20, 25 and 35% respectively. By employing these proposed water fractions, the concentrations of the polymer and filler can be varied over a wide range.

Secondly, the tests carried out showed following conclusions. The water retention capacity increased as the viscosity and the concentration of the polymer increased in the formulation. The density of the extrudates, which were lower than expected in comparison to the density of the raw materials, is mainly determined by the amount of dibasic calcium phosphate. The poor water solubility of this filler and water migration to the surface explain this observation. The porosity was inversely related to the percentage of polymer. However, a remarkable decrease in porosity was observed, which may be due to the behaviour of polymer as a binder instead of extended release matrix former explained. In addition, in this research no relationship between the porosity and the tensile strength could be defined. The observations of the swelling test showed that, generally a higher polymer content and degree of viscosity increased the shrinking and densification of the extrudate.

The drug release is characterized by a sustained release profile, which is most expressed when the most viscous polymer (MF HPC) was included in the formulation. 100% of drug release is obtained after 6 hours. The release mechanism occurred by diffusion of the drug through the swollen polymer matrix and by erosion of the matrix due to polymer swelling, which is known as the anomalous or non-Fickian transport.
6. FUTURE WORK

To find out if HPC is a possible alternative extrusion-spheronization aid to overcome the disadvantages of MCC, research of HPC in the production of extrudates using HME should be performed.

Successful samples of extrudates may be subjected to the spheronisation step, in which the extrudates are rounded into spheres or pellets.

The successful formulations employed in this study can be applied for the production of other shapes such as helical and laminar extrudates in the rod extrusion, tubular or cotubular extrudates.

The use of HPC in the formulations might be extended to the formation of extrudates with other drugs and therefore other drug properties.

Other research can make use of the higher viscosity polymer HF HPC (Ashland Klucel, Wilmington, USA). By creating a formulation with this polymer, better and longer sustained release profiles might be expected.
7. REFERENCES


44. MIRCIA S.I., BALACI T., AVRIGEANU V., HANCU G. Formulation and study of some controlled release tablets with pentoxifylline based on hydroxypropylcellulose matrix obtained by wet granulation method with peg 6000. *Broad research in artificial intelligence and neuroscience.* 2010;1(1):178-93.


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8. ANNEXES

Annex I: General info section about MCC
Annex II: General info section about HPMC
Annex III: General info section about HPC
Annex IV: Photos of the swelling process including LF HPC
Annex V: Photos of the swelling process including GF HPC
Annex VI: Photos of the swelling process including MF HPC
Annex I : General info section about MCC

MCC is a natural, purified cellulose prepared by treating alpha-cellulose with a partial hydrolysis derived from wood pulp. MCC particles adhere to each other without the use of a binding agent. It has applications in the pharmaceutical industry as tablet and capsule diluent used in wet granulation, as lubricant and disintegrant used in tablets but also in food and cosmetic industry.(82)
Annex II: General info section about HPMC

HPMC is a nontoxic partly O-methylated and partly O-hydroxypropylated cellulose derivative, as illustrated in figure 1.10. It finds its applications in the ophthalmology as eye tear film, in the food industry as thickening agent and as emulsifier, in the pharmaceutical industry as controlled release matrix for the active substance, as coating agent or as tablet binder. (82,84)

![Structure of hydroxypropylmethylcellulose](image)

Fig. 1.10 Structure of hydroxypropylmethylcellulose
HPC is a non-ionic water-soluble cellulose, in which some of the hydroxylgroups are hydroxypropylated using propylene oxide, as illustrated in figure 1.11. The viscosity is controlled by the degree of polymerization (DP) of the cellulose backbone, referring to the average number of substituted hydroxylgroups per glucose unit. Apart from the DP, the molar substitution (MS) describes the number of moles of hydroxylgroups per glucose unit. A value of 4 is required to obtain a good solubility in water. (82)
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### Annex V: Photos of the swelling process including GF HPC

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### Annex VI: Photos of the swelling process including MF HPC

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