Chapter 4

Contramid®: High-Amylose Starch for Controlled Drug Delivery

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Contramid® is a novel pharmaceutical excipient obtained by chemically and physically modifying a high-amylose corn starch. When a compressed tablet of Contramid® powder is placed in an aqueous medium, the material forms a hard gel displaying sponge-like viscoelastic properties. When observed by x-ray tomography, the gel reveals a membrane at its surface which governs the slow release of medication. Basic starch properties responsible for Contramid®'s slow release behavior are reviewed and used to explain the mechanism of self-assembly behind the controlled drug delivery technology. Characteristics of Contramid® such as diffusion and enzymatic susceptibility are also presented.
Introduction

The first publication on the Contramid® technology was reported by Lenaerts et al in 1991 (1). Starting from the well-understood principle postulated by Flory in 1953 (2) by which one can limit the swelling of a network by increasing its crosslink density, modified starches of different crosslinking degrees were prepared and theophylline release rate were evaluated. In doing so, the researchers attempted to prepare a crosslinked network of amylose to form a hydrogel able to control the release of medication, the rate of which would be a function of the crosslinking degree. Typically, by increasing the degree of crosslinking, one would create a tetrafunctional polymer network with a higher density of crosslinks and thus reduce its swelling capacity. It was soon discovered that crosslinking the natural polymer yielded a nonlinear response for swelling capacity and drug release (3,4,5,6). In fact, for higher crosslinking degrees, higher swelling capacity and faster drug delivery were observed. At moderate crosslinking degrees, the matrix efficiently sustained release of medications for 12-24 hours. This peculiar phenomenon sparked the interest of researchers and Contramid® was born (7).

Contramid® is a hydroxypropyl and crosslinked high-amylose starch pharmaceutical excipient used to prepare oral controlled release formulations. A brief review of starch composition and properties will allow the reader to efficiently capture the essence of this technology that relies essentially in harnessing the natural properties of starch. This paper provides an update and expands on the current level of knowledge reported over the years by the original inventors and researchers (8), using results from fundamental starch research to better explain and describe the Contramid® technology. Contramid® is used to prepare pharmaceutical tablets for controlled delivery of medication. This technology has been mainly applied to oral drug delivery but the reader may find interesting to know that Contramid® may also be used to prepare implants. The latter demonstrated excellent biocompatibility, biob sorption and are effective in controlling subcutaneous delivery of medication for several weeks (9,10,11,12).

Rationale for Controlled Oral Delivery

Soon after their discovery, drugs are formulated in their fastest, most convenient form for rapid access to market. With time however, their reformulation to the most convenient form for patients, posology and treatment is a trend that is undeniably logic-based. The significant increase in new products based solely on new formulations using existing or new technologies is a trend that has given
birth to a new face of the pharmaceutical industry: drug delivery companies. These companies generally use proprietary technologies to prepare value-added formulation of new or existing drugs. For drug delivery companies, oral delivery is a very competitive market as it represents the least invasive formulation, coupled with the highest patient compliance. However, this is not the end of the line, as prescriptions often require several tablets a day. Taking multiple doses of the same medication causes a series of highs and lows of the drug concentration in the blood, hitting the therapeutic window with alternating periods of limited efficacy and overdose (Figure 1). There is also the risk of forgetting to take one of the recommended doses, the result of which may alter treatment duration, cost and potentially the patient's health and safety. As presented in Figure 1, oral controlled release technologies such as Contramid® help to overcome these limitations by allowing slow release of the medication during its transit in the gastrointestinal tract in order to reach an efficient drug concentration in the blood and maintain it at therapeutic level for hours. Overall benefits of oral controlled drug delivery includes reduction in drug blood level variations, reduction in dosing frequency, enhanced patient convenience and compliance, reduction in adverse side effects and reduction in healthcare costs.

**Cellulose and starch: poly (D-glucopyranose) in Drug delivery**

The pharmaceutical industry has a long history of using cellulose and its derivatives as binders and adjuvants for tablet formulations (13,14,15,16). Nowadays, microcrystalline cellulose (MCC) is widely used because of its high compactibility property, i.e. its ability to form hard tablets at low compression force. This hardness is due in part to the numerous hydrogen bonds formed between particles of cellulose microcrystals. However, in tablet formulation, MCC readily disperses in water and instant drug release is obtained. Other cellulose derivatives (e.g. Hydroxypropylmethyl cellulose or HPMC) have been shown to allow controlled drug delivery due to continuously swelling matrix systems, i.e. drug release is governed by the kinetics of swelling. On the other hand, modified starches also possess great compactibility in the dry state, but adds the possibility of forming limited swelling gels to control the release of drugs. Because polysaccharides such as modified celluloses and starches are readily available "starting material" they hold an advantage over other more expensive synthetic polymer systems. In particular, the food industry has been using modified starches for a long time and has paved the way in terms of large-scale manufacturing. Starch is among the most important industrial biopolymers. It is the main nutrient consumed by humans worldwide, it is our main source of energy representing 70-80% of calories ingested (17). It is found in rice, pasta, bread, corn, potatoes and a wide variety of other grains, vegetables and plants. Because starches from various sources have different properties which can then
be modified by a large number of processes, there is a staggering variety of applications for starch based materials. Following is a brief overview of important aspects of starch chemistry that play important roles in the preparation and performance of Contramid®.

**Starch Composition**

Starch is composed of a mixture of two natural polymers: amylose and amylopectin (Figure 2). Amylose is a linear polymer of D-glucopyranose units joined by $\alpha$-1,4 acetal linkages. Depending on its botanical source, molecular weight of amylose strands are generally found to be less than 0.5 million and have degree of polymerization varying from 1,500 up to 6,000. Amylopectin molecules are much larger with typical molecular weights between 50 to 100 million and degree of polymerization of about 300,000 to 3,000,000 (17,18). Also, as shown in Figure 2, amylopectin has a racemose architecture where $\alpha$-
1,4-linked linear segments are branched together through α-1,6 linkages. Proportions of amylose and amylopectin vary according to their botanical source. Typically, corn and potato starches will have a 30%(w/w) content of amylose and 70% amylopectin. Contramid® is prepared from a high-amylose corn starch, a hybrid containing 70% amylose and 30% amylopectin.

Figure 2. Amylose and amylopectin schematic representations and molecular architecture.

In a native starch granule, amylose and amylopectin are found in intimate contact with each other, randomly interspersed (19). Furthermore, both are organized in a semi-crystalline arrangement where amorphous and crystalline regions are formed by neighboring amylose and amylopectin molecules (20). The hybrid high-amylose starch used to prepare Contramid® is found to exist as three main morphologies: Non-crystalline regions, V-type single helices and B-type double helices. The V-type is a single strand helix whose exterior is hydrophilic and interior is a hydrophobic cavity able to complex fatty acids (21) and small organic molecules (22,23). In fact, orientation of the glucose unit in the V-type helix is highly similar to a β-cyclodextrin molecule. This single helix is present in amorphous regions in starch. Crystal arrangements and packing in crystalline regions are made of clusters of double helices arising from the association of
neighboring branches of amylopectin molecules, and amylose chains, in such double helices (24). Figure 3 presents molecular models of a V-type single helix and a double helix made of linear segments of starch molecules (all molecular model graphics found in this chapter were graciously provided by Prof. Stefan Immel, Technical University of Darmstadt\(^1\)). More detailed molecular models of both these helical arrangements have previously been published by Immel et al. (25).

**Starch Gels**

The food industry has for a long time relied on starches for viscosity enhancement and gelling properties. At room temperature, starch granules are insoluble in water and swells relatively little. However, if a starch suspension is heated to temperatures above its gelatinization temperature and/or suspended in alkaline solution, starch undergoes an irreversible transition: gelatinization. Gelatinization is a general term used to describe a series of thermal events that occur in starch granules upon heating or in alkaline aqueous media. Most importantly, during gelatinization, the starch granule’s crystalline arrangement is destroyed and the granule swells to its maximum as an amorphous suspension (26). For an in-depth review on the complex subject of gelatinization of starches, please refer to (27). This transition is often referred to as being irreversible. However, if the order found in the native granule may never reform as once nature intended it, the formation of double helices is not entirely compromised. In fact, reformation of these double helices is a common phenomenon in starch science called retrogradation. Retrogradation of starch is a term used to define the changes that occur in gelatinized starch from an initially amorphous state to a more ordered or crystalline state (28). More importantly here, it is the process by which Contramid\(^\circledast\) self-assembles in water to form a gel.

Swelling of Contramid\(^\circledast\) tablets in water is presented as a self-assembly process that differs from other swelling polymeric systems: swelling increases with increasing crosslinking degree, which is opposite to typical crosslinked polymer networks (2). This is explained by starch retrogradation. When a tablet of Contramid\(^\circledast\) swells in water, self-assembly of its polymeric chains into double helices confers to the gel high mechanical strength and limited swelling capacity.

\(^1\) http://caramel.oc.chemie.tu-darmstadt.de/~lemmi
Figure 3. Molecular model representation of the V-type single helix (top) and double helical (bottom) arrangements found in starch.
In other words, the limited swelling and formation of a tridimensional network is caused by the formation of physical or pseudo-crosslinks: double helices and chain entanglement. By increasing the crosslinking degree, one is actually reducing the number of possible double helix formation, and thus oppositely reducing the number of physical crosslinks. Consequently, the tablet is able to swell more and, at an excessive crosslinking degree, no tridimensional network is formed and the tablet completely loses cohesion. This principle was previously observed by Hollinger et al. who measured an increase in water sorption in crosslinked starch (29), and by Moussa and Cartilier who measured an increase in swelling capacity of crosslinked starch tablets (30), with increasing crosslinking degree.

Contramid® Preparation

Contramid® is a crosslinked and hydroxypropylated high-amylose starch based excipient prepared according to a US patent (31). During the first preparation step (Figure 4), high-amylose starch is slurried in a weak sodium hydroxide suspension and heated to ca. 30°C. In these conditions, starch granules are partially swollen by the combined action of heat and sodium hydroxide, but are not gelatinized. At this point, hydroxyl groups on amylose and amylopectin molecules are available for modifications and an alkaline pH assures activation of future chemical reactions. This step is hereby referred to as activation step. Phosphorous oxychloride crosslinking agent is then added to the slurry, followed by propylene oxide. This reaction further functionalizes amylose and amylopectin molecules with hydroxypropyl side chains.

Crosslinking and hydroxypropylation

Crosslinking and hydroxypropylation of starch are both used to improve the stability and hardness of gels obtained from starch materials. Instability of starch-containing products is often associated with retrogradation of starch over time which changes the properties of the initial product. The best example of this is bread staling. Covalent crosslinks and hydroxypropyl side chains allow greater stability in terms of temperature and pH by hindering retrogradation over time (17). Crosslinking also plays the role of “grafting” amylose chains on the giant amylopectin molecules (32). As it will be seen further, both increased stability in the dry state and properties in the swollen state are important factors altered by chemical modifications such as crosslinking and hydroxypropylation.
Spray-Drying

The last step, and not the least important, is the drying of the material. After washing with water, the previous slurry is heated to a very high temperature (ca. 160°C) and gelatinized to an entirely swollen and amorphous state. Drying is then performed by spraying the hot slurry in hot air (>200°C). This results in rapid water evaporation and consequently, Contramid® is trapped in a non-crystalline state. The chemical modifications discussed above and the speed at which water is evaporated effectively prevents retrogradation. Resulting average

Figure 4. Contramid® preparation flow chart and progression of particle size representation.
particle size is around ten times larger than the starting material’s average granule size (Figure 4)

.Safety and regulatory acceptance

Modified starches, such as Contramid®, have a long history of safe use as food additives. Contramid® conforms to the specifications for modified starch under the Food Chemicals Codex and is considered a food additive by the FDA and the equivalent European authorities. Under these regulations, all modified starches are generally regarded as safe for oral administration and generally may be used with orally administered drugs without significant modification to the safety profile of the medication in unlimited quantities. Furthermore, the International Pharmaceutical Excipient Council guidelines indicate that pre-clinical toxicity and safety studies should not be required for the approval of Contramid® as a pharmaceutical excipient.

How Contramid® works

Most of the cited studies in this section were performed on starch suspensions. We believe these events also apply to a directly compressed starch tablet, albeit at a further extent because of the proximity of starch particles that allow more interparticular (intermolecular) interactions. This correlation between systems is also in line with the findings showing that an increase in starch concentration results in an increase of gel viscosity (33). Contramid® is prepared from high-amylose starch that is proven to yield stronger gels. Crosslinking and hydroxypropylation further increase the strength of gels (17). Rahmouni et al. (34) demonstrated that the mechanical strength of Contramid® gels, as measured by the force needed for a probe to penetrate the swollen tablets, was eight-fold greater than that of a widely used cellulose derivative. Ravenelle et al. (35) described swollen Contramid® tablets as sponge-like. In the latter study, a uniaxial unconfined compression of a tablet demonstrated the quasi reversible deformation of the gel. During a step compression, water slowly flows out of the tablet, and upon decompression, the water is sucked back in.

Visually, when a Contramid® tablet is swollen to equilibrium, its shape increases by 60-80% in thickness and 15-35% in width (8,35) depending on tablet preparation (compression force, tablet size). This anisotropy of swelling is simply explained by the flattening of the Contramid® particles in the axial direction during dry compression of the tablet. The flattened particles tend to adopt their initial shape and swell more in the axial direction than in the radial. More importantly, a Contramid® tablet swells to a limit, i.e. it holds its shape,
albeit bigger. This shape retention is a very important characteristic that allows for slow release of drugs. The shape retention is given by the propensity of starch to retrograde, i.e. to form double helices. These double helices are responsible for the efficient formation of a tri-dimensional network.

It has been recognized that interaction between amylopectin and amylose contribute directly to the gel properties of their mixtures (33,36,37,38). In order to obtain the necessary viscoelastic properties of a gel formed from a Contramid® tablet, a combination of important factors is considered. In a first instance, let's examine the role of chemical structures and molecular weight. Jane et al. (33) demonstrated how amylose molecular sizes and amylopectin branched chain length affected gel properties by analyzing the viscosity, clarity and strength of gels from different starch suspensions. Because high-amylose corn starches possess smaller amylopectin molecules and longer amylose chains (33), the authors concluded that a higher content of amylose in starches yielded stronger gel strength.

Water quickly penetrates the initially amorphous tablet and acts as a plasticizing agent. This plasticizing effect increases intermolecular space of free volume (39), and thus allows greater mobility to starch molecules which rapidly start reorganizing into their thermodynamically most stable conformations: double helices. While hydrogen bonding with water allows the plasticizing effect to occur, below its gelatinization temperature, hydrophobic interactions between starch molecules drive retrogradation. The reader is advised that it is often wrongly reported in literature that hydrogen bonding is the driving force behind retrogradation. In essence, hydrogen bonding allows for stabilization of the formed double helices. At room temperature, starch is insoluble in water and thus possesses intermolecular interactions (hydrophobic) and water-starch interactions (hydrophilic, plasticizing effect). If hydrogen bonding was the driving force, there would be no better molecule on earth than water to supply it and a solution would be formed, not double helices.

\( ^{13} \text{C Solid State NMR} \)

To investigate retrogradation in swelling tablets, \(^{13} \text{C Solid State NMR} \) experiments were performed. According to Veregin et al. (40) and Gidley & Bociek (41), starch crystalline and amorphous morphologies have characteristic resonance in the \(^{13} \text{C Solid State NMR} \) spectrum. Using \(^{13} \text{C Cross Polarization Magic Angle Spinning Nuclear Magnetic Resonance (}^{13} \text{C CP/MAS NMR) it is thus possible to identify the conformations present in samples of starch by observing the C1 resonance in the region of 100-104 ppm. Previous studies also
Figure 5. Retrogradation: Disordered V-type and amorphous Contramid® immersed in water for the indicated time converts to B-type double helix as shown by the C1 resonance changes in the $^{13}$C CP/MAS NMR spectra.
looked at this phenomenon by observing changes of spectra for powders exposed to 100% relative humidity for various times (7,42,43). In the present study, microtablets (pellets) of Contramid® were prepared and inserted in a CP/MAS NMR probe and spectra were acquired for different swelling times. For dry tablets, the C1 region is broad and is representative of an amorphous material. Figure 5 presents spectra obtained at different swelling times. The evolution of the C1 resonance with time presented in Figure 5 indicates a transition from amorphous and V-type single helix (broad peak) to a predominant B-type double helix upon hydration of the tablet. The narrowing of the peaks corresponding to V and B phases, as well as the entire spectrum in general, indicates an increase in degree of order.

**Differential Scanning Calorimetry (DSC)**

Differential Scanning Calorimetry (DSC) is often used to observe and quantify thermal events in aqueous starch suspensions. The most common determination is that of gelatinization temperature which is related to the extent of retrogradation in starch suspensions that have been heated and cooled (44,45). DSC was used to investigate the calorimetric profile of swelling Contramid® tablets. The experimental set up requires the use of small pellets. The latter are swollen for two hours at room temperature in excess water, removed from water, weighed for content of water and placed in a stainless steel hermetic pan for analysis. The two hours allow enough penetration of water to start swelling of the tablet while ensuring that the tablet is not at equilibrium, meaning the retrogradation of Contramid® is not complete and should thus be observed as an exothermic event. The reference cell contains an equivalent amount of water as the one absorbed by the tablet being analyzed. Samples are first brought to 0°C at equilibrium before being ramped at 10°C/minute up to 140°C. A typical thermogram for a Contramid® tablet is presented in Figure 6 (46). It is possible to observe the retrogradation exotherm (at ca. 40°C) caused by the formation of double helices.

From this thermogram we demonstrate that heating the tablet to body temperature (37°C) speeds up the formation of double helices as shown by the retrogradation exotherm in the range of 35-50°C. Although the plasticizing effect of water is present at room temperature, we can conclude that it is optimum at a temperature close to 40°C. It is noteworthy to mention that the exotherm was not present for a tablet swollen for more than 24 hours, supporting the interpretation. As we continue heating the swollen tablet, we observe a broad endotherm around 80°C characteristic for gelatinization temperature range. This is the temperature at which all organization is destroyed; pellets lose cohesion and become a homogenous suspension in water.
Figure 6. DSC thermogram of a Contramid® tablet swollen for 2 hours in water
In other experiments, Contramid® tablets were swollen at different temperatures (25, 37 and 55°C). After 12 hours of swelling, visual examination revealed that Contramid tablets slightly swelled at 25°C, and form a hard gel. However, the tablets split in two after a few hours due to the lack of cohesion between the swollen particles. At this temperature, the amylose chains have less mobility to self-assemble in a tri-dimensional network and maintain tablet integrity. At 37 and 55°C, tablet integrity is maintained but the gel strength of the swollen tablet, is much higher at 37°C than at 55°C. This means that the self-assembly structure of amylose that confers a high mechanical strength to the Contramid gel and maintains the tablet integrity reaches its maximum organization around 37°C, which concords with the DSC observations.

In-Situ Forming Membrane

Another interesting feature of a swelling Contramid® tablet is that a membrane is formed on the outer surface of the tablet in the first minutes of swelling. The instant rétrogradation of the surface of the tablet is visible to the eye. Moussa & Cartilier observed this membrane by optical microscopy and showed that it rapidly forms when the tablet is placed in water, but very slowly thickens over time (30). What is remarkable is that the organization formed at the surface of the tablet in the first few minutes is not propagated to its core; the core maintains a coarse porous texture. Recently, Nuclear Magnetic Resonance Imaging (NMRI) has been used to observe swelling of modified high-amylose starch tablets and the same membrane formation was observed (47,48). Recent results performed with Contramid® tablets using this technique are also presented in this book (cf. Thérien-Aubin and Zhu in this book). In the present chapter we introduce x-ray tomography as a new method for investigating this heterogeneous swelling of Contramid® tablets. These studies were initiated by Marchessault and Chauve (49) at McGill University’s Bone and Periodontal Research Center (Montréal, Canada). Similarly to NMRI, x-ray tomography is a non-destructive inspection technique that provides cross-sectional images in planes through a solid. It images relative electron density fluctuations in a material point by point in planes. Furthermore, using a mathematical algorithm, diffraction intensities of the x-ray beam transmitted through the tablet can yield grey level images that are directly proportional to local material density leading to a quantitative measurement of the porosity of the material (50). Using this non-invasive technique, we can image cross-sections of dry and swollen tablets of Contramid® and observe the membrane.

The relative density of planes selected approximately at mid height of both a dry (left) and 24-hour swollen tablet (right) are presented in Figure 7 (49). Tablets were made using a direct compression of 9.8 kN. The results once again demonstrate the heterogeneity of the swollen tablet and support previous observations of a membrane. It is clear that in the dry state (Figure 7, left), there
is no density variation between the interior and exterior of the tablet which could explain the membrane apparition. These results further indicate that the core of swollen tablets is less dense than the outer membrane formed. While the porosity of the dry tablet is around 10%, the swollen tablet shows an average porosity of 19%. This average over the entire tablet can be divided where the core has a porosity of 34% and the membrane has a varying porosity of 2-15%. When measuring the porosity of top or bottom surfaces, one finds a value around 2% porosity. This clearly confirms that the membrane is the diffusion rate-limiting step in the delivery of drugs. This in-situ formation of an outer membrane also allows for a quasi zero-order release kinetic. This is achieved when the release rate of the drug is directly proportional to time. According to Peppas and Franson (51), a limited swelling matrix having an outer membrane controlling the release of a drug could achieve zero-order kinetic release provided that the outer membrane or polymeric layer possesses a much smaller diffusion coefficient than the inner core of that same tablet. This is readily what happens when a Contramid® tablet is placed in an aqueous environment. In the case of a continuously swelling system (e.g. HPMC), changes in both the swelling kinetics and surface area with time, renders achieving zero-order kinetics an impossible task.

We explain the existence of this membrane in two different ways: Water availability and steric hindrance. First, when the tablet is placed in water, the outer surface is exposed to an unlimited supply of water. Diffusion of water inside the tablet is governed by rapid swelling of amorphous Contramid® particles and by capillary forces caused by the interparticle micropores. Both water supplies are slowed down when the outer surface rapidly retrogrades and forms a gel with low porosity. The kinetics of diffusion of water through this newly formed membrane limits the amount of water available for retrogradation of the core in such a way that it is not sufficiently fast to allow an efficient retrogradation. Secondly, the formation of the membrane also causes the particles located inside to swell and expand with steric limitation (52). This “encasing” is also believed to play a role in the existence of the outer membrane.

Membrane structure

Lenaerts et al. (8) presented the model where double helices formed between grafted amylose on amylopectin molecules. This model of starch is supported by rheological studies of Gidley (53) that demonstrated that amylose gels are semi-crystalline networks of double helices and amorphous regions. However, this model was simple and left out important pieces of the puzzle. The linear architecture of amylose and its backbone flexibility allows multiple double helices to form at different location along the backbone, either with other amylose chains or with amylopectin as postulated by Klucinek and Thompson (37). While linear segments of amylose have a greater tendency to self-assemble.
in double helices (17), amylopectin may also retrograde. In the case of Contramid®, a 30% proportion of amylopectin helps in obtaining stronger gels because of the gigantic size of amylopectin molecules that allow numerous attachment points for the formation of double helices and can be represented as “anchoring points” in tridimensional network formation. These “anchoring points” allow several double helical physical crosslinks to form between amylose and amylopectin outer branches. Also, because of covalent crosslinking, amylose chains were also grafted to amylopectin molecules. These amylose chains further increase the anchoring properties of amylopectin molecules by grafting longer side chains to its usually shorter ones. From their ability to form several double helices, coupled to crosslinking, amylose chains also get entangled. The combination of all factors allows the formation of a tridimensional network composed of the four following components:
• Amylose-amylose and amylose-amylopectin double helices
• Amylose chain entanglement
• Amylopectin anchoring points
• Amorphous regions

Since starch particles are closely packed together by compression, the proximity further increases the self-assembling and limited swelling through retrogradation. This increase in interparticle association counterbalances the limiting effects associated to chemical grafting and crosslinking. Figure 8 is a schematic representation of the different dynamics involved.

Drug Delivery Related Properties

Diffusion and permeability

The diffusion parameters of different drugs having various physical properties have been studied by Rahmouni et al. (52). The apparent permeability \( (P_{\text{app}}) \), partition coefficient \( (K) \) and diffusion coefficients \( (D_g) \) of drugs through the swollen Contramid® membranes were measured according to the 'lag-time' model, using the diffusion-cell technique (Figure 9).

The membranes were prepared by direct compression using a single station press (Stockes, F4), then swollen in desired buffer to equilibrium prior to use. Diffusion of solutes through hydrogels depends mainly on the solute size, the equilibrium water content of the hydrogel and its porosity (54). Factors affecting the physical properties of a gel such as degree of swelling and gel porosity may have an impact on its permeability. Compression force and particle size are known as factors that influence the porosity of dry Contramid® tablets. However, they have no significant effect on the permeation properties of the membranes obtained when swollen. The lack of a strong dependence of permeability on particle size and compression force was related to the mechanism of the transformation of Contramid® compact into a gel, as just presented.

While incorporation of hydrophilic additives such as 0.25 and 0.5% colloidal silicon dioxide or 10% hydroxypropylmethyl cellulose (HPMC) had no significant effect on the swelling and the permeation proprieties of Contramid® membranes (52), incorporation of hydrophobic additives such as magnesium stearate (0.25 and 0.5%), had a pronounced impact on these properties. This was probably due to the formation of complexes at the surface of particles between amyllose chains and these agents in forms of V-type single helix. This well-known phenomenon can reduce retrogradation and thus alter the gel properties. In fact, lipidic agents are used as antistaling agents in bread and other baked goods because of this retrogradation hindrance (55).
Figure 8. Schematic model representation of a Contramid® gel
Figure 9. Diffusion cell set-up
It was also reported that $P_{\text{app}}$ and $D_g$ of two model drugs, rhodamine B and tramadol decreased as the membrane thickness increased (56). The reduction of $P_{\text{app}}$ and $D_g$ was attributed to the loss of membrane homogeneity, as it becomes thicker in the range studied, due to the membrane and core structure discussed previously. However, the authors believe $P_{\text{app}}$ and $D_g$ remain stable above a certain thickness where the core's permeability is much higher than that of the membrane; the membrane becoming the rate limiting diffusion step.

Furthermore, the diffusion coefficient of small solutes through Contramid® gels is greatly affected by their solubility ($S_w$) and to a lesser extent by their molecular weight ($M_w < 500 \text{ g/mol}$) (52). When the partition coefficient of solute-Contramid® gel was less than unity ($K < 1$), the diffusion process occurred mainly via the 'pore' mechanism, and followed the Mackie-Meares theory. Estimation of the pore size of Contramid® gels according the Rankin equation gave a reasonable value of 22 Å. This average pore size value is in line with the findings of Ravenelle et al. (35) who reported a pore size of 16 Å from hydraulic permeability data, using the Navier-Stokes equation.

Finally, a relationship between $D_g$, $S_w$ and $M_w$ was studied according to an empirical model. Resistance to solute diffusion through Contramid® membranes was assumed to be dictated by chemical solute/gel interactions and by physical size exclusion of the gel network. Since Contramid® is a non-ionic polymer, solute/gel interactions should mainly depend on solute polarity, and thus on its $S_w$. The second factor, which reflects physical size exclusion by the Contramid® network, depends mainly on solute size and thus on its $M_w$. Good agreement was found between the experimental diffusion data and the values calculated with the proposed model.

**Enzymatic degradation and resistance**

Contramid® is unique in that it is based on starch, a usually highly digestible material. As mentioned above, starch is the main nutrient consumed by man. Because we have α-amylase in our gut, we are able to enzymatically degrade most starches to oligosaccharides and glucose for energy. However, there is abundant literature that discusses methods to prepare "resistant starches" (57). Eerlingen et al. reported that the higher the degree of organization, the higher the amount of double helices, the lower the enzymatic degradation (58). Hence, by partially gelatinizing starch and allowing retrogradation to occur, it is possible to reduce the enzymatic susceptibility. Generally, resistant starches are classified in
four different types, depending on the conditions leading to their resistance to enzymatic digestion (57). However, as it is described below, Contramid® holds the combination of all four types in a single system:

Type 1: Physical inaccessibility (surface area, addition of protective ingredients)

Surface area is greatly reduced by forming a tablet compared to free powder. Also, because there is a shape retention property, the tablet swells to a limit, restricting enzymatic attack to the surface of the tablet. As demonstrated earlier by x-ray tomography technique, the surface porosity is very low and allows limited access to enzymatic degradation.

Type 2: Due to refractory nature of some starch granules

High-amylose corn starches have for a long time being recognized as being less susceptible to enzymatic degradation (59).

Type 3: Due to retrogradation, increase in organization degree.

The quick formation of the membrane through retrogradation (double helix formation) just discussed considerably reduces the enzymatic degradation of the tablet.

Type 4: Due to chemical modifications and crosslinking

Contramid® is also chemically functionalized. Hydrolysis of amylose and amylopectin by α-amylase and the mechanism by which the enzyme attaches itself to and degrades starch to oligo and monosaccharides has been extensively studied and is now well understood (58,60,61). This comes from the fact that to hydrolyze the α-1,4 acetal linkage, the enzyme needs to attach itself to the substrate at a specific number of binding sites (62). Because of this, chemical modifications such as crosslinking and hydroxypropylation significantly reduce Contramid®'s susceptibility to enzymatic attack in comparison to the high amylose starch starting material.

In the paper by Rahmouni et al (63), many parameters and their effect on the enzymatic degradation were evaluated. An interesting factor is the compression force. It was shown that above a compression force of 6kN, the enzymatic degradation is independent of that parameter. At lower forces, the porosity of the dry and probably swollen tablet is enough to allow more enzyme activity.
because of a higher surface area. Neither ionic strength nor the gastric retention
time greatly affected the kinetics of enzymatic degradation.

Incorporation of gel forming polymers such as PEO and HPMC in the tablet
formulation has shown to reduce degradation and thus protect the matrix from
extensive erosion that would jeopardize controlled release (64). The addition of
about 5-10% of HPMC for example is enough to reduce the enzymatic
degradation to satisfactory levels. This indicates that addition of PEO or
HPMC does not significantly affect self-assembly of Contramid® and protects by
quickly swelling in water and forming a gel that further reduces the availability
of the substrate for enzymatic attack through an increase in viscosity.

Conclusion

Contramid is fabricated by altering the chemical and physical structure of starch,
leading to self-assembly of an amorphous powder to a gel matrix of double
helices upon swelling. An important equilibrium exists between restraining
retrogradation in the dry powder and allowing it to a sufficient extent to form a
viscoelastic gel. The gel formed on the surface of the tablet in the first few
minutes controls the rate of water diffusion inside and out of the tablet, i.e. it
allows controlled release of the drug. The intrinsic nature of high-amylose
starch, the high density of the surface membrane, its low porosity, along with
chemical modifications and crosslinking, significantly reduce the enzymatic
degradation expected in the intestine. While highly complex and expensive,
manufacturing of osmotic pumps is usually required to obtain zero-order release
kinetics. With this in-situ forming rate-controlling membrane, Contramid®
allows near zero-order release kinetics from a matrix tablet. Overall,
Contramid® is an excellent demonstration of how one can harness the natural
properties of a polysaccharide such as starch, and tune them just the right way as
to obtain a high performance specialty pharmaceutical excipient.

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