

Cyclodextrins as a new therapeutic approach to drug delivery in the colon

As ciclodextrinas como uma nova abordagem terapêutica para a administração de fármacos no cólon

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RESUMO

A veiculação de fármacos para o cólon tem-se tornado atrativa, na perspectiva terapêutica, quer pelo seu interesse no tratamento tópico de doenças intestinais, quer como local de absorção de moléculas proteicas. No entanto, os fármacos administrados por via oral têm um longo caminho a percorrer até atingirem o cólon e vários fatores dificultam a chegada do fármaco ativo a este local. Com o objetivo de ultrapassar estes obstáculos, as ciclodextrinas têm sido estudadas como veículos específicos para administração colónica de fármacos. Graças às suas características únicas e bioadaptáveis, as ciclodextrinas são capazes de complexar variadas moléculas ou parte delas, fornecendo um microambiente protetor à molécula complexada e atenuando as suas propriedades indesejáveis. Contudo, a complexação não é suficiente para garantir a entrega dos fármacos no cólon, visto que os complexos podem dissociar-se antes de atingi-lo. Recorrendo à conjugação dos fármacos com as ciclodextrinas, por estabelecimento de ligações covalentes, garante-se a libertação do fármaco apenas quando essas ligações forem destruídas, uma vez que as ciclodextrinas são degradadas no cólon, por ação da microflora aí existente. Este conhecimento deu lugar a uma nova abordagem terapêutica, potencializando a formação de conjugados de fármaco-ciclodextrina como profármacos para a administração colónica. Este artigo tem como objetivo fazer uma revisão de estudos já realizados nesta área, avaliando o potencial das ciclodextrinas como veículos para a administração de fármacos no cólon, assim como as perspetivas futuras da sua utilização.

Palavras-chave: ciclodextrinas, complexos de inclusão, administração colónica

ABSTRACT

Drug delivery to the colon has become attractive either for its interest in the topical treatment of intestinal diseases or for the delivery of peptide molecules. However, drugs administered through the oral route have a long way to go until reaching the colon and several factors can hinder the arrival of the active drug to this site. In order to overcome these barriers, cyclodextrins have been studied as specific vehicles for colonic administration. Due their exclusive and bioadaptable characteristics, cyclodextrins are capable of complexing various molecules or part of them, providing a protective microenvironment to the complexed molecule and decreasing its undesirable properties. However, complexation is not enough to ensure the delivery of drugs to the colon since the complex dissociates before it reaches it. Using the conjugation of drugs with cyclodextrins, through covalent bond formation, it is ensured that the drug is released only when these bonds are broken, according that, cyclodextrins are degraded only in the colon by the existing microflora. This knowledge gave rise to a new therapeutic approach, potentiating the formation of drug-cyclodextrin conjugates as prodrugs for colonic administration.

Keywords: cyclodextrins, inclusion complexes, colonic administration

INTRODUCTION:

The drug should be able to resist passing through stomach and small intestine and also the pH variations along the way, to finally get to the colon with the capacity to exert the desired therapeutic effect.

Many Placement systems have been studied for specific delivery of drugs in the colon, exploiting specific properties of this organ. The microflora present there, is one characteristic that has allowed the development of specific delivery systems to achieve better results.

Cyclodextrins are cyclic oligosaccharides consisting of a variable number of glucose units. It is known that these molecules are not absorbed through the upper gastrointestinal tract and are metabolized in the colon and in the cecum. This characteristic gives them interest as drugs vehicles to the colon.

Cyclodextrins have a frustoconical shape with a hydrophobic cavity able to incorporate many types of molecules and changing their physical-chemical and biological properties. In addition, because of their natural origin and saccharidic nature, they are considered by the FDA as safe molecules. Currently, drugs associated with cyclodextrins are already approved and commercially available, in addition to cosmetics and nutraceuticals.

The aim of this article is to review studies already carried out in this area, evaluating the potential of cyclodextrins as vehicles for delivery of drugs in the colon, as well as future prospects of their use.

The colon as a therapeutic target for oral administration of drugs

Colon morphology and physiology:

Colon is the portion of the digestive tract that extends from the ileocecal junction to the anus. It consists of the blind, colon, rectum and anal canal. Usually the content takes 18-24 hours to cover its entire length, in contrast to the 3-5 hours required in the small intestine) (SEELEY, STEPHENS & PHILIP, 2003.).

The colon measures 1.5-1.8 meters long and it is divided into four parts: the ascending, transverse and descending colon and the sigmoideu (SEELEY, STEPHENS & PHILIP, 2003.)

Histologically, the colon wall consists of four layers: the serosa, the outer muscle, mucosa and submucosa, which is the innermost layer. Mesenteric arteries irrigate the colon. Then, any drugs will be immediately absorbed by the liver, undergoing the first-pass effect (BARATA et al.,

2007).

During the colon motility, patterns vary, and the first part of the colon are characterized by their anti-peristalsis, which leads the fecal content to remain there for extended periods. Adding to this, the lower viscosity of the intestinal content, compared to the remaining areas of the colon, makes it an ideal zone for colonic drug absorption (BARATA et al., 2007).

The usage of drugs having the colon as a therapeutic target has become attractive, in the latest years, for investigators or its interest in topical treatment of intestinal diseases, such as ulcerative colitis, Crohn's disease and colorectal carcinoma, either local absorbing molecules protein (LEOPOLDO, 2001).

At first, this therapeutic approach did not seem to make sense due to the small absorption area and the strong colonic epithelium barrier. However, the Colon offers unique features that make it an attractive body for the transmission of drugs (LEOPOLDO, 2001).

However, the peptidase activity in the large intestine is significantly lower than in the stomach and small intestine and the intestinal transit time is much higher in the colon than in the upper gastrointestinal tract. This allows unstable peptide and low permeability drugs can be absorbed in this region (JAIN, GUPTA & JAIN, 2007).

Moreover, to topical treatment of inflammatory intestinal diseases it is expected a more selective action on the focus of the inflammation and the reduction of side effects that result, in the most of the cases, from the systemic absorption (SALMASO & SONVICO, 2011).

The other particular characteristic is the microflora of the colon, consisting mainly of anaerobic or facultative anaerobes microorganisms, which produce a large number of hydrolytic and reducing enzymes. This particularity of colon can be used in the formulation drug carriers systems for this intestinal region (PHILIP & PHILIP, 2010).

Factors That Difficult Drug Administration At Colon

The pH of the intestinal fluids affects drugs' efficacy conveyed to the colon after oral administration. In the stomach, the pH ranges between 1 and 2 when empty, but increases after meals. The pH in the duodenum is about 6.5 increasing to 7.5 in the distal small intestine. Colon pH is close to neutral (6.6 to 7) and may vary depending on the type of power practiced in the presence of certain diseases.

These pH changes are one of the obstacles

to deliver intact drugs in colon, once it affects the level of drug's ionization, which behaves as weak acids or weak bases.

Formulating systems to vehicle drugs based on colon pH differences has been one of the therapeutic approaches proposed. However, the difference between the small intestine and the large intestine is too small to ensure the specificity of the formulations, and that the individual differences may impair efficiency of vectoring (JAIN, GUPTA & JAIN, 2007).

The absorption of drugs into the colon depends on the transit time in this region. In healthy people, colonic transit time varies from 22 to 36 hours. However, this time is highly affected by different factors, such as diet, existing conditions, concomitant medications and sex (BARATA et al., 2007).

The intestinal transit time preceding the arrival of the drug in the colon is also variable and depends on several agents. One drug directed to the colon must be stable enough to reach the target organ but the long intestinal transit time may compromise this stability.

The microflora present in the human gastrointestinal tract is a mixture of aerobic, facultative anaerobic and anaerobic bacteria constituting a complex ecosystem (JAIN, GUPTA & JAIN, 2007)

The stomach and duodenum contain a few bacteria, all of them aerobic. Along the gastrointestinal tract, the number of bacteria increases and the number of anaerobic bacteria is growing. The predominant species into the colon are *bacteroides*, *bifidibacteria*, *eubacteria*, *clostridia*, *enterococcus* and *enterobacteria* (PHILIP & PHILIP, 2010). Many enzymes produced by these bacteria are able to metabolize drugs carriers systems, which constitutes a promising strategy for drug release in the colon.

Human intestinal flora is practically independent of diet, age and geographical location, in a manner that the enzymatic interindividual variation does not appear to be a serious problem for drug vectorization. However, certain diseases or treatment with antibiotics can alter the intestinal flora and call into question the effectiveness of these systems (JAIN, GUPTA & JAIN, 2007).

It is important to consider whether the use of microflora will be advantageous for the transmission of drugs to the colon since the drug release is dependent of the system degradation by this microflora. All these factors must be taken into account when developing specific delivery systems for drug release into the colon in order to have intended efficacy and show therapeutic advantages over conventional formulations.

Cyclodextrins For Drug Administration In Colon Inclusion complex with cyclodextrins:

Definition and short characterization

Cyclodextrins (CDs) are cyclic oligosaccharides consisting of a variable number of glucose units which are obtained by the action of cyclodextrin- α - glycosyltransferase enzyme on starch (7) The most common natural cyclodextrins consist of six, seven or eight units of D (+) - glucopyranose linked by α bonds (1-4) and are named as α , β and γ -CD, respectively (SALTÃO & VEIGA, 2001). All these molecules are crystalline, non-hygroscopic and frustoconical structures that have an apolar cavity which contrasts with the hydrophilic exterior.

Cyclodextrins containing less than six glucose units do not exist for steric reasons. Cyclodextrins containing more than eight glucose units are produced with low incomes and thus they have reduced pharmaceutical interest (SALTÃO & VEIGA, 2001)

Some of the most important physico-chemical properties of the natural cyclodextrins are summarized in Table 1:

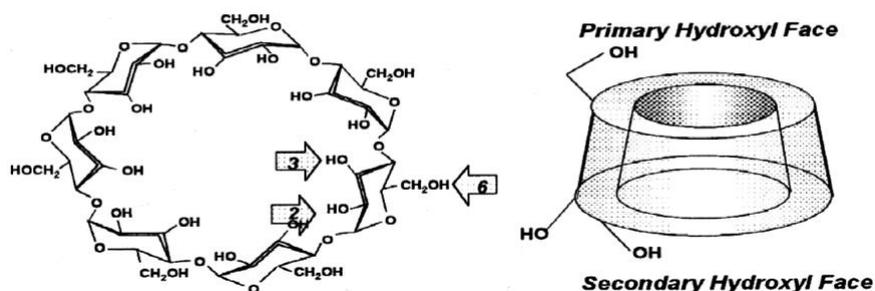
Table 1- Physical-chemical properties of the main natural cyclodextrins.

Cyclodextrins	α -CD	β -CD	γ -CD
Nº of glucose units	6	7	8
Molecular weight	972	1135	1297
Aqueous solubility (g/100 mL at 25 °C)	14,5	1,85	232
Cavity diameter (Å)	4,7-5,3	6-6,5	7,5-8,3
Cavity Volume	174	262	427
pK _a	12,332	12,202	12,081

Adapted from SALTÃO & VEIGA, 2001.

Cyclodextrins show in their structures, secondary hydroxyl groups at C-2 and C-3 atoms of glucose units, in the wider end, while the primary hydroxyl groups bonded to the C-6 atom of the glucose units are located at the opposite end, narrower. All of these hydroxyl groups can act as starting points for structural changes and various functional groups can be introduced into the macrocycle ring of cyclodextrins. (HIRAYAMA & UEKAMA, 1999). Figure 1 illustrates the location of the hydroxyl groups of β -CD.

Figure 1: Schematic representation of the location of the hydroxyl groups of β -CD.



Adapted from HIRAYAMA & UEKAMA, 1999

Inside the hydrophobic cavity of the cyclodextrins, many types of drugs may be included. From this association drug-cyclodextrin complex results, also called inclusion complexes. Therefore, the inclusion complexes are entities composed by two or more molecules, where one of the molecules - the host - wholly or partially includes one guest molecule without the establishment of covalent bonds (VEIGA, PECORELLI & RIBEIRO, 2006).

The formation of inclusion complexes is conditioned by the structure and the physicochemical properties of either the encapsulated drugs or cyclodextrins (VEIGA & FIGUEIRAS, 2012).

The minimum required condition is the geometric compatibility between the guest and the host molecules, the molecule guest has to penetrate and set up wholly or partly in the nonpolar cavity of the cyclodextrin (VEIGA, PECORELLI & RIBEIRO, 2006).

Thus, the inclusion of guest molecules into the cavity of cyclodextrins is conditioned not only by steric factors related to the shape and size of the guest molecules, but also by the polarity of these molecules. In aqueous solution, the apolar cyclodextrin cavity is occupied by water molecules which are in an energetically unfavorable environment, due to the nature of the polar-apolar interaction (VEIGA, PECORELLI & RIBEIRO, 2006).

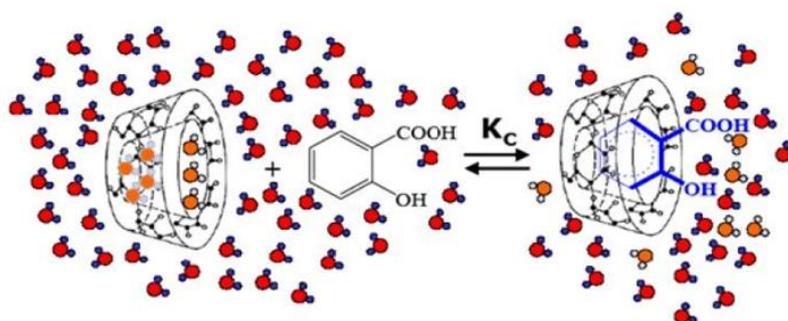
The formation of inclusion complexes happens through a process in which water molecules located in the central cavity of the cyclodextrin are substituted by a guest molecule or lipophilic groups in that molecule (VEIGA, PECORELLI & RIBEIRO, 2006). This event is depicted in Figure 2:

It is considered that the enthalpy released by the water molecules inside the cyclodextrin cavity is the primary force for complex formation. The system energy decreases when water molecules (high enthalpy) are replaced by guest molecules that are less polar than water (VEIGA & FIGUEIRAS, 2012). In addition to the proposed mechanism, van der Waals interactions, hydrogen bonding, hydrophobic interactions and changes in the surface tension of the solvent may be involved (VEIGA & FIGUEIRAS, 2012).

It is valid to point out that the links established between the host molecule and the guest molecule during the formation of an inclusion complex are not permanent. It creates a dynamic equilibrium between association and dissociation of both molecules.

The balance between the free drug's molecules and the complexed ones is quantitatively described by the association or stability constant, K_c , in which [drug-CD], [Drug] and [CD] represent respectively complexed drug, free drug and free CD and is diagrammed in figure 3 (OLIVEIRA,

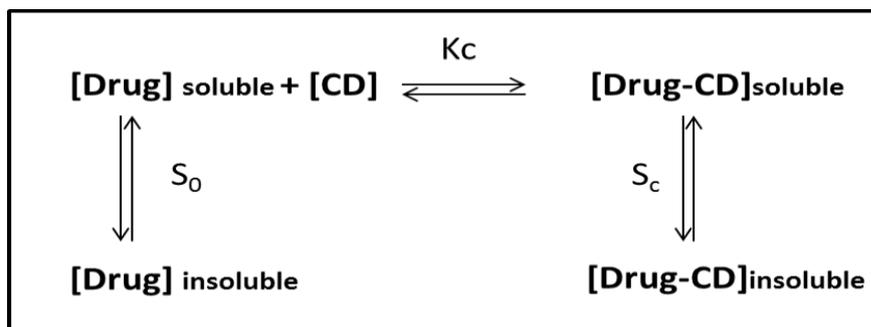
Figure 2 - Schematic representation of forming an inclusion complex with a guest molecule salicylic acid.



Adapted from (VEIGA & FIGUEIRAS, 2012)

decreasing the exposure of certain molecules of the biological tissue as a result of

Figure 3- Representation of the association and dissociation balance of inclusion complexes formation



Legend: S_0 is the solubility of drug and S_c the solubility of complex formed.
Adapted from OLIVEIRA, SANTOS & COELHO, 2009.

The magnitude of the constant K_c usually ranges between 0 and 10^5 M^{-1} . It is zero if drug is incapable to form an inclusion complex with CD and 10^5 for the already experimentally observed in drug-CD complex upper limit. The stronger the drug-CD bond, the slower is the kinetics of dissociation and, thus, the higher the value of K_c . (VEIGA & FIGUEIRAS, 2012).

However, the association and dissociation between drug molecules and CD are dynamic processes, which occur rapidly, in the order of milliseconds, even for complex with higher stability constants. Thus, the kinetics of drug's release from the CD is not a limiting factor in the absorption of it (OLIVEIRA, SANTOS & COELHO, 2009).

Advantages And Disadvantages Of Their Use

The formation of inclusion complexes significantly alter the characteristics of the substrate. These changes include changes in the chemical reactivity of the guest molecule, fixation of very volatile substances, improvements in the solubility of compounds, stabilization of substances that are sensitive to light, heat and oxidation, protection from degradation by microorganisms, masking colorants or pigments and catalytic activity with substrates (VENTURINI et al., 2008).

The most important direct consequences of a drug inclusion in a cyclodextrin relate to the increased solubility of the included drug (VENTURINI et al., 2008).

The formation of inclusion complexes reduces side effects, not only as a result of a decrease of the therapeutic dose, but also by

the therapeutic dose, but also by decreasing the exposure of certain molecules of the biological tissue as a result of molecular encapsulating in the cavity of the cyclodextrins.

Although the complexation may influence the drug release and its dissolution, it does not necessarily means that this results in an increase of the permeability and bioavailability of the drug, in that the cyclodextrins, because of their sheer size, do not penetrate biological membranes. Then it is necessary that the dissociation from the complex occur after free drug is absorbed.

Although inclusion complexes generally allow an increase of physical and chemical stability of the complexed drugs, there are some situations in particular in what cyclodextrins potentiate degradation of drugs (VEIGA & FIGUEIRAS, 2012). Furthermore, studies showed that, for many substances, the cyclodextrin complexation is impossible or did not show any advantages. The formation of inclusion complexes is strongly influenced by the structure and physicochemical properties of the drugs, and the complexed cyclodextrin, because for the inclusion complex to be formed, the drug molecule must fit wholly or partially within the interior of the cyclodextrin hydrophobic cavity (VEIGA, PECORELLI & RIBEIRO, 2006).

As noted above, an inherent characteristic to the formation of inclusion complexes is the generation of an equilibrium between the guest molecules and the free molecules in solution. The degree of dissociation from the complex is dependent on the magnitude of their constant of stability.

This property is a desirable characteristic for the complex to dissociate and for the drug to be found in its free form, capable to be absorbed. However, this balance is sometimes a disadvantage when it is desired to deliver the drug to target organs or tissues, since some poor stable complexes dissociate before they achieve them. One method to prevent the dissociation is to covalently link the drug to cyclodextrin. In this case, it is not inclusion complexes but drugs conjugated to cyclodextrins (HIRAYAMA & UEKAMA, 1999). This matter will be discussed in detail in the next topics.

Conjugates with Cyclodextrins

Definition and Short Characterization

Recently, strategies have been developed to increase the potential of cyclodextrins as specific delivery agents of drugs. However, the formation of inclusion complexes is insufficient to transport a drug into a target organ or tissue, since after administration the drug molecule can be easily released before reaching therapeutic target (RIZZARELLI et al., 2007).

One of the strategies studied to circumvent this problem is the synthesis of conjugates of drugs with cyclodextrins. The conjugation with cyclodextrins involves the establishment of covalent bonds between the drug and the hydroxyl groups of the cyclodextrin, which aims to secure the release of the drug only in places where it occurs the break of those links.

As mentioned above, cyclodextrins are not absorbed throughout the gastrointestinal tract. However, they are degraded by bacterial enzymes in the colon where they are assimilated as glucopyranose. This feature can be exploited for the drug release into the colon through the drug conjugation with cyclodextrin, acting as prodrugs.

The drug, covalently linked to the cyclodextrin, is a new molecule and therefore can lose or modify their pharmacological activity. Therefore, the synthesized derivative should guarantee the release of the drug in the area where absorption happens in its pharmacologically active form (RIZZARELLI et al., 2007). The synthesis of prodrugs for specific release in the colon requires several considerations, including the physicochemical properties of the drug and of the cyclodextrin, and the type of bond involved in the

conjugation.

Among the natural cyclodextrins, the β -cyclodextrin, consisting of seven glucose units, is the most used, because, although it has poor aqueous solubility, it has an inner cavity with suitable dimensions in order to incorporate a great number of pharmaceuticals and industrially and it is obtained with higher performance and lower costs if compared to other cyclodextrins (OLIVEIRA, SANTOS & COELHO, 2009). The drug molecules can be covalently linked to primary or secondary hydroxyls of the β -cyclodextrin, forming the cyclodextrin-drug conjugates (VIEIRA et al., 2013).

Studies using the anti-inflammatory drug, the biphenylacetic acid (BPAA), demonstrated that the ester conjugates exhibit a greater potential for drug release in the colon, compared to the amide conjugates.

The esters have reasonable chemical stability and it is an ideal characteristic for its formulating, beyond serving as substrates for esterase of existing in the colon. Thus, in the case of the ester conjugates, the drug release happens by the opening of the cyclodextrin ring, which allows specific delivery of the drug. Moreover, in amide conjugates, the drug is not released after the opening of the cyclodextrin ring in the colon, since the amide linkages are resistant to bacterial enzymes, leading to the formation of stable hydrophilic derivatives such as maltose and amide triose conjugates, which are not absorbed and remain in the intestinal contents (JAIN, GUPTA & JAIN, 2007).

In these same studies, using BPAA, it was found that the solubility of the conjugates was connected to the size of the hydrophobic cavity of the cyclodextrin. For example, the low solubility of β -cyclodextrin conjugates was attributed to the intermolecular association between the drug and the vicinity of the cyclodextrin cavity. On the other hand, the high solubility observed in conjunction with α -cyclodextrin may happen because the cavity is too small to accommodate BPAA molecule.

Advantages and Disadvantages of Their Use

Among the different approaches that aim for the delivery of drugs, the placement to target sites has always aroused fascination in researchers. Since the seventies, cyclodextrins and their derivatives have been proposed as pharmaceutical excipients, and

they have been applied in various products sold, due to their peculiar inclusion properties. Additionally, cyclodextrins began to be studied as functional excipients for controlled release systems and, in the last years, it is no longer considered only as functional excipients and began to be considered multifunctional supramolecular carriers (JAIN, GUPTA & JAIN, 2007).

As it was already mentioned, the combination of drugs with cyclodextrins through the establishment of covalent bonds has emerged as a new therapeutic approach for vector propagation of drugs which was not possible with the use of inclusion complexes with cyclodextrins.

The process of cyclodextrins to drug conjugation involves the synthesis of a new molecule, with the establishment of covalent bonds between the two initial molecules. This process involves external energy sources, toxic crosslinking agents and drastic conditions (high temperature, high pH, the use of organic solvents, etc.) which can affect the chemical structure of the encapsulated drug (MANAKKER et al., 2009). However, recent advances in biotechnology have contributed with significant improvements in conjugate synthesis and many techniques have been studied as alternatives to classical organic synthesis processes (MANAKKER et al., 2009).

About the therapeutic action of these agents, it is dependent on the break of the link between the two molecules to get the drug in its active form. Physiological factors that can question this process lead to therapeutic failure of the conjugate. For example, in the delivery of drugs to the colon, the drug efficacy is subject to the action of existing bacterial enzymes. It is known that certain diseases and the use of some antibiotics medicines, can affect the intestinal microflora and thus compromise the metabolism of cyclodextrins. Thus, there is the necessity of additional studies in affected individuals that prove the advantage of drugs release through its conjugation with cyclodextrins (KANAUCHI et al., 2005).

In the context of pharmacokinetics, drug-cyclodextrin conjugates exhibit a slower absorption compared to inclusion complexes with cyclodextrins and the free drug, because conjugates exhibit a slower onset of action. However, there is an increased bioavailability and reduced adverse effects when the drug is used conjugated to cyclodextrins, which makes attractive from the therapeutic point of view.

Application of conjugates with cyclodextrins in vectored and release drug`s

Examples of different therapeutic targets bone:

The repair of bone defects is costly and invasive, leading the scientific community to direct efforts to improve the effectiveness of existing therapies.

Recently, researchers at the University of Nebraska designed and synthesized a conjugate of alendronate and β -cyclodextrin (ALN- β -CD), in order to vectorize therapeutic agents for bones and teeth. This conjugate was then studied for the delivery of prostaglandin E1 (PGE1) in the treatment of bone defects. It consists on injecting the ALN- β -CD-PGE1 conjugate in mice's jaw, which would bind to the bone surface through the alendronate phosphonate group linking the rest of the complex to the site of injection. Due to the gradual release of PGE1 and its retention at the target site, systemic toxicity could be reduced. The viability of the hypothesis was studied using a control group to which was administered ALN- β -CD conjugate.

Surprisingly, the control group demonstrated the occurrence of a bone anabolic reaction higher than the group that was administered ALN- β -CD conjugated to PGE1 (LIU et al., 2008). One of the explanations suggests that, due to the versatile complexing ability of the β -CD, various endogenous compounds with anabolic properties may have suffered binding to the target site, such as prostaglandins, steroids, vitamin D, etc.

Although the mechanism of action is not clearly elucidated, it is known that β -CD-ALN conjugate has bone anabolic effects, which were not visible using alendronate alone (LIU et al., 2008). Additional studies are required to confirm the hypothesis. In a near future, the combination of various substances with cyclodextrins may turn out to be one of the therapeutic strategies in the treatment of bone diseases.

Tumor receptor:

Through the study of the characteristics of tumor cells, it is possible to develop cyclodextrin conjugates that specifically

recognize some tumor receptors. The folic acid is essential for cell growth and is involved in the synthesis of purines and pyrimidines. In normal cells, folic acid transporters only recognize reduced folate and not conjugates. Whereas in the tumor cells, due to accelerated cell growth, they recognize reduced and conjugated folates. These receptors are expressed in large quantities in many tumors (ANTONY, 1999).

Cyclodextrins have already been successfully modified, that specifically recognize tumor folate receptor, by conjugation with this vitamin and a polyethylene glycol spacer (PEG) which increases the flexibility of the molecule (ELKAMELA et al., 2008). Conjugates of folic acid with cyclodextrins enable to complex active molecules with cytostatic action within the cyclodextrin, increasing the specificity of these drugs to tumor cells, enhancing its therapeutic effect and reducing side effects (ELKAMELA et al., 2008).

Another receptor that is overexpressed in tumor cells is the transferrin receptor, since this molecule transports iron into the cell, essential for cell cycle progression. Studies have shown the efficacy of transferrin-PEG-CD conjugates complexed with oligonucleotides, resulting in increase on cellular recognition and internalization of oligonucleotides in tumor cells and thus increasing the therapeutic efficacy (ZOU et al., 2005).

Therapeutic Applications Of Conjugates With Cyclodextrins For Drugs Oral Administration In Colon

The use of oral administration as a mean of directing drugs to the colon is extremely useful for the treatment of a variety of intestinal diseases which are increasingly worrying, such as inflammatory bowel disease (Crohn's disease and ulcerative colitis) and placed rectal cancer, which is the third cause of cancer death worldwide (ELKAMELA et al., 2008).

Whether you want a systemic or local action, it is not easy to get the drug to reach the colon intact, without losing part or all of its properties. This is why it has been proposed the use of conveyor systems specifically targeted for colonic release, which should be able to protect the drug during its passage through the stomach and small intestine. The properties of the cyclodextrins mentioned above have shown interest in the development of pharmaceutical specific means of delivery of

drugs in the colon. Thus, the drug can act locally, without the occurring of an extensive systemic absorption, responsible for most of the adverse effects observed. Some already studied examples will be presented below.

Release of the conjugate 5-amino salicylic acid-CD in the colon:

The ulcerative colitis and Crohn's disease are chronic recurrent disorder that involve the mucosa and submucosa of the colon. The 5-aminosalicylic acid (5-ASA) is an active compound used in the maintenance therapy of these pathologies (SALMASO & SONVICO, 2011). However, when orally administered, a large amount of drug is absorbed before reaching the site of action, which causes systemic side effects.

A group of researchers at the University of Shenyang, China, studied the in vivo behavior of the 5-ASA conjunction with α -, β - and γ - cyclodextrins in the intestine of rats. The conjugate was orally administered and blood samples were collected after 4, 8, 12 and 24 hours. In the control group was administered 5-ASA. After the test, the animals were killed and collected some organs such as the stomach, small intestine, cecum and colon for subsequent analysis. The control group showed a peak of drug concentration in plasma and urine 4 hours after the administration (SALMASO & SONVICO, 2011).

The several conjugates showed that the rate of drug liberation of the conjugate depends on cyclodextrin used, was faster with γ -CD and more prolonged with the β -CD (SALMASO & SONVICO, 2011). The results obtained in the group to that it was administered the conjugate showed insignificant amounts of drug in blood and urine after the trial period. The drug in the free form was detected in the cecum and colon. It was therefore concluded that the conjugate resisted to the passage through the stomach and the small intestine, without significant systemic absorption and that the conjugate, in particular cyclodextrin ring, has been subjected to the opening process in the cecum and colon, where drug was found in the free form (ZOU et al., 2005).

Conjugates of Cyclodextrins with NSAIDs:

The non-steroidal anti-inflammatory drugs (NSAIDs) are widely used in the treatment of chronic inflammatory conditions. Moreover, they present a promising activity for the prevention and treatment of colon cancer

and ulcerative colitis (ELKAMELA et al., 2008). The side effects arising from the absorption in the upper GIT are a major consideration for its use, it is desirable to delivery to specific site of action.

Several NSAIDs such as naproxen, flurbiprofen, diclofenac, and ketoprofen were combined with cyclodextrins, in order to study their potential for colonic vectoring (SALMASO & SONVICO, 2011).

The flurbiprofen conjugated to α and β -cyclodextrins was tested in vitro and in vivo. Both conjugates were efficiently hydrolyzed in the colon of rats, except in cases where that was submitted prior treatment with clindamycin, which damaged the intestinal microflora, responsible for the degradation of the cyclodextrins (SALMASO & SONVICO, 2011).

Diclofenac was conjugated with the hydroxyl group of β -cyclodextrin and its stability and drug release in the colon capacity were determined (VIEIRA et al., 2013).

The results of the in vitro study showed, again, the resistance of the combined to the passage through the stomach and small intestine and the release of the active drug by action of the colonic microflora.

Conjugates of Cyclodextrins in chemotherapy of colorectal cancer:

Despite constant advances in medicine have increased the expectancy of life of cancer patients, colorectal cancer is still a leading cause of death in the US and Europe.

The current chemotherapy methods are far from ideal by administering high doses and the amount of side effects. It is intended to develop specific strategies for drug delivery to the tumor site without harming healthy tissue (SALMASO & SONVICO, 2011). As a result, cyclodextrins conjugates with substances with cytostatic or chemopreventive properties have been investigated to optimize the therapeutic oral administration.

For specific delivery in colon, in the treatment of colorectal cancer, it has been proposed the administration of a conjugate with β -cyclodextrin. Among the various properties of short chain fatty acids, their effect on tumors has been reported in several studies, particularly in colorectal cancer. Studies of cyclodextrins conjugated with these acids, such as β -CD / n-butyric acid conjugates, have focused in specific delivery into the colon. However, they have not yet

been reported in vivo studies using animal models with cancer (SALMASO & SONVICO, 2011). However, conjugates of cyclodextrins with various substances used in cancer treatment have been proposed and may arise as a response to the problems currently associated to this therapeutic area.

Cyclodextrins conjugates of corticosteroids:

To treat inflammatory bowel disease, corticosteroids, such as prednisolone, are used. However, after oral administration, large part of this is absorbed before reaching its site of action, which leads to the occurrence of severe systemic side effects, such as adrenal suppression, hypertension and osteoporosis (SALMASO & SONVICO, 2011). Through the combination of the drug with CD by ester linkage to one of the terminal hydroxyl groups, it was observed a substantially complete release of the drug in vitro, in conditions similar to those of the colon (YANO et al., 2000).

CONCLUSIONS AND FUTURE PROSPECTS

The placement of drugs to the colon provides a potential therapeutic interest, particularly in specific diseases on this organ, such as ulcerative colitis or Crohn's disease. In many analyzed studies, cyclodextrins are presented as potential vehicles in the development of prodrugs specific delivered into the colon through the formation of conjugates. The results are promising and show resilience to the passage through the upper gastrointestinal tract, with the possibility of using lower doses and thus minor side effects. However, these compounds are still an initial phase of research and studies will be made in humans to confirm its efficacy and safety. Taking into consideration the development over the past few years and the increasing efforts made in the study of their properties, it is probable that the first conjugated cyclodextrins for colonic administration arise in the market in the near future. Beyond serving for the colon and others mentioned therapeutic targets, other pathways open up by applying cyclodextrins for various therapeutic systems, making them promising compounds also in the the biotechnological area.

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