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Review article

Technological evolution of cyclodextrins in the pharmaceutical field

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ABSTRACT

We herein disclose how global cyclodextrin-based pharmaceutical technologies have evolved since the early 80s through a 1998 patents dataset retrieved from Derwent Innovation Index. We used text-mining techniques based on the patents semantic content to extract the knowledge contained therein, to analyze technologies related to the principal attributes of CDs: solubility, stability, and taste-masking enhancement. The majority of CDs pharmaceutical technologies are directed toward parenteral aqueous solutions. The development of oral and ocular formulations is rapidly growing, while technologies for nasal and pulmonary routes are emerging and seem to be promising. Formulations for topical, transdermal, vaginal, and rectal routes do not account for a high number of patents, but they may be hiding a great potential, representing opportunity research areas. Certainly, the progress in materials sciences, supramolecular chemistry, and nanotechnology, will influence the trend of that, apparently neglected, research. The bottom line, CDs pharmaceutical technologies are still increasing, and this trend is expected to continue in the coming years.

Patent monitoring allows the identification of relevant technologies and trends to prioritize research, development, and investment in both, academia and industry. We expect the scope of this approach to be applied in the pharmaceutical field beyond CDs technological applications.

1. Introduction

Cyclodextrins, cyclic oligomers linked by α-1,4 glycosidic bonds, are well known for their truncated cone structure, comprising a hydrophilic surface and a cavity bearing a hydrophobic microenvironment. CDs have been considered "all-purpose molecular containers" because their cavity can selectively accommodate a diversity of molecules through supramolecular host-guest interactions, giving rise to an IC (Fig. 1). CDs are chemically versatile and can be modified to get mono- or poly-substituted derivatives, which can improve their properties (i.e., solubility and stability), and tune their complexation abilities. The complexation process leads to significant changes in guest spectral properties, reactivity, volatility, solubility, and stability; thus, giving the CDs a great potential to be applied in a diversity of technological fields [1].

CDs have been of particular importance on drug delivery and pharmaceutical technologies. Undoubtedly, the most acknowledged application is the enhancement of aqueous solubility of poorly soluble drugs through the formation of CD/drug ICs. However, the complexation can also protect drugs from heat, light, hydrolysis, and oxidation, thereby improving the formulations stability. In other cases, it allows the manipulation of volatile compounds, reduces unpleasant tastes and odors, and decreases the effect of irritating compounds. Moreover, CDs can modify the release rate of drugs working as excipients for immediate or sustained release. Native CDs and several CD-derivatives are FDA-approved for pharmaceutical use and their success is evident with more than 50 medications containing CDs currently marketed [2–5]. The growth in the number of approved formulations over time suggests CDs are still a useful tool in the pharmaceutical field and that their applications could be expanding into a promising future.

Comprehensive reviews describing the CDs' abilities to enhance the solubility and stability of drugs, and the mechanisms of CD/drug complexation, have previously been reported [4,6–10]. However, an overview to understand the technological evolution of CDs in the pharmaceutical field is missing.

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Abbreviations

BCS	Biopharmaceutics Classification System
CDs	Cyclodextrins
DII	Derwent Innovation Index
EMA	European Medicines Agency
EPO	European Patent Office
FDA	U.S. Food and Drug Administration
FDI	Foreign direct investment
HIV	Human immunodeficiency virus
HPβCD	Hydroxypropyl-β-cyclodextrin
HPγCD	Hydroxypropyl-γ-cyclodextrin
IC	Inclusion Complex
IM	Intramuscular
IPC	International Patent Classification
IV	Intravenous
MAGL	Monoacylglycerol lipase
MERS	Middle East Respiratory Syndrome
MβCD	Methyl-β-cyclodextrin
NSAIDs	Nonsteroidal anti-inflammatory drugs
PGE2	Prostaglandin E2
RMβCD	Random methyl-β-cyclodextrin
SARS	Severe Acute Respiratory Syndrome
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SBEβCD	Sulfobutylether-β-cyclodextrin
GI	Gastrointestinal
VP	Vantage Point Software
WIPO	World Intellectual Property Organization

Patents are a significant source of technical and commercial knowledge, as well as a good indicator of innovation. Thus, their analysis is a useful approach for researchers interested in studying the evolution of technological trends and changing demands for technological forecasting. At the academic level, patent analysis has great potential for identifying relevant technologies, evaluating the competitiveness of projects, and prioritizing research, development, and investment. Moreover, the analysis of patent data becomes highly relevant when the innovation cycle becomes more complex and shorter and when the market demands rapid responses [11,12]. For instance, Liu et al. analyzed data from patents related to the SARS and MERS viruses, thereby providing a substantial background for the ongoing development of therapies to treat or prevent SARS-CoV-2 infection [13].

Some outstanding publications have included some technological breakthroughs of CDs in their discussion. For instance, the first patent for CDs pharmaceutical applications in the '50s, the first formulation launched on the market in the '70s, and some relevant patents registered by the early '80s [3,4,8,14]. In 2011, Deorsola et al. briefly presented the global industrial applications of CDs through the analysis of scientific literature and patents [15]. Also, some reports examine the current patenting of the use of CDs as applied to specific families of drugs [16–18]. Nonetheless, an extensive analysis of CDs patents to inform how the CD-based pharmaceutical technologies have evolved over time has not been published so far.

In the pharmaceutical field, CDs patents fall into four categories: 1) methods for the synthesis/production of CDs and their derivatives; 2) methods to improve the performance of CDs, for instance, formulation techniques to improve the solubilizing ability of CDs; 3) ICs of CDs with a specific type of drug to render a particular result; and 4) pharmaceutical applications of CDs and their derivatives [8]. Hereafter, the analysis presented in this paper is based on pharmaceutical applications.

Thus, we herein present the global technological landscape of CDs for pharmaceutical applications and the evolution of those technologies over time, through text-mining techniques, using patents as the technical source. We based our analysis on the patent's semantic content [11]. Patent text-mining systems are generally focused on the analysis of title and abstract of the patent documents. In our approach, we analyzed keywords in terms of the "novelty" and "use" of each document to extract crucial information that might be hidden in the claims and description sections, thus allowing us to correlate the CDs properties and their pharmaceutical technologies intended for specific administration routes. Bottom line, from the knowledge mined from patents, we aim to inform the progress of such technologies, the current trends, and opportunity areas in the pharmaceutical applications of CDs.

2. Methodology

2.1. CD pharmaceutical patents dataset

Patents were retrieved from the database DII (Clarivate, 2020; access through the National Autonomous University of Mexico). To obtain the initial patent dataset, the search considered all documents filed until

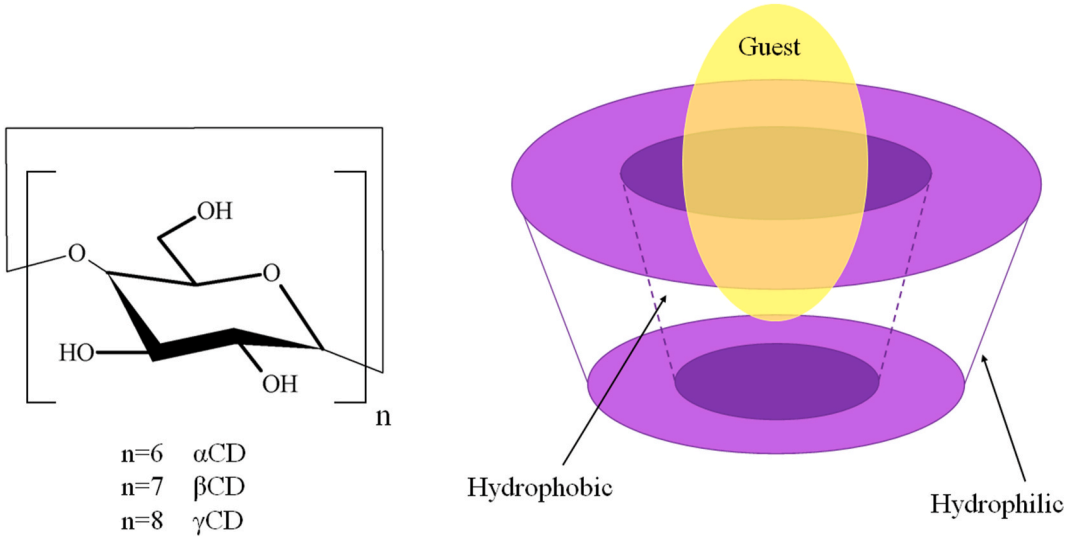


Fig. 1. Structural representation of α-, β-, and γ-CDs and the formation of an IC.

2019, the specific CDs' IPC codes [19,20], and the keyword *cyclodextrin* (Fig. 2a). Our query excluded the IPC A61Q, that refers to "Specific use of cosmetics or similar toilet preparations".

2.2. Solubility, stability, and taste-masking

A second search was performed, from the initial dataset, to identify the number of patents in which CD molecules were used as solubilizers, stabilizers, or taste-masking agents. For this end, the combination of truncated keywords (by using the wildcard asterisk, *) associated with solubility, stability, and taste-masking were entered, in addition to Boolean operators used as conjunctions to include or exclude keywords (Fig. 2b).

2.3. Technological development of CDs as functional excipients

To identify and count the number of patents related to a particular CD use as an excipient concerning administration routes, we conducted a text mining analysis. Furthermore, we analyzed the evolution of a particular technology by determining the change in the number of patents over time. For this aim, we used different tools for text and data processing implemented in Python's library pandas [21]. We first pre-processed the text (word lowering, removal of special symbols and punctuation) and then applied algorithms to identify specific words and logical Boolean operators like OR and AND, for the analysis of combinations of words in each patent (Fig. 2c). The text mining was performed in the fields of "novelty" and "use" for the documents retrieved from DII CDs patents dataset.

2.4. CD patents: Where and who?

VP [22] software was used to process, filter, classify, and analyze the dataset, for purposes of identifying assignees and geographical regions, as well as for ranking them and detecting the trends and behaviors with regard to CD patenting for pharmaceutical applications.

The matching rule was set as "General" for identifying priority year and countries. For this analysis, the top 10 countries were chosen because they encompass more than 99 registered patents each. It must be considered that each patent (e.g., the same technology) may be registered in more than one country, so the sum of patents in this section does not necessarily correspond to the total number of patents in the initial search. To retrieve the assignees, the matching rule was "Organization name (dept ignore)". In this case, our criteria were based on the selection of the top 20 assignees which are the ones having more than 10 patents each (Fig. 2d).

3. Results

3.1. Evolution of CD patents

Through our search, we retrieve an initial dataset of 1998 patents from DII. When analyzing the data, we identified two trends in patenting behavior over time. The first one, between 1983 and 2000, with a total of 125 records, corresponding to the 6.3% of total patents, and an average number of 6.9 patents per year. During this time, the rate of patenting was steady, with few changes. The second trend is from 2001 to 2019, with 1873 new filed patents, representing 93% of the total number of documents. Fig. 3 also shows that the highest increase in the number of patents registered, indicated by the steepest slope, occurred in the period from 2001 to 2007, with an average increment of 58.7 patents per year. Likewise, 2012 and 2018 stand out in patenting activity, with 157 and 170 registered patents, respectively, the highest numbers of registered patents over time.

The first patent retrieved from our dataset in DII dates from 1983. Before discussing this patent, we first briefly describe some relevant patents for a historical background before that year. In 1953, Freudenberg, Cramer, and Plieninger registered the patent entitled "Methods for preparation inclusion compounds of physiologically active compounds" [23]. This document discloses how CDs' ICs increase the stability of biologically active compounds and the precipitation method to obtain them [8,24]. By 1976, the apogee of CDs was just beginning with the Japanese approval of βCD/dinoprostone complexes for the induction of labor in childbirth, through the oxytocin-like effects formulated as a sublingual tablet [25]. As the investigations progressed, it was understood that αCD had a stabilizing effect on the parenteral use of some prostaglandins, allowing for the development of Alprostadil Alphadex™, approved for the treatment of Buerger's disease in 1979 and, later, for the treatment of male erectile dysfunction. After that, the interest on CDs for the development of pharmaceutical technologies was notable and since then, several formulations containing CDs, in diverse physical forms for its administration by different routes, have been approved in many countries [2–5,26].

As we mentioned before, the first patent of our dataset dates from 1983 and belongs to Teijin Limited. This document deals with the role of CDs as adjuvants for the stabilization of vitamin D_3 and its preparation process [27,28].

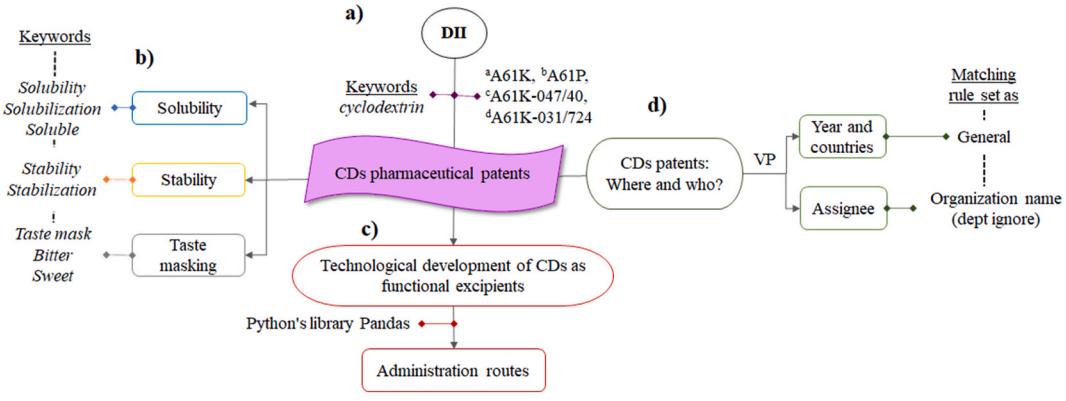


Fig. 2. Workflow showing a) general search to retrieve CD patents from DII; b) specific search to obtain CD patents disclosing solubility, stability, and taste-masking applications; c) text mining strategy to arrange the temporal evolution of patents according to the CD applications according to administration routes; d) procedure to analyze the CD patent dataset based on geographical region and assignee.
[a]A61K: Preparations for medical, dental, or toilet purposes
[b]A61P: Specific therapeutic activity of chemical compounds or medical preparations
[c]A61K-047/40: Cyclodextrins and derivatives thereof (medicinal preparations characterized by the non-active ingredients)
[d]A61K-031/724: Cyclodextrins (medicinal preparations containing organic active ingredients).

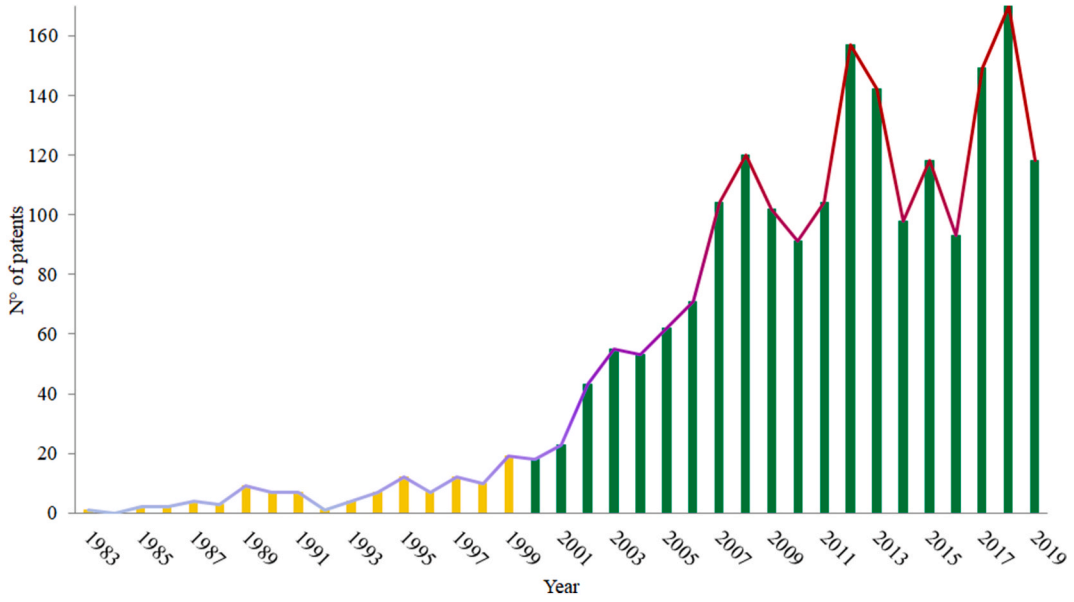


Fig. 3. Evolution of pharmaceutical CDs patents over time.

It is worth defining a couple of concepts related to patents. On the one hand, the term "priority art" refers to all the knowledge needed to develop the invention. In this case, all the priority art is linked to other patents or scientific papers that have demonstrated how CD complexation modifies the physicochemical properties of a given host, in particular, solubility and stability. It also refers to the relevance of the biological and physicochemical characterization of CD derivatives and their complexes [29–31]. Hence, this patent (No. US 4729895, Teijin Limited) and its corresponding priority art are directly related to the primary application of CDs, which is the solubility enhancement of a guest molecule as a result of the formation of an IC.

On the other hand, patent citations are the count of citations of the document in subsequent patents and, therefore, indicative of its impact on the development of new technology. In our search, the most cited patent, accounting for 413 citations, was registered by Kansas University in 1994. This document reports the successful functionalization of α, β, and γ CDs with sulfoalkyl substituents, for purposes of improving the physicochemical features of native CDs, their complexation capacity, and the decrease of their toxicity profile. This patent also mentions how CD derivatives can increase the solubility of drugs and, as a consequence, implement different administration routes such as oral, intranasal, parenteral, and rectal for ICs [32].

As we already mentioned, it was after the year 2000 when a breakthrough in CD patenting activity was observed. In fact, the most cited patent in the period between 2000 and 2019 corresponds to an innovation registered by CyDex Inc. in 2000, with a total of 193 citations. This patent describes sulfoalkyl ether CD-based controlled release solid pharmaceutical formulations, in which the CD derivatives were used, in combination with other components, to modify the bioavailability and/or rate of bioabsorption of therapeutic agents [33]. We consider this document to be a relevant innovation for several reasons. First, it introduces the terms "controlled release", "sustained release", "delayed release", and "targeted release", which are very popular in current CDs scientific papers but were revolutionary at that time, when CDs were pigeonholed as solubilizers/stabilizers. Second, it was based on modified rather than native CDs (sulfoalkyl ether moiety). Although the solubility enhancement could be implicit, the main goal of this invention was to control the delivery of drugs through CD-based solid platforms. All the priority art of this patent was published after 1989 and suggests a different driving force in the research and development activity related to CDs: the design of novel materials to control drug release and optimize the drugs' bioavailability by chemically modified CD derivatives, and the combination of different types of molecules and/or building blocks [34–36].

Thus, the milestone of CD patenting behavior is parallel to the emergence of intensive research activity in the drug delivery field, which in the last two decades has focused mainly on the design of versatile structures for carrying drugs and releasing them in a controlled manner. To date, this breakthrough has also integrated other disciplines into the field of CDs, such as supramolecular chemistry, materials sciences, and nanotechnology [37].

Despite the novelty projected for CDs in advanced drug delivery, their use in modifying the aqueous solubility of poorly soluble drugs has been—and continues to be—of great importance in the pharmaceutical industry. For instance, the use of CDs to solubilize an antineoplastic compound assigned to Pfizer Inc [38]. Fig. 4 summarizes the representative patents over time described above.

In 2004, Szejtli published a comprehensive review of CDs status in both, industrial and academic research, in which he forecasted that the use of CDs would expand in the coming years, due to more efficient forms of production. Also, he concluded that CDs in the pharmaceutical field would show slow but steady development [4]. Sixteen years later, we can say that the first two hypotheses were right. Contrary to what was thought, the interest in CDs has not grown slowly but, rather, has been rapidly increasing and is still engaging pharmaceutical and drug delivery research, with a boom stage starting in the early 2000s and continuing to the present day.

3.2. *Solubility, stability, and taste-masking*

CDs are primarily used for enhancing the aqueous solubility of poorly soluble drugs; improving the stability and masking unpleasant taste/odor of a formulation. Accordingly, we analyzed the CDs dataset to retrieve those patents devoted to each one of the mentioned attributes to then inspect their behavior over time.

3.2.1. *Solubility*

Aqueous solubility determines many aspects of drug discovery and development processes, including formulation, administration routes, and pharmacokinetics [39]. A poorly soluble drug cannot be formulated into a solution for parenteral or other administration routes (nasal, ocular, and otic). In addition, its bioavailability is limited if it is

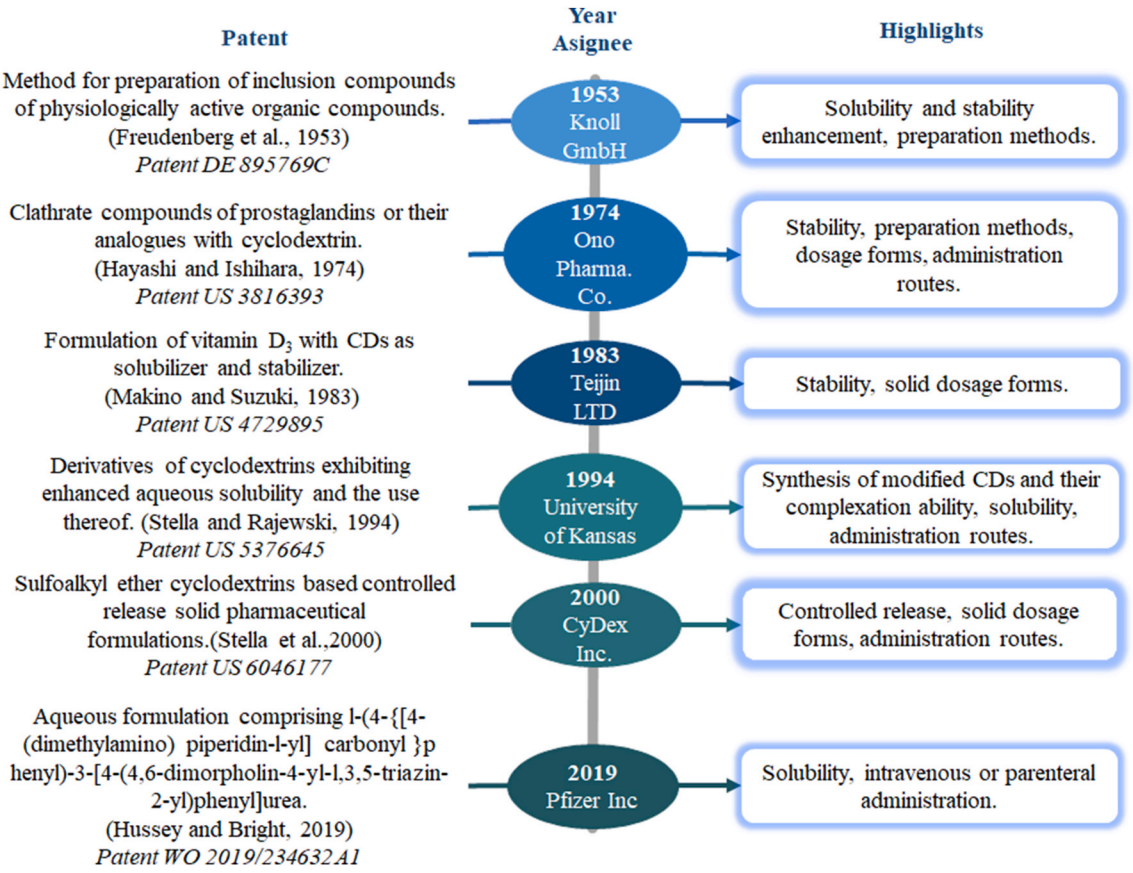


Fig. 4. Milestone patents of CDs with pharmaceutical applications over time.

administered orally.

CDs modify the apparent solubility of drugs through the formation of CD/drug ICs. In some cases, the solubility increase arises from non-inclusion aggregates, in which the CDs display the ability to form and stabilize supersaturated drug solutions [7]. Indeed, the supremacy of CDs is given by this attribute and the evolution of patents associated with solubility enhancement have substantially influenced the global trend of CDs pharmaceutical patents over time (Fig. 5).

Between the mid-80s and just before 1998, patenting activity was steady, reaching a peak in 1994, with 24 patents registered. After 2001, an inflection point marks the beginning of a very active period of patenting that is still observed to date; and 2013 outstands with 58 filed patents, the highest record in terms of solubility.

The first patent of our dataset is from 1983 and is related to water-soluble CD polymers substituted by ionic groups that, in addition to their abilities to complex with diverse guest molecules, they form salts

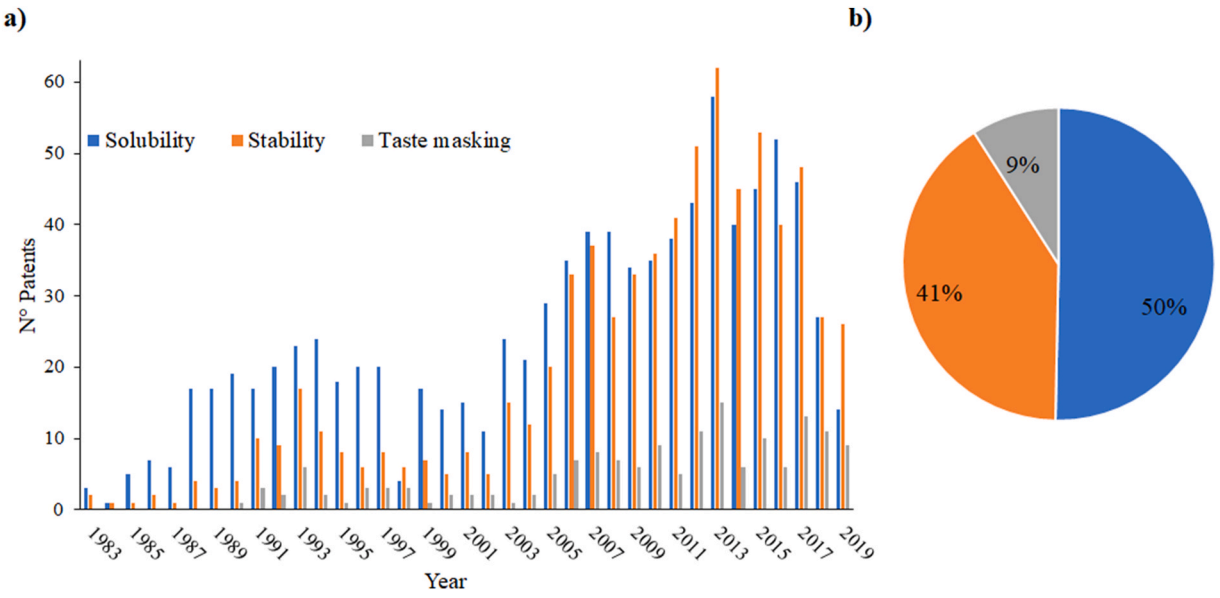


Fig. 5. a) Patenting trends of CDs and their uses for solubility, stability, and organoleptic properties enhancement; b) distribution of patents according to CD use.

thus broadening their applications [40]. The most cited patent regarding solubility enhancement corresponds to Stella & Rajewski, 1994, the most cited patent of the whole dataset (described in Section 3.1), just followed by a patent whose invention corresponds to Pitha, 1985, with 385 citations. The latter is another landmark in CDs history as it describes the preparation of alkylated CDs including HPβCD, one of the most important CD-derivatives, since its use has been approved for any administration route. The patent is also associated with the preparation of drug/alkylated-CD mixtures, emphasizing their amorphous state and high aqueous solubility [41].

Although Fig. 3 points out that 2018 was the year with the highest number of patents, Fig. 5 shows that, in this year, little activity was detected regarding solubility. After a while, the solubility enhancement of a poorly soluble drug was not a novelty anymore. Therefore, new effects, of course, associated or based on improved solubility, have had to be found. This may explain why the number of related patents started to decline.

Nonetheless, this does not mean that a simple IC to modify the solubility of a drug is not important. On the contrary, high-throughput screening strategies continuously propose new candidates, of which a large majority have low solubility. Therefore, CDs remain a valuable strategy for overcoming the challenges associated with these compounds. The same would happen with the repositioning of drugs, in which a change in their solubility, could be a trigger for their use in the treatment of a disease different from that for which they were originally created.

Similarly, CDs may enable formulations for the most convenient routes of administration, or reformulations for a relaunch of the product. For example, remdesivir, the drug that could be used to treat the SARS-CoV-2 infection, is poorly soluble in water—a limitation that has been overcome by the formation of an IC with SBEβCD for IV administration [42,43]. Other examples of patents using CDs for parenteral formulations are discussed in Section 3.3.1.

3.2.2. Stability

The effect of CDs on the chemical and physical stability of drugs has been well documented. In the solid state some CDs like MβCD can retard or suppress the degradation of some drugs. In addition, CDs can prevent thermal-sensitive drugs from degrading into oily products or, in turn, protect oily and volatile therapeutic molecules. Moreover, CDs can be used as a stabilizer agent for the whole formulation [10].

From 2002, an increase in the interest in the use of CDs as a stabilizing agent is seen, and 2010 is the year in which the number of patents of CDs as stabilizers, slightly exceeds the number of those for solubility. Today, the number of patents related to solubility and stability is comparable (Fig. 5). To note, a single patent can claim the use of both solubility and stability. This may be the case for patents that protect a vast number of drugs or formulations. Although less frequent, this could also happen for patents concerning a drug in which its hydrophobic part is also the sensitive part.

The first patent in this regard is related to the stabilization, conferred by CDs, of a solid formulation of vitamin D_3 [27,28]. An invention granted in 1985 by Janssen Pharmaceutica N.V. is on the preparation of HPβCD. The patent also describes the use of this derivative in pharmaceutical compositions to overcome the instability or low solubility of a variety of drugs, namely, non-steroid anti-rheumatic agents, steroids, benzodiazepines, imidazoles, and others. HPβCD is the most important CD-based solubilizer used on any type of administration, including the parenteral route, so far, which explains why this patent accounts for a significant number of citations (79 citations) and is the most cited patent concerning stability from our dataset [44]. Strikingly, it was few months later when the similar patent comprising pharmaceutical formulations using the alkylated CD-derivatives, discussed in Section 3.2.1, was filed [41]. The use of CDs as stabilizers to make a product last longer or to optimize the conditions of manufacturing, packing, and storage are examples of other CD applications [45].

When designing a formulation employing CDs as stabilizers, it must be considered that the formation of an IC can make some drugs more stable but some others more labile. Furthermore, it has been observed that drugs that are stabilized in aqueous solution by a CD can be destabilized by the same CD in a solid dosage form [10,46,47]. Therefore, the use of CDs to improve the stability of a given drug or formulation must be thoroughly studied and the formulation carefully designed.

3.2.3. Taste-masking

Many active pharmaceutical ingredients have undesirable taste and/or odor, which can lead to low patient compliance, thereby compromising the treatment efficiency, especially for geriatric and pediatric populations [48]. As the oral administration is the most accepted route, masking the unpleasant taste of drugs to an acceptable degree of palatability is important during formulation. Masking techniques can be integrated into three levels: 1) formulation level, through sweeteners and flavors; 2) particle level, by creating a physical barrier between the bitter component and the taste receptors; and 3) molecular level, through the complexation of the drug with CDs or ion-exchange resins [48,49].

In general, the global number of patents concerning taste-masking is considerably lower in comparison to solubility and stability applications and has slowly gained interest over time (Fig. 5).

The most cited patent (151 citations) describes a formulation of a nicotine lozenge for smoking cessation, to release nicotine in the buccal mucosa for reaching a maximum systemic level faster than the nicotine transdermal patch. Besides other components, the formulation involves an IC between βCD and an essential oil flavoring [50]. Another patent with a significant number of citations (35) is a technological innovation reporting βCD/ibuprofen complexes with an enhanced taste profile and bioavailability in comparison to sodium ibuprofen [51].

A patent published in 2002, entitled “Oral pharmaceutical compositions containing cyclodextrins as taste masking agent”, claims that CDs can mask the unpleasant taste of drugs without the preparation of an IC between the CD and the drug, which was thought to be essential. Besides the scientific contribution to the field, this was considered a breakthrough in terms of manufacturing processes, regarding simplicity and costs [52]. Later, in 2005 it was argued that the preparation of the CD/drug IC might not be necessary if the drug dose is small and the CD is in excess. If so, the CD will dissolve quickly in the saliva, giving rise to a saturated CD solution in which the bitter component instantly forms a complex with the CD [53]. CDs have also been useful as a taste-masking agent for chewable, fast-disintegrating, buccal, and sublingual tablets [54].

Taste-masking is also needed in nasal and pulmonary administration routes. Several potential drugs for inhalation therapy have an unpleasant taste, which, again, may result in incomplete therapy due to low patient compliance. For these formulations, bitter molecule encapsulation is the best option because other types of methodologies, such as coating, are not feasible. Some examples in this regard are reviewed in Section 3.3.4.

The use of CDs for taste-masking is still emerging and represents a great area of opportunity. Besides the improvement of organoleptic properties, CDs can simultaneously modify solubility and impart stability to the formulation, making them exceptional multifunctional excipients.

3.3. Administration routes

According to the previous sections, it is clear that CDs can be present in a variety of dosage forms intended for practically all administration routes. Hence, we were interested on knowing how the presence of CDs has evolved in formulations for different administration routes over time (Fig. 6).

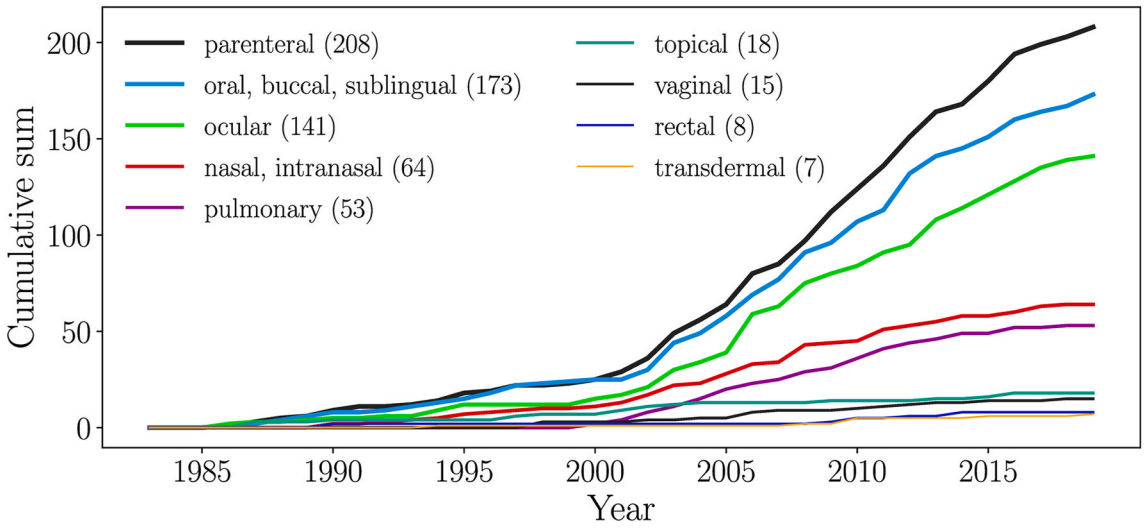


Fig. 6. Technological development of CDs in a variety of administration routes.

3.3.1. *Parenteral administration*

Certainly, the major strength of CDs is their ability to increase the apparent solubility of a drug through the formation of an IC. Therefore, their most attractive and robust application has been for preparing aqueous for parenteral administrations, clearly confirmed by the 208 patents observed in Fig. 6.

Although only αCD, HPβCD, and SBEβCD are approved for parenteral administration, their success is remarkable as there are numerous commercially available products for this aim. Some examples for IV administration are αCD/alprostadil (Caverject ™), HPβCD/itraconazole (Sporanox ™), SBEβCD/voriconazole (Vfend ™), and HPγCD/Tc-99 teoboroxime (Cardiotec ™). In terms of IM formulations are SBEβCD/aripiprazole (Abilify ™) and SBEβCD/ziprasidone mesylate (Geodon ™) [26,55–59]. As we have mentioned, the development of formulations for parenteral administration remains very active. Some examples of recent patents include: the parenteral formulation of clopidogrel through its complexation with sulfoalkyl ether CDs, patented by CyDex Inc. in 2019 [60]; the development of CD-based formulations for lansoprazole [61]; and sartans drug family [62].

This trend is expected to continue growing in the future as the formulation of new drugs, reformulations, and drug repurposing still strongly consider CDs technologies as an excellent tool for formulating low-water-soluble drugs, [42,63,64]. This scenario is possible only if research and development of pharmaceutical technology, as well as studies on pharmacokinetic and toxicological profiles of the ICs, are continuously conducted, as they have been so far. Because not all CDs or CD derivatives can be parenterally administered, the design and synthesis of new CD derivatives are highly desirable. Besides being biocompatible, a derivative must be water-soluble and present good complexation abilities. Furthermore, its production process should be robust and scalable to produce volumes that can fulfill the pharmaceutical industry's demands.

3.3.2. *Oral administration*

Oral route is the most accepted way to administer medications and, in turn, solid dosage forms, are the most common formulations intended for this aim. Despite its popularity, the oral route is challenging or sometimes not possible for several drugs, due to their low solubility/permeability, instability, degradation in the GI tract, extensive metabolism, and unpleasant organoleptic properties. CDs have demonstrated great potential to overcome these limitations directly or indirectly and even to modify a drug release profile.

Hydrophilic CDs can improve the oral absorption of the BCS Class II drugs (low solubility, high permeability), as CDs augment their solubility without altering their permeability to biological membranes. In the case of BCS Class IV drugs (low solubility, low permeability), CDs may increase their solubility and improve their availability at the mucosal surface to enhance their absorption. Lipophilic CDs such as MβCD are ideal to increase permeability through membranes, although their use for oral delivery is hampered by their toxicity. CDs can also be beneficial for BCS Class I drugs (high permeability, high solubility), not for modifying their bioavailability but for reducing gastrointestinal irritation, as in the case of some NSAIDs. The CDs effect on Class III drugs is negligible.

Although oral administration addresses liquid and solid forms, the success of CDs is reflected majorly in the latter, with several oral tablets already marketed: αCD/cefotiam-hexetil HCl (Pansporin T ™), βCD/omeprazole (Omebeta ™), βCD/piroxicam (Brexin ™), and βCD/tiaprofenic acid (Surgamyl ™). Although less common than tablets, capsules are also present included in the list of marketed CDs oral formulations, like Ulgut ™, a product based on a βCD/benexate IC [2,4,65]. In this context, our analysis will be focused on solid forms including conventional, sublingual and buccal tablets, and from here, with oral administration, we will only refer to these pharmaceutical forms.

Patents for CD-based oral formulations account for 173 files which makes them second in importance after parenteral formulations. The increasing number of patents (Fig. 6), especially from the early 2000, clearly indicates that they have been, and still are, a very attractive resource for oral pharmaceutical technologies. An example of a patent published in 1999 discloses the use of CDs in oral tablets for preventing sodium pravastatin degradation and isomerization by humidity or temperature before oral administration [66]. An example of a patent issued in 2019 discloses a CD-based oral tablet to enhance the bioavailability of meloxicam [67].

For a successful development of CD-based conventional tablets, some aspects must be carefully considered, for instance, whether CDs are used as ICs or as a physical mixture; their interaction with other components of the formulation; and the type of drug, its dose, and the size of the dosage form. In addition, the technologies to process them play a fundamental role in determining an outstanding performance [68]. Also, care must be taken in the amount of CD used in the formulation, as an excess of CDs could hinder the absorption of the drug through the GI tract [68,69]. Nonetheless, the fascinating recent research devoted to oral CD-based pharmaceutical technologies will certainly maintain the increasing trend observed herein [70–75].

Buccal formulations aim to deliver drugs through the buccal mucosa, which possesses a large surface area for absorption, to achieve a local or systemic effect. On the other hand, sublingual tablets, in which the drug

is placed beneath the tongue, seek a more rapid systemic absorption, in comparison to the conventional oral route, and avoids intestinal and hepatic first-pass metabolism of the drug. In this regard, CDs can enhance drug dissolution in the saliva, improve the organoleptic properties, or work at the absorption and bioavailability levels [76]. In fact, there are some buccal and sublingual medications containing CDs on the market: βCD/PGE2 (Prostarmon E ™), βCD/nitroglycerin (Nitropen™), and βCD/nicotine (Nicorette™), also formulated as a chewing gum (Nicogum™) [65,69].

Compelling research shows the promising potential of CDs for developing sublingual dosage forms [77–79]. Therefore, an important role of innovations in this matter is expected. The following are two examples of patents for sublingual formulations: 1) the use of CDs to provide faster dissolution times for reaching high levels of apomorphine in plasma to treat female sexual dysfunction [80]; 2) the use of CDs for the transformation of therapeutic oils into water-soluble dry powders for sublingual administration [81].

The combination with polymers has enabled the development of mucoadhesive buccal films, which appear to be emerging as a trending research area [82,83]. In this sense, very innovative approaches are being investigated and patented, like a CD-based hydrogel, which disintegrates at the human body temperature, to increase the bioavailability of aurantiin, with a good taste and suitable for children or particular patients [84].

CDs are an excellent resource for developing oral formulations and patents in this matter are expected to continue increasing in the next years. The progress in mucoadhesive materials is paving the way to design buccal mucoadhesive devices to provide convenient therapies to pediatric and geriatric patients, thus generating a very attractive research opportunity area.

3.3.3. Ocular administration

Ophthalmic preparations must allow the drug to permeate the structure of the corneal epithelium without irritating the ocular surface; otherwise, it will be rapidly cleared from the precorneal area a few minutes after administration, with an incomplete absorption. Suspensions, drops, gels, ointments, and solid inserts have been used to deliver drugs to the eye. Aqueous eye drops are the most common because they are the ones with the least adverse effects, especially irritation and blurred vision, which may influence the medication adherence. In eye drop formulations, the drug must be dissolved in a small aqueous volume, but at the same time, must preserve a moderately lipophilic character to penetrate the corneal epithelium and stroma into the aqueous humor.

CDs offer numerous advantages that can facilitate the development of convenient ocular formulations [69,85–87]. CDs enhance drug solubility, without interfering in its ability to permeate the lipophilic barriers, stabilize the formulation, and decrease irritation to the ocular surface. CDs do not cross the corneal epithelium; however, if they are complexing a lipophilic drug, they can keep it in the aqueous solution and afford a higher availability at the surface of the corneal barrier. There are currently two marketed ophthalmic drops employing CDs: the antibiotic Clorocil ™ containing MβCD/chloramphenicol, and the anti-inflammatory Voltaren Ophthalmic ™ comprising the HPγCD/diclofenac sodium IC [2,5]. Based on the number of patents, the use of CDs in ocular medications is one of the most important, just below parenteral and oral solid forms. Moreover, the interest on CDs has increased from the year 2000 and is still appealing, as evidenced by the rapid increase in the number of patents in the last 20 years. An example of a recent patent is the nano- and micro-suspensions containing αCD and γCD, where αCD forms an IC with cyclosporin A, while γCD promotes the formation of CD/cyclosporin A ICs aggregates. The formulation is intended to treat inflammatory ocular surface disorders and to enhance tear formation [88]. As we have discussed, the research on bioadhesive materials is driving the development of innovative technologies. Proof of this is a patented composition called nanoglue, comprising CDs, one or more bioadhesive polymers, one or more dendrimers, and (optionally) one or more therapeutic, prophylactic, or diagnostic agents. After external stimuli, like UV irradiation, the nanoglue forms a hydrogel at the target tissue that seals corneal wounds [89].

Recent research on ocular formulations containing CDs include: sustained-delivery eye drops [90,91]; in situ gelling systems [92,93]; mucoadhesive hydrogels [94,95]; CD/drug-loaded contact lenses [96,97]; and micro and nanosystems [86,98,99]. Also, CD-based formulations have shown potential to treat eye posterior segment diseases, such as diabetic retinopathy and age-related macular degeneration, which are commonly treated by intravitreal drug injections [100]. Certainly, the outcomes of such compelling investigations will be reflected in a higher patenting growth in the following years.

3.3.4. Nasal, intranasal, and pulmonary administration

The obvious and best way to treat nose and paranasal sinuses ailments is through nasal delivery medications. For a successful nasal delivery, drugs must dissolve in a very small volume of water, as the volume of the aqueous diffusion layer is small. Permeation enhancers and mucoadhesive components are highly desirable for nasal and intranasal formulations as they will promote the delivery of drugs before their clearance [101].

The promising role of CDs in formulations for nasal administration is associated to the modification of the absorption rate of the drugs at the site of delivery due to an increase of drug solubility and changes in nasal mucosa permeability [102,103]. For example, a patent disclosing a dry powder formulation of a group of indazoles, designed to inhibit the Janus dependent kinase for blocking the interplay of multiple inflammatory cells, in which CDs act as both solubilizers and bioadhesive components for the nasal mucosa [104]. Suitable formulations of corticosteroids are needed for rhinitis, sinusitis, asthma, and nasal polyps, among others. Several innovations have responded to this necessity through the implementation of CDs (especially sulfoalkyl ether derivatives) to enhance drugs solubility and permeability in nasal medications, while improving their organoleptic properties [105,106].

Intranasal delivery has gained great interest due to their potential to deliver drugs systemically, while avoiding phase I and II metabolism. Hence, is an attractive route for administering peptide drugs and hormones. Moreover, this route has been explored for brain delivery [107]. Recently, a new product called Baqsimi ™, used for the treatment of diabetes mellitus, has been approved by the FDA and EMA. It contains βCD as an inactive ingredient that improves the stability, solubility, and bioavailability of glucagon [108–110]. Another commercial product administrated nasally is RMβCD/17β-estradiol (Aerodiol ®) [2]. Thus, intranasal technologies using CDs have arisen over time. One example is a powder formulation containing glucagon or a glucagon analog for nasal administration, useful in the treatment of hypoglycemia, in which βCD performs as a filler and as a mucoadhesive agent to the nasal mucosal surface to promote the absorption of the active agent [111]. Another interesting patent is the intranasal formulation for the parathyroid hormone, in which βCD enables an aqueous formulation while preventing drug aggregation [112].

Patents of nasal and intranasal preparations employing CDs have evolved slowly over time. Although they have gained strength in the last 20 years, they can still be considered emerging. However, recent investigations [113–115] will generate new opportunities for innovations and a slow but steady increase in patents may be coming in the next years.

Although the pulmonary route has been mainly proposed for localized treatments, the large lung surface area and abundant blood supply make this route an alternative for systemic drug delivery. The efficacy of this route relies on the adequate aerosolization properties of the dosage form, as well as the drug permeability through the lung, its solubility in small aqueous volumes, and its suitable organoleptic properties. Both solid and dissolved CD/drug ICs have been formulated as dry powders and nebulizers, improving the aerosolization properties of formulations

and enhancing the drug dissolution in the lung fluids [116] and recent research continues showing the promising potential of using CDs for pulmonary medications [117–119].

Based on technological information, we found, for example, a preparation of a group of fluoroquinolones suitable for aerosolization for the treatment of pulmonary bacterial infections. In this formulation, CDs are complexing the therapeutic molecules to improve their solubility and stability [120]. Another example includes the CD complexation with compounds to treat inflammatory and fibrotic disorders at the protein kinase level, in which the CD is used as a solubilizer [121].

Innovations on pulmonary formulations containing CDs have progressed slower than nasal formulations (Fig. 6). Nonetheless, is notable that the interest in this regard has strengthened throughout the last decade, which will probably increase the number of patents in the short term.

3.3.5. Other administration routes

The number of patents regarding topical, transdermal, vaginal, and rectal routes is significantly lower than the number of patents for the administration routes already discussed and has remained unchanged over time (Fig. 6). The following section briefly discusses the roles of CDs for each of them.

3.3.5.1. Topical and transdermal. Topical delivery refers to medications that minimally penetrate the skin layer, creating a local effect. A meticulous selection of the vehicle is necessary for the CDs to display suitable performance. For example, hydrophilic CDs can increase the in vitro release rate of corticosteroids from water-based ointments but delay the drug release in oily-based vehicles. Moreover, some components of the ointments can displace the drug from the CD/drug IC [122]. These demanding requirements, however, have achieved fruitful results with Glymesason ™, an ointment containing dexamethasone and βCD. Our study revealed that only 18 patents disclose dermal formulations employing CDs. Some examples of them include a bio-adhesive film--forming pharmaceutical composition created for application directly to the skin or to a substrate to treat skin disorders, in which CDs perform principally as solubility enhancers [123]. Another invention uses the SBEβCD/silymarin IC for a composition useful in reducing facial redness in rosacea-prone skin, preventing skin aging, inhibiting oxidative stress in epidermal and dermal cells, and increasing collagen production. CD is used to enhance the solubility and availability of the active compound in the topical formulation [124]. Although the patenting behavior has remained without significant changes over time, the outcomes of recent research could change this trend as investigations range from ointments [125] to wearable biomimetic films for wound healing [126], including supramolecular gels [127] and nanosystems [128].

The transdermal route requires a formulation capable of penetrating the skin to exert its effect in deeper tissues or in systemic circulation. Transdermal formulations require penetration enhancers to enable the drug to cross the stratum corneum and reach systemic circulation. In this respect, CDs increase drug availability at the barriers surface, differently to penetration enhancers, which induce physicochemical changes within the barrier. However, the combination of both CDs and penetration enhancers results in additive effects. Thus, CDs can support the adequate performance of a transdermal preparation [129]. Only 7 patents were retrieved from the dataset, however, this behavior may change in the future due to the increasing interest in delivering drugs to systemic circulation with all the advantages that the transdermal route offers. Proof of this is the fascinating research for transdermal delivery using CDs: CD-based hydrogels [130]; CD/drug ICs loaded into microneedles [131] or patches [132]; and ICs with ionic CDs for iontophoretic transdermal delivery [133].

3.3.5.2. Vaginal and rectal administration. In vaginal formulations, drug absorption, distribution, and residence time may vary. The most common vaginal formulations are semisolid and fast-dissolving solid dosage forms, notwithstanding, bioadhesive systems have become highly desirable for local or systemic vaginal effects. Those drugs administered by this route include hormones, antibiotics, and antimycotics. However, other diseases, like those related to human papillomavirus, herpes simplex virus, and HIV, along with the unfortunate increase in the prevalence of cervix carcinoma, have recently driven the interest to develop vaginal formulations [134]. Several compelling investigations have shown that CDs are useful, as solubilizers, in the development of these type of formulations such as mucoadhesive gels, creams, and films for antifungal and antiviral activities [135–137]; gels for contraception purpose [138]; vaginal discs for the controlled delivery of antiretroviral drugs [139]; and mucoadhesive nanosystems for cervical cancer treatment [140]. Also studied are the mucoadhesive properties of CD derivatives in which CDs *perse* comprise the delivery systems [141].

From the 15 patents retrieved from the dataset we selected a recent invention for systemic effect: a vaginal formulation, in which CDs are used for solubility and stability enhancement containing MAGL inhibitors to treat systemic MAGL-mediated disorders such as pain, inflammatory disorders, traumatic brain injury, depression, anxiety, and Alzheimer's disease, among others [142].

The patenting pattern has remained without change, nevertheless, it is highly desirable to change the trend for the coming years. Likely the advances in the development of functional biomaterials will make an outstanding contribution to these technologies.

Rectal administration is an advantageous alternative to the oral route for children and for patients with difficulty for swallowing or those with intense nausea and vomiting. The constraints associated with this route are the limited surface area for drug absorption and the small volume of the rectal fluids in which the drug must be dissolved [143]. CDs and their derivatives have also been employed to optimize drug rectal delivery. CDs can improve drug stability in the suppository base and decrease the rectal irritation caused by drugs. Also, CDs can modify the release rate of drugs from the vehicles and promote their permeation through the rectal epithelium, with the subsequent optimization of the drug pharmacokinetic profile. If the formulation comprises a CD/lipophilic drug IC in an oleaginous vehicle, the IC will be well dispersed in it. Therefore, the drug dissolution at the interface of the oily base and the rectal fluids will improve. At the same time, the reverse diffusion of the drug into the vehicle is hindered [69,122,144].

As with ointments, the success of a formulation depends on the vehicle (aqueous or oleaginous), the physicochemical features of the CD in use, the drug, the CD/drug IC, and their interactions with the other components of the preparation. Despite these challenges, there are some rectal suppositories currently marketed: βCD/piroxicam (Cicladol ™ and Brexin ™), βCD/meloxicam (Mobitil ™), and HPβCD/cisapride (Prepulsid ™) [5]. According to our search, the number of patents concerning suppositories is relatively low (Fig. 6), nonetheless herein we discuss two recent examples of interesting technologies: 1) a novel rectal composition for the treatment of pediatric cancer in which CDs works as solubilizer [145]; 2) a rectal composition containing rifaximin, hydrocortisone, and CD, in which the latter is employed as a mucosal permeation enhancer improving the local retention and bioavailability of the drug for the treatment of anal diseases like anal fissure, ulcers, or hemorrhoidal diseases [146].

The number of academic publications is also low. A general search in the Scopus database for the last ten years (search criteria: cyclodextrin rectal delivery) revealed that only a few articles per year were published—or even no articles, as in the case of 2015. Fortunately, after that, compelling research has been done. For example, the study of HPβCD/budesonide ICs in the form of thermoreversible gels for ulcerative colitis [147]; or HPβCD/5-fluorouracil IC encapsulated in a thermoreversible gelling film for colorectal cancer [148]. Despite its low popularity, this administration route may still be hiding its potential to deliver drugs locally or systemically, and the use of mucoadhesive and

thermoresponsive materials whose development could be supported by CDs may provide interesting progress to the field.

3.4. CD patents: Where and who?

We aimed to identify those regions with high patenting activity around the world, as these may correspond to the regions with high market potential. This analysis was carried out using the dataset of 1998 patents. Fig. 7a shows the top ten countries that hold most of the CD pharmaceutical patents. Since 2011, China has become the nation with the highest patent filing activity in practically all kinds of technological fields [149]. CDs pharmaceutical innovations are no exception. According to our analysis, 1356 patents were filed in this country, just followed by the geographical region represented by WIPO, with 710 records. These numbers position China as the global technological leader in the field of CDs for pharmaceutical applications, as the number of patents registered here is 47% higher than that registered in the WIPO countries. Japan and the U.S. also stand out with 688 and 656 patents, correspondingly.

Besides the regions with the highest market potential, we aimed to provide information about the assignees—this is, the entities that have the right to exploit the patent. In accordance with what we have mentioned, Fig. 7b highlights that 7 out of the top 20 assignees are located in China, including both industry (five pharma companies) and academic institutions (two universities). Japan and Brazil (positions 3 and 8, respectively, in the top-10 countries) also appear in the top-20 assignees with patenting activity in both universities and pharma companies. Certainly, the holistic technological knowledge coming from industry and academia is highly relevant for the technological development of a region.

China, Japan, the U.S.A., and Brazil, each belonging to the top-10 ranking regions, are also present among the top-20 ranking of assignees. U.S.A has only 2 assignees in the top-20 list, Pfizer Inc. and CyDex Pharmaceutical Inc. Both companies have shown to have an active CDs patent portfolio (some of their patents have been discussed throughout this work). In particular, CyDex Pharmaceutical Inc. has played an important role in the development of CDs technologies, and owns one of the most influential patents in the area: Patent No.US 6046177 [33], which today is still a breakthrough in the evolution of CDs innovations in the pharmaceutical field.

There are several channels for spreading knowledge and technology across boundaries. Among them, FDI has been widely studied. FDI refers to an investment made by a firm or individual in one country into a business located in another country. This implies that patents that protect the same invention can be filed in different locations from where they were created, thereby generating different economic phenomena between developed and undeveloped countries [150,151]. FDI could be the reason why some countries in the top-10 ranking regions do not have an assignee backing up their position, as could be the case for Australia, the Korean Republic, Mexico, and Spain.

For the WIPO and the EPO regions, the dynamic is different because they encompass different cooperation treatments. On the one hand, the Patent Cooperation Treaty enables patents to be registered in the 193 countries that are part of the WIPO through only one procedure. On the other hand, EPO grants European patents in 44 countries and also facilitates the registration of a patent in different EPO countries in a single grant procedure. This explains why these two entities appear in the second and fifth positions of the top-20 ranking for geographical regions. Hence, it is expected that WIPO and EPO will remain at the top positions in terms of regions in which a certain technology is protected.

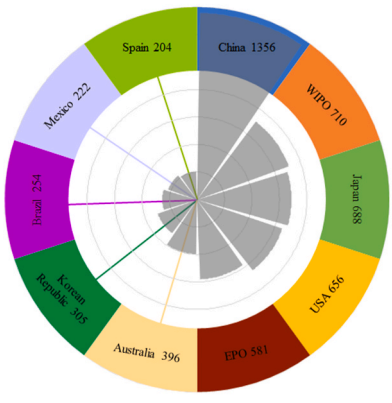
4. Conclusions

We analyzed the evolution of CD-based pharmaceutical technologies, using patent data as the technical source, through a text-mining approach based on the patents semantic content. In our dataset, the first-filed patent dated from the early '80s. During that decade, slow growth in CD patents was observed. However, the early 2000s saw very fast growth in the use of CDs for pharmaceutical applications.

The abilities of CDs to enhance the solubility and stability of drugs have determined their technological progress. Nonetheless, their abilities to modify organoleptic properties are emerging and represent a great area of opportunity. CDs are used in formulations for practically any route of administration. Although patents are majorly associated with the parenteral aqueous solutions, oral and ocular formulations are significantly growing, while nasal and pulmonary formulations seem to be promising. Of great importance was to revise patents associated with formulations for topical, transdermal, vaginal, and rectal routes. The interest on patenting these technologies seems to be neglected, however they may be hiding a great potential and represent opportunity research areas. Certainly, the better understanding of CDs, along with the progress in materials science, supramolecular chemistry, and nanotechnology, will drive a change in their patenting trend. Bottom line, the interest in CDs is still increasing and this trend is expected to continue in the coming years.

Patent monitoring allows the identification of relevant technologies and trends to prioritize research, development, and investment. Thus, knowledge mined from patents can be applied to foster technological innovations based on CDs or any other platform.

a)



b)

Assignee	N° Patents
1. Tianjin Tianshi Pharmaceutical Co.	26
2. CyDex Pharmaceuticals Inc.	25
3. Nanjing Normal University	21
4. Ono Pharmaceutical Co.	20
5. Nanjing University	20
6. Novartis AG	17
7. Taisho Pharmaceutical Co.	17
8. Pfizer Inc.	16
9. Federal University of Sergipe	15
10. CSPC Pharmaceutical Group Limited	14
11. Hainan Weikang Pharmaceutical Qianshan Co	13
12. Jiangsu Aosaikang Pharmaceutical Co	13
13. Bayer Schering Pharma	12
14. French National Centre for Scientific Research	12
15.Tianjin Hankang Pharmaceutical Biotechnology Co	12
16. Kumamoto University	12
17.Minas Gerais Federal University	11
18. Kunming Pharmaceutical Corporation	10
19. Chengdu Qiankun Veterinary Pharmaceuticals Co	10
20. The Institute of Chemical Sciences of Kazakhstan	10

Fig. 7. a) Top-10 ranking countries for CDs patents on pharmaceutical applications. b) Top-20 ranking CDs patents assignees (colors correspond to the country the assignees belong). (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

Author statement

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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