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EXPERT OPINION

Enhanced analgesic activity by cyclodextrins – a systematic review and meta-analysis

Renan G Brito, Adriano AS Araújo, Jullyana SS Quintans, Kathleen A Sluka & Lucindo J Quintans-Júnior[†]
[†]*Federal University of Sergipe, Department of Physiology, Sergipe, Brazil*

Introduction: Analgesics can be ineffective in treating some types of pain, hence, improved drug delivery systems could optimize their efficacy.
Area covered: The authors conducted a systematic review to evaluate the analgesic activity of compounds complexed in cyclodextrins, analyzing whether these complexes improved analgesic efficacy. The search terms 'analgesics', 'cyclodextrins' and 'drug effects' were used to retrieve articles in SCOPUS, PUBMED and EMBASE. A total of 22 papers were identified. In the clinical studies, there was greater efficacy in the complexed drug when compared with control groups, with differences ranging from 25 to 83%. Through a meta-analysis, the preclinical studies showed that the complexed drug had a significantly ($p < 0.01$) greater effect than the non-complexed drug.
Expert opinion: The use of cyclodextrins can improve the efficacy of analgesic compounds, and they are an important tool in the search for greater analgesic effect. They may also be a way to reduce the therapeutic doses, and hence increasing the potential of the drug.

Keywords: analgesics, cyclodextrins, drug effects, meta-analysis, pain, systematic review

Expert Opin. Drug Deliv. [Early Online]

1. Introduction

Pain is defined as an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms as such damage. Pain is recognized as a public health problem with significant physical and psychological consequences [1]. The average prevalence of acute and chronic pain in the adult population ranges around 15% [2,3], resulting in an annual spending, in the US alone, in the order of US $ 635 billion [4].

Pharmacotherapy is widely used in the treatment of pain. Several classes of drugs are common, including opioids, non-steroidal anti-inflammatories (NSAIDs), muscle relaxants, anticonvulsants and antidepressants are the most widely used drugs [5,6]. However, 40 – 60% of patients do not respond appositely to the therapy, and may have partial reductions in pain or significant side effects [7,8]. Thus, various types of drugs with an analgesic profile, such as NSAIDs, have been incorporated into drug delivery systems, such as cyclodextrins (CDs), to improve pharmacological properties [9].

CDs have been known for over 100 years. They were first discovered in 1891 by Villiers, a French scientist. He isolated about 3 g of a crystalline substance from 1000 g of starch and determined its composition as $(C_6H_{10}O_5)_2{\cdot}3H_2O$ [10]. The first patent on CDs and their complexes was registered in 1953 in the US. However, until 1970 only small amounts of CDs were produced and high production costs prevented their widespread usage in pharmaceutical formulations. With recent

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Article highlights.

- Cyclodextrins (CDs) are one of the most interesting drug encapsulation systems for analgesic and anti-inflammatory drugs already used in medicine.
- CDs can easily form complexes with analgesic drugs and they can improve the pharmacological efficacy.
- CDs can act using decreasing doses of analgesic drugs, which may reduce any side effects.
- There are few studies sufficiently providing evidence of why this improvement occurs.
- Preclinical studies have a key role to understand how the CDs can advance analgesic profiles.

This box summarizes key points contained in the article.

biotechnological advancements, the production of CDs has improved and production costs have been lowered [11].

CDs are cyclic oligosaccharides consisting of six (αCD), seven (βCD), eight (γCD) or more glucopyranose units linked by α-(1,4) bonds. The sugar units adapt to a $^4C_1$ chain conformation and are orientated in such a way that the molecule forms a toroidal truncated cone structure [12,13]. CDs are pharmaceutically useful due to the fact that they can interact with drug molecules to form inclusion complexes. In forming inclusion complexes, major changes in candidate drug properties, including enhanced solubility, pharmacological bioavailability, chemical stability and physical profile, have been reported [14-16]. Such changes have then resulted in a better biological performance, and thus in the use of CDs in various commercially successful pharmaceutical products [17,18].

In this context, the present study aimed to assess, through a systematic review and meta-analysis, the studies that evaluated the analgesic activity of analgesic compounds complexed in CDs, analyzing whether the drug encapsulation improves the analgesic profile.

2. Methods

2.1 Systematic review

This systematic review was conducted in accordance with the guidelines of Transparent Reporting of Systematic Reviews and Meta-Analyses (PRISMA statement) [19]. A literature search was performed in January 2014 and included articles published over a period of 14 years (January 2000 to January 2014). This literature search was performed through specialized databases (PUBMED, SCOPUS and EMBASE) using different combinations of the following keywords: 'Analgesics', 'Cyclodextrins' and 'Drug effects' either as MeSH terms or as free-text words. The inclusion criteria used were: both preclinical and clinical studies that investigated analgesic action and the use of CDs to improve analgesia, published between January 2000 and January 2014 and written in English.

For the selection of the manuscripts, two independent investigators (R.G.B. and J.S.S.Q.) first selected the articles according to the title. The abstract was used to consider inclusion criteria, and then assessment of the full-text publication confirmed the inclusion criteria and extracted data. The disagreements, which happened two times, were resolved through consensus. The resulting articles were manually reviewed with the goal of identifying studies that met the inclusion criteria described above.

2.2 Risk of bias in clinical studies included

In order to assess the 'risk of bias', clinical studies were judged on the following items: random sequence generation, allocation, blinding, incomplete outcome data and sources of funding bias using criteria outlined by the Cochrane Collaboration [20]. The overall risk of bias in the seven clinical studies was classified as high, low or unclear.

2.3 Data analyses

Clinical Studies: The clinical studies did not have enough similar data to perform a meta-analysis as comparison groups were mixed. We determined the extent to which the CD-complexed drug improved the analgesia when compared with placebo, standard drug, vehicle, baseline or the drug alone by calculating the percentage of the analgesic improvement (AI). For those clinical studies with Visual Analog Scale (VAS) scores provided, the following formula was used to calculate the percentage improvement in pain: $AI = ((\text{Mean } VAS_{Experimental} - \text{Mean } VAS_{Control})/\text{Mean } VAS_{Control})) \times 100$.

Preclinical studies: we performed a meta-analysis using the software Open Meta.[Analyst] 2013. The data from the published trials were divided into three groups and a separate analysis was performed for each one: thermal, chemical and nociceptive score. We extracted the sample size, means and standard deviations for each measure for the individual papers. When the same study had two or more assessments in the same group of animals, we used the assessment with the greatest effect. For the meta-analyses, we only included studies that compared the drug complexed with CD to the drug alone. Three studies were, therefore, not included in the meta-analysis as they compared the complexed drug to the vehicle. Two additional studies were also excluded because we could not extract all data required for the meta-analysis. For all studies when multiple doses were tested, we extracted data from the dose with the greatest analgesic effect.

3. Results

This review searched studies that evaluated the effectiveness of substances complexed in CDs in the analgesic activity. The primary search identified 329 articles: 190 from PUBMED, 81 from SCOPUS and 58 from EMBASE. After screening, 47 articles met the inclusion criteria: 14 from PUBMED, 14 from SCOPUS and 19 from EMBASE. Out of this total, 25 were indexed in two or more databases and were considered only once, resulting in 22 articles selected for final analysis. Seven publications were clinical and 15 were preclinical.

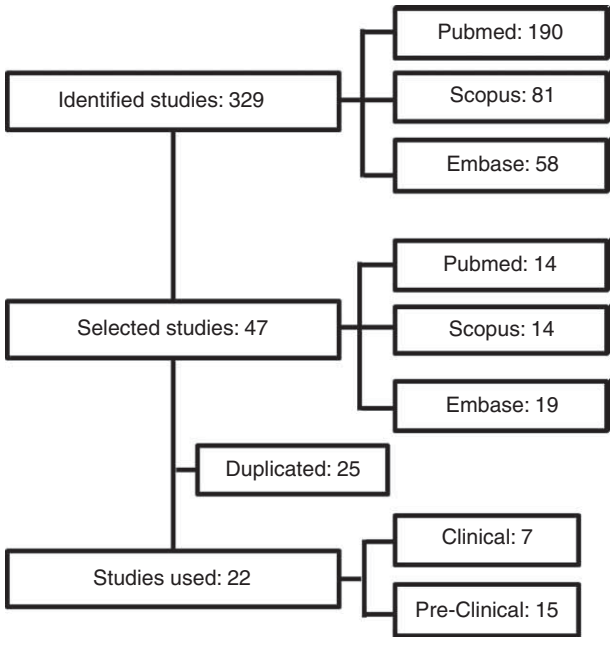

Figure 1. Flow chart of the search and selection results.

A flowchart illustrating the progressive study selection and numbers at each stage is shown in **Figure 1**. The general characteristics of the clinical and preclinical studies identified by this systematic review are described in **Tables 1** and **2**.

Using the assessment for risk of bias, sequence generation was judged to be adequate in six studies, incomplete outcome data were adequate in six studies, four had adequate assessor and participant blinding and the source of funding bias was clear in six. The allocation concealment was unclear in six studies and with high risk of bias in one. **Figure 2** provides details of the judgments about each methodological quality item for each study and **Figure 3** provides a summary of overall risk of bias in the seven studies as high, low or unclear.

The seven clinical studies selected by this systematic review compared the use of NSAIDs complexed with CDs (**Table 3**). Among those, three were compared with placebo, two were compared with the CD-free drug, one was compared with the baseline and one was compared with another NSAID, naproxen. Five of the seven studies provided VAS pain scores, for which we calculated percent reduction in pain. Of those that were compared with placebo, the CD-free drug, baseline or standard drug, there was (n = 5) a reduction in pain intensity between 25 and 83%. Two studies normalized VAS scores and provided total pain relief or pain intensity differences for each group, demonstrating an improvement in the analgesic effect by the complexed drug. One study did not find any difference in the analgesic profile when compared with another NSAID. However, there were fewer side effects related to gastrointestinal tract, suggesting an improvement in the gastrointestinal tolerability to the complexed drug.

The preclinical studies evaluated the analgesic effect of different complexed drugs including NSAIDs, natural products, opioids, local anesthetic and antidepressants. The preclinical studies compared complexed drugs in CDs with the vehicle or the drug alone. Several analgesic protocols were used and classified into three broad categories: thermal, chemical and nociceptive score. Thermal tests included the tail-flick and hot-plate tests in uninjured animals. Chemical tests included the acetic acid-induced abdominal constrictions and the formalin. In the nociceptive score group, a subjective nociceptive assessment of animal response to injury was used (neuropathic pain). The meta-analysis from the chemical group demonstrated that the complexed drug significantly decreased (Overall: 10.25; $I^2 = 89\%$; $p < 0.001$) the nociceptive behavior when compared with the drug alone (**Figure 4A**). In the thermal group, the complexed drug increased significantly (Overall: -9.02; $I^2 = 75\%$; $p < 0.01$) the time on the hot-plate or tail-flick tests when compared with the drug alone (**Figure 4B**). The nociceptive score group showed a significant (Overall: -1.5; $I^2 = 97\%$; $p < 0.001$) decrease in the pain score with the complexed drug compared to the drug alone (**Figure 4C**). Thus, all conditions clearly show an enhanced relief of pain behaviors for the complexed drug when compared to the drug alone.

Some clinical and preclinical studies also reported an improvement in other aspects. Among the clinical studies, one study showed an increase in the time of action when the complexed and non-complexed drugs were compared; another one demonstrated an increase in the gastrointestinal tolerability when the complexed drug was compared with the standard drug. In the preclinical studies, eight demonstrated an increase in the solubility, three in time of action, two in absorption, one in oral delivery, one in permeability, one in bioavailability and one in the drug release when compared with the drug alone. In addition, two preclinical studies showed a decrease in the cytotoxicity when the complexed drug was compared with the drug alone. The other improvement aspects are summarized in **Table 4**.

4. Discussion

The current systematic review showed that analgesics complexed with CDs were effective when compared with the drug alone, placebo or vehicle. Clinical studies have already tested the complexed-NSAIDs diclofenac (DF) [21,22], piroxicam (PX) [23-26] and nimesulide (NM) [27]. The clinical studies generally show good methodological quality and demonstrate the effectiveness of CDs in a variety of pain conditions. The preclinical studies used complexes with natural products (*Lippia grata* essential oil [EO] [28], (-)-linalool [LIN] [29], *p*-cymene [pCM] [14]), NSAIDs (indomethacin [30], acetyl salicylic acid [31], etoricoxib [32], meloxicam [33], etodolac [34,35] and ketoprofen [36]), cannabinoids (MDA7 [37]), steroids (allopregnanolone and alphaxalone [38]), local anesthetic (tetracaine (TTC) [39]), opioid (sufentanil (SUF) [40]) and antidepressant

Table 1. Description of the main aspects of the clinical studies included in the systematic review.

Author (year)	Substance	CD type	Doses	Sample	Assessment pain tools
Gan *et al.* (2012) [21]	Diclofenac	HPβCD	18.75 and 37.5 mg	265 adults between 18 and 65 years old scheduled undergoing abdominal or pelvic surgery. The first treatment was administrated 6 h after the surgery	VAS, SPID and PID
Christensen *et al.* (2011) [22]	Diclofenac	HPβCD	3.75, 9.4, 18.75, 37.5 and 75 mg	353 male and female subjects between 18 and 75 years old undergoing surgical extraction of 1 or more third molar	CPIS, VAS, TPR, TSPR, PPR, SPID, PID, PPID, SPRID.
Keles *et al.* (2010) [23]	Piroxicam	βCD	20 and 40 mg	75 male and female subjects aged between 18–65 years of age meeting physical status I or II of the American Society of Anesthesiologists and undergoing endoscopic sinus surgery. The subjects received the treatment before induction of general anesthesia	VAS
Chang *et al.* (2008) [24]	Piroxicam	βCD	20 mg	47 male and female subjects between the ages of 20 and 75 years old, who had low back pain for more than 3 months	VAS, ODI and the sway assessments
Chang *et al.* (2008) [25]	Piroxicam	βCD	20 mg	47 subjects between 20 and 75 years with low back pain for more than 3 months	VAS and ODI
Pijak *et al.* (2002) [26]	Piroxicam	βCD	20 mg	31 subjects of both sexes without age limitation that experienced back pain between the occipital region and gluteal fold, lasting during most days of the preceding 6 weeks	VAS and PID
Fioravanti *et al.* (2002) [27]	Nimesulide	βCD	400 mg	287 subjects aged 50 – 80 years with a diagnosis of osteoarthritis of the hip or knee according to the criteria of American College of Rheumatology	VAS, Pain on movement

βCD: β-cyclodextrin; CD: Cyclodextrin; CPIS: Categorical pain intensity scale; HPβCD: Hydroxypropyl β-cyclodextrin; ODI: Oswestry Disability Index; PID: Pain intensity differences; PPID: Peak pain intensity difference; PPR: Peak pain relief; SPID: Sum of pain intensity differences; SPRID: Summed pain relief intensity differences; TPR: Total pain relief; TSPR: Time-specific pain relief; VAS: Visual analog scale.

(doxepin (DOX) [41]). A variety of pain measures were used including chemical, thermal and nociceptive score tests. In all cases, there was a significantly better analgesic effect of CD-complexed drugs when compared with the drug alone.

4.1 Clinical studies

Several NSAIDs, including DF, PX and NM, have been complexed with CDs to improve analgesic efficacy in clinical populations. This class of drugs has analgesic, anti-inflammatory and anti-pyretic profiles. DF and PX inhibit prostaglandin synthesis by inhibiting cyclooxygenase-1 and cyclooxygenase-2 enzymes [42], whereas NM is a selective cyclooxygenase-2 inhibitor.

Gan *et al.* [21] demonstrated that DF complexed with DF-hydroxypropyl βCD (DF-HPβCD) provided significantly greater analgesic efficacy than did the placebo after abdominal or pelvic surgery; the study was not empowered to discern significant differences between the treatment groups. Christensen *et al.* [22] showed a substantially lower DF-HPβCD dose than that previously thought as necessary (37.5 vs 75 mg) to sufficiently reduce moderate to severe acute pain following the extraction of the third molar with a more rapid onset of action by several measures when compared with ketorolac [43].

PX has been widely prescribed for the treatment of low back pain, even though gastrointestinal mucosal injury reduces the incidence of favorable outcomes [44,45]. Keles *et al.* [23] demonstrated that oral preemptive analgesia with PX complexed with βCD (PX-βCD) decreased postoperative pain and morphine consumption after functional endoscopic sinus surgery. Chang *et al.* [24,25] showed that PX-βCD yielded greater improvement in pain than did the same dose of PX alone in people with chronic low back pain. Pijak *et al.* [26] demonstrated that patients with chronic back pain receiving PX-βCD once daily for 40 days showed an AI higher than with other NSAIDs. In addition, the PX-βCD complexes considerably increase the water solubility as well as the rate of dissociation of poorly soluble PX, leading to a higher rate of gastrointestinal absorption than PX [46,47]. Thus, the rapid onset of action, the long duration of activity, the favorable risk-benefit ratio and less gastrointestinal injury are the major clinical advantages of PX-βCD [12,48,49].

NM is commonly used for the treatment of acute pain and painful osteoarthritis, having a fast rate of oral absorption [50]. Fioravanti *et al.* [27] showed that NM-βCD (400 mg, orally) showed efficacy similar to that of naproxen (500 mg, orally) with a 41% reduction of pain in people with osteoarthritis of the hip and/or knee. The gastrointestinal tolerability of

Table 2. Description of the main aspects of the preclinical studies included in the systematic review.

Author (year)	Substance	CD type	Doses	N (per group)	Route	Animal	Nociception protocols used
Natural products							
Siqueira-Lima *et al.* (2014) [28]	*Lippia grata* essential oil	βCD	6, 12 and 24 kg/kg	6	p.o.	Male albino Swiss mice	Formalin-, glutamate- and capsaicin induced nociception.
Quintans-Júnior *et al.* (2013) [29]	(-)-Linalool	βCD	20 and 40 mg/kg	6	p.o.	Male albino Swiss mice	Acetic acid-induced abdominal constrictions, formalin-, glutamate- and capsaicin-induced nociception and hot-plate test.
Quintans *et al.* (2013) [14]	*p*-Cymene	βCD	20 and 40 mg/kg	8	p.o.	Male albino Swiss mice	Acetic acid-induced abdominal constrictions and hot plate test.
NSAIDs							
El-Feky *et al.* (2013) [30]	Indomethacin	HPβCD	15 and 20 mg/kg	6	p.o.	Albino rats	Tail-flick test
Dolita (2012) [31]	Acetyl salicylic acid	βCD	30 mg/kg	6	p.o.	Female albino Swiss mice	Acetic acid-induced abdominal constrictions
Singh *et al.* (2011) [32]	Etoricoxib	βCD and HPβCD	6 mg/kg	6	i.p.	Rats	Tail-flick test and Eddy's hot-plate apparatus
Janovsky *et al.* (2010) [33]	Meloxicam	βCD	3, 7, 10 and 15 mg/kg	6	p.o.	Rats and mice	Plantar test and writhing test
Sinha and Goel (2010) [34]	Etodolac	βCD	10 mg/kg	6	p.o.	LACA mice	Tail-flick test, Acetic acid-induced abdominal constrictions
Capello *et al.* (2009) [35]	Etodolac	βCD, HPβCD and γCD	3.5 mg/kg	6	p.o.	Male Swiss mice	Acetic acid-induced abdominal constrictions
Lu *et al.* (2004) [36]	Ketoprofen	βCD	4, 8 and 16 mg/kg	15	p.o.	Kun-Ming mice	Acetic acid-induced abdominal constrictions
Canabinoid							
Astruc-Diaz *et al.* (2013) [37]	MDA7	HPβCD	10 mg/kg	3	i.v.	Male Sprague-Dawley rats	Spinal nerve ligation neuropathic pain model and von Frey filaments
Steroids							
Svensson *et al.* (2013) [38]	Allopregnanolone, alphaxalone	βCD	10 µl	6	i.t.	Adult male rats (Holtzman)	Unilateral intraplantar delivery of carrageenan, Hargreaves system and von Frey filaments.
Local anesthetics							
Franco de Lima *et al.* (2012) [39]	Tetracaine	βCD and HPβCD	0.5%	7	i.n.	Male Wistar rats	Infraorbital nerve blockade technique
Opioid							
Volobuef *et al.* (2012) [40]	Sufentanil	HPβCD	1 $\mu g/kg^{-1}$	7	i.m.	Male Wistar rats	Tail-flick test
Antidepressants							
Sammeta *et al.* (2010) [41]	Doxepin	HPβCD	5%	3	t.o.	Male hairless rats	Pain avoiding response using a blunt needle.

βCD: β-Cyclodextrin; γCD: γ-Cyclodextrin; CD: Cyclodextrin; HPβCD: Hydroxypropyl β-cyclodextrin; i.m.: Intramuscular; i.n.: Infraorbital notch; i.p.: Intraperitoneal; i.t.: Intrathecal; i.v.: Intravenous; p.o.: Oral administration; t.o.: Topically.

NM-βCD was higher than that of naproxen during medium-term treatment on demand.

4.2 Preclinical studies

4.2.1 Natural products

Several EOs or related compounds from medicinal plants have been used in preclinical studies for their analgesic profile. For instance, the EO obtained from *Lippia grata* has anti-inflammatory and analgesic properties. Similarly, LIN and pCM, terpenes as main compounds of some EOs, have a diversity of pharmacological properties, including anticonvulsant, anti-inflammatory and analgesic [51-56]. The inclusion of volatile oils with βCD can protect the EOs against oxidation, heat and light degradation, evaporation and moisture; it also turns liquid EOs into water-dispersible and easy-to-handle powders [57,58].

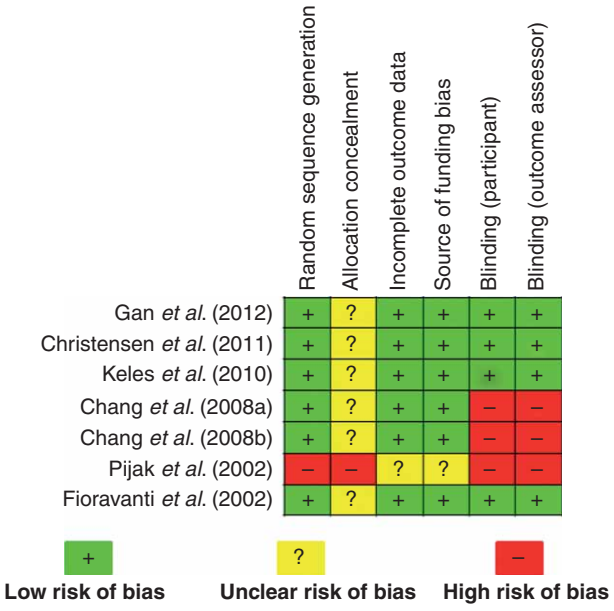

Figure 2. Methodological quality summary for clinical trials: review of authors' judgments about each methodological quality item for each study included.

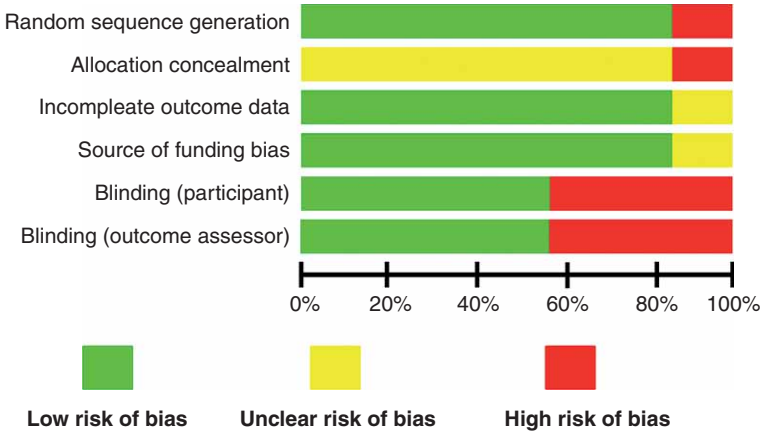

Figure 3. Methodological quality graph for clinical studies: review of authors' judgments about each methodological quality item presented as percentages across all studies included.

Table 3. Summary of the results of the clinical studies included in the systematic review.

Author (year)	Complexed substance	Analgesia	Comparison	Protocol assessed
Gan *et al.* (2012) [21]	Diclofenac	433%	vs placebo	Pain intensity differences from VAS
Christensen *et al.* (2011) [22]	Diclofenac	451%	vs placebo	Total pain relief from VAS
Keles *et al.* (2010) [23]	Piroxicam	83%	vs placebo	VAS score
Chang *et al.* (2008) [24]	Piroxicam	25%	vs piroxicam alone	VAS score
Chang *et al.* (2008) [25]	Piroxicam	42%	vs piroxicam alone	VAS score
Pijak *et al.* (2002) [26]	Piroxicam	66%	vs baseline	VAS score
Fioravanti *et al.* (2002) [27]	Nimesulide	No difference	vs naproxen	VAS score

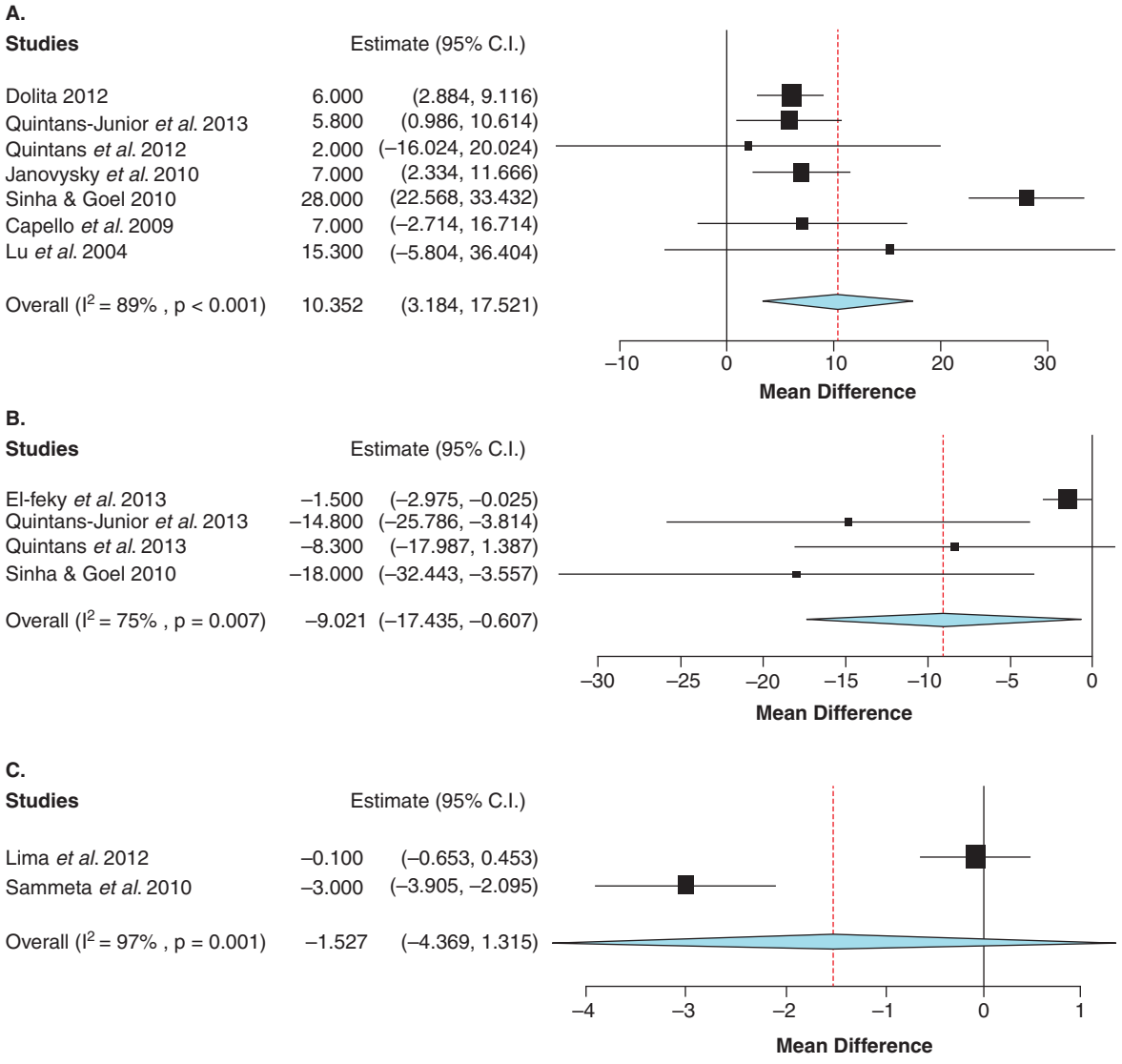

Figure 4. Effects of the meta-analysis of 12 studies comparing the change in the mean analgesic effect in the complexed drug group and the drug-alone group in different types of protocols. A. Chemical protocols, **B**. thermal protocols and **C**. nociception score.

Siqueira-Lima *et al.* [28] demonstrated that the treatment with *L. grata* EO complexed with βCD induced a significant antinociceptive effect in the orofacial formalin-, capsaicin- and glutamate-induced pain tests. Quintans-Júnior *et al.* [29] showed that the LIN and LIN βCD complex (LIN-βCD) reduced glutamate-induced nociceptive behavior and inflammatory cytokines in the carrageenan-induced peritonitis model. LIN-βCD when compared with LIN alone also showed enhanced water solubility, improved dissolution rate and enhanced stability of LIN [59,60]. Quintans *et al.* [14] demonstrated the antinociceptive effect of pCM and pCM-βCD complexed in the acetic acid-induced abdominal constrictions and hot-plate tests, and the anti-inflammatory property through the carrageenan-induced paw edema in mice. The study showed that pCM-βCD inhibited nociceptive behavior for 8 h when compared with pCM alone, which showed 2 h of inhibition in the acetic acid-writhing test. Thus, these studies show enhanced and prolonged analgesia and increased bioavailability with CD-complexed EOs.

4.2.2 NSAIDs

The NSAIDs are clinically used in different diseases, to reduce fever, pain, stiffness and swelling [30,61-69]. That class of drugs has been complexed in CDs and tested in different experimental models to optimize their pharmacological effects. When complexed with CDs, indomethacin, etoricoxib and etodolac show enhanced efficacy in the tail-flick test and hot-plate test [30,32,34]. Similarly, in the acetic acid-writhing

Table 4. Summary of the results of the preclinical studies included in the systematic review.

Author (year)	Complexed substance	Other aspects improved
Clinical		
Christensen *et al.* (2011) [22]	Diclofenac	Time action
Fioravanti *et al.* (2002) [27]	Nimesulide	Gastrointestinal tolerability
Preclinical		
Siqueira-Lima *et al.* (2014) [28]	*Lippia grata* essential oil	Solubility
Quintans-Júnior *et al.* (2013) [29]	(-)-Linalool	Solubility
Quintans *et al.* (2013) [14]	*p*-Cymene	Solubility and time action
El-Feky *et al.* (2013) [30]	Indomethacin	Solubility and oral delivery
Dolita (2012) [31]	Acetyl salicylic acid	Permeability and solubility
Singh *et al.* (2011) [32]	Etoricoxib	Solubility
Sinha and Goel (2010) [34]	Etodolac	Bioavailability and absorption
Capello *et al.* (2009) [35]	Etodolac	Gastrolesivity reduction and solubility
Lu *et al.* (2004) [36]	Ketoprofen	Solubility and absorption
Astruc-Diaz *et al.* (2013) [37]	MDA7	Solubility
Franco de Lima *et al.* (2012) [39]	Tetracaine	Time action and cytotoxicity decrease
Volobuef *et al.* (2012) [40]	Sufentanil	Time action and cytotoxicity decrease
Sammeta *et al.* (2010) [41]	Doxepin	Drug release

test, meloxicam, etodolac, ketoprofen and acetyl salicylic acid showed a greater reduction in nociception when complexed in CDs than when administered alone [31,33-36]. Furthermore, CDs improved the solubility of indomethacin [30], enhanced the solubility, dissolution and permeability of meloxicam [70,71], and enhanced absorption of etodolac [34]. For instance, Sinha and Goel [34] showed an increase in the $t_{1/2}$ and decrease in the elimination rate for CD-complexed etodolac compared to the drug alone. In addition, lower ulcerogenic activity occurs with CD-complexed etodolac alone as the average number of ulcerations was reduced in approximately 50% in the presence of the CDs examined. Thus, the NSAIDs complexed to CDs show enhanced analgesia, improved bioavailability and reduced side effects when compared with the drug alone.

4.2.3 *Other analgesic drugs*

Drugs from a variety of different classes have also been tested in the complexed form to check for a possible improvement in their analgesic activity. Those include studies with cannabinoids, steroids, local anesthetics, opioids and antidepressants.

MDA7, a selective CB_2 agonist, suppresses allodynia in rats with spinal nerve ligation or paclitaxel-induced neuropathic pain [72,73]. In animals with neuropathic pain induced by spinal nerve ligation, MDA7 formulated in HPβCD produces a greater reduction in mechanical hyperalgesia when compared with the vehicle [37].

Allopregnanolone and alphaxalone are neurosteroids that probably facilitate activation by γ-amino butyric acid (GABA) of the $GABA_A$ chloride ionophore and at higher concentrations by directly activating the ionophore, promoting the channel open state [74-76]. Svensson *et al.* [38] showed that the intrathecal delivery of 5α-reduced neurosteroid agonist allopregnanolone and alphaxalone in a CD-water-based vehicle shows a greater reduction in thermal and mechanical hyperalgesia in the unilateral intraplantar delivery of carrageenan model when compared with the vehicle.

TTC is a member of the ester class of local anesthetics that is used to anesthetize nasal tissues before diagnostic and surgical procedures [77]. Lima *et al.* [39] evaluated the antinociceptive effect induced by TTC complexes through the infraorbital nerve blockade test in rats and showed that the complexation with HPβCD and βCD increased the analgesic duration and intensity induced by TTC alone. The authors also demonstrated that the treatment of 3T3 cultured cells with TTC showed an increase in the LD_{50} following complexation, reflecting a reduction in the cytotoxicity of TTC upon the complexation of either βCD or HPβCD.

SUF is a synthetic opioid of the 4-anilidopiperidine group and is commonly used in the surgical room [78,79]. Volobuef *et al.* [40] demonstrated that the latency to the tail-flick was increased after the complexation of SUF with HPβCD when compared with the free drug. SUF-HPβCD also changed hemolytic concentrations, which is possible because the CDs change the drug permeation across the membranes or its distribution, prolonging the effects, decreasing the plasmatic levels and reducing the systemic toxicity [79,80].

DOX, a member of tricyclic antidepressant family, is used as analgesic in addition to depression and anxiety disorders [81-83]. Sammeta *et al.* [41] demonstrated that the electroporation of CD-complexed DOX resulted in the retention of significant amounts of drug in epidermis and sustained drug release from the epidermis. In the study, a prolonged analgesic activity measured with the pain avoiding response using a blunt needle model was observed in the CDs group of rats when compared with the pure drug solution group.

5. Conclusion

This systematic review found clinical and preclinical studies that tested a variety of drugs complexed with different types of CDs. Clinical studies showed greater efficacy of NSAIDs complexed with CDs in a variety of conditions. The preclinical studies demonstrated that the CD complexions were capable of producing analgesic profile in several animal models of nociception, having better effects than the drugs alone. These preclinical studies also showed greater bioavailability of the drug and reduced side effects. Thus, complexation of drugs with CD may be an important delivery method to improve analgesic efficacy by reducing therapeutic doses and the consequent side effects.

6. Expert opinion

The CDs have mainly been used for many purposes, as complexing agents to increase aqueous solubility of poorly soluble drugs, to increase their bioavailability and stability and also to improve drug delivery from almost any type of drug formulation. Along with that, the relatively low cost and easy acquisition are factors that place the CDs as continuously interesting drug delivery systems. Therefore, CDs continue to have different applications in different areas such as food and pharmaceutical industries.

All these promising characteristics of CDs have motivated the researchers to find a way to improve the effects of drugs with analgesic activity, which may also reduce the side effects and improve the pharmacological efficacy. Our systematic review found different clinical and preclinical studies that tested some drugs, with analgesic effect, complexed in different types of CDs. Therefore, it was possible to demonstrate that the use of these drug delivery systems was able to improve the pharmacological effects of drugs, provide a more rapid onset of action and increase the duration of activity in humans.

The preclinical studies demonstrated that the CD complexions were capable of producing analgesic profile in several animal models of nociception, having better effects than the drugs alone (non-complexed drug). The clinical studies showed that the CD complexation was able to increase the analgesic activity of compounds widely used nowadays, such as PX and DF.

Consequently, the use of new formulations with CDs is an important tool in the search for greater analgesic effect, and it may also be a way to reduce the therapeutic doses, increasing the potential of the drug. On the other hand, it is necessary to investigate possible interactions between these agents and other formulations, once the interaction can adversely affect the performance of both.

In summary, the use of CDs makes it possible to construct different pharmaceutical formulations, like capsules and gels, and optimize the chemical configuration of some drug molecules that can improve the pharmacokinetics and dynamic profiles, which can result in a better toxicity and side effect profiles. In this context, it is expected that the CDs can solve many problems associated with the delivery of different novel drugs through different delivery routes that may improve the prognosis of certain diseases, particularly those with severe pain as a symptom, like cancer, fibromyalgia, arthritis and neuropathy, offering a better quality of life to patients, caregivers and family members.

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Declaration of interest

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Affiliation

Renan G Brito[1,2], Adriano AS Araújo[3], Jullyana SS Quintans[1], Kathleen A Sluka[2] & Lucindo J Quintans-Júnior[†1,2]

[†]Author for correspondence

[1]Federal University of Sergipe, Department of Physiology, São Cristóvão, Sergipe, Brazil
Fax: +55 79 2105 6640;
E-mail: lucindojr@gmail.com; lucindo@pq.cnpq.br

[2]University of Iowa, Carver College of Medicine, Physical Therapy and Rehabilitation Science, Iowa City, IA, USA

[3]Federal University of Sergipe, Department of Pharmacy, São Cristóvão, Sergipe, Brazil