J Oral Med Oral Surg 2019;25:23
https://doi.org/10.1051/mbcb/2019008

https://www.jomos.org

JOMOS
Journal of Oral Medicine and Oral Surgery

Literature Review

Topic delivery of analgesics in oral surgery

Gildas Réthoré[1,2,3,*], Saïd Kimakhe[1,2], Alexandra Cloitre[1,2,3], Pierre Weiss[1,2,3], Philippe Lesclous[1,2,3]

[1] CHU Nantes, PHU4 OTONN, 44042 Nantes, France
[2] Université de Nantes, UMR 1229, UFR Odontologie, 44042 Nantes, France
[3] Inserm, U1229, RMeS "Regenerative Medicine and Skeleton", 44042 Nantes, France

(Received: 26 June 2018, accepted: 23 February 2019)

Keywords: analgesics / topical route / oral surgery

Abstract – Introduction: Following any oral surgery procedure, postoperative pain is an inevitable outcome and can be described as moderate to severe. The pain management is essential for the comfort and the well-being of the patients. Topical delivery and more specifically transmucosal delivery systems seem to be of great value for the development of new pain management strategies. **Method:** A systematic literature review was performed using PubMedCentral database. Only PubMedCentral indexed publications were selected and included if they described i) a human clinical study with pharmacokinetic and/or pain relief assessment a biomaterial for topic delivery, ii) the delivery of analgesics or NSAIDs for analgesic purpose and iii) a biomaterial for topic delivery. **Results:** Ten articles were selected among which 4 pharmacokinetic studies and 8 studies describing pain relief. Six of the selected articles were well defined with a good scientific level of evidence (level 2) and 4 of them with a low level of evidence. **Discussion:** The clinical investigations demonstrated a good analgesia, a rapid pain relief with a decrease of the administered doses compared to the oral administration. Moreover, these topic analgesics were well tolerated by the patients. Number of devices was developed for the topical delivery after oral surgery procedures. Excepting a gelatin sponge and a hydro alcoholic gel, most of the devices were made of cellulose and its derivatives. Authors reported that the materials showed a good maintenance at the site of application and the release of the analgesic was well controlled over the time. **Conclusion:** However, well conducted large clinical trials are still missing in order to validate the absence of side effects.

1 Introduction

According to the International Association for the Study of Pain (IASP), the pain can be described as "an unpleasant sensory or emotional experience associated with actual or potential tissue damage, or described in terms of such damage" [1,2]. The pain control, notably the postoperative pain control, is essential in the management of the patient. Indeed, postoperative pain is an unavoidable outcome of any surgical procedure and pain related to oral surgery is one of the most studied. Based on the predictability of the postoperative pain, a preventive treatment is recommended by several agencies including the French Health Agency: (HAS) [1].

In 2005, this agency published guidelines for the prevention and treatment of the postoperative pain management after oral surgery. This pain is described as "moderate to severe with a maximum of pain reached after 2 to 6 h post surgery followed by a slow relief ending after 6 to 10 days" (Fig. 1) [3]. Throughout this report, the expert panel stated that the prevention of the pain should encompass the predictive parameters of its appearance and intensity. These parameters include the difficulty of the surgery, the operating capacity of the surgeon (practice) and factors linked to the patient (age, cleanness, tobacco, anxiety, depression).

In addition, the world health organization (WHO) published a 3 steps ladder for analgesic prescription based on the pain intensity (Fig. 2) [4,5]. Moreover, for pharmacological reasons, the efficacy of the analgesics may vary depending on the analgesic used and from a patient to another. For these reasons, 2 types of prescription can be used: analgesia at constant interval or analgesia on demand of constant doses.

In pain relief treatment, it is well known that anticipated analgesia (avoiding the pain establishment) is more effective that curing. Consequently, after surgery, analgesics will be prescribed on a regular basis for 2 days (*e.g.* 1 g of paracetamol every 4 to 6 h), and then on demand if the symptoms remain. Several analgesic molecules can be found in the therapeutic

* Correspondence: gildas.rethore@univ-nantes.fr

panel for the treatment of post surgery pain. They can be classified in 3 steps based on their efficacy (I, II and III) or according to their family (analgesics, NSAIDs (nonsteroidal anti-inflammatory drugs), opioids).

According to the WHO, for the lower pain (visual analog scale (VAS) 0 to 4), step I analgesics should be used, and without notice, paracetamol will be prescribed to the adult at the posology of 1 g every 6 h for 3 days. Once the VAS increases above 4 (4 to 7), step II molecules should be used. Two possibilities can be chosen. In the first one, weak opioids (codeine, tramadol) are prescribed alone or combined with paracetamol. The second possibility consists in the prescription of NSAIDs alone or combined with paracetamol. Finally, in the context of high pain scores (VAS $>$ 7), opioids alone or in combination with other analgesics are recommended (Tab. 1).

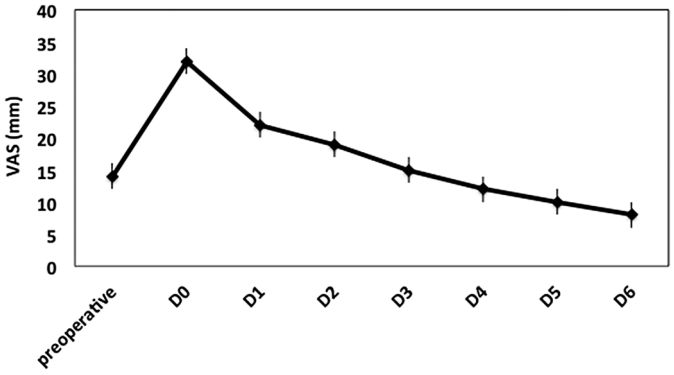

Fig. 1. Pain intensity profile over a 7 days period of time [3]. VAS: Visual Analog Scale; D: Day.

The management of the postoperative pain is mainly performed by the prescription of analgesics *per os* (rarely *via* intra venous administration). Even if this delivery route is very convenient (easy administration, low costs) and effective, it suffers from several drawbacks linked to the administration route, to the molecule used or to the patient's compliance (Tab. 1) [6,7].

Once the analgesic is delivered by oral route, it has to overcome limiting parameters such as i) the hepatic first pass effect with degradation and removal of the drug leading to a low plasmatic concentration, ii) systemic effect and iii) the compliance of the patient. On the top of these problems, some side effects linked to the molecule used have been reported such as i) peptic ulcer, ii) gastrointestinal toxicity, iii) hepatic toxicity and iv) nausea.

One approach to overcome these therapeutic limitations is to maximize drug delivery levels at the site of action and minimize systemic exposure by administrating the drug directly at the site of injury. Topical application of analgesics at very low dose (subtherapeutic) has been demonstrated to provide analgesia compared to placebo and systemic administration of the same dose [7–9]. For these reasons, topical delivery and more specifically transmucosal delivery systems seem to be of great value for the development of new pain management strategies.

This review firstly proposes to investigate the analgesic efficiency of the topical delivery systems used for transmucosal delivery in oral surgery postoperative pain management. Secondly, throughout this manuscript, we will describe the influence of the material device used to develop delivery systems. These effects will include the properties (adhesion, release, degradability) and the pharmacokinetic of delivered analgesics.

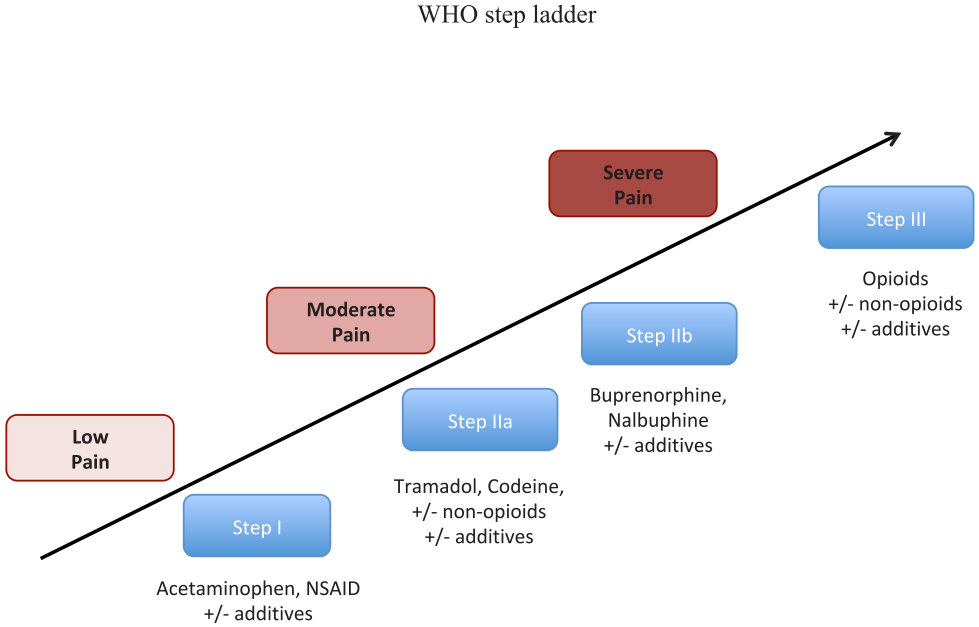

Fig. 2. Steps ladder for analgesic prescription according to the world health organization [4]. NSAID: Non-Steroidal Anti-Inflammatory Drugs.

Table 1. Analgesics prescribed in oral surgery according to the pain intensity, their side effects and their contraindications. NSAID: Non-Steroidal Anti-Inflammatory Drug; MAOI: Monoamine Oxidase Inhibitor.

Pain	Step	Treatment	Posology	Side effects	Contraindications
Low		Paracetamol	1 g/6h (max 4 g/j)	Rare allergies	Liver failure
Moderate to severe	I	NSAID	Analgesic posology, < 72 h	Hemorrhage, digestive troubles, allergies	Asthma and allergies history Pregnancy ($<$ 6th month) Hemorrhage Evolving ulcer
	IIa	Tramadol	50–100 mg/6h	Nausea, vertigo, vigilance disorder	Hypersensibility MAOI Lung failure Liver failure Children below 3 years old Breast feeding (long time medication) Pregnancy (caution)
		Paracetamol/Codeine	60 mg pour 1 g de paracetamol/6h	Constipation, drowsiness, alertness disorders	Same as paracetamol Respiratory failure Children below 12 Breast feeding
		Paracetamol/Tramadol	325/37.5 mg 1–2 pills/6h	Same as drugs alone	Same as drugs alone
	IIb	Buprenorphine	0.8–4 mg/j	Nausea, vomiting, head ache, insomnia	Liver failure Respiratory failure Alcohol consumption Children below 15
		Nalbuphine	0.25 mg/kg/4h	Drowsiness, nausea, vomiting	Abdominal pain Baby below 18 months
Resilient	III	SNAID + Paracetamol SNAID + Paracetamol/Codeine SNAID + Paracetamol/Tramadol SNAID + Codeine	Same posology as drugs alone	Same as drugs alone	Same as drugs alone
		Opioids	Non recommended without analgesic association	Constipation, nausea, metabolic and attention disorders	Kidney failure Lung failure Intracranial hypertension
Co-analgesics	Antidepressant	Amitriptyline	75 mg/j	Drowsiness Orthostatic hypotension Sexual impotence	Myocardial infarction MAOI
	Myorelaxant	Thiocolchicoside	4 mg twice a day	Diarrhea Allergy	Pregnancy Breast feeding
	Antispasmodic	Phloroglucinol/ Triméthylphloroglucinol	2 pills (62/80 mg) 3 times/j	Allergy	Phenylketonuria Breast feeding Pregnancy (caution)

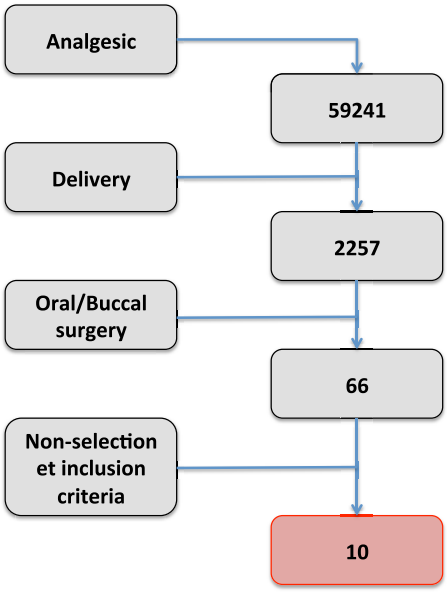

Fig. 3. Flow chart of the systematic literature review.

2 Method

2.1 Literature search

A systematic literature review was performed using PubMedCentral database into two steps. The first step was oriented towards classification using the following keywords: topic, delivery, controlled release, analgesic, oral surgery, transmucosal and mucoadhesive. The second step was performed manually to detect the missed articles in the step 1 (Fig. 3).

2.2 Article selection

PubMedCentral indexed publications were selected and included if they described i) a human clinical study with pharmacokinetic and/or pain relief assessment, ii) the delivery of analgesics or NSAIDs for analgesic purpose and iii) a biomaterial for topic delivery.

On the contrary, they were not included if they were related to i) only an *in vitro* study (no human clinical study), ii) the treatment of pain related to cancer, iii) the delivery of a non analgesic molecule, iv) an extra oral delivery and v) an analgesic therapy for veterinary purpose.

The authors independently extracted data and assessed study quality. The objective was to characterize the analgesia efficacy after transmucosal topical delivery. Following parameters were selected and systematically analyzed: the population studied, the sampling, the analgesia, the pharmacokinetics and the *in vitro* properties.

According to the HAS, the level of evidence aims to characterize the ability of a study to answer the scientific question of the paper (Tab. 2). This classification was important for the analysis and the discussion of the results from the selected articles.

Table 2. Recommendation grades and scientific level of evidence according to the HAS [1].

Recommendations grade	Scientific level of proof from literature
A Well established proof	Level 1 High power randomized comparative trials; Meta-analysis of randomized comparative trials; Analysis of well conducted studies.
B Scientific presumption	Level 2 Low power randomized comparative trials; Not randomized well conducted comparative studies; Cohort studies.
C	Level 3 Case-control studies.
Low scientific proof	Level 4 Comparative trials with number of bias; Retrospective studies; Case series; Descriptive epidemiological studies (transversal, longitudinal).

3 Results

3.1 Bibliometric analysis

The results of the systematic literature review are summarized in Tables 3 and 4 with 10 selected articles. First of all, a systematic search using key words was performed as describe in Figure 3. The entire review has been realized through a clinical trial filter. The first key word used was "Analgesic" reaching to 59 241 articles. Then this result was filtered with a second key word "Delivery" reaching to 2257 articles, and then a third one was used (oral/buccal surgery) to get 66 articles as a result. Ultimately, inclusion (biomaterial for topic delivery, delivery of analgesics or NSAIDs for analgesic purpose and human clinical study with pharmacokinetic and/or pain relief assessment) and non selection (no human clinical study, the treatment of pain related to cancer, the delivery of a non analgesic molecule, an extra oral delivery and an analgesic therapy for veterinary purpose) criteria were applied and led to 10 articles. The manual search realized in a second step, resulted in no additional articles. Finally, the non-selection and inclusion criteria (described above) were applied to get the final

Table 3. Selected article analysis.

Article	Clearly defined objectives	Methodology						Results linked to the objectives	Clinic		Level of proof
		Comparative study	Prospective study	Randomized study	Crossed study	Double blinded study	Adapted statistical analysis		Pharmacokinetic study	Pain relief study	
U.J. Moore *et al.* [14]	X	X	X	X	X		X	X		X	2
U.J. Moore *et al.* [13]	X	X	X	X	X		X	X		X	2
R.A. Dionne *et al.* [10]	X	X	X	X		X	X	X	X	X	2
L. Perioli *et al.* [15]	X							X	X		4
I.A. Alsarra *et al.* [16]	X	X	X	X		X	X	X		X	4
N. Vasisht *et al.* [11]	X	X	X	X			X	X	X		4
K. Al Hezaimi *et al.* [6]	X	X	X	X		X	X	X		X	4
S. Movassaghian *et al.* [17]	X	X	X	X		X	X	X		X	2
G. Pickering *et al.* [12]	X	X	X	X	X	X	X	X	X	X	2
S.R. Rajeswari *et al.* [7]	X	X	X	X	X	X	X	X		X	2

Table 4. Main information of the selected articles.

Year	Authors	Delivery biomaterial	Analgesic	Characterizations	Clinical population	Pharmacokinetic clinical trial	Pain relief clinical trial	Feeling of the patients
1992	U.J. Moore *et al.* [14]	Methyl cellulose gels	Aspirin Paracetamol	/	2 × 12 patients (Control: aspirin/oral paracetamol)	/	Pain decrease at the early time Decrease of the administered dose Rapid efficiency	/
1994	U.J. Moore *et al.* [13]	Methyl cellulose gels	Morphine	/	12 patients (Control: oral morphine)	/	No effect	/
2004	R.A. Dionne *et al.* [10]	Gelatin particles and sponges	Flurbiprofene	/	107 patients (Control: oral flurbiprofene)	50% decrease of the plasmatic concentration	Pain decrease	Good tolerability

Table 4. (continued).

Year	Authors	Delivery biomaterial	Analgesic	Characterizations	Clinical population	Pharmacokinetic clinical trial	Pain relief clinical trial	Feeling of the patients
2007	L. Perioli *et al.* [15]	Bilayer cellulose/ polyacrylic + cellulose/ hydrotalcite	Flurbiprofene	Rapid swallowing Good adhesion Good maintenance on the site Slow and sustained release, faster *in vivo* compared to *in vitro*	5 (Control: /)	/	/	/
2007	I.A. Alsarra *et al.* [16]	HPMC/Carbopo 934 Films	Ketorolac	/	Rat Mouse Human: 68 patients (Control: placebo)	/	Decrease of the edema//Pain decrease	/
2009	N. Vasisht *et al.* [11]	BEMA® (BioErodible MucoAdhesive) FBSF (Fentanyl Buccal Soluble Film)	Fentanyl	/	12 patients (Control: oral transmucosal fentanyl citrate)	Maximum and cumulated concentration and absorption time higher with the film compared to the pill controls	/	/
2010	K. Al Hezaimi *et al.* [6]	HPMC/polyacrylic acid gels	Ketorolac	/	68 patients (Control: placebo)	/	Pain decrease	/
2011	S. Movassaghian *et al.* [17]	HPMC et CMC tablets	Amitriptyline	The release and the mucoadhesion increase when the viscosity decreases	25 patients (Control: placebo)	/	Pain decrease compared to the placebo	/
2014	G. Pickering *et al.* [12]	Hydroalcoholic gels	Paracetamol	/	20 patients (Control: paracetamol IV et S)	Decrease of the paracetamol concentration in blood	Increase of the analgesia Faster analgesia	Satisfaction of the patients Slight bitter taste
2015	S.R. Rajeswari *et al.* [7]	HPMC films	Meloxicam	/	60 patients (Control: /)	/	Pain decrease Rapid efficiency	Good comfort Only 1 administration Satisfaction of the patients Slight bitter taste

10 selected articles among which 4 pharmacokinetic studies and 8 studies describing pain relief. Six of the selected articles were well defined with a good scientific level of evidence (level 2) and 4 of them with a low level of evidence (Tab. 3).

3.2 Literature analysis

Throughout the selected literature, few materials were developed for the topical delivery of few analgesic after oral surgery procedures. Most of the materials used to prepare the delivery device were cellulose-based polymers. However, couple of other materials were used.

In 2004, Dionne *et al.* developed a strategy to optimize the concentration of flurbiprofen at the site of interest [10]. Toward that goal, they prepared gelatin-based capsules loaded with flurbiprofen. These loaded capsules were then embedded within a gelatin sponge and placed into tooth socket after third mandibular molar surgery. They evaluated the applicability of their strategy by studying the clinical efficacy and the pharmacokinetics of their material within a double-blinded clinical study including 107 patients over a 6 h postoperative period of time. This clinical trial revealed a higher and faster analgesia associated with a lower plasmatic concentration (50% reduction) of their structures compared to the oral administration (*per os*). Moreover, this new strategy has been revealed to be well tolerated by the patients. Two other studies on materials other than cellulose have been realized. The first one, published by Vasisht *et al.* in 2009, evaluated the pharmacokinetics of a buccoadhesive bilayer material loaded with fentanyl called BEMA® (BioErodible MucoAdhesive) [11]. Unfortunately, no pain relief monitoring has been done. The last study, realized by Pickering *et al.* in 2014, was based on the use of a hydroalcoolic solution of paracetamol and compared to intravenous and sublingual administration [12]. The results demonstrate a higher and faster analgesia compared to the controls. Moreover, the pharmacokinetic investigation demonstrated a lower amount of paracetamol in the blood stream when the analgesic was administered topically.

As mentioned previously, most of the materials used to develop intra oral delivery device was the cellulose and its derivatives (methyl cellulose and carboxymethyl cellulose). However, the leading polymer used was the hydroxypropyl methylcellulose (HPMC). Indeed, three studies have been published using cellulose or methylcellulose and four clinical studies have been published using HPMC-based materials for topical delivery of analgesics. As soon as 1992, Moore *et al.* published 2 studies evaluating the clinical relevance of an analgesic material made of methylcellulose with or without aspirin or paracetamol placed directly into tooth sockets after bilateral third molar surgery [13]. The study was conducted within 12 patients per group and one group per analgesic with pain score evaluation over an 8 h period of time post-surgery using VAS scale. The patients were administered with analgesic into the tooth socket and a placebo *per os* or a placebo into the tooth socket and an analgesic *per os* leading to a good pain relief when aspirin or paracetamol were used. However, in the second study, the authors used morphine and demonstrated no efficacy of their device [14]. In 2005, Perioli *et al.* developed a bilayared cellulose tablet for the delivery of flurbiprofen [15]. Their structure has shown rapid hydration and swelling reaching 80% after 2 h and also great adhesion and maintenance even after 12 h. They have demonstrated a slow and constant release of the encapsulated flurbiprofen with a maximum of release (50%) reached after 12 h. They also demonstrated a good adhesion and maintenance on the site with a faster release of the encapsulated drug *in vivo* compared to *in vitro*.

Concerning HPMC, Alsarra *et al.* were the first to publish in 2007 its use as material to prepare delivery devices for ketorolac release [16]. They performed a clinical trial on 68 patients and demonstrated a pain relief. Then, Al Hezaimi *et al.* and Movassaghian *et al.* published in 2010 and 2011, respectively, clinical trials showing pain relief using ketorolac and amitriptyline respectively compared to a placebo [6,17]. Throughout their investigations, these authors demonstrated that the formulation of their tablets, in term of molecular weight of the polymers and HPMC/CMC ratio, plays a crucial role. Indeed, the increase of the concentration of CMC leads to a decrease of the stiffness and an increase of the fragility. Moreover, a decrease of the molecular weight of the HPMC induce an increase of the adhesivity of the material while favorating the release of the amitriptyline from 60 to 100%. More recently, in 2015, Rajeswari *et al.* described a mucoadhesive patch made of HPMC loaded with meloxicam for pain relief after periodontal surgery [7]. The clinical trial was a prospective double blinded randomized study conducted on a 60 patients population divided in 4 groups (10, 20, 30 and 45 mg of meloxicam). They described a good pain relief and a rapid efficiency. It is worth noted that their patients mentioned a good comfort and that they patients spontaneously asked for the use of this analgesia device for later surgeries.

Throughout these studies, it has been shown that cellulose-based materials presented good adhesion properties with a maintenance at the site for the duration of the investigation. The clinical trials demonstrated a high and rapid analgesia.

4 Discussion

4.1 Pain relief

The selected articles reported a good pain relief associated a rapid efficiency of the analgesic. However, in one study, Moore *et al.* described the delivery of morphine using a methylcellulose gel after mandibular third molar removal. No analgesia has been reported and an escape painkiller has been administered [13]. This failure has been explained because of no peripheral effect of their device. One of the explanations might be the low number of opioid receptors within the oral mucosa and also the lack of activity of these receptors. The lack of efficacy is due to the use of morphine rather than the device itself. Indeed, in a previous article, Moore *et al.* demonstrated the analgesic efficacy of their structure associating a methylcellulose gel with 2 different analgesics (aspirin and paracetamol) [14].

Globally, the clinical evaluations of the topical delivery of analgesics demonstrated the good comfort of the patients using these delivery devices.

4.2 Delivery device

For the design of intra oral delivery device, the material used can be from wide origins with natural (polysaccharides, proteins) and synthetic (polyvinyl alcohol, polyacrylic, alcohol, polyethylene glycol) polymers. However, on a clinical point of view, only a few of them have been evaluated. The main part of polymer used is composed of cellulose and its derivatives (cellulose, methylcellulose, carboxymethyl cellulose (CMC) and hydroxylpropyl methylcellulose HPMC)), which are formulated alone or with a copolymer [6,7,13–17]. The formulations aim at optimizing the encapsulation of the analgesic while controlling its leakage. They also should enhance the bioadhesivity onto the oral mucosa and maintain their integrity for a period of time compatible with the pain profile. Indeed, a large number of enzymes can be found in the oral cavity including aminopeptidases, carboxypeptidases, deshydrogenases and esterases which can degrade the polymer-based devices limiting their life time and therefore the controlled release of the analgesic over a long period of time.

4.3 Mucosa adhesion

Besides the protection, the remaining of the device on the site is a key factor for the success of such a strategy. Consequently, the use of mucoadhesive polymer is essential to maintain an intimate contact between the delivery device and the mucosa. Mucoadhesion is a complex phenomena and a number of theories has been argued such as a mechanical interlocking, diffusion/interpenetration, electrostatic interactions and adsorption [18]. Nowadays, the most studied theory is the formation of hydrogen bindings between the material and the mucosa [19]. Toward that goal, the materials used are mainly prepared with hydrophilic polymers incorporating functional groups with high potential of hydrogen bonds. The functional groups capable of such bindings can be hydroxyl, carboxyl and amine groups. These functions are found in a large amount within the synthetic polymer family and even more in polysaccharides such as cellulose (CMC, HPMC). This last one has demonstrated a great property of hydration in humid media and the possibility of making hydrogel structures, which can interact with the superficial layer of the mucosa creating a hydrogen bond network leading to the adhesion of the material onto the mucosa.

4.4 Drug release

Once administered, the device should allow the sustained release of the entrapped drug. Even if numerous *in vitro* studies, about the controlled released of drug from biomaterials, have been published, only 2 have been selected about the *in vivo* release of analgesics. Perioli *et al.* studied the properties of bilayer tablets [15]. They demonstrated a rapid swallowing, however, the behavior of their structure seemed to act differently once applied *in vivo*. Indeed, the constitution of the saliva combined with the friction forces leads to an increase of the erosion. These phenomenon lead to a constant release over the time and to an increase of the maximum rate of release of the encapsulated molecule enabling a sustainability local concentration. In addition, Movassaghian *et al.* demonstrated that the increase of the concentration of CMC leads to a decrease of the stiffness and an increase of the fragility and a decrease of the molecular weight of the HPMC induces an increase of the adhesivity of the material while favorating the drug release [17]. These properties could be explained by an increase of the hydrophilie leading to a better swelling of the material and to a higher diffusion within the scaffold. This last property is essential regarding the wettability and consequently to the adhesion onto the mucosa and on the release profile of the loaded drug.

In addition, it is worth noted that few authors such as Perioli *et al.* developed bilayered structures in order to promote the mucosa adsorption and to prevent the release of the analgesic into the oral cavity [15].

4.5 Drug delivery and diffusion

Despite the difficulties (saliva, mechanical stress, pH, enzymes), the oral mucosa is an administration route of great interest. Because of the high vascularization, the molecule diffusing through the mucosa have a direct systemic action avoiding the hepatic first pass effect which strongly reduce the bioavailability of the drug administered orally [9]. Number of authors have been studied the mucosa permeability and stated that oral mucosa presents a permeability 4 to 4000 times higher compared to the skin [20]. The molecules can be transported through the epithelial *via* passive diffusion, active transportation and specialized systems. The published studies stated that the main route for transportation is the passive diffusion of molecules through transcellular and paracellular routes [21–23]. The hydrophilic properties of the paracellular route seams to act as a barrier for hydrophobic molecules but is the main route for hydrophilic molecules. On the contrary, the transcellular route requires the crossing of cellular membrane (lipid bilayer membrane) and consequently represents a favorable route for hydrophobic drugs. Indeed, according to their amphiphilic properties, the molecules are able to use both routes simultaneously. From these findings, it is clearly stated that the pharmacokinetics of the analgesic encapsulated delivery devices should be monitored. Only 3 studies evaluating the pharmacokinetics properties have been selected. Usually, the doses of analgesics administered by locally are lower than the doses of analgesics *per os* [10–12]. Therefore, it is difficult to compare the plasmatic concentrations. Nevertheless, it seems clear that the analgesic absorption time is faster when used in local delivery compared to *per os* administration. On the contrary, Vasisht *et al.* published a pharmacokinetic study measuring the maximum concentration, the cumulated concentration and the absorption time of fentanyl delivered by buccal soluble film [11]. They have demonstrated that, at the same dose; the plasmatic concentration of fentanyl is

higher when a buccal film is used. Moreover, the absorption time decreases demonstrating a faster systemic diffusion of the fentanyl.

4.6 Limits and bias

Throughout this review, it has been revealed that the use of local delivery device for the administration of topic analgesia represents a great future in postoperative pain management. However, a number of limits has been noticed. It suffers from the lack of well conducted clinical trials. Indeed, the size of the studied population is too small to reach a good representativity. Moreover, the authors usually used placebo as control instead of the commonly used treatment (paracetamol *per os*).

Consequently, it would be of great interest to set up a well set, large clinical trial to increase the power of the study and using well defined parameters such as the analgesic control.

5 Conclusion

Throughout these data, the clinical interest is clear for the local delivery of analgesic for the pain management in oral surgery. This systematic literature review led to a selection of 10 original articles of which 8 of them about a clinical trial of pain management after oral surgery. Seven of them led to the conclusion that their delivery devices allow a significant pain relief. Moreover, the authors mentioned that their device provide a rapid pain relief with great efficacy at the early time. Only one article mentions a failure of this strategy.

Finally, 3 studies reported the acceptance and the well-being of the patients using this strategy [7,10,12]. Even if a bitter taste has been mentioned, the patients are satisfied of the analgesia of the device but also of the comfort and the absence of repeated drug taking. Rajeswari *et al.* even reported that the patients, who went under topical analgesia after surgery, requested spontaneously the same analgesia during the following procedures [7].

The results demonstrated a good analgesia of these structures with a decrease of the administered doses compared to the oral administration. Moreover, these topic analgesics are well tolerated by the patient. However, well conducted large clinical trials are still missing in order to validate the absence of side effects. A development phase will also be necessary to decrease the cost of such a strategy in order to make it applicable in oral surgery daily practice.

Conflict of interest

The authors declare that they have no conflicts of interest in relation to this article.

References

1. Haute Autorité de Santé. Prévention et traitement de la douleur postopératoire en chirurgie buccale. Recommandations pour la pratique clinique. 2005. Available from has-sante.fr.
2. Merksey HNB. Pain terms: A current list with definitions and notes on usage. In: Merksey HNB, Ed. IASP Task Force on Taxonomy, Seattle: IASP Press, 1994.
3. Siano H, Jolly D, Rinkenbach R, Furon V, Lefèvre B. Étude de la douleur post-opératoire en chirurgie buccale. 1e partie : observation de différents profils de douleurs post-opératoires. MBCB 2001;7(1):9–19.
4. Reid C, Davies A. The World Health Organization three-step analgesic ladder comes of age. Palliat Med 2004;18(3):175–6.
5. Reidenberg MM. Pain control and the world health organization analgesic ladder. JAMA 1996;275(11):835.
6. Rajeswari SR, Gowda TM, Kumar TAB, Thimmasetty J, Mehta DS. An appraisal of innovative meloxicam mucoadhesive films for periodontal postsurgical pain control: A double-blinded, randomized clinical trial of effectiveness. Contemp Clin Dent 2015;6 (3):299–304.
7. Al-Hezaimi K, Al-Askar M, Selamhe Z, Fu JH, Alsarra IA, Wang HL. Evaluation of novel adhesive film containing ketorolac for post-surgery pain control: A safety and efficacy study. J Periodontol 2010;82(7):963–8.
8. Boaz M, Abraham JD. Mucoadhesive polymers for delivery of drugs to the oral cavity. Recent Pat Drug Deliv Formul 2008;2(2): 108–19.
9. Patel VF, Liu F, Brown MB. Advances in oral transmucosal drug delivery. J Control Release 2011;153(2):106–16.
10. Dionne RA, Haynes D, Brahim JS, Rowan JS, Guivarc'h PH. Analgesic effect of sustained-release flurbiprofen administered at the site of tissue injury in the oral surgery model. J Clin Pharmacol 2004;44(12):1418–24.
11. Vasisht N, Gever LN, Tagarro I, Finn AL. Formulation selection and pharmacokinetic comparison of fentanyl buccal soluble film with oral transmucosal fentanyl citrate. Clin Drug Investig 2009;29 (10):647–54.
12. Pickering G, Macian N, Libert F, Cardot JM, Coissard S, Perovitch P, *et al.* Buccal acetaminophen provides fast analgesia: Two randomized clinical trials in healthy volunteers. Drug Des Dev Ther 2014;8:1621–7.
13. Moore UJ, Seymour RA, Gilroy J, Rawlins MD. The efficacy of locally applied morphine in post-operative pain after bilateral third molar surgery. Br J Clin Pharmacol 1994;37(3):227–30.
14. Moore UJ, Seymour RA, Rawlins MD. The efficacy of locally applied aspirin and acetaminophen in postoperative pain after third molar surgery. Clin Pharmacol Ther 1992;52(3):292–6.
15. Perioli L, Ambrogi V, Giovagnoli S, Ricci M, Blasi P, Rossi C. Mucoadhesive bilayered tablets for buccal sustained release of flurbiprofen. AAPS Pharm Sci Tech 2007;8(3):E20–7.
16. Alsarra IA, Alanazi FK, Mahrous GM, Abdel Rahman AA, Al Hezaimi KA. Clinical evaluation of novel buccoadhesive film containing ketorolac in dental and post-oral surgery pain management. Pharmazie 2007;62(10):773–8.
17. Movassaghian S, Barzegar-Jalali M, Alaeddini M, Hamedyazdan S, Afzalifar R, Zakeri-Milani P, *et al.* Development of amitriptyline buccoadhesive tablets for management of pain in dental procedures. Drug Dev Ind Pharm 2011;37(7):849–54.
18. Andrews GP, Laverty TP, Jones DS. Mucoadhesive polymeric platforms for controlled drug delivery. Eur J Pharm Biopharm 2009;71(3):505–18.

19. Lee JW, Park JH, Robinson JR. Bioadhesive – Based dosage forms: The next generation. J Pharm Sci 2000;89(7): 850–66.
20. Galey WR, Lonsdale HK, Nacht S. The in vitro permeability of skin and buccal mucosa to selected drugs and tritiated water. J Invest Dermatol 1976;67(6):713–7.
21. Nielsen HM, Rassing MR. Nicotine permeability across the buccal TR146 cell culture model and porcine buccal mucosa in vitro: Effect of pH and concentration. Eur J Pharm Sci 2002;16(3): 151–7.
22. Xiang J, Fang X, Li X. Transbuccal delivery of 2′, 3′-dideoxycytidine: In vitro permeation study and histological investigation. Int J Pharm 2002;231(1):57–66.
23. Deneer VHM, Drese GB, Roemelé PEH, Verhoef JC, Lie-A-Huen L, Kingma JH, *et al*. Buccal transport of flecainide and sotalol: Effect of a bile salt and ionization state. Int J Pharm 2002;241(1):127–34.