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Advanced formulations for improving therapies with anti-inflammatory or anaesthetic drugs: A review

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ABSTRACT

The development of new more effective therapeutic treatments for pain relief is essential for enhancing the patient quality of life and safety and avoiding or limiting risks of abuse, addiction or serious injuries posed by some of the present pain therapies. With this aim, in the last years, several advanced delivery systems have been developed to increase bioavailability, therapeutic efficacy and safety of well known analgesics, overcoming limits and drawbacks of traditional formulations. Among the different kinds of drugs used in the treatment of pain, non-opioid drugs such as local anaesthetics, corticosteroids and non steroidal anti-inflammatory drugs are preferred in the treatment of mild or moderate pain. However, each of these classes is associated with different adverse events and inconveniences, most of which could be reduced or overcome by appropriate drug carrier systems. This review is focused on recent drug delivery strategies based on micro- and nano-technologies developed for improving the effectiveness in pain management through non-opioid agents, exploiting different approaches such as: cyclodextrin complexation, solid dispersions with hydrophilic polymers, mechano-chemically activated systems, micro and nanoparticles, micro and nano-emulsions, vesicular systems. Combined approaches, simultaneously exploiting the relative advantages of such systems in a single drug delivery device, were also reviewed.

1. Introduction

Pain is a persistent and widely diffuse medical problem, both in hospitals and society in general, and relief from pain is an important therapeutic goal. Pain limits the functional status of patients, adversely impacts their quality of life, and hinders their ability to work.

The treatment of pain is still a challenge, despite the considerable efforts involved in this regard from both the scientific and economic points of view, and it is essential that the techniques and therapies utilized to treat pain continue to improve. The development of new more effective therapeutic treatments would be important for enhancing the quality of life and safety of the patients and avoiding or limiting the risks of abuse, addiction or serious injuries posed by some of the present pain therapies [1]. Moreover, inefficient treatments of pain have serious negative consequences from the economic face, and the disability by pain represents a great cost for the society [2]. Therefore, effective treatments to lessen pain symptoms with minimal side effects should allow for relieving the burden of such problem on the society's resources, in terms of both direct and indirect costs [3].

The search for enhancing the effectiveness of pain management is presently directed not only to the development of new chemical entities, but especially to the possible improvement of the therapeutic efficacy of well known and safe analgesics through the development of advanced delivery systems. It is known that conventional dosage forms present a series of drawbacks such as, in particular, the short duration of action, with the consequent need for repeated administrations and frequent appearance of undesired side-effects dose-related, the incomplete and/or variable bioavailability, with consequent unsatisfactory pain management.

The great technological progresses achieved in the drug delivery field claim for several benefits such as improved drug dissolution and/or absorption properties, improved stability, reduction of drug dosage and side-effects dose-related, controlled or prolonged release with reduced frequency of dosing and consequent improved patient compliance, reduced occurrence of breakthrough pain, possibility of site specific delivery, possible reduction of systemic toxicity in case of topical treatments, and so on. All these

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benefits should allow for overcoming the limits and inconvenient of traditional formulations, and give rise to enhanced drug therapeutic effectiveness and safety in use, as a consequence of the improved bioavailability and increased therapeutic index. Moreover, the more favourable and safer conditions in their use could make opening of new therapeutic applications of known drugs possible.

Drugs used in the treatment of pain are generally classified as non-opioid and opioid agents: the first ones are preferred in the treatment of mild or moderate pain, while the use of opioid drugs is necessary and vital in more severe cases.

The actual advantages achievable by the use of advanced drug delivery systems for improving the therapeutic effectiveness and reduce side effects of opioid drugs have been well illustrated [4].

As for non-opioid agents, glucocorticoids and non-steroidal anti-inflammatory drugs are the most commonly prescribed drug categories for the treatment of pain associated with inflammation. Although glucocorticoids can be highly effective in treating inflammation, their systemic application is limited due to the high incidence of serious adverse effects, particularly in long-term treatment. On the other hand, non-steroidal anti-inflammatory drugs are a heterogeneous group of compounds and most of them have unfavourable pharmacokinetic and pharmacodynamic properties, and their usefulness is often limited by dose-dependent adverse events such as gastrointestinal disturbances, cardiovascular events, and renal toxicity.

Anaesthetic drugs are another fundamental class of non-opioid agents widely used for pain control in many areas of clinical practice, including general surgery and post-operative treatments, ophthalmology and dentistry, and also in management of acute, chronic, and cancer pain. Local anaesthetics are able to induce pain relief by causing physicochemical disturbance of the neuron myelin sheath and thus inhibiting the opening and closing of sodium ion channels in neural membranes. Local anaesthesia is preferred, when possible, to general anaesthesia for different reasons, including wider safety margin, greater ease of use, good patient's compliance. A frequent drawback presented by several local anaesthetics is their poor aqueous solubility, which often limits their parenteral administration. Another diffused inconvenient is represented by the short duration of the anaesthetic effect, compared with the potential duration of pain. Moreover, the consequent need for repeated administrations, to prolong the analgesic effect, clearly improves the risks of systemic toxicity [5].

Therefore, it is particularly important to develop new effective drug delivery systems (DDS) able to overcome the above drawbacks of both anti-inflammatory and anaesthetic drugs, make their use safer and enhance their therapeutic efficacy in pain management.

This review is focused on recent drug delivery strategies based on micro- and nano-technologies developed for improving the effectiveness in pain management by the use of non-opioid agents, namely local anaesthetic, corticosteroids, non steroidal anti-inflammatory drugs (NSAIDS), by exploiting different possible approaches, whose selection is depending on both the physicochemical properties of drug to be carried out and the specific goal to be reached. The main technological approaches based on micro- and nano-technologies include:

- Cyclodextrin (CD) complexation
- Solid dispersions with hydrophilic polymers
- Mechano-chemically activated systems
- Vesicular systems
  - Liposomes
  - Niosomes
  - Micelles
- Micro and nanoparticles:
  - Nanoparticles based on synthetic or natural polymers
  - Solid lipid nanoparticles (SLN)
  - Nanostructured lipid carriers (NLC)
- Micro and nanoemulsions
- Combined approaches
  - Drug in CD in vesicular systems
  - Drug in CD in micro or nanoparticles
  - Drug-in CD-in micro or nanoemulsions

2. Complexation with cyclodextrins

Cyclodextrins (CDs) are cyclic oligosaccharides able to form inclusion complexes with a variety of hydrophobic guest molecules, positively modifying their physicochemical properties [6]. CD complexation is mainly utilized in pharmaceutical field to enhance water solubility and dissolution rate of poorly-soluble drugs, which is the critical factor limiting their absorption rate and bioavailability [7–10]. Furthermore CD molecular encapsulation can also be used to mask unpleasant taste or odour, improve the stability of the included host molecules from hydrolysis or enzymatic degradation in gastric environment, and reduce drug local irritation phenomena.

CD complexation has been successfully exploited to increase the dissolution rate and bioavailability of a series of NSAIDS, including ibuproxam [11], naproxen [12], flurbiprofen [13], oxaprozin [14], flufenamic acid [15], ibuprofen [16], piroxicam [17], ketoprofen [18]. The improved bioavailability obtained by CD complexation would also allow to reduce the dose of drug to be administered, and decrease the appearance of dose-related side-effect. Furthermore, inclusion into the CD cavity of NSAIDS reduces the local concentration of free drug molecule, thus reducing their irritant effects on gastrointestinal mucosa [19].

The use of flufenamic acid as complex with hydroxypropyl-βCD allowed for developing a muco-adhesive buccal film formulation, able to assure an effective sustained drug release useful in the treatment of inflammatory diseases of the oral cavity [15]. Moreover, it has been proved that CD complexation of NSAIDs is also effective in allowing a quicker drug absorption rate, which translates into a faster onset of analgesic activity [17]. Thus CD complexation can offer a safer and more effective alternative to the use of free NSAIDs.

In a similar way, CD complexation has been successfully exploited to increase the dissolution rate and bioavailability of a series of corticosteroids such as betamethasone [20], prednisolone [21], dexamethasone [22,23], hydrocortisone [24]. Moreover, inclusion in CDs enabled to mask the unpalatable taste and after taste of hydrocortisone in pediatric formulations [25]. CDs revealed to be very useful carriers of corticosteroids in eye drop formulations, increasing their water solubility, enhancing the drug absorption into the eye, improving their aqueous stability and reducing effects of local irritation [26,27].

However, due to various reasons (such as their high molecular weight and consequent dosage problems, possible toxicity, relatively high cost), the amount of CDs that can be used in most pharmaceutical formulations is rather limited. Therefore, different strategies have been undertaken to improve their performance and reduce the amount necessary to obtain the desired solubilizing and/or stabilizing effect. Among these, it has been proved that the addition of small amounts of some hydrophilic polymers substances can significantly increase the CD solubilising and complexing abilities through the formation of ternary drug-CD-hydrophilic polymer complexes [28,29]. Addition of basic amino-acids can be useful to increase the CD performance towards NSAIDs of acidic nature as a result of the combined effects of salt formation