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Polymer Based Therapies for the Treatment of Chronic Pain

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1. Introduction

Since chronic pain manifests functional limitation, it is the leading cause of longer term disability [1, 2]. In the US alone, an estimated 75 million people suffer from chronic pain [3]. In addition to chronic pain, proper management of postoperative acute pain impacts the clinical outcome of patients undergoing surgery [4]. Opioid family of analgesics and non-steroidal anti-inflammatory drugs (NSAIDs) are the main stays of current pharmacological agents available for the management of chronic pain [5, 6]. However, current therapies for pain management show modest efficacy and are associated with significant side effects. The major adverse effects of oral NSAIDs are gastrointestinal bleeding, gastric ulcer, renal failure and cardiovascular risks (in particular with selective COX-2 inhibitors) [7, 8]. The side effects of opioid family therapies include constipation, nausea, cognitive impairment and most importantly addiction [9, 10]. Thus, development of safer and effective treatment of chronic pain is an important goal of current pharmaceutical research.

In recent years numerous efforts have been made to develop long-acting opioid analgesics and NSAIDs to modulate their pharmacokinetic profiles. Some of these include sustained release formulations and topical gels [11, 12]. Biological agents such as antibody against nerve growth factor (NGF) have also been evaluated as therapies for chronic pain. The anti-NGF antibody acts by sequestering NGF and thus inhibits its interaction with the NGF-receptor on the sensory neurons [13].

Polymeric approach offers an attractive route to develop novel therapeutic agents for effective management of chronic pain. Interesting physical and chemical characteristics of synthetic and natural polymers enable them as promising materials for biomedical applications such as therapeutic agents, drug delivery carriers, and medical devices [14, 15]. A number of polymer derived therapies have been commercialized in the marketplace [16, 17]. The present article reviews the current state of research and development efforts to discover and develop biomedical polymer as therapeutic agents for the treatment of chronic pain. While use of polymer-derived agents for the treatment of different kinds of pains will be highlighted, the primary focus of the present article pertains to management of pain arising from osteoarthritis. Furthermore, role of polymers as intrinsically pain relieving agents either alone or as chemical conjugates of low molecular weight pain modulating agents are described in this article. The research and development efforts to develop control release formulations of low molecular weight pain therapies are outside the scope of this article. There are in fact a number of interesting articles that describe this aspect of pain management therapies [18, 19].

2. Osteoarthritis pain

Osteoarthritis (OA) is one of the most prevalent musculo-skeletal degenerative diseases [20]. Although OA affects joints of the knee, hip, hand, and spine, knee is the most affected joint [21]. As a result of pain and reduced mobility, OA leads to significant loss of quality of life. Since OA is generally considered to be a result of mechanical “wear and tear” of joints, it typically affects people over the age of 60. However, its onset can be expedited at younger age due to other factors including obesity, genetic factors, and joint injury [22, 23]. Approximately 10% of the world’s adult population over the age of 60 has been affected by OA [24]. Therefore, the economic burden of this disease, which includes healthcare costs and loss of productivity, is significant. These expenditures are likely to escalate with aging population. At present approximately 27 million people in the US suffer from OA and it has been estimated that by the year 2030 25% of the US adult population (a third of which of working age) will be affected by OA [25].

Although OA manifests a broad clinical syndrome, its primary cause has been attributed to the progressive breakdown of articular cartilage and chondrocytes within the synovial joints. This degeneration leads to narrowing of the joint space, subchondral sclerosis, and synovial inflammation. Breakdown of the cartilage results in alternation in joint mechanics, which further exacerbates the disease [26, 27]. In OA, concentrations of a number of mediators of inflammation such as cytokines, chemokines, and proteolytic enzymes like matrix metalloproteinases (MMPs) as well as free radicals are elevated in the synovial fluid that catalyze further degradation of cartilage [28, 29]. This process results in a self-sustaining degenerative circle that hinders the natural process of cartilage repair.

In spite of years of intensive research in tissue engineering, there has been no breakthrough to regenerate physiologically viable articular cartilage [30]. Also, no therapeutic agent has been developed that demonstrates structure modifying efficacy in OA patients [31]. The current therapies for OA are largely symptomatic in alleviating the chronic pain. These agents largely include anti-inflammatory agents, NSAIDs, and opioid family of analgesics. The relative efficacies of these therapies to relieve OA associated chronic pain have been modest at best [32, 33]. As mentioned earlier, long term use of these pharmacological agents results in major side effects (see above). In order to minimize systemic side effects associated with oral NSAIDs, topical agents containing the active agents have been developed. These delivery systems are expected to deliver the drugs in high concentrations locally and would reduce systemic side effects [34]. However, efficacy of these topical therapies is modest. In recent years, other novel therapeutic approaches for the management of OA pain has been pursued that include antibodies targeting NGF and antagonist of Transient Receptor Potential Vanilloid (TRPV) family of ion channels [35, 36]. One of the attractive therapeutic options for treating OA associated pain are polymer based viscosupplements. The following section describes the state of viscosupplement based treatments for OA pain.

3. Hyaluronic acid derived viscosupplements

3.1 Hyaluronic acid and its biology

Hyaluronic acid or hyaluronan (HA) is a polysaccharide that belongs to the glycosaminoglycan class of biological macromolecules. This highly viscous anionic biopolymer is composed of β -1, 3-D-glucuronic acid and β -1, 4-N-acetyl-D-glucosamine

arranged in an alternate fashion along the polymer backbone (Fig. 1). HA is ubiquitous in nature and is produced by every tissue of higher organisms and some bacteria. The biopolymer is found in the extracellular matrices (particularly in soft connective tissues), synovial fluid, and cartilage. HA is endogenously synthesized by chondrocytes and synoviocytes [37-39]. After being released into the synovial space, HA accumulates on the surfaces of cartilage and ligament. Endogenously synthesized HA is generally of very high molecular weight (in the range of 3 -5 million Dalton) and its fully hydrated form assumes a globular shape [40]. Unique viscoelastic properties of HA enables it to maintain rheological homeostasis of the synovial fluid in the joints and plays a critical role in providing lubrication, elasticity, and shock absorption to joint tissues. Furthermore, by providing a coat on the surface of articular cartilage, HA protects the cartilage and blocks the loss of proteoglycan from the cartilage matrix into the synovial space [41]. In healthy joint of human knee, the normal concentration of HA in the synovial fluid is in the range of 2.5 - 4.0 mg/mL. However, under pathological conditions such as osteoarthritis, the concentration of HA is significantly reduced (estimated to be ~ 1 - 2 mg/mL) [42]. Furthermore, the biopolymer undergoes degradation under diseased conditions with substantial reduction in molecular weight. A combination of lowering in concentration and molecular weights leads to lowering in viscosity and elasticity of synovial fluid and consequently adverse impact on joint function. Thus, catabolic degradation of HA directly correlates with the onset OA.

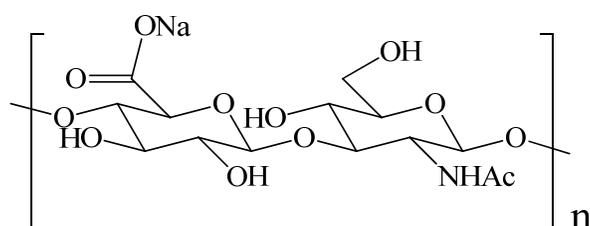


Fig. 1. Chemical structure of hyaluronic acid.

3.2 HA derivatives for the treatment of osteoarthritis

In addition to acting as a lubricant for the joint, HA has been reported to impart anti-inflammatory, anabolic, and chondroprotective effects [43, 44]. Since OA onset is attributed to degradation of high molecular weight HA and its concentration in the synovial fluid, increase in HA concentration either by increasing the rate of the proteoglycan biosynthesis or by incorporating HA exogenously to the joint space would improve joint function and relieve OA associated chronic pain. Therefore, the effect of intraarticular administration of exogenous HA to restore rheological properties of the synovial fluid have been extensively studied [45].

In order to maintain desired viscoelastic property of synovial fluid, the exogenous HA needs to have high molecular weight. It has been observed that the frequency and the amount of exogenous HA injected can be lowered by increasing the molecular weight of HA based exogenous viscosupplement. Towards that end, a variety of synthetic approaches have been undertaken to engineer high molecular weight HA derivatives [46]. In general, the desired rheological properties of HA based viscosupplements are achieved by crosslinking of naturally occurring linear HA to produce higher molecular weight compounds.

Functional group richness of HA has rendered it to be an important precursor material for the design and synthesis of numerous biomaterials with tuned physicochemical and biological properties that have found broad applications in biomedicine and biosurgery [47, 48]. HA offers three kinds of functional groups that can be used for chemical modification: carboxylic acid, primary and secondary hydroxyl, and N-acetyl (after removal of acetyl group to generate primary amine). While carboxyl groups can be modified to introduce amide and ester bonds, the hydroxyl groups can be subjected to reaction with various electrophiles such as epoxides, alkyl halides, alkyl tosylates, vinyl sulfones, etc. However, since HA is unstable at low pH, the chemical reactions employed for its modification must be selected very carefully so that they are mild and compatible to HA. This is necessary to avoid undesired degradation of HA to lower molecular weight. Furthermore, the byproducts of these reactions must be benign for both short- and long-term uses. Over the years, a great deal of research efforts have been put forth to synthesize chemically modified HA [49].

In order to synthesize HA derived viscosupplements, linear HA has been subjected to crosslinking reactions with a number of bifunctional reagents such as diepoxides, divinyl sulfone, epichlorohydrin etc [50, 51]. Some representative examples of crosslinking chemistries that were carried out to prepare HA based hydrogels are shown in Figure 2.

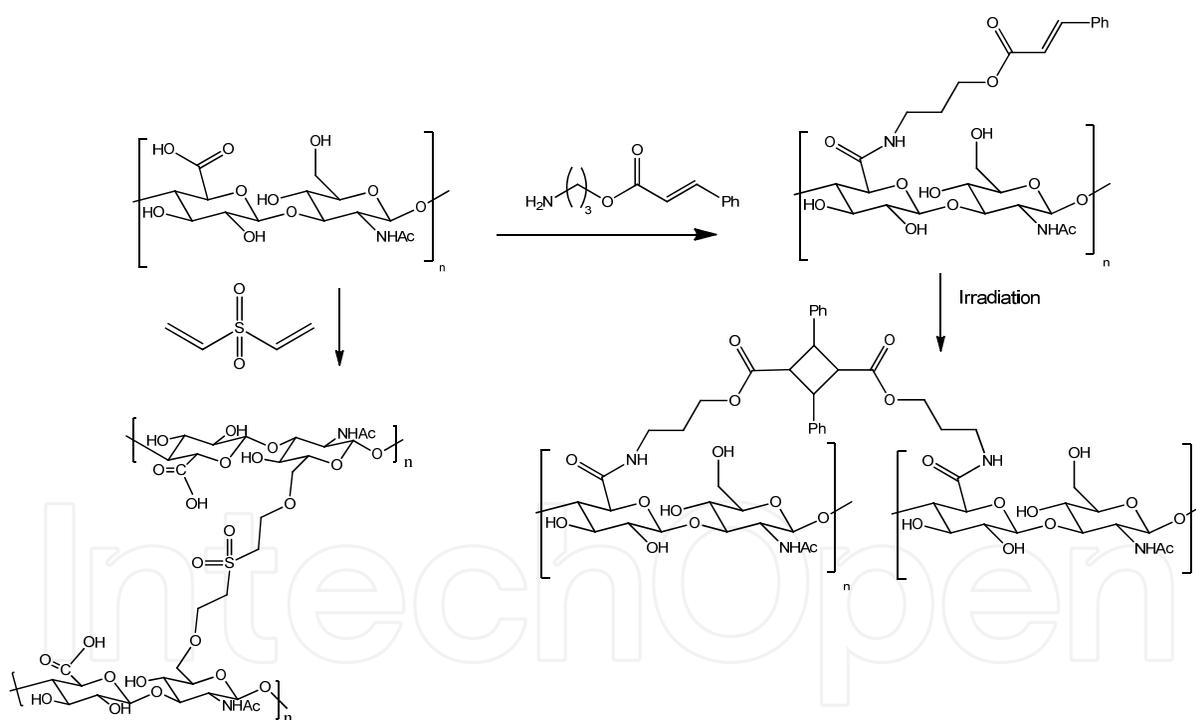


Fig. 2. Representative examples of crosslinking chemistries used to prepare HA hydrogels.

Several factors need to be taken into consideration while optimizing HA derived viscosupplementation products. For example, the rheological properties need to be tuned so that they match with those of native synovial fluid. The hydrogels must be free from any reagents that could trigger an inflammatory response associated with an exogenous material. The molecular weight of the hydrogel is critical to obtain desired clinical benefits since HA is prone to degradation and this process is accelerated in a diseased joint. A variety of HA derived crosslinked viscosupplements have been approved for human use.

The precursor HA for these preparations are obtained either from avian sources or by biofermentation in bacteria. Table 1 summarizes some important features of representative HA based viscosupplements that are marketed for intraarticular injection in the knee to relieve OA pain [52]. Particularly, these products differ by their molecular weights, which influence their rheological properties and hence residence time in the joint.

Brand name	Generic name	HA source	Modification type	Molecular weight (kDa)
Artz®/Supartz®	Sodium hyaluronate	Avian	N/A	600 - 1,200
Euflexxa®	Sodium hyaluronate	Biofermentation	N/A	2,400 - 3,600
Hyalgan®	Sodium hyaluronate	Avian	N/A	500 - 730
Intrigel®	Sodium hyaluronate	Biofermentation	N/A	800 - 1, 200
Orthovisc®	High mol. Wt. hyaluronan	Biofermentation	Chemical Modification	1,100 - 2,900
Synvisc®	Hylan G-F 20	Avian	Cross-linked	6,000

Table 1. Representative examples of clinically approved hyaluronic acid (HA) based viscosupplementation products (reference 45).

One of the most effective viscosupplement that has been approved for clinical use is Synvisc® (Hylan G-F 20) and its single injection formulation, Synvisc-One® [53]. The main components of Synvisc® are HA lightly crosslinked with formaldehyde (Hylan A) and divinyl sulfone crosslinked hylan A (Hylan B). Synvisc® contains 90% (v/v) of Hylan A and 10% (v/v) of hylan B and its chemical structure is shown in Figure 3. Synvisc® has been approved for the treatment of pain associated with mild to moderate OA. In subsequent clinical studies it has been observed that intraarticular injection of Synvisc® resulted in significant pain relief in the carpometacarpal joint, temporomandibular joint and the hip [54]. These findings suggest that pain relief from the intraarticular injections of HA-derived viscosupplements is not limited to knee. Since, OA of the hip is the second most common form of arthritis after OA of the knee, additional clinical investigation of the role of viscosupplements in relieving chronic pain arising from hip arthritis is warranted.

The biological mechanisms underlying the pharmacological action of HA derived viscosupplements to relieve OA pain are not completely understood. It was initially thought that since there is a reduced level of HA in OA joints, intraarticular injection of exogenous HA restores the rheological properties of synovial fluid to the level present in healthy joints. However, while the half-life of exogenous HA in the synovial fluid is only

few days, its clinical effect in reducing OA pain has been found to be maintained for several months [55]. This indicates that mechanism of action of HA derived viscosupplements is of multifactorial nature and is a combination of physical and biological effects. A number of *in vitro* studies have been carried out to investigate the biological activities of HA [56]. The results of these studies suggest that HA exhibits chondroprotective and anti-inflammatory effects in the synoviocytes by preventing invasion of inflammatory cells to the joint space. Biological activity of HA has also been attributed to down regulation of the gene expression of various inflammatory cytokines and catabolic enzymes like aggrecanase. Furthermore, being a natural ligand of the cell surface receptor CD44, HA has been thought to impart its effect by modulating CD44-mediated metabolism. In another *in vitro* study, when synovial fibroblasts were cultured with high molecular weight HA, newly synthesized HA molecules were found. These biological effects of exogenous HA may result in overall cartilage protection [57, 58]. Thus, well controlled clinical studies would shed further light on the chondro-protection properties of exogenous HA like Synvisc and lead to the discovery of novel therapies with disease modifying properties.

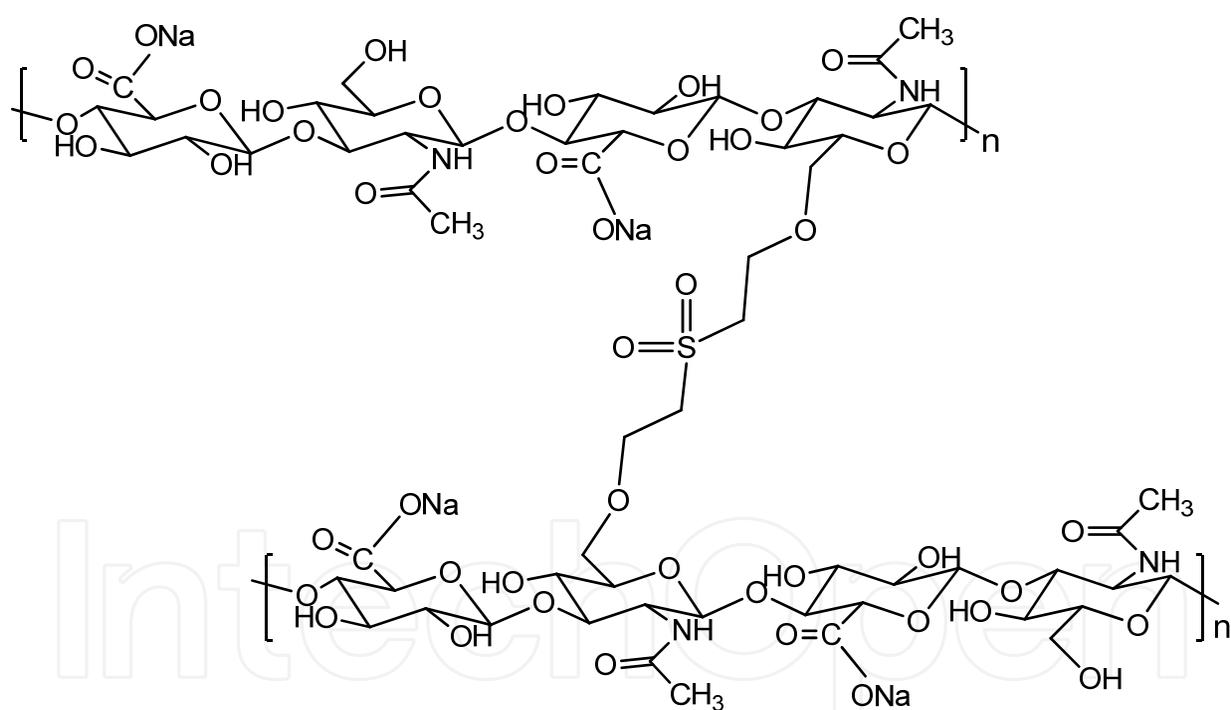


Fig. 3. Structure of Hylan B component of Synvisc®.

3.3 HA-steroid combinations for the treatment of chronic pain

One of the shortcomings of HA derived viscosupplements is their slower onset of action to reduce OA pain relative to low molecular weight drugs such as NSAIDs and steroids. Therefore, the viscosupplements are generally administered weekly over a course of three to five weeks. As described earlier, unlike traditional pain killers, pain relief from viscosupplements lasts much longer (up to several months). Although intraarticular injection of corticosteroids achieves maximum benefit within few days of injection,

repeated injection of these catabolic agents can have adverse effect [59]. In order to achieve fast and longer lasting pain relief while minimizing the side effects of steroids, combination therapy of HA and corticosteroids have been envisioned. Non-covalently bound admixtures of HA gel with steroids, where the steroid is dispersed within the HA hydrogel matrix have been investigated as combination therapy to treat OA pain. This approach allows sustained local delivery of the steroid at OA site and would overcome the side effects associated with steroid overdose. Figure 4 shows the structures of representative corticosteroids that have used to prepare HA derived drug-viscosupplement composites.

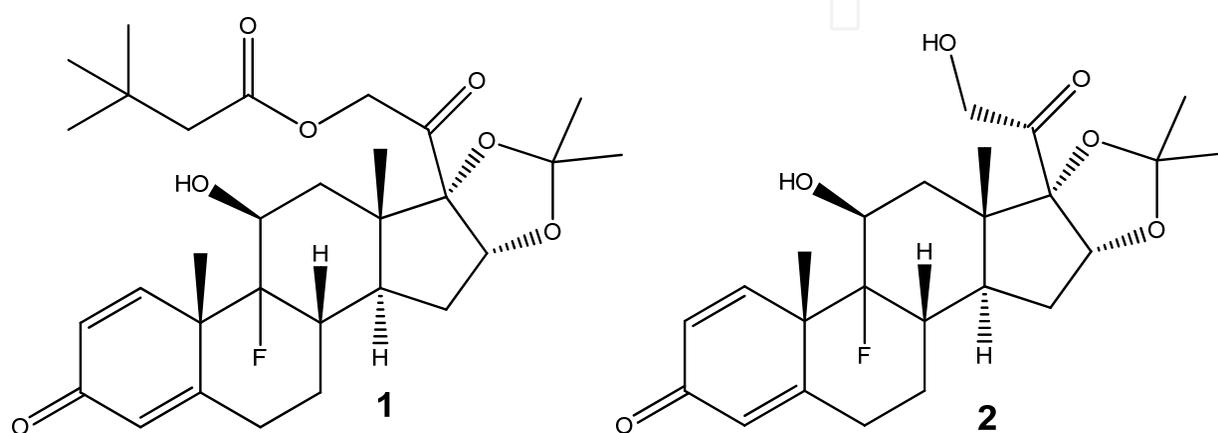


Fig. 4. Corticosteroids used to prepare HA-steroid composite hydrogel viscosupplements.

Preparation stable formulation of crosslinked HA hydrogel, Synvisc® with triamcinolone hexaacetonide (TAH) (Figure 4, 1) was investigated by dispersing Tween-80 stabilized TAH colloidal suspension within a swollen gel of Syvisc® [60]. By optimizing the ratio of Synvisc® to TAH in the formulation mixture, a stable composite was obtained. The rheological properties of Synvisc® were not adversely affected by the presence of the hydrophobic corticosteroid and the composition was found to be stable in an accelerated shelf life test.

Another steroid-viscosupplement composite was prepared by crosslinking linear HA in the presence of triamcinolone acetonide (Figure 4, 2). In this study, divinyl sulfone was allowed to react partially with HA to generate a linear HA structure with pendant vinyl sulfone group. To a solution of this vinyl sulfone functionalized HA was added a suspension of 2 and resulting reaction mixture was treated with α,ω -dithio polyethylene glycol (PEG) as the crosslinking agent. A crosslinked HA gel with relatively homogeneously distributed steroid particles within the gel matrix was obtained. The synthetic strategy adopted for the preparation of this dual-acting viscosupplement is shown in Figure 5 [61]. In a preliminary clinical study, this steroid-HA composite (Hydros-TA) showed faster pain relief compared to the corresponding native viscosupplement alone. Long term clinical study involving larger patient population needs to be carried out to demonstrate the clinical efficacy of such steroid-viscosupplement composites to treat OA associated chronic pain.

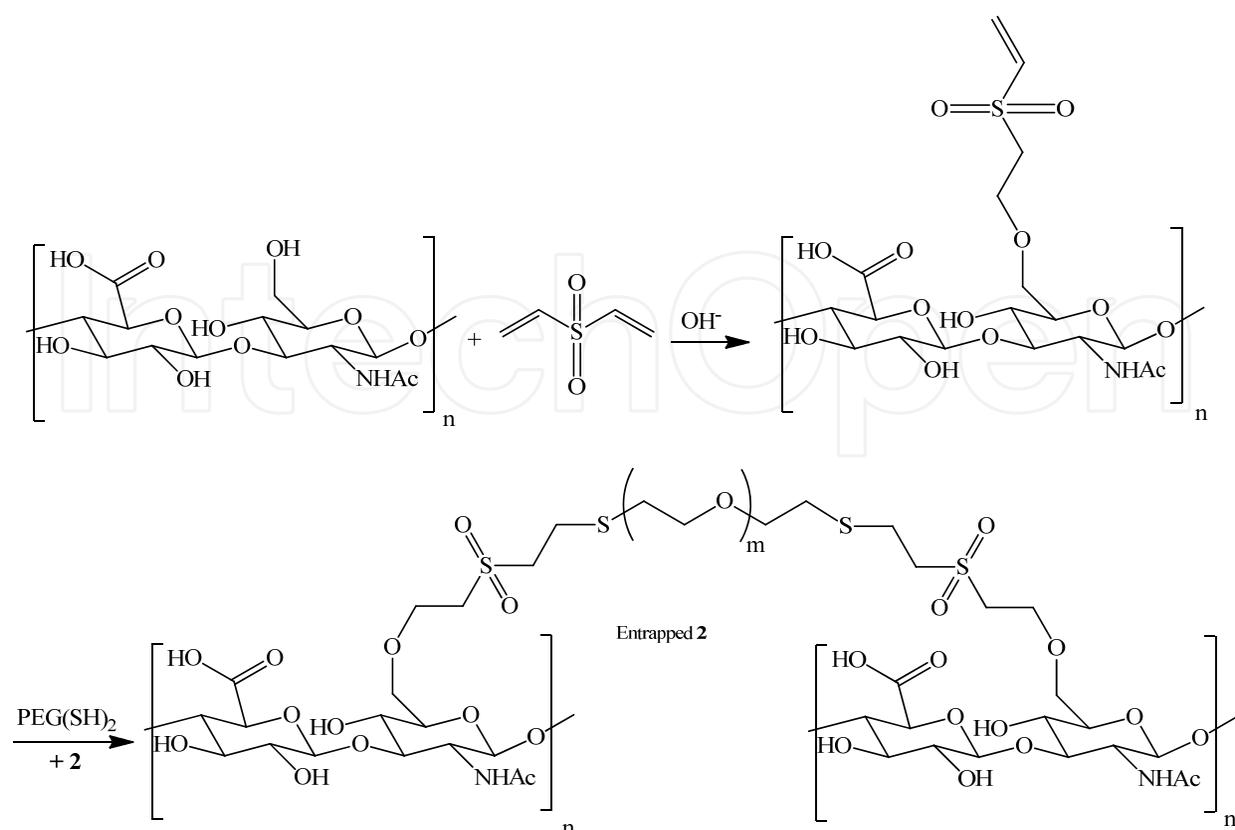


Fig. 5. Crosslinking of HA in the presence of a dispersion of triamcinolone acetonide to prepare viscosupplement-steroid composite hydrogel

3.4 Covalent conjugates of HA and low molecular pain killers

Intrinsic biocompatibility and its versatility for chemical modification make HA an attractive biomaterial to synthesize conjugated drug delivery systems. Chemical modification of HA has allowed the preparation of an array HA-drug conjugates and HA-protein conjugates as sustained-release carriers for drugs and biotherapeutics [62, 63]. Covalent conjugates of HA containing hydrogels with pain relieving agents have been explored as dual acting agents to treat chronic pain. This approach would offer a number of potential clinical benefits, that include: i) retaining viscosupplementation property of soluble HA, ii) minimizing the systemic exposure of NSAIDs and opioid family pain killers by localizing administration to the target site, iii) modulating the duration of action of these pain killers by incorporating appropriate conjugation chemistry to control the rate of cleavage of the drug from the HA gel, and iv) minimizing the frequency of administration of viscosupplement and the pain killer in the clinic. These features of the HA-drug conjugates could lead to better patient compliance and improved quality of life.

A series of HA derived functional hydrogels conjugated with local analgesics (e.g. bupivacaine) and opioid drugs (e.g. morphine) were synthesized in our laboratories as long acting treatments for chronic pain [64, 65]. Divinyl sulfone crosslinked HA hydrogel (Hylan B) was used as the polymer matrix for the synthesis of these drug conjugates. Appropriate linker arms were designed to tether these pain relieving agents to the HA

matrix. Bupivacaine was conjugated to HA through a hydrolysable imide bond (Figure 6A). On the other hand, opioid drugs such as morphine, naloxone analogs were conjugated via a hydrolysable ester bonds (Figure 6B). A number of conjugates were synthesized by varying the nature of the linker arm, spacer length, and the amount of the drug loading. A systematic evaluation of the release kinetics of the drugs from the HA gel was carried out under *in vitro* conditions to identify an optimum composition. The optimum drug-HA conjugate from each class was evaluated *in vivo* for its biological activity. These drug-conjugated HA hydrogels exhibited therapeutic benefits by prolonging pain relief and were more effective than the individual agents and their admixtures. These preclinical research findings suggest that development of HA based viscosupplements conjugated with traditional pain relieving agents might lead to a promising new generation of long acting therapies for the treatment of OA associated chronic pain.

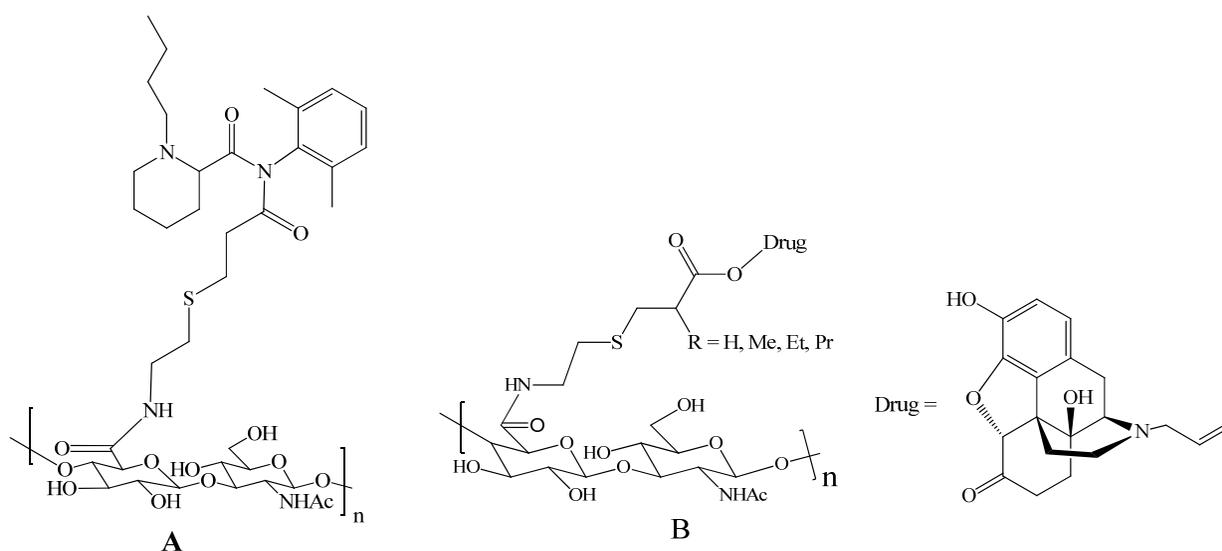


Fig. 6. HA conjugated local analgesics (A) and opioids.

In related work, conjugates of HA with methotrexate (MTX) were synthesized to achieve viscosupplementation and anti-inflammatory effect concurrently intraarticularly [66]. Increased levels of TNF- α have been found in the synovium of OA affected joints that can be mitigated by oral administration of MTX [67]. However, systemic administration of MTX is associated with certain side effects such as pneumonitis and myelosuppression [68]. Therefore, by localizing MTX to target joint by delivering it as a polymer conjugate, the systemic side effect could be minimized. After a careful structure-activity study by screening various linker arms and enzyme target groups, an optimized HA conjugate of MTX was identified (Figure 7). A peptiditic linker was chosen as target for cathepsin enzymes, which are over-expressed in OA joints. The polyethyleneglycol (PEG) linker was chosen to enable the peptide target to be accessible to the cathepsin enzyme in the joint environment. *In vitro* and *in vivo* studies revealed that the HA-MTX conjugate is capable of reducing joint pain and swelling of the knee. On the other hand, admixture of HA and MTX showed marginal efficacy.

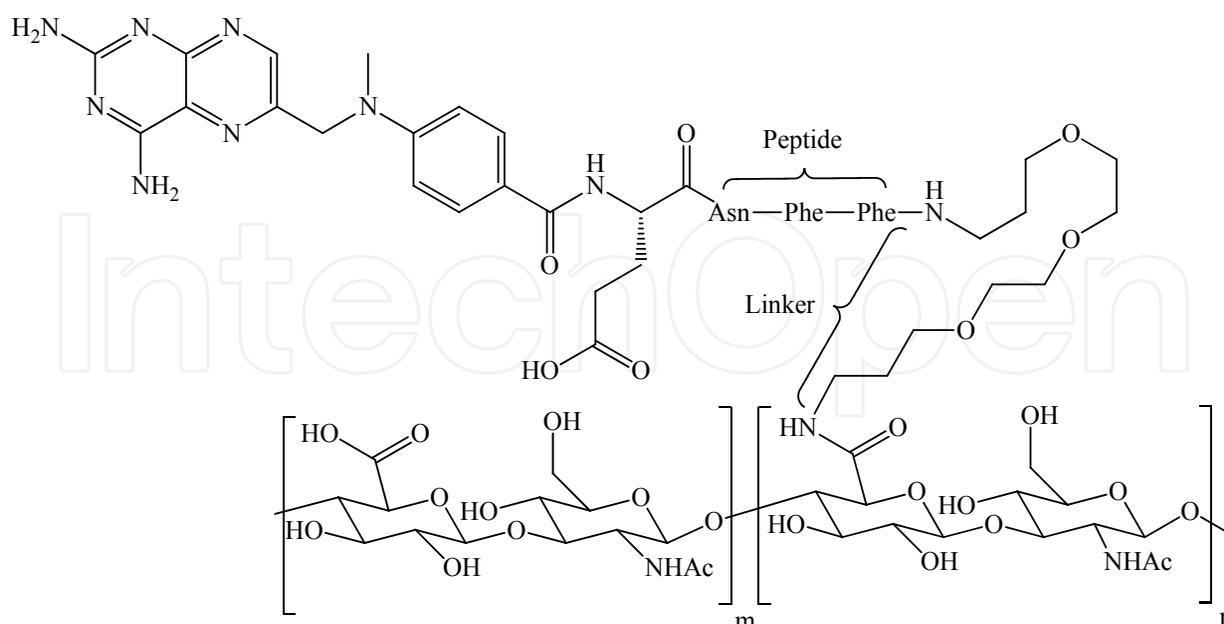


Fig. 7. HA conjugate of methotrexate as an intraarticular combination therapy for the treatment of OA pain.

4. Polymer-opioid conjugates and polymeric opioid derivatives

Besides being a first-line analgesic therapy for acute pain, opioids have been found to be useful in treating chronic pain. However, the adverse effects associated with their long term use limit the therapeutic benefits of opioid analgesics, thus leading to discontinuation of the therapy. Constipation (opioid-induced bowel dysfunction (OBD)) is one of the significant side effects associated with opioid therapies. OBD affects up to 80% of the patients undergoing opioid therapy. While other side effects associated with chronic use of opioids resolve with time, constipation continues to persist [69].

Efforts have been made to utilize polymeric approach to design and develop new generation of opioid analogs as pain killers. These polymeric compounds enable the patients to overcome OBD without losing the benefits of opioid therapy by limiting drugs' systemic absorption. Pegylation chemistry was utilized to synthesize these macromolecular opioids. The technology of pegylation has been successfully utilized to improve pharmacokinetic properties of a number of (bio)pharmaceutical agents [70]. Two representative polymer conjugated opioid derivatives are shown in Figure 8. These compounds consist of naloxol analogs linked to PEG chains through hydrolytically stable ether linkage [71, 72]. In preclinical studies, these pegylated opioid derivatives were found to maintain their centrally mediated analgesia, while antagonizing peripherally mediated constipation. One of the key conjugates, NKTR-118 (Figure 8A, $n = 7$) has proceeded to advanced clinical trial. In the phase II clinical trial, patients receiving NKTR-118 exhibited significant increase in bowel movement compared to patients receiving native naloxol, without compromising the analgesic property of the opioid [73]. NKTR-118 is currently undergoing phase III clinical trial.

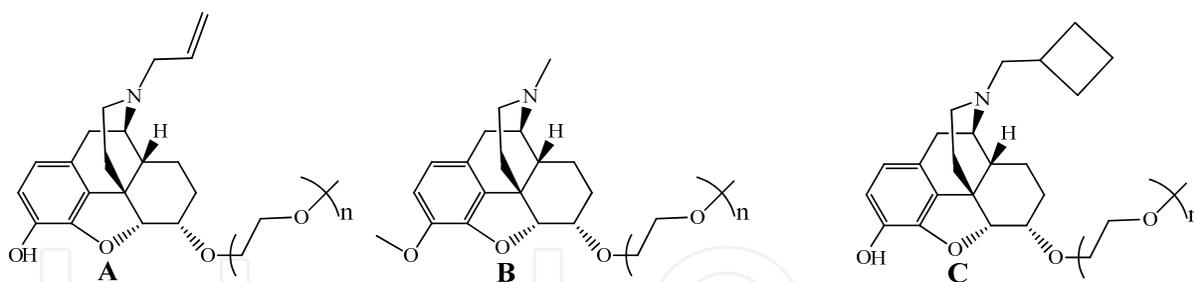


Fig. 8. Polymer modified naloxol derivatives to prevent opioid induced constipation.

Another interesting approach to develop polymeric pain relievers has been reported that utilizes a polymerization chemistry to synthesize poly(anhydride-esters), where the bioactive drug becomes part of the polymer backbone [74]. The general structure of this class of polymeric pain relievers is shown in Figure 9. Following this strategy, they were able to incorporate significant amounts (~ 62%) of the deliverable drug to the polymer chain. Hydrolytic degradation of these poly(anhydride-ester) polymers under physiological pH conditions releases the drug in a controlled manner. As a result, the side effects associated with the native drug (if released immediately) can be minimized. Some of the polymeric pain relievers reported are poly(anhydride-esters) containing the anti-inflammatory agent, salicylic acid and the opioid drug, morphine (Figure 10). Although syntheses of polymeric pain relievers based on these poly(anhydride-ester) scaffolds have been studied extensively, there is limited information about the biological activities of these polymers as treatments for chronic pain [75, 76]. Nevertheless, these polymeric opioids and anti-inflammatory agents offer a new perspective to develop novel treatments for chronic pain.

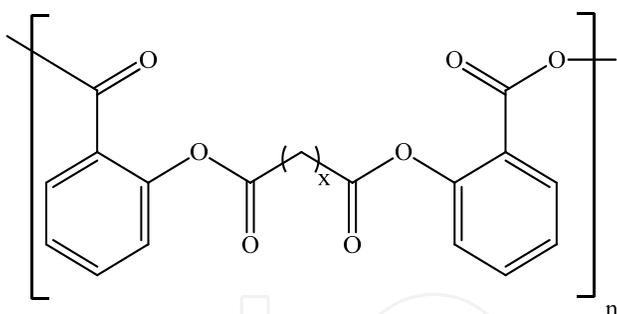


Fig. 9. Structure of salicylic acid-based poly(anhydride-esters) as polymeric anti-inflammatory agents.

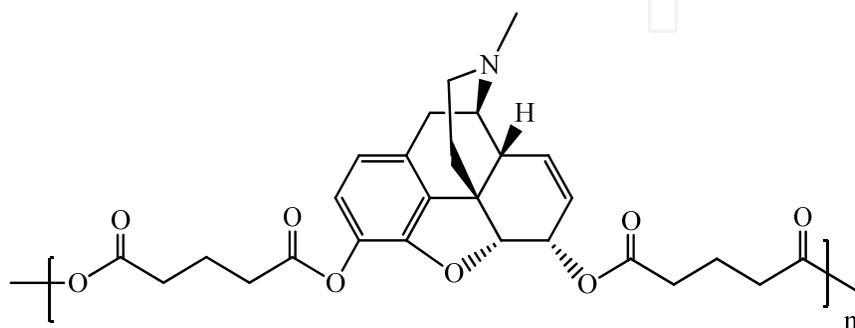


Fig. 10. Structure of morphine-based poly(ester-anhydride).

5. Conclusion

Because of its clinical relevance, development of novel pharmacologic agents for effective management of chronic pain continues to be an important goal of pharmaceutical research. Although numerous therapeutic agents with different modes of action have been developed to treat chronic pain, no single agent exhibits the most desired profile. For example, while opioids and NSAIDs remain the main stay of therapeutic options, concerns over their associated side effects have begun to limit their use. Polymeric approach offers a variety of options to develop a new generation of pain relievers, which include intrinsically bioactive polymers to different delivery systems for traditional pain killers. HA derived viscosupplements offer an attracting option to treat chronic pain due to excellent biocompatibility and various biological functions of HA. The ability to trigger various biological functions makes HA based viscosupplements as promising agents to not only relieve symptomatic effects of chronic OA pain, but also to bring about potentially disease modifying effects. Therapies comprising of polymers in combination with traditional pain killers (either as conjugates or as stable non-covalent formulations) have been found to minimize the side effects of the latter. By targeting the disease via different mechanisms of actions, these combination agents could become superior therapeutic options to treat chronic pain. With increasing understanding of the pathobiology of chronic pain and intense research in biomedical polymers, it will be possible to develop novel polymer based therapies in the near future that are safe and could act as structure modifying treatments for chronic pain.

6. References

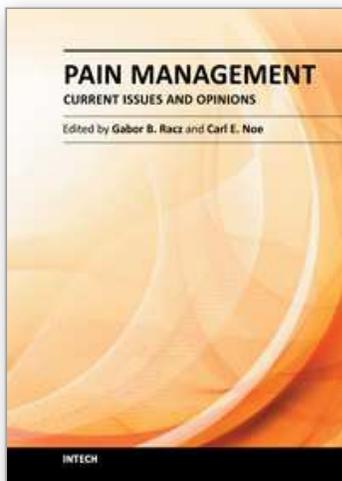
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