

SUMMARY AND CONCLUSION

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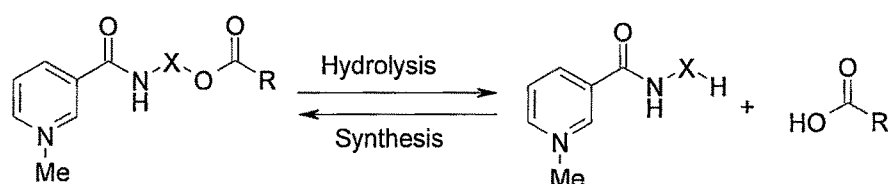
Arthritis is a group of conditions involving damage to the joints of the body. Rheumatic diseases are estimated to affect up to 1.1 % of world's population and these patients are often treated with steroids, NSAIDs, DMARDs and/or immunosuppressive drugs. Currently available therapy for the arthritis focuses on reducing inflammation of the joints with NSAIDs and steroids.

After studying the various options for the treatment of arthritis it was felt that it should be possible to deliver therapeutic agents with improved therapeutic efficacy, longer duration of action with minimal side effects which is very essential in chronic diseases such as arthritis. It was planned to adopt the following four strategies to achieve the above defined goals:

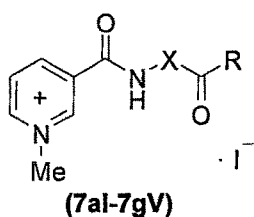
1. Intra-Articular Chemical Delivery Systems (IA-CDS)
2. Percutaneous Drug Delivery Systems (PDDS)
3. Intra-Articular Liposomal Drug Delivery Systems (IA-LDDS)
4. Oral Drug Delivery Systems (ODDS)

1. Intra-Articular Chemical Delivery Systems (IA-CDS)

Literature survey revealed that a drug in solution form is rapidly expelled from the joint cavity upon IA administration; so various drug delivery systems such as suspensions, liposomes, microspheres etc. have been developed and tested but till date no drug delivery system having longer duration of action without side effects has been developed. Hence there is a need to develop delivery system with improved drug residence time in joints on IA administration. CDS of various NSAIDs have been designed, synthesized and evaluated as shown below:



From the obtained data it is clear that the synthesized CDS (**7aI-7gV**) showed high retention time in joints after IA administration as compared to the parent drug (**5IV**). Further, radioactivity obtained for the synthesized CDS after 24h was about 4 times higher in Region of Interest (ROI) compared to the parent drug.



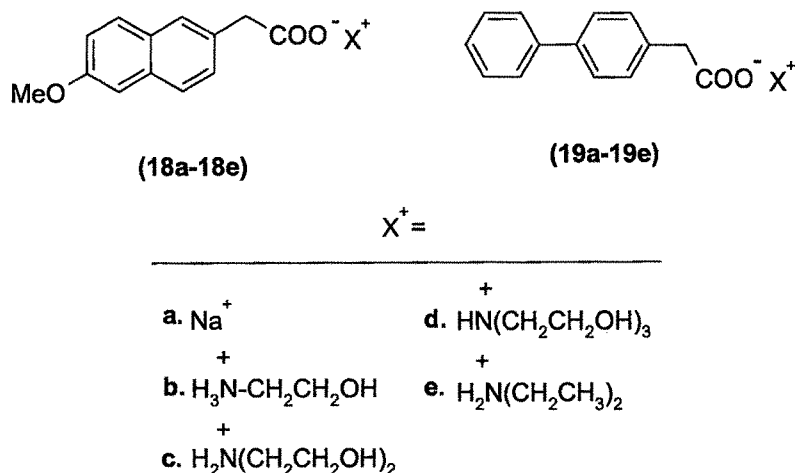
X=	R=	
a. $-\text{CH}_2\text{CH}_2\text{O}-$		
b. $-\text{CH}_2\text{CH}(\text{CH}_3)\text{O}-$	(I)	(II)
c. $-\text{CH}(\text{CH}_2\text{CH}_3)\text{CH}_2\text{O}-$		
d. $-\text{C}(\text{CH}_3)_2\text{CH}_2\text{O}-$	(III)	(IV)
e. $-\text{CH}_2\text{CH}_2\text{CH}_2\text{O}-$		
f. $-\text{CH}_2\text{CH}_2\text{NH}-$		(V)
g. $-\text{CH}_2\text{CH}_2\text{CH}_2\text{NH}-$		

So, it can be concluded that cationic molecules are retained for a longer period of time in joint cavity by ionic interaction and hence in the initial phase we can extend residence time of the drug by these CDS.

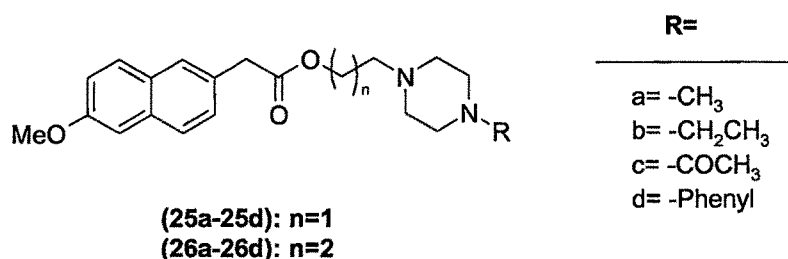
2. Percutaneous Drug Delivery Systems (PDDS)

The bioavailability of topically applied NSAIDs is only up to 1-2 % in humans. To improve the percutaneous delivery of NSAIDs the usefulness of the salt formation and prodrug approach for NSAIDs has been evaluated.

Amongst all of the synthesized salts of NSAIDs, the ethanolamine salts of MNA and BPA (**18b**, **19b**) displayed 9-10 times higher flux than the parent NSAIDs. The result also showed that salts with higher flux have a balance between solubility and partition coefficient. Further, except for sodium salt all the salts have shown lower melting points than the parent drugs and higher permeability through the skin, which support previous reports indicating that a decrease in melting point or conversion of solid state to liquid state improves the permeability of drugs through skin.



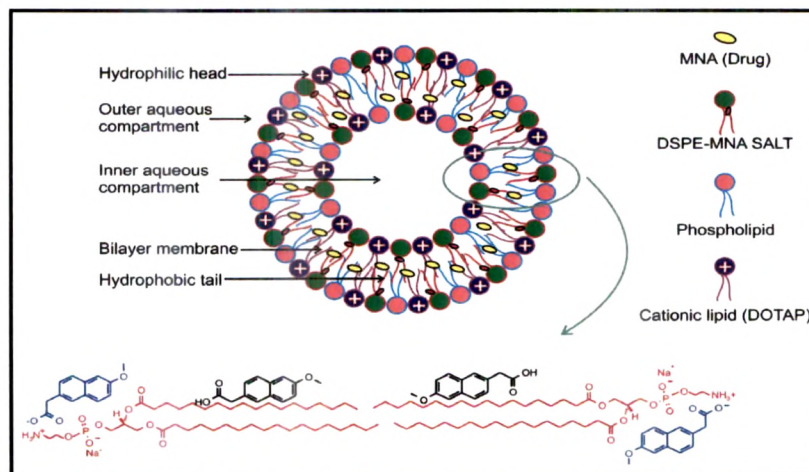
In case of prodrugs the diffusion experiments showed that both 6-MNA and its prodrugs were able to permeate rat abdominal skin *in vitro*. The steady-state flux (J_{ss}) of prodrugs showed higher flux values than the parent NSAID.



Among all of the prodrugs, prodrug (26b) has exhibited the highest steady state flux while 25b the lowest. Prodrugs (25a and 26a) have shown intermediate flux values but still both the values were 5-fold and 7-fold higher than the parent NSAIDs. Prodrug (26b) having the highest flux was 12-fold higher than the parent NSAID. The result indicated that lipophilic piperazinyl prodrugs with adequate aqueous solubility increased the flux of 6-MNA.

3. Intra-Articular Liposomal Drug Delivery Systems (IA-LDDS)

Another objective of the present work was to develop cationic liposomal formulations of NSAIDs having long half life, selectivity towards COX-II enzyme and affinity towards joint cavity producing less gastrointestinal side effects.



The encapsulation of an NSAID possessing all these ideal features into liposomes with further modifications of liposomal properties such as size, lamellarity, charge etc. could improve the overall therapeutic efficacy of the agent after IA injection in patients with OA. As shown in the above figure cationic liposomes were prepared and evaluated.

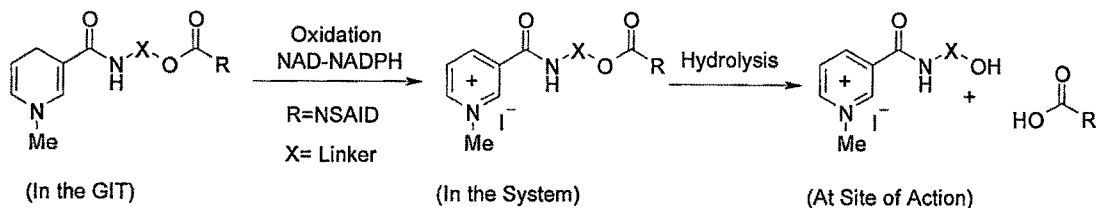
From the obtained data it was clear that liposomes showed higher retention in joints after IA administration as compared to the parent drug and the quaternary ammonium chemical delivery system. Further, radioactivity obtained for the prepared liposomes after 24 h was about 5 times higher in ROI compared to the parent drug. So it could be concluded that liposomal drug delivery systems having cationic charge are retained for a longer period of time in joint cavity by ionic interaction. Hence residence time of the drug in the joint can be extended by these drug delivery systems. Moreover, sustained release of the drug will give anti-inflammatory effect for still longer duration reducing frequency of administration of IA injections.

4. Oral Drug Delivery Systems (ODDS)

It was evident from the literature that a cationic molecule possesses higher affinity towards cartilage tissue. But such molecules show poor bioavailability on oral administration. Hence it was planned to convert the conventional NSAIDs into neutral chemical delivery systems which could be easily absorbed from the GIT.

Once the CDS enters into the systemic circulation it should be metabolized/converted into a cationic species. The designed CDS was synthesized and evaluated. From the results it could be concluded that dihydropyridine CDS were quite unstable in phosphate buffer pH 2 as well as 7.4; the primary route of hydrolysis of these

compounds was ester bond cleavage. All the synthesized CDS have undergone enzymatic hydrolysis in human serum to cleave the ester bond present in CDS.



Further, it could be concluded that the synthesized CDS were found to be comparatively more stable in human serum than in buffer of *pH* 2.0 and 7.4. It may be due to protonation of dihydropyridine ring which might stabilize the dihydropyridine ring. Biodistribution studies clearly indicated that the designed dihydropyridine CDS were not suitable for oral administration as these were not properly absorbed from the GIT, may be due to their fast conversion to various oxidation products which were not absorbed through oral route.