ABSTRACT

Neuropathic pain is a type of chronic pain condition that generally arises due to certain type of nerve damage or lesions. The pharmacological treatment options for neuropathic pain are generally based upon their symptoms and are managed by various classes of drugs such as anti-depressants, anti-convulsants, anti-spasmodic, opioids etc. However, since majority of these drugs are given by oral route, drugs undergo hepatic metabolism and enzymatic degradation. These drugs are generally hydrophobic and their distribution profiles to various peripheral organs leads to unwanted side effects. Further, blood brain barrier (BBB) restricts the entry of these drugs in brain via systemic circulation leading to low bioavailability in brain. Nose-to-brain delivery has been reported to bypass the BBB however, limited absorption through nasal mucosa and muco- cilliary clearance still remains a challenge. Nano-carrier based drug delivery provides an alternative delivery approach where pharmaceuticals encapsulated in delivery carriers. Polymers or emulsion based nanoparticle or nano-emulsion based systems provide an alternative approach where their small size leads to rapid absorption while their coating leads to prolonged release of drugs and avoids their quick degradation. When these nanoparticles/nano-emulsions are delivered via intranasal route, they can quickly be absorbed and deliver drugs in brain unlike the conventional delivery systems.

In our study, Baclofen (anti-spasmodic), Lamotrigine (anti-convulsant) and Capsaicin (phyto-therapeutic) were selected for development of nano-carrier systems for managing neuropathic pain. Four formulations were prepared: Capsaicin loaded oil-in-water nano-emulsion (Caps-NE), Baclofen loaded PLGA nanoparticles (Bcf-PLGA-NPs), Lamotrigine loaded PLGA nanoparticles (Ltg-PLGA-NPs) and Baclofen+Lamotrigine loaded PLGA nanoparticles (Bcf-Ltg-PLGA-NPs). The formulations were found to be in homogenous, stable and in nano-metric range when characterized for particle size, polydispersity index, zeta-potential and Transmission Electron Microscopy. Caps-NE was additionally analyzed for other physical parameters and anti-oxidant assays where Caps-NE showed high anti-oxidant potential. *In vitro* mammalian cell lines based cytotoxicity (MTT assay) and staining assays (Giemsa and DAPI staining) revealed that nano-emulsion exhibited cytotoxicity whereas prepared nanoparticles exhibited good cell viability (%). Further, ELISA based cytokines analysis of nano-carriers showed high anti-inflammatory potential of Caps-NE while prepared nanoparticles were found to be potential pro-inflammatory cytokines inhibitors. *In vivo* pharmacokinetics studies were carried on Sprague Dawley rats for prepared nanoparticles

where initial drug (baclofen and lamotrigine) radiolabelling was done using technetium-99m followed by gamma scintigraphy and bio-distribution studies. Various routes of administration (intra-nasal, intra-venous and oral) were studied for delivery of radiolabelled nanoparticles and aqueous drugs. As hypothesized and based upon evaluation of various pharmacokinetic parameters, intra-nasal delivery of nanoparticles was found to be most effective in delivering the drugs in brain regions. Further, preliminary pharmacodynamics studies on C57BL/6 mice was done by formalin test and vonFrey test where the combination nanoparticles (Bcf-Ltg-PLGA-NPs) showed synergistic action during tonic phase significantly reducing the no. of licks and bites as compared to other NPs and control group suggesting synergistic action of the drugs when co-delivered. Bcf-Ltg-PLGA-NPs also showed reduction in withdrawal threshold in vonFrey test as compared to other groups. This study concluded that prepared nanoparticles when delivered intra-nasally can effectively reach brain (unlike the conventional intra-venous or oral route) and have potential in management of neuropathic pain.