Chapter 7

7.1 Conclusion

In this thesis strong emphasis has been given on the development of Cyclodextrin-Polyurethane based controlled drug delivery carriers for cancer treatment. Cyclodextrin has been chosen as the starting material, which is a oligosachharide containing six (α–CD), seven (β–CD), eight (γ–CD), or more (a-1,4-)-linked D-glucopyranose units, consist of a relatively hydrophobic inner cavity and a hydrophilic outer face, obtained by the enzymatic hydrolysis of starch. Cyclodextrin is the well known biopolymer, due to its high biocompatibility it is widely used in biomedical field. Our aim of this investigation is to prepare different polymeric architectures which can deliver the drug in sustained pattern. In order to do so, polymers with different graft density and graft length have synthesized. Grafting of polyurethane on Cyclodextrin imparts greater thermal and mechanical stability making them suitable for their application in biomedical field.

Chemical modification of Cyclodextrin has been carried out by grafting with long chain polyurethanes on Cyclodextrin backbone. Polyurethanes are grafted with varying degree of substitution. Cyclodextrin is hydrophilic in nature and on grafting with polyurethane it becomes hydrophobic. Hydrophilic-hydrophobic balance is maintained and the less substituted graft is more hydrophobic as compared to highly grafted system which is due to wrapping of polyurethane onto cyclodextrin backbone. Controlled hydrophilic/hydrophobic nature of copolymers make them suitable drug delivery systems. Thermal and mechanical properties of copolymers were enhanced. Dexamethasone is used as a model anticancer

drug to understand the drug release phenomenon from pure polymers and their grafts. In vitro drug release study reveals that burst release was observed from pure cyclodextrin while sustained release was observed in graft copolymers. This sustained release from graft copolymers is attributed from the wrapping of polyurethanes chains making it hydrophobic and creating a tangled path which slows the diffusion of drug from polymeric network. Thus the release can be easily tuned by altering the degree of substitution. Biocompatibility and cell killing efficiency of graft copolymers has been checked through MTT assay, revealing better biocompatible nature and higher cell killing from graft with time due to sustained release. Further the efficacy of sustained drug release has been revealed from in vivo melanoma studies where significant suppression in tumor volume from graft patch has been observed with any side effects on vital organs. Therefore polyurethane grafted cyclodextrin copolymers are promising controlled drug delivery vehicles.

In this study grafting of polyurethane has been done on cyclodextrin backbone with slight variations in reaction conditions of previous technique. Polyurethanes of short chain length have been grafted with different degree of substitution to demonstrate the effect of chain length on drug release. Verification of grafting have been done using NMR spectroscopy and GPC technique. The extent of interactions between polyurethane chains with cyclodextrin has been revealed through FT-IR and UV-Vis spectroscopy Improved thermal and mechanical properties of graft copolymers with respect to pure polymer have been revealed through TGA and UTM testing. Conversion of particle nature of CD to strip like morphology in graft copolymers is revealed from atomic force microscopy. Sustained drug release has been observed from graft copolymers against burst release from native CD or prepolymer. The wrapping of polyurethane onto CD backbone hinders the release of drug

and thus slower diffusion is observed in graft copolymers. Biocompatibility assessment of graft copolymers investigated through MTT assay, cell adhesion and fluorescence images revealed their better biocompatible nature than pure CD. Importantly the cell killing efficiency from drug loaded graft copolymers was higher causing mortality rate of 75 %, while meager killing of 25 % was observed in pure drug/ drug loaded CD. The reason is well understood from sustained release of drug from the graft copolymer vis-vis burst release from pure systems. Thus controlled release along with better biocompatibility of these graft copolymers make them captivating biomaterial for drug delivery applications.

In this study an injectable hydrogel based controlled drug delivery systems has been developed for prolonged drug release by assembling different generations of CD followed by grafting with hydrophobic polyurethane to control the drug release for better cancer treatment. Three generations of CD has been designed using small spacer HMDI,which is wrapped with a hydrophobic layer of polyurethane through grafting leading to an intricate superstructure. Sustained drug (Paclitaxel) release was observed from this superstructure which follows non fickian mode of diffusion. Further the developed superstructure was biocompatible and massive killing of cancer cells was observed as compared to pure drug in similar concentration and time. The interaction between superstructure and drug has been revealed from spectroscopic and calorimetric measurements which are prominently responsible for sustained drug release from superstructure. Drug loaded superstructure is embedded in methyl cellulose to make whole system injectable hydrogel which can be placed subcutaneously at the tumor for its better efficacy through effective delivery at the tumor site. In vivo studies in melanoma bearing mice treated with this injectable gel resulted in complete melanoma healing and no side effects were observed as opposed to

conventional systems due to sustained drug release from the super structure. Therefore a biocompatible superstructure is designed which is versatile controlled drug delivery vehicle for subcutaneous delivery of chemotherapeutic for cancer treatment without imposing any side effects.

In this study dextrin and polyurethane based brush polymers have been designed and its injectable hydrogel is prepared for regulating the release of hydrophobic anticancerous drug dexamethasone. The efficacy of brush polymers and its gel is visualized from their sustained drug release which follows Fickian kinetics, a diffusion controlled phenomenon. Biocompatible nature of developed brushes has been revealed from MTT assay, drug embedded brushes exihibited higher killing efficiency towards Hela cells as compared to native drug in similar concentration and time. The interactions between drug and brushes have revealed through calorimetric and spectroscopic studies. In-vivo studies using albino mice clearly demonstrate the efficacy of significant tumor suppression within one month time due to sustained drug release without any side effect. Hence, biocompatibility and efficient cell killing property of drug loaded brushes make them versatile drug delivery carrier for subcutaneous delivery of therapeutic agents particularly for tumor treatment without any side effect.

In summary, we have designed different polymeric architectures based on Cyclodextrins/dextrins and polyurethanes, their spectroscopic characterizations and thermal and mechanical measurements were done. Their applications in *In vitro* drug release study, cellular studies (biocompatibility and cytotoxicity) and melanoma treatment were carried out.

7.2 Scope for future work

The present work has reported synthesis, characterizations and biological applications of Cyclodextrins grafted polyurethanes. The different polymeric architectures have been developed for exploring the drug release mechanism from developed materials. Biocompatibility and in vivo cytotoxicity of developed polymers is also studied. However, there are some scopes for future studies, few are listed below.

- Modification of CD with different hydrophobic systems for controlled drug release.
- Host guest interaction of modified CD with drug and their hydrogels for control drug release.
- Cellular studies using different cell lines and efficacy of cell killing from control release.
- Application of prepared polymers for breast cancer and colon cancer treatment.

Contribution of above work

- Different polymeric architectures are designed for controlling the drug release.
- Sustained drug release is obtained from prepared polymeric architectures.
- Efficacy of sustained release is visualized in animal model using different treatment methods like

  a) Dermal patch.
  b) Intravenous injections.
  c) Injectable gels locally at the tumor site which effectively reduces tumor volume.