Chapter 4

4.1 Introduction

Cyclodextrins (CD) are the most versatile materials produced in nature. Its special cyclic structure composed of 6 to 8 glucopyranose units with hydrophilic exterior and hydrophobic interior confers unique quality. They are crystalline, homogenous and non hygroscopic substances. The cavity size of CD is appropriate for drug loading and complexation.[156] CD is generally considered as first drug carriers used ever with remarkable ability to sustain hydrophobic molecules within the cavity and as a consequence tune their therapeutic efficacy.[157-159] It is demonstrated that simple cyclodextrin limits the improvement of solubility of drugs which means some additional steps are required to increase their solubility in stable and biocompatible solvent. In such delivery systems, natural cyclodextrin are grafted with some other polymers and then drug delivery is carried out. Grafting is carried out by conjugating many units of cyclodextrin in polymer chain or reverse may be done to enhance the binding ability of drugs on the surface of polymers. Graft copolymerization is the most suitable technique that introduces hydrophobic and bulky groups in CD chain which plays important role in retarding the drug release from polymeric matrices. Grafting of acrylic polymers on guar gum is reported for sustained drug release.[160, 161] Attention has been paid towards the synthesis of well defined graft copolymers with desired functional groups, chain length on polymer backbone and their graft densities for wide range of applications in biology and other medical fields.[162, 163] CD bears a large number of hydroxyl groups having different reactivities. Primary hydroxyl group at C_6 position is directed away from the cavity and

exhibit more reactive which can be easily functionalized with other polymers. Aldehydes, ketones, isocyanates or epoxides (*e.g.* epichlorohydrine or glycidylethers) have been used as cross-linking agents for CDs.[164-166] Diisocyanates have been used to a great extent as a cross linker forming macro size CD networks.[167-169].

Here, in this chapter, we have grafted NCO terminated short prepolymer chain on cyclodextrin backbone with an aim of preparing polymers with different graft density with short prepolymer chain to make them thermally and mechanically stable materials to be used in control drug delivery for cancer treatment. Grafting has been verified through spectroscopic methods and its structural details are obtained from XRD studies to understand the importance of different architecture. In vitro sustained release of drug has been presented using graft copolymer against burst release in pure CD and PP. Biocompatibility analysis along with its complete cytotoxicity studies at different drug concentration and different time interval reveal their biocompatibility and corresponding drug loaded copolymers showed significant cell killing with increasing drug concentration. Thus the PP grafted CD copolymers displayed sustained drug release and were biocompatible biomaterials.

4.2 Results and discussion

4.2.1 Spectroscopic evidence for grafting

Grafting of polyurethane onto CD is done via chemical reaction between hydroxyl groups on CD and isocyanate (-NCO) terminated prepolymer. The general reaction scheme is presented in ***Scheme 2.2*** in experiment section where copolymers with two different graft density are prepared by varying the CD weight ratio which in turn alter the hydrophilicity

of CD. Mostly the reaction occurs at primary hydroxyl group of CD with NCO of prepolymer due to its high reactivity which is verified through NMR **(*Figure 4.1a*).**

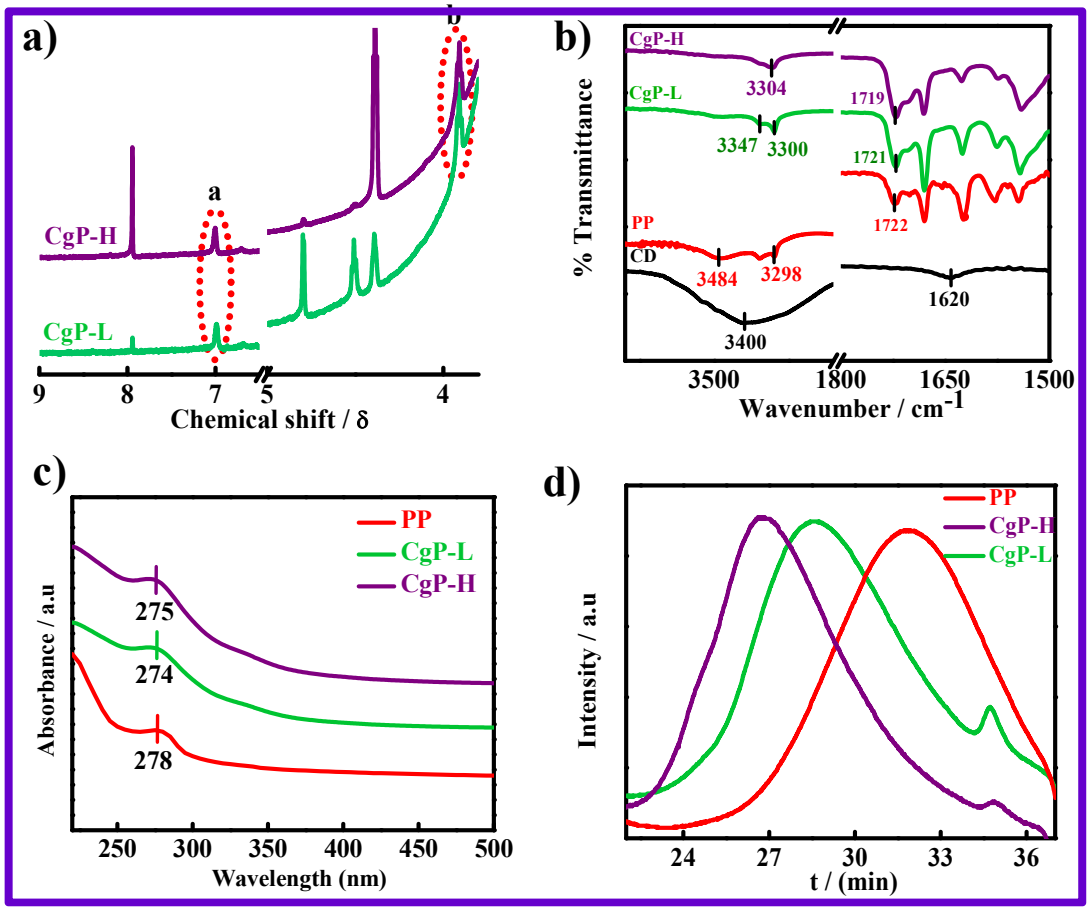

Figure 4.1: *a) ^{1}H NMR Spectra of CD, prepolymer (PP) and their indicated grafts. Occurrences of new peak due to grafting are marked as 'a' and another peak at δ~8 ppm demarcates the intermolecular hydrogen bonding. Calculation of degree of substitution from integrated peak area is presented in the text; b) FTIR spectra of pure CD, PP and their graft copolymers as indicated; c) UV- Vis spectra of CD and indicated graft copolymers. Vertical lines indicate the peak position for n-π^{*} transition of carbonyl peak; d) Molecular weight analysis through gel permeation chromatogram of graft copolymers.*

Appearance of the signal at δ~7 ppm which is labelled as '*a*' in spectrum indicates the urethane proton form NHCOO group, particularly caused by the reaction of -NCO with –OH group. The intensity of NH peak at 7 ppm is enhanced as the number density

prepolymer chains increase on CD leading to higher content of hard segment. The intense peak at δ~1.5 ppm and 3.9 ppm corresponds to the methylene proton of PTMG ***(Figure 4.1a)*** and HMDI, respectively, further supports the grafting of polyurethane on CD ring. The extent of grafting /degree of substitution is calculated by the ratio of integrated peak area of -OH at δ~4.4 ppm and CH at δ~1.5 ppm from PTMG. Degree of substitutions are found to be 45 and 20 % and samples are thus termed accordingly CgP-H and CgP-L, respectively, where H and L after P represents high and low graft density of prepolymer. Grafting is further confirmed through FTIR spectroscopy where the absorption peaks at ~1720 and 1540 cm^{-1} are characteristic peaks for urethane carbonyl and urethane NH bending, respectively. Another intense peak at 1680 cm^{-1} in both the copolymers is assigned for hydrogen bonded >C=O which is also present in prepolymer and its intensity is reduced in highly grafted systems indicating predominant intermolecular hydrogen bonding (***Figure 4.1b***). While slight shifting in free >C=O peak is attributed to interactions with neighboring >NH groups. Broader peak in the region 3300 - 3500 cm^{-1} is predominantly due to -OH stretching vibration of CD which is narrowed and shifted to lower wavenumber in graft copolymers. Peak in this range further splits in two peaks at 3497 and 3334 cm^{-1} assigned for free and hydrogen bonded >N-H stretching vibrations, respectively, for PP which are shifted to 3304 cm^{-1} in CgP-H due to extensive intermolecular hydrogen bonding between PP chains in high graft density copolymer as opposed to doublet peaks at 3306 and 3447 cm^{-1} in CgP-L, a low graft density copolymer, where interaction of grafted PP chain with CD (intramolecular hydrogen bonding predominates). UV-Vis absorption peak for CgP-H has shifted to lower wavelength as compared to PP whose peak appears at 275 nm, assigned for $n \rightarrow \pi^*$ transition (***Figure 4.1c***).

This blue shift in graft copolymers is presumably due to wrapping of polyurethane chains around CD molecule making it a constraint system. Molecular weight distribution analysis is done through gel permeation chromatography. The synthesized graft copolymers show high molecular weight having low elution time than that of prepolymer, highly grafted copolymers CgP-H exhibit highest molecular weight of 53k as compared to less grafted copolymers CgP-L having molecular weight of 28k (***Figure 4.1d***).

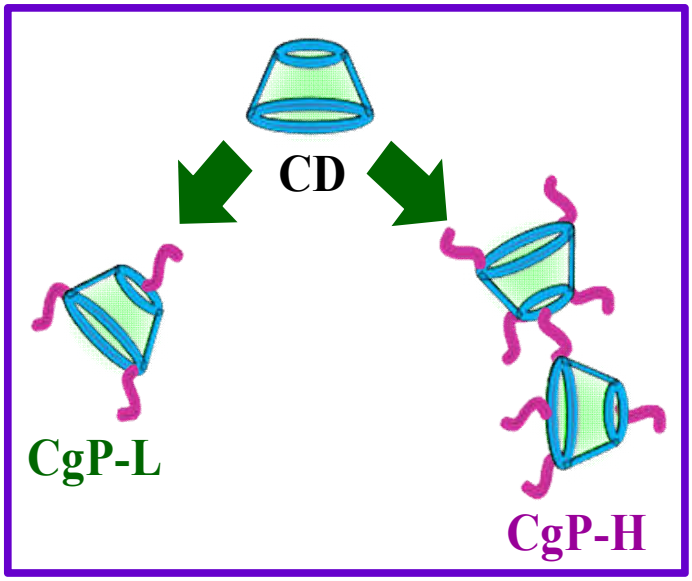

Figure 4.2: *Model showing formation of two different graft density copolymers.*

Both the grafted copolymer displayed unimodal distribution with relatively low polydispersity index of ~1.5. It is worthy to mention that graft density increases the molar mass of the copolymers as expected. A representative cartoon for the graft copolymer is presented in ***Figure 4.2*** showing varying graft density and expected to have different properties from the molecular architecture.

4.2.2 Thermal and mechanical responses in graft copolymer

Thermal stability of the graft copolymer is compared from the weight loss measurement under heat treatment using thermogravimetric analyzer. Native cyclodextrin starts decomposing at ~300 ^{o}C due to degradation of glucose units while weight loss at 100 ^{o}C is due to evaporation of adsorbed water.[135] Thermal stability is enhanced in graft copolymers and the degradation temperature increases by 35 ^{o}C after grafting with prepolymer chain on CD (***Figure 4.3a***). Degradation temperatures for CgP-H and CgP-L are found to be 348 and 343 ^{o}C, respectively, illustrating better thermal stability of graft copolymers as compared to pure CD. Wrapping of PP chain having greater thermal stability on CD is responsible for improved thermal stability of the graft copolymers. Temperature corresponding to 5 % weight loss is considered as the degradation temperature. Further from DSC analysis, pure PP showed endothermic peak at 38 ^{o}C due to the melting of its soft segment content while both the graft copolymers exhibited single endothermic peak at 23 ^{o}C and 22 ^{o}C for CgP-H and CgP-L, respectively (***Figure 4.3b***). It is important to mention that lowering of melting point in graft copolymer is due to strong interactions as discussed in above sections while relatively higher heat of fusion (ΔH_m) in CgP-H (27 $J.g^{-1}$) vis-à-vis CgP-L (22 $J.g^{-1}$) further strengthen the strong intermolecular interactions in highly graft copolymer (CgP-H) against intramolecular interactions in less grafted copolymer (CgP-L). Lower melting point and reduced heat of fusion is the indicator of strong interaction in polymers.[136] Intermolecular interaction in high graft density copolymer lead to the formation of crystalline aggregate through hydrogen bond formation between hard segments of two neighboring molecules.[170]. Hence, better thermal stability and strong interactions in copolymers is evident from thermal study.

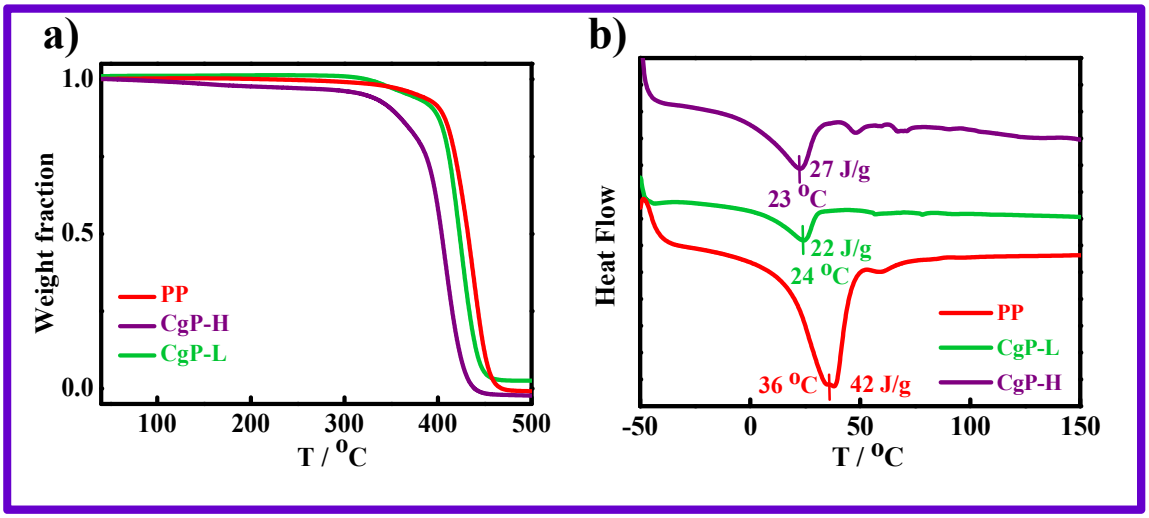

***Figure 4.3**: a) Thermal stability (TGA thermogrammes) of pure CD, PP and their indicated grafts; b) DSC thermograms of PP and its indicated graft copolymers showing melting temperature and heat of fusion.*

Stress-strain curve measured through uniaxial stretching of both the graft copolymers is presented in (***Figure 4.4a)***. Higher elongation at break is observed in high graft density copolymer (CgP-H) along with stiff rise of stress under uniaxial tension indicating its superior mechanical strength than that of low graft density copolymer (CgP-L). Toughness, as measured from area under stress strain curve, and stiffness, as calculated from the initial linear slope, clearly show higher value for high density graft copolymer vis-à-vis low density graft copolymer (***Figure 4.4b&c***). This enhanced toughness and elongation at break can be accounted for larger chains of PP in CgP-H which provide flexibility and also suppress the crack propagation which depends on the concentration of the hard segment and intermolecular hydrogen bonding within the hard domain.[137] Mechanical testing of PP and pure CD could not be studied using UTM due to low molecular weight of PP and powdery nature of CD. Amorphous nature of copolymer is further supported by XRD measurement where pure CD displayed crystalline peaks and PP as well as graft

copolymers are found to be amorphous since the PP chain is quite small and wrapping up over CD molecule convert the graft copolymer as amorphous (***Figure 4.4d***).

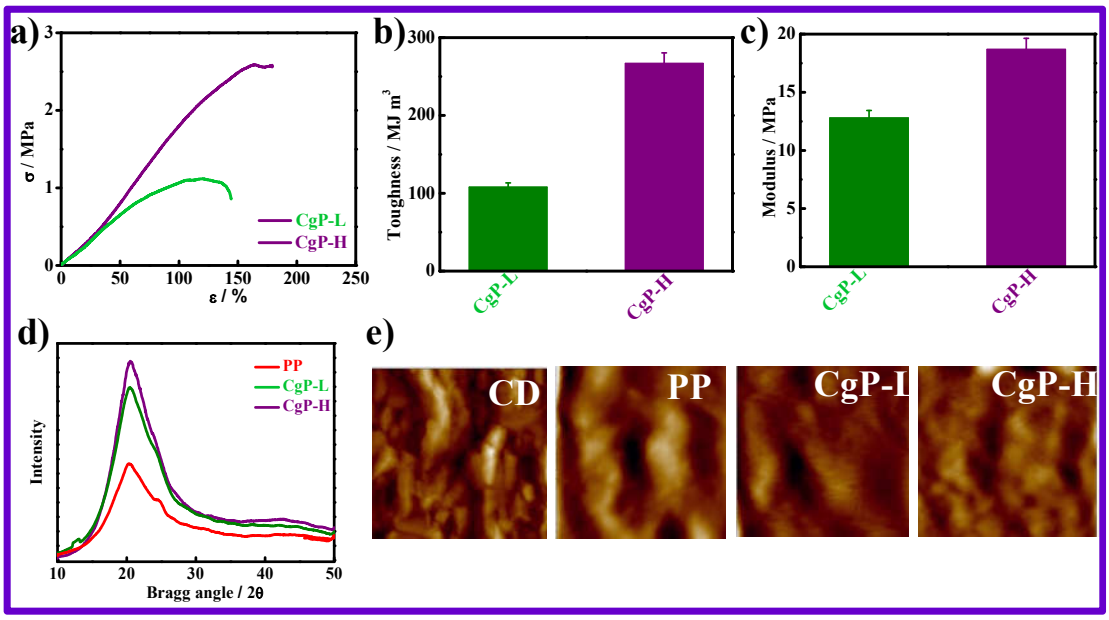

Figure 4.4: *a) Stress–strain curves of graft copolymers under uniaxial stretching showing elongation at break; b) Toughness of indicated graft copolymers; c) Modulus of the graft copolymers; d) XRD patterns of pure CD, PP and their graft copolymers; and e) AFM images of CD, PP and their indicated grafts in semi contact mode (5×5 μm^2).*

The mechanical properties of grafted copolymers are appropriate and thereby make them suitable for drug delivery vehicle especially for implant purpose. Surface morphology is assessed through AFM imaging where surface topography along with roughness and average size of inhomogeneities. Pure CD displayed granular /particle morphology with average dimension of ~400 nm (***Figure 4.4e***). Graft copolymers display strip like morphology which is prominent in CgP-H presumably due to hydrogen bonded agglomeration in the hard segmented zone as discussed earlier. Alternate bright and dark strip pattern in graft copolymers arises due to hydrogen bonding interactions among polar

groups between >C=O and >N-H which govern the morphology of graft copolymers. Distinct phase separation observed between dark phase and bright phase which are characteristics for softer matrix and hard segment in CgP-H supports greater intermolecular hydrogen bonding.[140] The average roughness values of entire micrograph of both the grafted copolymer are 22 and 52 nm for CgP-L and CgP-H, respectively, and this contrast indicates the induced self assembly in polyurethane chains and extensive hydrogen bonding[170] between polymer chains through urethane linkages. The shifting in stretching frequencies of the N-H bond in PP from 3334 to lower frequency range of ~3306 and 3304 cm^{-1} for grafted copolymers as discussed above firmly supports the extensive hydrogen bonding in high density graft copolymers.[138, 171]

4.2.3 In-vitro drug release and polymer drug interaction

The prime importance of drug release system is to deliver the therapeutic molecule at specific target on the need of the physiological environment over a period of time maintaining the appropriate drug concentration in the body. *In-vitro* drug release kinetics of dexamethasone (5 wt % w.r.t. polymer weight is embedded in polymer matrix) from CgP-H and CgP-L are carried out in PBS solution (pH~7.4). The total amount of drug release from pure CD and graft copolymers are calculated and release kinetics are presented in (***Figure 4.5a)*** as a function of time. Pure CD and PP release the drug in a very short span of time (within 2 h). On the other hand, sustained release is observed in graft copolymers. Around 10 % initial burst release is noticed in both the grafted systems due to drug adhered at the surface. However, the burst release phenomena of pure CD is subdued through grafting it with suitable graft density of PP chain over CD molecule causing the release of 56 and 40% of drug from CgP-H and CgP-L, respectively, in 42 h. The initial slow release

in high density graft is presumably due to more prepolymer chains covering the CD molecule creating a barrier and thereby causing initial slow release. As discussed before, intramolecular hydrogen bonding in low density graft copolymer forms a relatively confined structure in CgP-L where interactions of CD with PP is predominant, so the drug molecules persists in a better way between chains resulting significant sustained release against open structure in highly grafted system where intermolecular hydrogen bonding occurs causing relatively slight fast release. Based on this architecture, controlled release is understood from the varying diffusion phenomena and is presented in a carton in ***Figure 4.5b,*** which explains reasonably well the relative drug release kinetics from various architectures of graft copolymers. There are certain steps involved in release of drug from polymer matrix like penetration of solvent in the matrix, dissolution of the drug and diffusion of the drug from the matrix and amongst these steps any of them could be rate determining for the overall kinetics of drug release.[172]

For understanding the mechanism the release kinetics of drug, the data points are fitted with various models like zero order, first order, Higuchi and Korsmeyer-Peppas model presented in ***Figure 4.6*** *and* ***table 4.1*** but the kinetics are well fitted with Korsmeyer-Peppas model with (r^2 ~0.99) leading to exponent n values of 0.52, 0.31, and 0.7 for CgP-H, CgP-L and PP, respectively, indicating non Fickian diffusion (n> 0.45) behavior for high graft density copolymer as opposed to Fickian diffusion for low graft density copolymer (***Figure 4.5a***). However, sustained drug release from grafted copolymers is due to wrapping of polyurethane chains around CD ring which hinders the drug release from the polymer matrix and overall grafted systems acts as the good delivery vehicle. Further the less grafted copolymers CgP-L exhibited better sustained release as

compared to highly graft system which is mainly due to intramolecular interactions as discussed earlier. A schematic representation of drug release is shown in ***Figure 4.5b*** indicating fast release from pure CD against sustained release in grafted systems.

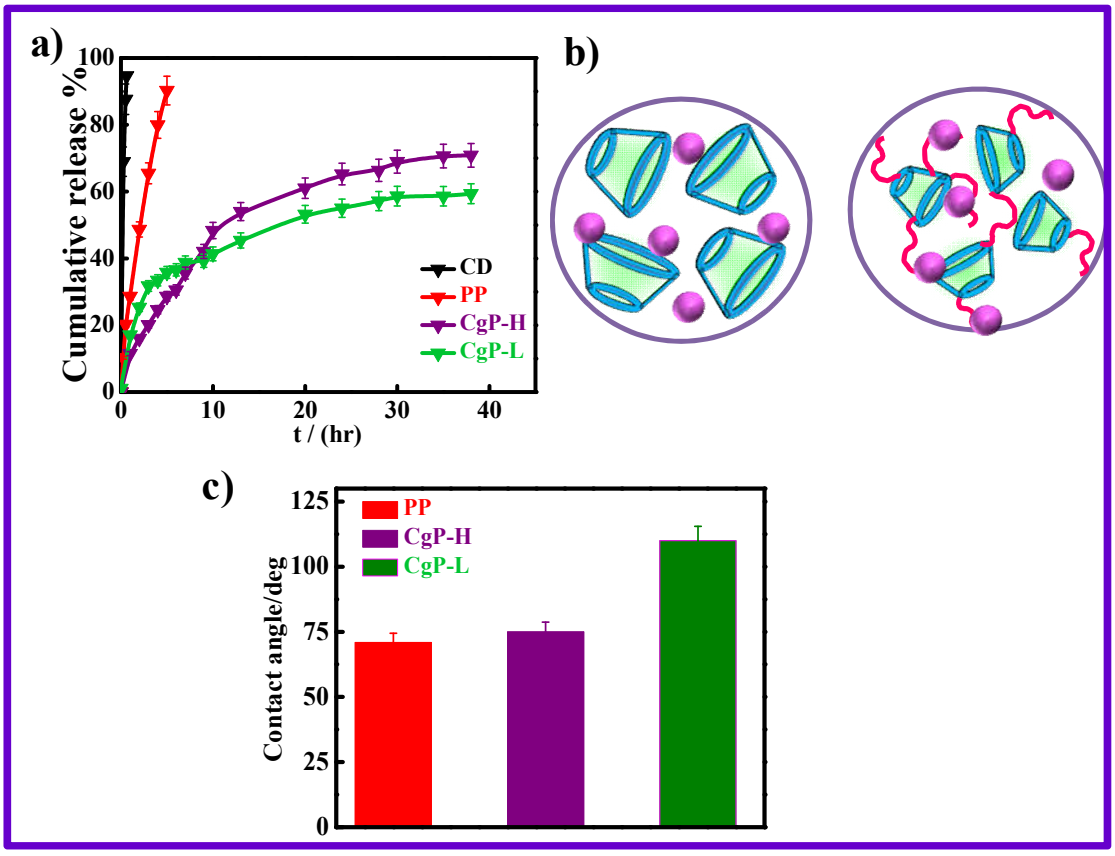

Figure 4.5: *a) Cumulative release profiles of drug loaded graft copolymers indicated, showing controlled drug release profile from graft copolymers; b) Schematic model showing the drug release from pure CD and graft copolymer. c) Contact angle of graft copolymers and PP showing low graft density copolymers are hydrophobic as compared to high graft density copolymer.*

Nevertheless, slower diffusion of drug is the rate determining step which is controlled by the wrapping of CD ring with PP chain and also by making it hydrophobic from the original highly hydrophilic nature of pure CD. Contact angle predicts the hydrophilicity of

the test sample and higher value of CgP-L (120^o) suggests hydrophobic character against considerably lower value of CgP-H (90^o) which further strengthen the schematic/cartoon structure and resulting hydrophilic-hydrophobic balance, by controlling the graft density using prepolymer graft, which finally regulate the drug release behavior from graft copolymer matrix (***Figure 4.5c***). Incorporating hydrophobic component on polymer surface interrupts the polymer packing in solution phase creating free passage arising from intermolecular hydrogen bonding which leads to faster drug release. Greater swelling of low graft density copolymer (CgP-L) as compared to high graft density (CgP-H) copolymer also corroborate the greater hydrophobic character with less graft density of PP on CD.

Interactions between drug and copolymers also control the drug release form polymer matrices which are revealed through spectroscopic and thermal analysis. Native drug (dexamethasone) in solid state exhibits the characteristic UV-Vis absorption peaks at 273 and 340 nm and the peaks are shifted to lower wavelength in CD-d (drug loaded CD) to 271 nm (***Figure 4.7a***). Further blue shift has been observed in CgP-H-d (drug loaded CgP-H) to 270 nm clearly indicate stronger interaction between drug and graft copolymer as compared to CD and drug interaction. Blue shifting of drug absorption peak appears from its confinement within the CD core or grafted CD core.[173] Similar trends are observed in low density graft copolymer with slight shifting (3 nm) indicating interaction between polymer and drug. Differential scanning calorimetry is employed to understand the interaction between drug molecules and graft copolymers as a carrier matrix. DSC thermogrammes of pure and drug loaded copolymer (CgP-H-d) are presented in ***Figure 4.7b.***

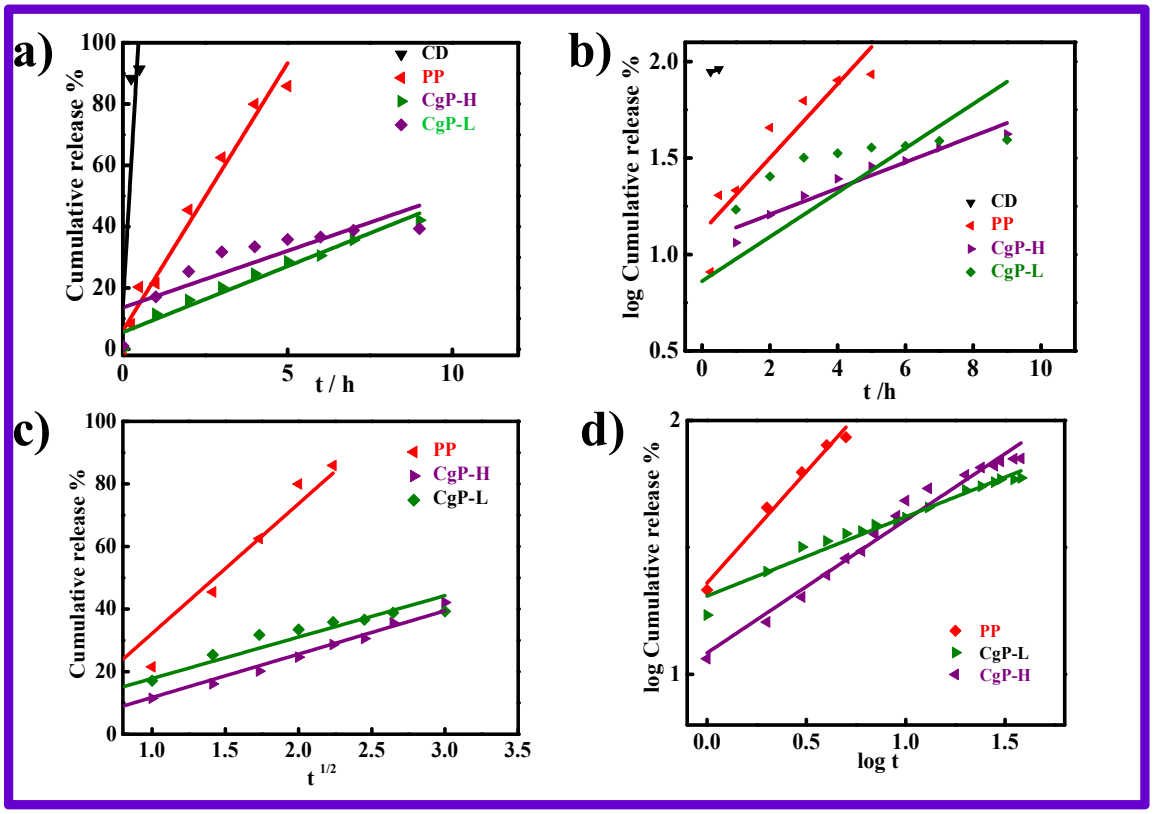

Figure 4.6: *Mathematical models for drug release kinetics. a) Zero order model, b) First order model, c) Higuchi model, d) Korsmeyer- Peppas model. The correlation coefficients along with other parameters for each model are presented in table below*

Table 4.1: *Release constant k, correlation coefficient (r), release exponent (n) calculated from various models for short chain PU graft*

Sample	First order		Zero order		Higuchi		Korsmeyer Peppas	
	k	r^2	k	r^2	k	r^2	n	r^2
PP	0.2±0.03	0.83	15.14±1.2	0.96	38.45±0.32	0.95	0.85	0.97
CgP-H	0.06±0.03	0.93	4.3±0.12	0.95	13.8 ±1.6	0.98	0.52	0.98
CgP-L	0.1±0.01	0.38	0.1±0.45	0.70	13.2±0.45	0.94	0.31	0.99

The depression in melting point along with reduced heat of fusion clearly indicates interaction between two components.[174] Slight reduction in melting point of drug loaded copolymer to 21°C from the pure copolymer of melting at 23 °C is observed. This decrement is due to interaction arising from the components and further, the reduction in heat of fusion (ΔH) of the said reduces in presence of drug to 20 $J.g^{-1}$ as compared to pure copolymer value of 27 $J.g^{-1}$. Thus, from both spectroscopic and thermal measurements provide information about interactions between drug and copolymers which contributes in the steady release of drug from graft copolymers and the sustained release of drug is visualized from these relative interactions with drug and polymer matrix.

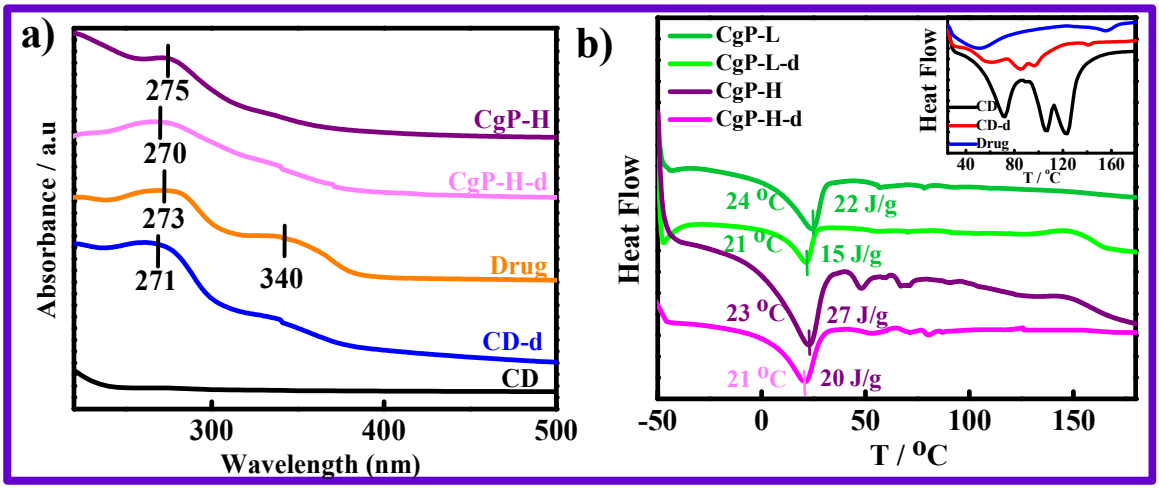

Figure 4.7: *a) UV-Vis spectra of drug loaded graft copolymer and CD showing polymer-drug interaction. Vertical lines indicate the respective peak positions; b) DSC thermogrammes of representative CgP-H and its drug loaded sample showing depression of melting peak and heat of fusion in presence of drug.*

4.3 Biocompatibility and in-vitro toxicity

Effective drug delivery systems should be biocompatible in quality for its application in biomedical fields. Here, MTT assay has been used for biocompatibility assessment of graft

copolymer using HeLa cells. The cell viability of HeLa cells on polymeric film surfaces is studied through MTT assay. Cultured cells without polymers are taken as control. Cell viabilities of graft copolymers are almost similar for 1, 3 and 5 days of cell culture (***Figure 4.8a***). Interestingly, the cell viabilities for graft copolymers are higher than control revealing their biocompatible nature. Cell viability data is further supported by the fluorescent images of cell proliferation on polymer films using acridine orange and ethidium bromide dye (***Figure 4.8b***). Cell morphology displays good health of cells as compared to pure CD. Further, biocompatibility is studied through optical density of adhered HeLa cells on polymer film surfaces (***Figure 4.8c***). Graft copolymers exhibit better cell adhesion property as compared to pure CD as evident from the spreaded morphology on graft copolymers vis-à-vis slightly squeezed morphology on pure CD. Cell adhesion is almost similar in both the graft copolymers indicating better biocompatibility of graft copolymers over pure CD. CD and polyurethanes are well known biocompatible material.[147, 175] Thus, time dependent MTT assay unveils the anti toxic nature of graft copolymers and better biocompatibility of CgP-H and CgP-L over CD as explained from their respective surface morphology which is further confirmed from the cell morphology using fluorescence imaging of HeLa cell after staining with acridine orange and ethidium bromide.

In-vitro sustained drug release is presented above using drug loaded graft copolymers. Now, it is pertinent to understand the efficacy of control release of drug in synthesized biocompatible copolymer using cell line *i.e.* the killing efficiency of the drug loaded polymer vehicle. Cytotoxicity against HeLa cells after 24, 48 and 72 h treatment using free drug, drug loaded CgP-H and CgP-L carriers are evaluated using MTT assay. In day 1, the

cell killing efficiency of pure drug and drug embedded in CD is relatively high (low cell viability) mainly due to fast release of drug from CD matrix (***Figure 4.8e***). On the other hand, initially the cell killing efficiency of drug embedded in graft copolymers is low (25%) but over a period of time that goes steadily very high (low cell viability (75%) while the cell viability of pure drug or CD-d keep on increasing with time. The increasing tendency of cell viability of pure drug and CD-d over time is due to non-availability of drug in longer time period (as most of the drug is consumed within one day). In contrary, slow release of drug from graft copolymers constantly supply drug to media and efficiently kill the cancerous cell for longer period of time (up to 5 days).

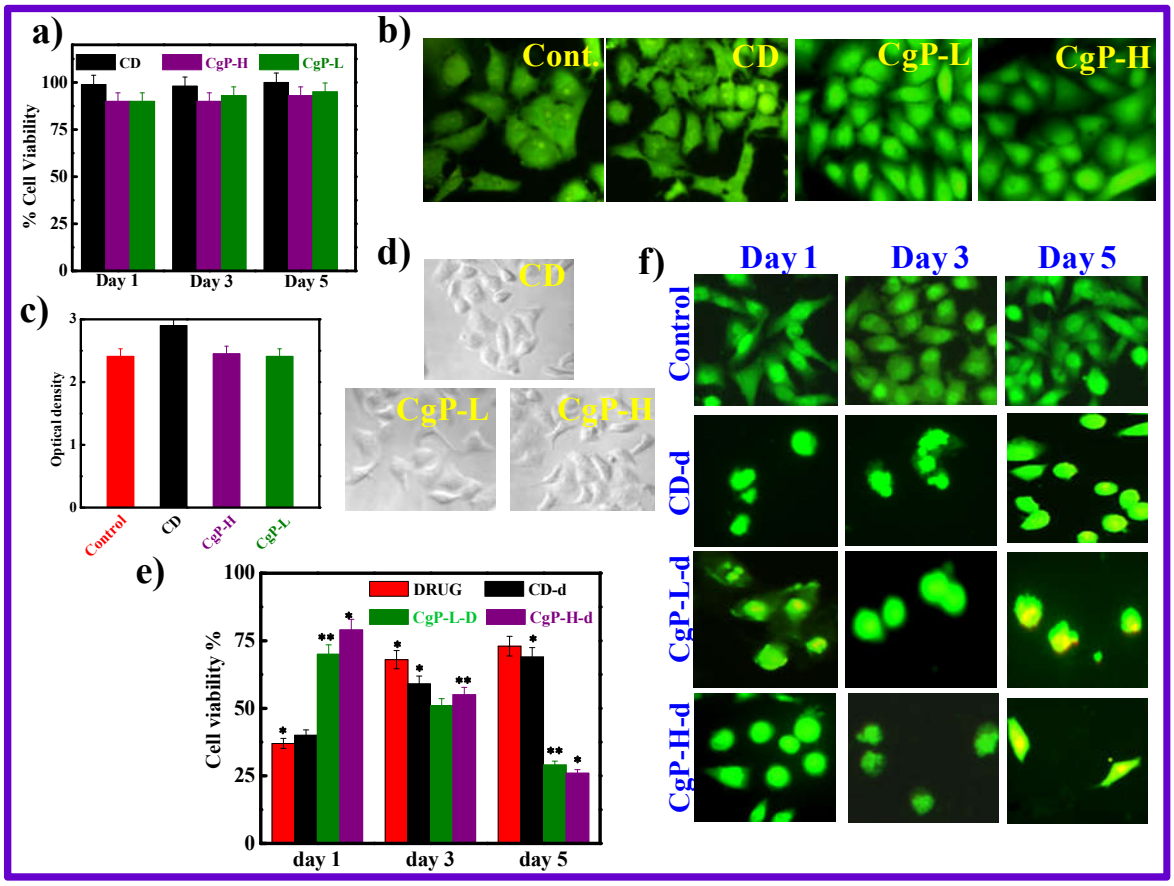

Figure 4.8: *Biocompatibility assessment through cellular studies: a) Cell viability of indicated samples at three different time interval through MTT assay measurement of pure CD and indicated graft copolymers; b) Fluorescence microscopic images of cell cultured on indicated grafted copolymers and images are taken after 24 h of incubation (mag 40×); c) Cell adhesion, depicting morphology of the cells over polymer/graft copolymer surfaces; d) Phase contrast images of adhered cells over various indicated sample surfaces; e) In-vitro cytotoxicity of native drug and drug loaded graft copolymers against HeLa cells after 1, 3 and 5 days of incubation time interval; and f) Fluorescence images after AO/EB staining of cells treated with pure drug and indicated drug loaded graft copolymers showing relative number density of cells and their health after treatment as mentioned.*

Hence, the efficacy of slow release from graft copolymer is realized to kill the cancer cells. Cell viability declined gradually with time and as low as 25 % viability indicating 75% cell mortality after 5 days of treatment with drug loaded graft copolymers while for pure drug cell viability has increased. Due to burst release in pure drug into the medium causing rapid

cell death within 24 h, while in case of grafted copolymers the initial cell viability was quite higher but significantly reduced up to 72 h mainly due to sustained delivery of drug for longer period of time as observed *in-vitro* drug release study (***Figure 4.5a***).

Nevertheless, at the end of 5 days the mortality rates are 73 and 25% for pure drug and drug embedded in graft copolymer, respectively, indicating the importance of sustained release of drug from copolymers against burst release in drug loaded CD. It is the amount of drug released with time that controls the cell killing as reflected from varying time interval with higher killing at 5 days of incubation. Furthermore, EB/AO staining results demonstrate directly the cell compatibility with drug loaded copolymers. Cells in control, where no treatment is given, are healthy having green nuclei with uniform chromatin and intact cell membrane (***Figure 4.8f***). On the contrary, cells treated with grafted systems displays apoptosis having yellow nuclei and condensed chromatin with shrinkage of nucleus. AO/EB staining is a rapid and quite simple technique for detecting live and apoptotic cells. Acridine orange is permeable to membrane of live and dead cells both while ethidium bromide only binds to DNA of dying cells or cells that have lost membrane cleavage.[176] The fluorescent images of native drug showed a significant cell killing on day 1 which is due to burst release of drug and after day 3 there is cell growth due to non availability of drug in the media at longer time. Treatment with drug loaded CgP-H shows the presence of both viable as well as apoptotic cells at both 3 and 5 days of incubation and significant decrease in cell density is observed which is attributed to sustained release of drug (availability of drug) in the media for longer period of time. It is important to mention that healthy cells are observed in control up to 5 days. It is pertinent to mention that the amount of pure drug and the total content of drug in each copolymer are kept constant for

these comparative studies. However, controlled cellular studies supports the rapid and consistent killing of cells with time in drug loaded graft copolymers as compared to pure drug or drug embedded in CD only exhibit meager decrease in cell density showing the efficacy of sustained drug release from the grafted copolymers.

4.4 Conclusion

Polyurethane grafted cyclodextrin are synthesized by varying graft density of polyurethane on CD backbone. The chemical tagging is confirmed through NMR and molecular weight measurement studies. The chemical properties of graft copolymers are compared with pure prepolymer or CD. Greater interactions in the graft copolymers are revealed through FTIR and UV-Vis spectroscopic techniques and comparison is done with pure CD / prepolymer.

Grafting of polyurethane has enhanced the thermal stability as compared to pure CD. Graft copolymers are tougher and stiffer by design as evident from high elongation at break and Young's modulus measured through uniaxial stretching. Inter and intra molecular hydrogen bonding is established from FTIR studies which induce open and closed architectures of high and low graft density copolymer, respectively, which in turn control the drug release kinetics. Sustained drug release is achieved from graft copolymers as opposed to burst release from pure CD or prepolymer. The wrapping of polyurethane onto CD backbone hinders the drug to come out to media and, thereby, slow diffusion is observed in graft copolymers. Biocompatibility of these graft copolymers is investigated through MTT assay, cell adhesion and fluorescent images indicating the developed materials as biocompatible controlled drug delivery vehicle. Significantly high cancer cell killing efficiency is achieved using drug loaded graft copolymers as compared to initial fast killing followed by cell proliferation at longer time using pure drug or drug embedded in CD.

Thus control and sustained drug delivery along with excellent biocompatibility of these graft copolymers with its superior thermal and mechanical properties make it as captivating biomaterial for drug delivery and tissue engineering purpose.