



Cyclodextrin Modified Block Polymer for Oral Chemotherapy

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Author's contribution

The sole author designed, analysed, interpreted and prepared the manuscript.

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ABSTRACT

Cationic polymers have received much attention for their potential use as nonviral gene delivery agents. Under certain conditions, these polymers self-assemble with poly(nucleic acids) via electrostatic interactions and condense them into submicron size particles that can be endocytosed by cells. Many drugs are commercially available for cancer treatment but most of them lacks in terms of poor solubility thereby resulting in inappropriate treatment. This research was planned and tested to ensure the preservation of product safety in our body for enhancing bioactivity of hybrid cyclodextrine nano-capsules, wherein cyclodextrin molecules are modified with Poly(e-Caprolactone)-Poly(Ethylene Glycol) (PCL-PEG), wherein nanocapsules were prepared from cyclodextrin and further were coated with PCL-PEG for enhancing cellular uptake and interacting with biological films in order to provide drug delivery of anti-cancer agent i.e. camptothecin. The nanocapsules were then further subjected to characterization studies which comprises zeta potential, drug release profiles, in-vitro toxicity and transfection effectiveness.

Keywords: Anti-cancer; Cyclodextrin; Nanocapsules; Poly(e-Caprolactone)-Poly (Ethylene Glycol).

1. INTRODUCTION

Cancer is the world's main deadly illness, as cardiovascular diseases are the leading cause of

death worldwide. With improvements in chemotherapy for decades, it is recognized that inadequate breakthroughs occur in therapeutic diagnosis of cancer. Usefulness and health of

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cancer treatment are still limited by some restrictions. The main disadvantage is poor water solubility as most chemotherapeutic agents are hydrophobic [1]. Another essential consideration is that chemotherapeutic medications easily spread throughout the bloodstream that are consumed by both tumor and normal cells leading to their non-specific cytotoxic effects. However, low therapeutic metrics of chemotherapeutic agents, a dramatic growth in blood level and its apparent decay is among the limits of cancer treatment [1].

During chemotherapy surge in drug amount with blood decreases at the time of cooling span thereby limiting the therapeutic effect and contributing to tumor cell proliferation. Cationic polymers got tremendous publicity on their usage as non-viral genomic transmission agents is possible [2]. Such polymers self-organize under suitable conditions with poly(nucleic acids) electrostatically followed by condensing into particles of small size. Polymeric gene delivery carriers comprise many significances over non-immunogenicity, resiliency and easy manufacturing of viral counterparts which increase their attention for cancer gene therapy [3]. But because of their instability and propensity to accumulate certain gene-supply nanoparticles are not appropriate for systematic administration within conditions in physiology [3].

Although, intravenous path of cancer treatment is more popular than other methods, oral medication is considered to be a cornerstone in potential treatment [4]. The oral path permits pain free self-medication through the patient's point of view and therefore is the crucial practical path. Drug delivery mechanisms for Nano particulates are successful. Nanoparticles are referred to as Nano spherical or Nano capsular particles in nano size. Nanosphere are classified as matrix systems, while nano capsules are central shell forms made up of the internal liquid centers which are enclosed by a polymeric sheath [5]. Nanocapsules have many benefits such as increased water solubility, maintenance of product quality by environmental safety, targeted release, and enhancement of optimal pharmaceutical profile. The oily nucleus offers a better solubilization in hydrophobic drugs, while the polymeric sheath surrounding it offers shelter of molecules in action towards the brutal environment, taking account of significance of nanocapsules according to their structure [5,6].

Cyclodextrins (CDs) referred to as cyclic oligosaccharides comprises of glucopyranose

blocks linked via α -1,4-glycoside bonds [7]. The broad use of CDs in various fields, such as medication and polymers. The interesting capacity is to develop food technology integration clusters with different active ingredients. The surface alteration of blood vessels graft and bone implantations has been investigated in recent years with Cyclodextrin (CD) polymeric materials [8]. Polyester blends of cyclodextrins and different types acids such as citric acid and 1,2,3,4-butanetetracarboxylic acid have been included in these experiments [9]. The above changes lead to end-stage showing enhanced sorption features for instance, variety of common antibiotics including vancomycin, rifampin and Ciprofloxacin and so forth. The effect on sorption features of final product of polymer blend and free carboxylic groups is, nevertheless, not disclosed [10].

In the present paper, cyclodextrin is coated with biodegradable block polymers to provide a modified polymer that enhances the retention of the drug within the body of cancer patients at the time of chemotherapy and provide targeted drug delivery. Till date many researches have been performed on anti-viral drug but to the best of knowledge combination of cyclodextrin with Poly (ε-Caprolactone)-Poly (Ethylene Glycol) is a topic of interest.

Research in different areas of globe have been ongoing that show that oral cancer has been badly or incorrectly identified by dentists. Early diagnosis of oral carcinoma is most successful way to boost the recovery and decrease patient morbidity. The goal would be to research specific dentists' awareness, views or perceptions regarding oral carcinoma in general clinical procedure in Spain [11]. In U.K., oral carcinoma and esophagus are 42,400; fewer than 1 quarter in reported case of lung carcinoma. In a strong comparison, oral mucosa and pharyngeal carcinoma account for approx. 14-35 per cent of all carcinomas in men and 4-15 per cent of all carcinomas in women as per population dependent cancer report released by "Indian Council of Medical Research" (ICMR). Though cancer occurs for just about 6-15% of all man and approx. 1.5-3% in female cancers. This is too a disparity between the various areas of world in prevalence of carcinoma on specific locations of the upper arm. Oral carcinoma is very common disease by far [12].

Recent advances in the oral chemotherapy have been done, both conventional cytotoxic and new target inhibitors, from perspective of patients,

doctors, medication manufacturers and healthcare professionals. Clever medications, tailored to intracellular signaling components like protein kinases, could be more effective medium and long-terms [13]. Some treatments are known as oral imatinib and iressa drugs that point the nation. Imatinib activates tyrosine kinases of c-abl and c-kit. The oral organic material of both Chronic myelogenous leukemia (CML) [14] and Gastrointestinal (G.I) has outstanding bioavailability and exceptional behavior. The stromal tumors 'powered' by the signal peptide and c-kit [15]. Iressa (ZD 1839) known as oral EGFR tyrosine kinase inhibitor delivered once a day through the mouth and involved in glioma carcinoma [16]. Another oral quinazolinhas been found in iressa and tarceva respectively EGFR tyrosine kinase inhibitor that is also responsible for glioma carcinoma and headache cancers [17]. Substances of specific molecular properties stress the contamination in 'class effect' cannot automatically be minimized by the path of implementation alone. Although the above mentioned research was effective but faced problems lacks in terms of stability. For example imanitib is stable for 1 week. Thus, the present paper involves the formulation with improved drug stability and enhanced bioavailability.

Poorly hydro-soluble drugs are still a concern, but a major category of drugs for treating a broad range of illnesses. The exploration is still small, and it is often restricted by the failure of a full knowledge of the impacts on bioactivity of the complex chemistry, physiology and biochemistry processes which take place independently together and throughout execution and absorption. The researchers described the problem such medications side-effects, discusses current approaches to overcome this and also tests the distribution of poorly water-soluble pharmaceutical goods through silicon and in laboratory. In order to enable improvements to be made in development of poorly hydro-soluble substances, a blueprint for future research is suggested [18].

From the above cited prior work of the researchers it may be concluded that, although conventional available medications are effective but still lacks in delivery of adequate amount of drug at the target site and also lacks in maintaining required amount of drug levels as well as enhanced bioavailability [19]. The anticancer agent used herein i.e. camptothecin is poorly hydro-soluble drug but is effective anti-cancer agent. Hence to enhance

the drug delivery of the hydro-soluble drug there is a need to develop a formulation that aids in delivering required amount of drug at the target site [20].

2. RESEARCH QUESTION

How to enhance drug delivery for oral chemotherapy?

3. MATERIALS AND METHODS

3.1 Design

To prepare cyclodextrin modified biodegradable block polymer, Poly(ϵ -Caprolactone)-Poly (Ethylene Glycol) i.e. PCL-PEG is coated with cyclodextrin by utilizing different solvents followed by which the final product is subjected to various characterization studies and their effect was observed in order to prove their effectiveness.

3.2 Sample

Samples involved in the development of the product includes: Iron oxide nanoparticles which are used herein as a core molecule, cyclodextrin (2.16g, from cyclodextrin manufacturing unit), Dimethyl Sulfoxide, Poly(ϵ -Caprolactone)-Poly (Ethylene Glycol).

3.3 Instrument

Instruments required for testing of the developed product includes: particle size analyzer, zeta potential analyzer.

The methodology involved in the synthesis of cyclodextrin modified Poly(ϵ -Caprolactone)-Poly (Ethylene Glycol) comprises of three steps: the first step involved synthesis of iron oxide nanoparticles and the second step involved fabrication of cyclodextrin on iron oxide particles and the third step involved synthesis of polymer.

3.4 Synthesis of Iron Oxide and Fabrication of Cyclodextrin on Iron Oxide Particles

Iron oxide (Fe_2O_3) was synthesized by a known co-precipitation method, wherein $\text{FeCl}_2 \cdot 4\text{H}_2\text{O}$ and $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$ were dissolved in 0.5 M of degassed HCl followed by frequent addition in 300 ml of 0.5 M ammonia solution to

obtain a reaction solution and was mechanically stirred in a nitrogen environment for 25 minutes at 50 degrees Celsius with a pH of 9.5 to obtain nanoparticles [4]. The nanoparticles were further collected and washed with deionized water and ethanol followed by freeze drying. Cyclodextrin was fabricated on iron oxide particles, wherein Fe_2O_3 acts as a core molecule [21].

3.5 Synthesis of Polymer

279 mg of Poly(ϵ -Caprolactone)-Poly (Ethylene Glycol) is mixed with 2.20 of cyclodextrin to obtain a mixture, Camptothecin was loaded by a penetration method [1]. The mixture was then dissolved in 100 ml of DMSO solvent to obtain a solution [22]. The solution obtained was then stirred at 75 degrees Celsius for 48 hours followed by transferring to a dialysis membrane of low molecular weight in order to dialyze the solution against water for a period of 7 days. The dialyzed solution was subjected to lyophilization to obtain a final product i.e. a solid of light color [23].

The final product thus obtained was then subjected to characterization studies in order to determine its efficacy. The characterization studies involved herein include: zeta potential, drug release profiles, in-vitro toxicity and transfection effectiveness [24].

3.6 Particle Size and Zeta Potential Calculation

Mean iron oxide incorporated cyclodextrin particle sizes and PDI profile were characterized by dynamic light scattering (DLS) (Malvern Zetasizer sequence, UK). Dispersion angle of 175° is used to assess nanocapsules. In mV along with Malvern Zetasizer, with angle approx. at 13° and 24°C , the zeta potential of the same was calculated [1]. That analysis has been done three times.

3.7 In-Vitro Cytotoxicity Test

In vitro toxicity test was done on MCF cell lines that possess great intestinal medicine absorption and is also capable of mimicking gastrointestinal hurdle to provide chemotherapy by MTT Assay. In this, MCF cell lines with circulation quantity 37-35, were cultivated on polycarbon films filters with seed density of 6.5×10^3 at seeding. Apical (455 μL) and basolateral (2 ml) filter insert were introduced to culture medium and substituted for 15 days every second day following the maintenance of cells under 96% air and 6%

CO_2 in a 96% humidity level incubator at room temperature [7].

3.8 Drug Release Profiles

Drug release profile of the nanocapsule was calculated in phosphate buffer saline with two distinct pH (7.5 and 6.5) at 37°C within three separate mass ratios. Within specific periods, new solution has been used to substitute solution for each sample. For determining the released amount, absorbance of individual solutions was measured at 495 nm. Figure represents drug release profiles of resultant modified drug. All the prepared samples can be identified as having a pH-responsive activity in the release sequence. In addition, release approach describes a continuous release pattern to allow for release rate also after 2 weeks [4].

3.9 Transfection effectiveness (Cyclodextrin-Modified Polyethylenimine Polymers for Gene Delivery)

Plating of a cells of PC3 i.e. (human prostate epithelial adenocarcinoma cells via ATCC) was done at 60000 cells/well in 25 plates 25 hrs before proceeding for transfection, wherein cells in every well were further rinsed at least for once by PBS prior to addition of 300 μL of Opti-MEM. Comprising polyplexes (2 μg of DNA incorporated with polycations at 15 N/P). Following this after 5 hrs, transfection culture was separated and substituted with 2 ml of accomplished media. After a period of 2 days the transfected cells were thoroughly washed from PBS and subjected to lysis by adding 105 μL of cell culture lysis buffer (Promega, Madison, WI) [7].

3.10 Statistical Analysis

The statistical analysis was performed using OriginPro software and data representation was done accordingly. Analysis of Variance (One way ANOVA) was performed to establish statistical difference and probability threshold below 0.05 (p value) was considered as statistically significant.

4. RESULTS AND DISCUSSIONS

In view of both pharmacodynamics and pharmacokinetics profiles, nanoparticles have great benefit, for example release patterns, bio-distributions, absorption rate and cellular uptake. The particles size will thus be in an ideal range that allows it possible for particulate

matter to disperse and infiltrate biologically across its films, as well as for efficient product encapsulation potential and long release. In order to refine the nanocapsules composition, the effect of CD concentrations, oil phase concentrations and the organic-aqueous liquid volume ratio was investigated. Table 1 demonstrates the influence of the synthesized polymer concentration over particle size, polydispersity index (PDI). Element size decreases sequentially with polymer volume, which further relates to decreased organic amount viscosity with decreased concentration of polymer.

Table 1. Cyclodextrin modified PCL-PEG impact on particle sizes and polydispersity index. The information below represents average result \pm SD values of different classes. The table shows the particle size and polydispersity index (PDI) of different concentration of polymer

Polymer amount (% w/v)	Particle size	PDI \pm SD
0.04	155 \pm 2.4	0.15 \pm 0.03
0.1	160 \pm 2.4	0.20 \pm 0.43
0.3	280 \pm 2.5	0.45 \pm 0.29
0.6	391 \pm 3.5	0.52 \pm 0.34

It was inferred that at 0.04% w/v polymer, amount of polymer achieved was small. Average particle size did not rise by two fold, even when the amount of polymers rises from 0.04 percent w / v to 0.3 percent w / v. The selection of the polymer amount may be critical to provide stabilization since polymer framework is a crucial protecting factor and stabilizing of embedded substances. Cyclodextrin nanocapsules were developed in the absence of any stabilizing agents. This implies that drug stabilization is mostly accomplished by polymeric layer. Hence, the polymer content, which is likely connected to polymeric film thickness, is a critical parameter throughout terms of area and durability of prepared nanocapsules. At \pm greater CD concentrations, PDI values demonstrated monodispersed particle spread and low polydispersity. Table 1 represent impact of polymer concentration on particle size and polydispersity index.

This pre-formulation analysis was undertaken to determine the ideal oil amount in order to reduce particle size and to optimize the potential to remove medication, specifically influenced by nanocapsules' oily core. Rise of oil concentration contributed to enhancement in

nanoparticle sizes as seen in Table 2. Improvement in viscosity of organic phase was due to such effect, provided that the greater the oil content is, more viscous the organic state. But the amounts 0.4% v / v and 2% v / v ($p < 0.05$) are significantly different from that of the normal size of the molecule.

Table 2. Impact of oil on particle sizes and polydispersity index. The information below represents average result \pm SD values of different classes. The table represents that 6.5% v/v of oil enhanced the nanoparticle size and PDI

Oil Concentration (%v/v)	Particle size	PDI \pm SD
0.4	180 \pm 2.4	0.08 \pm 0.03
2.0	210 \pm 2.3	0.10 \pm 0.42
5.0	250 \pm 2.5	0.25 \pm 0.20
6.5	386 \pm 3.5	0.32 \pm 0.31

Study of nanocapsule particles utilizing organically-aquaous layer density ratio 1:2, 1:3, 1:4 and 1:5 revealed the influence of growing aqueous state volume. Table 3 reveals that the total partial volume is constant from 1:3 and 1:5 to 2 organic volume ratios, which implies there really is no significant discrepancy in such ratios ($P > 0.05$) in respect of particle size. On the another side, for a lower amount of water (6 mL), the maximum particle size amount was produced, which implies that ratio from organic to aqueous form 1:1 was presumably mostly improved owing to weak separation.

Table 3. Effect of organic to aqueous phase ratio on particles size and polydispersity index

Oil Concentration	Particle size	PDI \pm SD
1:2	175 \pm 2.4	0.32 \pm 0.03
1:3	134 \pm 2.2	0.09 \pm 0.40
1:4	125 \pm 2.1	0.07 \pm 0.22
1:5	110 \pm 3.3	0.07 \pm 0.21

In-vitro cytotoxicity of the modified cyclodextrin was calculated by determining the IC₅₀ Value of the cyclodextrin- PLC-PEG at different concentrations.

Cell viability of MCF cancer cell lines cultured with modified cyclodextrin nanocapsules were also analyzed, wherein MCF cells were subjected to incubation for 3 days along with DMSO diluted compositions at dilution rate of 1:10 (Fig. 2). Following this, cytotoxic effects of nanocapsules were investigated. Incubation time is further dependent on exponential duration of

MCF cells line and also over-release features of formulations [25]. MCF cells possess an exponential period of about 40 hrs and an anticancer agent released through nanocapsules within 3 days in a sustainable way. This can be inferred from this that aggregation within cells requires long exposure. Both CD-nano carrying methods have demonstrated that further cancer cell death has occurred. The surface area of PCL-PEG coating content can be due to cytotoxic influence (Fig. 2). If the electrostatic contact between cell membranes and the nanoparticle is favorable, the modified polymer will improve the probability of cellular absorption by measuring the duration of residence throughout the cellular surface. Fig. 1. represents the cell viability of modified cyclodextrin.

Drug release outcomes are represented by Fig. 3. pH-responsive activity in their release cycles can be observed by all 3 trials. Findings show the most important change within pH-responsive behavior is related to the first sample with approx.76 percent of medications produced in acidic pH and approximately 34 percent in regular environments for 2 weeks as they have the higher level of release. It was observed that if the concentration of drugs is increased, the competition among drug molecules also increases to protect bursting of drugs and also increases duration of drug manumit. Although longer release time was observed but the concentration of drug released was same or greater than first sample during two weeks indicating that they possess a toxicity effect for greater duration of time. X-Axis represents time and Y axis represents %drug release.

Cell lysis and examination for 48 hours following transfection for gene expression was performed.

Expression of luciferase was identified near 5 N / P for certain composites and enhanced with load ratio up to potency (usually about 15 N / P; findings not demonstrated) in all composites. A 11 N / P analysis of transfectant behavior has been developed. Overall genome sequence-level (RLU / mg) behaviors are not standardized as the procedure selectively produces elevated values for tests with small protein concentrations arising from Polymer sensitivity. Full sampling luciferase (RLU / well) behavior is then recorded with independently analyzed polymer sensitivity.

The combination of cyclodextrins to CLP-PEG increases the performance of transfection. Improvement to just 4% to CLP-PEG reduced luciferase activity. Degree of cyclodextrin combination is related to reduced transfection; effects of 11 percent shift reduced transfection to one of 3 orders of magnitude.

From the above results it can be inferred that cyclodextrin modified with Poly (ε-Caprolactone)-Poly(Ethylene Glycol) (PCL-PEG) resulted in enhanced cellular uptake and easily interact with membranous layers for providing delivery of the anti-cancer agent i.e. Camptothecin thereby enhancing bioactivity of the hybrid cyclodextrin nano-capsules and aiding in treatment of oral cancer. The biodegradability of PCL-PEG makes it effective for not providing any damage to the formulation. Also production of PCL-PEG is easy and most importantly serves important role in delivering poorly soluble drugs (here, Camptothecin). The present formulation is

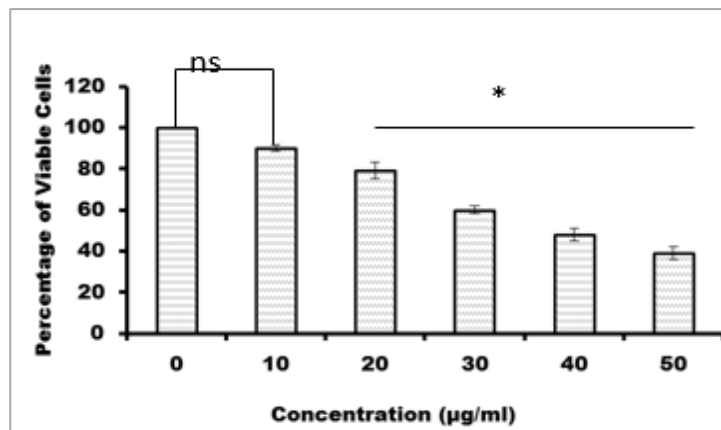


Fig. 1. Representation of Cell viability assay of Modified cyclodextrin at different concentrations for calculation of IC₅₀ Value. (ns- non-specific and *p< 0.05)

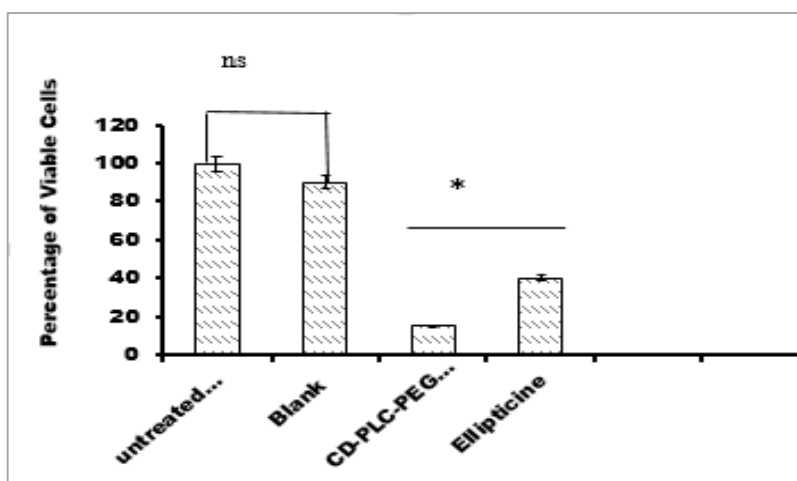


Fig. 2. Competitive representation of MFC cell viability assay of Ellipticine and CD-PLC-PEG nanocapsule. In this figure untreated group represents vehicle control, Blank represents cell treated only with Cyclodextrin shell, ellipticine represents in a free form (not enclosed in any shell), and CD-PLC-PEG represents the modified nanocapsule for enhanced delivery of drug to the target site. (ns- non-specific and * $p < 0.05$)

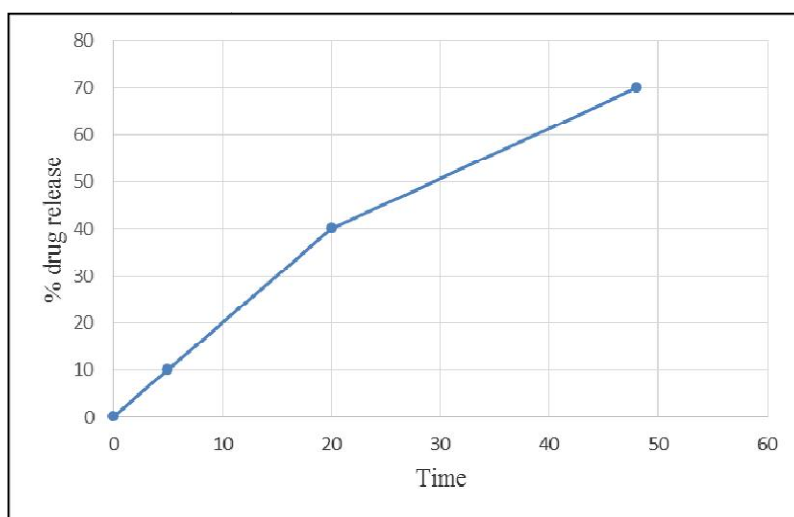


Fig. 3. Representation of Drug release % at pH 7.4, wherein the graph represents 70% drug release in 48 hours

advantageous than other known formulation used for drug delivery as many practices have been performed for delivery of hydrophilic drugs such as muco-penetration centered delivery. The muco-penetration centered delivery example include incorporation of Pluronic F127 (PF127) within liposomal matrix for inducing hydrophilicity [19]. However, they are not suitable for enhanced delivery of hydrophobic drugs thereby reducing the bioavailability of the formulation. The proposed cyclodextrin modified PCL-PEG is advantageous over aforementioned nano-

carriers in terms of enhanced delivery and increased bioavailability of hydrophobic drugs.

5. CONCLUSION

In this research nanocapsules of CPT-loaded amphiphilic cyclodextrin were first designed and tested in-vitro by performing different procedures. Particles size analysis indicates that polymer of 0.04% w/v was found to be convenient for improved solubility of the drug. Further, cytotoxicity analysis of the modified polymer

indicated that the cells were found to decrease the polymer toxicity. Cell viability analysis of the MFC cancer cells were performed where a decline in cancer cells were found. Drug release profiles also indicate that increase in drug concentration leads to increase in drug manumit duration. Finally, the transfection efficiency of the modified drug was also found to be enhanced. As a potential medicinal agent that will remove the impact on human cells and a substantial reduction in the dosage of opioid consumption contributing to the avoidance, cytotoxicity impact on tumor cells at quite low doses opposite the medication release trend and increase in medicine medicinal performance. The findings from these studies indicate that cyclodextrin nanocapsules have a naive approach for creating a secure and efficient oral therapies. Cyclodextrin nanocapsules may be an important technique for enhancing the efficacy of an anti - tumor medication CPT and its bioactivity. The confirmation of the results can be derived from in vivo studies involving animal models of oral cancer.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Author has declared that no competing interests exist.

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