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ANALYSIS ON BRAIN TUMOR TREATMENT BASED ON NANOCARRIER TARGETED DRUG DELIVERY SYSTEM

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ABSTRACT

Cancer is a group of diseases characterised by uncontrollable, abnormal cell growth. Research scientists have had a difficult time dealing with cancerous brain tumours. Furthermore, the lack of early-stage symptoms delays its diagnosis, resulting in a worsening of the condition. Surgical, radiation, and chemotherapy treatments still have a number of drawbacks. It is difficult for most anticancer drugs to cross the blood–brain barrier, because of their low solubility and limited therapeutic window. Solid tumours can be targeted with nanoparticles that take advantage of the enhanced permeability and retention effect. Using surface membrane proteins that are over expressed in cancer cells as targets for active targeting, which involves altering the nanoparticles' surfaces, it is possible to reduce uptake in healthy tissue while increasing accumulation in tumours. Antibodies, their fragments, aptamers, oligopeptides, or small molecules are commonly used as target molecules. Several FDA-approved nanomedicines are currently available, but none of them has been approved for the treatment of brain tumours. The surface modified nanoparticles will lead to enhanced delivery of the drug to the brain by prevention of the clearance by reticuloendothelial system and probable inhibition of the efflux mechanism of brain and ultimately enhance drug concentration towards target site. This targeted drug delivery will lead to reduction in dose and also will reduce drug related toxicity towards normal cells.

1. INTRODUCTION

1.1 Brain tumor

Primary and metastatic tumours of the central nervous system include brain tumours, which are one of the most dangerous diseases with a poor prognosis. Around 296,851 new cases of brain and nervous system tumours were discovered, and 241037 people died as a result, according to GLOBOCAN 2018. Every year, India sees 28142 new cases of brain tumours, with 24003 deaths in 2018 alone. India has a prevalence of 2.5 percent for men, 2.7 percent for women, and 1.6 percent for those with a 5-year survival rate of less than five years for brain tumours. Since the discovery of over 120 different types of brain tumours, tumours of neuroepithelial tissue, cranial and spinal nerve tumours, meningeal tumours, heamopoietic origin cancers and lymphomas, and tumours of the sellar region are among the most common. Meningiomas, intracranial metastases from systemic cancers, and glioblastomas, in particular, are the most common types of brain tumours. 29 percent of all primary brain and CNS tumours and 80 percent of malignant brain tumours are gliomas, the most common primary brain cancer. There are approximately 70 percent of new cases of primary brain cancer diagnosed as malignant gliomas, which originate from glial cells.

1.2 Current treatment approaches for brain tumor

In the fight against brain cancer, there are a variety of treatment options that are tailored to the patient's specific tumour characteristics and overall health, such as the patient's age and overall health. The multidisciplinary approach for treatment of brain tumor includes combination of surgery, radiation and chemotherapy. Most common initial therapy for brain tumor is chemotherapy. Various therapeutic moieties indicated in brain tumor are available in oral and parenteral dosage form in market. Currently, oral temozolomide, a first-generation drug for treating brain tumours, is administered. There are a number of other therapeutic drugs that have been suggested for use in the treatment of brain tumours, including irinotecan, carmustine, cisplatin, and lomustine. For brain tumours, most of the drugs have demonstrated enhanced anticancer activity. Insufficient barrier passage has been found to be a cause of clinical failure with these medications.

1.3 Limitations associated with chemotherapeutic agents

Prognosis for brain tumours is complicated by the tumor's self-protective nature (the BBB and cell alignment), genetic changes in the cells, transporters on the blood-brain barrier, and the properties of chemical agents used in treatment. A few hydrophobic agents and particles with a molecular weight of less than 500 Da can pass through the brain's blood vessels. The lipophilicity of a drug is an important consideration when designing new entities for the treatment of cancer. Increasing the lipophilicity of a drug can help it cross the BBB more easily, but this can also lead to increased drug uptake by other tissues, increasing the burden on the BBB. Because the toxicity of cytotoxic agents would be higher at non-target sites, this non-selectivity in drug delivery is detrimental. Another major drawback of increased lipophilicity is that it may lead to poor tissue retention and short biological action due to increased efflux and loss of CNS activity. The pharmacological properties of the drug can be modulated to improve treatment.

2. LITERATURE REVIEW

2.1 Brain tumor

Tumors of the brain, cranium, spinal cord, and meninges comprise a diverse group of diseases affecting the central nervous system. Depending on the cell type and other histopathologic features, there are more than 100 different histologic subtypes of these tumours according to the WHO Classification of Tumors of the Central Nervous System (CNS). Malignant and nonmalignant (or benign) brain tumours can be broadly divided into two categories. Nonmalignant meningiomas account for the vast majority of brain and CNS tumours diagnosed in the United States (Figure 2.1).

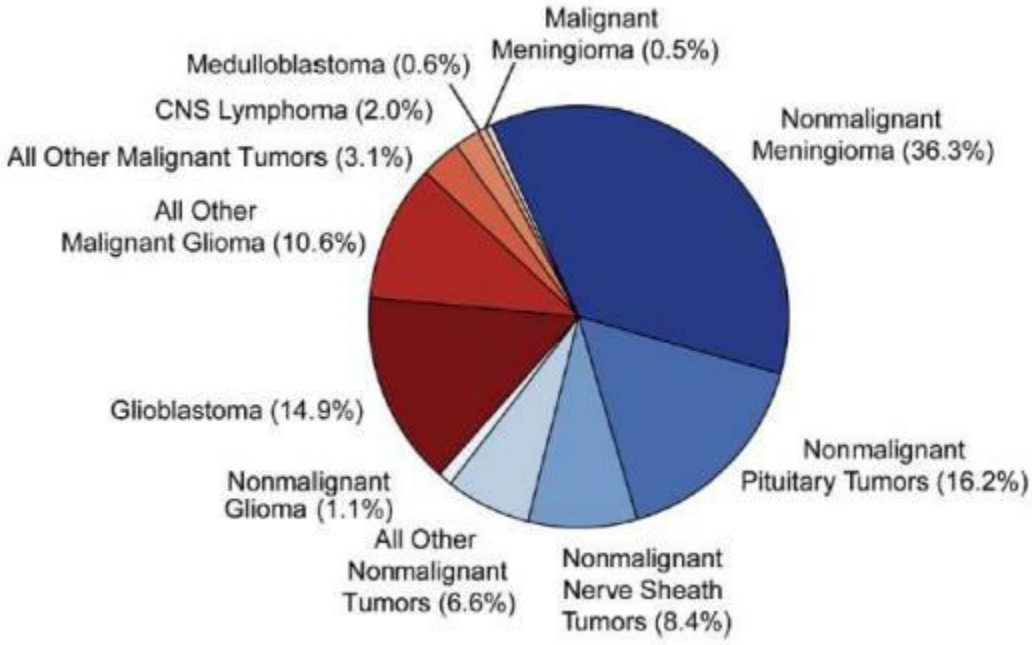

Figure 2.1: Distribution of primary brain and other CNS tumors by behavior and histology

2.2 Blood–brain barrier

In order to protect the brain, a layer of membranes known as the meninges surrounds it. One of the brain's other defence mechanisms is referred to as the BBB. Brain tissue is made up of blood vessels, nerve cells, and other substances. The BBB acts as a formidable barrier to pathogens and pollutants that cause disease and can be found in the blood. Small particles, fat-soluble molecules, and many gases cannot enter the brain because of the endothelial tight junctions present in the BBB. In contrast, the BBB and maintaining an optimal therapeutic concentration are difficult for large-sized drug molecules. Shown here in Figure 2.2 are the BBB's fundamental components.

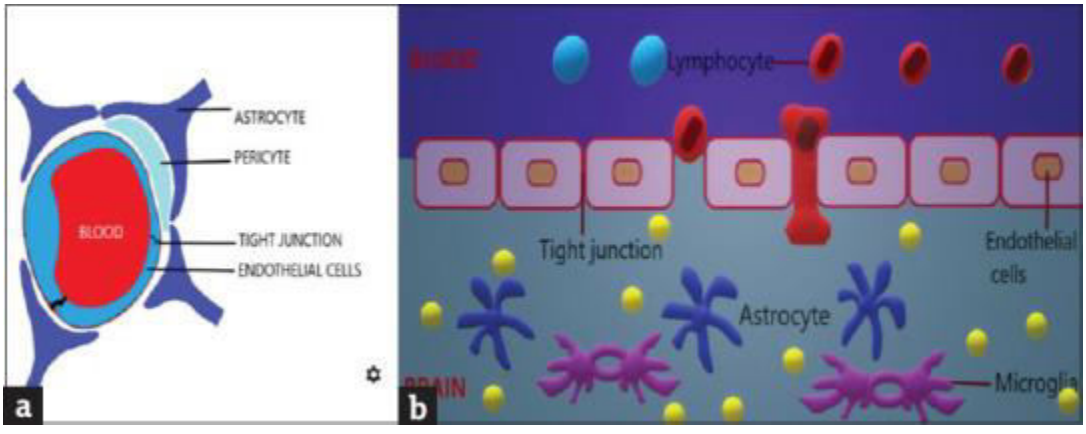

Figure 2.2 (a) LS of Blood Brain Barrier. (b) Sectional view of Blood Brain Barrier

Brain targeting strategies

Passive and active targeting of brain tissue can be discussed in relation to nanocarrier-based platforms.

2.3 Passive targeting

Nanocarriers loaded with anticancer drug(s) are able to remain at the tumour site for a reasonable period of time because of unique tumour characteristics such as punctured vasculature, leaky, and low lymphatic drainage systems. Small size and high lipophilicity are essential for passing the BBB. Nanocarriers with the required lipophilicity are expected to cross the BBB effectively and accumulate in the brain due to the BBB's lipophilic nature. The most effective systems for bypassing macrophages and remaining in the bloodstream for an extended period of time have been found to be nanocarriers with a preferred size below 100 nm, allowing them to pass through the BBB.

2.4 Active targeting

Increasing the medication's selectivity at a specific site of action through active targeting is the primary goal. Targeting the protein/receptor that is overexpressed in cancer cells is one of the methods for active tumour targeting. Aptamers, antibodies, small molecules, peptides, and DNA fragments are some of the ligands that can be used to target a particular protein. These surface ligands can be targeted to specific tissues that express specific receptors or antigens that can recognise the ligands, allowing for precise targeting. As a result, the loaded cargo is delivered precisely where it is needed, and the potentially harmful side effects of conventional chemotherapeutics are reduced to a minimum.

3. METHODOLOGY

3.1 Methods

Surface modification of TNPs with Hyaluronic acid (HA)

Carbodiimide chemistry was used to link HA to TNPs. In a nutshell, 1 mole of HA was dissolved in pH 4.7 MES (2-(N-morpholino) ethane sulfonic acid) buffer, and 2 moles of EDC and NHS were added and stirred for 4 hours. A subsequent incubation with TNPs at room temperature was performed while the mixture was constantly stirred. Centrifugation at 15000 rpm for 30 minutes collected the conjugated HA-TNPs, which were then washed three times with water to remove any excess HA. The CTAB turbidimetric method was used to gauge the amount of HA that could be conjugated to TNPs.

Surface modification of TNPs with Chondroitin sulphate (CS)

Carbodiimide chemistry was used to attach CS to TNPs (3) CS, EDC, and NHS were dissolved in 0.01 M MES (pH 4.7) at a molar ratio of 1: 2: 2 to activate the carboxylic groups of CS. For the next 12 hours at RT, TNPs were added to the mixture (CS: TNPs ratio = 1:1 w/w). Centrifugation at 15,000 rpm for 30 minutes separated the conjugated CS-TNPs, which were then washed three times in water to remove any unreacted materials.

Optimization of surface modified TNPs (HA-TNPs)

It was discovered that the molecular weight of the HA, stirring time, and the ratio of HA to TNPs all had an impact on the quality attributes of particle size (size distribution index), PDI (zeta potential), and percent conjugation efficiency (percentage of conjugation efficiency).

3.2 Paracellular Transport and Transcytosis

Paracellular transport and transcellular transport must be considered in terms of how the BBB functions. Intracranial mass and equilibrium can be described more accurately thanks to the CSF "sink" in the brain's interior. Blood-brain connections are so strong that paracellular transit is severely limited. It is known as "unidirectional transcytosis" in polarised cells when a macromolecule travels from the apical membrane to the basolateral one. In addition to endocytosis, this pathway also includes intracellular vesicular trafficking and exocytosis. CNS barrier properties were maintained at low transcytosis levels due to the presence of specialised tight junctions in the CNS. We now know that BBB transcytosis suppression occurs, and that CNS-targeted genetic programmes work to keep this barrier intact, as demonstrated by this new discovery. Every single brain endothelial cell has a transcytosis receptor. Reduced permeability of the blood–brain barrier to macromolecules could explain the lower expression levels of certain receptors in comparison to transcytosis pathway inhibition.

3.3 Double salting out assisted liquid-liquid extraction (SALLE)

The drug was extracted from plasma samples using sodium chloride and potassium sulphate as salts. For this experiment, we used a 10-milliliter glass tube to add 1 millilitre of TMZ solution (10g/ml) dissolved in 0.1 percent acetic acid to 5 millilitres of plasma. After that, 0.5 ml of 1 M sodium chloride solution was added and vortexed for 2 minutes. To separate the supernatant from the precipitate, 2 ml of acetonitrile was added, and the centrifuged for 10 minutes. Finally, the supernatant was centrifuged at 5000 rpm for 20 minutes with 0.5 ml potassium sulphate (1 M solution) added and vortexed for 2 minutes to separate plasma proteins and other residual materials.

4. RESULTS AND DISCUSSION

TMZ showed a characteristic spectrum when scanned in ultraviolet range between 200-400 nm. The λmax was found to be 330 nm and linearity range was found to be 2.0 – 16.0 µg/ml (Table 4.1). Regression analysis was performed on the experimental data and results are shown in table 3.2 and figure 4.1. Results of regression analysis indicated linear relationship between absorbance and concentration of TMZ.

Table 4.1: Calibration curve of TMZ in DD water by UV-visible spectrophotometer

Sr. No.	Concentration (µg/ml)	Absorbance mean ± SD
1	2.0	0.17572 ± 0.0015
2	4.0	0.27827 ± 0.0020
3	6.0	0.37439 ± 0.0023
4	8.0	0.47171 ± 0.0029
5	10.0	0.59511 ± 0.0031
6	12.0	0.71262 ± 0.0035
7	14.0	0.84122 ± 0.0029
8	16.0	0.93266 ± 0.0031

Table 4.2: Calibration data of TMZ in DD water

Solvent	**Amax**	**Range**	**Regression Equation**	**Regression Coefficient (R^2)**
Water	330 nm	2-16 µg/ml	y = 0.055x + 0.052	R^2=0.997

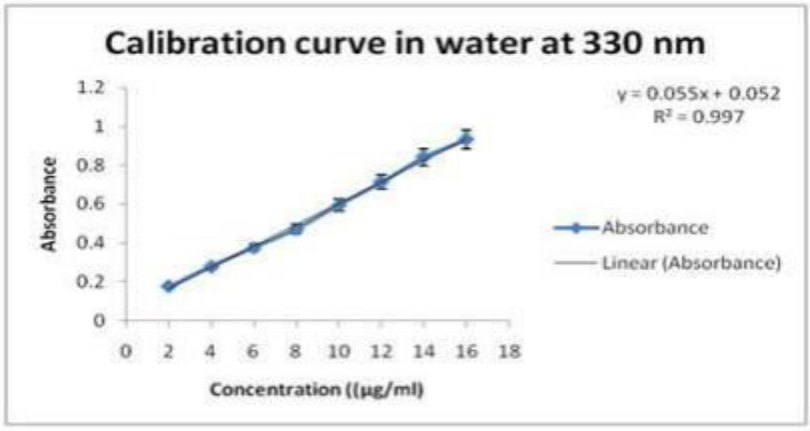

Figure 4.1: Calibration plot of TMZ in DD water

4.1 Drug-excipient interaction studies

To assess TMZ-excipient interactions, different FTIR spectrum was generated and analysed (Figure 4.2).

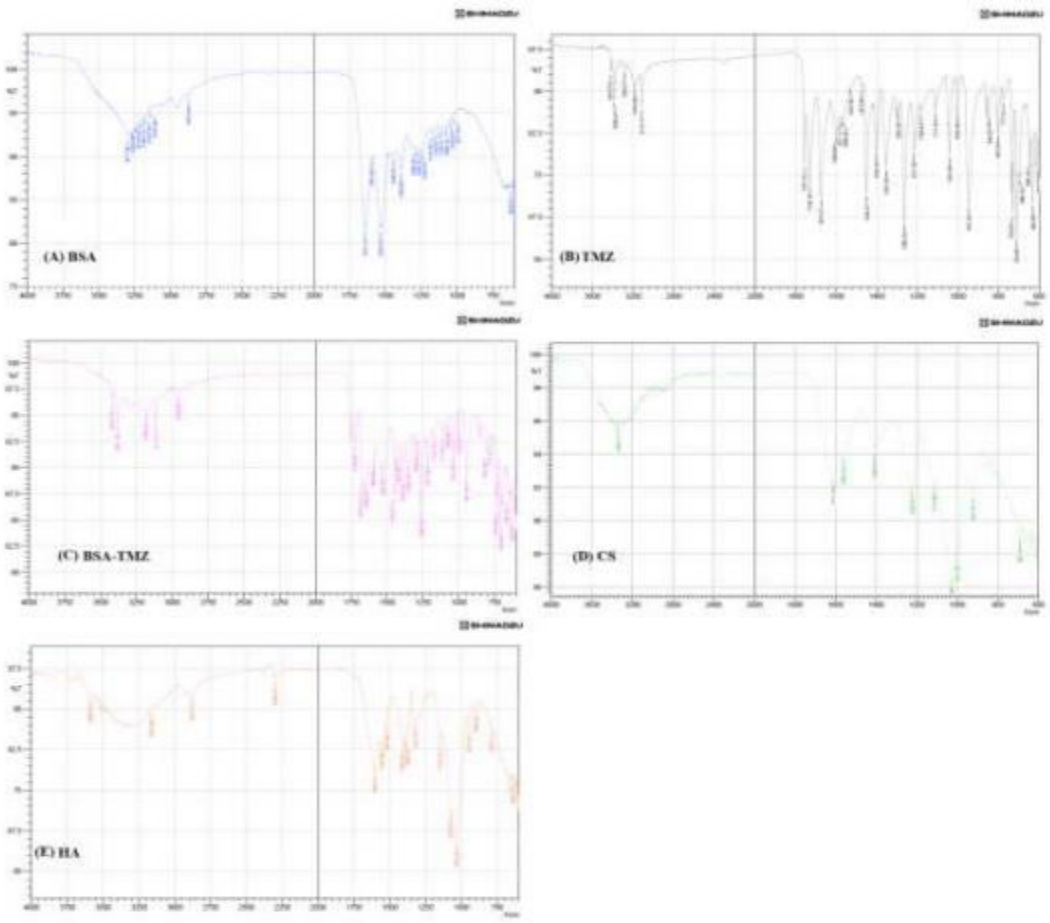

Figure 4.2: TMZ-excipients compatibility study by FTIR where (A) Spectrum of BSA, (B) Spectrum of TMZ, (C) Spectrum of Physical mixture of BSA-TMZ, (D) Spectrum of CS and (E) Spectrum of HA

4.2 Stability of TMZ in different solvents

TMZ showed pH dependent stability. At neutral and alkaline pH it rapidly degraded and converted in AIC (5-amino-imidazole-4-carboxamide) which can be detected by the UV-Visible spectrophotometry because it shows characteristic absorption maximum at 265nm. So before selecting solvent for the development of formulation, stability of TMZ in various solvents were assessed by the UV-Visible spectrophotometry method and results are shown in table 4.3. The results indicated that in water, TMZ was stable up to 5-6 hrs and after that degradation of TMZ started as the absorbance at 265 nm increased which corresponded to AIC (Figure 4.9). In case to methanol, TMZ was stable only for 1 hr while in ethanol and IPA stability was higher (more than 15 hr and 7 hr respectively) (Figure 4.3).

Table 4.3: Stability of TMZ in different solvents

Sr. no.	Solvent	Stability	Time
1	Water	Stability decrease with time	5-6 hr
2	Ethanol	stable	15 hr and more
3	Methanol	unstable	1 hr
4	IPA	stable	7 hr and more

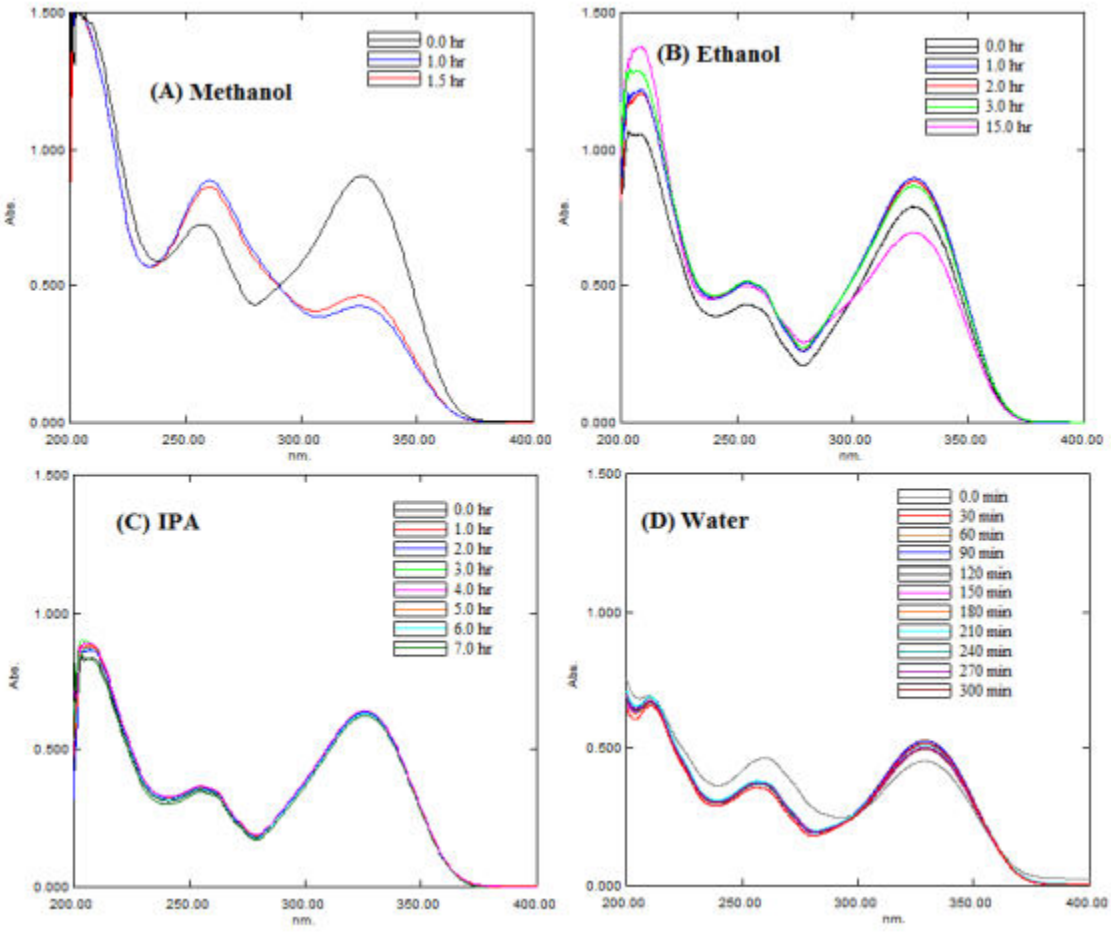

Figure 4.3: Stability of TMZ in different solvents where (A) Spectrum in methanol, (B) Spectrum in ethanol, (C) Spectrum in IPA and (D) Spectrum in water

4.3 Particle size and PDI determination

Particle size and PDI of HA-TNPs were found to be 375.1 ± 1.57 nm 0.181 ± 0.013 respectively (figure 4.4). In case of CS-TNPs, particles size and PDI was found to be 222.3 ± 1.57 nm and 0.217 ± 0.05 respectively (figure 4.5).

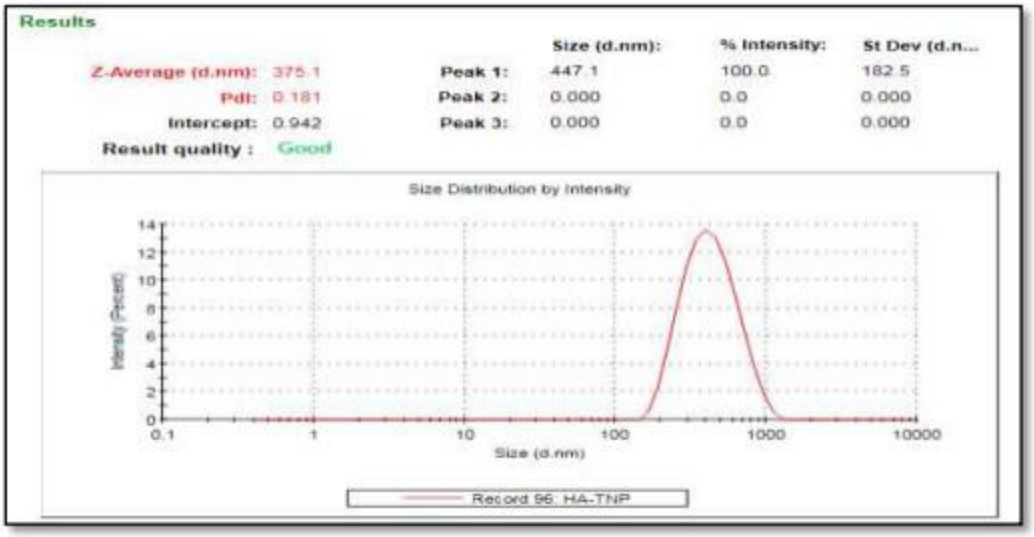

Figure 4.4 Particle size and PDI of HA-TNPs

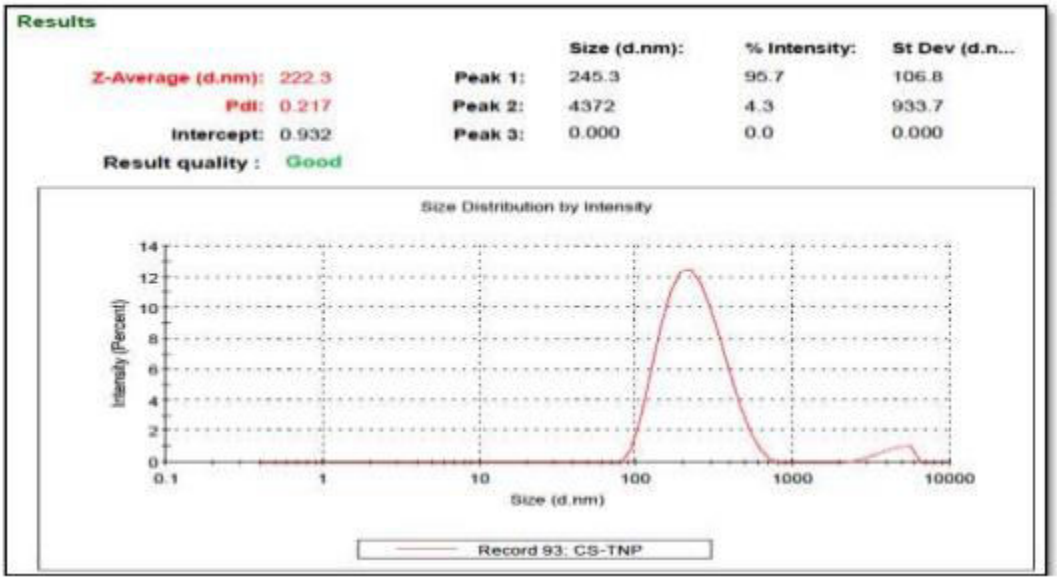

Figure 4.5 Particle size and PDI of CS-TNPs

CONCLUSION

The goal of treatment of diabetes involves the oral delivery of anti-diabetic drugs. The drug delivery by the conventional dosage form is usually associated with the problems like high gastrointestinal drug concentration, fluctuating peaks of plasma drug concentration which might cross the therapeutic window and enter in the toxic level or reverse could happen by diminished peaks and loss of therapy. Tolbutamide

belongs to BCS class II drug i.e. with low aqueous solubility and high permeation capacity and demands high doses (250-1000 mg) with frequent drug administration. Keeping in view of these limitations, TBM was selected as a drug for the study. In the recent years, nanotechnology based formulation like nanoparticles has generated new hopes for better therapeutic efficacy for the drugs having poor aqueous solubility. Nanoparticles drug delivery system promises these better results due to some unique characteristics viz. high surface to volume ratio, lower toxicity, higher dissolution profiles, increased bioavailability, effective crossing of biological barriers, diminished plasma peaks and reduction in dosing which leads to patient compliance. In conclusion, a study aimed to produce nanotechnology based TBM-PC particles by quasi-emulsion solvent evaporation technique has been presented. These investigations have also lead to better understanding of the effects of critical formulation and process parameters on the particle size (PS), drug entrapment efficiency (DEE) and cumulative drug release (CDR) of the formulation.

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