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Fabrication and Evaluation of Micellar Structure of Pluronic Copolymer Nanoaggregates of Cabazitaxel

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A B S T R A C T

Conventional therapy available for lung cancer has untended consequences and oral dosage forms has limitations such as low bioavailability of drug due to first pass metabolism which need high dose to treat disease. Polymeric micelles' low toxicity and quick rate of bodily elimination make them excellent for intravenously given drug delivery systems. Additionally, the chemical makeup of the medications does not need to be changed. The study was undertaken for development and characterization of Cabazitaxel loaded lyophilized block co-polymeric micelles for treatment of cancer therapy with effective use of Pluronic F127 and TPGS in polymeric micelles to improve Cabazitaxel solubility. Formulation CBT9 has the highest entrapment rate at 79.12 percent, as the quantity of polymer increases, fraction of drug loading and entrapment also enhances, which is related to the production of additional micelles over the CMC value. The optimized batch's Z averages were 103.5 and 113.6 nm, respectively, with PDI of 0.011 and 0.055. At pH 5.5, Cabazitaxel-loaded polymeric micelles release 87.49 percent of the drug. At pH 7.4, Cabazitaxel-loaded polymeric micelles release 83.19 percent of the drug.

Keywords: Cabazitaxel, Polymeric micelles, CMC, Pluronic co-poymer, Pluronic F68, Pluronic F127

A R T I C L E I N F O

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CONTENTS

1. Introduction

Lung Cancer is the second most leading cause of cancer in both men and women with highest mortality rate. 19 % of all the cancer deaths are only due to lung cancer [1]. Early-stage diagnosis is also a hurdle leading to typically progress if the disease is not controlled. Treatment causes additional symptoms. Targeted therapy is a method of cancer treatment that employs drugs that are specifically engineered to kill cancer cells while leaving healthy cells alone[2,3]. Polymeric micelles are nanostructured polymeric carriers formed by self-assembly of amphiphilic polymer[4]. Above CMC value polymer arranged in such manner that hydrophobic potion arranged in core and hydrophilic portion remain outer side. Hydrophobic core able to encapsulate hydrophobic drug which will enhance its solubility and dissolution. Encapsulation of BCS class II and IV drugs in polymer matrix will help to target disease site in lower amount of dose with enhanced bioavailability. Unlike bigger drug carriers, nanoscopic size reduces the risk of embolism in capillaries[5,6]. Utilizing stimuli-sensitive (pH, temperature sensitive) nanocomposites in micelles could result in the creation of "excellent carriers." The use of such excellent carriers to achieve controlled

drug delivery and targetability are now being investigated.

Hence in the present research, derivatives of poly(ethylene oxide)-poly(propylene oxide)-poly(ethylene oxide) (PEO-PPO- PEO) block copolymers were used which are among the most researched amphiphilic materials to make polymeric mixed micelles. The linear and bifunctional PEO-PPO-PEO triblocks or poloxamers (Pluronic®) and their branched 4-arm equivalents known as poloxamine (Tetronic®) are two of the families that are commercially available and used in the research for targeted delivery of cabazitaxel.

2. Materials and Methods

Materials" The drug Cabazitaxel was purchased from Drugs India LTD, Hyderabad. Pluronic F127 and TGPS were purchased from Sigma-Aldrich, Mumbai, Creamophor from BASF, Mumbai, other chemicals and reagents used were of analytical grade.

Pre-formulation Studies:

Preformulation studies like fundamental characterization studies (Organoleptic properties, melting point, solubility, and pH) and spectroscopic studies (UV and IR) were performed on Cabazitaxel drug sample.

Formulation Methodology:

Preformulation study for polymer: Six different types of polymers were used for screening i.e. Pluronic F68, Polycaprolactone (PCL), Pluronic F127, Creamophor EL, tween 80, sodium lauryl sulphate (SLS).

Screening of polymer ratio for self-assembled mixed micelles: Pluronic F127 and TPGS were selected based on the ratio selection 1:1, 2:3, 3:7, 4:1, 9:1 for Pluronic F127 and TPGS. All the batches were prepared by solvent evaporation method.From all the ratio, optimised ratio was selected based on micellar size and entrapment efficiency [7-10].

Preparation of self-assembled mixed micelles

Cabazitaxel loaded mixed micelles were prepared by a solvent evaporation method. Cabazitaxel has low water solubility so that an organic solvent is selected which is common to both the polymers and the drug (such as Ethanol, dimethyl sulfoxide, N,N-dimethyl formamide, acetonitrile, THF, acetone or dimethyl acetamide). The mechanism by which micelle are self- assembled depends on the process of solvent removal. The requisite amount of Cabazitaxel is added in different mass ratios of Pluronic F 127 and TPGS. The resultant mixtures were ultrasonically dissolved in Ethanol (a water miscible organic solvent). After the complete dissolution of polymers, the dispersion was dropped into clean water using a micropipette and agitated for 3 hours until the methanol had evaporated. To eliminate any big aggregates, the final solution was filtered with a 0.2µM filter. [11]

Characterization of Self-assembled Mixed micelles:

Size determination: DLS measurements were carried out in all cases utilizing a photon correlation spectrometer in Zetasizer NanoZS, Malvern Instruments Ltd., UK. All measurements were made in triplicate at 25°C after 5 minutes of equilibration, and all results are the average of three separate samples. To prevent losing particles such as bigger vesicles, the generated samples were often examined without dilution or filtration to get information on all species that appeared during sample preparation. The polydispersity index was studied to determine the distributionof the molecular mass in the polymer[12].

Encapsulation Efficiency and drug loading:

The drug concentration of Cabazitaxel in micelles were measured by HPLC Analysis at maximum absorption wavelength of 332 nm. Cabazitaxel loaded micelles were passed from a 0.22-micron syringe filter to remove the unentrapped drug. To dissolve the core-shell structure, methanol was transferred to Cabazitaxel mixed micelles, which culminated in the release of Cabazitaxel. 1 ml of filtered micellar solution was pipetted out and made up to 10 ml with Methanol and allowed to sonicate for 15 minutes to further break the micelles[13].

Critical micelles concentration:

The dynamic light scatter technique was used to estimate the critical micelle concentration of micelles using Zetasizer. From design matrix we have taken different ratio. Dilutions of samples ranging from 0.01 mM to 0.05 mM were made for 4:1 ratio in deionized water and ethanol, and changes in light intensity were measured for each sample. The light intensity and the sample's molar concentration were plotted on a graph. The CMC was calculated from the point where the slope of the intensity increased dramatically, indicating micelle production [14].

Surface Morphology:

Surface morphology of polymeric micelles of drug, dispersion of drug containing polymer and pure drug powder was captured using a Transmission electron microscope (Philips, Philips XL 30 ESEM).(85) Samples is to be fixed on an aluminum stub with conductive double-sided adhesive tape and coated with gold in an argon atmosphere (50 Pa) at 50mA for 50 sec[15].

In vitro release:

To explore the in-vitro drug release behaviour, the validated method was used. The optimized batch of drug loaded mixed micelles was evaluated for in vitro drug release using franz diffusion cell via dialysis bag methodology, in phosphate buffer (pH 7.4 as well as pH 5.5). Lyophilized mixed micelles were weighed accurately such that equivalent to 75 mg of the drug and further reconstituted in 10 ml of phosphate buffer (pH 7.4 and 5.5). The diffusion cell was put in a shaker incubator at 37.0±0.5°C with moderate shaking at a speed of 100 rpm. To keep the sink conditions, 1ml of the sample was removed and the incubation medium was replaced with freshly produced release medium at specified time intervals. The method of distribution was chosen to match the in vivo condition of the site of administration and site of action in the receiver chamber [16]. The release profile of Cabazitaxel was evaluated by plotting curve of cumulative drug release vs. time. The experiment was carried out in triplicate to check reproducibility.

3. Results and Discussion

FTIR Study: The characteristic absorption peaks of Cabazitaxel in FTIR spectrum of Cabazitaxel was shown in fig 01. From the spectrum it was observed that, obtained Cabazitaxel was a pure compound by observing the standard spectrum of Cabazitaxel.

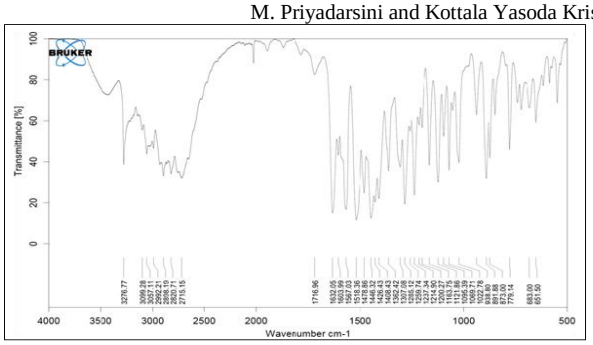

Fig: 01 FTIR of Cabazitaxel

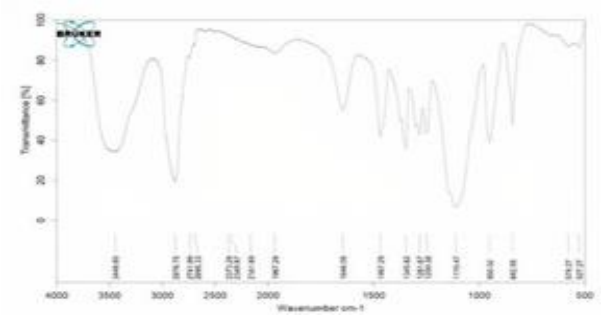

Fig: 02 Identification of Pluronic F-127 using FTIR spectroscopy.

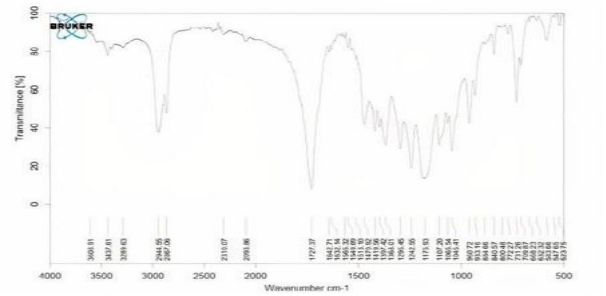

Fig: 03 Identification of TPGS using FTIR spectroscopy.

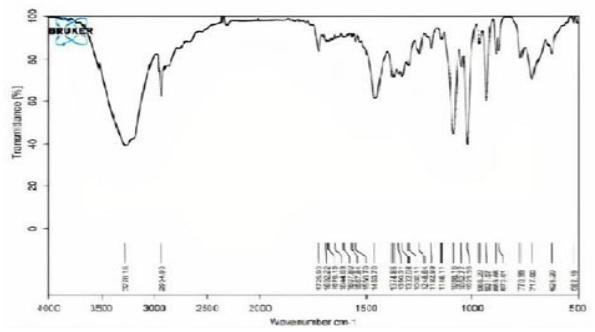

Fig 05: FT-IR of drug and excipients

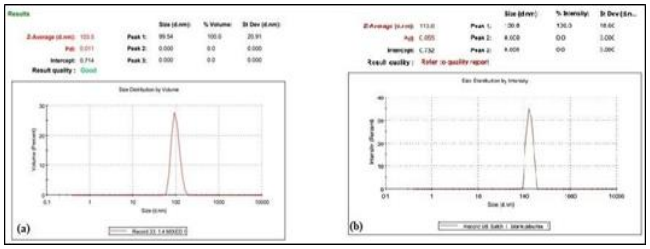

Figure 6: Micellar size of optimized batch of self-assembled mixed micelles.

Screening of polymers and different preparation methods for micelles: Pluronic F68 polymeric micelles were prepared form three different method which are direct dissolution, evaporation and dialysis. From dialysis method the micellar size observed is 1084nm and PDI 0.483. By evaporation and direct dissolution the micellar size observed 493 and 353nm with PDI 0.163 and 0.112 respectively. Also, other polymers like Pluronic F127, PCL were used for screening where Micellar size of Pluronic F127 was found 22.06 nm and PDI 0.2. PCL and Pluronic F68 mixed micelles were prepared which shows micellar size of 564nm and PDI 0.7. Surfactant like Creamophor, Tween 80, SLS were used to prepare micelles gives micellar size 68.88nm, 396.1nm and 250.2nm with PDI 0.3, 0.6 and 0.8 respectively.

Screening of polymer ratio for self-assembled mixed micelles: From 1:1, 2:3, 3:7, 4:1, 9:1 ratio, optimised ratio selected based on micellar size and Entrapment efficiency. As the amount of Pluronic F127 and TPGS increases entrapment of drug and with that micellar size also decreases. From all the ratio 9:1 is selected for better entrapment and micellar size as shown in Table.02.

Cabazitaxel loaded self-assembled micelles

Cabazitaxel loaded self-assembled micelles was analysed for miscellar size and % EE. CBT1 to CBT9 batches showing the range of 103-316 nm size shown in Table 03. which is suitable for the targeting at the cancerous site; hence this pH 7, solvent type and its volume, polymer concentration, Sonication time were selected as critical variables respectively to obtain the range of particle size with uniform distribution and high entrapment of drug. EE% from CBT1-CBT9 ranges from 59% - 79 %. [17,18] From the results we can interpret that as amount of polymer get increases micellar size decreases. Amount of TPGS has high impact when compared to other. Various analysis shows reduction in core radii at high TPGS concentration. This was accompanied with a reduction in the aggregation number, and increased number density of micelles (N). These observations imply the micellization with lower number of surfactant units, wherein remnants assembled to create additional micelles. More over reduction could be attributed to the presence of a greater amount of TPGS polymers, which may enhance the interaction between the hydrophobic chains and the components of both polymeric mixtures, thus resulting in a more compact structure. Combined influence of polymer concentration and solvent volume on particle size, demonstrating that when polymer concentration rises, particle size decreases.

Interpretation for % EE:

From the results we can predict that as amount of polymer increases entrapment efficiency increases. As concentration of polymer increases drug loading also increases due to more carrier available to entrapment the requisite fraction of drug. Hydrophobic- Hydrophobic interaction of drug with polymer is also one of the mechanism which increases entrapment. However, when this factor interact with solvent volume leads to the negative outcome of the response (%EE). Combined effect of polymer concentration and solvent volume on entrapment efficiency which shows that as the polymer concentration and solvent volume increases

the entrapment efficiency increases. [19]. The optimized batches of Cabazitaxel loaded Pluronic F127 and TPGS mixed micelles was shown in Table-04.

Furthermore, design batches ranged from 43.22 to 133.7 nm. The increase in Pluronic F127 concentration was related to the increase in particle size. The greater chain length of PEO provides higher hydrophilicity, which increases micellar size, which is linked to the ratio of PEO to PPO block. TPGS, on the other hand, has the opposite effect on Micellar size as Pluronic F127. One of the reasons is that TPGS has a hydrophobicity that interacts with the PEO block, resulting in a more compact structure. Micelles of a smaller size aggregate more efficiently in tumours and enable more consistent medication release.

Encapsulation Efficiency and drug loading

The effectiveness of entrapment is given in Table 04. As the quantity of polymer increases, fraction of drug loading and entrapment also enhances, which is related to the production of additional micelles over the CMC value. F9 has the highest entrapment rate at 79.12 percent. Pluronic F127 and TPGS levels are greatest in the F9 batch. Only greater amount Pluronic is not able to improve drug loading. Pluronic F127 is not able to provide much hydrophobicity [20]. Addition of TPGS to the mixed micelles enhanced percent DL and percent EE. Because of the hydrophobic - and van der Waals contacts between the aromatic ring and hydrocarbon chain of TPGS, the PPO segment of Pluronic, and the Cabazitaxel. More polymer means more interaction with the medication and the production of micelles.

Surface morphology

Optimized check point was evaluated for surface morphology. Cabazitaxel loaded self- assembled micelles found to be spherical in shape. Morphology is shown in figure.07

Because of the hydrophobicity of the Cabazitaxel, solution just releases 25.32 percent which indicate very poor drug release. At pH 5.5, Cabazitaxel-loaded polymeric micelles release 87.49 percent of the drug. At pH 7.4, Cabazitaxel-loaded polymeric micelles release 83.19 percent of the drug. There was an initial burst discharge. Polymeric micelles first release 44.25 percent in 12 hours. The fast breakdown of the micellar system caused by cohesion, a greater concentration gradient, and sink conditions in the system might explain the burst release of Cabazitaxel from mixed micelles [21]. This release could be able to reach the therapeutic concentration, and the steady rise might be able to keep it there.

Table 1: Formulation Table

Formulation Code	Amt of Pluronic F 127 (mg)	Amt of TPGS (mg)	Solvent volume (ml)
CBT1	45	7.5	7.5
CBT2	45	7.5	10
CBT3	45	10	7.5
CBT4	67.5	7.5	7.5
CBT5	67.5	7.5	10
CBT6	67.5	10	7.5
CBT7	90	7.5	7.5
CBT8	90	7.5	10
CBT9	90	10	7.5

Table 02: Micellar Size and %EE of Cabazitaxel loaded self-assembled micelles

F. Code	Amt of Pluronic F 127 (mg)	Amt of TPGS (mg)	Solvent volume (ml)	Micellarsize (nm)	%EE (%)
CBT1	45	7.5	7.5	316.2±2.25	59.21±0.12
CBT2	45	7.5	10	205±1.23	68.71±0.15
CBT3	45	10	7.5	200.2±1.66	62.45±0.35
CBT4	67.5	7.5	7.5	185.33±2.3	72.83±0.22
CBT5	67.5	7.5	10	185.33±1.34	72.83±0.21
CBT6	67.5	10	7.5	113.6 ± 2.76	73.33±0.25
CBT7	90	7.5	7.5	162.84±1.23	71.32±0.32
CBT8	90	7.5	10	148.36±3.1	79.3±0.15
CBT9	90	10	7.5	103.5 ± 1.45	79.12±0.17

Table 03: Assembled micelles

S.no	Amt. of Pluronic F127(mg)	Amt. of TPGS(mg)	Micellar size(nm)	% EE(%)
CBT6	67.5	10	113.6 ± 2.76	73.33±0.25
CBT9	90	10	103.5 ± 1.45	79.12±0.17

Table 04: In vitro drug release

Time (Hrs)	% Cumulative Drug Release of Cabazitaxel mixed miscelles				
	Cabazitaxel Solution	CBT 6 (pH 5.5)	CBT 9 (pH 5.5)	CBT 6 (pH 7.4)	CBT 9 (pH 7.4)
2	18.65±2.5	8.65±4.8	11.49±5.8	10.38±6.8	12.85±0.5
4	21.49±1.1	12.49±3.9	18.65±4.5	18.58±5.4	15.47±4.5
8	26.48±3.8	32.48±7.5	31.15±6.6	31.85±7.2	29.45±5.3
12	30.19±4.8	42.15±3.6	44.25±7.8	49.49±4.7	47.35±2.5
16	39.58±4.8	54.19±2.5	55.28±5.7	57.48±3.2	54.19±5.8
20	41.19±2.7	65.19±5.8	66.48±3.6	64.55±3.7	62.06±2.5
24	44.19±4.6	82.48±3.6	87.49±5.4	79.74±3.5	83.19±8.9

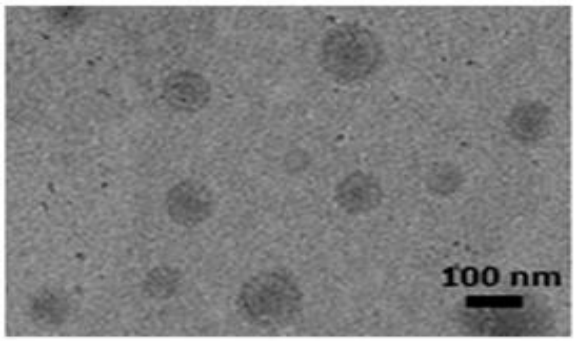

Figure 07: TEM image of self-assembled mixed micelles

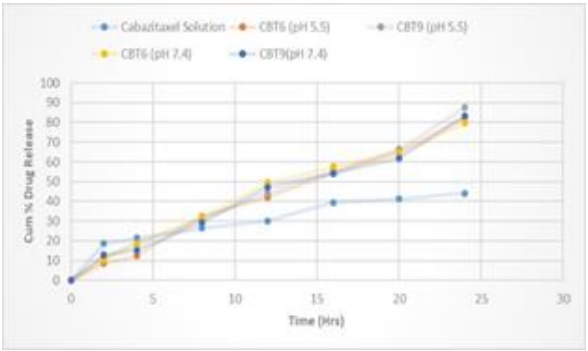

Figure : 08 In-vitro drug release of Drug, drug loaded mixed micelles at pH 7.4 and 5.5

4. Conclusion

The study demonstrates that for micellar size, shape, zeta potential and other characteristics of lyophilized polymeric micelles are appropriate, which further minimizes the toxicity and side effects due to the encapsulation by polymer and ability to sustain the drug release. Block co-polymeric micelles provide better solubility and high drug loading capacity which may enhance the bioavailability. The notion of using block co- polymeric micelles in the solubility improvement of hydrophobic medicines has a significant potential to serve as a viable platform for intravenous drug administration, according to this research. Although the results are promising, the Cabazitaxel-loaded block co-polymeric micelles must be further evaluated for In-Vivo studies to check the targeted drug delivery.

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