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PREPARATION AND OPTIMIZATION OF TEMOZOLOMIDE LOADED SOLID LIPID NANOPARTICLES BY CENTRAL COMPOSITE DESIGN

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ABSTRACT

The present research study was aimed to formulate, evaluate and optimize temozolomide solid lipid nanoparticles by central composite design for treatment of Glioblastoma multiforme. The temozolomide solid lipid nanoparticles were prepared by solvent injection method using palmitic acid as lipid and tween 80 as surfactant. The independent variables used in the formulation were surfactant concentration (X1) and drug: lipid (X2), their effects were observed with regard to dependent variables like % entrapment efficiency (R1) and % drug release (R2). Total 13 formulations were prepared and evaluated. The Differential scanning calorimetry and Fourier transform infrared studies indicated compatibility between drug and excipients. All temozolomide solid lipid nanoparticle formulations showed sizes in nanometre range, with high % entrapment efficiency and prolonged drug release up to 24 hours. The optimized formulation showed an entrapment efficiency of 85.65% and 95.343 ± 0.88% drug release for an extended period of 24 hours. Scanning electron microscopic studies revealed discrete spherical shape of temozolomide solid lipid nanoparticles. This study indicates that solid lipid nanoparticles could be a feasible carrier for temozolomide delivery to brain for treatment of glioblastoma multiforme. However further studies are required to endorse their potential as an effective drug delivery system.

KEYWORDS

Temozolomide, Brain targeting, Solid lipid nanoparticles and Palmitic acid.

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INTRODUCTION

Glioblastoma multiforme (GBM) also called as glioblastoma is fast growing glioma that develops from star shaped glial cells (astrocytes and oligodendrocytes) that support the health of nerve cells within the brain. It is often referred as grade-IV astrocytoma. It is the brain cancer typically results in death in the first 15 months after diagnosis. Overall, GBM accounts for about 17% of

all tumours of brain. The main stay of treatment for GBM is surgery, followed by radiation and chemotherapy. Chemotherapy with the drug temozolomide (TMZ) is the current standard of treatment of GBM. TMZ was found to be the most effective antineoplastic agent for treating high-grade metastatic melanoma and glioma[1]. TMZ is an alkylating agent with the ability to cross the Blood Brain Barrier. It is derived from a series of modified imidazotetrazinones. TMZ must be administered in high systemic doses due to its short half-life 1.8 hours; only 20% of TMZ with respect to its systemic dose reaches the brain. It requires high systemic doses to reach therapeutic levels in the brain, which simultaneously brings about a number of side effects like headache, nausea, vomiting, fatigue, bone marrow depression and oral ulcerations[2,3].

Many novel drug delivery systems have been designed to improve the bioavailability of drug to brains including nanoparticles, micellar systems, microemulsion, solid lipid nanoparticles, liposomes, niosomes etc. Among them, nanoparticles based delivery of drugs to the brain has shown significant potential. Nanometric size of these particulate carriers not only improves the permeation and availability of drugs to the brain, but also provides a large surface area, improves solubility and ability to encapsulate both hydrophilic and lipophilic drugs[2]. Recently, increasing attentions has been focused on the solid lipid nanoparticles (SLNs); because SLNs are ideal for brain targeting because of the rapid uptake, bio-acceptability, bio-degradability, reduce dose related toxicity, side effects during chemotherapy, possibility of controlled drug release and long-term stability. SLN are sub-micron colloidal carriers ranging from 50 to 1000nm, which are composed of physiological lipid, dispersed in water or aqueous surfactant solution[4].

Central Composite Design (CCD) was developed by box and Wilson; it is also called as Box-Wilson Design. A better design that encompasses the advantages of factorial design or fractional factorial design or the star design, is the CCD. It is composed of +2k factorial design or fractional factorial design. A two factor CCD is identical to a 3^2 factorial design with the rectangular experimental domain at $\alpha = +1$ or $\alpha = -1$, on the other hand, the experimental domain is spherical in shape for $\alpha = \sqrt{2} = 1.414$. The CCD is quite popular in response surface optimization during pharmaceutical product development[5].

Hence, in the present research work, solid lipid nanoparticles were explored as carrier for the delivery of temozolomide. Furthermore central composite design is applied for optimization of critical process parameters.

MATERIAL AND METHODS

Materials

Temozolomide was obtained as a gift sample from Hetero Labs Pvt. Ltd, Hyderabad. Palmitic acid was purchased from SD fine-Chem Ltd, Mumbai. Soya lecithin was purchased from Yarrow Chem Products, Mumbai. All other chemicals and solvents were of analytical grade.

Methods

Formulation approach with experimental design

SLNs batches were formulated according to the Central Composite Design (CCD) to study the effect of different variables on the entrapment efficiency and % drug release. A CCD with 2^3 factorial studies in which 2 factors were evaluated at randomized 3 levels (5 centre points and 8 non centre points), generated 13 formulations. Concentration of surfactant (X1), Drug: Lipid ratios (X2) are the critical process parameters, hence selected as independent variables. Entrapment efficiency (R1), *In-vitro* drug release (R2) are critical quality attributes for SLNs, hence were selected as dependant variables. The coded value -1.0 indicates lower limit of concentration and +1.0 indicates higher limit. The star points represent new extreme values of low (-2) and high (+2) for each factor in the design. The minimum and maximum specifications of the processing variables are entered in to the software (Design Expert, Version 12.0.12.0, Stat -Ease) to obtain a suitable design. The design summary and formulation table are shown in Table No.1 and Table No.2 respectively.

Preparation of TMZ SLNs

Temozolomide loaded Solid lipid nanoparticles were prepared by solvent injection method followed by ultrasonication. In this method TMZ and palmitic acid (lipid) were dissolved in ethanol which constitute organic phase. The aqueous phase consists of equal ratios of tween 80 as surfactant and soya lecithin as emulsifier in water. The organic phase was injected rapidly through an injection needle into continuously stirred aqueous phase at 1500rpm for 120 min. The resultant SLNs suspension was subjected to sonication using probe sonicator at 50W for 20 min. The obtained nanosuspension was cooled at 6^{o}C for the formation of TMZ SLNs. Further SLNs were separated by centrifugation. The obtained SLNs were stored in cold condition. 13 formulations of TMZ SLNs were prepared by varying drug: lipid ratios and concentration of surfactant[6].

EVALUATION PARAMETERS OF SLNS

Drug excipient compatibility studies

Fourier Transform Infrared (FTIR) studies

FTIR spectroscopy was done to identify the functional groups present and interaction between drug and excipients. FTIR spectra were developed for pure drug and formulations by preparing potassium bromide disks. Taking few mg of temozolomide drug or formulation with potassium bromide, the disk was prepared by compression of 10 tons pressure for 5 min. Finally, disk was placed in a holder of FTIR machine and a spectrum was recorded from 4000cm^{-1} to 500cm^{-1} band width.

Differential scanning calorimetry (DSC) studies

DSC is a thermo analytical technique gives an insight into the melting behaviour of substance. Generally, the temperature program for a DSC analysis is designed such that the sample holder temperature increases linearly as a function of time. The pure drug and formulations were subjected to DSC studies using Perkin Elmer pyres 4 series DSC equipment (Massachusetts USA) samples were sealed in 40µl aluminium pans an identical empty pan was used as a reference; all samples were scanned at 5^{o}C/min with a 20ml/min nitrogen purge from 20-320^{o}C.

Drug Entrapment Efficiency

TMZ-SLN's were centrifuged at 3000 rpm for 30 minutes using REMI centrifuge C-854/8. Entrapment of TMZ in TMZ-SLN's was determined using below equation:

$$\% \text{ Entrapment Efficiency} = \frac{W1 - W2}{W1} x100$$

Where W1 is the total amount of drug added during TMZ-SLN's preparations. W2 is the amount of drug present in the clear supernatant layer, determined by UV-VISIBLE spectrophotometer at 325nm[7].

Particle Size, Polydispersity Index and Zeta Potential

The mean particle diameter and Polydispersity index (PDI) were determined with the aid of Malvern Zetasizer nano ZS -V2.0 at 25^{o}C after appropriate dilutions in Milli Q water filtered through 0.22µm poly vinylidene difluoride filters. Size measurement was carried out using DTS-5.10 clear disposable sizing cuvettes with measurement position set at 4.65mm. Zeta potential is an important parameter to evaluate and establish an optimum condition for stability of colloids or disperse systems. It is also determined by the above mention equipment before the measurements, the samples were diluted and probe sonicated to avoid possible interference during the measurements means of results. Measurements were carried out at 25^{o}C using water as a dispersant (refractive index: 1.330) in a clear disposable zeta cell.

Surface morphology by SEM

The morphology of the nanoparticles was investigated by scanning electron microscopy (Carl Zeiss- Supra 55) at an accelerating voltage of 10 Kv. The sample was fixed on a SEM-stub using double-sided adhesive tape and conductive carbon paint is applied along the edges of coverslips and the sample is allowed to air dry. The samples were coated with thin layer of gold under vacuum using Sputter Coater vacuum coater (JEOL, JFC 1600, auto fine Coater) to minimize electrostatic charging. The images as different magnification were captured.

***In-vitro* drug release studies**

In vitro release of the drug and TMZ SLN's was studied in USP-II apparatus using pH 6.8 phosphate buffer saline as dissolution medium. The medium was stirred at 50 rpm at 37^{o}C ± 0.5^{o}C. TMZ SLN's equivalent to 100mg of TMZ was transferred into dissolution medium. At predetermined time intervals (0, 1, 2, 4, 6, 8, 12 and 24hrs) 5ml of the sample medium was taken and the same amount of fresh medium was replaced. The amount of TMZ released was determined using its absorbance at 325nm. *In-vitro* drug release profiles of all formulations were constructed by taking time in hours on X-axis and % drug release on Y-axis[6].

Statistical Analysis

Analysis of variance test (ANOVA) was applied to determine whether the results obtained from the experiment were significant or not. A probability level of $p<0.05$ was considered to be significant.

Prediction of optimized formulation

Using the design expert software, the obtained data for each response were analysed and after optimization of multiple responses, the optimized TMZ SLNs formulation was predicted, prepared and evaluated for all responses.

***In-vitro* drug release kinetics**

The drug release kinetics and mechanism of drug release of optimized TMZ SLNs was determined by fitting *in-vitro* release data in to various models such as zero order, first order and Higuchi equations, Korsmeyer-Peppas models[8].

RESULTS AND DISCUSSION

Drug-Excipient compatibility studies

FTIR studies

FTIR spectrum of TMZ and its formulation is depicted in Figure No.2, it showed N-H stretching at 3180.16cm^{-1}, C-H stretching at 3124.99cm^{-1}, C=O stretching at 1744.32cm^{-1}. The TMZ SLNs formulation showed no major shifting of any functional peaks of drug. Hence it was indicated that there was no interaction between drug and used excipients.

DSC studies

DSC thermogram of pure drug TMZ and formulation are shown in Figure No.3. In DSC study of pure drug, a peak observed at 210^{o}C indicates the drugs melting point. DSC thermogram of formulation showed excipients peak at 79.25^{o}C and did not show any peak near the melting point of the drug. This indicated that TMZ was not in its crystalline state but rather present in an amorphous state and that the drug was completely entrapped within the SLNs. Furthermore, none of the formulation's excipients showed any interference with the drug.

Physicochemical characteristics of TMZ SLNs

The formulated SLNs were evaluated for parameters like entrapment efficiency, particle size, PDI, zeta potential to study the effect of concentration of surfactant and ratio of drug: lipid. The entrapment efficiency of all formulations was in the range of 74.706 to 89.44%. It was found that with an increase in the concentration of lipid, the entrapment efficiency increased. It was also observed that an increase in the surfactant concentration first increases and then decreases the entrapment efficiency of the drug in the SLNs. An increase in lipid concentration increased the entrapment efficiency significantly by providing more space for the accommodation of the drug as an increment of the lipid content and also reducing the escape of the drug into the external phase. The decreasing effect of surfactant may be attributed to the entrapment of surfactant molecules into the SLNs at higher concentrations of surfactant. The particle sizes of TMZ SLNs were in the range of 177.1 to 5093nm. The PDI is a measure of the heterogeneity of a sample based on size. Polydispersity can occur due to size distribution in a sample or agglomeration or aggregation of the sample. The PDI values of TMZ SLNs are in range of 0.452 to 1.000. Zeta Potential analysis is a technique for determining the surface charge of SLNs in solution. The magnitude of the zeta potential is predictive of the colloidal stability. Zeta potentials of prepared SLNs are in the range of -

17.8 to -70mv. All the results are tabulated in Table No.3.

***In-vitro* drug release studies of TMZ SLNs**

The *in-vitro* drug release profile of all TMZ-SLNs showed a sustained release of the drug for 24 hrs. The formulation F-8 with 1:3 drug: lipid ratio and 1.5% (w/v) surfactant concentration has shown high drug release of 98.588% up to 24hrs. The release from SLNs was found to be fast over the initial time period, followed by prolonged release over a period of 24 hrs. The initial release of the drug may be due to the release of TMZ from the SLNs surface, whereas at a later stage, TMZ may be constantly released from the core of nanoparticles, which is responsible for the prolonged release. Increasing the amount of lipid causes a significant decrease in the cumulative drug release percentage. This is due to the fact that increasing the lipid concentration increases the size of the nanoparticle, thereby decreasing the effective surface area available to interact with the releasing medium and hence decreasing the drug release.

Statistical analysis

ANOVA with multiple regression analysis of the responses (R1, R2) using Design Expert software were implemented for statistical analysis of CCD formulations. The estimated factors effects with *p*-values on the responses were presented in Table No.4 and Table No.5. The effects of these factors on the responses were displayed in contour and 3D response surface plots (Figure No.5 and Figure No.6).

The Model F-value of 11.24 implies the model is significant. P-values less than 0.0500 indicate model terms are significant. In this case B is a significant model term. Values greater than 0.1000 indicate the model terms are not significant. Higher proximity of R^2 value towards 1, highlights the model strength, R^2 value for designed model system was recorded as 0.8892 confirming the higher interdependence of the model parameters. Adequate Precision ratio greater than 4 is desirable. Obtained ratio of 10.4209 indicates this model can be used to navigate the design space.

The Model F-value of 108.42 implies the model is significant. P-values less than 0.0500 indicate model terms are significant. In this case A and B are significant model terms. Values greater than 0.1000 indicate the model terms are not significant. Higher proximity of R^2 value towards 1, highlights the model strength, R^2 value for designed model system was recorded as 0.9873 confirming the higher interdependence of the model parameters. Adequate Precision ratio greater than 4 is desirable. Obtained ratio of 33.3228 indicates this model can be used to navigate the design space.

The above contour graph and 3D surface plots of response-1 (% Entrapment Efficiency) illustrates that high entrapment efficiency of 89.44% is attained by formulations, it is indicated as red zone. Higher drug: lipid ratio of 1:4 to 1:5 and less surfactant (Tween 80) concentration of 0.5 to 1.5% w/v achieves high entrapment efficiency zone.

The above contour graph and 3D surface plots of response-2 (% Drug Release) illustrates that high drug release of 98.588% is attained by formulations, it is indicated as yellow zone. Lower drug: lipid ratio of 1:1 to 1:1.5 and surfactant (Tween 80) concentration of 0.5 to 1% w/v represents high drug release zone.

Mathematical modelling of experimental data

Depending on the analysis of the observed values of the responses; a mathematical model for each response was generated and presented in the form of equations.

Quadratic equation for % Entrapment efficiency

% EE (R1) = 85.240-0.5062*A + 3.87*B + 0.3320*AB + 0.1322*A^2 - 1.35*B^2 (A=Surfactant concentration, B= Drug: Lipid ratio)

The equation in terms of coded factors can be used to make predictions about the response for given levels of each factor. The coded equation is useful for identifying the relative impact of the factors by comparing the factor coefficients. In the above equation factor- A *i.e.* Surfactant concentration has -ve sign. This indicates that as surfactant concentration increases entrapment efficiency decreases. Factor-B is drug: lipid ratio has a +ve sign. This indicates as drug: lipid ratio increases

entrapment efficiency increases. For interaction effect AB, the sign is +ve indicating a synergistic interactive effect on entrapment efficiency.

Quadratic equation for % Drug release

% DR (R2) = 85.44 -1.47*A - 7.66*B -0.3675*AB + 0.4780*A^2 + 1.11*B^2

(A=Surfactant concentration, B= Drug: Lipid ratio)

The equation in terms of coded factors can be used to make predictions about the response for given levels of each factor. The coded equation is useful for identifying the relative impact of the factors by comparing the factor coefficients. In the above equation factor-A *i.e.* Surfactant concentration has -ve sign. This indicates that as surfactant concentration increases drug release decreases. Factor-B is drug: lipid ratio has a –ve sign. This indicates as drug: lipid ratio increases drug release decreases. For interaction effect AB, the sign is –ve indicating antagonistic effect on drug release.

OPTIMIZATION OF TMZ SLNs

The resultant experimental data of all prepared formulations F1 to F13 were used to develop an optimized TMZ SLNs with maximum % EE and % DR by using CCD in Design Expert software. The suggested optimized formulation has 0.5%w/v concentration of surfactant Tween-80 and 1:1 ratio of drug: lipid. To validate these values, the optimized TMZ SLNs formulation was prepared and evaluated. The observed responses of this formulation were 85.65% entrapment efficiency, particle size of 388.4nm, PDI of 1, -41.4mV zeta potential and 95.343% drug release for 24hours. These observed values are in a close agreement with the predicted values. This proved the feasibility of the optimization procedure using CCD in developing a new TMZ SLN formulation with controlled release.

Surface morphology by SEM

The morphology of TMZ SLNs was observed and the results were shown in Figure No.9. The results displayed almost spherical and smooth morphology of SLNs with mean particle size of 388.4nm.

***In-vitro* drug release kinetics**

The *in-vitro* drug release kinetics of optimized formulation followed first order (r^2=0.9896). The obtained value of diffusion exponent (n) is 0.5681, indicating that the release behavior was non-Fickian diffusion as depicted in Figure No.10.

Table No.1: Design summary of formulation variables

S.No	Variables	Low level (-1)	Mid-level (0)	High level (+1)
1	X_1=Surfactant (Tween80) %W/V	0.5	1.5	2.5
2	X_2=Drug: Lipid	1:1	1:3	1:5

Table No.2: Formulation table obtained from Central Composite Design

S.No	Formulation code	Ingredients				
		Organic phase		Aqueous phase		
		Drug: Lipid	Ethanol (ml)	Tween-8 (%w/v)	Soya lecithin (g)	Water (ml)
1	F-1	1:3	5	1.5	1.5	45
2	F-2	1:5	5	2.5	2.5	45
3	F-3	1:1	5	2.5	2.5	45
4	F-4	1:3	5	1.5	1.5	45
5	F-5	1:0.17	5	1.5	1.5	45
6	F-6	1:5.82	5	1.5	1.5	45
7	F-7	1:1	5	0.5	0.5	45
8	F-8	1:3	5	1.5	1.5	45
9	F-9	1:3	5	1.5	1.5	45
10	F-10	1:5	5	0.5	0.5	45
11	F-11	1:3	5	2.914	2.914	45
12	F-12	1:3	5	1.5	1.5	45
13	F-13	1:3	5	0.085	0.085	45

Table No.3: Evaluation results of TMZ SLNs

S.No	Formulation code	*Entrapment efficiency (%)	Particle size (nm)	PDI	Zeta potential (mV)
1	F-1	85.621±0.34	389.9	1.000	-70
2	F-2	86.96 ±0.45	313.3	1.000	-64
3	F-3	81.24±0.53	5093	1.000	-52.2
4	F-4	85.52±0.29	387.2	1.000	-68
5	F-5	74.706±0.62	627.5	0.452	-42
6	F-6	89.44±0.78	177.1	1.000	-19.5
7	F-7	82.68±0.16	220.2	1.000	-17.8
8	F-8	84.90±0.91	386	1.000	-66
9	F-9	85.42±0.20	387.5	0.950	-67.8
10	F-10	87.072±0.88	235.9	1.000	-25
11	F-11	84.15±0.92	396.1	1.000	-43.4
12	F-12	84.72±0.56	388.2	0.825	-69.2
13	F-13	85.916±0.82	1064	0.885	-27

*All the values are calculated as Mean, ± S.D, n=3

Table No.4: Anova Table for % Entrapment Efficiency

S.No	Source	F-value	p-value	
1	Model	11.24	0.0031	**Significant**
2	A-Surfactant (Tween-80)	0.8500	0.3872	
3	B-Drug : Lipid	49.65	0.0002	
4	AB	0.1828	0.6818	
5	R^2	---	---	0.8892
6	Adequate Precision	---	---	10.4209

Table No.5: Anova Table for % Drug Release

S.No	Source	F-value	p-value	
1	Model	108.42	< 0.0001	**Significant**
2	A-Surfactant (Tween-80)	18.85	0.0034	
3	B-Drug : Lipid	512.50	< 0.0001	
4	AB	0.5904	0.4674	
5	R^2	---	---	0.9873
6	Adequate Precision	---	---	33.3228

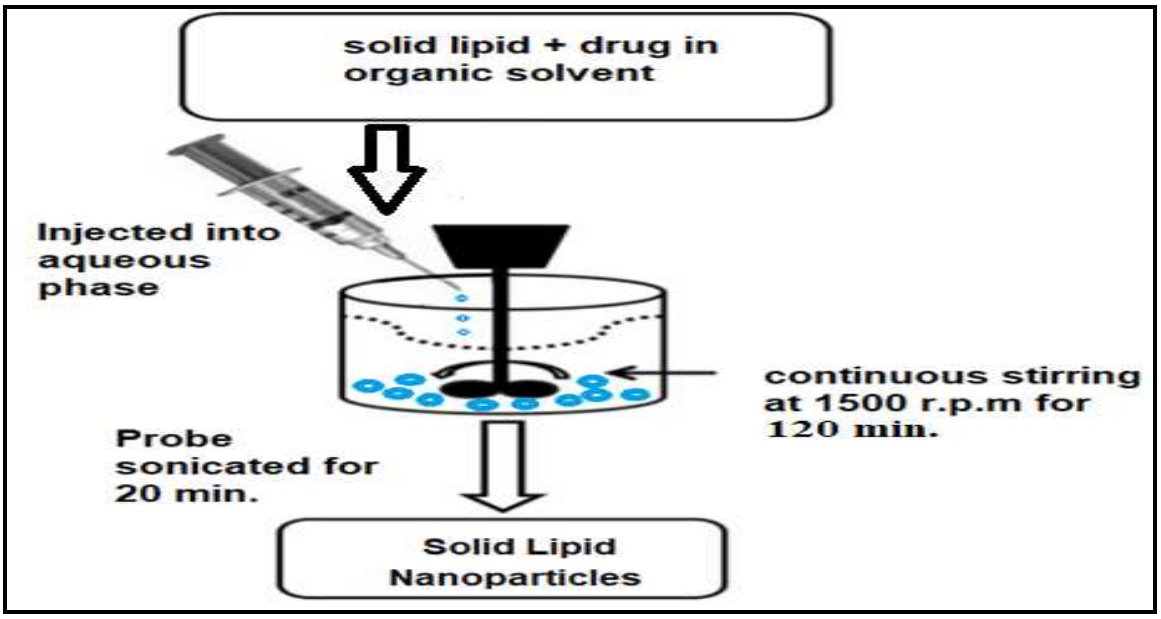

Figure No.1: Solvent Injection Method

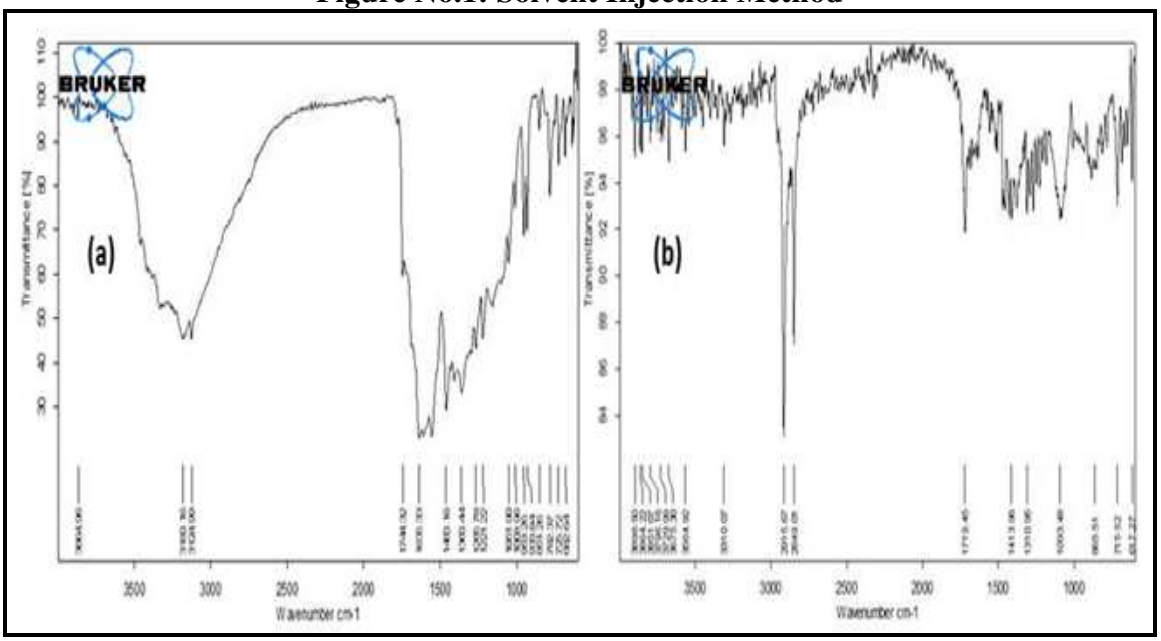

Figure No.2. FTIR spectrum of (a) TMZ (b) TMZ Formulation

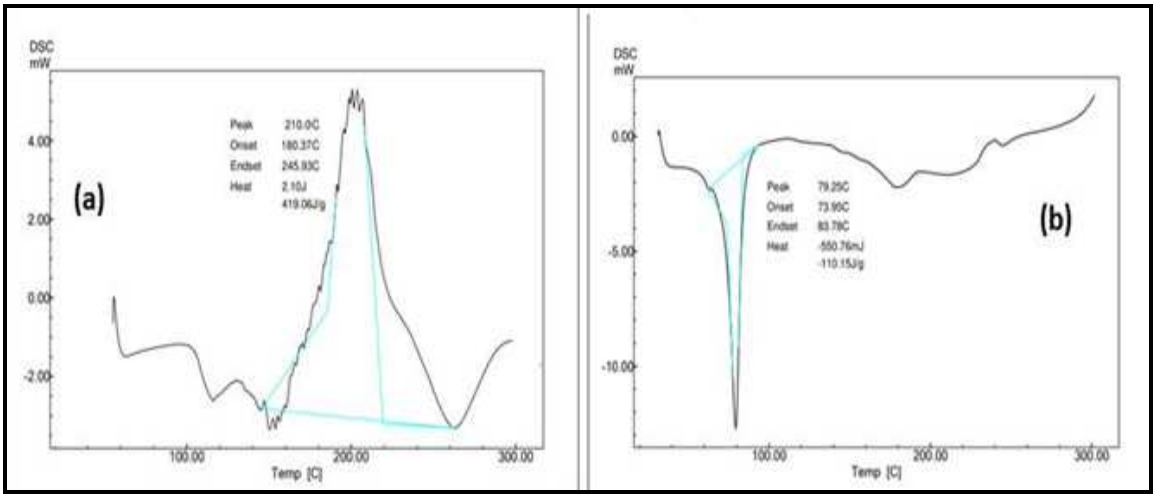

Figure No.3: DSC thermograms of (a) TMZ (b) TMZ Formulation

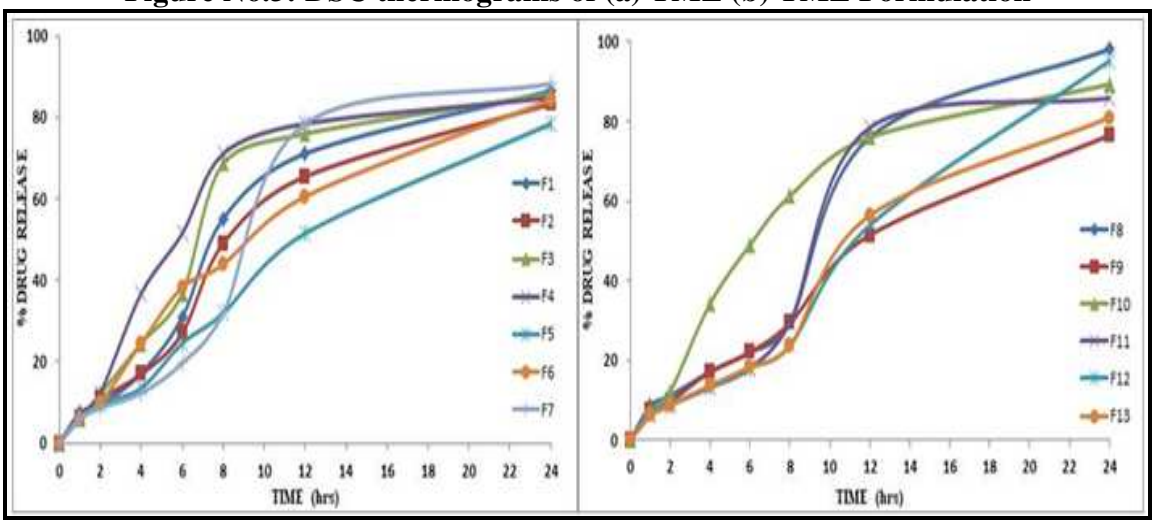

Figure No.4: *In-vitro* drug release studies of all formulations from F1-F13

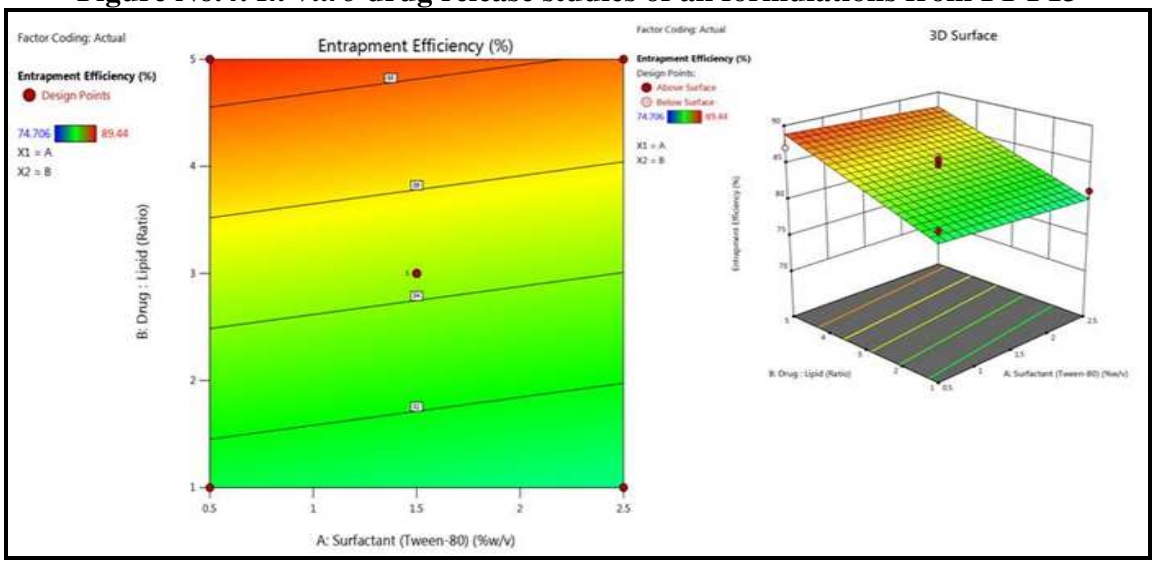

Figure No.5: Contour and 3D surface plots of Response-1 (%EE)

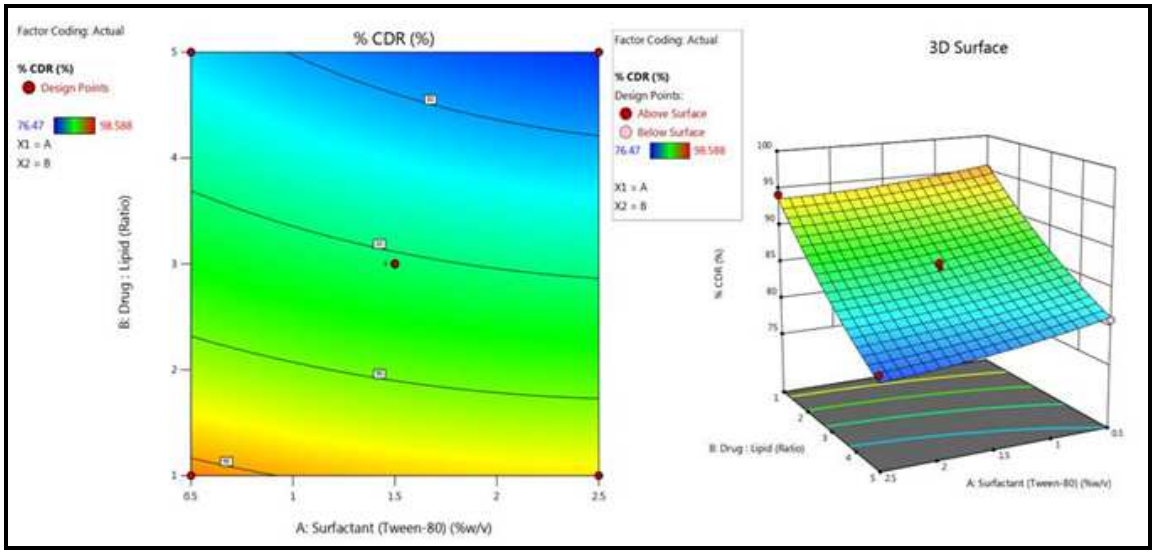

Figure No.6: Contour and 3D surface plots of Response-2 (% DR)

Figure No.7: Particle size, PDI and Zeta potential of Optimized formulation

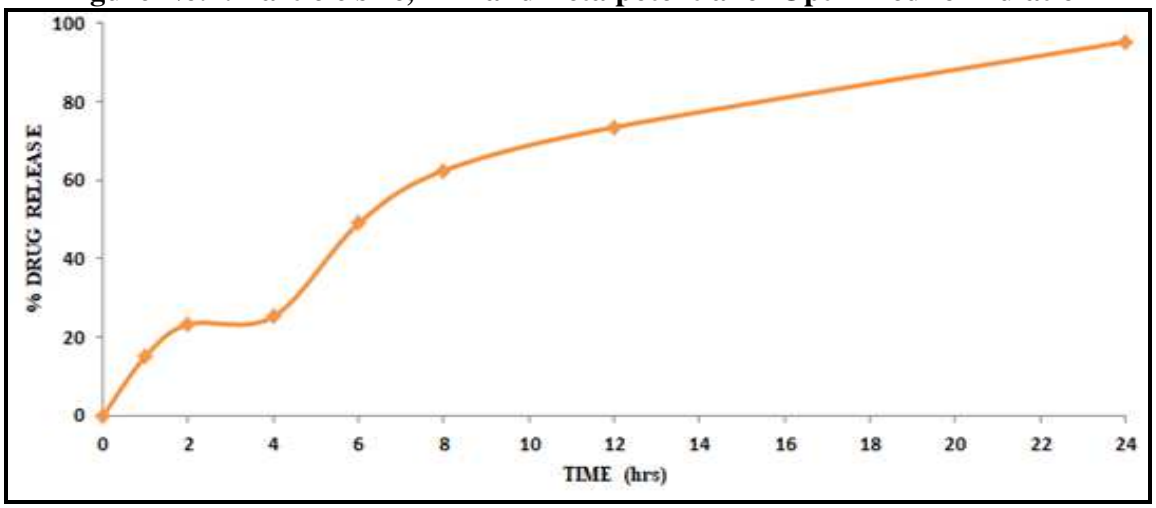

Figure No.8: *In-vitro* drug release plot of Optimized formulation

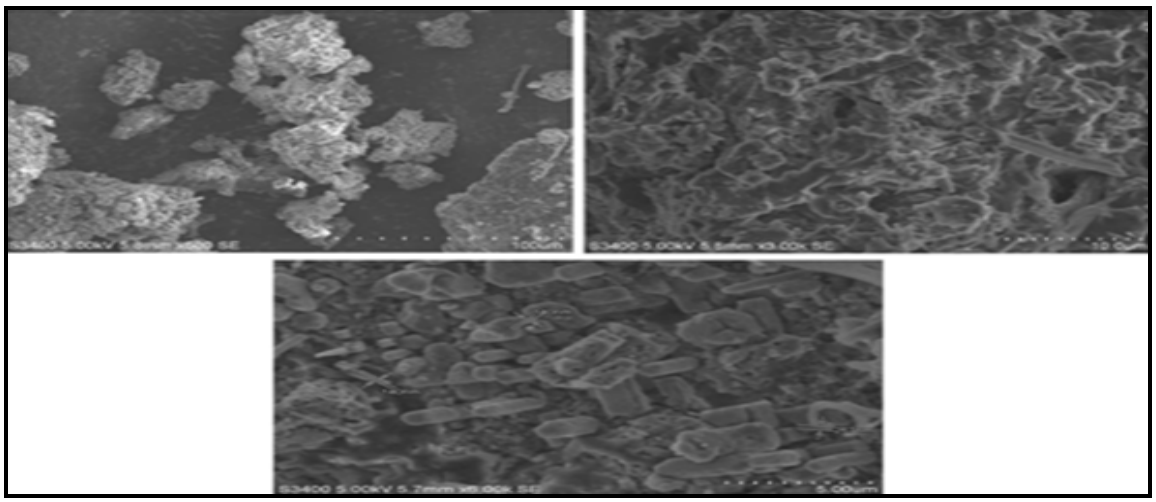

Figure No.9: SEM studies of TMZ optimized formulation

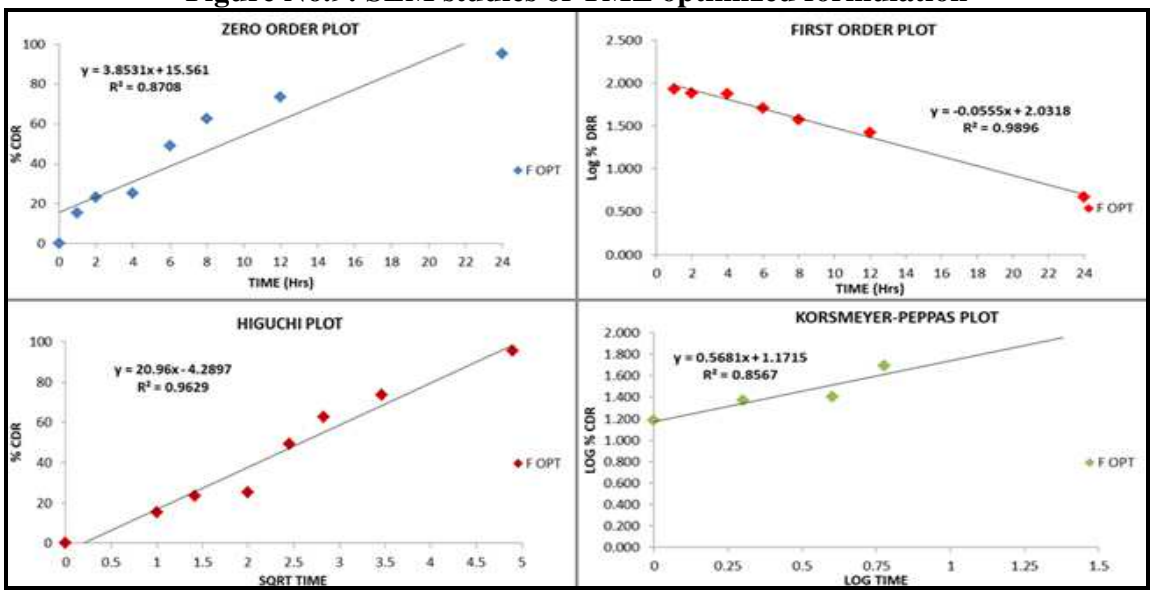

Figure No.10: *In-vitro* drug release kinetics of Optimized formulation

CONCLUSION

TMZ loaded SLNs were successfully developed using central composite statistical design, which gave optimum concentration of surfactant and drug: lipid ratio in the formulation to obtain maximum entrapment efficiency and drug release for extended period of 24hrs. The release of TMZ was found to follow first order kinetics with non-fickian diffusion. The prepared formulation may also reduce the toxicity of chemotherapy. However, further studies are required to endorse their potential as an effective drug delivery to brain in treatment of glioblastoma multiforme.

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CONFLICT OF INTEREST

We declare that we have no conflict of interest.

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