Formulation and Evaluation of Temozolomide Oral Suspension for Brain Tumor Therapy

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ABSTRACT

Temozolomide (TMZ) is an alkylating agent widely used in the treatment of glioblastoma multiform and other malignant brain tumors. However, the commercially available capsule dosage form presents challenges in pediatric, geriatric, and dysphagia patients due to swallowing difficulty and dose inflexibility. The present study aims to develop and evaluate a stable, patient-friendly oral suspension of temozolomide using a Quality-based pharmaceutics approach. A novel citrate-buffered, polymer-stabilized suspension was formulated to enhance chemical stability and dosing accuracy.

Keywords: *Temozolomide, Oral suspension, Brain tumor, Glioblastoma, Pediatric formulation, Stability study.*

INTRODUCTION

Glioblastoma multiforme (GBM) is the most common brain tumor in adulthood. Uniformly fatal, it arises from astrocytic cells and provides the ability to proliferate extensively. Maximum treatment leads to a median survival of primary GBM of 14 to 15 months. (Lee et al., 2017) Its infiltrative character combined with molecular heterogeneity hallmark the tumor's aggressiveness. (Huang et al., 2015) Despite substantial efforts in order to identify novel therapeutic strategies, tumors invariably recur after surgery. (Ellis et al., 2015) GBM is comprehensively delineated in its genomic characteristics. However, the transfer to effective treatment options has failed to appear until now.

MATERIALS AND METHODS

Materials

Ingredients	Procured Drug Location
Temazolamide (TMZ)	Cipla, Hyderabad.
Sodium carboxymethyl cellulose (NaCMC) Xanthan Gum, Polysorbate 80 (Tween 80) Methyl paraben, Propyl paraben,	Sigma Aldrich, Mumbai.

METHODS

Liquid Chromatographic Method

The liquid chromatographic system consisted of a Supercoil ABZ (Supelco, Toronto) C18 column with 30% acetonitrile and 70% 0.05M phosphoric acid with 0.01 M sodium lauryl sulfate as the mobile phase with a flow rate of 1 mL/min and UV detection at 330 nm.

Assay Validation

Following development of the chromatographic system capable of separating temozolomide from its degradation products (Figure 1), the accuracy and reproducibility of standard curves was then tested over 5 days.

Data Reduction and Statistical Analysis

Analysis of variance was used to test differences in concentration on different study days, at different temperatures, in different bottle containers and with different formulations. The 5% level was used as the a priori cut-off for significance.

FORM ULATION BATCHES

Formulation	Temazolamide (TMZ)	Sodium carboxymethyl cellulose	Xanthan gum	Polysorbate 80	Methyl Paraben,	Propyl Paraben,
F1	70	0.1	0.1	05	0.4	0.7
F2	70	0.6	0.6	09	0.6	0.4
F3	70	0.7	0.7	04	0.4	0.6
F4	70	0.8	0.8	06	0.9	0.9
F5	70	0.18	09	0.1	06	0.6
F6	70	0.14	04	0.6	09	0.8
F7	70	0.16	06	0.7	04	0.9
F8	70	0.17	0.5	0.8	07	0.6

EVALUATION PARAMETERS

PH MEASUREMENT

pH was measured using a calibrated digital pH meter.

DRUG CONTENT UNIFORMITY

Drug content was analyzed using a validated UV-spectrophotometric method at 329 nm. Drug content determination of the film was carried out by dissolving the films of required size in pH 1.2 phosphate buffer (0.1N HCl) using magnetic stirrer for 1hour.

VISCOSITY

Measured using a Brookfield viscometer to ensure pourability and uniform dosing.

IN-VITRO DRUG RELEASE

Dissolution studies were conducted using USP Type II apparatus in pH

STABILITY STUDIES

Stability studies were performed at: 4 °C (Refrigerated) 25 °C / 60% RH
Samples were evaluated over 30 days for assay, pH, and physical stability.

Statistical analysis

Proteins of interest on Western Blots were normalized by relative normalization control values of respective GAPDH lanes. Error bars indicate the mean densitometric value ± standard deviation.

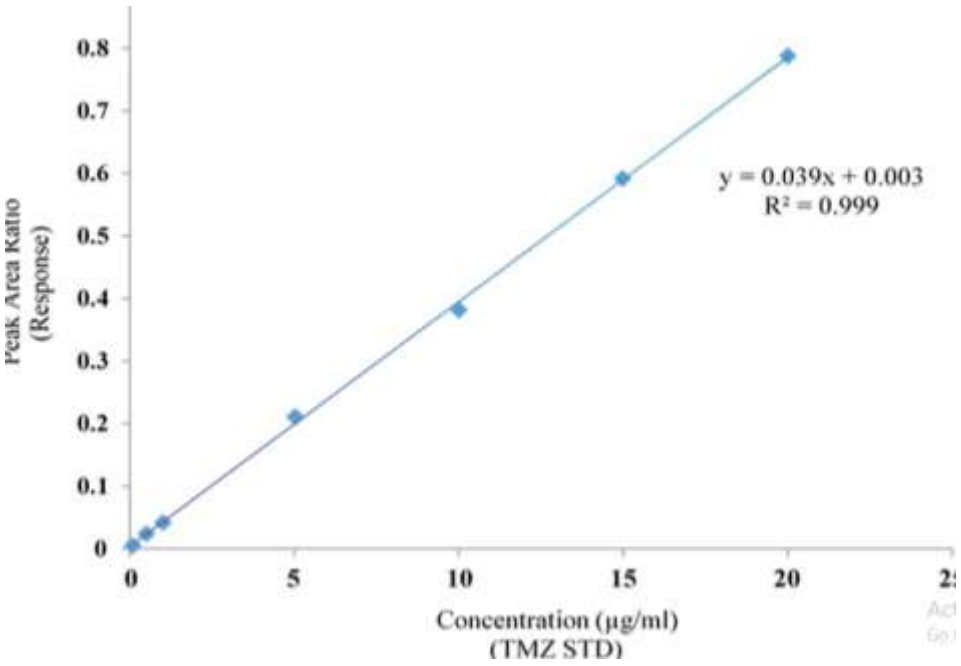
Detection of proteins

Brief staining with Ponceau solution allowed cutting the blots at the right lanes. Blocking of unspecific binding sites was performed with 5% milk for 1h. Antibodies were diluted as recommended or tested in 5% milk or 5% BSA.

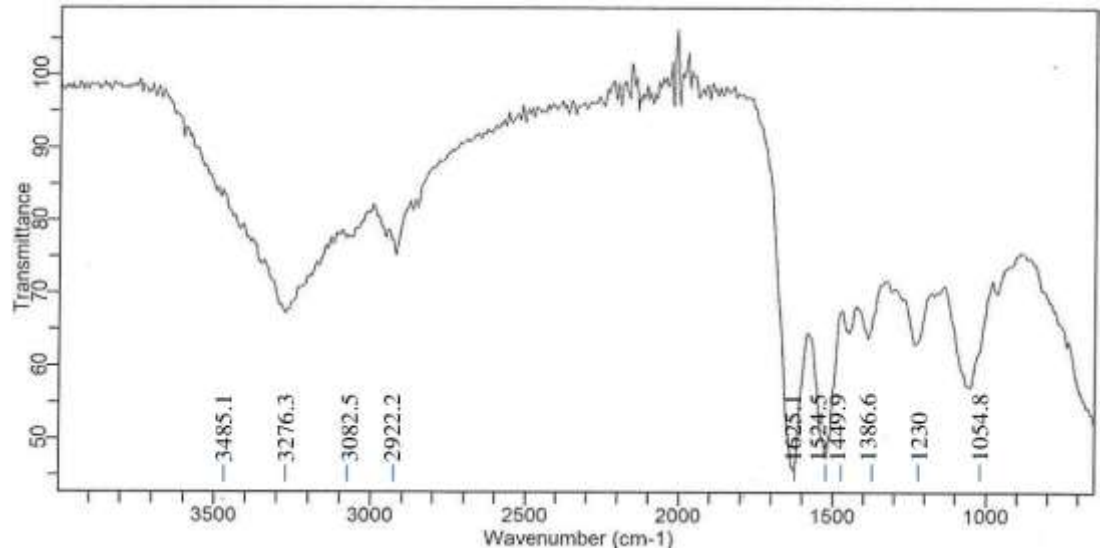
Semi-Dry blotting

The transfer system was set up from anode to cathode with 1-2 sheets of Whatman-paper previously plunged in anode I / II buffer, a PVDF membrane moistened with methanol, the acrylamide gel and 3 sheets of Whatman-paper plunged in cathode buffer.

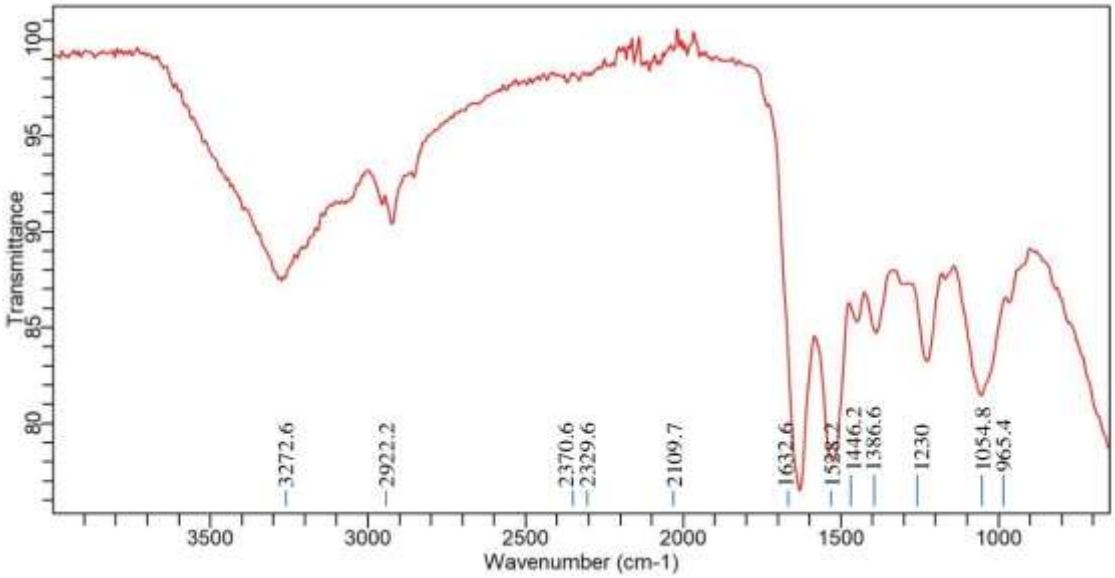
CALIBRATION CURVE OF TEMAZOLAMIDE (TMZ)



FTIR OF PURE DRUG

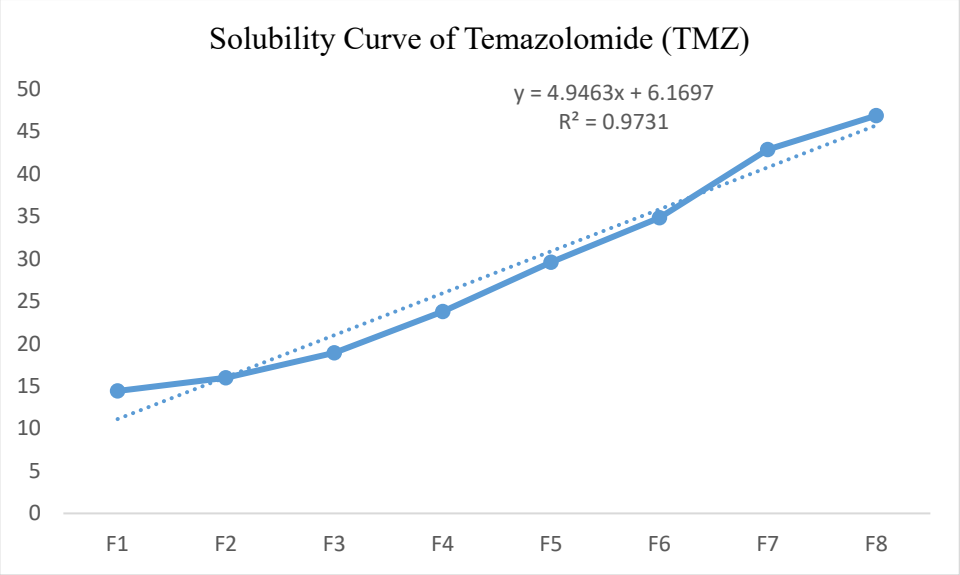


FTIR OF DRUG WITH POLYMERS



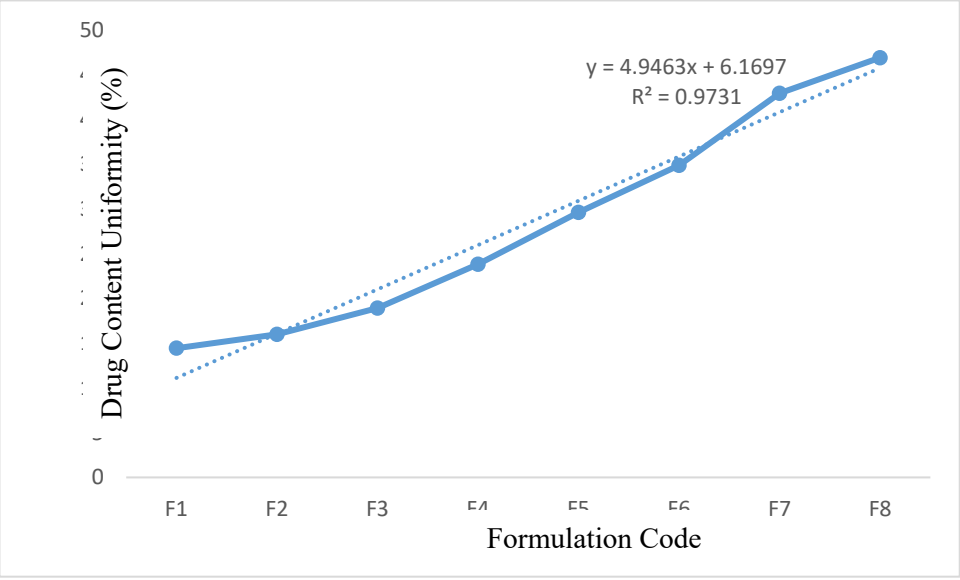
SOLUBILITY

FORMULATION CODE	SOLUBILITY
F1	14
F2	16
F3	19
F4	24
F5	30
F6	35
F7	43
F8	47



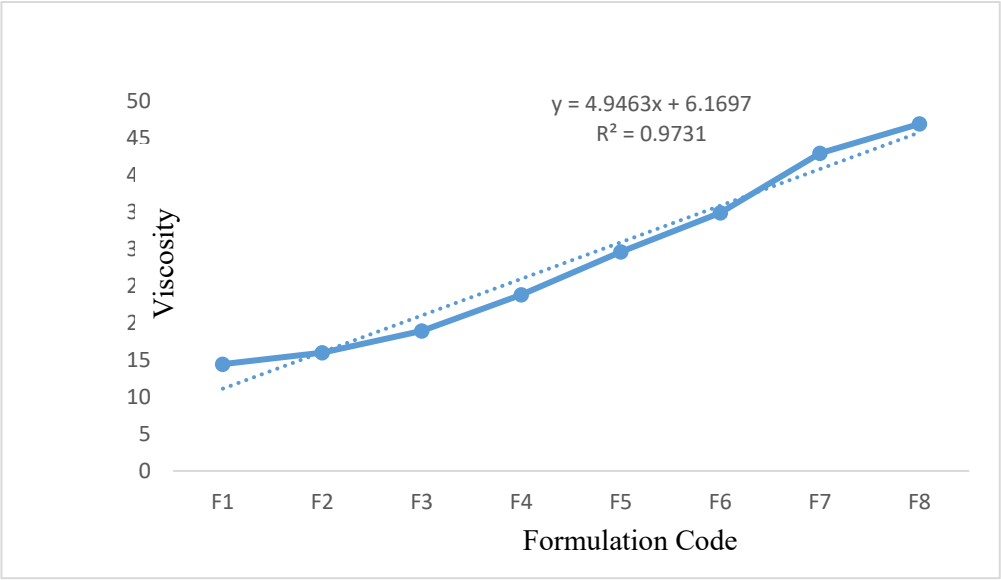
DRUG CONTENT UNIFORMITY

FORMULATION CODE	DRUG CONTENT UNIFORMITY
F1	85
F2	88
F3	91
F4	93
F5	95
F6	96
F7	98
F8	99



VISCOSITY

FORMULATION CODE	SOLUBILITY
F1	24
F2	30
F3	35
F4	43
F5	24
F6	38
F7	40
F8	43



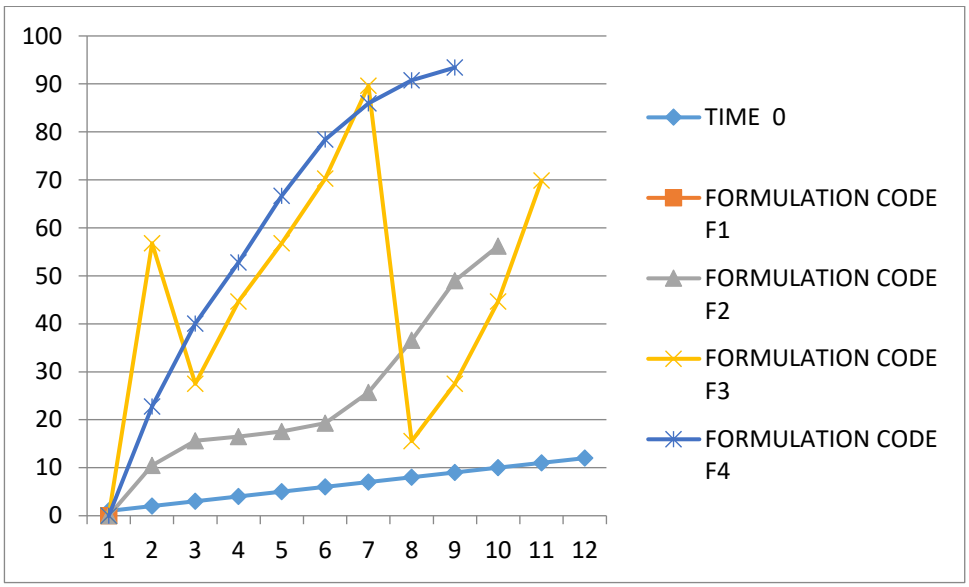
IN-VITRO DRUG RELEASE

It was noticed that the suspension hydrated rapidly and began to dissolute the drug within minutes. Orally dissolved formed by higher quantity of polymer had shown slower dissolution rate this might be due to the increase level of polymer, results in formation of high viscosity gel layer caused by more intimate contact between the particles of polymer results in decreased in mobility of drug particles in swollen matrices, which leads to decrease in release rate. From the In vitro drug release, it was observed that in formulation containing low concentration of polymer, the drug release was found to be faster and higher from oral suspension of F8 when compared with the other films, i.e. 99.49 ± 0.36. F8 is considered as an optimized formulation based on in vitro release studies and other evaluation parameters.

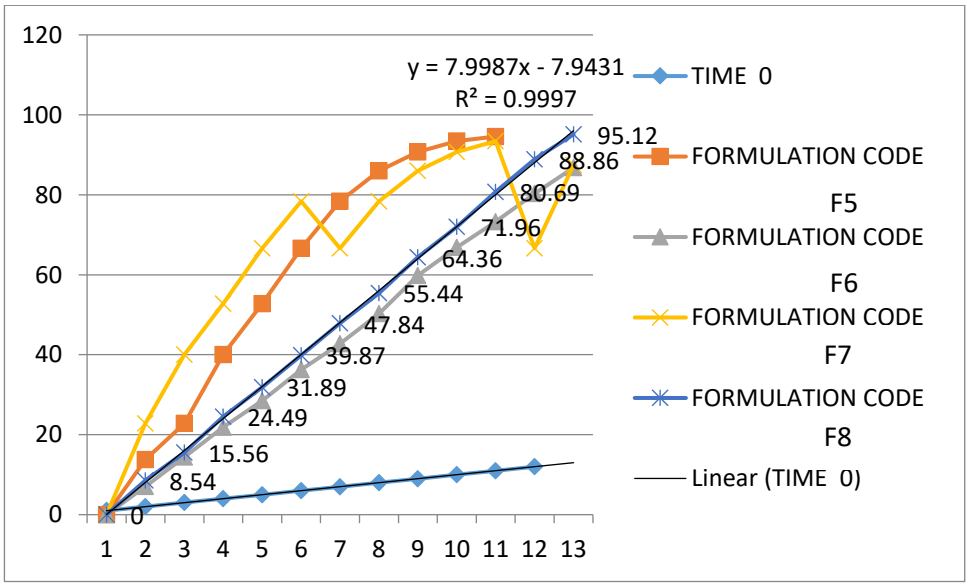
Time (hrs.)	**Percent Drug Release**							
Formulation								
0 min.	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**
1	Failed	10.52	56.77	13.79	13.79	7.02	22.78	8.54
2	-	15.62	27.53	22.78	22.78	14.43	40.06	15.56
3	-	16.48	44.62	40.06	40.06	21.83	52.78	24.49
4	-	17.54	56.77	52.78	52.78	28.48	66.64	31.89
5	-	19.32	70.25	66.64	66.64	36.26	78.41	39.87

6	-	25.67	89.62	78.41	78.41	42.72	66.64	47.84
7	-	36.57	15.56	85.96	85.96	50.31	78.41	55.44
8	-	48.96	27.53	90.75	90.75	59.81	85.96	64.36
9	-	56.21	44.62	93.41	93.41	66.83	90.75	71.96
10	-		69.87	-	94.58	73.29	93.41	80.69
11	-		-	-	-	80.31	66.64	88.86
12	-		-	-	-	86.77	87.41	95.12

FORMULATION BATCH (F1-F4)



FORMULATION BATCH (F5-F8)



SUMMARY

The high stability of a TMZ solution prepared from the powder for infusion formulation makes it suitable for oral administration. Oral use of a TMZ solution facilitates administration of the drug to patients with difficulties to swallow capsules and also enables a more flexible and precise dosing.

CONCLUSION

The interplay with other pathways possibly interacting with autophagy like the important mTOR pathway and EGFR should be clarified as well. Particularly studies about inactive EGFR in different cellular locations might help to surpass ambiguities of the EGFR – autophagy interaction. Patient material like primary cell lines held under different culture conditions might play a major role in future cellular autophagy research.

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