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TEMOZOLOMIDE AFLOAT MICROSPHERES FOR CARCINOMA OF THE BRAIN: FABRICATION AND CHARACTERIZATION

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ABSTRACT

Floating microspheres (FM) of Temozolomide (TZM) were made to build its scope to achieve good blood concentration and to show lengthened medication discharge. FM of TZM was set up by Ion gelation strategy utilizing ethyl cellulose, Carrageenan gum, and sodium alginate. The medication stacked FM were structured and evaluated for its physicochemical attributes including drug-excipient inviting conduct by Differential Scanning Calorimetry (DSC) and Fourier Transform Infra-red (FTIR). The DSC and FTIR study uncovered the similarity of TZM with the excipients utilized. The rate yield of FM from all details was acceptable and demonstrated palatable lightness and coasting time. % TZM discharge for the FM was found up to 98.25% (F-8) till tenth h. The investigation infers that FM with TZM can be figured utilizing sodium alginate, ethyl cellulose, and carrageenan gum by exfoliation technique.

Keywords: Temozolomide, carrageenan, microspheres, buyout

INTRODUCTION

The floating drug delivery systems (FDDS) is intended for gastrointestinal maintenance for a long length (Ahad *et al.,* 2011). Gastro holding of solid dosage forms can be accomplished by the creations of adjusted density, bodily fluid attachment, development, unfurling, and so on (Meka *et al.,* 2008). Floating Microspheres (FM) with low-density polymers are getting intriguing for many researchers (Harsha *et al.,* 2020).

Temozolomide (TZM) is an alkylating agent given orally to tackle carcinoma of the brain (Barvaux *et al.,* 2004). TZM is of imidazotetrazine derivative, contains imidazole ring fused to tetrazine ring. TZN is a prodrug and converts into an active form in the body. It mainly eliminates by renal and traces by feces (Ashley *et al.,* 2009).

MATERIALS AND METHODS

Material

The materials required in this work are delineated in Table 1.

Table 1: List of materials

Materials	Suppliers/Manufacturer
Temozolomide	A gift from Cipla, Hyderabad, Telangana
Sodium alginate	Fischer Chemic Ltd, Hyderabad
Ethyl Cellulose	Fischer Chemic Ltd, Hyderabad
Carrageenan	Fischer Chemic Ltd, Hyderabad
Calcium chloride	Fischer Chemic Ltd, Hyderabad
Double distilled water	Own distillation unit

The equipment utilized was (table 2) listed.

Table 2: List of equipment used in the study

Devices	Manufacturers
Digital balance	Vibra technologies, Bangalore
Magnetic stirrer	Remi, Secunderabad
Melting point apparatus	Sisco Ltd. Hyderabad, India
DSC scanner	Perkin Elmer
FTIR	Bruker alfa
UV visible spectroscopy	Shimadzu-S1210
Membrane filter	Millipore

Probe sonicator	Power sonic, Mumbai
Dissolution test apparatus	Electro lab USP Tdl-081

Drug excipient compatibility studies

Differential scanning calorimetry (DSC)

The DSC examinations of TZM and definition mix were performed with Perkin Elmer, FTIR spectrophotometer to check any medication excipient collaboration. Each sample was situated in an aluminum skillet discretely with warming paces of 10°C/min from 50-300°C under nitrogen (50 ml/min).

FTIR study

FTIR spectra of TZM and its combination with excipient blend were made by Bruker IR spectrophotometer.

Preparation of FM

The FM of the TZM was set up by the exfoliation method. The sodium alginate cross-connecting polymers were inundated in water for 24 h. The TZM taken in 10 ml of water broke up and afterward blended in with the above polymer blend. The above arrangement was poured gradually utilizing a 24-measure carrageenan needle containing calcium chloride (3%). The shaped FM was left for 30 min in the above arrangement with mixing to finish the response and to frame round MS. The readied MS were separated, sprinkled with refined water lastly dried at 45°C (Hennink and Franssen, 2002). The dried MS safeguarded in a water/air proof holder (Table 3) (Abdul *et al.,* 2011).

Table 3: Formulations of various FM

Ingredients (mg)	Formulations								
	F-1	F-2	F-3	F-4	F-5	F-6	F-7	F-8	F-9
Temozolomide	100	100	100	100	100	100	100	100	100
Sodium alginate	10	20	30	10	20	30	10	20	30
Ethyl Cellulose	-	-	-	10	20	30	10	20	30
Carrageenan	5	5	5	10	10	10	15	15	15
Calcium chloride	3	3	3	3	3	3	3	3	3

Characterization of FM

Determination of Entrapment Efficiency

A 100 mg of FM were taken, cautiously ground, and suspended in HCl (0.1 N). In this way, the substance suspended in the water was kept up by test sonication (Power sonic 505) for 20 min and mixed with a magnetic instigator (Remi) for the entire extraction of the TZM from the FM. The ensuing arrangement was explained through a 0.45µ film channel (Millipore). The TZM was

hounded by a UV-visible spectrophotometer (Shimadzu-S1210) at 329 nm. The entrapping was determined by utilizing the accompanying formula (Srivastava *et al.,* 2005).

$$\text{Drug entrapment efficiency} = \frac{\text{Experimental drug content}}{\text{Theoretical drug content}} X100$$

Particle size distribution

Sieve analysis with the help of sieves # 16, #20, #30, #40, #60, and #80 was used to determine by passing the MS from coarse size to finer sieves (Muneer *et al.,* 2017; Kumae *et al.,* 2010).

Buoyancy percentage

The FM (0.3g) was put in USP XXIV dissolution assembly (type II) loaded up with 900 ml of 0.1M HCl with Tween 80 (0.01%). The medium was inspired at 100 rpm for 12 h. The drifting and balanced out part of the FM was recouped independently. The FM were emaciated and contemplated. The buoyancy rate was planned as the extent of the majority of the FM that persevered through fluctuating and the complete mass of the FM (Ma *et al.,* 2008; Hindustan *et al.,* 2010).

$$\% \text{ Buoyancy} = \frac{\text{Weight of the FM s}}{\text{Weight of the settled FM}} X100$$

***In Vitro* Release studies**

TZM release from FM was performed by the USP basket dissolution apparatus. FM of the required amount was suspended in 900 ml of HCl (0.1 M of pH 1.2). The medium was enthused (100 rpm) and maintained at 37±0.5°C by keeping up sink conditions. After sufficient dilution, the samples were investigated for measurement of the TZM at 329 nm utilizing the Shimadzu UV-VIS double beam spectrophotometer (model: S1210) (Ishaq *et al.,* 2013; Rani *et al.,* 2011). The TZM was measured from the calibration curve as describes by Ishaq *et al.,* 2014.

RESULTS AND DISCUSSIONS

The TZM thermogram was described by a solitary intense endothermic at 211.78°C and the TZM blend demonstrated an endothermic top at 201.84°C. These thermograms showed that a little change to one side when joined with excipients, this could be attributable to the TZM liquefying or to its transformation into a nebulous structure. These thermograms show that there are no indications of contrariness among TZM and excipients (Fig.1).

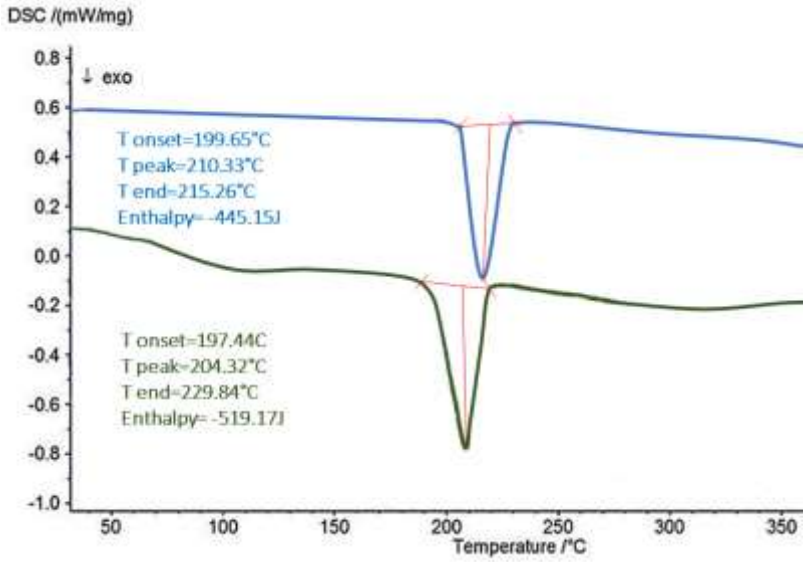

Fig. 1. DSC thermograms of drug and excipient

The FTIR spectra of TZM demonstrated stretches and peaks were likewise in FTIR of TZM-excipient mix represents no remarkable contra issues of TZM with the excipients of the study.

Drug entrapment efficiency (DEE)

It was discovered that the DEE was acceptable in all the FM at the awakening of 500 rpm (Table 4). The DEE was from 55.95±0.35 to 78.07±0.32% for F-1 to F-9. The DEE was expanded by climb the polymer focus in FM s. This might be attributable to the low dissolvability of TZM in water, which encourages the dissemination of a piece of the TZM caught in the encompassing during the FM preparation.

Particle size analysis

The size of the FM differed based on composition (Table 4). The F-1 demonstrated a moderately enormous level of huge size (299.54±1.48µ) and the F-8 detailing indicated fluctuating FM of generally little size (278.84±2.69µ) as the viscidness of the medium raised to a higher polymer fixation, bringing about the improved interfacial strain. The FMs were globular with no noteworthy obvious inconsistency on a superficial level (Table 4).

The Buoyancy Percentage

The buoyant rate for all FM was >75% (for 10 h), and ranged from 75.09±0.02% to 91.36±2.16%. The uppermost% was gained with the plan F-8.

Table 4: Efficiency of FM s of Temozolomide FM

Formulation	Yield	Particle	Drug	Buoyancy	Floating

	(%)	Size (µ)	Entrapment (%)	Percentage (%)	time (h)
F-1	65.48±0.58	299.48±1.45	56.48±1.20	75.09±0.02	5.0±0.07
F-2	64.58±1.49	298.54±1.48	55.95±0.35	76.26±1.38	4.8±0.07
F-3	69.54±1.05	297.49±2.25	72.19±0.68	80.28±1.65	3.8±0.05
F-4	71.35±2.15	287.03±7.84	68.25±2.25	81.41±0.26	5.1±0.01
F-5	68.57±1.15	295.98±2.36	74.49±0.49	85.22±0.38	7.3±0.05
F-6	81.10±0.65	294.91±1.20	69.55±0.31	86.84±0.13	8.5±0.11
F-7	69.05±0.48	299.30±1.26	67.22±0.95	78.58±1.48	7.0±0.05
F-8	75.84±0.29	278.84±2.69	76.04±0.25	91.36±2.16	8.9±0.09
F-9	80.11±1.49	285.65±0.67	78.07±0.32	87.65±1.49	8.5±0.05

Values are in mean± SD; Trials made=3

Calibration curve

The TZM concentrations were estimated by the regression equation (y = 0.017x-0.0007, R^2 = 0.9976) of the calibration curve of TZM in 0.1 N HCl (pH 1.2). The calibration curve of TZM was tabulated in table 5 and shown in fig. 2.

***In-vitro* dissolution study**

The FM s showed a prolonged emission of the TZM in an acidic medium and the release of the TZM was approximately linear. About 40% of TZM was initially released. Furthermore, the release of the TZM from the FM s matrix was regulated by the polymer. This can reduce the total drug release (DR) from the polymer matrix. Furthermore, the smaller FM are designed at a minor polymer level and has a wider surface wide-open to the dissolution medium, which results in a faster DR (fig.3).

Table 5: Calibration data of drug

Concentration (µg/ml)	Absorbance (nm)
0	0.000
10	0.156
20	0.356
30	0.526
40	0.658
50	0.852

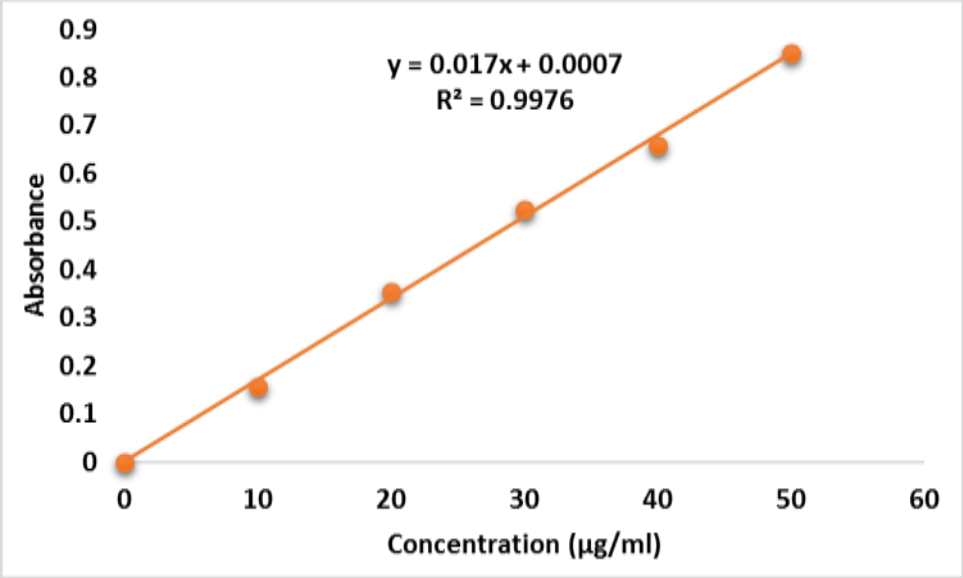

Fig.2. Standard calibration curve of TZM

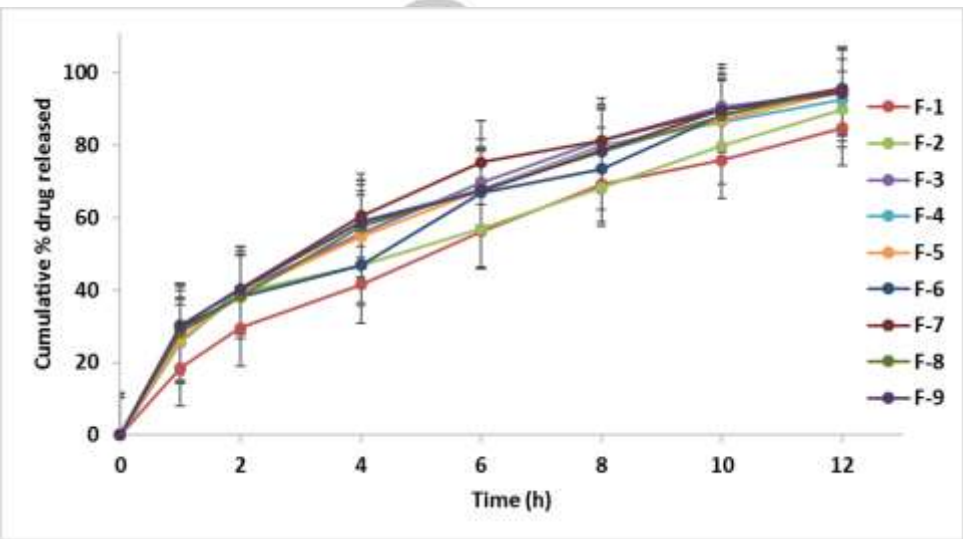

Fig.3. Zero-order plots of TZM

CONCLUSION

In-vitro data obtained for floating microspheres (FM) of Temozolomide (TZM) displayed good incorporation effectiveness, good buoyancy, and lengthy drug release. The microspheres of various sizes and TZM content could be attained by fluctuating the ingredients. The study concludes that TZM can be formulated as FM using sodium alginate, Ethyl cellulose and carrageenan gum by ionotropic gelation method. The FM disclosed better buoyancy, and TZM discharge.

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