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Research Article

**DESIGN AND DEVELOPMENT OF TRIMETAZIDINE  
HYDROCHLORIDE SUSTAINED RELEASE MICROSPHERES**<sup>1</sup>Vadla saipreethi, <sup>2</sup>Dr Alladi Saritha

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**Article Received:** August 2022**Accepted:** September 2022**Published:** October 2022**Abstract:**

The meaning of microencapsulation is converting liquids to solids, altering colloidal and surface properties, providing environmental protection and controlling the release characteristics by using the coating materials. Trimetazidine is indicated for the symptomatic treatment of stable angina pectoris in patients inadequately controlled or intolerant to first line therapies. Aim of the study is to formulate Trimetazidine hydrochloride double walled microspheres using different polymers by solvent evaporation method. In the present work, twofold walled microspheres of Trimetazidine hydrochloride utilizing Sodium alginate alongside Carbopol 934 and HPMC K100, Guar gum as copolymers were planned to convey Trimetazidine hydrochloride by means of oral course. Among all plans F7 shows Maximum medication discharge in 12hrs when contrasted and different details. Examination of medication discharge system showed that the medication discharge from the definitions followed the Non fickian dissemination instrument and follows zero request kinetics. In light of the consequences of assessment tests definition coded F7 was closed as best plan.

**Key words:** Trimetazidine hydrochloride, Sustained release microspheres, Formulation, Evaluation.**Corresponding author:****Dr Alladi Saritha**

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**INTRODUCTION:**

Conventional oral drug administration does not usually provide rate-controlled release or target specificity. In many cases, conventional drug delivery provides sharp increase in drug concentration often achieving toxic level and following a relatively short period at the therapeutic level of the drug concentration eventually drops off until re-administration. In order to obtain maximum therapeutic efficacy, it becomes necessary to deliver an agent to the target tissue in the optimal amount for the required period of time, thereby causing little toxicity and minimal side effects [1]. Desired drug release can be provided by rate-controlling membranes or by implanted biodegradable polymers containing dispersed medication. Microparticulate drug delivery systems are considered and accepted as a reliable one to deliver the drug to the target site with specificity, to maintain the desired concentration at the site of interest without untoward effects [2]. Microencapsulation is a useful method which prolongs the duration of drug effect significantly and improves patient compliance. Eventually the total dose and few adverse reactions may be reduced since a steady plasma concentration is maintained [3]. In recent years much research in drug delivery has been focused on degradable polymer microspheres. Administration of medication via such systems is advantageous because microspheres can be ingested or injected, can be tailored for desired release profiles and in some cases, it can provide organ-targeted release [4,5,6,7,8]. The meaning of microencapsulation is converting liquids to solids, altering colloidal and surface properties, providing environmental protection and controlling the release characteristics by using the coating materials. Emulsion solvent [5], phase-separation method [10] and spray drying method [11] are commonly used for the preparation of microspheres. The success of any microencapsulation method depends on many factors such as the drug solubility, partition co-efficiency, polymer composition, molecular weight etc. Among the various microencapsulation methods, emulsion solvent evaporation technique is often widely used to prepare microcapsules of water insoluble drugs (within the water insoluble polymer). Microspheres are formed by the evaporation of an organic solvent from dispersed oil droplets containing both polymer and drug.

Trimetazidine is indicated for the symptomatic treatment of stable angina pectoris in patients inadequately controlled or intolerant to first line therapies.<sup>12</sup> During myocardial ischemia, anaerobic metabolism takes over, increasing levels of lactic acid. The decreased intracellular pH and increased

concentration of protons activates sodium-hydrogen and sodium-calcium antiport systems, raising intracellular calcium concentrations, finally leading to decreased contractility. This injury to the myocardium raises concentrations of catecholamines, which activate hormone sensitive lipase, and increasing fatty acid concentrations in plasma.<sup>5</sup> When the myocardium is repurged, fatty acid oxidation becomes the dominant form of ATP production, maintaining an acidic pH, and further exacerbating the injury.<sup>13</sup>

Aim of the study is to formulate Trimetazidine hydrochloride double walled microspheres using different polymers by solvent evaporation method.

**MATERIALS AND METHODOLOGY:****MATERIALS:**

Trimetazidine hydrochloride Procured from, Provided by Chandra labs Hyderabad. Sodium alginate, Guar gum, Carbopol, HPMC, Eudragit are Standard chemical Reagents

**ESTIMATION OF TRIMETAZIDINE HYDROCHLORIDE:****STANDARD GRAPH OF TRIMETAZIDINE HYDROCHLORIDE:**

Standard Stock solution: 100 mg of Trimetazidine hydrochloride was broken down in little amount of ethanol and make up to 100 ml 0.1N HCL to give a convergence of (1000 µg/ml)

**Examining:**

From the stock arrangement 100µg/ml was ready and UV filter was taken between 200 to 400 nm. The assimilation most extreme was viewed as 270nm and was utilized for the further logical investigations.

**Calibration curve of Trimetazidine hydrochloride in 0.1 N HCL:**

The standard arrangements were ready by legitimate weakenings of the essential stock arrangement with cushion to acquire working norms in the focus scope of 30-150µg/ml of unadulterated example of Trimetazidine hydrochloride. The convergence of Trimetazidine hydrochloride present in the microspheres was acquired from the alignment bend.

**Calibration curve of Trimetazidine hydrochloride in pH6.8 Phosphate buffer:**

Standard Stock solution: 100 mg of Trimetazidine hydrochloride was broken up in little amount of ethanol and make up to 100 ml of pH 6.8 Phosphate support to give a centralization of (1000 µg/ml)

The standard arrangements were ready by legitimate weakenings of the essential stock arrangement with

cradle to get working guidelines in the fixation scope of 30-150µg/ml of unadulterated example of Trimetazidine hydrochloride. The centralization of Trimetazidine hydrochloride present in the microspheres was gotten from the alignment bend.

#### Drug-Excipients Compatibility study:

Trimetazidine hydrochloride was mixed with all excipients, used in the formulation in different ratios and subjected to Physical observation/FTIR.

#### Drug-Excipient Compatibility study (FTIR):

Preceding the improvement of the measurement shapes the preformulation study was completed. IR phantom examinations lies more in the subjective ID of substances either in unadulterated structure or in mix with polymers and excipients and goes about as an apparatus in foundation of synthetic association. Since I.R. is connected with covalent bonds, the spectra can give itemized data about the design of sub-atomic mixtures. To set up this point, examinations were made between the range of the substances and the unadulterated compound. The above conversations infer that infrared information is useful to affirm the character of the medication and to recognize the cooperation of the medication with the transporters. FTIR spectra were recorded with a Thermo Nicolet. Japan In the reach 400-4000 cm<sup>-1</sup> utilizing a goal of 4 cm<sup>-1</sup> and 16 outputs. Tests were weakened with KBr blending Powder, and squeezed to get self-supporting circles. Fluid examples definitions were investigated to shape a meager fluid film between two KBr circles.

#### EXPERIMENTAL METHODS:

#### PREPARATION OF DOUBLE WALLED MICROSPHERES OF TRIMETAZIDINE HYDROCHLORIDE:

#### FORMULATIONDESIGN:

**Table : 1 Formulation of Microspheres**

Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Trimetazidine hydrochloride	400	400	400	400	400	400	400	400	400	400	400	400
Sodium alginate	400	400	400	400	400	400	400	400	400	400	400	400
Guar gum	400	--	--	600	--	---	200	--	200	300	--	300
Carbopol	--	400	--	--	600	--	200	200	--	300	300	--
HPMC	--	--	400	--	--	600	--	200	200	--	300	300
Drug: polymer	1:2	1:2	1:2	2:5	2:5	2.5	2:5	2:5	2:5	2:5	2:5	2:5

q.s – Quantity sufficient

The twofold walled microspheres were ready by two stage process. In initial step the center microspheres of turf. Alginate and HPMC or Carbopol, Guar gum were formed. The microspheres then scattered in the natural stage. The natural stage containing polymer in which medication was broken up then the natural stage was emulsified with fluid paraffin. The dissolvable was permitted to vanish and twofold walled microspheres were gathered.

#### Formulation of Core Microspheres with Drug:

Microspheres were ready by water in oil emulsification dissolvable vanishing method. A polymeric fluid arrangement was made in which the medication was scattered and afterward the arrangement filled light fluid paraffin containing length 20 as an emulsifying specialist. The watery stage was emulsified in slick stage by blending. Steady blending was done utilizing attractive stirrer. The measuring glass and its substance were warmed, blending and warming were kept up with. The fluid stage was vanished. The microspheres were washed with n-hexane, isolated and dried at room temperature.

#### Formulation of Double Walled Microspheres:

The recently planned microspheres were scattered in the natural stage. The second polymer carbopol was broken up in a similar natural stage. The subsequent natural stage arrangement was emulsified in fluid paraffin. 1% range 80 arrangements were utilized as emulsifying specialist. Above emulsion was blended for complete dissipation of the natural arrangement. After complete vanishing of the natural arrangement the twofold walled microspheres were gathered by vacuum filtration and washed with n-hexane. The came about twofold walled microspheres were freeze dried for 24hrs.

**EVALUATION OF MICROSPHERES****Swelling Index Studies:**

$$\text{Swelling index} = \frac{(\text{Wet weight of microspheres} - \text{Dry weight of microspheres})}{\text{Dry weight of microspheres}}$$

**Drug Entrapment Efficiency:**

$$(\text{Drug entrapment efficiency (\%)}) = \frac{\text{Amount of drug actually present}}{\text{Theoretical drug load expected}} \times 100$$

**Determination of percentage yield**

The dried microspheres were weighed and percentage yield of the prepared microspheres was calculated by using the following formula.

$$\text{Percentage yield} = \frac{\text{Practical yield (mg)} \times 100}{\text{Theoretical yield}}$$

**In-vitroReleaseStudy:**

Details of dissolution testing:

- Apparatus: Lab India DS 8000
- Dissolution media:0.1 NHCl(pH-1.2), Ph6.8 Phosphate buffer
- Speed: 50 rpm
- Volume of medium: 900 ml
- Aliquots taken at each time interval: 5ml
- Temperature: 37±0.5°C
- Wavelength: 270 nm.

Release Kinetics:

Zero Order Kinetics

First Order Kinetics

Higuchi Model

Peppas Release Model

**STABILITY STUDIES:**

Strength of a medication has been characterized as the capacity of a specific definition, in a particular compartment, to stay inside its physical, compound, remedial and toxicological determinations. The reason for security testing is to give proof on how the nature of a medication substance or medication item fluctuates with time affected by an assortment of ecological factors like temperature, dampness, light, and empowers suggested capacity conditions. In general perceptions from various assessment concentrates, for example, drug-polymer cooperations, assessment of arranged definitions and medication discharge studies were completed. In view of the got results best definition was oppressed for additional dependability study. The solidness study was led according to ICH rules for the time of a half year at different sped up temperature and stickiness states of 25°C/60%RH, 40°C/70%RH, 60°C/80%RH.The sped up security investigation of the best definitions was done according to the ICH rules.nThe chose detailing F7 was examined for the medication capture productivity and in vitro discharge learn at various temperatures.

**RESULTS AND DISCUSSION:****PRE-FORMULATION STUDIES****Description****Table: 2 Description of Trimetazidine hydrochloride (API)**

Test	Description
Colour	White to almost white crystalline powder

Odour	odourless
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**Solubility****Table: 3** Solubility of Trimetazidine hydrochloride (API) in various solvents

Solvents	Solubility
Water	Practically insoluble
chloroform	Freely Soluble
Methanol	Freely Soluble
Ethanol	Soluble

**Melting Point**

These tests results were illustrated below:

**Table: 4 Melting point of API'**

Material	Melting Point
Trimetazidine hydrochloride	139 <sup>0</sup> c

**SPECTROSCOPIC STUDIES:****Calibration curve of Trimetazidine hydrochloride in 0.1N HCL**

Table shows the adjustment bend information of Trimetazidine hydrochloride in 0.1N HCL at 270nm. Fig. shows the standard adjustment bend with a relapse worth of 0.9972, slant of 0.005 and block of - 0.010. The bend was viewed as straight in the focus scope of 30-150µg/ml.

**Table: 5 Calibration curve data for Trimetazidine hydrochloride in 0.1N HCL**

CONCENTRATION (µg /ml)	ABSORBANCE
0	0
30	0.117
60	0.270
90	0.411
120	0.589

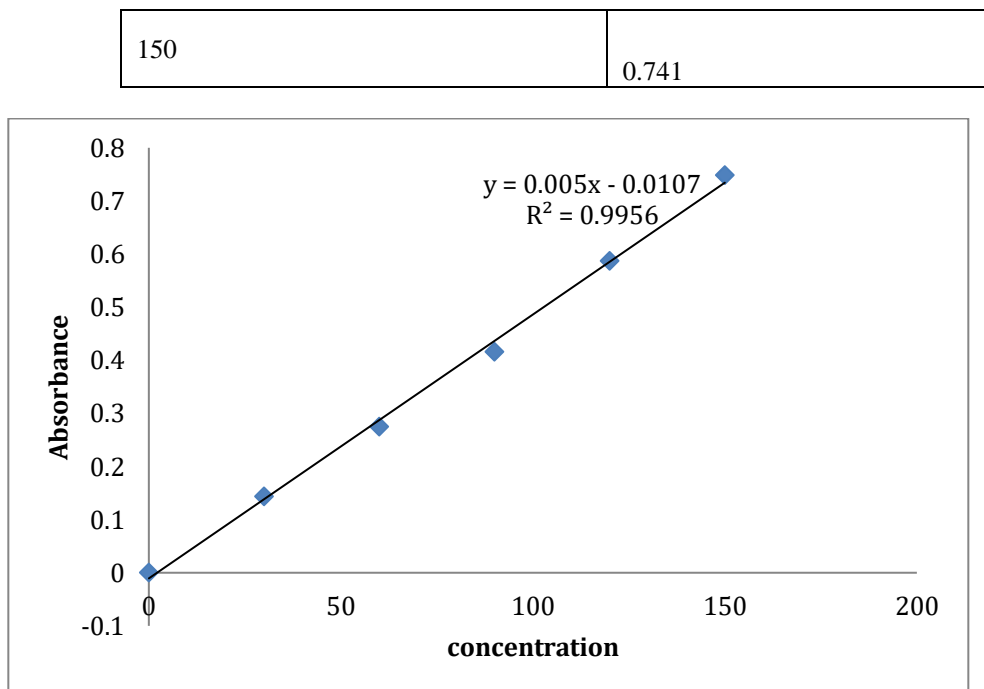


Figure: 1 Standard graph Of Trimetazidine hydrochloride in 0.1 N HCL

**Calibration curve of Trimetazidine hydrochloride in 6.8 pH phosphate buffer:**

Table shows the alignment bend information of Trimetazidine hydrochloride in 6.8 pH phosphate buffer at 270nm. Fig. shows the standard alignment bend with a relapse worth of 0.9987, incline of 0.005 and block of -0.010. The bend was viewed as straight in the focus scope of 30-150µg/ml.

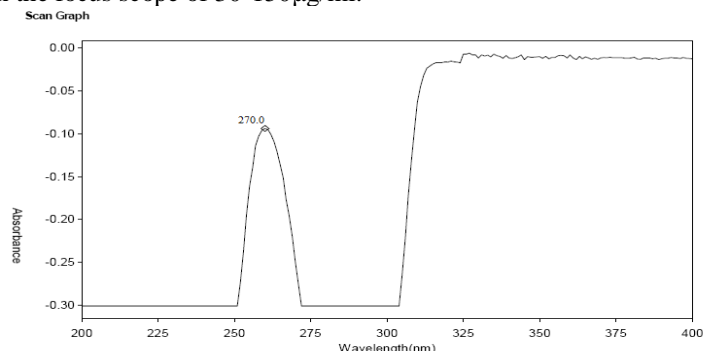


Figure: 2 UV Spectrum for Trimetazidine hydrochloride at 270nm

Table:6 Calibration curve data for Trimetazidine hydrochloride in 6.8 pH phosphate buffer

CONCENTRATION (µg/ml)	ABSORBANCE
0	0
30	0.132

60	0.289
90	0.418
120	0.586
150	0.745

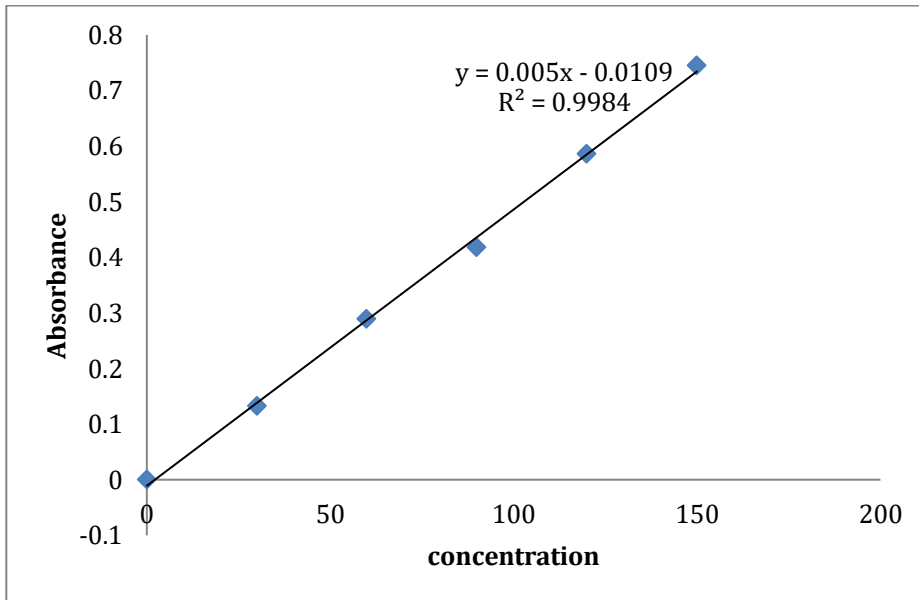


Figure: 3 Standard graph Of Trimetazidine hydrochloride in 6.8 pH phosphate buffer

#### DRUG AND EXCIPIENT COMPATABILITY STUDIES:

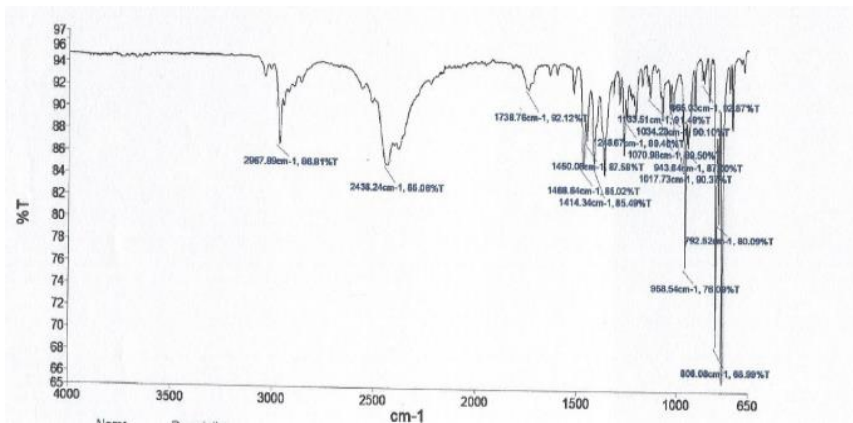


Figure: 4 FTIR graph for Trimetazidine hydrochloride pure drug

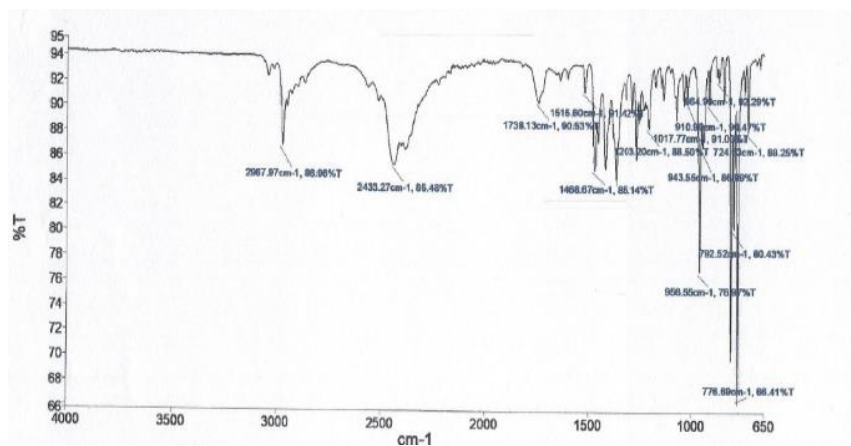


Figure: 5 FTIR graph for Trimetazidine hydrochloride drug with optimized formulation

**EVALUATION AND CHARACTERISATION OF MICROSPHERES**  
**PERCENTAGE YIELD**  
**DRUG ENTRAPMENT EFFICIENCY**

Table: 7 Percentage yield and percentage drug entrapment efficiency of the prepared microspheres

S.No.	Formulation code	% yield	% Drug entrapment efficiency
1	F1	82.2	77.1
2	F2	85.3	75.4
3	F3	86.1	85.1
4	F4	84.5	85.4
5	F5	79.7	82.7
6	F6	85.1	82.1
7	F7	88.4	87.8
8	F8	84.8	84.5
9	F9	85.1	79.7
10	F10	85.1	84.5
11	F11	84.5	86.1
12	F12	82.9	82.5



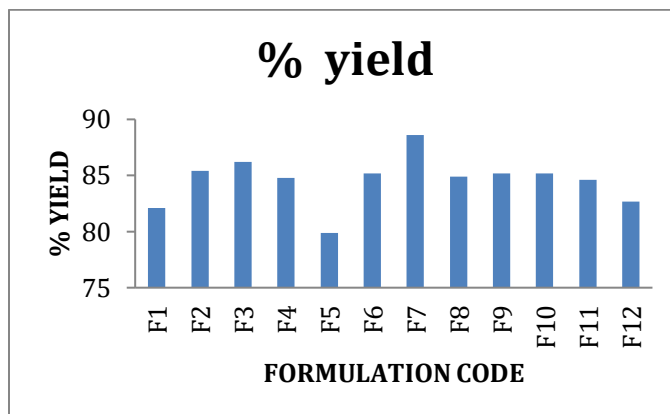


Figure: 6 Graphical representation of percentage yield of formulations F1-F12

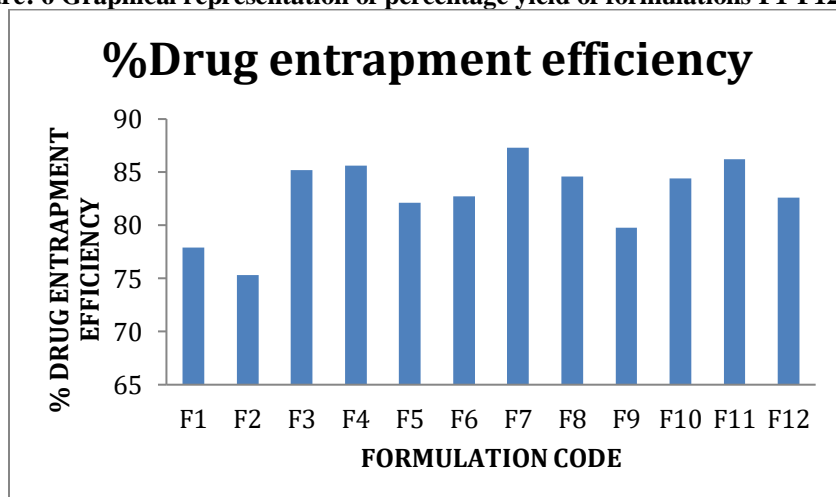


Figure: 7 Graphical representation of percentage drug entrapment efficiency of formulations F1-F12

#### PARTICLE SIZE ANALYSIS

Table: 8 Average Particle Size analysis for formulation F1-F12

Formulation code	Average particle size( $\mu\text{m}$ )
F1	647
F2	657
F3	667
F4	621
F5	624

F6	634
F7	612
F8	647
F9	651
F10	661
F11	629
F12	641

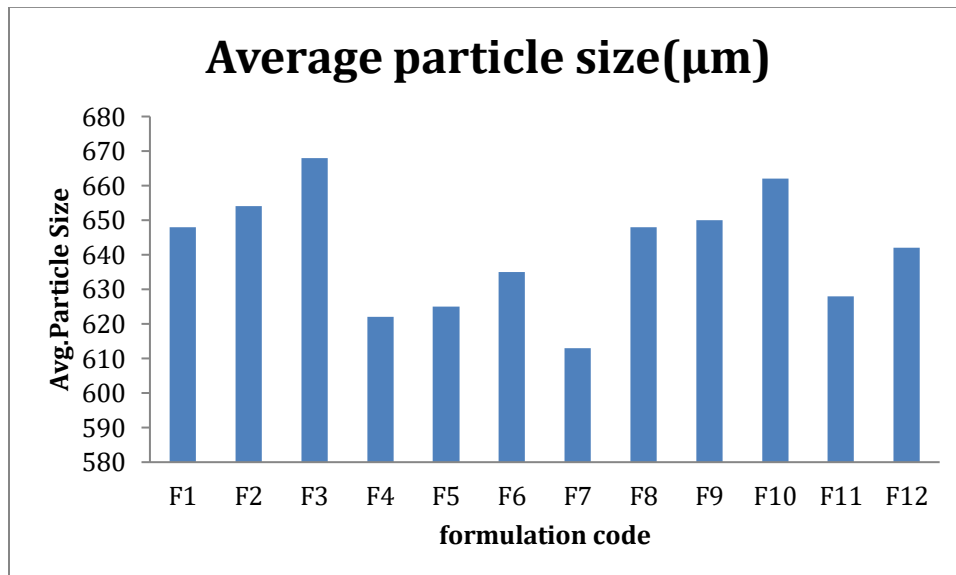


Figure: 8 Graphical representation of average particle size for formulations

#### IN-VITRO DRUG RELEASE STUDIES

Table: 9 In-Vitro drug release data of Trimetazidine hydrochloride microspheres

TIME (hrs)	Cumulative Percent Of Drug Released			
	F1	F2	F3	F4
0	0	0	0	0
1	5.08	4.5	6.81	1.77
2	9.7	12.11	16.52	11.05
3	22.65	28.7	26.66	28.81
4	44.20	41.58	38.74	41.41

5	56.33	52.23	50.1	54.68
6	72.71	63.59	68.38	62.75
7	86.41	76.81	80.15	70.95
8	98.71	92.35	95.65	82.51
10	--	--	----	94.28
12	--	---	----	---

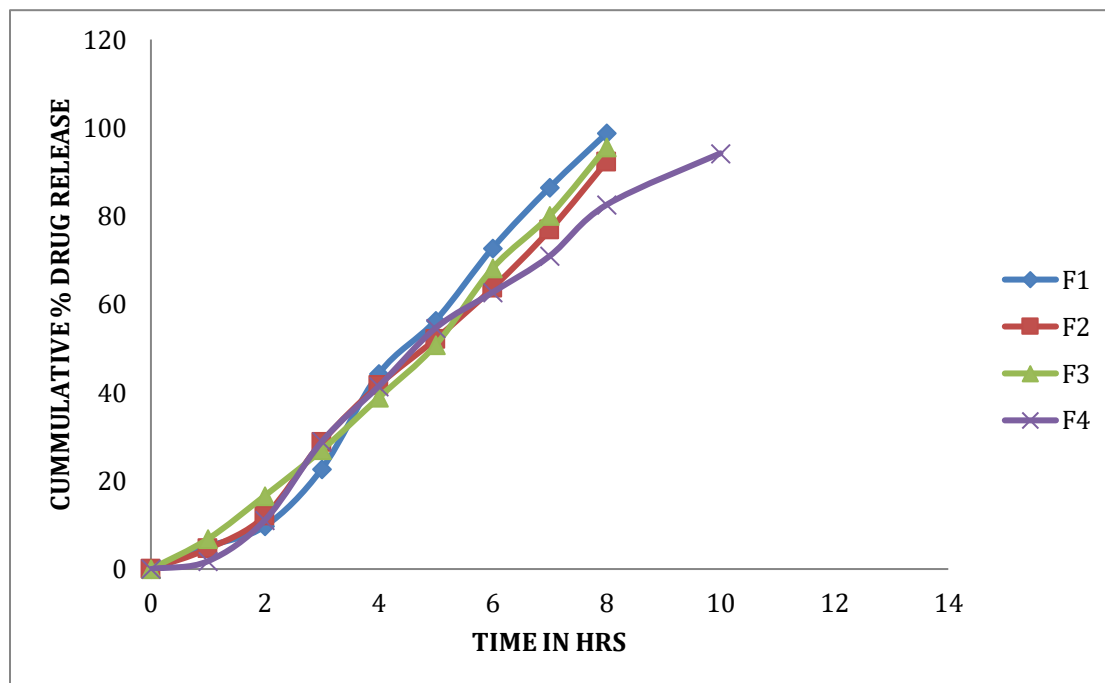


Figure: 9 In-Vitro drug release profile of Trimetazidine hydrochloride microspheres For F1-F4 formulations

Table: 10 In-Vitro drug release data of Trimetazidine hydrochloride microspheres

TIME (hrs)	Cumulative Percent Of Drug Released			
	F5	F6	F7	F8
0	0	0	0	0
1	4.7	8.2	7.61	5.6
2	15.62	16.6	14.07	10.2
3	22.4	24.3	26.46	16.46
4	36.16	36.31	38.6	24.31
5	43.8	45.52	52.9	35.58
6	54.91	55.61	62.22	47.15
7	69.4	62.9	74.07	56.9
8	82.12	70.44	86.09	67.42

10	96.51	82.6	94.58	80.8
12	--	89.56	97.8	88.16

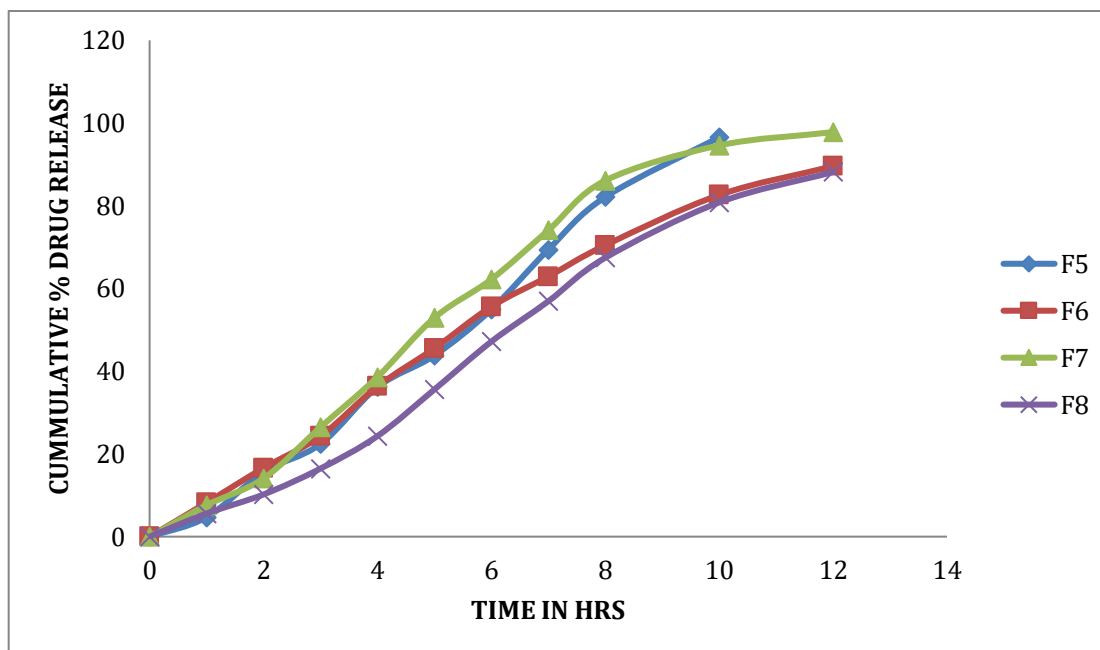


Figure: 10 In-Vitro drug release profile of Trimetazidine hydrochloride microspheres For F5-F8 formulations

Table: 11 In-Vitro drug release data of Trimetazidine hydrochloride microspheres

TIME (hrs)	Cumulative Percent Of Drug Released			
	F9	F10	F11	F12
0	0	0	0	0
1	6.6	5.4	8.4	8.31
2	10.4	12.1	18.7	11.14
3	20.2	24.6	29.8	18.49
4	31	36.22	45.7	26.65
5	41.36	45.5	56.1	36.6
6	52.27	56.1	65.8	43.14
7	65.7	62.6	74.7	54.55
8	71.13	72.24	80.8	63.5
10	83.3	89.12	89.2	72.61
12	87.21		91.4	84.40

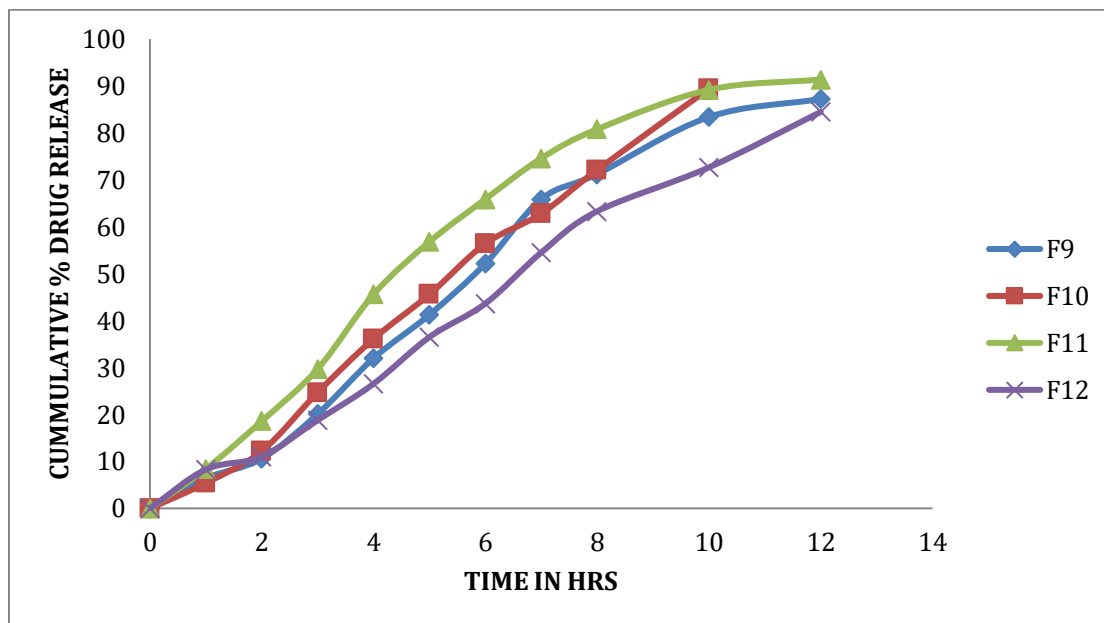


Figure: 11 In-Vitro drug release profile of Trimetazidine hydrochloride microspheres For F9-F12 formulations

Table: 12 IN-VITRO DRUG RELEASE KINETICS

	ZERO	FIRST	HIGUCHI	PEPPAS
	% CDR Vs T	Log % Remain Vs T	%CDR Vs $\sqrt{T}$	Log C Vs Log T
Slope	9.21811995	0.13533304	0.02780548	0.570787071
Intercept	1.79123506	0.76867477	0.71123660	-0.23910595
Correlation	0.97825756	-0.9395964	0.946195226	0.9097214
R 2	0.96007759	0.70835944	0.91687405	0.855254831

**RELEASE KINETICS FOR OPTIMIZED FORMULATION (F7)  
ZERO ORDER KINETICS**

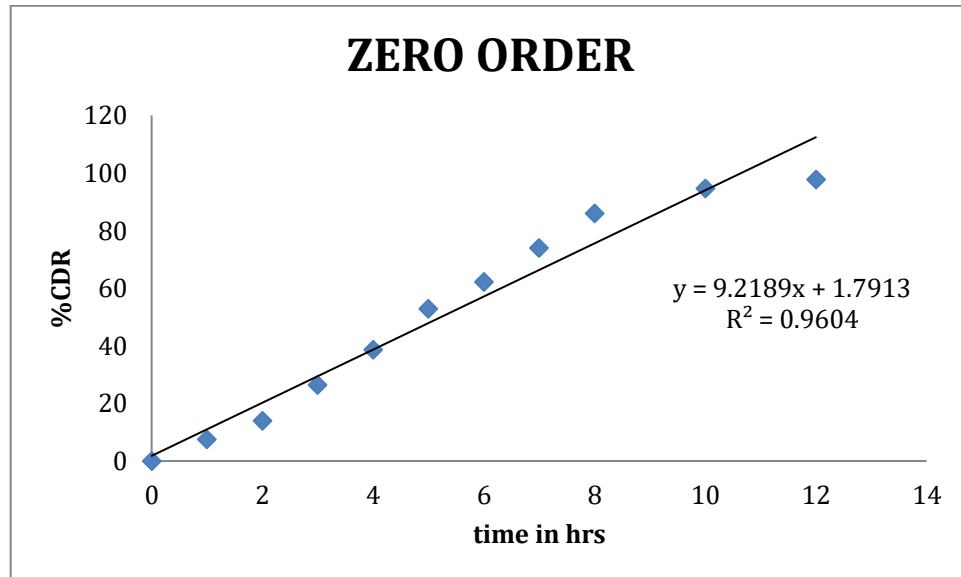


Figure: 12 Zero order kinetics for Trimetazidine hydrochloride microspheres F7 formulation

#### FIRST ORDER KINETICS

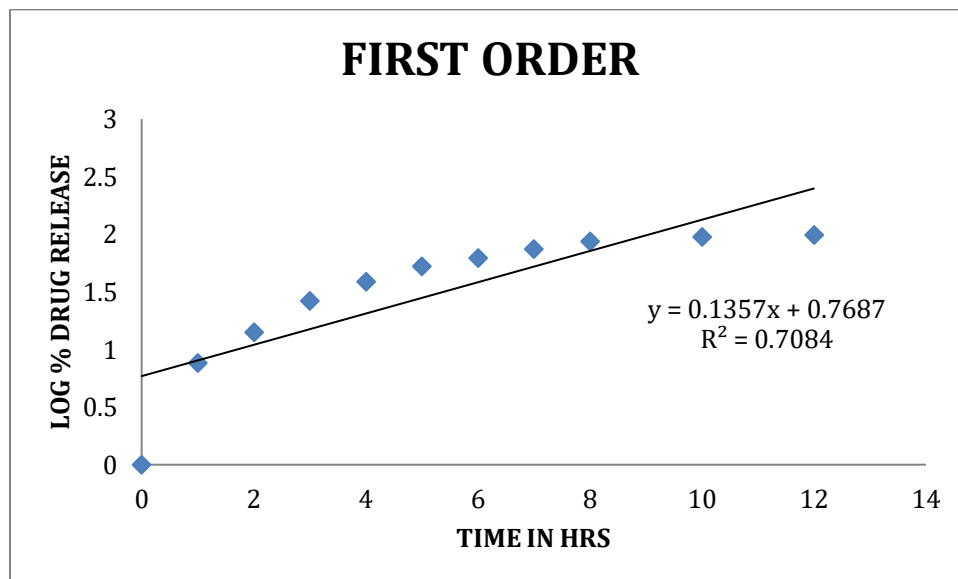


Figure: 13 First order kinetics for Trimetazidine hydrochloride microspheres F7 formulation

#### HIGUCHIS PLOT

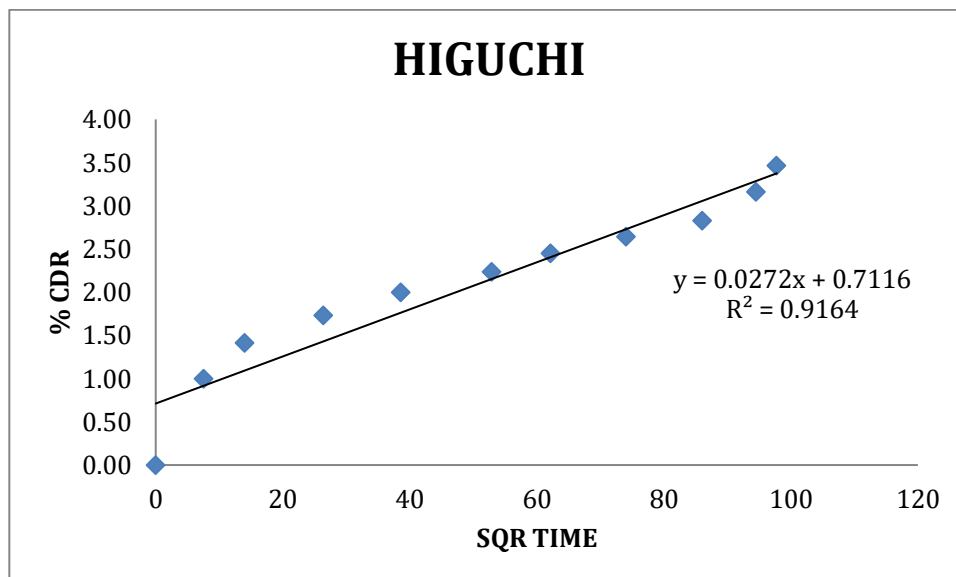


Figure: 14 Higuchis kinetics for Trimetazidine hydrochloride microspheres F7 formulation

#### PEPPAS PLOT

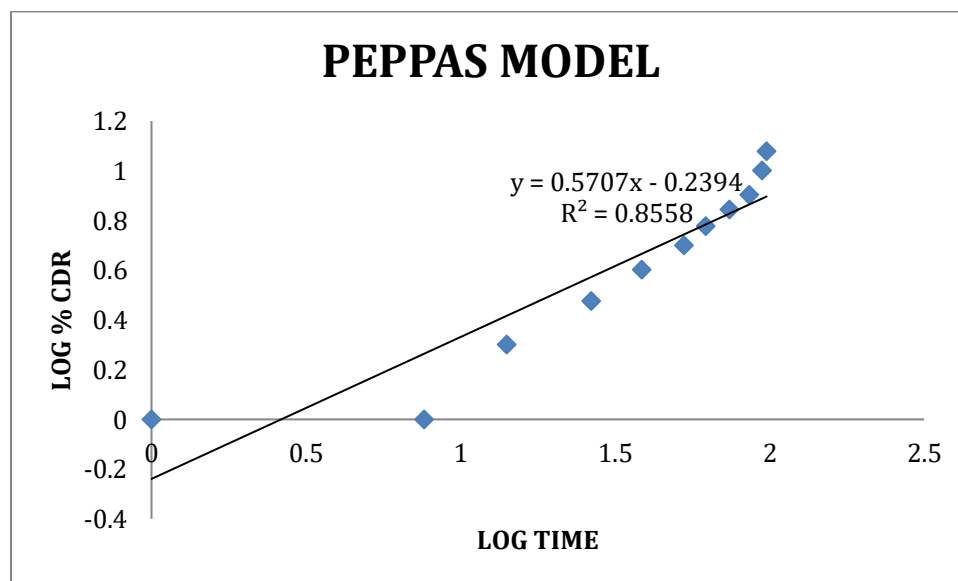


Figure: 15 Peppas kinetics for Trimetazidine hydrochloride microspheres F7 formulation

#### SUMMARY AND CONCLUSION:

In the present work, twofold walled microspheres of Trimetazidine hydrochloride utilizing Sodium alginate alongside Carbopol 934 and HPMC K100, Guar gum as copolymers were planned to convey Trimetazidine hydrochloride by means of oral course.

Insights about the arrangement and assessment of the definitions have been examined in the past section. From the review following ends could be drawn: -

- The aftereffects of this examination show that Solvent Evaporation strategy can be effectively

utilized to create Trimetazidine hydrochloride microspheres.

- FT-IR spectra of the actual blend uncovered that the medication is viable with the polymers and copolymer utilized.
- Microspheres containing sodium alginate alongside carbopol and Guar gum in 5:2 proportion had a least size scope of 613µm.
- Expansion in the polymer fixation prompted expansion in % Yield, % Drug ensnarement effectiveness, Particle size.

- The invitro drug discharge diminished with expansion in the polymer and copolymer fixation.
- Among all plans F7 shows Maximum medication discharge in 12hrs when contrasted and different details.
- Examination of medication discharge system showed that the medication discharge from the definitions followed the Non fickian dissemination instrument and follows zero request kinetics.
- In light of the consequences of assessment tests definition coded F7 was closed as best plan.

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