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DESIGN AND DEVELOPMENT OF TRIMETAZIDINE HYDROCHLORIDE SUSTAINED RELEASE MICROSPHERES

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ABSTRACT
Trimetazidine hydrochloride-loaded Gelatin microspheres were prepared by the ionic cross-linking technique using TPP as cross-linking agent. The process induced the formation of microspheres with the incorporation efficiency of 47% to 77%. The effect of Gelatin concentration, cross-linking agents and conditions was evaluated with respect to entrapment efficiency, particle size, surface characteristics and in vitro release behaviors. Infrared spectroscopic study confirmed the absence of any drug-polymer interaction. Differential scanning colorimetric analysis revealed that the drug was molecularly dispersed in the Gelatin microspheres matrices showing rough surface, which was confirmed by scanning electron microscopy study. The mean particle size and entrapment efficiency were found to be varied by changing various formulation parameters. The in vitro release profile could be altered significantly by changing various formulation parameters to give a sustained release of drug from the microspheres. The kinetic modeling of the release data indicate that trimetazidine hydrochloride release from the Gelatin microspheres follow anomalous transport mechanism after an initial lag period when the drug release mechanism was found to be fickian diffusion controlled.

KEYWORDS: Trimetazidine hydrochloride, sustained release, Microspeares.

INTRODUCTION
Angina pectoris, commonly known as angina, is a clinical manifestation of ischemic heart disease, generally arising from obstruction or spasm of the coronary arteries.[1],[2] In patients with angina pectoris, myocardial ischemia induces lower exercise capacity, more frequent angina attacks and reduces quality of life.[3] Trimetazidine dihydrochloride, 1-[(2,3,4-trimethoxyphenyl) methyl] piperazin is a clinically effective antianginal agent that has been used in the prophylaxis and management of angina pectoris.[4] Unlike other classical antianginal drugs, such as beta-blockers, calcium-channel antagonists, and long-acting nitrates, trimetazidine dihydrochloride displays anti-ischemic effects without inducing hemodynamic changes and thus protects the heart from the deleterious consequences of ischemia. So it is generally well tolerated and accompanied by minor side effects. Besides, trimetazidine dihydrochloride is freely soluble in water and has a relatively short half-life of 6 ± 1.4 h. Therefore, it is considered as an ideal candidate for sustained drug delivery.[5]

In the market, trimetazidine dihydrochloride is available as both immediate release oral formulations (Vastarel IR, 20 mg) and modified release tablets (Vastarel MR, 35 mg). The optimal dosage regimen of IR tablets is approved three times a day while MR tablets is twice a day.[6] However, repeated administration of the IR tablets leads to poor compliance for angina pectoris patients who need a long term therapy. MR tablets with sustained drug release behaviors could maintain their therapeutically effective concentrations in systemic circulation for prolonged periods of time, which decreases the number of daily administrations, minimizing local and systemic side effects. Thus it improves the patient compliance with prescribed dosage regimens.[7]

Hydrophilic polymers are becoming very popular in formulating oral sustained release tablets, such as xanthan gum, cellulose derivatives, alginate sodium or carbopol.[8] Hydroxypropyl methylcellulose (HPMC) is the most commonly and successfully used hydrophilic material for sustained drug delivery.[9] It possesses some important characteristics including nontoxicity, pH independence and high water swellability, which contribute to obtain a desirable drug sustained release profile. In this investigation, HPMC was used as a release retardant carrier in the design of sustained release matrix tablets for trimetazidine dihydrochloride.

Besides, a point-to-point in vitro–in vivo correlation was developed for relating percentage of drug dissolved to percentage of drug absorbed. The Food and Drug Administration (FDA) defines in vitro–in vivo correlation as a predictive mathematical model describing the relationship between an in vitro property of a dosage form and a relevant in vivo response.[10] A good correlation could predict the rate and extent of drug absorption in vivo.[11] Developing an in vitro–in vivo correlation for a sustained release tablet is an important object to facilitate product development and serves as a quality control procedure during product manufacture. This reduces the need for expensive bioavailability testing in animals and humans.[12] Hence the objective of the work was to prepare oral administration of sustained release microspears.

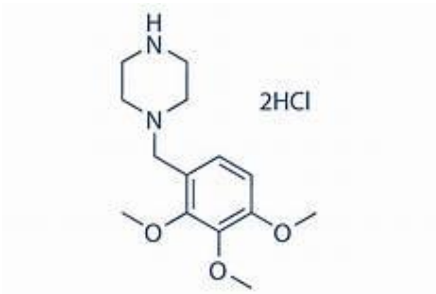

Fig 1: Chemical structure of Trimetazidine hydrochloride.

MATERIALS

The Trimetazidine hydrochloride was supplied by Chandra labs Hyderabad, India, Sodium alginate, Guar gum, Carbopol, HPMC, Eudragit are from Standard chemical reagents. Methanol was of high performance liquid chromatography (HPLC) grade. All other reagents and solvents were of analytical reagent grade.

METHODOLOGY

ESTIMATION OF TRIMETAZIDINE HYDROCHLORIDE

STANDARD GRAPH OF TRIMETAZIDINE HYDROCHLORIDE

Standard Stock solution: 100 mg of Trimetazidine hydrochloride was dissolved in small quantity of ethanol and make up to 100 ml 0.1N HCL to give a concentration of (1000 µg/ml)

Scanning: From the stock solution 100µg/ml was prepared and UV scan was taken between 200 to 400 nm. The absorption maximum was found to be 270nm and was used for the further analytical studies.

Calibration curve of Trimetazidine hydrochloride in 0.1 N HCL

The standard solutions were prepared by proper dilutions of the primary stock solution with buffer to obtain working standards in the concentration range of 30-150µg/ml of pure sample of Trimetazidine hydrochloride. The concentration of Trimetazidine hydrochloride present in the microspheres was obtained from the calibrationcurve.

Calibration curve of Trimetazidine hydrochloride in pH6.8 Phosphate buffer

Standard Stock solution: 100 mg of Trimetazidine hydrochloride was dissolved in small quantity of ethanol and make up to 100 ml of pH6.8 Phosphate buffer to give a concentration of (1000 µg/ml)

The standard solutions were prepared by proper dilutions of the primary stock solution with buffer to obtain working standards in the concentration range of 30-150µg/ml of pure sample of Trimetazidine hydrochloride. The concentration of Trimetazidine hydrochloride present in the microspheres was obtained from the calibrationcurve.

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)

Prior to the development of the dosage forms the preformulation study was carried out. IR spectral studies lies more in the qualitative identification of substances either in pure form or in combination with polymers and excipients and acts as a tool in establishment of chemical interaction. Since I.R. is related to covalent bonds, the spectra can provide detailed information about the structure of molecular compounds. In order to establish this point, comparisons were made between the spectrum of the substances and the pure compound. The above discussions imply that infrared data is helpful to confirm the identity of the drug and to detect the interaction of the drug with the carriers. FTIR spectra were recorded with a Thermo Nicolet. Japan In the range 400–4000 cm−1 using a resolution of 4 cm−1 and 16 scans. Samples were diluted with KBr mixing Powder, and pressed to obtain self-supporting disks. Liquid samples formulations were analyzed to form a thin liquid film between two KBr disks.

EXPERMENTAL METHODS

PREPARATION OF DOUBLE WALLED MICROSPHERES OF TRIMETAZIDINE HYDROCHLORIDE

The double walled microspheres were prepared by two step process. In first step the core microspheres of sod. Alginate and HPMC or Carbopol, Guar gum were formulated. The microspheres then dispersed in the organic phase. The organic phase containing polymer in which drug was dissolved then the organic phase was emulsified with liquid paraffin. The solvent was allowed to evaporate and double walled microspheres were collected.

Formulation of Core Microspheres with Drug

Microspheres were prepared by water in oil emulsification solvent evaporation technique. A polymeric aqueous solution was made in which the drug was dispersed and then the solution poured into light liquid paraffin containing span 20 as an emulsifying agent. The aqueous phase was emulsified in oily phase by stirring. Constant stirring was carried out using magnetic stirrer. The beaker and its content were heated, stirring and heating were maintained. The aqueous phase was evaporated. The microspheres were washed with n-hexane, separated and dried at room temperature.

Formulation of Double Walled Microspheres

The previously formulated microspheres were dispersed in the organic phase. The second polymer carbopol was dissolved in the same organic phase. The resulting organic phase solution was emulsified in liquid paraffin. 1% span 80 solutions were used as emulsifying agent. Above emulsion was stirred for complete evaporation of the organic solution. After complete evaporation of the organic solution the double walled microspheres were collected by vacuum filtration and washed with n-hexane. The resulted double walled microspheres were freeze dried for 24hrs.

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

EVALUATION OF MICROSPHERES

Swelling Index Studies

Swelling index =

(Wet weight of microspheres – Dry weight of microspheres)

Dry weight of microspheres.

Drug Entrapment Efficiency

(Drug entrapment efficiency (%) = Amount of drug actually present × 100

Theoretical drug load expected

Determination of percentage yield

The dried microspheres were weighed and percentage yield of the prepared microspheres was calculated by using the following formula[37].

Percentage yield = Practical yield (mg) ×100

Theoretical yield

***In-vitro* Release Study**

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

Stability of a drug has been defined as the ability of a particular formulation, in a specific container, to remain within its physical, chemical, therapeutic and toxicological specifications.

The purpose of stability testing is to provide evidence on how the quality of a drug substance or drug product varies with time under the influence of a variety of environmental factors such as temperature, humidity, light, and enables recommended storage conditions. Overall observations from different evaluation studies such as drug-polymer interactions, evaluation of prepared formulations and drug release studies were carried out. Based on the obtained results best formulation was subjected for further stability study. The stability study was conducted as per ICH guidelines for the period of six months at various accelerated temperature and humidity conditions of 25°C/60%RH, 40°C/70%RH, 60°C/80%RH. The accelerated stability study of the best formulations was carried out as per the ICH guidelines.

RESULTS AND DISCUSSION

SPECTROSCOPIC STUDIES

Calibration curve of Trimetazidine hydrochloridein 0.1N HCL

Table shows the calibration curve data of Trimetazidine hydrochloride in 0.1N HCL at 270nm. Fig. shows the standard calibration curve with a regression value of 0.9972, slope of 0.005 and intercept of -0.010. The curve was found to be linear in the concentration range of 30-150µg/ml.

Table 2: Calibration curve data for Trimetazidine hydrochloride in 0.1N HCL.

CONCENTRATION (µg /ml)	ABSORBANCE
0	0
30	0.114
60	0.275
90	0.416
120	0.587
150	0.749

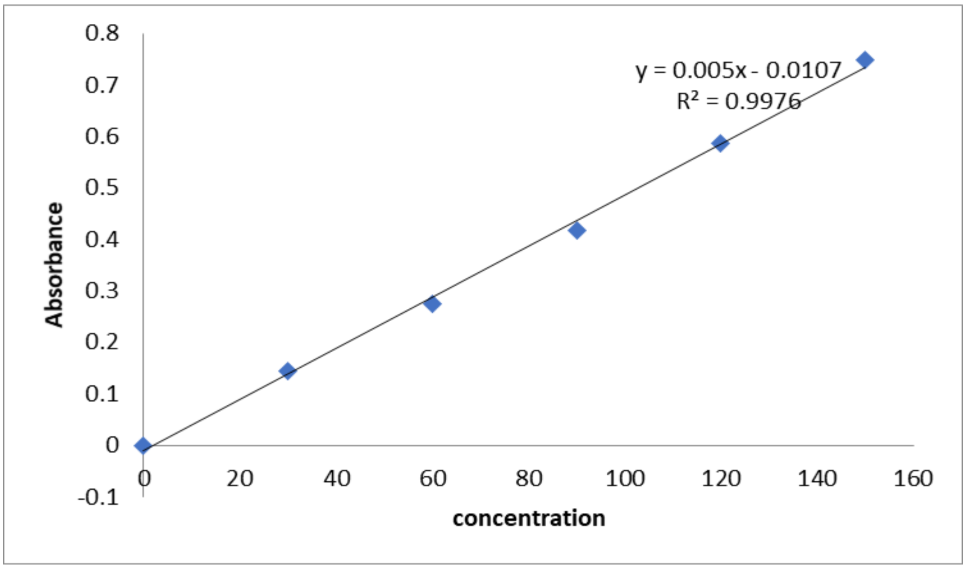

Fig. 2: Standard graph of Trimetazidine hydrochloride in 0.1 N HCL.

Calibration curve of Trimetazidine hydrochloridein 6.8 pH phosphate buffer

Table shows the calibration curve data of Trimetazidine hydrochloridein 6.8 pH phosphate buffer at 270nm. Fig. shows the standard calibration curve with a regression value of 0.9987, slope of 0.005 and intercept of-0.010. The curve was found to be linear in the concentration range of 30-150µg/ml.

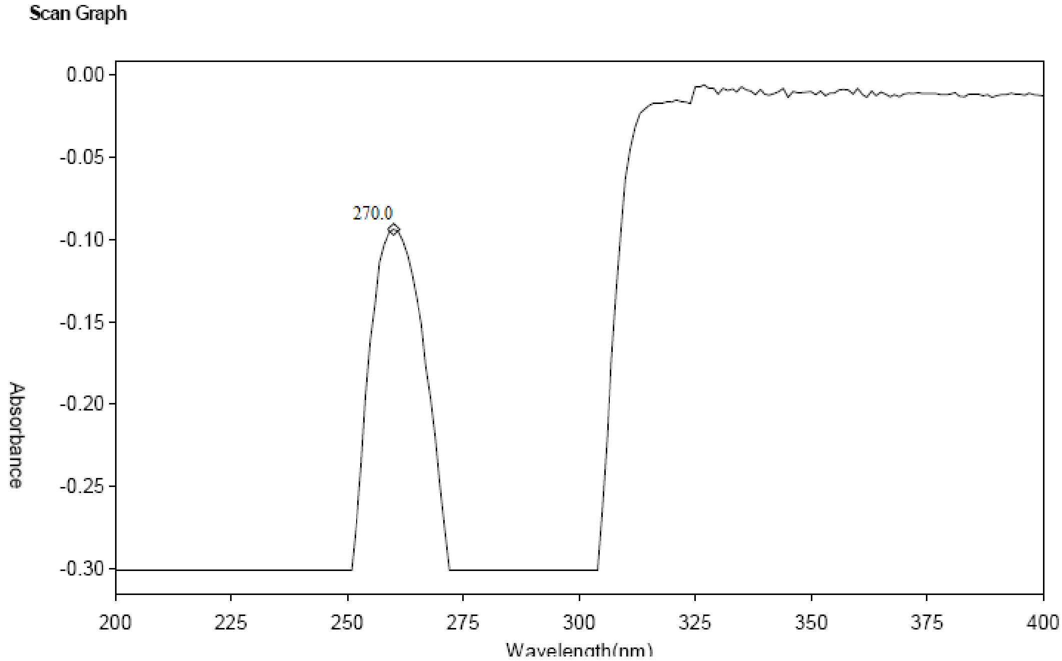

Fig. 3: UV Spectrum for Trimetazidine hydrochloride at 270nm.

Table 3: Calibration curve data for Trimetazidine hydrochloridein 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

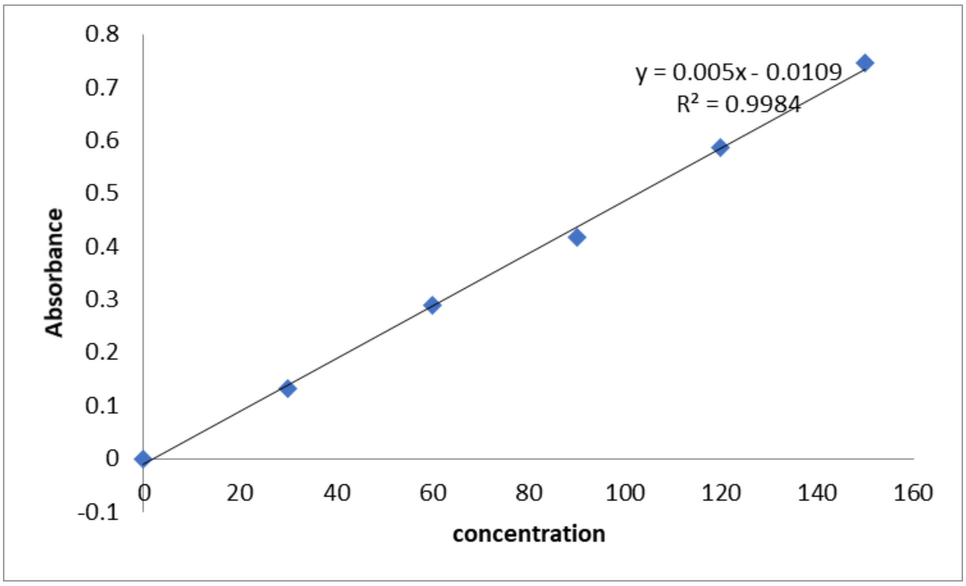

Fig. 4: Standard graph of Trimetazidine hydrochloridein6.8 pH phosphate buffer.

DRUG AND EXCIPIENT COMPATABILITY STUDIES

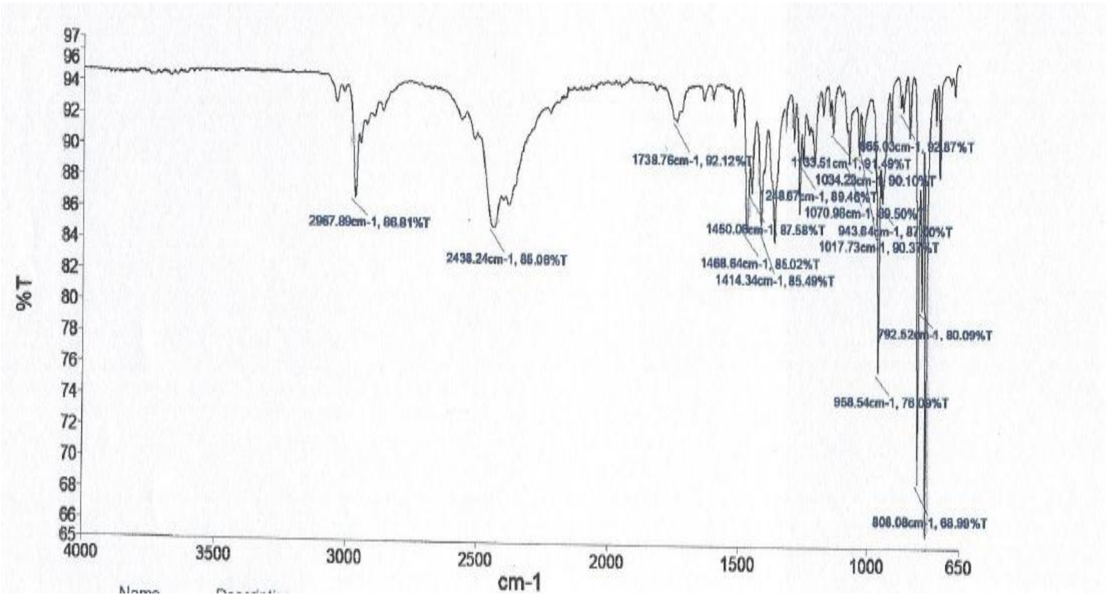

Fig. 5: FTIR graph for Trimetazidine hydrochloride pure drug.

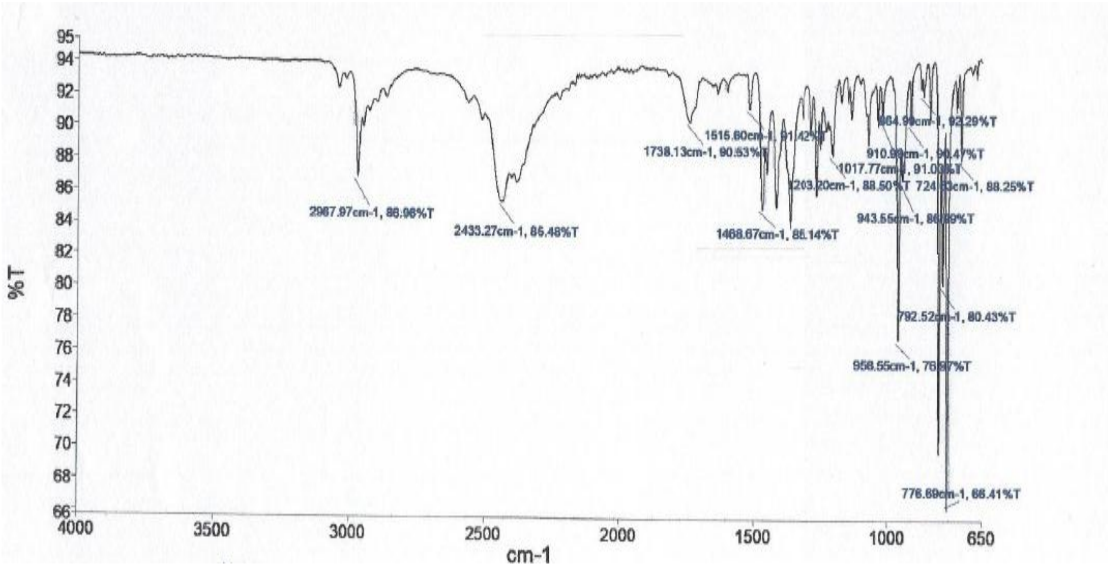

Fig. 6: FTIR graph for Trimetazidine hydrochloride drug with optimized formulation.

EVALUATIONANDCHARACTERISATION OF MICROSPHERES

- **PERCENTAGE YIELD**
- **DRUG ENTRAPMENT EFFICIENCY**

Table 4: Percentage yield and percentage drug entrapment efficiency of the prepared microspheres.

S.No.	Formulation code	% yield	%Drug entrapment efficiency
1	F1	82.1	77.9
2	F2	85.4	75.3
3	F3	86.2	85.2
4	F4	84.8	85.6
5	F5	79.9	82.1
6	F6	85.2	82.7
7	F7	88.6	87.3
8	F8	84.9	84.6
9	F9	85.2	79.8
10	F10	85.2	84.4
11	F11	84.6	86.2
12	F12	82.7	82.6

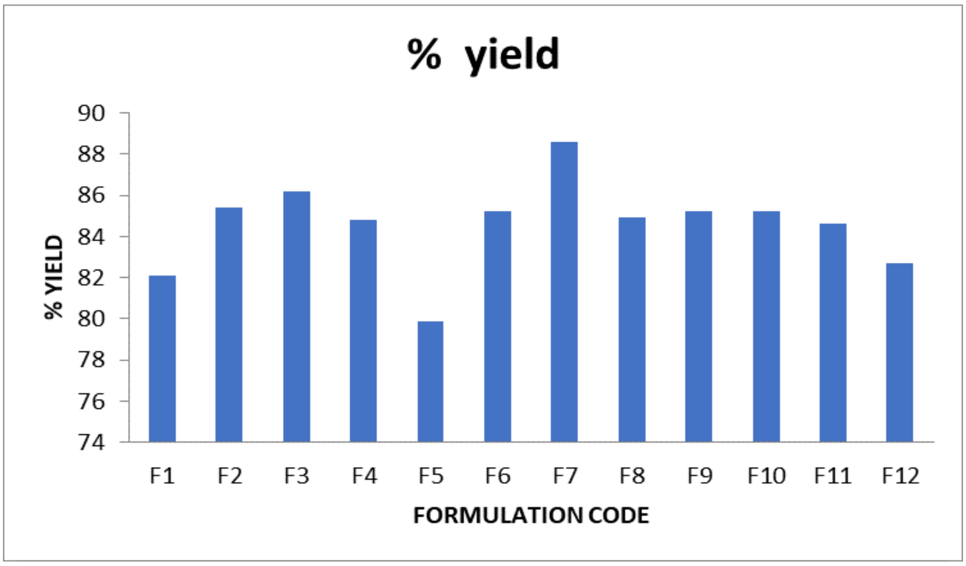

Fig. 7: Graphical representation of percentage yield of formulations F1-F12.

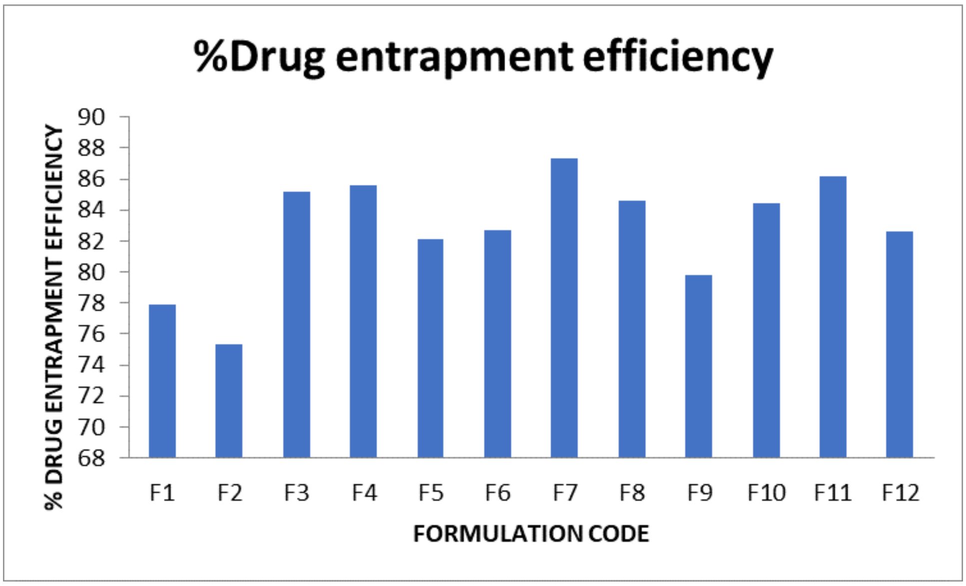

Fig. 8: Graphical representation of percentage drug entrapment efficiency of formulations F1-F12.

PARTICLE SIZE ANALYSIS

Table 5: Average Particle Size analysis for formulation F1-F12.

Formulation code	Average particle size(µm)
F1	648
F2	654
F3	668
F4	622
F5	625
F6	635
F7	613
F8	648
F9	650
F10	662
F11	628
F12	642

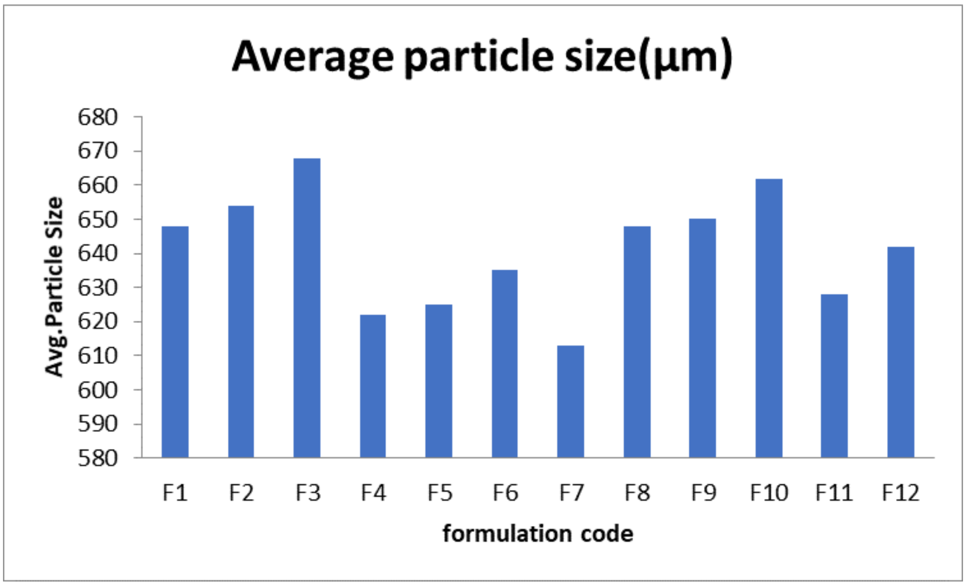

Fig 9: Graphical representation of average particle size for formulations.

IN-VITRO DRUG RELEASE STUDIES

Table 6: 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	4.6	6.82	1.78
2	9.7	12.01	16.62	11.07
3	22.68	28.8	26.96	28.86
4	44.25	41.68	38.84	41.42
5	56.36	52.13	50.8	54.62
6	72.74	63.69	68.18	62.71
7	86.47	76.82	80.11	70.92
8	98.74	92.31	95.62	82.54
10	--	--	----	94.21
12	--	---	----	---

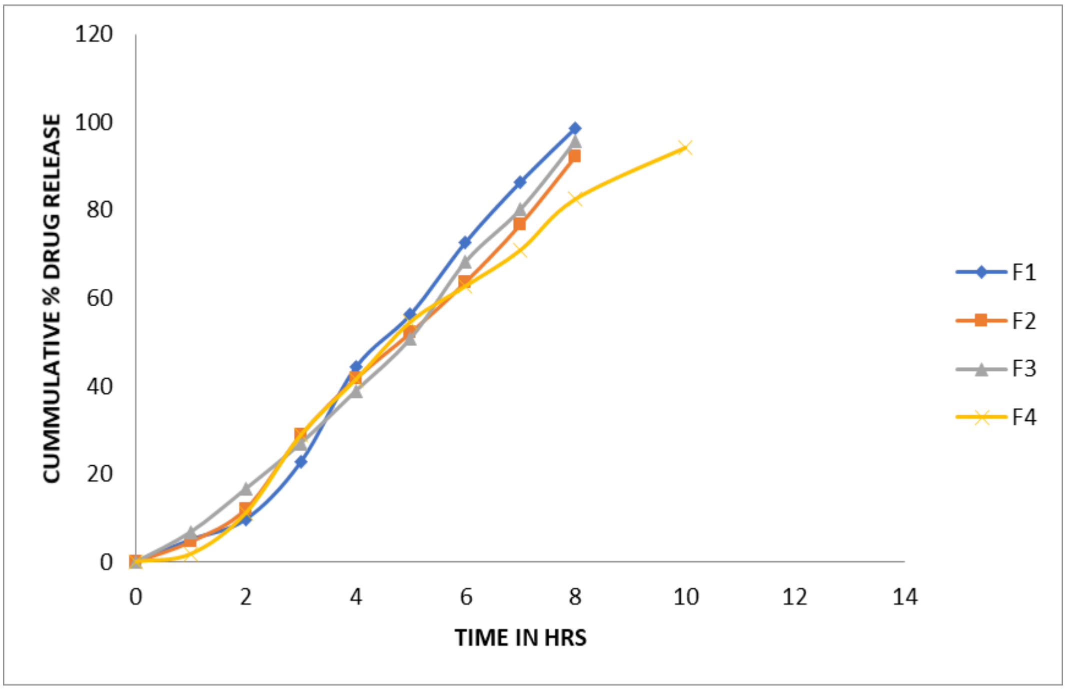

Fig. 10: In-Vitro drug release profile of Trimetazidine hydrochloride microspheres For F1-F4 formulations.

Table 7: In-Vitro drug release data of Trimetazidine hydrochloridemicrospheres.

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

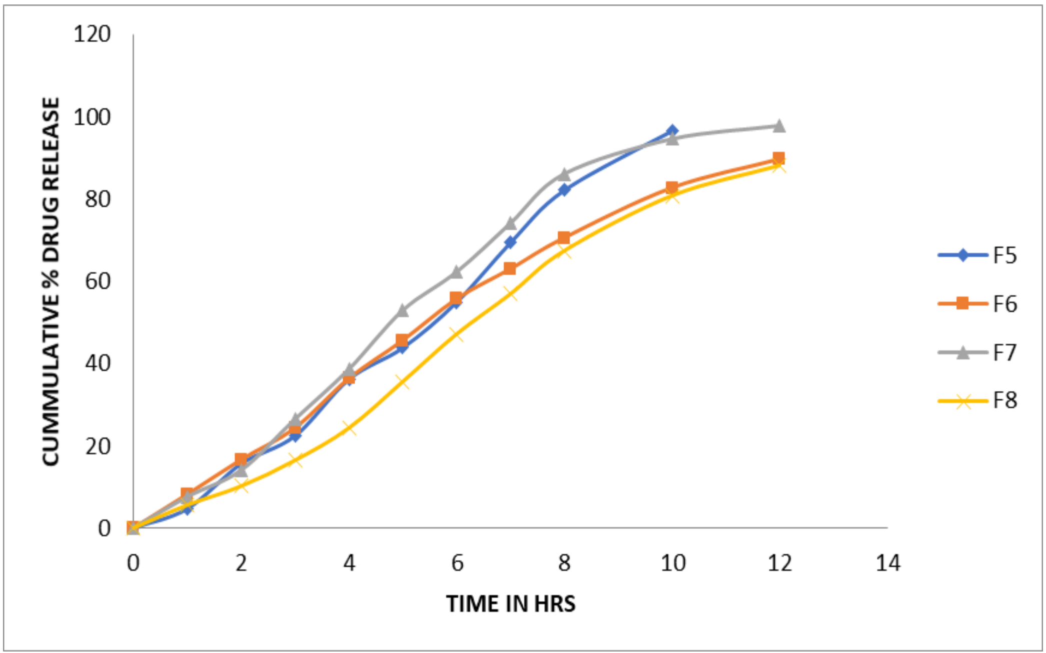

Fig. 11: In-Vitro drug release profile of Trimetazidine hydrochloride microspheres For F5-F8 formulations.

Table 8: In-Vitro drug release data of Trimetazidine hydrochloridemicrospheres.

TIME (hrs)	Cumulative Percent Of Drug Released			
	F9	F10	F11	F12
0	0	0	0	0
1	6.4	5.4	8.4	8.29
2	10.6	12.2	18.6	11.04
3	20.1	24.7	29.7	18.79
4	32	36.12	45.6	26.55
5	41.26	45.6	56.8	36.5
6	52.17	56.4	65.9	43.64
7	65.9	62.8	74.6	54.52
8	71.23	72.14	80.8	63.3
10	83.4	89.42	89.2	72.66
12	87.24		91.4	84.48

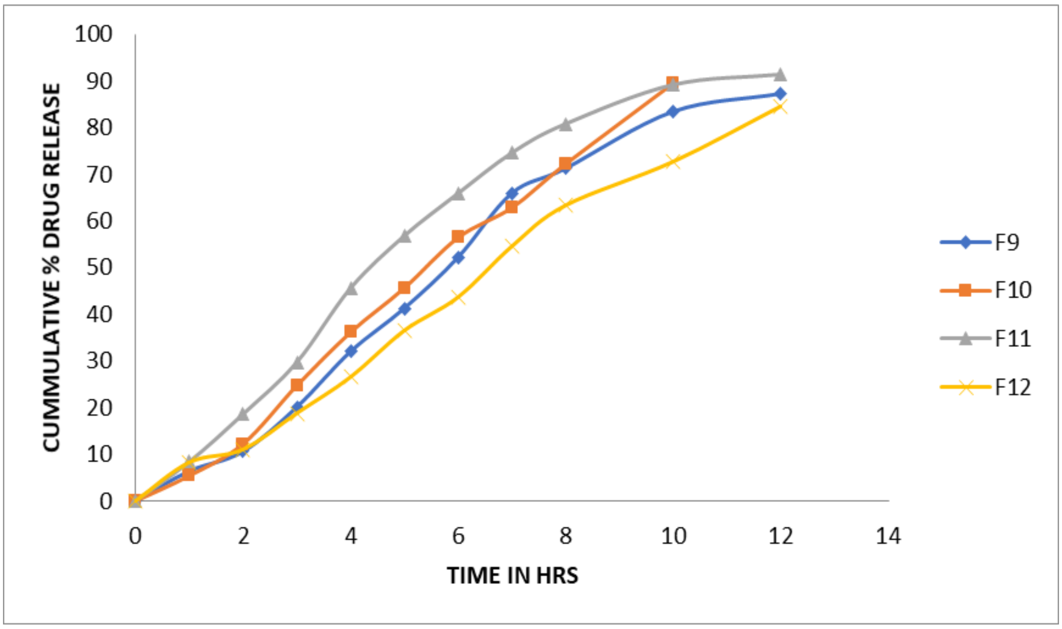

Fig. 12: In-Vitro drug release profile of Trimetazidine hydrochloride microspheres For F9-F12 formulations.

Table 9: IN-VITRO DRUG RELEASE KINETICS.

	ZERO	FIRST	HIGUCHI	PEPPAS
	% CDR Vs T	Log % Remain Vs T	%CDR Vs √T	Log C Vs Log T
Slope	9.21821995	0.13543304	0.02780648	0.570708071
Intercept	1.79122506	0.76867477	0.71123660	-0.23920595
Correlation	0.97828756	-0.9395964	0.946195226	0.9097114
R 2	0.96009759	0.70815944	0.91685405	0.855274831

RELEASE KINETICS FOR OPTIMIZED FORMULATION (F7)

ZERO ORDER KINETICS

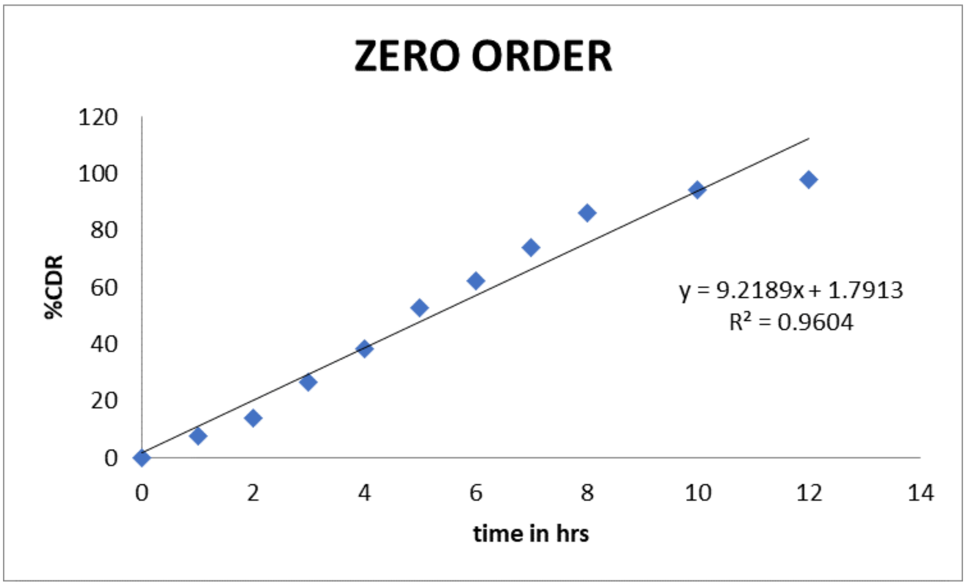

Fig. 13: Zero order kinetics for Trimetazidine hydrochloride microspheres F7 formulation.

FIRST ORDER KINETICS

Fig. 14: First order kinetics for Trimetazidine hydrochloride microspheres F7 formulation.

HIGUCHIS PLOT

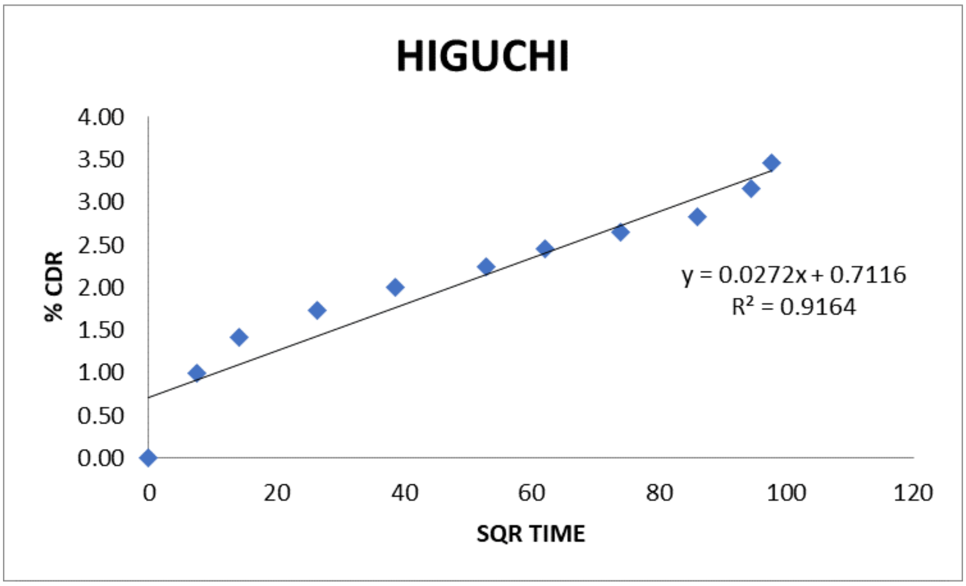

Fig. 15: Higuchis kinetics for Trimetazidine hydrochloride microspheres F7 formulation.

PEPPAS PLOT

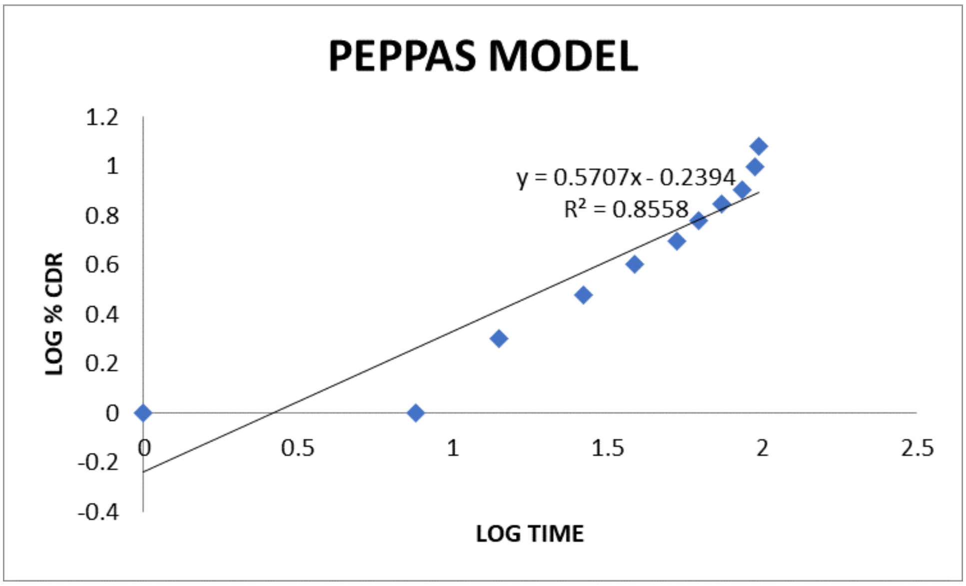

Fig. 16: Peppas kinetics for Trimetazidine hydrochloride microspheres F7 formulation.

SUMMARY AND CONCLUSION

In the present work, double walled microspheres of Trimetazidine hydrochloride using Sodium alginate along with Carbopol 934 and HPMC K100, Guar gum as copolymers were formulated to deliver Trimetazidine hydrochloride via oral route.

Details regarding the preparation and evaluation of the formulations have been discussed in the previous chapter. From the study following conclusions could be drawn:-

- The results of this investigation indicate that Solvent Evaporation method can be successfully employed to fabricate Trimetazidine hydrochloride microspheres.
- FT-IR spectra of the physical mixture revealed that the drug is compatible with the polymers and copolymer used.
- Microspheres containing sodium alginate along with carbopol and Guar gum in 5:2 ratio had a least size range of 613µm.
- Increase in the polymer concentration led to increase in % Yield, % Drug entrapment efficiency, Particle size.
- The *invitro* drug release decreased with increase in the polymer and copolymer concentration.
- Among all formulations F7 shows Maximum drug release in 12hrs when compared with other formulations.
- Analysis of drug release mechanism showed that the drug release from the formulations followed the Non fickian diffusion mechanism and follows zero order kinectics.
- Based on the results of evaluation tests formulation coded F7 was concluded as best formulation.

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