



**TRIMETAZIDINE HYDROCHLORIDE MICROSPHERES FOR THE MANAGEMENT
OF STABLE ANGINA PECTORIS: INFLUENCE OF PROCESS PARAMETERS**

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ABSTRACT

The present study was undergone to investigate the effect of two major process parameters such as drug polymer concentration and stirring rate in the formulation of Trimetazidine hydrochloride microspheres. Nine different batches (F1-F9) of Trimetazidine loaded eudragit microspheres were developed using a novel W/O/O double emulsion solvent evaporation technique. Effect of process parameters on morphology, percentage yield, particle size, percentage drug content, encapsulation efficiency, *in vitro* drug release and release kinetics of all batches were investigated. From the analysis, it was observed that, the two process parameters have played important roles in controlling the performance of formulated microspheres such as percentage yield, particle size distribution, encapsulation efficiency, *in vitro* drug release but little effect on micromorphology, percentage of drug content and release kinetics. From the outcome of results, it was concluded that the experimental parameters have greater influence on microspheres and the formulation F5 with drug: polymer ratio of 1:2 prepared at 500-700 rpm as stirring speed showed a spherical shaped microspheres with narrow particle size distribution, maximum encapsulation efficiency and release up to 24h with non-fickian zero order release kinetics.

KEYWORDS: Trimetazidine Hydrochloride, Eudragit microspheres, Drug: polymer concentration, Stirring rate.

INTRODUCTION

In this contemporary world of pharmaceutical research, offering modern vitality to the existing drugs by innovative dosage form development methods for treating some chronic diseases have been come to light undoubtedly. From a few decades ago, Ischemic cardiac disease is becoming one of the leading causes of death. Earlier findings suggested that the drug Trimetazidine hydrochloride which is the first known cytoprotective anti - anginal drug and is proven to reduce the severity of anginal attacks with non – haemodynamic effects in contrast to the traditional anti- anginal drugs prevailing in the pharma market. Undeniably, clinical studies demonstrated that use of metabolic agents have been emerging as a novel assuring path for the management of stable angina pectoris.^[1,2]

Chemically, the drug Trimetazidine Hydrochloride is (1-[2,3,4 trimethoxybenzyl]- piperazine hydrochloride) which is a freely soluble in water. Generally 40 – 60 mg of drug is administered orally in three divided doses. It is absorbed quickly and eliminated with a half life of 6 h and Tmax of 1.8 h. After administration, the immediate release dosage forms lead to maximum plasma levels rapidly and to very low plasma level at the time of next dose, resulting in great differences at steady state concentration. Since, Trimetazidine hydrochloride is witnessed as a safe drug in the chronic treatment of

Ischemic disorders, this urge the necessity of designing the sustained release once daily dosage form for accomplishing regular and constant plasma levels which is also favourable for better patient compliance.^[3,4]

In current times, microencapsulation by double emulsion technique have been transpiring as a boon for the better encapsulation of water soluble drugs.^[5] However, experimental parameters have significant aspect in the formulation of microspheres. In connection with that, this research work was intended to analyse the influence of major process variables such as drug polymer concentration and stirring speed on Trimetazidine loaded eudragit microspheres and to optimize a more desirable formulation for the better management of stable angina pectoris.

MATERIALS AND METHODS

The drug Trimetazidine hydrochloride (Active Pharmaceutical Ingredient) was received as gift sample from Strides Shasun Ltd., Pondicherry, India. Polymers such as Eudragit (L100 & S100) were obtained from HiMedia Laboratories Ltd., Mumbai, other chemicals and solvents used were of analytical Grades procured from different manufacturers.

Microspheres preparation

Different batches of Trimetazidine hydrochloride microspheres were developed using W/O/O double emulsion solvent evaporation technique with different drug: polymer concentration and stirring rate as process variables and the composition were given in the Table 1. Drug (equivalent to 60 mg) was dissolved in water and added slowly to the polymer mixture containing Eudragit L & S 100 in the ratio of 1:1.5 which was dissolved in the mixture of solvent system acetonitrile &

dichloromethane in the ratio of 1:1 and Tween 80 (0.5% w/v) as surfactant with constant stirring for 10 minutes. The resulting W/O primary emulsion was slowly dispersed in the oil processing medium containing 90 ml of light liquid paraffin, Span 20 (0.5% w/v) as surfactant and 10 ml of n-heptane as viscosity retarding agent with constant stirring for 1 h. After that the microspheres were decanted, washed with n-hexane thrice and air-dried for 12 h.^[6,7]

Table: 1 Composition of Trimetazidine Hydrochloride Microspheres and the Process Parameters.

S.No.	Process parameters	F1	F2	F3	F4	F5	F6	F7	F8	F9
1.		1:1	1:2	1:3	1:1	1:2	1:3	1:1	1:2	1:3
2.	Drug: Polymer concentration	200-400	200-400	200-400	500-700	500-700	500-700	1000-1200	1000-1200	1000-1200
3.	Volume of processing medium (ml)									
	Liquid paraffin	90	90	90	90	90	90	90	90	90
	n-heptane	10	10	10	10	10	10	10	10	10
4.	Solvent system									
	Acetonitrile – Dichloromethane	1:1	1:1	1:1	1:1	1:1	1:1	1:1	1:1	1:1

Microspheres Characterization

Morphological studies by Scanning Electron Microscopy (SEM)

The prepared microspheres were subjected to Scanning Electron Microscopy (SEM) studies. The morphology of microspheres (size and shape) was examined with SEM (Zeiss, Model- EVO 18, Germany) operating at 15kv.^[8]

Percentage yield

Percentage yield of Trimetazidine microspheres were determined by using the following formula Practical yield.

Percentage yield=

$$\frac{\text{Practical Yield}}{\text{Theoretical Yield}} \times 100$$

Practical yield – Amount of microspheres recovered from each batch

Theoretical yield – Amount of starting materials used for the formulating the each batch of microspheres.

Average particle size

The Average particle size of all the formulations (F1-F9) were determined by particle size analyzer.

Drug content and Percentage Encapsulation efficiency

The drug content in the prepared microspheres was determined by pulverizing the weighed amount of Trimetazidine Hydrochloride loaded microspheres equivalent to 60mg followed by immersing them in 100ml of pH 6.8 Phosphate buffer with agitating at room temperature for 12 h. After filtration, the drug

concentration was determined spectrophotometrically at the wavelength of 269nm. The filtered solution from the empty microspheres (without drug) was taken as blank. All samples were analysed and from the absorbance value, Percentage Drug content (DC) was determined. Percentage Encapsulation efficiency (EE) was calculated according to the following formula.^[9,10]

Actual drug content in microspheres

Encapsulation Efficacy (%) =

$$\frac{\text{Actual drug content in microspheres}}{\text{Theoretical Drug Content}} \times 100$$

In vitro release profile

The *in vitro* dissolution studies were carried out using USP basket (Type I) apparatus at 100RPM and 37±0.5°C. Required amount of microspheres equivalent to 60 mg drug was filled in a dialysis bag and placed in the basket containing 900ml of phosphate buffer pH 6.8 (simulated colonic fluid) as dissolution medium and the drug release was observed for 24 h. 5 ml samples were withdrawn at specified time intervals and replaced immediately with an equal volume of fresh medium. Samples were assayed by using UV-spectrophotometer (Shimadzu 1700, Japan) at wavelength of 269 nm, against phosphate buffer pH 6.8 as blank. From the absorbance values, the cumulative percent drug release were determined.^[11,12]

Drug Release Kinetics

The release mechanism of all the formulations were analyzed mathematically using Zero order, First order, Higuchi and Koresmeyer - Peppas model.^[13,14]

Stability studies

The stability studies for the optimized formulation was carried out as per ICH guidelines for six months and were packed in high density poly ethylene containers and kept in stability chamber at $40^{\circ}\text{C} \pm 2^{\circ}\text{C}/75 \pm 5\%$ RH.^[15]

RESULTS AND DISCUSSION EVALUATION OF MICROSPHERES

Surface morphology and particle size

Both shape and size of all the batches were based on the concentration of drug & polymer and the stirring rate. SEM Micrographs resulted with complete encapsulation

of microspheres with highest polymer concentration but increased viscosity leads to greater sized particles whereas lowest polymer content showed improper encapsulation with small particle size of microspheres. According to stirring rate, small and porous microspheres were observed at high stirring rate with narrow particle size distribution. Non- aggregated, much large spherical shaped microspheres were observed at moderate speed. However, aggregated, rough surfaced, asymmetrically shaped microspheres were observed at low speed may be due to coalescence of emulsion droplets. The results are given in the Fig.1-3.

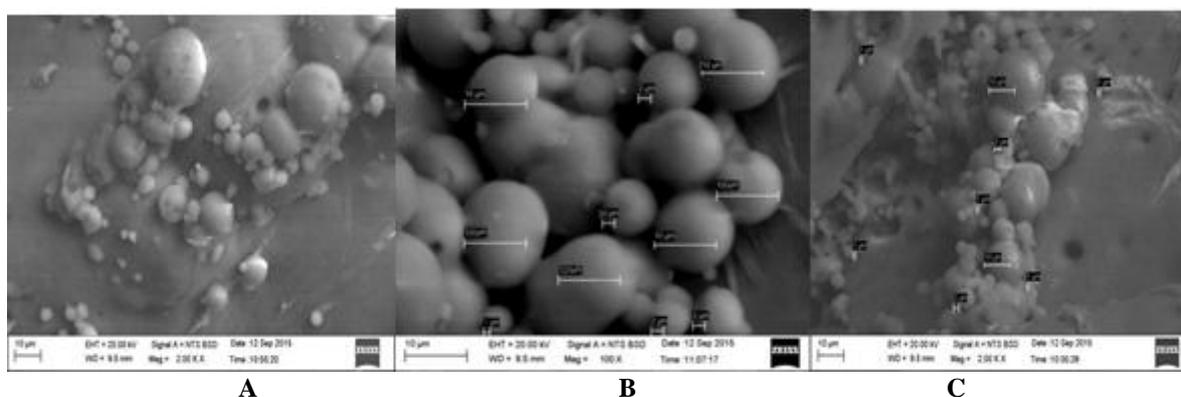


Fig: 1-3. SEM photographs of formulation F3, F5, F7 prepared at a) Low stirring rate b) Moderate rate c) High rate.

Percentage yield

The percentage yield of all the formulations (F1 – F9) ranged from 66.4% - 79.23%, which was increased with increase in concentration of drug polymer ratio from 1:1 to 1:3. This may be due to increase in viscosity of the primary emulsion

Drug content and Encapsulation efficiency

Irrespective of process variables such as drug-polymer concentration and stirring rate, the drug content of all the formulations (F1-F9) were ranged from $90.64 \pm 0.212\%$ to $98.83 \pm 0.144\%$.

Encapsulation efficiency of all the formulations were varied according to concentration of polymer used and stirring rate. Increase in drug – polymer concentration increased the % Encapsulation efficiency, this effect

might be due to increase in viscosity of the preparation which caused hindrance for the migration of drug towards the continuous phase and thereby reduction in drug loss by diffusion during the formulation of microspheres. Formulations prepared at highest stirring rate (1000 – 1200 rpm) showed lowest % encapsulation efficiency which was observed due to the formation of smaller emulsion droplets which enhanced the drug diffusion out of the microspheres before they harden. Among the 9 formulations, formulations F5 and F6 prepared at moderate stirring rate (500 – 700 rpm) showed highest encapsulation efficiency of 80.12% and 79.22% respectively.

The results of particle size, percentage yield, % drug content and encapsulation efficiency were given in the Table. 2.

Table: 2 - Particle size, Percentage yield, % Drug content and % Encapsulation efficiency of formulations.

Formulation code	Avg. Particle Size (μm)	% Yield	% *Drug content	% *Encapsulation efficiency
F1	202.35	67.24	90.64 ± 0.211	53.68 ± 0.204
F2	214.60	70.11	95.65 ± 0.234	69.32 ± 0.167
F3	223.16	73.20	97.33 ± 0.189	76.14 ± 0.196
F4	128.20	68.72	92.20 ± 0.156	71.83 ± 0.122
F5	144.56	78.80	98.83 ± 0.128	80.12 ± 0.131
F6	159.43	79.23	97.22 ± 0.265	79.22 ± 0.282
F7	89.12	66.40	94.50 ± 0.152	44.35 ± 0.141
F8	100.50	71.53	95.43 ± 0.231	59.24 ± 0.266
F9	109.78	77.45	96.22 ± 0.192	68.15 ± 0.187

*All the values are expressed as Mean \pm S.D, n = 3

In vitro release profile

From the results, it was noticed that *in vitro* drug release pattern of all the formulations depended on the change in drug- polymer concentration and stirring speed. Among the nine formulations, formulations F2, F5, F7 with drug-polymer concentration (1:2) showed a maximum release of 80.94%, 97.65% and 94.13 at the end of 20, 24 and 14 h respectively. Further increase in drug polymer ratio to 1:3 showed no significant increase in drug release. This might have occurred due to system saturation.

According to the change in stirring speed, formulations prepared at lower speed showed a decreased % cumulative drug release due to increased particle size and imperfect entrapment of drug by the polymer. Stirring at moderate rate, the formulation F4 showed a cumulative % drug release of 96.11% at the end of 22 h. Formulations F5, F6 released up to 24 h with cumulative % drug release of 97.65% and 95.25% respectively. The formulations prepared at highest stirring rate showed initial burst release and drug release sustained to a maximum of 16 h. This may be due to small size and increased surface area of microspheres at high stirring rate. The results of cumulative % drug release of the all the formulations were depicted in the Fig.4,5,6.

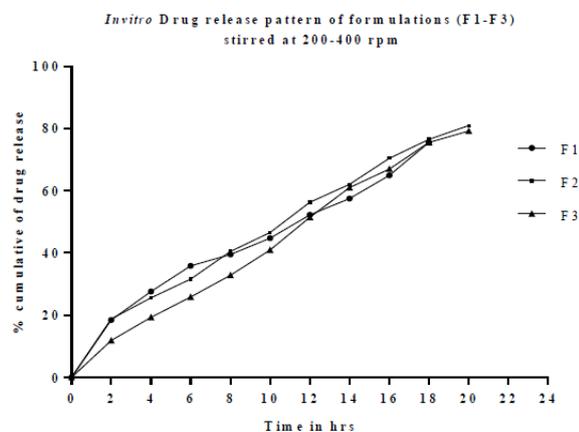


Fig: 4 *In vitro* drug release pattern of the microsphere formulations (F1-F3).

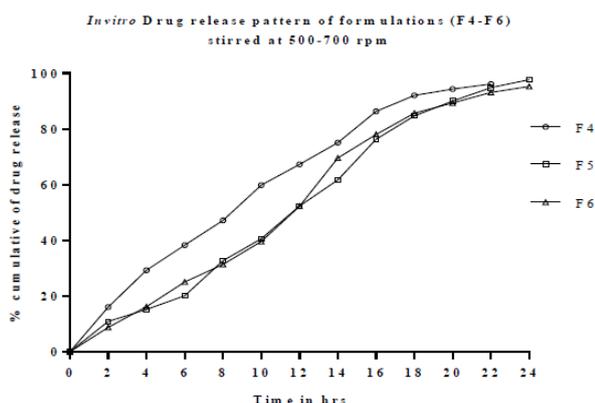


Fig.5 *In vitro* drug release pattern of the microsphere formulations (F4-F6).

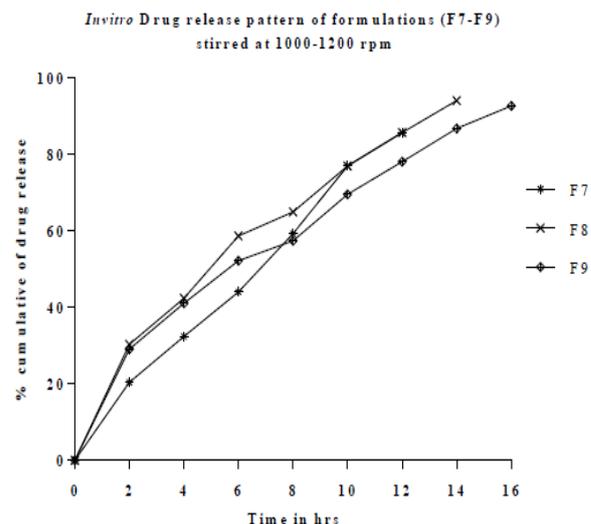


Fig. 6 *In vitro* drug release pattern of the microsphere formulations (F7-F9).

Release kinetics

The Cumulative % release data of all the batches obtained were fitted to various kinetic equations to determine the mechanism of drug release. The formulation F5 was best fitted to zero order kinetic equation with r^2 value of 0.986. Further Korsmeyer – peppas model showed a good linearity of 0.953 with a n value of 0.942 which implies that the formulation follows non-fickian Zero order kinetics.

Stability study

Results of stability studies for the optimized formulation F5 inferred that there was no significant changes when stored at $40^{\circ}\text{C} \pm 2^{\circ}\text{C}/75\% \pm 5\% \text{RH}$ after 6 months.

CONCLUSION

From the results obtained, it was concluded that the two process parameters such as drug polymer concentration and stirring rate had significant effect on percentage yield, particle size percent encapsulation efficiency and *in vitro* drug release of Trimetazidine hydrochloride microspheres prepared by novel W/O/O double emulsion solvent evaporation technique. Therefore, the formulation F5 with drug- polymer ratio of 1:2 prepared at moderate stirring speed was optimized as a more desirable microsphere preparation for the long term management of stable Angina pectoris.

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