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Formulation characterization and invitro evaluation of double walled microspheres loaded with metoproplol succinate

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ABSTRACT

In the present work, double walled microspheres of Metaprolol succinate using Sodium alginate along with Carbopol 934 and HPMC K100,Guar gum as copolymers were formulated to deliver Metaprolol succinate via oral route[1,2]. The results of this investigation indicate that Solvent Evaporation method can be successfully employed to fabricate Metaprolol succinate microspheres. FT-IR spectra of the physical mixture revealed that the drug is compatible with the polymers and copolymer used. 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.

Key words: Metaprolol succinate, Sodium alginate, Carbopol 934 and HPMC K100

INTRODUCTION

Microencapsulation

Microencapsulation is a rapidly expanding technology. As a process, it is a means of applying relatively thin coatings to small particles of solids or droplets of liquids and dispersions[1]. Microencapsulation is arbitrarily differentiated from macrocoating techniques in that the former involves the coating of particles ranging dimensionally from several tenths of a micron to 5000 microns in size.[6]

Microencapsulation provides the means of converting liquids to solids, of altering colloidal and surface properties, of providing environmental protection, and of controlling the release characteristics or availability of coated materials[4].

Microenacapsulation is a process whereby small discrete solid particles or small liquid droplets are surrounded or enclosed, by an intact shell. Two major classes of microencapsulation methods have evolved i.e. chemical and physical[6].

The first class of encapsulation method involves polymerization during the process of preparing the microcapsules. The second type involves the controlled precipitation of a polymeric solution where in physical changes usually occur.[7, 8]

AIM AND OBJECTIVE

Aim of the study is to formulate Metoprolol succinate double walled microspheres using different polymers by solvent evaporation method

The objective of the present study is

- To conduct preformulation studies by analytical methods.
- To develop dosage forms whose bioavailabilities of drugs are significantly greater than those observed from conventional solid forms such as tablets and capsules
- To formulate the Metoprolol succinate double walled microspheres using different polymers in different ratios.
- To evaluate the prepared double walled microspheres.
- To choose the better formulation among the prepared formulations which shows better release

METHODOLOGY

Expermental methods

Preparation of double walled microspheres of metaprolol

The double walled microspheres were prepared by two step process. In first step the core microspheres of sod. Alginate and HPMC 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 7%Eudragit 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.

Formulation design

Table No 1: Formulation of Microspheres

Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8
Metaprolol	500	500	500	500	500	500	500	500
Sodium alginate	500	500	500	500	500	500	500	500
Guar gum	1000	--	--	1500	--	1000	--	500
Carbopol	--	1000	--	--	--	500	1000	500
HPMC	--	--	1000	--	1500	--	500	500
Drug: polymer	1:3	1:3	1:3	1:4	1:4	1:4	1:4	1:4

q.s – Quantity sufficient

RESULTS AND DISCUSSION

Preformulation

Table No 2: Melting point determination test of drug

Drug	Reported melting point	Observed melting point
Metoprolol	120 $^{\circ}$C	120 $^{\circ}$C

Table No 3: Solubility studies

Solvent	Metoprolol
Water	Freely Soluble
Ethanol	Slightly Soluble
0.1N HCl	Soluble
pH 6.8 buffer	Soluble

Drug and excipient compatibility studies

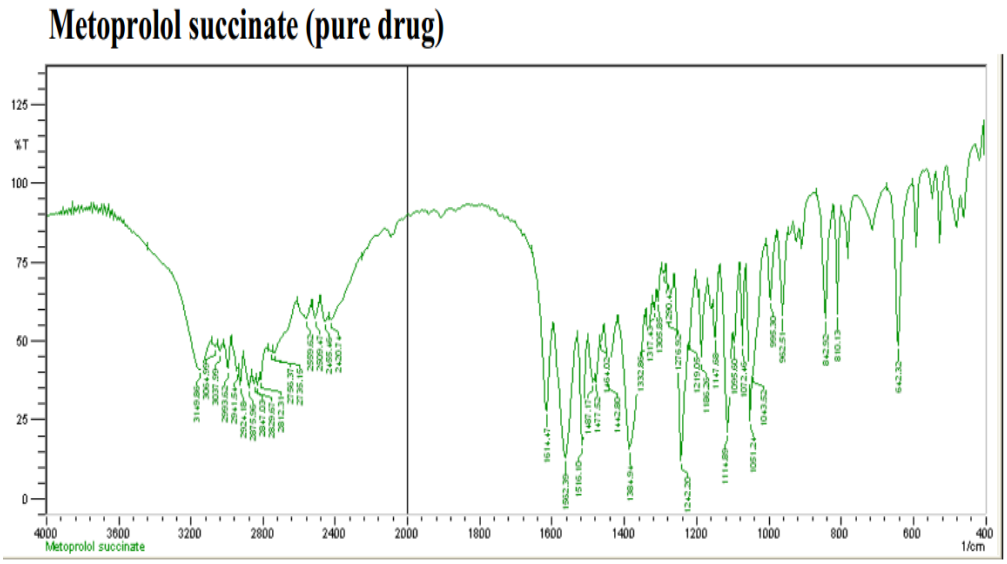


Fig No1: FTIR Spectra of Metoprolol pure drug

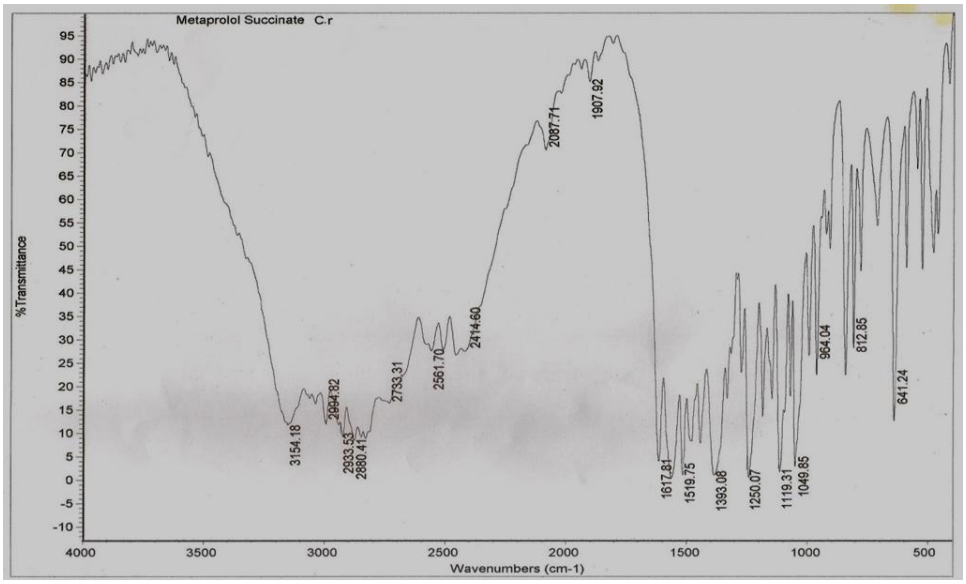


Fig No 2: FTIR Spectra of Metoprolol controlled release optimized formulation

Evaluation and characterisation of microspheres

Percentage yield

It was observed that as the polymer ratio in the formulation increases, the product yield also increases. The low percentage yield in some formulations may be due to blocking of needle and wastage of the drug- polymer solution, adhesion of polymer solution to the magnetic bead and microspheres lost during the washing process. The percentage yield was found to be in the range of 85 to 95% for microspheres containing sodium alginate along with different ratios of polymers. The percentage yield of the prepared microspheres is recorded in Table --4

Drug entrapment efficiency

Percentage Drug entrapment efficiency of Metaprolol ranged from 86 to 96% for microspheres containing sodium alginate along with different ratios of polymers. The drug entrapment efficiency of the prepared microspheres increased progressively with an increase in proportion of the respective polymers. Increase in the polymer concentration increases the viscosity of the dispersed phase. The particle size increases exponentially with viscosity. The higher viscosity of the polymer solution at the highest polymer concentration would be expected to decrease the diffusion of the drug into the external phase which would result in higher entrapment efficiency. The % drug entrapment efficiency of the prepared microspheres is displayed in Table --4,

Table No 4: Percentage yield and percentage drug entrapment efficiency of the prepared microspheres

S.No.	Formulation code	% yield	%Drug entrapment efficiency
1	**F1**	88	86
2	**F2**	85	89
3	**F3**	86	88
4	**F4**	88	89
5	**F5**	89.9	92.1
6	**F6**	87.2	92.7
7	**F7**	94.6	92.3
8	**F8**	95	96

Particle size analysis

The mean size increased with increasing polymer concentration which is due to a significant increase in the viscosity, thus leading to an increased droplet size and finally a higher microspheres size. Microspheres containing sodium alginate along with carbopol and Guar gum in 4:1 ratio had a least size range of 403µm. The particle size data is presented in Tables – 5 the particle size as well as % drug entrapment efficiency of the microspheres increased with increase in the polymer concentration.

Table No 5: Average Particle Size analysis for formulation F1- F8

Formulation code	Average particle size(µm)
F1	448
F2	454
F3	468
F4	422
F5	425
F6	403
F7	445
F8	448

In-vitro drug release studies

Dissolution studies of all the formulations were carried out using dissolution apparatus USP type I. The dissolution studies were conducted by using dissolution media, 0.1 N HCl for 2hrs and 6.8 pH phosphate buffer for next hours. The results of the in-vitro dissolution studies of formulations F1 – F8, shown in table no.6-- The plots of Cumulative percentage drug release Vs Time. Figure -- shows the comparison of % CDR for formulations F1 – F8.

The formulations F1, F2 showed a maximum release of 98.12, 95.16 % at 7 hours, respectively, While F3 and F4 showed a maximum release of 98.12, 98.21% at 10hrs respectively.

The formulations F5, F6, F7 and F8 showed a maximum release of 88 %,90 %,97 % and 84 % at 12 hours respectively. Among all formulations F7 shows Maximum drug release in 12hrs when compared with other formulations.

This shows that more sustained release was observed with the increase in percentage of polymers. As the polymer to drug ratio was increased the extent of drug release decreased. A significant decrease in the rate and extent of drug release is attributed to the increase in density of polymer matrix that results in increased diffusion path length which the drug molecules have to traverse.

Table No 6: In-Vitro drug release data of Metaprolol double walled microspheres

TIME (hrs)	Cumulative Percent Of Drug Released			
	F1	F2	F3	F4
0	0	0	0	0
1	6.08	6.60	3.82	4.78
2	9.70	12.01	10.62	19.07
3	26.68	34.80	21.96	30.86
4	40.25	50.68	32.84	42.42
5	59.36	70.13	53.80	50.62
6	86.74	81.69	68.26	67.71
7	98.12	95.19	79.18	72.92
8	--	--	86.11	83.54
10	--	--	98.12	98.21
12	--	--	--	--

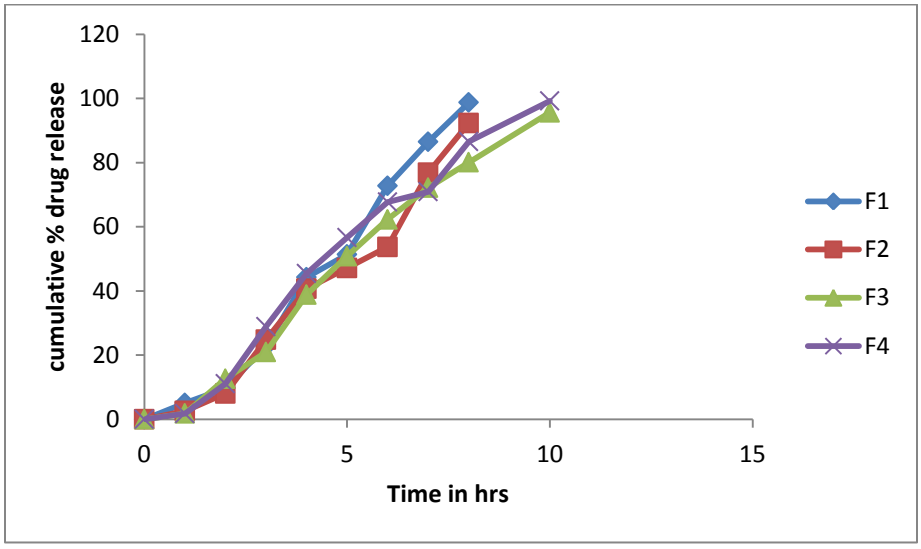


Fig No: 3 Comparison of In-Vitro drug release profile of Metaxalone microspheres

Table No: 7 In-Vitro drug release data of Metaxalone microspheres

TIME (hrs)	Cumulative Percent Of Drug Released			
	F5	F6	F7	F8
0	0	0	0	0
1	4.70	8.20	5.61	8.29
2	15.62	12.60	12.07	11.04
3	22.40	20.34	22.46	18.79
4	36.16	28.00	38.60	26.55
5	43.80	34.31	46.90	36.50
6	50.91	45.52	57.22	43.64
7	65.40	55.61	75.07	54.52
8	71.82	57.70	88.09	58.30
10	85.51	65.98	94.58	62.66
12	88.7	90.11	97.80	84.48

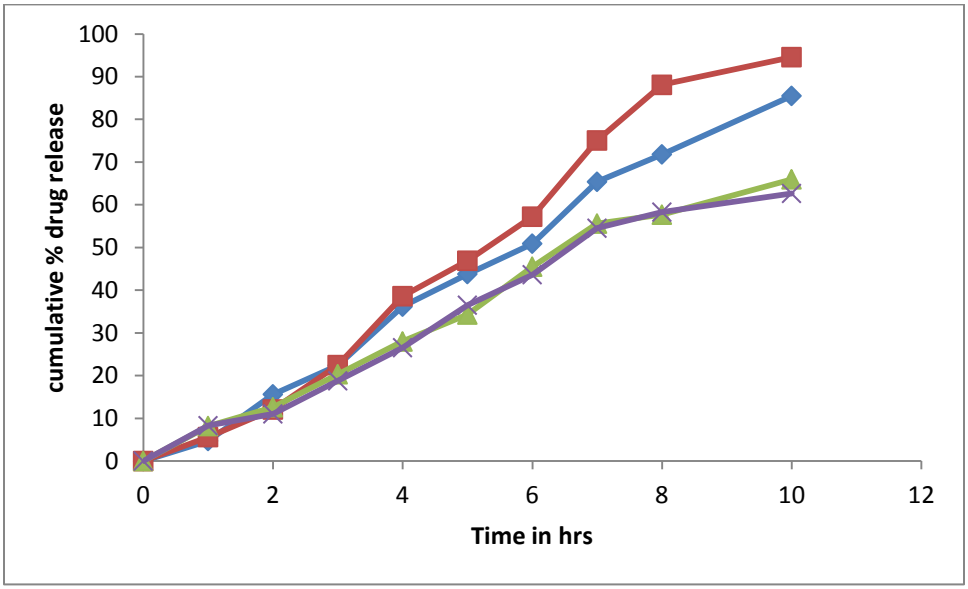


Fig No 4: Comparison of In-Vitro drug release profile of Metaxalone microspheres

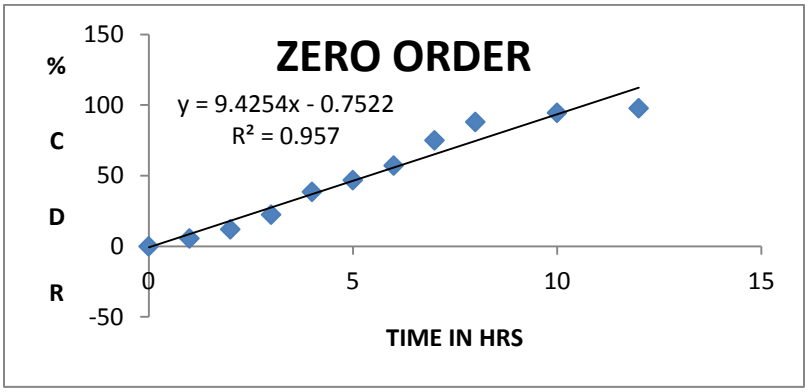
In-vitro drug release kinetics

Table No 8: Release kinetics for optimized formulation (f7)

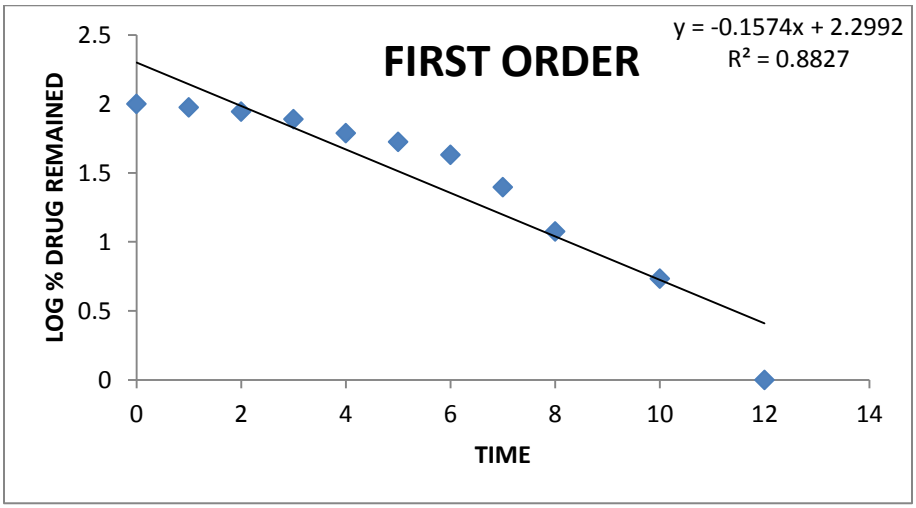
	ZERO	FIRST	HIGUCHI	PEPPAS
	% CDR Vs T	Log % Remain Vs T	%CDR Vs √T	Log C Vs Log T
Slope	9.425421995	-0.15743304	34.05080648	2.257708071

Intercept	-0.75222506	2.299167477	-22.0423660	-0.20820595
Correlation	0.978268756	-0.93952964	0.946195226	0.9097114
R 2	0.957009759	0.882715944	0.895285405	0.827574831

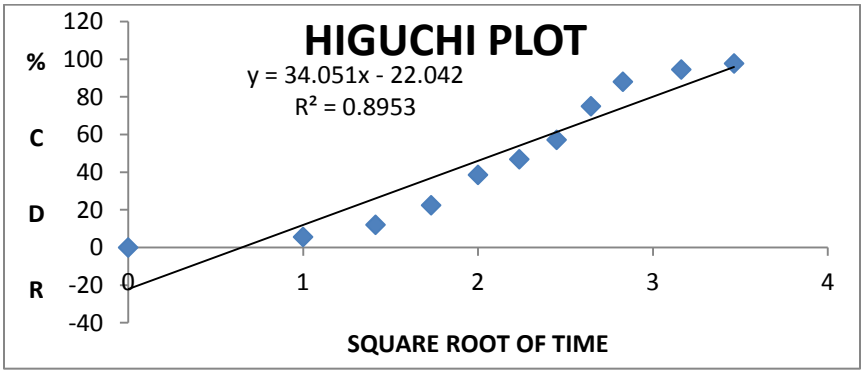
Zero order kinetics



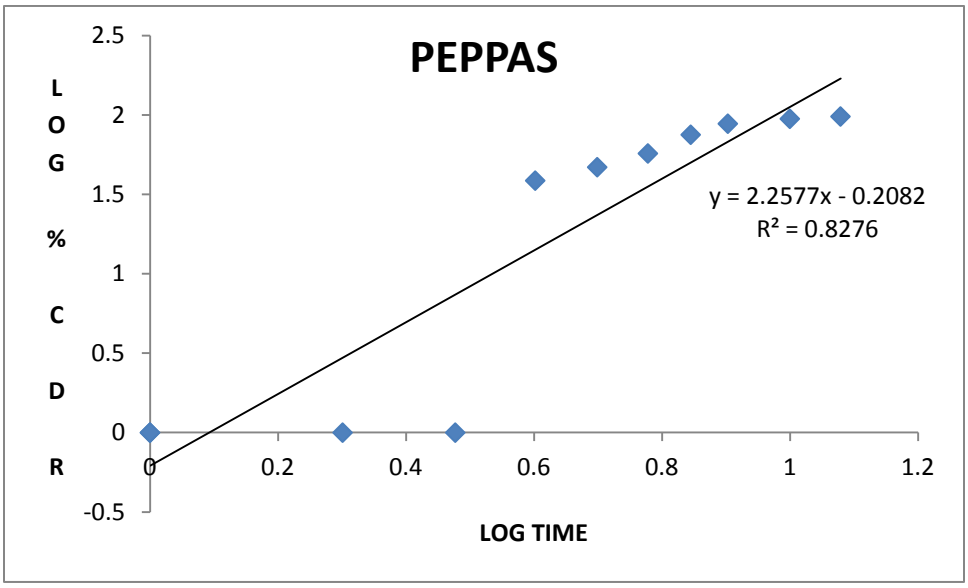
First order kinetics



Higuchis plot



Peppas plot



Release kinetics studies of the prepared formulations

For understanding the mechanism of drug release and release rate kinetics of the drug from dosage form, the in-vitro drug dissolution data obtained was fitted to various mathematical models such as zero order, First order, Higuchi matrix, and Krosmeyer-Peppas model. The values are compiled in Table --. The coefficient of determination (R2) was used as an indicator of the best fitting for each of the models considered. From the coefficient of determination and release exponent values, it can be suggested that the mechanism of drug release follows Zero order kinetics which is independent on concentration and Peppas model shows Non fickian diffusion mechanism which leading to the conclusion that a release mechanism of drug followed combination of diffusion and spheres erosion.

Stability studies

Table No 18: Stability studies of bilayered tablet at room temperature

Time	Colour	Assay		Cumulative % drug release at 12 hrs	
		25±2^{0}c and 65±5%RH	40±2^{0}c and 75±5%RH	25±2^{0}c and 65±5%RH	40±2^{0}c and 75±5%RH
First day	White	100	99	99	99.5
30 days	White	99.88	98.18	99.8	98.1
60 days	White	99.85	99.75	99.84	99.63
90 days	White	98.30	99.50	100.76	99.22

DISCUSSION

Microspheres containing sodium alginate along with carbopol and Guar gum in 1:4 ratio had a least size range of 403µm. 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. The formulations F5, F6, F7

and F8 showed a maximum release of 88 %,90 %,97 % and 84 % at 12 hours respectively. Among all formulations F7 shows Maximum drug release in 12hrs when compared with other formulations.

CONCLUSION

In the present work, double walled microspheres of Metaprolol succinate using Sodium alginate along with Carbopol 934 and HPMC K100,Guar gum as copolymers were formulated to deliver Metaprolol succinate via oral route. The results of this investigation indicate that Solvent Evaporation method can be successfully employed to fabricate Metaprolol succinate microspheres. Microspheres containing sodium alginate along with carbopol and Guar gum in 1:4 ratio had a least size range of 403µm. 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.

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