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Formulation characterization and invitro evaluation of bio-adhesive microspheres loaded with metoproplol succinate

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ABSTRACT

The present work was designed to formulate metoprolol succinate microspheres by using ethyl cellulose polymer by solvent evaporation method and by using sodium alginate by ion gelation method and comaprision was made and evaluated that solvent evaporation method proves to be best method than ion gelation method. Preformulation studies were done for bulk drugs. The Metoprolol succinate microspheres were formulated and evaluated. The ethylcellulose microspheres of Metoprolol succinate were successfully prepared by solvent evaporation technique and confirmed that it is a best method for preparing Metoprolol succinate loaded microspheres from its higher percentage yield. For all the formulations dissolution profile graph and percentage of drug release Vs time was plotted. From all the parameters mentioned above were taken, including surface characteristics of the formulation, drug polymer ratio and time F3 Shows the reliable results.

Key words: ion gelation method, Metoprolol succinate and ethylcellulose

INTRODUCTION

Gastroretentive drug delivery systems

Gastro retentive drug delivery is an approach to prolong gastric residence time, thereby targeting site-specific drug release in the upper gastrointestinal tract (GIT) for local or systemic effects. Gastro retentive dosage forms can remain in the gastric region for long periods and hence significantly prolong the gastric retention time (GRT) of drugs.[5]

Floating systems or hydrodynamically controlled systems are low-density systems that have sufficient buoyancy to float over the gastric contents and remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time.[6]

After the ingestion of a mixed meal, the pattern of contractions changes from fasted to that of fed state. This is also known as digestive motility pattern and comprises continuous contractions as in phase II of fasted state. These contractions result in reducing the size of food particles (to less than 1 mm), which are propelled toward the pylorus in a suspension form. During the fed state onset of MMC is delayed resulting in slowdown of gastric emptying rate.[9]

Factors affecting gastric retention

Gastric residence time (GRT) is affected by several factors, including size and shape of dosage forms, density, concomitant intake of food and drugs, such as anticholinergic agents (e.g. atropine, propanthelin), prokinetic agents (e.g. cisapride, metoclopramide) and opiates (e.g. codeine). Similarly, Biological factors, which affect gastric emptying, including age, gender posture, body weight and

diseases state (e.g. diabetics). Food affects the gastric residence time of the dosage forms depending on its nature, caloric content, and the frequency of intake. It has been reported that the mean GRT of bilayer of floating capsules misoprostol was 199 ± 69 min after a single light meal.[10]

Most of the studies related to the effect of food on GRT of FDDS indicated that food intake influences gastric emptying to a large extent, whereas specific gravity has only minor role to play in gastric emptying.[11, 12]

The resting volume of the stomach is 25 to 50 ml. Volume of liquids administered affects the gastric emptying time. When volume is large, the emptying is faster. Fluids taken at body temperature leave the stomach faster than colder or warmer fluids. Studies have revealed that gastric emptying of a dosage form in the fed state can also be influenced by its size. Small-size tablets leave the stomach during the digestive phase while the large-size tablets are emptied during the "housekeeping waves." [9]

METHODOLOGY

Preformulation studies

Preformulation was the first step in the rational development of dosage forms of a drug substance. It can be defined as, "An investigation of physical and chemical properties of a drug substance alone and when combined with excipients".

Organoleptic properties

The Organoleptic character of the drug like color, odor and appearance play an important role in the identification of the sample and hence they should be recorded in a descriptive terminology. The results were given in results and discussion section.

Solubility Studies

Very soluble in water, freely soluble in alcohol, chloroform, acetone. The results were given in results and discussion section.

Melting point

Melting point of Metoprolol succinate drug was determined by melting point apparatus. The results were given in results and discussion section.

Drug and excipient compatibility study

The Fourier transform infra-red analysis was conducted for the analysis of drug and polymer interactions. FTIR spectra of the drug, ethyl cellulose, polyvinyl alcohol and formulated microspheres were recorded using Shimadzu FTIR spectrophotometer. The samples were prepared as KBr (potassium bromide) disks compressed under a pressure of 10 Ton/nm2. The wave number selected ranged between 4000 - 400 cm-1.

METHOD OF PREPARATION

Solvent evaporation method[15]

Metoprolol succinate microspheres were prepared by solvent evaporation technique. For this, Metoprolol succinate was dissolved in dichloromethane and then ethyl cellulose was dissolved in ethanolic solution .Both drug and polymer solutions were mixed well to form a uniform solution. The obtained drug and polymer solution was added drop wise to the PVA solution under constant stirring at1500 rpm. The constant stirring was obtained using homogenizer at 1500rpm. The beaker and its content were heated at 80 ^{o}c with constant stirring for 1hr until the aqueous phase was completely removed by evaporation. The microspheres formed were collected by whatmann filter paper and washed three times with distilled water and dried at room temperature for one day. By varying this drug: polymer ratio, three batches of microspheres were prepared.

Table No 1: Formulation table of Metoprolol succinate microspheres

S.No	Ingredients	Batches of Metoprolol succinate microspheres prepared		
		F_1	F_2	F_3
1	Metoprolol succinate	100mg	100mg	100mg
2	Ethyl cellulose	100mg	150mg	200mg
3	Dichloromethane	10ml	10ml	10ml

4	Ethanol	10ml	10ml	10ml
5	Poly vinyl alcohol	300mg	300mg	300mg
6.	Distilled water	25 ml	25 ml	25 ml

Ionotropic gelation method

Ionotropic gelation is based on the ability of polyelectrolytes to cross link in the presence of counter ions to form hydrogel beads also called as gelispheres. Gelispheres are spherical crosslinked hydrophilic polymeric entity capable of extensive gelation and swelling in simulated biological fluids and the release of drug through it controlled by polymer relaxation. The hydrogel beads are produced by dropping a drug-loaded polymeric solution into the aqueous solution of polyvalent cations. The cations diffuses into the drug-loaded polymeric drops, forming a three dimensional lattice of ionically crosslinked moiety. Biomolecules can also be loaded into these gelispheres under mild conditions to retain their three dimensional structure.

RESULTS AND DISCUSSION

Preformulation studies

Table No 2: Metoprolol succinate preformulation studies

S.NO	PARAMETERS	REPORT
1	Physical appearance	White crystalline power.
2	Solubility	Very soluble in water and Freely soluble in acetone, chloroform and alcohol,
3	Melting point	118-120^{o}C

In Preformulation studies drug characteristics was performed and results were complies with pharmacopoeial values.

Drug and Excipients Compatibility Studies

Fourier Transform Infrared Spectroscopy

FTIR spectroscopy was used to ensure that no chemical interactions between the drugs and polymer had occurred. The wave numbers of final formulation and individual ingredients were compared. Hence it was concluded that no chemical interactions were found between drug and polymer.

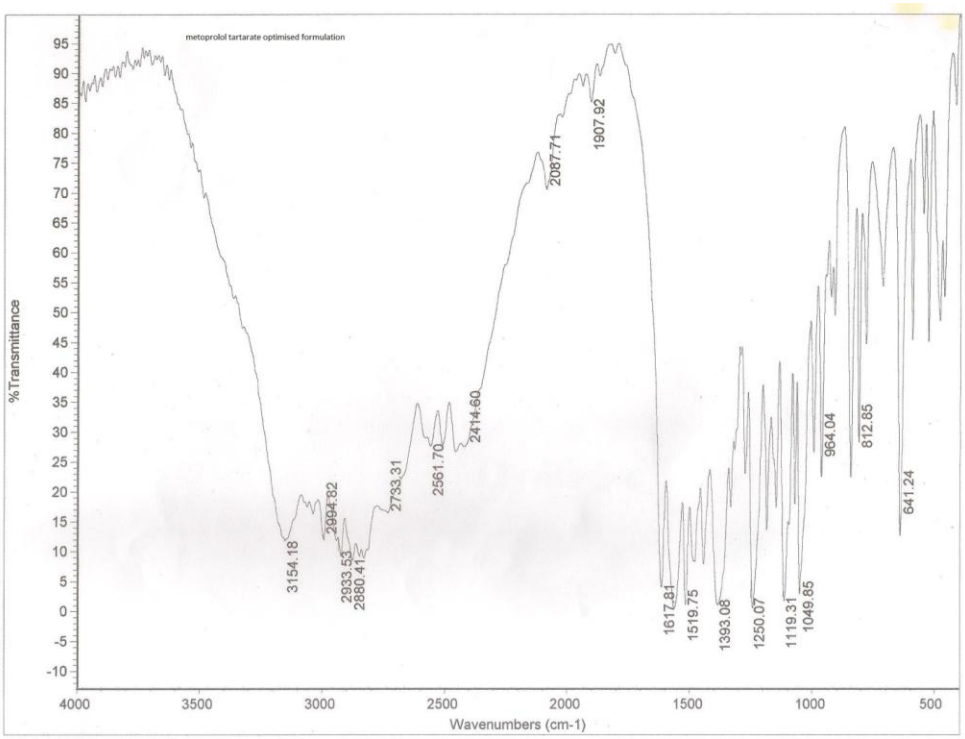

Fig No 1: FTIR of Metoprolol tartarate pure drug

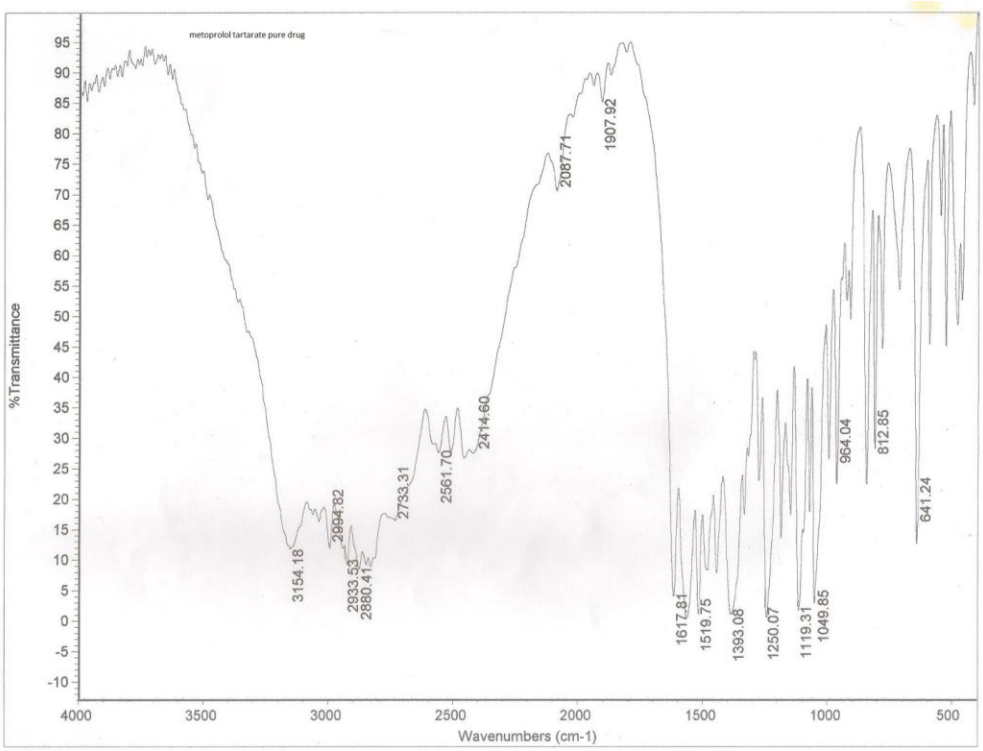

Fig No 2: FTIR of Metoprolol tartarate optimized formulation

Evaluation of Microspheres

Table No 3: Pre Formulation Studies

Formulation code	Angle of repose	Flow property
F1	31.32^0	Good
F2	33.42^0	Good
F3	34.52^0	Good
F4	26.32^0	Excellent
F5	26.54^0	Excellent
F6	27.65^0	Excellent
F7	28.65^0	Excellent

The fllow properties of all the formulationsby solvent evaporation method(F1-F3) shows good flow property where as by ion gelation method (F4-F7) shows excellent flow properties.

Percentage yield, entrapment efficiency, drug loading of microspheres by solvent evaporation method

Table No 4: Percentage yield, entrapment efficiency, drug loading of microspheres (Table: 9)

Solvent evaporation method		
Formulations	**Percentage yield (%)**	**Entrapment efficiency(%)±SD**
F_1	66.7	71.3±0.378
F_2	70.4	76.8±0.208
F_3	74.6	88.2±0.1527
Ion Gelation Method		
F_4	70	70.6±0.378
F_5	74.1	81.8±0.208
F_6	75.92	83.2±0.1527
F7	76.25	84.3±0.156

Table No 5: Mucoadhesive property

Solvent Evaporation Method	
S.No	**Percent Mucoadhesive**
F1	60
F2	72
F3	79
Ion Gelation Method	
F4	45
F5	59
F6	68
F7	75

Among all the other formulation F3 was optimized as it has highest percent of mucoadhesive nature.

Swelling index

Table No 6: Swelling index parameters for microspheres by two different methods

Solvent Evaporation Method	
S.No	**Swelling index**
F1	25
F2	27
F3	33
Ion Gelation Method	
F4	28
F5	32
F6	38
F7	42

The swelling index for all microspheres formulations were in the order F7>F6>F3>F5>F4>F2>F1.The optimized formulation F3 showed 33 percentage of swelling index. It purely depends on the amount of polymer and nature of polymer where as polymer concentration increases swelling index increases and percent of drug release decreases.

Mean Particle Size

Mean particle size was determined by optical microscopy and the average particle size was calculated .The results were shown in table-7 and figure -7

Table No 7: Mean particle size of Metoprolol tartarate microspheres

Solvent Evaporation Method		
S.No	**Batches**	**Mean Particle Size(µm)**
1	F_1	39.72
2	F_2	46.69
3	F_3	57.26
Ion Gelation Method		
4	F4	83
5	F5	94
6	F6	103
7	F7	102

Scanning Electron Microscopy

The microspheres prepared by solvent evaporation method showed a good sphericity, with smooth surface and the particles were distributed uniformly without any lumps.

In-vitro release studies

The in-vitro release profile of Metoprolol succinate microspheres were conducted in 0.1 N Hcl for 12 hours for ion gelation method.

Dissolution conditions

Medium : 0.1 N Hcl.
Apparatus : basket (USP Apparatus I)
RPM : 50
Temperature : 37.0 ±0.5ºC
Time : 12hrs
Volume : 900ml
Sampling times : 1hr,2hr,3hr,4hr,5hr,6hr,7hr,8hr,9hr,10hr,11hr,12hr

Table No 8: Cumulative drug release of Metoprolol tartarate microspheres

Time (hrs)	% Cumulative drug release		
	$F_{1\pm SD}$	$F_{2\pm SD}$	$F_{3\pm SD}$
0	0	0	0
1	9.98±0.012	8.62±0.102	7.32±0.01528
2	38.61±0.005	33.70±0.085	31.06±0.02517
3	42.47±0.068	39.84±0.342	34.54±0.03055
4	53.18±0.305	45.26±0.0643	38.79±0.03512
5	67.52±0.512	58.55±0.921	45.93±0.03055
6	70.05±0.482	67.31±0.007	58.84±0.1101
7	76.33±0.053	73.28±0.0181	67.18±0.09713
8	83.14±0.810	80.73±0.146	76.80±0.09849
9	-	82.62±0.0273	79.14±0.1
10	-	-	81.05±0.283
11	-	-	83.8±0.429
12	-	-	94.9±0.245

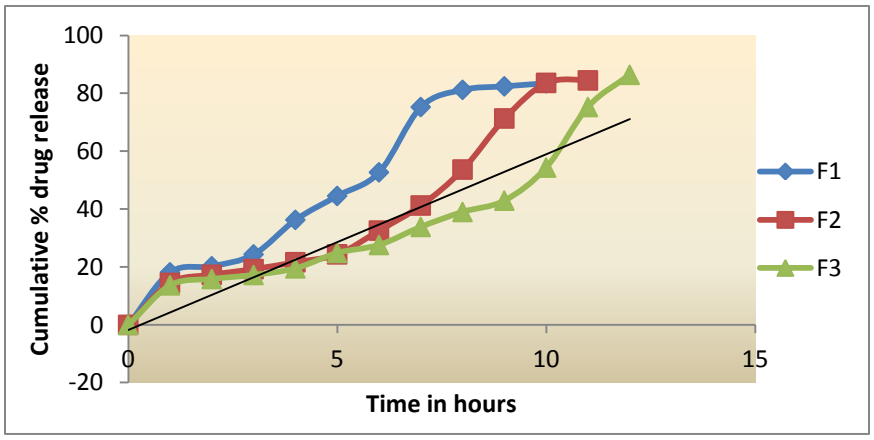

Fig No 3: In vitro drug release of Metoprolol tartarate microspheres

In-vitro release studies

The in-vitro release profile of Metoprolol tartarate microspheres were conducted in 0.1 N Hcl for 12 hours for ion gelation method.

Dissolution conditions

Medium : 0.1 N Hcl.
Apparatus : basket (USP Apparatus I)
RPM : 50
Temperature : 37.0 ±0.5ºC
Time : 12hrs
Volume : 900ml

Sampling times : 1hr,2hr,3hr,4hr,5hr,6hr,7hr,8hr,9hr,10hr,11hr,12hr

Table No 9: Cumulative drug release of Metoprolol tartarate microspheres

Time (hrs)	% Cumulative drug release			
	$F_{4\pm SD}$	$F_{5\pm SD}$	$F_{6\pm SD}$	$F_{7\pm SD}$
0	0	0	0	0
1	23.43±0.012	18.34±0.042	16.34±0.01528	14.21±0.067
2	32.13±0.005	27.08±0.067	24.42±0.02517	20.43±0.030
3	41.52±0.068	36.13±0.342	31.29±0.03055	33.09±0.631
4	57.45±0.305	45.16±0.0543	42.65±0.03512	39.31±0.068
5	63.67±0.512	51.34±0.631	49.53±0.03055	42.43±0.068
6	68.86±0.482	56.39±0.054	51.32±0.1101	45.06±0.012
7	74.56±0.053	62.42±0.068	54.09±0.09713	48.322±0.068
8	86.26±0.810	69.56±0.123	57.21±0.342	51.32±0.053
9	89.31±0.030	72.45±0.0253	59.34±0.1	57.32±0.342
10	92.06±0.025	75.32±0.1	67.54±0.283	62.65±0.631
11	-	85.43±0.005	72.65±0.429	66.34±0.342
12	-	93.29±0.512	76.34±0.245	70.23±0.283

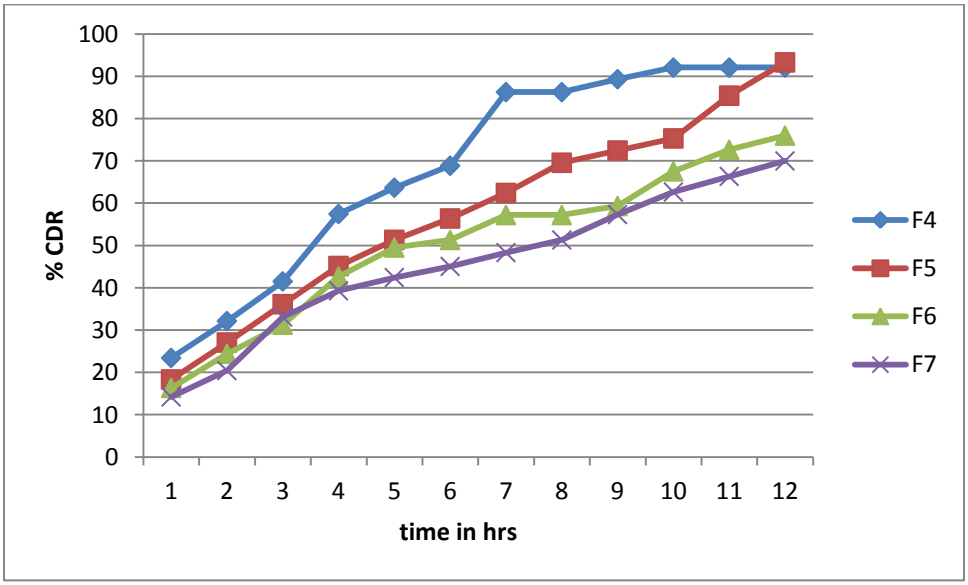

Fig No 4: Dissolution graph for F4, F5, F6, and F7 of ion gelation method

From the above inference F3 was optimized based on drug release and entrapment efficiency, the formulation F5 also show s similar characteristics but depending on all criteria there made a comparissoin between two methods and it was concluded that F3 of solvent evaporation method was optimized and showed better results than F6 of ion gelation method.

Release Kinetics Plots for Ethyl Cellulose Microspheres Containing Metoprolol succinate F3

The dissolution of microspheres formulation follows Zero order and Higuchi models.

ZERO ORDER

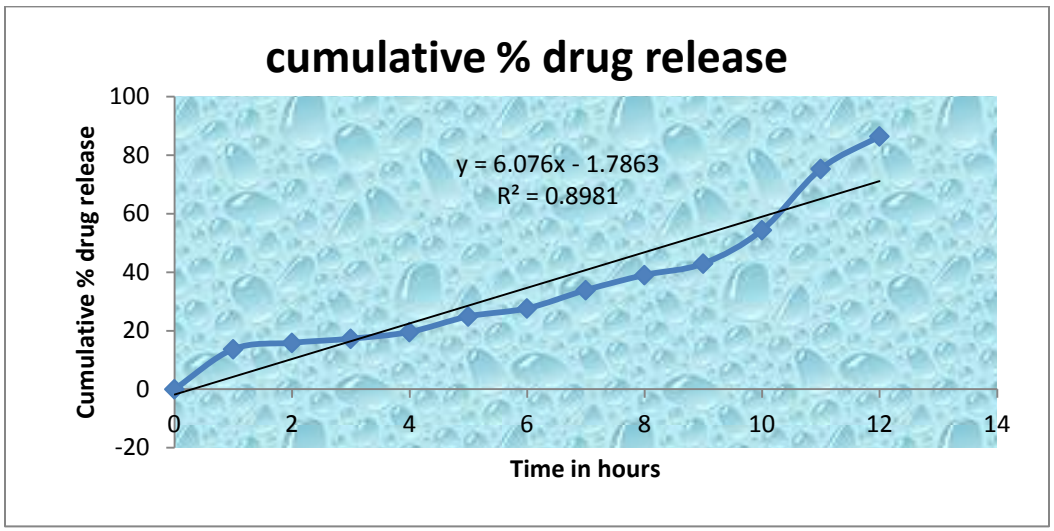

Fig No 5: Zero order release of Metoprolol tartarate microspheres F3

FIRST ORDER

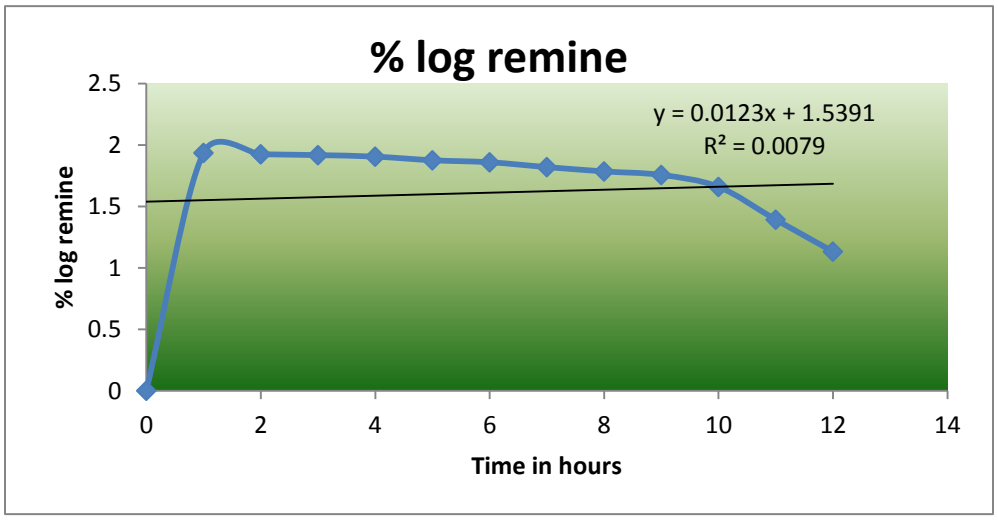

Fig No 6: First order release of Metoprolol tartarate microspheres F3

HIGUCHI PLOT

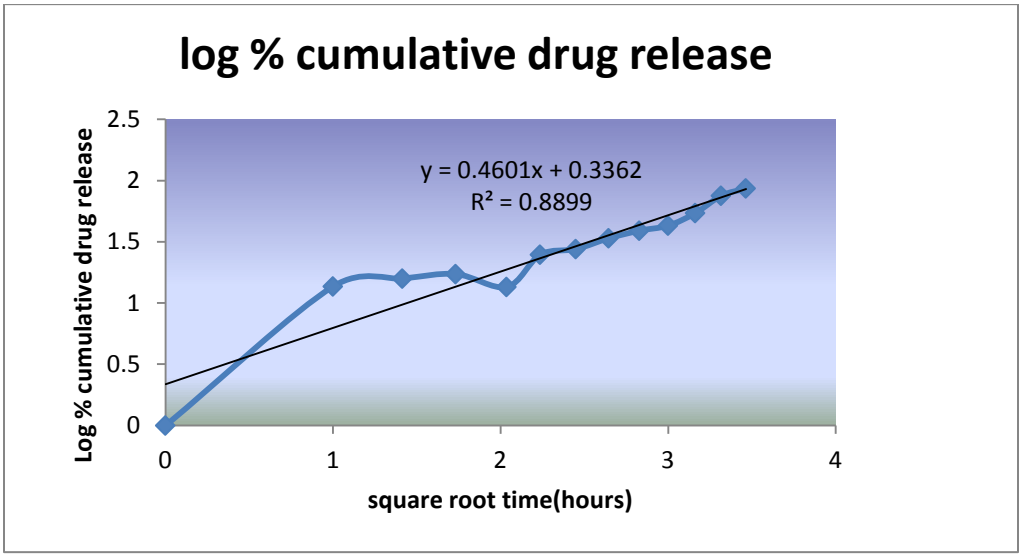

Fig No 7: Higuchi plot of Metoprolol tartarate microspheres F3

PEPPAS PLOT

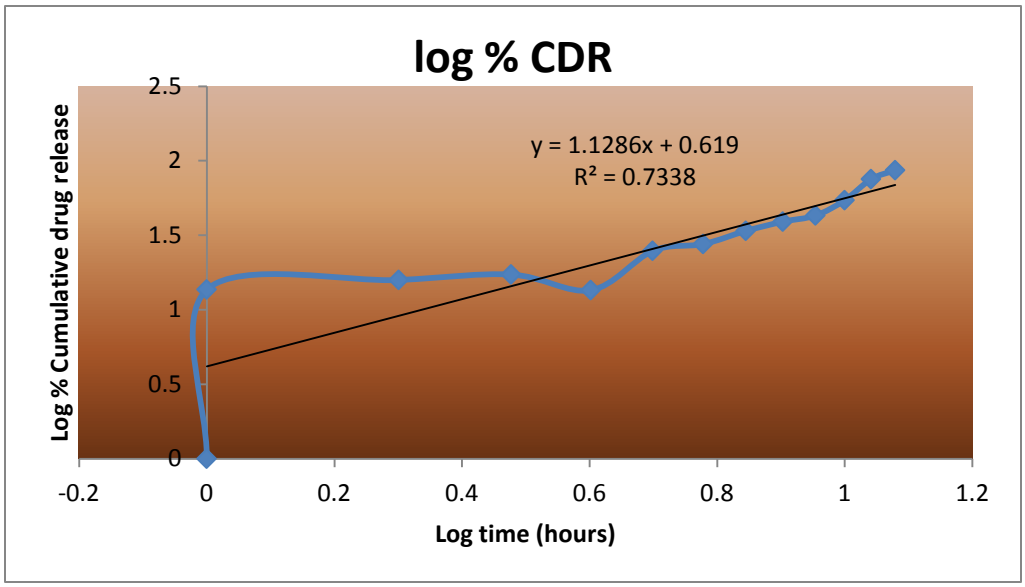

Fig No 8: Peppas plot of Metoprolol tartarate microspheres F3

Table No 10: Drug release kinetics of Metoprolol succinate microspheres

Formulations	Zero order	First order	Higuchi plot	peppas plot
	R^2	R^2	R^2	R^2
F_3	0.898	0.007	0.889	0.733

DISCUSSION

The formulation F3 has the highest entrapment efficiency. The drug loading was found to decrease with increase in the amount of polymer related to drug. The particle size of a microsphere was determined by optical microscopy and all the batches of microspheres show uniform size distribution. The particle size was found to be in the range of 39.72 to 57.26 µm. The prepared microspheres had good spherical geometry with smooth surface as evidenced by the scanning electron microscopy. The invitro dissolution studies that the Metoprolol succinate microspheres formualation F3 showed better controlled release over a period of 12hrs than the other formulations. It was concluded that as the polymer concentration increases, density of polymer increases that results in increased diffusion path length, which the drug molecules have to traverse so, the drug release of F_3 formulation takes long time than other formulations.

CONCLUSION

The present work was designed to formulate metoprolol succinate microspheres by using ethyl cellulose polymer by solvent evaporation method and by using sodium alginate by ion gelation method and comaprision was made and evaluated that solvent evaporation method proves to be best method than ion gelation method. Preformulation studies were done for bulk drugs. The Metoprolol succinate microspheres were formulated and evaluated. The ethylcellulose microspheres of Metoprolol succinate were successfully prepared by solvent evaporation technique and confirmed that it is a best method for preparing Metoprolol succinate loaded microspheres from its higher percentage yield. The formulation F3 has the highest entrapment efficiency. The drug loading was found to decrease with increase in the amount of polymer related to drug. The particle size of a microsphere was determined by optical microscopy and all the batches of microspheres show uniform size distribution. The particle size was found to be in the range of 39.72 to 57.26 µm. The prepared microspheres had good spherical geometry with smooth surface as evidenced by the scanning electron microscopy. The invitro dissolution studies that the Metoprolol succinate microspheres formualation F3 showed better controlled release over a period of 12hrs than the other formulations. It was concluded that as the polymer concentration increases, density of polymer increases that results in increased diffusion path length, which the drug molecules have to traverse so, the drug release of F_3 formulation takes long time than other formulations.

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