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Research Article

FORMULATION AND EVALUATION OF SUSTAINED RELEASE MICROSPHERES OF METOPROLOL

Surendranath Betala [1]*, M.Mohan Varma [2], K.Abbulu [3]

[1]Sri Vasavi Institute of Pharmaceutical Sciences, Tadepalligudem, Andra Pradesh. India

[2]Sri Vishnu College of Pharmacy, Bhimavaram, Andra Pradesh. India

[3]CMR College of Pharmacy, Hyderabad, Telangana, India

*Corresponding Author Email: surendrapharma05@gmail.com

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ABSTRACT

Formulated Metoprolol sustained release microspheres. Microspheres are prepared by Ionic-Gelation method using Hydroxy Propyl Methyl Cellulose (HPMC), Ethyl cellulose and Sodium CMC for sustained release in view to prolong drug release. Metoprolol is an adreno receptor beta blocking agent used in the treatment of hypertension and characterized by high solubility and high permeability which corresponds to BCS class I drug. Plasma half life ranges from 3 to 7 hours & oral bioavailability is 50% hence require frequent oral administration for adequate treatment of hypertension. Administration of conventional tablet of Metoprolol has been reported to exhibit fluctuations in plasma drug levels resulting in either manifestation side effects reduction in drug concentration at receptor site. so that oral sustained dosage form was developed. The microspheres were evaluated for various characteristics like encapsulation efficiency, percentage yield, partial size and the *In vitro* release for 12 hours. The Microspheres were found to be discrete, spherical, and free-flowing. The microspheres were uniform in size, and the microencapsulation efficiency was in the range of 91.7%. Microspheres had good spherical geometry.

Keywords: Microspheres, Hypertension, *In vitro* release, Encapsulation efficiency

INTRODUCTION

Oral Drug Delivery System [1,2]

Oral drug delivery has been known for decades as the most widely utilized route of administration among all the routes that have been explored for the systemic delivery of drugs via various pharmaceutical products of different dosage forms.

Sustained Release Drug Delivery

Sustained release, sustained action, prolonged action controlled release, extended released, depot release are the terms used to identify drug delivery systems that are designed to achieve a prolonged therapeutic effect by continuously releasing medication over an extended period of time after administration of single dose of drug.

Microspheres[1,2]

Microspheres are small spherical particles, with diameters in the micrometer range (typically 1 µm to 1000 µm (1 mm)). Microspheres are sometimes referred to as microparticles.

MATERIALS AND METHODS

Table 1: List of Materials used for the study

INGREDIENTS	SUPPLIER
Metoprolol Succinate	Yarrow Chem, Mumbai
Hydroxyl propyl methyl cellulose K100M	Ozone International, Mumbai.
Sodium carboxy methyl cellulose	Ozone International, Mumbai.
Ethyl cellulose	Loba Chemie Pvt Ltd., Mumbai.
Calcium chloride	Sd Fine-Chem Limited, Mumbai.
Sodium alginate	Loba Chemie Pvt Ltd., Mumbai.

DRUG PROFILE

METOPROLOL SUCCINATE

Chemical Name: 1-[4-(2-Methoxyethyl)phenoxy]-3-[(propan-2-yl)amino]propan-2-ol

Systematic (IUPAC) Formula: $C_{15}H_{25}NO_3$

Molar. Mass: 267.364 g/mol

STRUCTURE

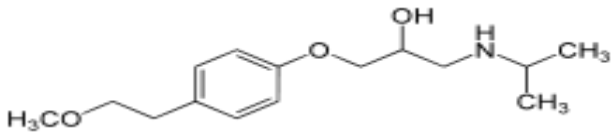

Figure 1: Structure of Metoprolol hydrochloride

Description
Metoprolol hydrochloride is a stable, white, crystalline solid which is readily soluble in water and ethanol. Its molecular weight is 267.364 g/mol

Physico-chemical Properties:

Melting point: 120 °C (248 °F)

Solubility soluble in water, and alcohol; slightly soluble in chloroform; practically in soluble in ether. As for acid, alkali or organic solvent like diethyl ether.

Spectral Properties: λmax (Metoprolol): 296.

FORMULATION OF SUSTAINED RELEASE MICROSPHERES[3,4,5]

PROCEDURE: The following steps involved in preparation of Metoprolol microspheres.
1. Preparation of Polymer Solution by dissolving in distilled water.
2. Dissolve Drug (Metoprolol) in above Solution.
3. Sonicate the Drug-Polymer Solution for proper mixing.
4. Above solution was added drop wise by a 26G hypodermic needle into 50ml of 5% w/v $CaCl_2$ solution.
5. Formed Metoprolol Microspheres were stirred in the cross linking agent for 1hr at 100rpm.
6. Wash the Microspheres with de-ionized water and dried at 80ºC for 2 hour.
7. Transfer prepared Microspheres to desiccators to maintain the constant Humidity conditions.
All Formulations were prepared by Ionic Gelation method using different polymers.

Table No. 2: Trail formulations composition

Trail Formulations	Metoprolol (mg)	HPMC K100M (mg)	Sodium CMC (mg)	Ethyl Cellulose (mg)	Sodium Alginate (mg)	$Cacl_2$ %(W/V)
F1	100	_	50	_	1000	5
F2	100	_	100	_	1000	5
F3	100	200	150	_	1000	5
F4	100	100	_	50	1000	5
F5	100	150	_	50	1000	5

RESULTS AND DISCUSSIONS
PREFORMULATION STUDIES[8,9]
Drug excipient compatibility studies

The compatibility of drug and formulation components is important prerequisite before formulation. It is therefore necessary to confirm that the drug does not react with the polymers and excipients under experimental conditions and affect the shelf life of product or any other unwanted effects on the formulation.

The compatibility study between the drug and the polymer was done by I.R studies. No major peak shift was observed in the I.R graphs in major functional groups. Based on the compatibility studies obtained by I.R studies, polymers, HPMC,EC.Sod.CMC ware taken for the optimization of the formulation, which is compatible with the drug.

EVALUATION TESTS[14,17,18]
PARTICLE SIZE

SEM photograph of formulated Microspheres

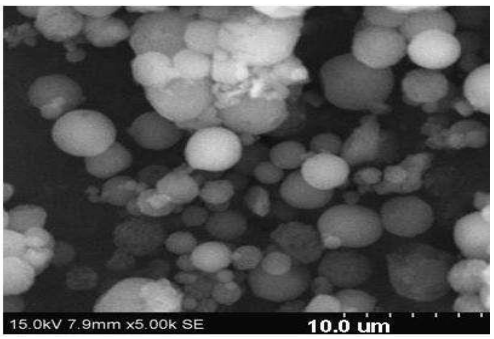

Figure SEM of formulated Microspheres

IN-VITRO DISSOLUTION DATA: DISSOLUTION KINETICS

Table 4: Percentage drug release for optimized formulation

Time(hours)	Absorbance	% Cumulative drug release
0	0	0
1	0.135	35.1
2	0.146	41.2
3	0.231	50.6
4	0.265	56.2
5	0.314	61.7
6	0.336	69.8
7	0.384	73.4
8	0.472	76.5
9	0.518	79.6
10	0.621	87.2
12	0.692	96.8

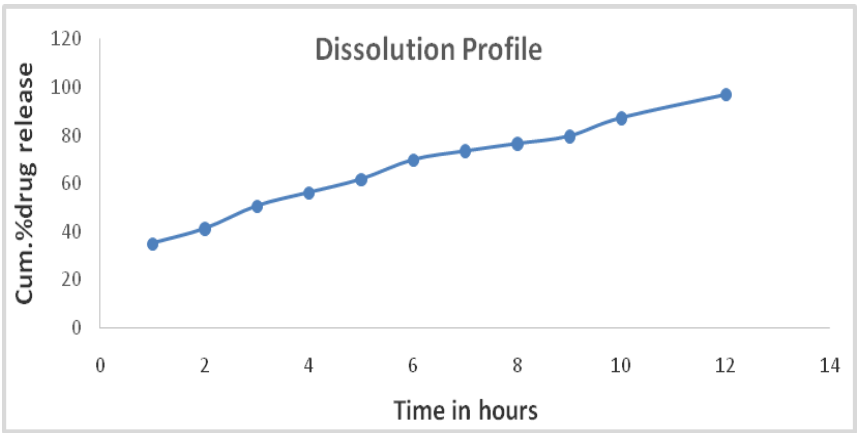

Figure 4: Dissolution profile of formulation F-5

COMPARATIVE DISSOLUTION PROFILE

Table 5: Comparative dissolution profile for different formulations F1-f5

Time(hours)	F-1 % CDR	F-2 % CDR	F-3 % CDR	F-4 % CDR	F-5 % CDR
0	0	0	0	0	0
1	24.2	36.0	21.2	22.3	35.1
2	36.5	45.0	30.4	36.2	41.2
3	39.4	50.5	36.4	62.6	50.6
4	50.1	53.4	40.8	63.0	56.2
5	59.4	54.0	56.7	64.2	61.7
6	64.5	59.3	59.4	64.8	69.8
7	70.2	65.0	65.2	66.6	73.4
8	80.9	76.3	70.4	68.0	76.5
9	94.8	99.7	79.8	97.8	79.6
10	99.7	--	96.7	99.7	87.2
12	---	--	--	--	96.8

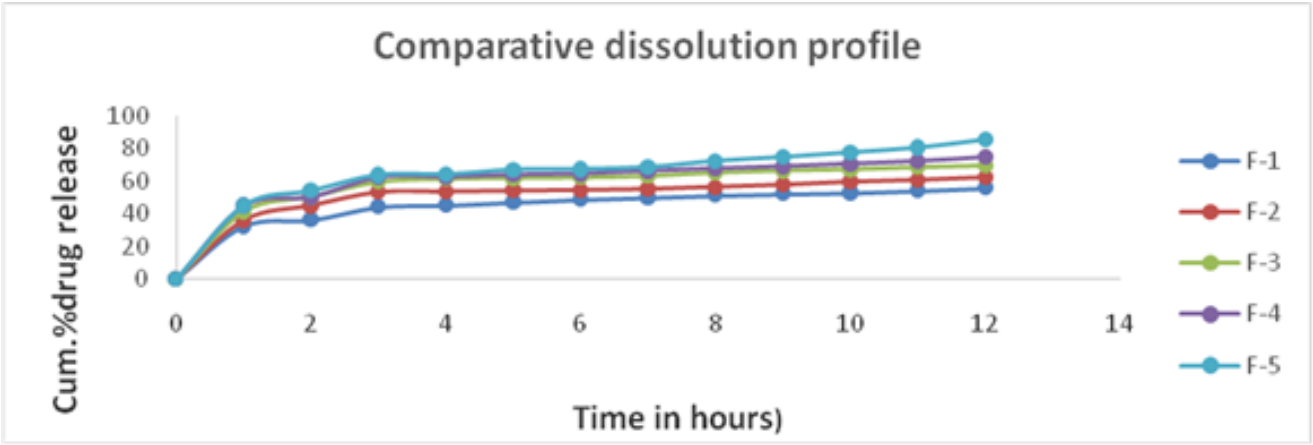

Figure 5: Comparative dissolution profile for formulation F1-F5.

Inference: From the above fig the dissolution profile for the formulation F-5 was found to be have the more cumulative % drug release.

ZERO ORDER PLOT

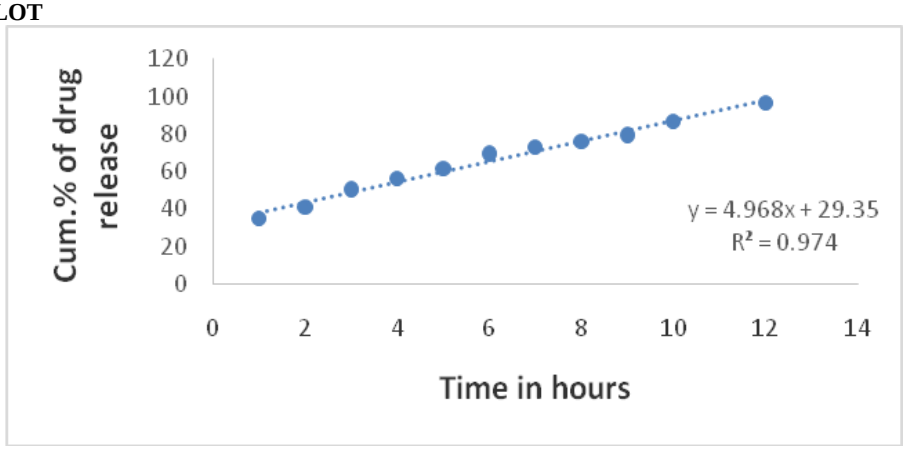

Figure 6: Zero order plot for optimized formulation F-5

FIRST ORDER PLOT

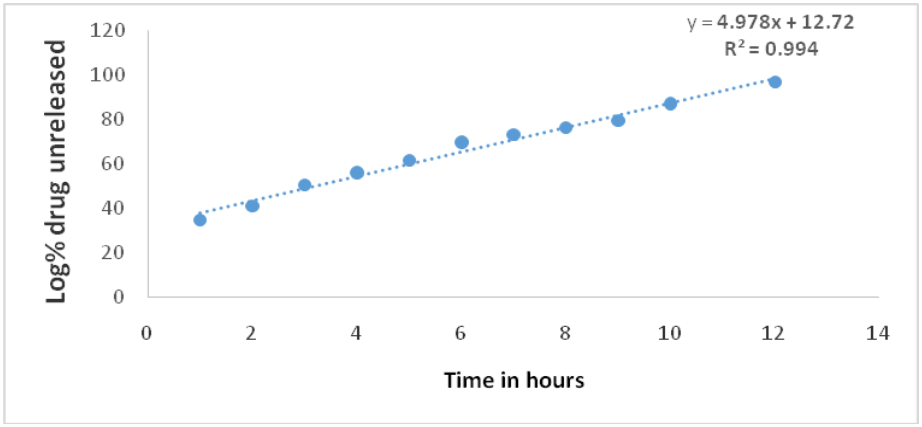

Figure 7: First order plot for optimized formulation F-5

Inference: From the above graph R^2 value is (0.931) and for zero order plot R^2value is (0.919) which indicates that the order of release was first order.

HIGUCHI'S PLOT

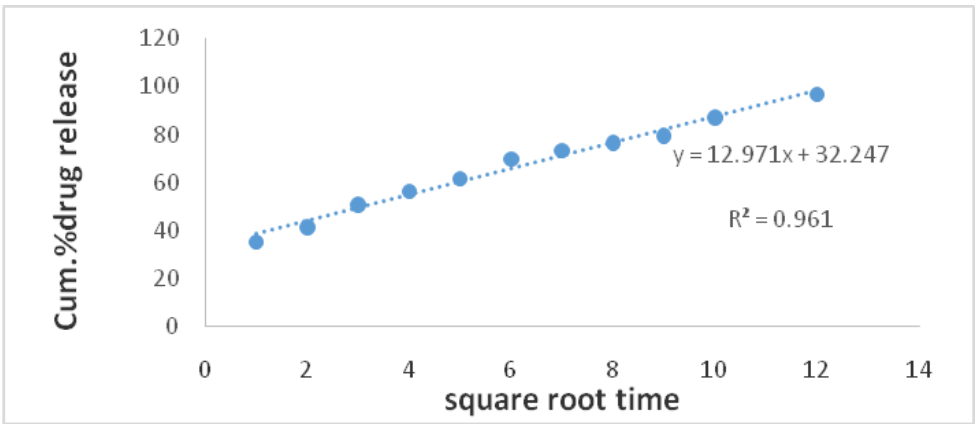

Figure 8: Higuchi's plot for optimized formulation F-5

KORSEMEYER-PEPPAS PLOT

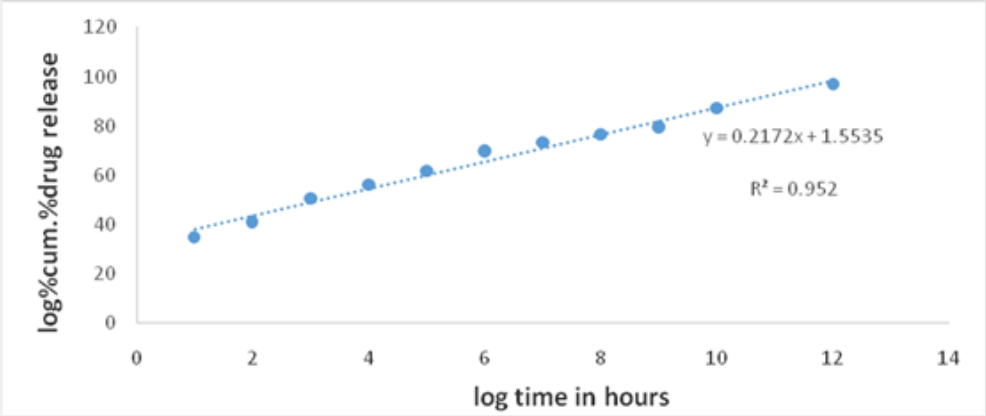

Figure 9: Korsemeyer- Peppas plot for optimized formulation F-5

Inference: As per the above plot the R2 value for Higuchi (0.919) and for Korsemeyer – peppas plot (0.961), showing that the mechanism of drug release from the formula was found to be diffusion controlled release.

Stability studies

The accelerated stability study for the formulation at 40 ± 2^0 C and 75 ± 5 % RH was conducted for the 6 months, which includes the testing of parameters like identification of physical characters, identified by IR studies, dissolution profile and assay throughout period.

CONCLUSION

Thus, Microspheres with a coat consisting of Sodium alginate and other polymers (Sodium CMC, HPMC K100M and Ethyl Cellulose) could be prepared by an Ionic gelation process. The microspheres exhibited good sustained release in an *in vitro* test. Metoprolol release from these sustained release microspheres was slow and extended over a longer period of time (12hours) and depended on composition of the coat. Drug release was diffusion controlled and followed zero-order kinetics. In the *in vitro* evaluation, EC-HPMC K100M microspheres could sustain the drug release over a 12-hour period. . Based on results the best formulation F5 can successfully employed as a controlled release drug delivery system. These sustained release microspheres are thus suitable for oral sustained release of Metoprolol.

- FTIR studies revealed no interactions between the drug and polymers used.
- Formulated Microspheres gave satisfactory result for various physico-chemical evaluations like physical appearance, surface morphology, entrapment efficiency, percentage drug loading and *in vitro* drug release.
- The prepared beads showed required drug release in about 12 hours.
- From the research, it can be concluded that Metoprolol can be formulated as microspheres for the desired use in treatment of Hypertension.

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