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DEVELOPMENT AND EVALUATION OF METOPROLOL SUCCINATE MICROPARTICLE-HYDROCHLOROTHIAZIDE SUSTAIN RELEASE MATRIX TABLET

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ABSTRACT

This study reports the properties of Tableted microparticles based on ethyl cellulose blend polymers as sustain release system for Metoprolol succinate. Ethyl cellulose blend microparticles are prepared through a solvent evaporation process which is widely used microencapsulation technique in the pharmaceutical industry. The Microparticle were spherical & free flow in nature. The Entrapment Efficiency was based on the ratio of polymer in formulation. The Tableted Microparticle based on 1:3 ratios was found to better formulation. Since they exhibit effective sustain release compare to other formulation. The blend microparticles of Metoprolol succinate were compressed with combination of Hydrochlorothiazide. This fixed dose combination of Metoprolol succinate and Hydrochlorothiazide is used as Antihypertensive agent. Drug Release from compressed tablet was always faster than from uncompressed Microparticles. The Drug release rate increased at higher compression pressure due to the rupture of a greater proportion of Microparticle. Generally the least compression pressure that gives Tableted with acceptable properties is preferred.

KEYWORDS: Microparticles, Metoprolol succinate, Hydrochlorothiazide, Sustain Release Matrix Tablet.

INTRODUCTION

The goal of any drug delivery system is to provide a therapeutic amount of drug to the proper site in the body to achieve promptly and then maintain the desired drug concentration.

The oral route of drug administration is most appealing route for the delivery of the drug among various dosage form tablet is one of the most preferred dosage form.

Combination therapy has various advantages over a mono therapy a low dose combination of two different agents reduced the dose- related risk minimize the clinical and metabolic effects that occur with maximal dosage of individual components. The Metoprolol succinate and Hydrochlorothiazide both are having antihypertensive agents.

Ethyl cellulose is a polymer of β-anhydrous-glucose building block joined together by acetal bonding it is generally considered as a non toxic, biocompatible and biodegradable polymer EC coated Microparticle have also demonstrate their capability to absorb pressure and therefore save the coating from fracture during tablet manufacturing process.

Sustain Release multiple-unit oral dosage form are effective in achieving optimal therapy with drugs that have a narrow therapeutic range of blood concentration or that eliminate rapidly and reduce the risk of gastric irritation at one particular site because of the uniform distribution of the drug throughout the GIT. Polymeric microparticles are widely studied carriers for the sustain release application of drugs. Encapsulation of drugs into polymeric matrix can be achieved by techniques, such as solvent evaporation .sustain release characteristics of microparticles reduce the need for frequent administrations and enhance patient compliance by maintaining in drug levels in the therapeutic range. This Microparticle can be compressed into tablets. However, the formulation of multiple units into tablets has

The advantage of preventing tampering, as in the case of capsules, but the merger of these multiple systems during compression can produce variations in the sustain release of the drug.

MATERIALS AND METHODS

Materials

Metoprolol succinate, Hydrochlorothiazide was received as a gift sample from Ajanta Pharamaceutical Ltd, kandivali, Mumbai. Ethyl Cellulose and other ingredients were procured from balaji drug supplier. Chemicals used in this study were of analytical grade.

Methods

Preparation of Microparticle of Metoprolol succinate by solvent Evaporation Method

- Prepare an aqueous solution of the drug (may contain a viscosity building or stabilizing agent.).
- Then added to an organic phase consisting of the polymer solution in solvents like dichloromethane or chloroform with vigorous stirring to form the primary water in oil emulsion.
- This emulsion is then added to a large volume of water containing an emulsifier like PVA or PVP to form the multiple emulsion (w/o/w).
- The double emulsion is then subjected to stirring until most of the organic solvent Evaporates, leaving solid microspheres.
- The Microparticle can then be washed and dried.

Table: 1 Composition of Trial Batches

Sr.No.	Name of Ingredients	T_1	T_2	T_3	T_4	T_5	T_6	T_7	T_8	T_9
1	Metoprolol succinate	100	100	100	100	100	100	100	100	100
2	Eudragit RL-100	100	-	-	200	-	-	300	-	-
3	Eudragit RS-100	-	100	-	-	200	-	-	300	-
4	Ethyl Cellulose	-	-	100	-	-	200	-	-	300
5	Methanol	30	30	30	-	-	-	-	30	-
6	Chloroform	30	-	-	-	30	30	-	-	-
7	Acetone	-	30	30	30	-	-	-	-	-
8	Methylene chloride	-	-	-	-	-	-	30	30	30
9	Magnesium stearate	-	-	-	0.5	0.5	-	-	-	-
10	n-Hexane/liquid paraffin	q.s	q.s	-	-	-	-	-	q.s	-
11	Water	-	-	q.s	q.s	q.s	q.s	q.s	-	q.s

Evaluation of Microparticles

Percentage Yield

The prepared microparticles of all batches were accurately weighed. The measured weight of prepared microparticles was divided by the total amount of all the excipients and drug used in the preparation of the microparticle, which give the total percentage yield of microparticles. It was calculated by using following equation,

$$\% \text{ Yield} = \frac{\text{Actual weight of product}}{\text{Total weight of Excipients and drug}} \times 100$$

Micromeritic Studies

The prepared microparticles are characterized by their micromeritic properties, such as microparticles size, tapped density, Carr's compressibility index, Hausner's ratio and angle of repose.

Drug Loading and Drug Entrapment

Microparticles equivalent to 50 mg of the drug were taken for evaluation. The amount of drug entrapped was estimated by crushing the microparticles and extracting with aliquots of 0.1N HCl (pH-1.2) repeatedly. The extract was transferred to a 100ml volumetric flask and the volume was made up using 0.1N HCl (pH-1.2). The solution was filtered and the absorbance was measured after suitable dilution spectrophotometrically at 274nm against appropriate blank. The amount of drug loaded and entrapped in the microspheres was calculated by the following formulas.

Drug loading = weight of drug in microparticles/ microparticles sample weight × 100

(Drug entrapment efficiency (%) = Amount of drug actually present/ Theoretical drug load expected × 100

In-vitro Release Study

The drug release study was performed for microparticles containing quantity equivalent to 100mg of Metoprolol succinate by using USP dissolution apparatus Type I in 900 ml of 0.1N HCl dissolution media (pH-6.8) at 100 rpm and 37^0C temperature. 5 ml of sample was withdrawn at predetermined time interval for 1 hours and same volume of fresh medium was replaced to maintained sink condition. Withdrawn samples were assayed spectrophotometrically at 275 nm. Drug release was also performed for pure drug. The cumulative % drug release was calculated using standard calibration curve.

Table: 2 Composition of Tablet

Sr. No.	Ingredients	Quantity (mg)
1	Microparticle containing Metoprolol succinate	300
2	Hydrochlorothiazide	12.5
3	Dried Starch	X1
4	Talcum	5
5	MCC	X2
6	Propyl Paraben	10
7	Magnesium stearate	X3
8	Lactose	Q.S to 415

Table: 3 Codes of Independent Variables

Coded Level	Independent Variables		
	X1=Starch (mg)	X2= MCC (mg)	X3=Magnesium stearate (mg)
Low Level(-)	15	10	5
High Level (+)	30	20	10

Dependent Variable

Y1=Drug Release

Y2=Disintegration Time

Optimization of formulation

The F9 composition containing Metoprolol succinate and Ethyl cellulose in the Ratio 1:3 and HCTZ, other Excipients is subjected to compressed Tablet. The Experimental Design of processing parameter of tableted microparticles

Physical Evaluation of Tableted microparticles

In vitro disintegration time

The process of breakdown of a tablet into smaller particles is called as disintegration. The in-vitro disintegration time of a tablet was determined using disintegration test apparatus as per I.P. Specifications.

The disintegration time for the tablet was determined using the disintegration apparatus. One tablet was placed in each of six tubes placed in a beaker containing 1000 ml of purified water maintained at 37 ± 5^0 C and the apparatus was operated. The time taken for the tablets to disintegrate and pass through the mesh was noted.

In vitro Drug Release

Drug release from the pure Metoprolol succinate (MS) Microparticle and HCTZ matrix tablet was studied by using a dissolution tester (Electro lab) at a stirring speed of 100 rpm. Three tablets from each batch were tested using 900mL of dissolution medium (phosphate buffer, pH 6.8), maintained at 37^{o}C. An aliquot of the release medium (5mL) was withdrawn through a sampling syringe attached with 0.2 mm filtrate predetermined time intervals (0.5, 1, 2, 3, 4, 5, 6and 7 h) and an equivalent amount of fresh dissolution medium, which was pre warmed at 37^{o}C, was replaced. Collected samples were then analyzed for MS & HCTZ content by measuring the absorbance at 274nm & 272 nm using a UV spectrophotometer. In vitro release studies were performed in triplicates in an identical manner

RESULTS AND DISCUSSION

Metoprolol succinate Microparticles were prepared by solvent evaporation technique with different polymeric concentrations of ethyl cellulose. Effect of different concentrations of EC Metoprolol succinate microparticles were successfully examined with respect to microparticles, % yield, particle size, drug loading efficiency.

In Metoprolol succinate Microparticle exhibit a smooth surface (figure no.1) The particle size of MS microparticle was found to be in the Size range of 10 µm by SEM. Compressibility index (less than 15%) indicated fine flow properties. Hausner's ratio (volume before taping/volume after taping), for all formulations, was below 1.29 again indicating free flow of all formulations of microparticles. Similarly angle of repose for all formulations were below 30° indicating once again free flowing nature of microparticles. It was found that the encapsulation efficiency is influenced by core to wall ratio. With increasing EC ratio, more particles of Metoprolol succinate are coated which leads to a higher encapsulation efficiency An increase in EC concentration caused a slight increase in production yield of microparticles.

Hence Drug polymer ratio 1:3 is having an ideal requirement for producing the tableted microparticles by direct compression this 1:3 Ratio to be better formulation Since they Exhibited Sustain Drug Release, compare to other to other formulation.

Table: 4 Rheological properties of microparticles

Formualtion	Bulk Density	Tapped Density	Hausner's Ratio	Angle of repose
F_3	0.30	0.24	1.14	21.82^0
F_6	0.27	0.32	1.02	24.14^0
F_9	0.22	0.34	1.26	28.35^0

Table: 5 Evaluation of physical Characteristic of MS Microparticles.

Sr.No.	Parameters	Formulation								
		F_1	F_2	F_3	F_4	F_5	F_6	F_7	F_8	F_9
1	Percent Yield(%)	NA	NA	60	10	13	72	19	21	82
2	Particle size	NA	NA	20-22	NA	NA	21-24	30-34	40-48	12-14
3	Entrapment Efficiency	NA	NA	49	NA	NA	65	NA	NA	79
4	Carr's Index (Flow Property)	NA	NA	19	NA	NA	17	NA	NA	14

Surface morphology og Microparticles

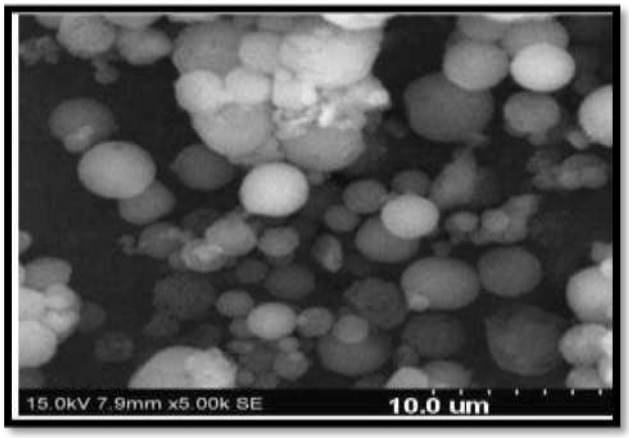

Figure: 1 Scanning Electromn microscopy of microparticle

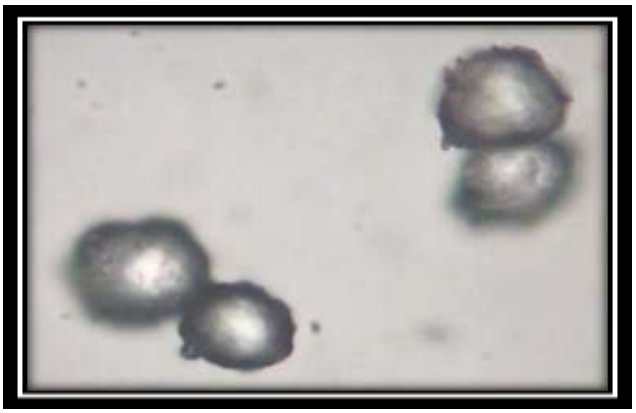

Figure: 2 Binocular microscopic photographs of MS microparticles

Preparation of Matrix Tablet

The microparticle thus prepared were compressed into tablets by direct compression method. Tablet microparticles exhibit sustain release of the drug. However, the cumulative amount of drug release was affected by the ratio between Drug and polymer ,the Tableted microparticles based on 1:3 ratios were found to be better formulation since they exhibit effective sustain drug release compare to other formulation.

Optimization of formulation

Response surface methodology (RSM) is a widely practiced approach in the development and optimization of drug delivery devices. Based on the principle of design of experiments (DoE), the methodology encompasses the use of various types of experimental designs, generation of polynomial equations, and mapping of the response over the experimental domain to determine the optimum formulation(s).The technique requires minimum experimentation and time, thus proving to be far more effective and cost-effective

than the conventional methods of formulating dosage forms. Various computations for the current optimization study were performed using Design Expert® software (Design Expert trial version 8.0.1; State-Ease Inc., Minneapolis, MN, USA).a three factors Box-Behnken design was used for systemic study of processing parameters of Tableted microparticles A three factor three level Box-Behnken design was constructed where the Starch (X1), MCC (X2) and Magnesium Sterate (X3) were selected as the independent variables i.e. factors. The levels of these factors were selected on the basis of initial studies and observations. The composition of Matrix Tablet was kept invariant throughout the study period.

Optimization of processing parameters of Matrix Tablet

The optimization of the processing parameters of Matrix Tablet was done on the basis of the results obtained in the above parameters and required Disintegration and Dissolution. The optimized batch (O_1) was having the composition containing Starch (15mg), MCC (20mg), Magnesium stearate (7.50mg) which showed a good desired results. The optimized batch (O_1) was identified to provide desired values for tablet disintegration (20.56), dissolution (57.25) the details of solution for optimized batch is given in table No.

Table No. 6 Actual Design Layout

Std	Factor 1 A:Starch Mg	Factor 2 B:MCC Mg	Factor 3 C: Mg Stearate mg	Response 1 Disintegration Min.	Responce2 Dissolution %
1	30.00	10.00	7.50	19	60
2	15.00	20.00	7.50	22	62
3	22.50	20.00	10.00	16	39
4	22.50	10.00	10.00	19	41
5	15.00	10.00	7.50	20	65
6	22.50	10.00	5.00	15	96
7	30.00	15.00	5.00	16	80
8	30.00	15.00	10.00	16	42
9	30.00	20.00	7.50	17	50
10	22.50	15.00	7.50	18	51
11	15.00	15.00	5.00	15	75
12	22.50	15.00	7.50	19	52
13	22.50	20.00	5.00	20	71
14	15.00	15.00	10.00	18	40
15	22.50	15.00	7.50	19	53
16	22.50	15.00	7.50	20	54
17	22.50	15.00	7.50	21	54

Table: 7 Optimized Batch

Sr.No.	Parameters	Solution for optimized batch	Optimized batch O1
1	Starch	15 mg	15 mg
2	MCC	20 mg	20 mg
3	Magnesium stearate	7.50 mg	7.50 mg
4	Disintegration	20.56	19.42
5	Dissolution	57.25	60.4
6	Desirability	1	-

Evaluation of optimized batch of Matrix Tablet

Table: 8 In Vitro dissolution profile of Metoprolol succinate and HCTZ

Min.	Hydrochlorothiazide (%)	Sustain Release Metoprolol Succinate(%)
15	23.41	-
30	48.37	-
45	65.20	-
60	96.82	35.6
120	-	37.7
180	-	42.9
240	-	46.1
300	-	50.8
360	-	56.9
420	-	60.4

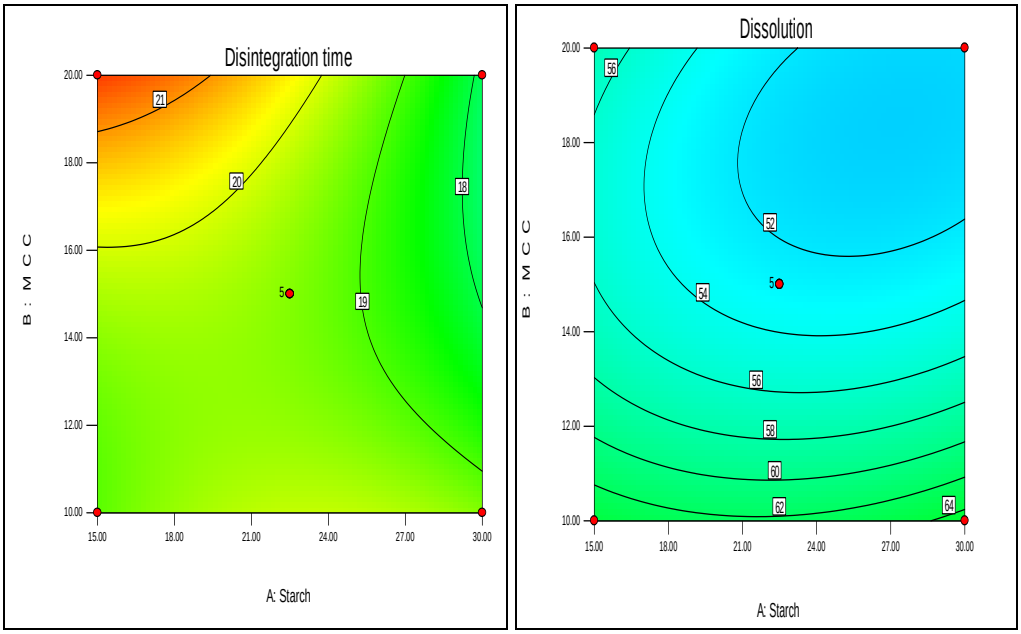

Figure No. 3: Contour Plot

a) Plot between Starch, MCC Disintegration Time.

b) Plot Between Starch, MCC Dissolution.

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CONCLUSION

This study elaborate that the solvent evaporation technique is an appropriate method to microencapsulated the Metoprolol succinate into Ethyl cellulose coats and to prepare the Fixed dose combination of Metoprolol succinate Microparticle and Hydrochlorothiazide matrix Tablet by Direct compression Method. The result clearly show the prepare formulation is sustain release profile & stability. The optimize batch was found to be stable for a period of Two month at 40°C/75%R.

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