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# DESIGN AND EVALUATION OF SUSTAINED RELEASE METAPROLOL SUCCINATE SUPPOSITORY BY NON- AQUEOUS SOLVENT EVAPORATION TECHNIQUE

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**ABSTRACT:-**

The aim of the present study is to prepare a sustained release suppository of an antihypertensive drug suitable for rectal administration.

Firstly, the microspheres of metaprolol succinate were formulated using ethyl cellulose as polymer to sustain the drug release for longer time to conquer the short half life of the drug. The microspheres using ethyl cellulose were prepared by non-aqueous solvent evaporation technique. The microspheres were evaluated for micromeritic properties, particle size, percentage yield, entrapment efficiency, drug polymer compatibility, scanning electron microscopy and *in-vitro* drug release studies.

**KEYWORDS:- Polymer, Suppository, Microsphere.**

## INTRODUCTION

- **SUSTAINED DRUG DELIVERY SYSTEMS:**

It has been used to describe a pharmaceutical dosage form formulated to retard the release of a therapeutic agent such that its appearance in the systemic circulation is delayed and or prolonged and its plasma profile is sustained in duration.

- **MICROSPHERES:**

They are defined as homogeneous, monolithic particles in the size range of about 0.1-100 μm and are widely used as drug carriers for controlled release. Administration of the drug in the form of microspheres usually improves the treatment by providing the localization of the active substances at the site of action and by prolonging release of drugs.

- **SUPPOSITORIES:**

"Suppositories" are solid dosage forms intended for insertion into body orifices (rectum, vagina and urethra) where they melt, soften, or dissolve and exert a local or systemic effect.

**OBJECTIVES OF THE STUDY**

Performing the descriptive preformulation studies of metaprolol succinate individually as well as in physical blend to ascertain the compatibility by characterization of IR, UV-Spectroscopy and construction of standard calibration curve.

- Formulation of metaprolol succinate microspheres using microsphere forming polymer ethyl cellulose.
- Physico-chemical characterization of the prepared microspheres.
- In-vitro evaluation of the sustained release metaprolol succinate.

**METHODOLOGY**

- **DRUG PROFILE**

- **METAPROLOL SUCCINATE:-**

Metoprolol Succinate is the succinate salt form of metoprolol, a cardioselective competitive beta-1 adrenergic receptor antagonist with antihypertensive properties and devoid of intrinsic sympathomimetic activity. Metoprolol succinate antagonizes beta 1-adrenergic receptors in the myocardium, thereby reducing the rate and force of myocardial contraction, and consequently a diminished cardiac output.

**Empirical formula:** C19H31NO7
**Melting point:** 120-122º C
**Half-life:** 4 to 5 h
**Color:** White crystalline powder
**Odor:** Odorless
**Solubility:** Soluble in water and alcohol, Slightly soluble in chloroform, Insoluble in ether, benzene, ethyl acetate.

- **PHARMACOKINETICS**

**Absorption**

Metapralol is rapidly and completely absorbed; with peak plasma levels achieved approximately 3–4 h after ingestion. Co-administration with food appears to enhance bioavailability. Despite complete absorption, metaprolol has a variable bioavailability due to extensive first-pass metabolism. Hepatic impairment will therefore increase its bioavailability.

**Distribution**

Metaprolol is a highly lipophilic drug achieving high concentrations in the brain.
Protein Binding is approximately 95 %.

## POLYMER PROFILE

- **ETHYL CELLULOSE**

**Synonym:** Aqua coat; Aqualon; E462; Ethocel; Surelease.
**Functional Category:** Coating agent; tablet binder; tablet filler; viscosity increasing agent.

- **POLYETHYLENE GLYCOL**

**Synonyms:** Carbowax; Carbowax Sentry; Lipoxol; Lutrol E; macrogola; PEG; Pluriol E; polyoxyethylene glycol.
**Chemical Name:** α-Hydro-ω-hydroxypoly(oxy-1,2-ethanediyl)
**Functional Category:** Ointment base; plasticizer; solvent; suppository base; tablet and capsule lubricant. Applications in pharmaceutical formulation or technology

- **STEARIC ACID**

**Synonyms:** Acidum stearicum; Cetylacetic acid; Dervacid; E570; Edenor; Emersol; 1-heptadecanecarboxylic acid; Hystrene; Industrene; Kortacid 1895; Pearl Steric; Pristerene; stereophanic acid; Tegostearic.
**Functional Category:** Emulsifying agent; solubilizing agent; tablet and capsule lubricant.

## ANALYTICAL METHOD DEVELOPMENT

- **Determination of $\lambda_{max}$:** Most drugs absorb light in the ultraviolet wavelengths (200-400 nm), since they are generally aromatic or contain double bonds. The solution containing 12 µg/ml of Metaprolol succinate in 0.1N HCl was scanned over the range of 200 to 400 nm against 0.1N HCl as blank respectively using double beam UV spectrophotometer. The maximum peak obtained in the graph was considered as $\lambda_{max}$ for the pure drug.

- **FTIR Study:** The drug and polymer interactions were studied by Fourier Transform Infrared Spectroscopy by KBr disc method. FTIR spectra help to confirm the identity of the drug and to detect the interaction of the drug with the carriers.

- **Differential Scanning Calorimetry:** The DSC analysis of pure drug, polymer and the physical mixture of both drug and polymer were carried out to evaluate any possible interaction between drug and polymers using Mettler-7 DSC, Germany.

## FORMULATION DEVELOPMENT

### PREPARATION OF METAPROLOL SUCCINATE ETHYL CELLULOSE MICROSPHERES

- Microspheres containing metaprolol succinate as core material were prepared by *non-aqueous solvent evaporation* technique.
- Drug and Ethyl cellulose in varying ratios (1:1 to 1:5) were weighed and dissolved in 3:2 ratio of acetone: ethanol with agitation to form uniform drug-polymer dispersion.
- This dispersion was slowly introduced into the medium consisting of 100 ml heavy liquid paraffin while being stirred at 1000 rpm by a mechanical stirrer.
- Liquid paraffin was decanted and the microspheres were collected by filtration through Buchner funnel.
- The microspheres were washed thrice with petroleum ether until free from oil and dried at room temperature overnight and stored in desiccator.

### FORMULATION OF SUSTAINED RELEASE METAPROLOL SUCCINATE SUPPOSITORIES

**MOLD CALIBRATION:**

The blank suppositories are prepared using a clean, dries and lubricated mold, of various bases, which are weighed. In each case the average weight was taken as the true capacity of that particular mold.

### CHARACTERIZATION OF PRPEPARED MICROSPHERE FORMULATIONS

**YIELD OF MICROSPHERES:** The percentage yield of microspheres was calculated by the following formula

$$\% \text{ yield} = \frac{\text{Actual weight of Product}}{\text{Total weight of drug and excipient}} \times 100$$

- **MICROMERITIC STUDIES:** The microspheres were characterized for their micromeritic properties such as particle size and shape. All the analysis was carried out in triplicate.
- **Particle size and shape:** The surface morphology and internal structure of the products were observed by, Scanning electron microscopy.

- **Optical microscopy**

The microspheres were observed under 100X magnification in an optical microscope (Olympis LITE Image) and an average of 100 particles were counted. Finally average mean diameters were obtained.

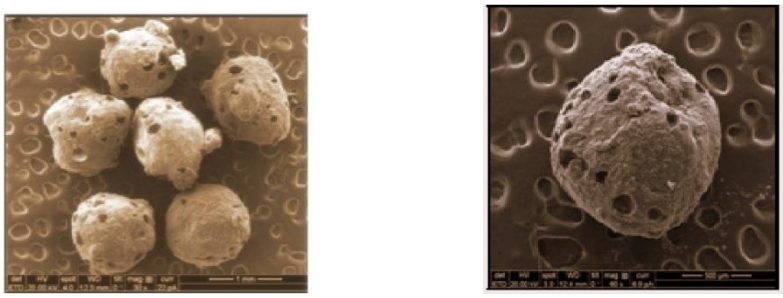

**Fig:- Optical Microscopy of Microspheres**

- **DRUG ENTRAPMENT EFFICIENCY:** Accurately weighed quantity of microspheres equivalent to 50 mg of metaprolol succinate was taken in 50 ml volumetric flask and dissolved in 25 ml of 0.1N HCl using sonication for 5 min and the volume was made up to 50 ml with 0.1N HCl. The resulting solution was diluted suitably with 0.1N HCl and filtered through Whatmann filter paper. The absorbance of the resulting solution was measured at 292 nm, using 0.1N HCl as blank. All the analysis was carried out in triplicate.
- ***In-Vitro* drug release studies**
- *In-vitro* drug release was studied using dissolution test apparatus USP XXIII type I method (rotating basket method). The drug loaded microspheres equivalent to 50 mg of metaprolol succinate are introduced into 900 ml of pH 7.4 phosphate buffer, which was maintained at 37±0.5 $^0$C and stirred at 100 rpm. 2 ml of aliquot was withdrawn at regular predetermined intervals and sink conditions were maintained throughout the study by replacing equal volume of fresh dissolution medium. The samples were diluted to 25 ml with 0.1N HCl and analyzed spectrophotometrically at 292 nm using 0.1N HCl as blank.

**CHARACTERIZATION OF FORMULATED METAPROLOL SUCCINATE SUPPOSITORIES**

- **SURFACE AND APPEARANCE:** Suppositories were inspected for physical appearance on its outer surface for smoothness or gritty conditions
- **UNIFORMITY OF MIX:** Formulated suppositories are inspected for uniformity of mix by slicing longitudinally. Checked for the uniformity of drug, microspheres and also base.
- **WEIGHT VARIATION (IP):** Weigh individually 20 suppositories taken at random and determined the average weight. The percentage deviation from the mean was subsequently determined. Not more than 2 of the individual weight deviate from the average weight by > 5 % and none deviate by > 10 %.
- **MECHANICAL STRENGTH/ HARDNESS TEST:** The hardness of suppository formulation was tested using a tablet crushing strength tester. It signifies the mechanical force necessary to break a suppository and denotes whether it is brittle or elastic. The mechanical strength should not be less than 2 kg/cm$^2$.
- **DISINTEGRATION TIME:** The disintegration times were recorded utilizing USP tablet disintegration apparatus. The suppository was completely immersed in a constant water bath (37 ºC) and the time taken for the suppository to melt or disperse in phosphate buffer pH 7.4 was recorded.

**RESULTS**

**ANALYTICAL METHOD :**

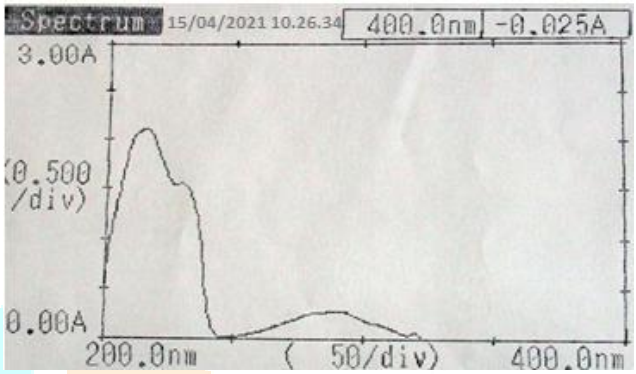


**Fig.** Spectrum showing the λmax of Metaprolol Succinate in 0.1N HCL

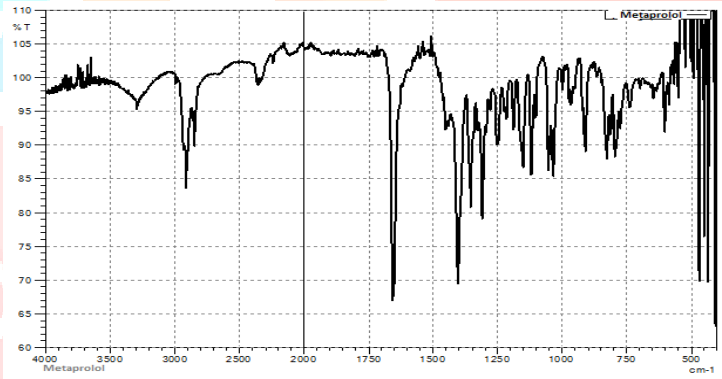


**Fig**. IR spectrum of pure drug Metaprolol succinate

**Results of DSC studies**

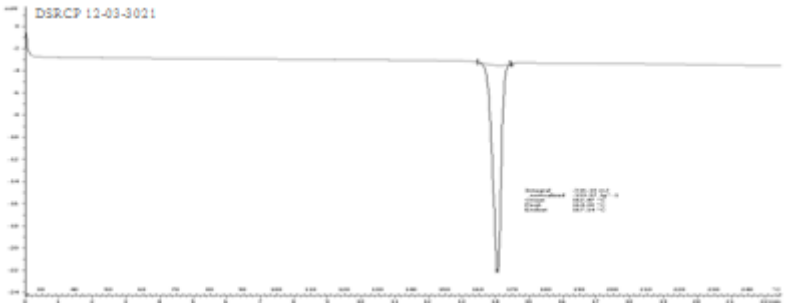


**Fig.** DSC thermogram of pure drug Metaprolol Succinate

**In-vitro drug release profile of metaprolol succinate microspheres in 0.1N HCl**

| Formulation code | Softening temperature ± S.D (°C) | Liquefaction temperature ± S.D ( °C) | Liquefaction time (min) |
|---|---|---|---|
| MP | 41 ± 0.891 | 52 ± 1.154 | 49 |

| Time (h) | Absorbance | Conc. (µg/ml) | Amt. in 25 ml (µg) | Amt. in 900 ml (mg) | DR (%) |
|---|---|---|---|---|---|
| 1 | 0.076 | 3.0 | 75 | 33.75 | 68.50 |
| 2 | 0.085 | 3.2 | 80 | 36.00 | 73.15 |
| 3 | 0.098 | 3.8 | 95 | 42.75 | 84.81 |
| 4 | 0.100 | 4.0 | 100 | 45.00 | 90.50 |
| 5 | 0.104 | 4.0 | 100 | 45.00 | 90.70 |
| 6 | 0.107 | 4.2 | 105 | 47.25 | 95.40 |
| 7 | 0.110 | 4.4 | 110 | 49.50 | 100.10 |

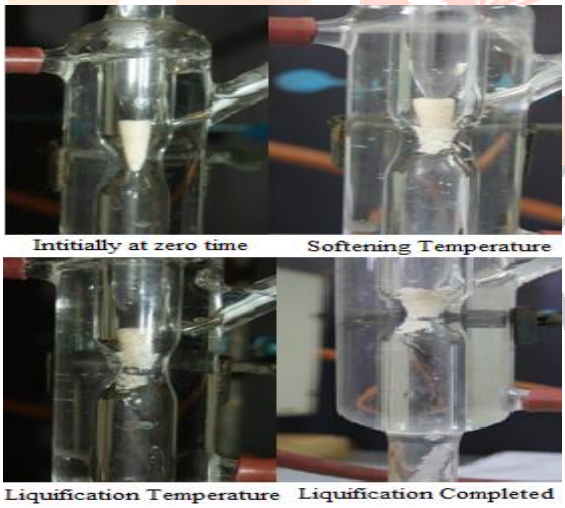


**Fig. Explaining about the sequence of softening and liquefaction temperature.**

**RESULTS OF *IN-VITRO* DRUG RELEASE STUDIES**

| Time (h) | Absorbance | Conc. (µg/ml) | Amt. in 25 ml (µg) | Amt. in 900 ml (mg) | DR (%) |
|---|---|---|---|---|---|
| 1 | 0.042 | 1.69 | 41.00 | 18.000 | 38.00 |
| 2 | 0.063 | 2.50 | 62.50 | 28.125 | 56.26 |
| 3 | 0.088 | 3.54 | 88.50 | 39.825 | 80.78 |
| 4 | 0.117 | 4.71 | 117.75 | 52.987 | 106.28 |

***In-vitro* drug release profile of MP suppositories**

**CONCLUSION**

The microspheres of Metaprolol succinate, an antihypertensive drug had been successfully developed with ethyl cellulose as a coating polymer to improve the bioavailability with prolonged drug release for 8 h. The prime importance of developing the microspheres was to formulate in to sustained release suppositories to provide the sustained release of the drug, as its half life is very short. From the results obtained from the experimental studies, it can be concluded that;

- FTIR spectra of physical mixture of drug and the polymers showed no significant shifting of principle peaks. Hence the drug is compatible with the polymers used.
- Microspheres of Metaprolol succinate with biocompatible polymer like ethyl cellulose were successfully prepared by solvent evaporation method.
- The particle size analysis revealed that the size of the prepared microspheres was found to increase with increase in the concentration of the polymer.
- From the SEM studies it was found that the microspheres were smooth and spherical in shape with a porous outer surface.
- The percentage drug entrapment efficiency was found to be in the range of 97.5 % -101.8 %.
- *In-vitro* drug release studies showed that the drug release was prolonged up to 8 h.

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