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Formulation and Evaluation of Injectable In-Situ Gelling Matrix System for Controlled Drug Release

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ABSTRACT

The aim of the present study was to formulate injectable in situ gel matrix containing metoprolol succinate by cold method, using the thermosensitive polymer Pluronic F 127 (20%) together with carbopol 934P, HPMC and SCMC. The drug polymer compatibility was studied by FTIR. The formulations were evaluated for clarity, sterility, gelation temperature, gelation time, viscosity, drug content and drug release. Gelation temperature for the formulations was found in between 34-41ºC with gelation time varying from 1-6 mins. The drug content for the prepared formulations was found to be 97 to 100%. The non-irritant nature of the developed formulation was confirmed by the HET-CAM test. In vivo appearance studies were conducted on dead calf ear. The optimized formulation C12 had viscosity suitable for injecting, formulation C12 showed controlled drug release and it was found to be 99.53% upto 12 h. The stability studies performed on C12 showed no single change in physical appearance and drug release. It was concluded that the drug release performance was greatly affected by the polymer used in the preparation of injectable in situ gel.

Keywords: *Metoprolol succinate, injectable in situ gel, intramuscular route, HET-CAM, thermosensitive.*

1. INTRODUCTION

There are many possible routes of drug administration such as oral, transdermal and parenteral. Oral route is not effective because of first pass metabolism [1-2]. Transdermal drug delivery has advantage over oral route which is first-pass effect. But main problem with drug penetration in transdermal drug delivery is stratum corneum [3]. Parenteral route has more advantages over both oral & transdermal routes. In parenteral drug delivery system, drug reaches to systemic circulation with rapid absorption. But main problem with parenteral route is rapid decline of drug concentration in systemic circulation. To overcome this problem, Extended-release & Controlled-release drug delivery systems have been developed.

The development of injectable drug delivery system has received considerable attention over the past few years. The reason to receive attention is advantages of new injectable drug delivery system. These advantages are ease of application, site-specific action, prolonged drug release, decreased drug dose and better patient compliance & comfort. Modified Release injectable delivery systems such as microspheres, liposomes, gels, suspensions, in situ forming implants, lipophilic solutions, solid lipid nanoparticles (SLN) and drug eluting stents [4].

In recent years, the development of *in situ* gel systems has received a considerable attention as polymeric drug delivery systems.The importance of *in situ* forming matrix systems is related to several advantages such as, for instance, easy application, use of non-toxic carriers, simple and economical elaboration, prolonged residence time and controlled drug release. Moreover these systems avoid painful surgical procedures to insert solid implants [5-7]. The *in situ* forming gel systems are designed such that they are fluid prior to injection. Once injected, the formulation responds to a change in the environment to give a

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high viscosity or solid depot at the injection site. The most studied thermosensitive polymers are the pluronics which are poly (ethylene oxide)-poly(propylene oxide)-poly(ethylene oxide) block copolymers [8]. Those polymers exist as a mobile viscous liquid at reduced temperatures but form a rigid semisolid gel network with an increase in temperature. Unfortunately, pluronic gels are obtained at high polymer concentrations only (between 20 and 30%) and have been shown to erode rapidly [9].

The aim of this study is to prepare biodegradable hydrogels that are rapidly formed in situ under physiological conditions. The hydrogels should be based on biocompatible materials and should degrade into biocompatible products [10]. The hydrogel degradation time should be well-controlled by the choice of the base polymers and their concentration, thus allowing design of a hydrogel for a particular application. The hydrogels should have good mechanical properties to withstand the forces which act upon the gel after its formation in the body[11-13]. Furthermore, the hydrogels should allow easy incorporation of bioactive moieties, to obtain biomimetic hydrogels.

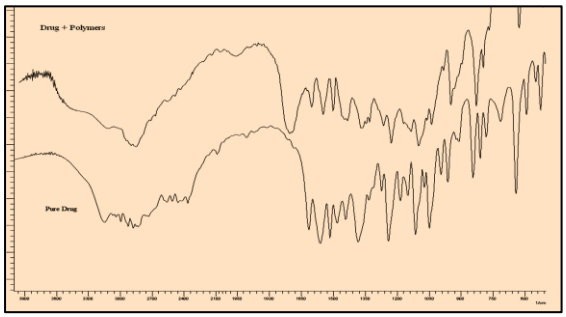

Figure 1: FTIR spectra of metoprolol succinate pure drug and drug with polymers.

2. EXPERIMENTAL

2.1. Materials And Equipments

Drug Metoprolol succinate was purchased from Astra Zeneca Pvt. Ltd, hydroxyl propyl methyl cellulose (HPMC) , sodium CMC, pluronic F 127NF, carbopol 934 were obtained from Sigma Aldrich, USA. Equipments used were digital pH meter (Elico-LI120pH (type 003) Hyderabad), orbital shaking incubator (Remi, CIS 24 BL, Mumbai), FTIR spectrophotometer (FTIR- 8400-S, Shimadzu, Japan), UV-Visible Spectrophotometer (Shimadzu-1800 S, Japan)

2.2 Methods

2.2.1. Preparation of injectable in situ gels, containing metoprolol succinate.

Injectable *in situ* gel was prepared by cold method. Metoprolol succinate and polymers except pluronic F127 were completely dispersed in distilled water with continuous agitation at room temperature and cooled down to 4ºC. Pluronic F127 was then slowly added to the solution with continuous agitation. The resulting solution was then left at 4ºC until a clear solution was obtained.

2.2.2. Biocompatibility test (HET-CAM)

The Hen's Egg Test- Chorio-allointoic Membrane is used to determine the potential irritancy using an alternative to the Draize methodology [14]. A fertile, 10 day old, white Leghorn egg is used in the HET-CAM as an alternative to the Draize Rabbit Eye Test. The results are tabulated in Table 1.

2.2.3. Sol-Gel transition temperature

The gelation temperature was estimated by heating the solution in a thin walled tube with gentle shaking until it got converted to gel. Gel formation was taken as the point where there was no flow when the test tube was overturned.

2.2.4. Gelation time

The gelation time was determined by test tube inverting method. Solution was taken in a thin walled tube and kept at the respective gelation temperature on a water bath. The test tube was taken out every 1 min and inverted to observe the state of the sample. The gelation time was determined by flow or no-flow criterion with the test tube inverted.

2.2.5. Determination of drug content

The prepared formulations were analyzed for drug content by taking 1 mL of gel in 10 mL volumetric flask and the volume was adjusted with pH 6.8 phosphate buffers. From the above solution 0.1 mL was pipetted out in a 10 mL volumetric flask and volume was adjusted with pH 6.8 phosphate buffer. Absorbance was measured at 274.0 nm.

Table 1. Irritancy Potential of Test Materials used in the HET-CAM Tests for Non-Aqueous Solvents and Polymers under Consideration

Test material		Average Score	Irritancy Potential
Non Aqueous solvent	Ethanol	12	Strong
	PEG 400	5	Moderate
	Glycerine	5	Moderate
	Propylene glycol	3.5	Slight
Polymer	Pluronic F 127	0	Practically None
	Sodium CMC	0	Practically None
	HPMC	0	Practically None
	Carbopol 934	0	Practically None

2.2.6. In vitro drug release study

The *in vitro* release study of metoprolol succinate from Injectable *in situ* gels was carried out at 37ºC and with the stirring rate of 100rpm using an orbital shaking incubator. Formulation equivalent to 50mg of drug was placed into a 50mL beaker and incubated at 37ºC to form gel. Then 100mL of pH 6.8 phosphate buffer was added to the beaker and the medium was stirred at 100rpm. At predetermined time interval, 1mL of the medium was collected and replenished by 1mL of fresh medium. The amount of released metoprolol succinate was analyzed at 274 nm by UV spectrophotometer.

3. RESULTS AND DISCUSSIONS

3.1. Drug-Excipients compatibility studies by FTIR

Metoprolol succinate pure drug and polymers were subjected for FTIR spectroscopic analysis for compatibility studies and to ascertain whether there was any chemical interaction between the drug and the polymers used. The IR spectra of pure metoprolol succinate and polymers was found to be identical and presented Fig 1. The characteristic IR absorption peaks of metoprolol succinate at 2934 cm^{-1} (C-H stretch), 1242 cm^{-1} (Aromatic ether), 1189 cm^{-1} (Isopropyl group), 1115 cm^{-1} (ether), 845 cm^{-1} (1,4-disubstituted benzene) were present. FTIR spectra of the formulation with polymers showed all the metoprolol succinate characteristics absorption bands suggesting there is no chemical interactions between the drug and polymers used in the formulation (Figure 1).

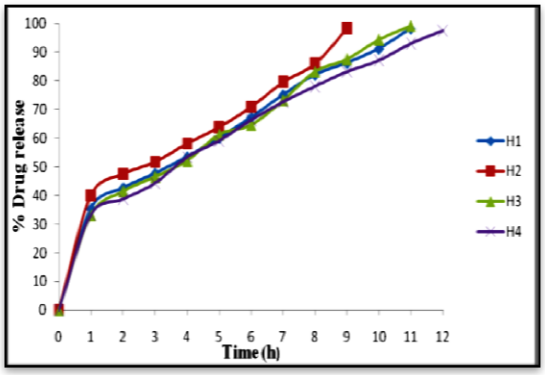

Figure 2: Cumulative % drug release from formulations H1-H4.

3.2. Gelation temperature

During preliminary work it was observed that the formulation containing less than 20 % w/w PF-127 did not gel over the temperature range tested (up to 50ºC) and that increasing PF-127 concentration, by increments of 2-3%, the gelation temperature of solution was decreased. A modulation of the gelation temperature to reach the desired range (30-37ºC) could be achieved through the use of a combination of the pluronic F127 with polymers (Figure 3). The addition of polymers lowered the gelation temperature of all formulations. The impact of polymers on the gelation temperature was found to depend on their nature and concentrations. Increase in the concentration of polymers decreased the gelation temperature.

3.3. Drug release studies

The in vitro drug release studies were carried out for all formulations in 6.8 pH. The *in vitro* drug release of metoprolol succinate formulations are reported in Figure 2. From the *in vitro* drug release studies it was observed that the concentration of polymers affected the drug release from the formulations. The addition of polymers like SCMC, carbopol and HPMC retarded the drug release from the formulations. The retardation of drug release increased with increase in the concentration of polymers.

From Table 1 it can be seen that of all the non-aqueous solvents tested, ethanol gave strong reaction according to the scoring system. In contrast, glycerin and PEG 400 produced moderate effects. Propylene glycol produced a very weak effect. None of the solid polymers used elicited any immunological response, polymers which were used in the formulations were tested and it was found that no single polymer had irritant effect on the embryo and there was no sign of lysis, haemorrhage and coagulation [15].

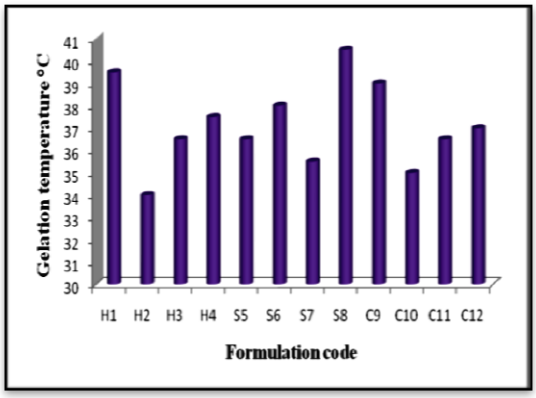

Figure 3: Gelation temperatures for formulations H1-C12.

4. CONCLUSION

From the study, it can be concluded that the temperature sensitive injectable *in situ* gel can be used to achieve controlled drug release. Formulation of aqueous phase into which both hydrophilic polymer and drug incorporation was successful. All the gels formulated had gelation temperature well below body temperature thus they readily became gels, making them ideally suited to function as drug depot. The research work proves

the practical demonstration of the conceptual idea of IGSM system and all the ingredients used were biocompatible. Through the research work we have successfully assessed the resultant suspensions for their physical stability. Thus the developed dosage form was found easy to administer, simple, comfortable, with increased patient compliance.

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