ASSESSMENT OF MICROPARTICULATE DRUG DELIVERY SYSTEM OF PROPRANOLOL HYDROCHLORIDE PREPARED BY MULTIPLE SOLVENT EMULSION TECHNIQUE

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ABSTRACT
Objective: In the current work the sustained release micro particles of an antihypertensive drug propranolol hydrochloride was prepared due to its short half life and high water solubility.
Method: The sustained release micro particles of propranolol hydrochloride with ethyl cellulose of different ratios 1:1, 1:2, 1:3 and 1:4 (wt/wt) was prepared using different surfactants like polyvinyl alcohol and Tween 80 through the W/O/W double emulsion solvent evaporation method.
Results: The effect of polymer and surfactant concentration on the particle size, encapsulation efficiency and the drug release rate were studied. The obtained particles were characterized by Motic microscope, FE-SEM and FT-IR. In vitro release study was carried out using eight station dissolution test apparatus and UV-visible spectrophotometer at 289 nm. This study revealed that the maximum encapsulation efficiency was 78.22±0.59 %, no drug-polymer interaction and drug released from the microparticles was up to 12 h.
Conclusion: From obtained results it was concluded that this dosage form maintained the drug level in therapeutic window which may help to minimize the side effects, number of dosage and improve patient compliance.

Keywords: Propranolol hydrochloride, Ethylcellulose, Encapsulation efficiency, Sustained Release, Drug Release kinetics.

INTRODUCTION
Microencapsulation is defined as the application of an emaciated coating of individual core materials that have a random particle size range from 1 to 1000 μm [1]. Propranolol hydrochloride [1-(isopropylamino)-3-(1-naphthoyl) -2-propanol hydrochloride] is a nonselective beta-adrenergic receptor blocking agent with a biological half life of about 3-5 hours [2]. Propranolol hydrochloride is commercially available in the form of conventional formulations with dose 10 to 40 mg in 3-4 times daily. It is also indicated in the long term management of patients with angina pectoris. However, Propranolol hydrochloride usefulness is limited due to its short half-life. Hence, it requires three-four times a day dosing which produce the patient’s noncompliance. To reduce the frequency of dose administration and to improve patient compliance, a controlled/sustained release formulation is popular [3]. Microparticles also offer advantages such as limiting fluctuate within a therapeutic range, reduction in side effects, decreased dose frequency and hence improved patient compliance [4,5]. Ethylcellulose, a non-biodegradable and biocompatible polymer is one of the extensively studied encapsulating materials for the controlled release of pharmaceuticals [6] was selected as the retardant material for Propranolol hydrochloride. Several researchers have investigated the utilization of ethylcellulose as a polymer to microencapsulate a drug by coacervation phase separation technique, emulsion solvent evaporation technique and spherical crystallization technique [7]. Generally, the solvent evaporation method is inappropriate for the microencapsulation of water soluble drugs as the associated efficiency of drug entrapment within the microparticles is low. This is primarily due to drug loss from the polymeric phase to the aqueous phase prior to solidification of the microparticles [8,9]. The purpose of the present work was to prepare and evaluate oral sustained release micro particulate drug delivery system of Propranolol hydrochloride using ethyl cellulose by W/O/W double emulsion solvent evaporation method with high entrapment capacity and extended release. Various parameters such as a drug-polymer ratio, surfactant concentration were optimized to maximize the entrapment. These micro particles were evaluated for encapsulation efficiency, drug content and in vitro drug release. Drug-polymer interactions in the solid state were studied by Fourier transform infrared spectroscopy (FT-IR), the size distribution and surface morphology were evaluated by Motic microscope and FE-SEM respectively.

MATERIALS AND METHOD
Materials
Propranolol hydrochloride was gifted from Micro Advanced Research Center, Pvt. Ltd., Bangalore and Ethyl Cellulose was received as a gift sample from Colorcon Asia Pvt. Ltd., Goa. Gelatin, extra pure was purchased from Himedia Laboratories Pvt. Ltd., Mumbai. PVA (MW 1, 25,000), Tween 80, Dichloromethane and n-hexane were procured from Merck Specialties Pvt. Ltd., Mumbai. Dissolution medium was prepared by using triple distilled water filtered with 0.22 μm membrane filter.

Method
Preparation of microparticles
Weighed amount of ethyl cellulose was dissolved in dichloromethane. Deionized aqueous drug solution was added in above polymeric organic solution to preparing a primary emulsion (W/O) with constant stirring at 500 rpm for 15 min. Gelatin (% w/v) was added in aqueous solution of drug to improve the viscosity of the solution. This primary emulsion was added drop by drop to the aqueous solution of pH 12 containing polyvinyl alcohol (% w/v) or Tween 80 (% w/v) as a surfactant with 1000 rpm constant stirring for 2 h using a lab stirrer (Remi Elektrotechnik Ltd. Mumbai). The n-hexane was added to harden the formed microparticles and the stirring was continued for further 1 h. The resulting microparticles were collected by filtration. The product was then dried at room temperature for 24 h and stored in desiccators for 74 h. All batches were prepared in triplicate [10, 11].

Particle size measurement
Motic microscope (B1 series, Motic, China) was used to determine the size microparticles. A drop of suspended microparticles was spread on a glass slide and observed at 40x and 100x resolution power using a microscope installed with a digital camera and image analysis software. Three areas on the slide containing about 100 particles were randomly snapped and used to determined the average particle size range [12].

Determination of encapsulation efficiency
Weighed quantities of respective samples were added in dichloromethane to dissolve polymer and then add the required
volume of double distilled water to extract the drug in it and precipitated the polymer. Finally this drug containing dichloromethane-aqueous solution was stirred until complete evaporation of dichloromethane. The remained aqueous solution of the drug was filtered through 0.45 μm pore size Whatman filter paper and analyzed spectrophotometrically at wavelength 289 nm using UV-visible spectrophotometer (UV-1800 Shimadzu Co. Ltd., Japan). The drug encapsulation efficiency was calculated using following equation 1:

\[ \text{EE} \% = \frac{D_a \times 100}{D_b} \quad \text{(1)} \]

Where D, is the theoretical amount of drug loaded to polymer solution and Db, is the practical amount of drug encapsulated in the prepared microparticles [13]. Determinations of encapsulation efficiency were run in triplicate.

**Surface morphology**

The shape and surface properties of microparticles were investigated by using Field Emission-Scanning Electron Microscopy (S4800, Hitachi, Japan). An appropriate sample was mounted on stub, using double sided adhesive carbon tapes and observed for morphology at acceleration voltage.

**Fourier transform infrared spectroscopy**

Propranolol hydrochloride, Ethyl cellulose and drug loaded microparticles were mixed with KBr and pressed to disk. Infrared spectra of the samples were scanned in the range from 400 to 4000 cm⁻¹ and recorded on a Fourier transform infrared spectrometer (Shimadzu Co. Ltd., Singapore) to study the possible interaction between propranolol hydrochloride and ethyl cellulose. All measurements were taken at room temperature. The spectra of water and KBr were subtracted from the sample spectrum and the procedure was done under nitrogen gas to prevent humidity interference [14].

**In-vitro drug release study**

*In vitro* dissolution studies were performed using USP Type II dissolution test apparatus (Paddle) at 75 rpm (Electrolab, India). The dissolution medium was used as double distilled deionized water and KBr were subtracted from the sample spectrum and the measurements were taken at room temperature. The spectra of water and KBr were subtracted from the sample spectrum and the procedure was done under nitrogen gas to prevent humidity interference. The absorbance of the withdrawn samples was measured at 289 nm against blanks. The concentration of Propranolol hydrochloride in test samples was corrected and calculated using a regression equation of the calibration curve. The dissolution studies were carried out in triplicate and the mean values were plotted as percentage cumulative drug release versus time.

**In-vitro release kinetics**

The *in vitro* release profiles were fitted to zero order, first order, Higuchi square root and Hixon-Crowell model. Regression coefficients (R²) were determined from the slope of the all obtained plots. Mechanism of drug release according to Korsmeyer-Peppas model was evaluated by fitted first 60% of drug release in its equation and release exponent "n" was calculated from plot $\log$ cumulative % drug release vs $\log$ time [15].

**RESULTS AND DISCUSSION**

In this work the effect of drug-polymer ratio and surfactant concentrations on particle size, entrapment efficiency and release pattern of propranolol hydrochloride from ethyl cellulose microparticles prepared by solvent evaporation method was examined. Propranolol was highly soluble in water therefore to reduce its solubility in external phase the pH of the external aqueous solution was increased up to 12. Due to decreased in solubility of Propranolol HCl in external water phase the drug loss was reduced and enhance the encapsulation efficiency [16]. Gelatin was used as an emulsifier and viscosity enhancer of the primary emulsion. Ethyl cellulose, also acts as a self emulsifier to stabilize this emulsion. Dichloromethane is less soluble and having more interfacial tension with water, therefore formed stable multiple emulsion (W/O/W). The emulsion droplets containing propranolol hydrochloride get transformed into solid state due to ethyl cellulose hydrophobic property and dichloromethane evaporation during stirring. This evaporation rate was maintained by stirring at 1000 rpm and 25 °C temperature. Table 1 shows the influence of drug-polymer ratio, surfactant and its concentration on particle size, percentage yield and encapsulation efficiency of different formulation trials.

**Table 1: Effect of content concentration variables on Propranolol HCl loaded microparticles.**

<table>
<thead>
<tr>
<th>Formulation Code</th>
<th>Drug:Polymer Ratio</th>
<th>Surfactant concentration</th>
<th>Yield (%)</th>
<th>Encapsulation Efficiency</th>
<th>Particle Size (µm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>1:1</td>
<td>0.2% PVA</td>
<td>72.46±0.42</td>
<td>48.56±0.41</td>
<td>100-150</td>
</tr>
<tr>
<td>F2</td>
<td>1:2</td>
<td>0.2% PVA</td>
<td>75.46±0.43</td>
<td>63.75±0.31</td>
<td>150-200</td>
</tr>
<tr>
<td>F3</td>
<td>1:3</td>
<td>0.2% PVA</td>
<td>78.44±0.43</td>
<td>66.79±0.49</td>
<td>170-240</td>
</tr>
<tr>
<td>F4</td>
<td>1:4</td>
<td>0.2% PVA</td>
<td>78.41±0.57</td>
<td>73.74±0.44</td>
<td>230-300</td>
</tr>
<tr>
<td>F5</td>
<td>1:1</td>
<td>0.5% PVA</td>
<td>69.57±0.60</td>
<td>52.61±0.43</td>
<td>50-100</td>
</tr>
<tr>
<td>F6</td>
<td>1:2</td>
<td>0.5% PVA</td>
<td>77.5±0.52</td>
<td>66.72±0.51</td>
<td>100-150</td>
</tr>
<tr>
<td>F7</td>
<td>1:3</td>
<td>0.5% PVA</td>
<td>82.56±0.53</td>
<td>72.04±0.73</td>
<td>125-200</td>
</tr>
<tr>
<td>F8</td>
<td>1:4</td>
<td>0.5% PVA</td>
<td>82.83±0.65</td>
<td>78.22±0.59</td>
<td>200-250</td>
</tr>
<tr>
<td>F9</td>
<td>1:4</td>
<td>0.2% T80</td>
<td>68.60±0.73</td>
<td>66.22±0.79</td>
<td>280-400</td>
</tr>
<tr>
<td>F10</td>
<td>1:4</td>
<td>0.5% T80</td>
<td>79.48±0.51</td>
<td>69.99±0.64</td>
<td>250-300</td>
</tr>
</tbody>
</table>

**Fig. 1:** (a) Motic microscope image and (b) Surface morphology of recovered microparticles.
The obtained results concluded that the particle sizes were directly proportional to ethyl cellulose concentration may be due to increased in viscosity of the internal phase [15], and inversely with the surfactant concentration may be due to the formation of new surfaces for the small emulsion globules [17]. The Motic microscope image is shown in Fig. 1a. Encapsulation efficiency was directly proportional to both the polymer and surfactant concentration. Because the polymer concentration may help to enhance the holding capacity for drug and surfactant decreased the interfacial tension between aqueous drug solution and polymeric organic solution [18].

The particles formulated by Tween 80 were less encapsulated and more size than the formulations prepared with polyvinyl alcohol because PVA has a better propensity to drift towards the surface of microparticles and stabilized it more efficiently. All recovered microparticles were spherical in shape and slightly porous in nature (Fig. 1b). The porous structure was responsible for the sustained release of drugs.

Drug polymer interaction was determined by comparing the IR spectra of propranolol hydrochloride loaded ethyl cellulose microparticles with the IR spectrum of pure drug.

As shown in Figure 2, propranolol hydrochloride (A) gives peaks in IR spectrum nearby at 2965 cm−1 due to the presence of a secondary amine group, 3283 cm−1 due to the hydroxyl group (secondary), the aryl alkyl ether shows a stretching band at 1267.27 cm−1 and the peak at 798 cm−1 due to a substituted naphthalene [19]. Frequencies of functional groups of pure drug remained intact or overlapped by polymer in physical mixture containing polymer.

Hence, there was no major interaction between the drug and polymer used in the study.

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Hence, there was no major interaction between the drug and polymer used in the study.

Figure 3. Illustrate in vitro release of selected formulations in double distilled water, by representing the cumulative percentage of propranolol hydrochloride released with respect to the amount of drug encapsulated. The formulations were selected on the basis of higher encapsulation.

The formulation F8 was more sustained than formulation F4 because the maximum number of particles may extend the time to release the drug from F8 formulation. In F8 formulation the 0.5%, w/v PVA surfactant was used which gives small size particles than F4 formulation (0.2%, w/v PVA). So, the same weight of particles of both formulations (F4 and F8) contained maximum number of particles in F8 formulations. When we compared the effect of surfactant on dissolution profile it was concluded that the formulations prepared by using PVA was more sustained than Tween 80 used formulations. Because PVA may stabilize the surface more effectively and encapsulates the drug at the core of particles. At the end of 12 hours F8 formulation released 74.88±0.39, F4 released 95.92±0.65 and F10 released 101.04±0.52 per cent propranolol hydrochloride. Formulation F10 and F4 released 25.79±0.87 %, 23.02±0.56 % drug at the first hour, may be due to the drug present at the surface of particles. The burst release effect may be due to the adsorption of the drug on the surface of the particles or due to concentrating the drug at the surface of the
particles because insufficient concentration or ineffectual surfactant unable to encapsulate drug at the core of particles and drug moved towards the interface of both phases. In F10 formulation the reason was Tween 80 not efficiently stabilized the surface of the particles during solidification step and in F4 formulation the PVA was in deficient concentration to stabilize the surface of the particles. Therefore the drug was not encapsulated in the core of the particle but stabilized or adsorbed at the surface of the particles.

The release kinetics of all selected formulations explained in Table 2. The obtained results revealed that the most sustained F8 formulation best fitted in zero order kinetics. The zero order rates describe the system where the drug release rate is independent of time and its concentration within microparticles. In this kinetics drug releases constantly over time, minimizing side effects and maintained drug concentration within the therapeutic window. Therefore preserve the drug level in blood throughout the delivery period [20].

<table>
<thead>
<tr>
<th>Formulations</th>
<th>Zero Order</th>
<th>First Order</th>
<th>Higuchi</th>
<th>Hixon-Crowell</th>
<th>n-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>F4</td>
<td>0.9847</td>
<td>0.8947</td>
<td>0.9555</td>
<td>0.9664</td>
<td>1.7192</td>
</tr>
<tr>
<td>F8</td>
<td>0.9944</td>
<td>0.9740</td>
<td>0.9833</td>
<td>0.9880</td>
<td>1.3735</td>
</tr>
<tr>
<td>F10</td>
<td>0.9630</td>
<td>0.9290</td>
<td>0.9923</td>
<td>0.8613</td>
<td>1.7419</td>
</tr>
</tbody>
</table>

Formulations F4 and F10 follows Higuchi model. Many controlled release products are designed on the principle of implanting the drug in a porous matrix. The release of solid drug from a granular matrix involves the simultaneous penetration of surrounding liquid, dissolution of the drug, and leaching out of the drug through interstitial channels or pores. The volume and length of opening were also accounted in the diffusion theory [21]. The mechanism of drug release according to Korsmeyer-Peppas model results (n-value) revealed that the overall solute diffusion mechanism follows Super case-II transport. Case-II relaxation release is the drug transport mechanism associated with stresses, state transition in polymers which swell in water, polymer Disentanglement and erosion [22-24]. From all above evaluations it was concluded that the prepared micro particles were successfully sustained for 12 h.

**CONCLUSION**

From the above results it was concluded that propranolol hydrochloride was successfully encapsulated into ethylcellulose micro particles using W/O/W double emulsion solvent evaporation method. Polyvinyl alcohol was more suitable surfactant than Tween 80 with a concentration of 0.5%, w/w. The 1:4 drug-polymer ratio obtained highest encapsulation and sustained the Propranolol hydrochloride for 12 h. It follows zero order release kinetics therefore this dosage form maintain the drug level in therapeutic window which may help to minimize the side effects, number of dosage and improve patient compliance.

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