Formulation and In vitro Characterization of Novel Sustained Release Microballoons of Anti-hypertensive drug

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ABSTRACT

The objective of the current investigation is to reduce dosing frequency and improve patient compliance by designing and systematically evaluating sustained release microballoons of Propranolol hydrochloride. An anti-hypertensive drug, Propranolol hydrochloride, is delivered through the microparticulate system using ethyl cellulose as the controlled release polymer. Microballoons were developed by the emulsion solvent diffusion-evaporation technique by using the modified ethanol-dichloromethane co-solvent system. The polymer mixture of ethyl cellulose and Eudragit® S100 was used in different ratios (1:0, 1:1, 2:3, 1:4 and 0:1) to formulate batches F1 to F5. The resulting microballoons were evaluated for particle size, densities, flow properties, morphology, recovery yield, drug content, and in vitro drug release behavior. The formulated microballoons were discrete, spherical with relatively smooth surface, and with good flow properties. Among different formulations, the fabricated microballoons of batch F3 had shown the optimum percent drug encapsulation of microballoons and the sustained release of the Propranolol hydrochloride for about 12 h. Release pattern of Propranolol hydrochloride from microballoons of batch F3 followed Korsmeyers-peppas model and zero-order release kinetic model. The value of ‘n’ was found to be 0.960, which indicates that the drug release was followed by anomalous (non-fickian) diffusion. The data obtained thus suggest that a microparticulate system can be successfully designed for sustained delivery of Propranolol hydrochloride and to improve dosage form characteristics for easy formulation.

Keywords: Microballoons, Propranolol hydrochloride, ethyl cellulose, Eudragit® S100, emulsion solvent diffusion-evaporation technique.

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INTRODUCTION

The limitations of the most obvious and trusted drug delivery techniques, such as conventional drug delivery system (DDS), have been recognized for some time now, the most important limitation of them being the patient incompliance due to frequent medication. This limitation can be overcome by modifying existing DDS. An appropriately designed sustained release (SR) or controlled release DDS can be a major step toward solving the problem associated with conventional DDS [1,2] The SR DDS also have solutions for other limitations of the conventional DDS such as undesirable side effects due to fluctuating plasma drug level, inability to maintain adequate drug concentration in plasma for therapeutic effect, larger doses than those required by the cells have to be administered in order to achieve the therapeutic concentration, causing the undesirable, toxicological and immunological effects in non-target tissues.

Some drugs are readily absorbed from the GI tract, but easily eliminated from the body via excretion on account of its short half-life, requiring concomitant drug administration. Formulating an oral controlled release dosage form for these classes of drugs can be most beneficial as they release drug slowly in GIT and maintain constant drug levels in plasma for the extended period [3] SR dosage forms, based on multiparticulate systems have attracted much attention due to their several benefits in reducing risk of dose dumping, and local irritation as the individual units can pass randomly through the pylorus and distribute widely in the GI tract [4] producing more predictable drug release profiles.

Gastric emptying studies revealed that orally administered controlled release dosage forms are subjected to basically two complications: that of short gastric residence time and unpredictable gastric emptying rate (5). Propranolol is a nonselective beta-adrenergic receptor blocking agent possessing no other autonomic nervous system activity. It specifically competes with beta-adrenergic receptor agonist agents for available receptor sites. It is used as antihypertensive, antianginal, antiarrhythmic, and in treatment of migraine (6). Propranolol is reported to be of value in cardiovascular disorders, many of which are associated with central nervous system (7). Propranolol is highly lipophilic and almost completely absorbed after oral administration. However, it undergoes high first-pass metabolism by the liver, and on average, only about 25% of propranolol reaches the systemic circulation. Approximately 90% of circulating propranolol is bound to plasma proteins. Propranolol is extensively metabolized with most metabolites appearing in the urine.

Peak plasma concentrations occur about 1 to 4 h after an oral dose. $t_{1/2}$ of propranolol is 3–4 h (8). Thus, propranolol has relatively short half-life. Consecutively, for an optimum effect, the administration of propranolol hydrochloride as conventional tablets (with rapid disintegration and dissolution) must be carried out several times a day. Therapy with immediate release propranolol hydrochloride tablets typically requires 40–160 mg as daily dose given in three to four divided doses (9).

Presence of food increases the bioavailability. The secretory transporter P-glycoprotein (P-gp) located on the epithelium cells is responsible for low and variable bioavailability of various compounds such as propranolol. Although P-gp appears to be distributed throughout the gastrointestinal tract (GIT), its levels are higher in more distal regions (stomach < jejunum < colon). Absorption through P-glycoprotein prolongs the drug exposure to CYP3A4.
The objective of the present invention is to develop and evaluate a sustained release microparticulate system of Propranolol hydrochloride in order to extend the drug release for about 12 h of duration and. The microballoons were evaluated for particle size, densities, flow properties, morphology, recovery yield, drug content, and in vitro drug release behavior.

MATERIALS AND METHODS

Materials

The active ingredient Propranolol hydrochloride was obtained as gift sample from IPCA Lab., Mumbai. Eudragit® S100 was procured from Evonik Degussa India Pvt. Ltd., Mumbai and Ethyl cellulose from Central Drug House (P) Ltd., New Delhi. Polyvinyl alcohol (PVA) was obtained from Research Lab., Mumbai. Ethanol, n-butanol, and dichloromethane used were of analytical grade purchased from S.D. Fine chemicals Limited, Mumbai, India. Double distilled water was used throughout the study.

Methods

Formulation of sustained release Propranolol hydrochloride microballoons

Before initiating formulation of microballoons, compatibility of Propranolol hydrochloride with different excipients was studied using the techniques like compatibility test for solid dosage form on lab scale [10] and DSC testing. Excipients used in formulation batches were found to be compatible with Propranolol hydrochloride.

Formulation of drug-loaded microballoons was carried out by the emulsion solvent diffusion-evaporation method. The polymers ethyl cellulose and Eudragit® S100 were used in different ratios with formulation batches F1 to F5, these ratios were shown in Table 1. The preferred ratio of 1:19 of Propranolol hydrochloride to polymer was used for all batches. Initially a solvent mixture of ethanol: dichloromethane: n-butanol was prepared in the ratio of 8:5:2 considering their volumes. An accurately weighed quantity of Propranolol hydrochloride (50 mg) and enteric polymer Eudragit® S100 along with ethyl cellulose was co-dissolved at room temperature in a solvent mixture.

This solution was introduced into 1000 ml of 0.4% PVA aqueous solution at room temperature and dispersed to form emulsion at stirring rates of 200 rpm using a mechanical stirrer equipped with 4-blade propeller. Agitation provided by stirrer breaks the poured polymer solution to form an oil-in-water (O/W) type emulsion. This emulsion was then stirred for about 20 min at room temperature. After stirring, the solidified microballoons were recovered by filtration, washed with phosphate buffer (pH 7.4 ± 1) to remove all non-encapsulated drug, and further with distilled water to wash off PVA solution. Recovered microballoons were dried at 50°C for 12 h to remove solvents.

Evaluation of microballoons

Micromeritic properties

Microballoons were characterized for their micromeritic properties such as particle size, shape, bulk density, tapped density, compressibility index, Hausner’s ratio, and angle of repose. The size was measured using an optical microscope with the help of a calibrated ocular and stage micrometer, and the particle size range was obtained by measuring size of about 100 particles [11] Densities were derived as follows: An exact quantity ‘M’ of microballoons was taken and was placed into a measuring cylinder. Volume ‘V’ occupied by the microballoons was noted without disturbing the cylinder and bulk density was calculated using the following equation [11].

\[
\text{Bulk Density (P_b)} = \frac{M}{V}
\]
The tapping method was used to determine the tapped density in which the cylinder containing known amount (M) of microballoons was subjected to a fixed number of taps (approximately 100) until the bed of microballoons had reached the minimum. The final volume after tapping ‘V₀’ was recorded and the tap density was calculated by the following equation:

\[
\text{Tapped Density (Pₜ)} = \frac{M}{V₀}
\]

Angle of repose, Hausner ratio, and Carr index (% compressibility index) were determined to predict flowability. A higher Hausner ratio indicates greater cohesion between particles, while a high Carr index is indicative of the tendency to form bridges. Angle of repose [11] of the microballoons, is the maximum angle possible between the surface of the pile of microballoons and the horizontal plane, was obtained by fixed funnel method using the formula:

\[
\text{Angle of repose} (\theta) = \tan^{-1} \left( \frac{2h}{d} \right)
\]

Where, h is height and d is the diameter of the microballoons pile that is on a paper after making the microballoons flow from the glass funnel.

Hausner ration and Carr index were calculated using the formulae:

\[
\text{Carr index or } \% \text{ Compressibility index or } C = \left[ 1 - \frac{V₀}{V} \right] \times 100
\]

\[
\text{Hausner ratio} = \frac{100}{100 + C}
\]

Here, V and V₀ are the volumes of the sample before and after the standard tapping, respectively and C is Carr index.

**Morphology**

The surface topography, particle size, morphology, and internal cross-sectional structure of the microballoons were explored by using the technique like scanning electron microscopy (SEM) [12]. The ultra-structural features were analyzed by JEOL Scanning Electron Microscope (JSM-5400). Before the samples were analyzed, dry microballoons were placed on an electron microscope brass stub and coated with gold in an ion sputter. Pictures of microballoons were taken by random scanning of the stub.

Percent recovery yield and encapsulation efficiency of microballoons

Percent recovery yield [12] of microballoons was calculated from the formula:

\[
\% \text{ Yield} = \left( \frac{\text{Total weight of microballoons}}{\text{Total weight of drug/polymer and other materials if added}} \right) \times 100
\]

Encapsulation efficiency of the microballoons was evaluated by deriving percent drug encapsulation. The drug content of drug-loaded microballoons was determined by dispersing 100 mg of microballoons in 50 ml ethanol followed by agitation with a magnetic stirrer for about 30 min to dissolve the polymer and to extract the drug. After filtration through a 5 μm membrane filter, the drug concentration in the ethanol phase was determined by taking the absorbance of this solution spectrophotometrically at 290 nm. Eudragit® S100 and ethyl cellulose did not interfere under these conditions. Drug concentration was then calculated. Thus, the total drug encapsulated in total yielded microballoons from the procedure was calculated. It was expressed in percentage called as “Percent drug encapsulation” calculated as:

\[
\% \text{ Drug Entrapment} = \left( \frac{\text{Actual drug content}}{\text{Theoretical drug content}} \right) \times 100
\]

In vitro drug release studies and comparison of release profile with marketed formulation. The drug release rate from microballoons was determined using USP XXIV basket-type dissolution apparatus [13]. A weighed amount of microballoons equivalent to 5 mg drug was filled into a capsule (size 0) and placed in the basket. Dissolution medium used was 0.1 N HCl (pH 1.2, 900 ml) for first hour and maintained at 37 ± 0.5°C at a rotation speed of 100 rpm. Prefect sink
conditions prevailed during the drug release studies. 5 ml of sample was withdrawn at each 1 h interval; later this interval was extended to 2 h. Sample was then passed through a 5 µm membrane filter, and analyzed spectrophotometrically at 290 nm to determine the concentration of drug present in the dissolution medium. The initial volume of dissolution medium was maintained by adding 5 ml of fresh dissolution media after each withdrawal. The dissolution study was continued with using simulated intestinal fluid (pH 7.5 ± 1, 900 ml) for next 12 h. All experiments were conducted in triplicate.

RESULT AND DISCUSSION

Formation of microballoons

In the formulation of Propranolol hydrochloride microballoons, Eudragit® S100 and controlled release polymer ethyl cellulose polymers were used, and mixture of ethanol, dichloromethane, and n-butanol was chosen as the solvent system. After introduction of drug and polymer solution in the aqueous PVA solution, an oil-in-water emulsion gets formed. Agitation provided by stirrer breaks the poured polymer solution into discrete droplets, forming oil-in-water (O/W) type emulsion where polymer and drug were still in their solution form in organic solvent. In the emulsion, the organic dispersed phase was drug with polymer solution and aqueous dispersion phase was PVA solution. As the stirring continued, the ethanol and n-butanol started to diffuse out from organic phase to aqueous phase, co-precipitating the drug and polymer at the interface of emulsion droplet. This co-precipitation of drug and polymer resulted into a shell around droplet. Dichloromethane remained entrapped within the shell of the droplet.

Kawashima et al. [14] reported that when the diffusion rate of solvent from the organic phase emulsion droplet was too slow, microballoons coalesced together. In another study [15] he reported that when it was too fast; the solvent may diffuse into the aqueous phase before stable emulsion droplets were formed, causing the aggregation of embryonic microballoons droplets. Here, incorporation of n-butanol in the solvent system declined the rate of diffusion of solvent into outer phase to achieve the critical diffusion rate. Appropriate rate of solvent diffusion gave desired porosity and morphology of microballoons. The alteration in this diffusion rate was due to different molecular weight of solvents. Higher the molecular weight, more time it will take to diffuse. Slower diffusion rate of n-butanol than that of ethanol provides more time for diffusion and ultimately for droplet formation. It improved the yield and decreased the losses due to aggregation of non-spherical emulsion droplets caused by rapid solvent diffusion.

Apart from this, Lee et al. [16] had made another such effort in which ethanol was replaced by isopropanol to improve the method of microballoons preparation by controlling the diffusion rate of solvent, and the effect on the formation of microballoons was evaluated. In this study, it was also reported that yield of microballoons depended on the diffusion rate of ethanol and/or isopropanol into the aqueous phase. Kawashima et al. [17] documented that the stable formation of an O/W emulsion at the initial stage and the precipitation of polymer on the surface of the dispersed droplet were the key elements in formulation of microballoons with desirable morphological characteristics.

Larger amount of aqueous dispersion phase (1000 ml) was used with the intention to harden the microballoons in shorter period of time. As reported by Jain et al. [18] using larger amounts of aqueous phase (400-500 ml), the diffusion of dichloromethane into the aqueous phase and hence solidification of particles occurs faster as compared to 200 ml. Thus, using large volumes of aqueous phase had potential
advantage of reduction in required stirring times. Hence, diffusion of the organic solvents completed in the time span of 20 min and the microballoons get hardened.

**Micromeritic properties**

Microballoons were found to be spherical and discrete. But the particle size of microballoons varied in range. The particle size increased with increase in ethyl cellulose concentration. The particle sizes of various batches of microballoons were in the range of 71µm to 474µm. Particle size range, densities, and flow properties of microballoons of batches F1-F5 are shown in Table 2.

Flow properties of batches were evaluated by measuring the angle of repose and compressibility index. In the evaluation of flowability of dry solid, the substance shows excellent flowability and performance, when the angle of repose have the value less than 25°, while when compressibility index has value below 9%, no aid is needed for enhancing the flowability of powder [19] Thus, angle of repose and compressibility index are indicative of good flowability of microballoons, showing no need for addition of glidants to enhance flowability. The better flow property of microballoons indicates that the microballoons produced were non-aggregated. The improved micromeritic properties of formulated microballoons when compared to that of the pure drug alone suggest that they can be easily handled and filled into a capsule.

**Morphology**

Surface properties and internal structure of microballoons had been revealed by scanning electron microscopy (SEM). The microphotographs of cross section and surface view of microballoons of batch F3 are shown in Figures 1 and 2.

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Figure 1. Scanning electron photomicrographs of Propranolol hydrochloride-loaded microballoons with cross-sectional area, (a) resolution 200 times, (b) resolution 500 times.

Figure 2. Scanning electron photomicrographs of Propranolol hydrochloride-loaded microballoons with surface view, (a) resolution 75 times, (b) resolution 350 times.

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The cross-sectional photomicrograph of the microballoons are shown in Figure 1, part (A) shows the round cavity surrounded by the thick shell of the microballoons, while part (B) shows the thick shell having about 80 µm length. Smooth outer surface of the microballoons appearing from the part (B) of the Figure 2 indicates no precipitation of drug on the surface of microballoons. SEM indicated that the microballoons produced by the emulsion solvent diffusion-evaporation method are spherical with smooth surface and not aggregated. Their smooth surface indicated that Propranolol hydrochloride was embedded in the shell, as the drug particles were not present on the surface.

Percent recovery yield and encapsulation efficiency of microballoons
Percent recovery yield was found to be increased from batches F1 to F5 with an increase in concentration of Eudragit® S100. It ranges from 74.81% to 96.26%, with highest recovery yield with batch F5. Percent recovery yield and percent encapsulation efficiency of the batches F1-F5 are shown in Table 3.

The effect of the combination of the polymers over encapsulation efficiency was convincing. The encapsulation efficiency was found to be abruptly increasing when both polymers were used together. Encapsulation efficiencies of batches F1-F5 ranged from 26.79% to 94.84%. Maximum encapsulation efficiency was observed of the batch F3, where ratio of 2:3 of the ethyl cellulose and Eudragit® S100 was used. It was about three times higher than that of batches F1 and F5 where ethyl cellulose and Eudragit® S100 were used alone, respectively. This ratio of polymers was found to be the efficient of encapsulating maximum drug than any other batches. It was reported in the literature that the encapsulation efficiency depends on the solubility of the drug in the solvent and continuous phase. An increase in the concentration of polymer in a fixed volume of organic solvent resulted in an increase in encapsulation efficiency [20] As we have seen in the formulation, alcohol diffused out first to the external aqueous phase, thus when the drug was soluble in alcohol, it was possible that the drug may diffuse out of emulsion droplets together with alcohol before the droplet solidification, leading to a low loading efficiency. This tendency of the drug would become more prominent when the solubility of the drug in dichloromethane was low, since the drug preferentially partition into the alcohol phase when it moved into aqueous phase from a solvent mixture.

**In vitro drug release studies**

Different release profiles were observed with each combination of polymers. The effect of changes in polymer proportion in batches F1 to F5 has been shown in Table 3 and Figure 3. When ethyl cellulose alone was used (F1), no drug release was observed till 8th hour of dissolution study. When 1:1 proportion of ethyl cellulose: Eudragit® S100 was used (F2), 70-75% drug release was observed in 12 h. This batch was controlling drug release more than 12 h. In batch F4, total drug release observed merely after 8 h. Eudragit® S100 alone gave formulation (F5) which released the entire drug only in 4-5 h. One of these formulations (F3) prepared using 2:3 ratio of polymer (Ethyl cellulose: Eudragit® S100) gave the most satisfactory results with extended drug release for approximately 12 h and highest encapsulation efficiency. Figure 3 had shown that increase in concentration of ethyl cellulose decreased the drug release rate. The appropriate combination of these two polymers had been achieved in batch F3 where extended release of drug for approx. 12 h had been attained.

![Figure 3. In vitro drug release study of batches F1(-♦-), F2(-■-), F3(-▲-), F4(-●-), F5(-x-). Reproduction size should be column width](image)
appropriate model for the dissolution data. The best fit with the highest correlation coefficient was observed in the Korsmeyers-peppas model and zero-order release kinetics followed by Higuchi model, as given in Table 4. The ‘n’ value of formulation was found to be 0.960 indicating that the drug release was followed by anomalous (non-fickian) diffusion.

Table 1. Formulae of Propranolol hydrochloride microballoons with variable polymer ratios

<table>
<thead>
<tr>
<th>Formulation Bathches*#</th>
<th>Ratio of ethyl cellulose to Eudragit S100</th>
<th>Quantity of polymer used (mg)</th>
<th>Quantity of propranolol hydrochloride</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Ethyl cellulose</td>
<td>Eudragit S100</td>
</tr>
<tr>
<td>F1</td>
<td>1:0</td>
<td>950</td>
<td>0</td>
</tr>
<tr>
<td>F2</td>
<td>1:1</td>
<td>475</td>
<td>475</td>
</tr>
<tr>
<td>F3</td>
<td>2:3</td>
<td>380</td>
<td>570</td>
</tr>
<tr>
<td>F4</td>
<td>1:4</td>
<td>190</td>
<td>760</td>
</tr>
<tr>
<td>F5</td>
<td>0:1</td>
<td>0</td>
<td>950</td>
</tr>
</tbody>
</table>

Stirring carried out at room temperature;
*Ratio of solvent used in each formulation was 8:5:2 (Ethanol:DCM:n-butanol)

Table 2. Effect of various polymer ratios over micromeritic properties of microballoons

<table>
<thead>
<tr>
<th>Formulation codes</th>
<th>Particle size range (µm)</th>
<th>Bulk density* (g/ml)</th>
<th>Tapped density* (g/ml)</th>
<th>Angle of repose* (degrees)</th>
<th>% Compressibility*</th>
<th>Hausner’s ratio*</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>142-474</td>
<td>0.324 ± 0.009</td>
<td>0.346 ± 0.009</td>
<td>21.52 ± 1.911</td>
<td>6.37 ± 1.720</td>
<td>1.056 ± 0.041</td>
</tr>
<tr>
<td>F2</td>
<td>113-457</td>
<td>0.339 ± 0.012</td>
<td>0.359 ± 0.007</td>
<td>21.68 ± 1.785</td>
<td>6.51 ± 1.913</td>
<td>1.061 ± 0.058</td>
</tr>
<tr>
<td>F3</td>
<td>92-422</td>
<td>0.341 ± 0.016</td>
<td>0.361 ± 0.011</td>
<td>21.18 ± 1.613</td>
<td>6.55 ± 1.896</td>
<td>1.047 ± 0.068</td>
</tr>
<tr>
<td>F4</td>
<td>86-326</td>
<td>0.348 ± 0.009</td>
<td>0.375 ± 0.009</td>
<td>22.47 ± 1.574</td>
<td>6.69 ± 2.045</td>
<td>1.072 ± 0.034</td>
</tr>
<tr>
<td>F5</td>
<td>71-289</td>
<td>0.351 ± 0.011</td>
<td>0.382 ± 0.006</td>
<td>21.55 ± 2.148</td>
<td>6.73 ± 1.843</td>
<td>1.067 ± 0.037</td>
</tr>
</tbody>
</table>

Average of three preparations ± SD
Table 3. Effect of various polymer ratios on characteristics of microballoons

<table>
<thead>
<tr>
<th>Formulation batches</th>
<th>% Recovery yield*</th>
<th>% Encapsulation efficiency*</th>
<th>% Drug release at 12th hour*</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>74.81 ± 2.72</td>
<td>30.12 ± 2.23</td>
<td>25.19 ± 1.58</td>
</tr>
<tr>
<td>F2</td>
<td>86.18 ± 3.02</td>
<td>78.91 ± 2.34</td>
<td>72.18 ± 2.11</td>
</tr>
<tr>
<td>F3</td>
<td>89.12 ± 3.41</td>
<td>94.84 ± 2.41</td>
<td>96.76 ± 2.58</td>
</tr>
<tr>
<td>F4</td>
<td>94.14 ± 2.82</td>
<td>67.37 ± 2.06</td>
<td>99.54 ± 2.18</td>
</tr>
<tr>
<td>F5</td>
<td>96.26 ± 2.15</td>
<td>26.79 ± 2.57</td>
<td>100.91 ± 2.86</td>
</tr>
</tbody>
</table>

*Average of three preparations ± SD

Table 4. ‘r²’ values of various kinetic models and value of ‘n’

<table>
<thead>
<tr>
<th>Kinetic models</th>
<th>Zero order</th>
<th>First order</th>
<th>Higuchi</th>
<th>Hixon crowell</th>
<th>Korsmeyers-peppas</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>r²</td>
<td>r²</td>
<td>r²</td>
<td>r²</td>
<td>r², n</td>
</tr>
<tr>
<td></td>
<td>0.988</td>
<td>0.941</td>
<td>0.970</td>
<td>0.954</td>
<td>0.989, 0.960</td>
</tr>
</tbody>
</table>

CONCLUSION
In this study, stable sustained release Propranolol hydrochloride microballoons were prepared successfully using the emulsion solvent diffusion-evaporation method. This study has been a satisfactory attempt to formulate a microparticulate system of an anti-hypertensive drug Propranolol hydrochloride with a view of sustained delivery of the drug. Moreover, the developed product is less complex with regards to formulation components and processing aspects.

It may be concluded that capsules of sustained release Propranolol hydrochloride microballoons would be a promising drug delivery system for oral administration of Propranolol hydrochloride to sustain the drug release for about 12 h enhancing the patient compliance. In the formulation, the combination of cost-effective and biocompatible polymers Eudragit® S100 and Ethyl cellulose had been successfully used and there is scope of scale up of the batches to the commercial level. The formulation was found to be efficient with good recovery yield and percent drug entrapment. The surface structure, particle size, and flow analysis revealed that the microballoons showed good flow and packability, indicating that it can be successfully handled and filled into a capsule dosage form.

Hence, the SR microballoons formulation of Propranolol hydrochloride may provide a convenient dosage form for achieving best performance regarding flow, drug entrapment, and release. Further, their potential to improve Propranolol hydrochloride
bioavailability in humans needs to be investigated in further studies.

REFERENCES


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