INTRODUCTION
Extensive applications of polymers in drug delivery have been realized because they make it easier to achieve a desirable drug release profile and are cost effective. The hydrophilic polymers are used to control the drug release rate from the formulations. Natural polymers remain attractive primarily because they are readily available, capable of multiple of chemical modifications, potentially degradable and compatible due to their origin. Transdermal drug delivery is one of the most promising methods for drug application. The drug release duration and order of drug release profile from polymeric films embedded with drug is important for its biomedical applications. It is well known that the release mechanism is dependent on the carrier used. For immediate release formulations the entire quantity of solid drug particles becomes available upon disintegration of the device. On the other hand, for controlled release formulations, there are several mechanisms that can be envisaged. In vitro diffusion has been recognized as an important element in drug development. Under certain conditions it can be used as a surrogate for assessment of bioequivalence. The aim of the present study was to develop different transdermal matrix films with varied ratios of two polymers Chitosan and Pullulan containing Metoprolol Succinate as model drug and to perform Physicochemical and in-vitro evaluation of the prepared films to know the influence of blending.

Chitosan is a nontoxic biocompatible and biodegradable polymer used in various fields of medicine and cosmetics as a drug carrier. Pullulan is an extra cellular bacterial polysaccharide produced from starch by Aurobasidium pullulans. Due to its bioadhesive, non-toxic, non-immunogenic, non-mutagenic and non-carcinogenic nature, has been used for many biomedical applications including targeted drug and gene delivery and surface modification. Metoprolol Succinate is a beta-selective beta-adrenergic receptor blocker useful in treatment of hypertension, angina and heart failure. It is a white crystalline powder with high aqueous solubility. Half-life of Metoprolol Succinate ranges from 3 to 7 hours. So an investigation has been made to elucidate the release profile, kinetics and mechanism of release of Metoprolol Succinate from the transdermal films of the blends found to be Fickian mechanism. The release of drug in pure Chitosan and Pullulan is fast, whereas blending results in decrease of release rate. Hence Chitosan-Pullulan blend can be useful for diffusion controlled drug release for transdermal applications.

MATERIALS AND METHODS
Materials
Polymers employed for the present study were Chitosan (CHI) [HiMedia Laboratories, Mumbai] and Pullulan (PU) [Nutriscience Innovations LLC, USA, Molecular weight 100 cst (10 wt%, 30°C)]. Metoprolol Succinate was obtained as gift sample from Aarti drugs Mumbai.

Preparation of CHI-PU films with Drug
The drug bearing films were prepared by using solution casting method by using 1% (w/v) solutions of Chitosan and Pullulan in different compositions (80:20, 50:50, 20:80). Chitosan and Pullulan were dissolved in water to get 1% (w/v) clear and homogeneous polymeric solution. 0.5% (w/v) drug was incorporated and the solution was stirred until the drug gets dissolved. Glycerol was incorporated as plasticizer. The prepared polymeric solution was poured onto Teflon coated Petri dish and dried under dust free environment for 24 hours.

Physicochemical Evaluation of the Transdermal Film
The prepared films were evaluated for physicochemical properties like uniformity of thickness, weight variation, percentage moisture uptake, percentage moisture loss and folding endurance.

Thickness and mass of the film
The thickness of the film was determined by screw gauge at different positions and average thickness was calculated. For weight variation test, Specimens of 1cm² were weighed individually and kept in a desiccator. Repeated measurements were made and average values were reported.

Percentage of Moisture Content
Patches of 2cm² were weighed individually and kept in a desicator containing Calcium chloride at room temperature for 24 hours. After 24 hours the patches were taken out and weighed again. The percentage of moisture uptake was calculated as the difference between final and initial weights with respect to initial weight. Percentage of Moisture Content = \( \left( \frac{W_f - W_i}{W_i} \right) \times 100 \)

Where, \( W_i \) and \( W_f \) are the initial and final weights of the films, respectively.

Folding Endurance
Folding Endurance was determined by repeatedly folding one film at the same place till it gets broken. The number of times the film could be folded at the same place without breaking gave the value of folding endurance. Repeated measurements were made and average values were reported.
Estimation of Drug
An Ultraviolet Spectrophotometric method based on measurement of absorbance at wavelength \( \lambda_{\text{max}} \) for Metoprolol succinate. The wavelength of maximum absorption \( \lambda_{\text{max}} \) for Metoprolol succinate was determined by scanning a known amount of drug solution in wavelength region 200-400 nm by using UV-VIS double beam spectrophotometer (Systronics-2202, India).

Estimation of content uniformity of drug
In order to ascertain the distribution of drug in the polymeric membrane, the content uniformity test was performed. Specimens of 1 cm² were cut from the film in three different places and dissolved separately in 50 ml of phosphate buffer (pH 7.4). The content of drug in the polymer film was determined spectrophotometrically and the average drug content of three replicate samples was presented.

Drug-Polymer Interaction Study
In order to evaluate the integrity and compatibility of the drug with carrier polymers in polymer-drug matrix, IR spectra of drug and its formulation were obtained by NICOLET AVATAR FTIR Spectrophotometer.

In –Vitro Drug diffusion studies
Drug diffusion studies were carried out in an open glass diffusion tube. A specimen of dimension 1 cm² was fixed to hydrated cellophane membrane at one end of open glass tube and placed in the receptor compartment containing buffer (pH 7.4) solution. The assembly was placed on a magnetic stirrer and speed was set at 100 rpm. The temperature of the system was maintained at 37±1°C. A known amount of receptor medium was withdrawn at regular intervals of time and sink condition was maintained by replacing equal volume of fresh buffer. The drug concentration was determined by measuring the absorbance of the solution at 220.8 nm. Amount of drug diffused at various time intervals was calculated and plotted against time.

Kinetic Analysis of Drug Release
In order to understand the mechanism and kinetics of drug release, the results of in vitro drug release study were fitted to kinetic equations, Higuchi model (Eq.1) as % cumulative drug release vs. square root of time and Koresmeyer- Peppas model (Eq.2) WHERE \( R^2 \) values were calculated for the linear curves obtained by regression analysis of the plots.

\[
\frac{M_t}{M_\infty} = k \sqrt{t} \quad \text{(1)}
\]

\[
\frac{M_t}{M_\infty} = \frac{k}{n} t^n \quad \text{(2)}
\]

Where \( M_t/M_\infty \) is the fractional solute release, \( t \) is the release time, \( k \) is a kinetic constant characteristic of the drug/polymer system, and \( n \) is diffusion exponent that characterizes the mechanism of release. When numerical value of \( n \) > 0.5, the solvent diffuses through and the drug is released through film with fickian diffusion mechanism and the value between 0.5-1.0, indicative of anomalous or non-fickian diffusion.

RESULTS AND DISCUSSION
Physicochemical Evaluation of the Transdermal Film
The prepared films were evaluated for Physicochemical properties like uniformity of thickness, weight variation, percentage of moisture content and folding endurance. The obtained values are presented in the Table 1.

Table 1: Physicochemical properties of Chitosan/Pullulan transdermal patches containing Metoprolol Succinate

<table>
<thead>
<tr>
<th>Composition</th>
<th>Thickness in μm±SD*</th>
<th>% Moisture Content</th>
<th>Folding Endurance</th>
<th>Weight (mg)±SD</th>
<th>Drug content (mg)±SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chitosan</td>
<td>126 ± 5.5</td>
<td>23.0559</td>
<td>145 ± 2.5</td>
<td>11.5333 ± 0.28</td>
<td>3.595 ± 0.39</td>
</tr>
<tr>
<td>CP 80:20</td>
<td>110 ± 6.3</td>
<td>22.781</td>
<td>155 ± 2.0</td>
<td>12.0933 ± 0.12</td>
<td>5.3194 ± 0.48</td>
</tr>
<tr>
<td>CP 50:50</td>
<td>118 ± 7.5</td>
<td>22.3458</td>
<td>140 ± 3.7</td>
<td>13.1466 ± 0.08</td>
<td>5.1199 ± 0.28</td>
</tr>
<tr>
<td>CP 20:80</td>
<td>136 ± 4.2</td>
<td>17.7906</td>
<td>141 ± 3.5</td>
<td>11.66 ± 0.21</td>
<td>3.841 ± 0.21</td>
</tr>
<tr>
<td>Pullulan</td>
<td>130 ± 6.1</td>
<td>20.9259</td>
<td>132 ± 2.5</td>
<td>12.416 ± 0.17</td>
<td>4.125 ± 0.31</td>
</tr>
</tbody>
</table>

*Standard deviation, n=3

All patches had a smooth, flat surface and the thickness ranged between 110 ± 6.3 μm to 136 ± 4.2 μm, which indicates that they are uniform in thickness. The weights ranged between 11.533 ± 0.28 mg to 13.1466 ± 0.08 mg, which indicates that different composition patch weights were relatively similar. Folding endurance test results indicated that the patches would not break and would maintain their integrity with general skin folding when applied. Moisture content studies indicated that the increase in the concentration of Chitosan was directly proportional to the increase in moisture content of the patches. Among the various compositions moisture content of the CP 20:80 formulation was low, which could help the formulation remain stable and reduce brittleness during long term storage.

Estimation of Drug
The wavelength of maximum absorption \( \lambda_{\text{max}} \) for Metoprolol succinate was determined by scanning a dilute solution of drug in wavelength region 200-400 nm by using UV-VIS double beam Spectrophotometer (Systronics-2202). The \( \lambda_{\text{max}} \) was found to be 220.8 nm. A standard graph is prepared by measuring the absorption of series of drug solutions of known concentrations. This method obeys the Beer’s law in concentration 5 to 50 μg/ml, with good correlation co-efficient.

Content uniformity
The values of the amount of drug present in 1 cm² of films were presented in the Table 1. It was observed that the content uniformity value lies in the range 3.595 - 5.3194 mg/cm². The results of content uniformity studies clearly indicate that the drug was uniformly distributed throughout the polymer film and were in the expected range as per Indian Pharmacopoeia [IP] standards (1- 9 mg/cm²).

Drug-Polymer Interaction Study
The FTIR spectra of metoprolol succinate and its formulation with polymer blend are shown in the figure 1. The IR spectra of drug containing polymer blend was compared with that of the metoprolol succinate. FTIR spectrum of Metoprolol Succinate is characterized by the absorption of -COOH group at 1612.5 cm⁻¹, -OH stretching absorption at 3061.0 cm⁻¹ and -NH deformation at 1375.5 cm⁻¹. In IR spectra of drug- polymer film, these bands shows same absorption patterns as that of pure drug. These evidences thus indicated that there is no chemical interaction occurred between the drug and polymers used.

In –Vitro Drug diffusion studies
Diffusion studies were carried out in an open glass diffusion tube. Figure 2 presents the drug release profile from patches with different compositions of Chitosan and Pullulan. The study shows that the release of Metoprolol Succinate from the two pure polymers was found to be fast and in irregular pattern (Fig.2). By blending the two polymers in different compositions gave promising results of release behavior and release rate was found to be decrease. The composition CP 20:80 gave minimum release rate, this may be due to the miscibility of the two polymers which hinders the diffusion of drug particles from the polymer matrix due interaction between two polymers. It indicated that blending of the polymers gave the good release profile for the drug Metoprolol Succinate.
Kinetic analysis of Drug release

Drug release results were analyzed using Higuchi’s method by plotting the amount of drug released as a function of square root of time (Figure 3). The plot should be linear if the drug release from the system is diffusion controlled. The plots indicated good linearity and inferred that the drug release from the system was by diffusion.

The data obtained from in vitro drug release studies was fit into Koresmeyer-Peppas model (Figure 4). From the plot of log $M_t/M_\infty$ versus log time, parameters such as the values of diffusional exponent $n$, and constant $k$, were determined and are presented in the Table 2. In all the cases the values of intercept, $k$ were found to be more than 0.5 and $n$<0.5. This indicates that the release of drug from all formulations was found to be by Fickian diffusion mechanism.\textsuperscript{22-24}
Fig. 4: Koresmeyer-Peppas kinetics (log cumulative percent drug released vs log time)

Table 2: In-vitro data of the drug release from Higuchi and Koresmeyer Peppas methods

<table>
<thead>
<tr>
<th>Composition</th>
<th>$R^2$ value of Higuchi plot</th>
<th>$R^2$ value of Koresmeyer-Peppas model</th>
<th>Intercept [k]</th>
<th>Diffusional exponent, n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chitosan</td>
<td>0.9631</td>
<td>0.9761</td>
<td>1.5378</td>
<td>0.2029</td>
</tr>
<tr>
<td>CP 80:20</td>
<td>0.8526</td>
<td>0.8645</td>
<td>0.9642</td>
<td>0.3954</td>
</tr>
<tr>
<td>CP 50:50</td>
<td>0.9906</td>
<td>0.987</td>
<td>0.7342</td>
<td>0.4711</td>
</tr>
<tr>
<td>CP 20:80</td>
<td>0.9955</td>
<td>0.959</td>
<td>1.3564</td>
<td>0.1876</td>
</tr>
<tr>
<td>Pullulan</td>
<td>0.8901</td>
<td>0.8716</td>
<td>1.7935</td>
<td>0.1828</td>
</tr>
</tbody>
</table>

CONCLUSIONS

Present study confirms the influence of blending Chitosan and Pullulan on their drug release behavior. Among various combinations of Chitosan-Pullulan, CP 28 (20% Chitosan and 80% Pullulan) was found to give promising results for all the evaluated parameters using the drug Metoprolol Succinate. The release of drug was found to be diffusion controlled and follows Fickian mechanism.

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REFERENCES

19. Mukesh G Gehel, Rajesh K. Fabrication of Modified Release Tablet Formulation of Metoprolol Succinate using


