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Chitosan/HPMC Polymer Blends for Developing Transdermal Drug Delivery Systems

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Chitosan and hydroxy propyl methyl cellulose (HPMC) blends in different compositions viz., 100/0, 80/20, 60/40, 40/60, 20/80 and 0/100 by wt/wt ratio have been prepared with and without the incorporation of propranalol HCl by the solvent casting method. The films were casted using 1% glacial acetic acid and glycerine as the solvent and plasticizer, respectively. Distilled water was used as a solvent for the drug. The mechanical properties such as tensile strength and percentage elongation at break and optical properties of chitosan/HPMC have been reported. The drug diffusion behavior of chitosan/HPMC drug films in buffer solution (pH 7.4) has been established by open glass diffusion cell at 37 ± 1°C. The diffusion rate of drug from the polymer blends was determined by UV/Visible spectroscopy. It may be concluded that a chitosan/HPMC blend could be a promising approach for formulating a transdermal drug delivery system (TDDS) as they have good film forming property.

Keywords chitosan, HPMC, propranalol HCl, solvent cast, mechanical property, drug delivery

Introduction

The polymeric technologies have been honed and refined over the past several years and currently great interest has been focused on the development of novel drug delivery systems. The controlled release dosage forms essentially involve polymers in their construction since the therapeutic efficacy of many low molecular weight drugs may be improved by combining them with polymer (1). The simplest way to combine polymer with the drug involves the formation of polymer matrices in which drugs are mixed physically or blended, and the drug release is achieved by diffusion from the surrounding polymeric matrix or by disintegration of the polymeric matrix (2). In addition to its simplicity, the main advantage of this type of delivery system is that the drug remains unchanged in the polymer matrix and therefore, its pharmacological properties after the release remain identical as that of the native drug. In recent years, transdermal drug delivery system (TDDS) applications of the drug have been given considerable

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attention. The drug release in TDDS follows the law of passive diffusion and the mechanism through which it takes place can be understood by controlled drug release mechanism. TDDS offer many advantages over the conventional dosage forms, for instance, it provides constant drug to blood ratio for a longer period of time, avoids-first pass metabolism, enzyme activity, gastro-intestinal absorption and increases patient compliance (3).

A literature review of chitosan based TDDS systems revealed that several researchers had worked using chitosan gel as the drug reservoir (4–8). Thacharodi et al., obtained chitosan membranes with different permeability to propranalol hydrochloride by controlled crosslinking with glutaraldehyde to regulate the drug release (4). Krishna et al. formulated a carboxy methylcellulose sodium based TDDS for propranalol drug and evaluated for *in vitro* and *in vivo* performance (5).

Chitosan is a naturally occurring polymer that exhibits favorable biological properties such as nontoxicity (6), biocompatibility (7), biodegradability (8) and low chemical-reactivity. It is highly insoluble in common solvents (solubility profile is in dilute acid). It exhibits some of the pharmacological properties like an antacid, anti-ulcer agent, hypocholesterolemic acid and wound-healing agent (9, 10). The presence of reactive functional groups opens up possibilities for their applications in controlled drug delivery (11). It has gel-forming ability at low pH. Hydroxy propyl methylcellulose (HPMC) is modified cellulose soluble in water. It is used as a coating agent, film former, stabilizing agent, suspending agent, tablet binder and a viscosity-increasing agent. HPMC is widely used in oral and topical pharmaceutical formulations. In oral products, HPMC is primarily used as a tablet binder and as an extended release tablet matrix (12). The drug, propranalol HCl is a non-selective β-adrenergic blocking agent. It is reported to have a broad spectrum of uses such as an anti-hypertensive and anti-arrhythmic action. It is also used as a solution for migraine.

Chitosan/HPMC is chosen in order to study the release profile of the drug, propranalol HCl from the membranes made of natural and synthetic polymers respectively. In continuation of our previous research work (13), we have reported here the physico-mechanical, optical and drug diffusion studies of chitosan/HPMC/drug systems by spectroscopic studies.

Experimental

Materials

Chitosan (practical grade) was obtained from Marine Chemicals, Cochin, India. Chitosan is a principal derivative of chitin (14). Chitin is a linear polycationic polymer of N-acetyl D-glucosamine (N-acetyl-2-amino-2-deoxy-D-glucopyranose) unit linked by β-D ($1 \rightarrow 4$) bonds. Chitosan is an amorphous yellow powder with density, glass transition temperature and melting point of 1.27 g/cc, 75–80°C and 200°C, respectively. Chitosan used was 80% deacetylated. HPMC is a partly o-methylated and o-(2-hydroxypropylated) cellulose. It is odorless and tasteless with the pH of 5.5–8 for 1% W/W aqueous solution. Its density, melting point and glass transition temperature (T_g) are 0.50–0.70 g/cc, 190–200°C and 170–180°C, respectively. It is soluble in cold water, aqueous acetone, dichloromethane and propane–2-ol mixture. The drug used was propranalol HCl. The molecular formula is $C_{16}H_{22}NO_2$ HCl and molecular weight 295.84. Its IUPAC name is 1-isopropylamino-3-(1-naphyloxy) propan-2-ol hydrochloride. It is a white, odorless crystalline powder, which is soluble in a water-alcohol mixture; slightly soluble in chloroform and practically

insoluble in ether. It is stable at acidic pH and decomposes rapidly in alkaline media. The solutions are most stable at pH-3; in aqueous solutions propranalol decomposes with oxidation of the isopropylamine side-chain.

Preparation of Chitosan/HPMC Blends

A series of chitosan/HPMC blends with different composition viz., 100/0, 80/20, 60/40, 40/60, 20/80, and 0/100 by wt/wt ratios were casted. Chitosan and HPMC solutions of 2% concentration of each were prepared by dissolving them in 1% glacial acetic acid. 15% of glycerine (as plasticizer) to the weight of polymer was added to the above solution mixtures. After complete dissolution, the solutions were filtered to remove impurities and degassed to remove entrapped air. The prepared polymer mixture was poured into a cleaned glass mold ($12 \times 5\,cm^2$) and allowed to dry at room temperature for about 30–48 h. Films of excellent clarity were obtained. The chitosan/HPMC/drug films were prepared by dissolving 600 mg of propranalol HCl in 5 mL of distilled water and blending it into 20 mL of the above 1% polymer solutions. A similar procedure was adapted to prepare films of drug incorporated chitosan/HPMC. The obtained films were conditioned to 65% RH (relative humidity) at room temperature. These films were stored in aluminum foil until further characterization.

Measurements

The mechanical properties such as tensile strength and percentage elongation at break provide an indication of the strength and elasticity of the film. It is suggested that films suitable for wound dressing should preferably be strong and flexible. These properties were measured as per ASTMD-638 using a Universal testing machine (UTM) UK (Model 4309, Instron). Minimum of six samples were tested for each composition at room temperature and average value was recorded.

Optical properties viz., light transmittance and haze was measured as per the ASTMD-1003 using a Suga test Haze meter (Model 206, Japan). The drug release studies were carried out using a UV/Visible spectrophotometer (model no. 1601). This involves the determination of λ_{max} of propranalol λ_{max} was determined by preparing a stock solution in pH 7.4 of a known concentration (10 mg/mL) in distilled water and a UV/Visible scan was taken between the wavelength of 200–500 nm. The absorption maximum was observed at 290 nm for propranalol.

Content Uniformity

In order to ascertain the uniform distribution of the drug in the film, the content uniformity test was carried out utilizing the pharmaceutical standard by means of a UV/Visible spectrophotometer. A specimen size of $1\,cm^2$ was cut and dissolved in 100 mL of 1% glacial acetic acid mixture. The drug concentration was determined by measuring the absorbance at 290 nm using a UV/Visible spectrophotometer and calibration plot. The content uniformity was calculated by the equation:

$$\text{Content uniformity} = \frac{\text{Concentration from the graph} \times \text{dilution factor}}{1000} \times 100\,mg/cm^2 \quad (1)$$

Drug Diffusion Studies

Drug diffusion behavior from the polymer membrane has been carried out in an open glass tube diffusion cell using hydrated cellophane paper as a membrane. A specimen size of 1 cm^2 was fixed at one end of the open glass tube and placed in the donor compartment containing a phosphate buffer solution of pH 7.4. The cell was placed such that it just touches the surface of the buffer. This assembly was placed on a magnetic stirrer and stirred at 100 rpm. The temperature was maintained at $37 \pm 1^{\circ}C$. A known volume of the (receptor medium) buffer was withdrawn at regular intervals of time up to 5 h and the sink condition was maintained by replacing an equal volume of fresh buffer. The drug concentration was determined by measuring the absorption at 290 nm. The percentage drug release was calculated using the formula:

$$\text{Percentage drug release} = \text{Cumulative concentration/Content uniformity} \times 100 \quad (2)$$

Results and Discussion

Mechanical Properties

The tensile strength of chitosan and HPMC were 5.3 and 21.53 Mpa, respectively. From Table 1, it was noticed that the chitosan showed lower tensile strength compared to HPMC. This may be due to a high degree of entanglement, molecular weight and high degree of hydrogen bond in HPMC. Both theoretical and experimental tensile strength values of blends are shown in Table 1. A marginal reduction in tensile strength was noticed with an increase in chitosan composition in the blend. Tensile strength values of the blends were in the range of 8.5–18.2 MPa. From Table 1, it was noticed that experimental tensile strength values lie above the theoretically calculated tensile strength values. These results revealed that some kind of interaction between chitosan and HPMC and these blends might be miscible in nature.

Table 1
Mechanical properties of chitosan, HPMC and their blends with and without drug

Composition (chitosan/HPMC) (wt/wt, %)	Tensile strength (MPa) ± 1%		Percentage elongation at break
	Without drug		
	Experimental	Theoretical	
0/100	5.2	—	38
20/80	8.5	10.5	36
40/60	11.7	12.5	20
60/40	15.0	17.5	18
80/20	18.2	18.6	20
100/0	21.5	—	22

Table 2
Optical properties and content uniformity of chitosan/HPMC blends with and without drug (propranalol HCl)

Composition (chitosan/HPMC) (wt/wt, %)	Transmitted light (T_t)		Total diffuse (T_d)		Content uniformity (mg/cm^2)
	Without drug	With drug	Without drug	With drug	
0/100	89.0	87.7	9.5	39.3	7.87
20/80	85.4	85.0	8.1	71.3	6.79
40/60	82.6	82.2	19.0	72.5	6.54
60/40	82.4	81.0	22.9	71.5	9.25
80/20	76.5	75.5	20.7	68.8	6.00
100/0	79.7	75.3	9.5	68.8	8.04

The highest percentage elongation at break (38%) was noticed for HPMC compared to chitosan (22%). The percentage elongation at break decreases from 38 to 8%, with an increase in the chitosan content from 0 to 50% in the chitosan/HPMC blends.

Optical Properties

The measured optical properties such as light transmittance and total diffuse data for chitosan/HPMC blends with and without drug are given in Table 2. From the table it was noticed that there was no systematic variation in total diffuse with composition of blends. The percentage transmittance for the blends lies in the range 76.5–85.4 which indicated that chitosan, HPMC and their blends are transparent in nature. A drastical change in total diffuse values was noticed after incorporation of the drug in the blends.

Drug Release Studies

Content Uniformity

From Table 2 it is noticed that the content uniformity values lie in the range of 6.0–9.25 mg/cm^2. The measured content uniformity lies in the expected range as per

Table 3
Propranalol HCl diffusion data from chitosan, HPMC and their blends at 37°C in pH 7.4

	% Drug release from chitosan, HPMC and their blends					
Time (min)	0/100	20/80	40/60	60/40	80/20	100/0
30	30.0	47.3	26.6	21.7	52.1	70.4
60	64.5	60.4	37.7	36.3	64.4	86.8
90	81.8	74.1	45.9	39.7	73.0	88.5
120	90.9	74.2	46.4	40.6	68.5	89.0
180	95.5	79.1	56.8	42.1	80.2	90.9
240	97.2	89.2	67.3	44.8	80.3	93.9
300	98.4	91.3	77.7	47.3	83.3	94.0

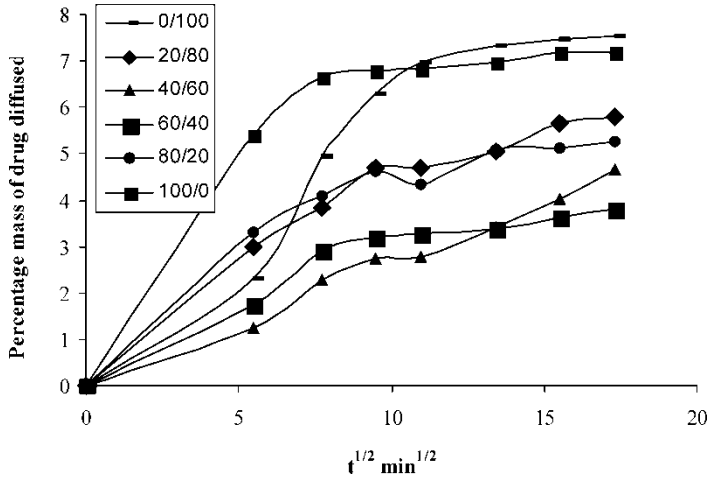

Figure 1. (a) Percentage mass of drug diffused versus square root of time for different chitosan, HPMC and thier blends at 37°C in pH 7.4.

pharmaceutical industry standard (2–8 mg/cm^2), which indicates that the drug is uniformly distributed in the film. The theoretical drug incorporation is about 10 mg/cm^2. When compared to the theoretical incorporation, the experimental data obtained has not varied much. This indicates that the drug is distributed uniformly throughout the polymer matrix.

Diffusion Studies

Table 3 gives the diffusion data for the drug with chitosan, HPMC and their blend systems. The rate of drug delivery is very fast in the case of pure chitosan and in the case of HPMC, the drug delivery steadily increases with time. Chitosan and HPMC films showed maximum drug release after 90 min. Also, the rate of drug release was almost identical for both polymers after 90 min, and maximum compared to their blends. From the table, it was observed that after 30 min, the 20/80 and 80/20 (chitosan/HPMC) blends shows maximum drug release compared to other blends. The percentage mass of drug diffused (Q_t) from the chitosan, HPMC and their blends vs. square root of time at 37°C in pH-7.4 is depicted in Figure 1. From Figure 1 it was noticed that, a very slow diffusion of drug from 60/40 (chitosan/HPMC) membrane compared to other membranes. From this study, we can conclude that, by changing the composition of blends, the rate of drug delivery can be controlled. Depending upon the requirement of pharmaceutical or band-aid designer, they can select suitable formulation. These polymer membranes were recommended for transdermal drug delivery system (TDDS) in the form of band-aid because these have good film forming properties.

Conclusions

The following are the conclusions that can be drawn from the afore said research data:

- Comfortable films and membranes can be prepared from chitosan, HPMC and their blends because they possess good mechanical performance. When high mechanical

performance is required, higher compositions of HPMC in the blends have to be used.

- The added advantages of these films are that they possess good optical clarity/transparent nature. Optical properties reveal that the incorporated drug had dispersed throughout the matrix without any change in its characters. After incorporation of the drug, the percentage transmittance was retained, but a drastic change in total diffuse was observed. This result indicates that the drug has not interacted chemically with the polymer.
- The content uniformity results indicated that the drug was uniformly distributed throughout the film and the values obtained (6.00–9.25 mg/cm^2) was in close accordance with the expected value that is 2–8 mg/cm^2. This indicates that the obtained content uniformity values lie in a narrow range compared to the expected range.
- The diffusion studies showed that the drug diffusion rate was more for HPMC and chitosan when compared to their blends. But as the present study aimed at studying the release of the drug using blends and their suitability, emphasis has been given to generate the data for blend systems.

From the above results, a general conclusion that can be drawn is that selection of a particular blend formulation can vary the diffusion of the drug (propranalol HCl) significantly. It may also be concluded that the HPMC/chitosan systems could be a promising approach for formulating TDDS as they have good film forming property and mechanical strength.

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