Chapter II

Experimental

Materials

All materials employed in this study were obtained from commercial sources and used as received except chitin and chitosan which were milled before used.

Active Ingredient :

Propranolol HCl BP, batch No. 08.90.019 (S & D Chemicals Co., Ltd., England).

Commercial Preparation :

Inderal LA 80, lot LS 809 A (ICI Pharmaceuticals, England)

Tablet Diluents :

Lactose, hydrous USP (Wyndale, New Zealand)

Polyvinylpyrrolidone, PVP K 30 (GAF, Singapore)

Talcum (Guangxi, China)

Magnesium stearate (Peter Greven Fett-Chemie GmbH, Germany)

Colloidal silicon dioxide, Aerosil® HDK type N 20 (Wacker Chemie GmbH, Munchen, Germany).

Film Formers :

Chitin (Kyowa Technos Co., Ltd., Japan)

Chitosan, m.w.of 300,000 - 500,000 (Kyowa Technos Co., Ltd., Japan).

Methylcellulose, Methocel® A 15 LV Premium (batch No. MM 87070921 A, Colorcon Ltd., England).

Hydroxypropyl methylcellulose, Methocel® E 15 LV Premium (batch no. MM 90082522 E, Colorcon Ltd., England).

Hydroxypropyl cellulose, HPC-L (lot No. BC-101, Nippon Soda Co., Ltd., Tokyo, Japan).

Ethylcellulose pseudolatex, Surelease® (batch No. 600007, Colorcon Ltd., England).

Miscellaneous :

Hydrochloric acid (Farmitalia Carlo Erba, Italy)

Sodium chloride AR (E.Merck, Darmstadt, Germany)

Disodium hydrogenphosphate, anhydrous AR (E.Merck, Darmstadt, Germany)

Citric acid, anhydrous AR (Fluka Chemika, Switzerland)

Methanol AR (BDH Laboratory Supplies, England)

Methanol HPLC (J.T.Baker Inc., Phillipsburg, NJ, USA)

Acetonitrile HPLC (J.T.Baker Inc., Phillipsburg, NJ, USA)

Potassium dihydrogen phosphate AR (E.Merck, Darmstadt, Germany)

Pindolol (Sigma Chemical Co., St. Louis, MO, USA)

Polyethylene glycol 400 NF XIV (supplied by Srichana United Dispensary Ltd., Bangkok, Thailand)

Hexafluoroisopropanol (Fluka Chemika, Switzerland)

Simethicone (supplied by Pharmaceutical Traders Co., Ltd., Bangkok, Thailand)

Equipment

Nest of sieves (Endecotts, London, England)

Harvard Trip balance (Ohaus Florham Park, NJ, USA)

Balance (Berkel AG, Zurich, Switzerland)

Planetary paddle mixer (Crypto-Peerless model EB 20 F, London, England)

Oscillating granulator (Viuheng Engineering, Bangkok, Thailand)

Hot air oven (Memmert type UL 80, Germany)

V - shape mixer (Kan Seng Lee Machinery Ltd., Part, Bangkok, Thailand)

Single punch tabletting machine (Viuheng Engineering, Bangkok, Thailand)

Analytical balance (Sartorius model A 200 S, Germany)

Tablet hardness tester (Schleuniger model 2E/205, Switzerland)

Disintegration apparatus (Hanson Research model QC-21, USA)

Dissolution apparatus (Hanson Research model SR 2, USA)

pH meter (Hanson Research model HI 8417, USA)

Spectrophotometer, Spectronic 2000 (Bausch and Lomb, NY, USA)

High performance liquid chromatography (HPLC) :

- pump : multiple solvent delivery system (Milton Roy model CM 4000, LDC division, FL, USA)

- ultraviolet absorption detector : programmable wavelength detector (Milton Roy model SM 4000, LDC division, FL, USA)

- integrator : computing integrator (Milton Roy model CI 4100, LDC division, FL, USA)

HPLC-reversed phase column : Spherisorb, octadecylsilica particle size 5 μm., 25 cm. length, 4.6 mm. I.D., serial No. 104817 (Phase Separations Ltd., UK) equipped with guard column : packed with C_{18} Corasil, particle size 37-50 μm (Millipore Corp., Milford, MA, USA)

Microsyringe, 100 μL. (Unimetrics. Storewood, IL, USA)

Scanning electron microscope (Jeol model JSM 35 CF, Japan)

Fitz mill (Kan Seng Lee Factory Ltd., Part, Bangkok, Thailand)

Blender, National Blender model MXT 31 GN, serial No.920918, (Matsushita Electric Co., Ltd., Taiwan)

Simple distillation set (Quickfit, England)

Thermolyne stirrers and stirring hot plates, Nuova 7 model No. SP-18420 (Thermolyne Sybron Corp., Dubuque, IA, USA)

Viscometer, Haake Rotovisco RV 20 equipped with Haake Rheocontroller RC 20 and computerized system (Haake Mess-Technik GmbH, Karlsruhe, Germany)

Particle size analyzer : Coulter Multisizer II, serial No.P 1100963 equipped with Sampling Stand II, serial No. P 0600135 (Coulter Electronics Ltd., England)

Tensometer, Instron model 4301, serial No. H3333 (Instron Corp., Canton, MA, USA)

Micrometer (Tecklock Corp., Japan)

Conventional coating pan (Fuji Electric Co., Ltd., Japan) equipped with nozzle model 970/0 (Glatt GmbH, Hamburg, Germany)

Peristaltic pump, Verder type VRX 88 No.3455 (Glatt GmbH, Hamburg, Germany)

Air compressor type VA 65 AA, serial No. 00151 (Fu Sheng Industrial Co., Ltd., Taipei, Taiwan)

Methods

The experiment was divided into 5 main sections as followed.

1. Preparation and Evaluation of Propranolol HCl Core Tablets.

1.1 Preparation of Propranolol HCl Core Tablets.

Propranolol HCl core tablets were prepared by means of wet granulation method. The core tablets composition was shown in Table 3.

Propranolol HCl and lactose were individually passed through a 40-mesh screen in order to eradicate the agglomerates. Required

Table 3 The Compositions of Propranolol HCl Core Tablets.

Materials	Weight (mg.)
Propranolol HCl	80.00
Lactose	174.48
PVP K 30	8.10
Talcum	5.40
Magnesium Stearate	1.34
Aerosil®	0.68
Total Weight	270.00

amount of each material was weighed and then thoroughly mixed together in a planetary paddle mixer by geometric dilution. PVP K 30 solution of 20% w/w in purified water was freshly prepared. It was then gradually added to the mixture and agitated with a fixed speed of No.1 until wet mass was obtained.

The wet mass was later granulated through an oscillating granulator with a 16-mesh sieve to obtain long granulates of about 3-4 cm. The granulates were tray dried in a hot air oven at the temperature of 65°C for 3-4 hours. They were then again sieved through the oscillating granulator with the same screen to obtain uniform-size granules.

Talcum, Magnesium stearate and Aerosil®, were all separately sieved through a 60-mesh screen and weighed as required in the formula. They were then thoroughly mixed with the dried granules in V-shape tumbling mixer for 5 minutes.

Finally, the lubricated solid mixture was compressed into 270 mg. tablets using 8 mm. in diameter, round standard concave punch on a single punch tabletting machine. The compression force as well as tablet weight were controlled in order to obtain the tablet hardness within the acceptable range of 10 ± 2 kps.

1.2 Evaluation of Propranolol HCl Core Tablets.

The following properties of the core tablets were investigated.

1.2.1 Average Weight and Weight Variation.

Each of twenty tablets was accurately weighed on

an analytical balance. The average weight and standard deviation were calculated.

1.2.2 Tablet Hardness.

Ten propranolol HCl tablets were sampled and individually subjected to the hardness tester. The tablet hardness was expressed in kilopounds (kp.) unit. Mean and standard deviation of the tablet hardness were determined.

1.2.3 Disintegration Time.

Disintegration time was measured from six tablets using disintegration apparatus. Deionized water, maintained at the temperature of $37\pm2^{\circ}C$ throughout the experiment, was used as an immersion fluid. The test was performed with disk. Mean as well as standard deviation were calculated.

1.2.4 Drug Release.

The procedure for studying the release of propranolol HCl tablets was based on the monograph of Propranolol Hydrochloride Extended-release Capsules USP XXII, using dissolution apparatus method I.

Nine hundred mL. of pH 1.5 buffer solution which was prepared by dissolving 20 gm. of sodium chloride in water, adding 7.0 mL. of hydrochloric acid, diluting with water to 1 liter, and mixing, was used as dissolution medium during the acid stage. The dissolution medium was allowed to equilibrate and maintain at temperature of $37\pm0.5^{\circ}C$ throughout the experiment. The tablet was

placed in the apparatus and operated for 1.5 hr. at a rotating speed of 100 rpm. For the buffer stage, 900 mL. of pH 6.8 buffer solution, prepared by dissolving 21.72 gm of dibasic sodium phosphate and 4.94 gm. of citric acid in water, diluting with water to 1 liter, and mixing, equilibrating to the temperature of $37\pm0.5^{\circ}C$, was then substituted for the acid solution in the vessel. The apparatus was continued to operate for the time specified or until propranolol HCl was completely released.

A 5-mL aliquot of dissolution medium was withdrawn and simultaneously filtered at various predetermined time interval. To maintain constant volume of the dissolution medium, the aliquot withdrawn for analysis was replaced immediately with an equal volume of fresh dissolution medium. A portion of the solution under test was then assayed spectrophotometrically in a 1-cm cell, to determine the amount of propranolol HCl dissolved, using an ultraviolet spectrophotometer, at the wavelength of maximum absorbance at 318.7 nm. for both stages of the test. The amount of propranolol HCl released was then calculated from absorbance-concentration calibration curve and corrected for the amount previously withdrawn for assay. The reported data were averaged from three determinations.

Preparation of Calibration Curve

Calibration curves of propranolol HCl were individually generated in both dissolution media, i.e. pH 1.5 and pH 6.8 buffer solution. About 250 mg. of propranolol HCl was accurately weighed and transferred to a 100-mL volumetric flask. It was dissolved, diluted with the dissolution medium to volume and thoroughly mixed.

This was used as stock solution containing about 2.5 mg. of propranolol HCl per mL.

An accurately measured volume of the stock solution was then quantitatively diluted with the same dissolution medium to provide the propranolol HCl solution within the concentration range of about 25-250 $\mu g/$ mL. The absorbances of known drug concentration solutions were determined in a 1-cm cell using the spectrophotometer at the wavelength of maximum absorbance at 318.7 nm. for both dissolution media which were used as the blank solution. Each concentration was determined in triplicate.

The absorbance concentration relationships of known drug concentration solutions in both acid and buffer dissolution media are presented in Table 27 and 28 (Appendix A) with both correlation coefficients of 0.9999. The calibration curve of propranolol HCl in both dissolution media after regression analysis were illustrated in Figure 43 and 44 (Appendix A) according to the equation $y = 0.0061x + 0.0047$ and $y = 0.0063x + 0.0046$, respectively, where y represented the absorbance and x represented the drug concentration in $\mu g/mL$.

1.2.5 Uniformity of Dosage Units.

The method was modified from the monograph of Propranolol Hydrochloride Tablets USP XXII. Propranolol HCl tablet was sampled and transferred to a 100-mL. volumetric flask. Five mL of diluted hydrochloric acid (1 in 100) was added. The tablet-containing volumetric flask was allowed to stand and occasionally swirled until the tablet was disintegrated. About 80 mL. of methanol were then added and thoroughly mixed. The mixture was then sonicated for about

1 minute and swirled for an additional 30 minutes. After that, it was diluted with methanol to volume and mixed.

A portion of the mixture was later filtered through a filter paper and the first 10-mL of the filtrate were dicarded. An accurately measured volume of the clear solution was further quantitatively diluted with methanol to obtain a solution containing about 30 μg of propranolol HCl per mL.

The absorbance of the solution was measured spectrophotometrically in a 1-cm. cell at the wavelength of maximum absorbance at 289.1 nm. using methanol as the blank solution. The quantity, in mg., of propranolol HCl in the tablet was then calculated from absorbance concentration relationship. The average and standard deviation of the drug content were determined from ten tablets.

Preparation of Calibration Curve.

Calibration curve of propranolol HCl in methanol was produced. An accurately weighed portion about 80 mg. of propranolol HCl was transferred to a 100-mL. volumetric flask. The drug was then dissolved, diluted with methanol to volume and thoroughly mixed, in order to obtain the stock solution containing about 0.8 mg of propranolol HCl per mL.

An accurately measured aliquot of the stock solution was further quantitatively diluted with methanol to provide the solutions within the concentration range of about 8-40 μg/mL. The absorbances of these known drug concentration solutions were determined in a 1-cm cell with the spectrophotometer, at the wavelength of maximum absorbance at 289.1 nm., using methanol as the blank solution. Each concentration was also determined in triplicate.

The absorbance concentration relationship was expressed in Table 29 (Appendix A). The calibration curve of propranolol HCl in methanol after least squares analysis was plotted and presented in Figure 45 (Appendix A), according to the equation $y = 0.0204x + 0.0017$, where y was the absorbance and x was the concentration, in $\mu g/mL$, of propranolol HCl. The good linear relationship was obtained with the correlation coefficient of 0.9998.

1.2.6 Percentage of Labeled Content.

The content of propranolol HCl tablet was determined with high performance liquid chromatography (HPLC), using the isocratic reversed phase technique. The chromatographic system was modified from the monograph of Propranolol Hydrochloride Extended -release Capsules USP XXII and set as followed.

column	: Spherisorb-octadecylsilica, particle size 5μm, 25 cm long and 4.6 mm I.D.
guard column	: Corasil-C_{18}, particle size 37-50 μm.
detector	: ultraviolet absorption detector set at 220 nm, peak area was calculated using an computing integrator.
mobile phase	: degassed mixture of phosphate buffer and acetonitrile (650 : 350).

diluting solvent	: degassed mixture of reversed osmosis treated water and acetonitrile (650 : 350)
flow rate	: 2.0 mL per minute
pressure	: 4,600 psi
injected volume	: 20 μL.
run time	: 15 minutes
chart speed	: 1 mm per minute
column temperature	: room temperature 25 $\pm$ 1° C

The mobile phase, a mixture of phosphate buffer prepared by dissolving and mixing 13.6 gm of monobasic potassium phosphate in 2 liters of reversed osmosis treated water, and acetonitrile (650 : 350) was freshly prepared and filtered through a 0.45 μm membrane filter. It was then degassed by sonication for about 30 minutes prior to use.

The diluting solvent was also freshly prepared with the same procedure as preparing the mobile phase, except for the phosphate buffer was replaced with reversed osmosis treated water.

Preparation of Calibration Curve

The stock solutions of propranolol HCl and pindolol, as and internal standard, in methanol were separately prepared. The certain quantity about 100 mg. of propranolol HCl and pindolol were individually transferred to 100-mL volumetric flasks. Both drugs were dissolved, diluted with methanol to volume and mixed, in order to obtain the stock solutions with the concentration of about 1 mg/mL.

Both stock solutions were then quantitatively and stepwise diluted with methanol or diluting solvent in the final step to obtain the standard solutions containing various concentrations of propranolol HCl within the range of about 5-25 μg/mL and 2 μg/mL of internal standard in every dilution. A 20-μL aliquot of these standard solutions was injected into the chromatograph and the chromatogram was recorded. Each dilution was average from two determinations.

The calibration curve, as illustrated in Figure 46 (Appendix A), was obtained by plotting the peak area ratio of propranolol HCl and pindolol against the concentration of propranolol HCl from the data in Table 30 (Appendix A). The least square fitted equation, $y = 0.4229x - 0.0419$ which was used to calculate the quantity of propranolol HCl in each elution sample, was obtained from regression analysis, where y was the peak area ratio of propranolol HCl and pindolol, and x was the concentration, in μg/mL, of propranolol HCl. The good linear relationship was received with the correlation coefficient of 0.9994.

Assay Preparation.

Twenty tablets were weighed and finely powdered. an accurately weighed portion of the powder, equivalent to about 80 mg of propranolol HCl, was transferred to a 50-mL volumetric flask. Fourty mL of methanol were added. The mixture was shaked by mechanical mean for about 1 hr. and then diluted with methanol to volume and mixed.

A portion of the mixture was later filtered through a filter paper and the first 10-mL filtrate was discarded. An accurately

measured volume of the clear filtrate was quantitatively and stepwise diluted with methanol and diluting solvent in the final step to obtain a sample solution having a concentration of about 20 μg of propranolol HCl per mL. The internal standard was also added into the sample solution, having a concentration of about 2 μg of pindolol per mL.

A 20 μL aliquot of the sample solution was injected into the chromatograph and the chromatograam was recorded. The retention time of propranolol HCl and the internal standard were about 9 minutes and 3 minutes, respectively. The peak area ratio of propranolol HCl and the internal standard was calculated to determine the quantity of propranolol HCl in each sample from the calibration curve. Each sample was determined in duplicate.

1.2.7 Surface Topography

Propranolol HCl tablet was coated with gold using ion sputtering prior to the microscopic examination with scanning electron microscope. The gold coated tablet was imaged using a 15-20 kV.electron beam and then photographed at an appropriate magnification. The surface topography was observed.

2. Preparation and Evaluation of Film Coating Formulations.

2.1 Preparation of Film Coating Formulations

All of the film coating formulations employed in this investigation were prepared as aqueous system of solutions or dispersions, depended on solubility property of the film formers, in the concentration unit of weight by weight.

2.1.1 Water-soluble Film Formers.

Chitosan (CS) was first pulverized with a Fitz mill and passed through a 100-mesh screen. Required quantity of CS was gradually dispersed in one part of the required volume of water until all particles were thoroughly wetted. The required amount of citric acid in the film coating formulations was dissolved in another part of water and then added. The mixture was mixed or agitated until clear viscous solution was obtained. It was left standing overnight as well.

Film coating formulations of cellulose derivatives i.e. methylcellulose (MC), hydroxypropyl methylcellulose (HPMC), and hydroxypropyl cellulose (HPC), were prepared as in the following procedure.

Certain amount of the film formers was first dispersed by mixing thoroughly with about one third of the required total volume of hot water (80 - 90°C) and agitated unitl all particles were thoroughly wetted. The remainder of the water was then added as cold water or even as ice to obtain the proper temperature. The mixture was again continuously agitated until it was smooth. The viscous solution obtained was left standing overnight in order to eliminate air bubbles and provide maximum degree of hydration.

2.1.2 Water-insoluble Film Formers.

Chitin (CT) was also first pulverized with the Fitz mill and then sized through a 200-mesh screen. Because of its ionic character with ammonium groups, CT pseudolatex aqueous dispersions was prepared by solvent change and self-dispersible technique as followed.

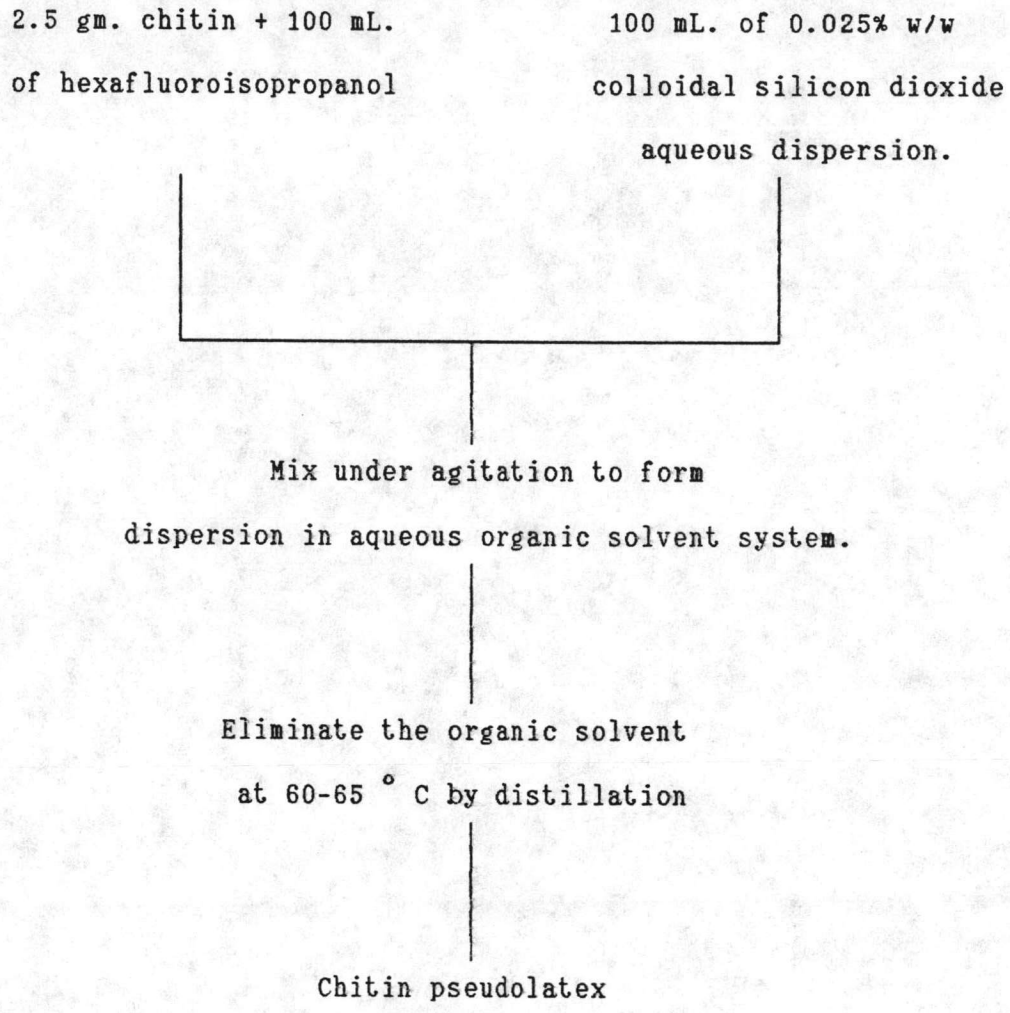

Figure 6 Schematic process for preparation of chitin pseudolatex aqueous dispersion.

About 2.5 gm of CT was first allowed to swell in 100 mL of hexafluoroisopropanol and left overnight to obtain the maximum degree of swelling. Certain amount of colloidal silicon dioxide as an antiadherent, equivalent to about 1% by weight of CT, was dispersed in about 100 mL of deionized water. The pseudolatex was

obtained by gradually dispersing the viscous liquid into the colloidal silicon dioxide dispersion under agitation using a blender for about 15 minutes and then transferred to a distillation set. The organic solvent was subsequently eliminated from the aqueous organic dispersions at the temperature of boiling point of the solvent (about 60-65°C) to leave a stable pseudolatex (Figure 6). The water, dispersion medium of the pseudolatex, was further evaporated to obtain more concentrated aqueous dispersions about 5% solids content. The organic solvent was collected up and reused, as necessary.

Ethylcellulose (EC), as concentrated pseudolatex aqueous dispersions (25% solids content), was further diluted to obtain less viscous and easily handled film coating formulations.

In addition to studying the application of film coating formulations containing one film former, the application of coupled film formers between water-soluble and water-insoluble film formers at some predetermined ratios was also investigated. Some kinds of the additives or other ingredients could be added into the film coating formulations, if necessary, to obtain the desired film properties.

2.2 Evaluation of Film Coating Formulations.

2.2.1 Water - soluble Film Formers.

- Viscosity Coefficient Determination

To determine the viscosity coefficient, the film coating formulations containing CS or a cellulose derivative

with the concentration of 3,4,5,6 and 7% by weight were individually subjected to a cup and bob type viscometer equipped with a computerized system. Each shear stress (F) at various rate of shear (G) in the predetermined range (0-200 1/sec.) within the specified time (4 minutes) was recorded.

Log G was then plotted as a function of Log F. The viscosity coefficient of each sample was obtained from the intercept on the log G axis (Appendix B). The viscosity coefficient, average from 3 determinations, at each concentration of the film former in the film coating formulations was then plotted against the concentrations of the film formers.

As informed in the product information (Dow Chemical Company, n.d.), the most appropriate concentration of HPMC (Methocel E 15) in the film coating formulations is between 4.5-6.5%, thus in this study, the concentration of about 5% by weight was selected as reference concentration. From the linear relationship between the average viscosity coefficient and the film former concentration, the concentration of other film formers, which had the same viscosity coefficient as 5% w/w HPMC coating formulations, was determined and selected to use for further steps of this study.

2.2.2 Water - insoluble Film Formers.

- Particle Size Determination.

The particle size of dispersed phase of both CT and EC pseudolatex was separately determined by particle volume measurement technique using the Coulter® counter, instrumented

with a computerized system. The pseudolatex was extremely diluted and suspended in 5 mmol of sodium chloride solution which was prefiltered through a 0.45 μm membrane filter and used as a conducting liquid. The dispersed particles were then pumped one by one through a small orifice with an aperture size of 50 μm, within 1 minute. Mean of the particle size were recorded.

- Solids Content.

This property was studied only in the CT pseudolatex. The dispersion was dried in a hot air oven at the temperature of 45°C for about 3 days. The dried residue was kept in the desiccator and weighed everyday until the weight was constant. The solids content was calculated from the last weighing and averaged from 3 determinations.

3. Tablets Coating Process.

3.1 Pan - spray Methods.

All film coating formulations were applied with the following method except for CT aqueous dispersion. A batch size of about 500 gm of core tablets were loaded into the conventional coating pan equipped with 4 baffles. An air-atomized spray nozzle model 970/0 was attached and adjusted to spray on the upper half of the tablet bed. The core tablets were then warmed by turning on the drying air temperature of 60-65°C, the exhaust air and the atomizing air pressure of 2 bars, for about 15 minutes. The pan was intermittently jogged while the core tablets were warming.

The film coating formulation was later applied with continuous spraying feed rate No. 0.6-0.8 using a Verder peristaltic pump type VRX 88 No. 3455. The amount of coating applied to each batch was determined from percentage coating level that had precedingly been set. The tablets were allowed to be dried in the pan with drying air and heat on for 10 to 15 minutes. The film coated tablets were stored in the desiccator for further evaluation.

3.2 Dip Coating

This method of coating applied was specially adapted for tablets coating with CT aqueous dispersion. The individual core tablet was dipped into the coating liquid and the wet tablet was then immediately dried as well as in a conventional manner in coating pan. Alternate dipping and drying were repeated several times to obtain the desired coating quantity. The coated tablets were kept in the desiccator until used.

4. Evaluation of Propranolol HCl Film Coated Tablets.

The following properties i.e. the average weight and weight variation, the tablet hardness, the disintegration time, the drug release test and the surface topography (either before or after the drug release test), as described in 1.2.1 - 1.2.4 and 1.2.7, were examined.

5. Preparation and Evaluation of Cast Films.

5.1 Preparation of Cast Films.

The selected film coating formulations were carefully cast onto the clean smooth surface glass plates with a diameter of 15 cm. The glass plates were thinly pretreated with simethicone and dried at the temperature of 65°C for about 24 hours. They were left cool down to the room temperature before the films were cast. The spread films were then slowly dried on the level surface at room temperature and dust-free atmosphere for about 2-3 days. Dried films were consequently removed from the glass surface and stored in the desiccator until used.

5.2 Evaluation of Cast Films.

5.2.1 Physical Characteristics.

The cast films were evaluated for different physical characteristics, such as appearance, colour, transparency, easily detachable, cracked on folding and stickiness.

5.2.2 Tensile Properties.

The method used for evaluating the mechanical properties was based on the guidelines of the American Society for Testing and Materials method D 882-80 a (American Society for Testing and Materials, 1981). Almost the central portion of the circular cast film samples were used because particle orientation at the edges of the film would differ from that found in the central part (Gibson, Rowe and White. 1988). The samples were cut into strips of 10 cm x 5 mm. The utmost care should be exercised in cutting specimens to prevent nicks or tears which were likely to cause premature failure.

The film thickness was ranged from 100-200 μm. depending on poured volume of the film coating formulations. Thickness was measured at 5 different points along the guage length (the middle 2-cm section of the samples) using a micrometer. In all cases, the test specimens should be selected so that thickness was uniform within 10% of the average thickness over the length of the specimens and there was no visible imperfection.

Each film specimen was placed between the grips of an universal testing machine. No extensometer was used because it was considered that the attachment of such a device could cause enough damage to this very delicated sample to produce premature breakage. The grips were tightened evenly and firmly to the degree necessary to minimize slipping of the specimen during test. A specific tested area, i.e. 2.0 cm. guage length, was marked in the middle section of the specimen, which was set to 0% elongation. The test was carried out using rate of grip separation 12.5 mm/min in an air-conditioned room at 25 $\pm$ 1 °C and about 50 $\pm$ 2% relative humidity. A minimum of 5 samples was extended and the displacement of the edge boundary lines with respect to each other was followed with a suitable test scales until they were broken. Stress-strain parameters, including the maximum load (breaking force) from the digital display and the elongation at the moment of rupture of the specimens from reading on the test scales for each sample were recorded.

The ultimate tensile strength was calculated by dividing the maximum load by the original minimum cross sectional area of the specimens. The result was expressed in force per unit area. The percentage elongation at break was calculated as the change in the

length at the time of sample failure divided by the original length and expressed as a percent. The arithmetic mean and standard deviation of both values obtained were also calculated from 5 determinations.

5.2.3 Moisture Sorption.

The cast films from selected film coating formulations were cut into rectangular size of 5 x 5 cm^2 and accurately weighed on a tared and numbered watch glass. They were then stored in a securely closed desiccator containing the saturated sodium chloride solution (with excess crystals) in the well, at controlled room temperature of 25 $\pm$ 2°C and about 75% relative humidity (American Pharmaceutical Association and The Pharmaceutical Society of Great Britain, 1986). The moisture uptake was measured periodically over 60 days with the aid of an analytical balance. All measurements were in triplicate.