INFORMATION TO USERS

This reproduction was made from a copy of a manuscript sent to us for publication and microfilming. While the most advanced technology has been used to photograph and reproduce this manuscript, the quality of the reproduction is heavily dependent upon the quality of the material submitted. Pages in any manuscript may have indistinct print. In all cases the best available copy has been filmed.

The following explanation of techniques is provided to help clarify notations which may appear on this reproduction.

1. Manuscripts may not always be complete. When it is not possible to obtain missing pages, a note appears to indicate this.

2. When copyrighted materials are removed from the manuscript, a note appears to indicate this.

3. Oversize materials (maps, drawings, and charts) are photographed by sectioning the original, beginning at the upper left hand corner and continuing from left to right in equal sections with small overlaps. Each oversize page is also filmed as one exposure and is available, for an additional charge, as a standard 35mm slide or in black and white paper format.*

4. Most photographs reproduce acceptably on positive microfilm or microfiche but lack clarity on xerographic copies made from the microfilm. For an additional charge, all photographs are available in black and white standard 35mm slide format.*

*For more information about black and white slides or enlarged paper reproductions, please contact the Dissertations Customer Services Department.
FORMULATION, DRUG RELEASE AND ANIMAL BIOAVAILABILITY FOR AN ORAL CONTROLLED-RELEASE DOSAGE FORM OF PROPRANOLOL HYDROCHLORIDE

St. John's University

Ph.D. 1986

Copyright 1986
by
Majeed, Muhammed
All Rights Reserved
PLEASE NOTE:

In all cases this material has been filmed in the best possible way from the available copy. Problems encountered with this document have been identified here with a check mark \( \checkmark \).

1. Glossy photographs or pages _____
2. Colored illustrations, paper or print _____
3. Photographs with dark background _____
4. Illustrations are poor copy _____
5. Pages with black marks, not original copy _____
6. Print shows through as there is text on both sides of page _____
7. Indistinct, broken or small print on several pages \( \checkmark \)
8. Print exceeds margin requirements _____
9. Tightly bound copy with print lost in spine _____
10. Computer printout pages with indistinct print _____
11. Page(s) ___________ lacking when material received, and not available from school or author.
12. Page(s) ___________ seem to be missing in numbering only as text follows.
13. Two pages numbered _______. Text follows.
14. Curling and wrinkled pages _____
15. Dissertation contains pages with print at a slant, filmed as received _______
16. Other ____________________________________________________________________

__________________________________________________________________________

__________________________________________________________________________

__________________________________________________________________________

University
Microfilms
International
FORMULATION, DRUG RELEASE AND ANIMAL BIOAVAILABILITY FOR AN ORAL CONTROLLED-RELEASE DOSAGE FORM OF PROPRANOLOL HYDROCHLORIDE

by

MUHAMMED MAJEED

A DISSERTATION SUBMITTED IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE DEGREE OF

DOCTOR OF PHILOSOPHY

TO THE FACULTY OF THE GRADUATE DIVISION COLLEGE OF PHARMACY AND ALLIED HEALTH PROFESSIONS at ST. JOHN'S UNIVERSITY NEW YORK (JUNE 1986)

SUBMITTED
BY

MUHAMMED MAJEED

DATE April 25, 1986

APPROVED
BY

DATE 4/25/86
ABSTRACT


This research work involves the formulation of an oral sustained release bead formulation of propranolol hydrochloride using Eudragit® polymers. Subsequently a comparison of its in vitro release profile and in vivo plasma levels with the marketed long acting bead formulation of Inderal LA® (ICI, England) was performed.

A mixture of propranolol hydrochloride and microcrystalline cellulose were mixed together and the mixture was applied to non-pareil seeds in a centrifugal granulator. A 10% solution of hydroxypropyl cellulose was used as the binder. Upon developing the beads to the desired potency, a solution containing Eudragit® polymers in non-aqueous solvents was sprayed onto the beads to retard drug release from the beads. Various combinations of Eudragit® polymers and different levels of coating were examined. The selected formulation which showed a similar in vitro release profile, as compared to the commercial long acting formulation, was used in the bioavailability study.
Six dogs in an "incomplete randomized block crossover design" were utilized in the study. Inderal® 40 mg immediate-release tablets, Inderal LA® (ICI, England) and the controlled-release formulation manufactured in the study were evaluated. Results of the study indicate that both Inderal LA® and the controlled-release formulation manufactured in this study show comparable bioavailability. Both of these dosage forms have lower bioavailability compared to the immediate-release dosage form.

Muhammad Majid
4/25/1986
TABLE OF CONTENTS

Abstract i
Dedication vi
Acknowledgements vii
List of Tables viii
List of Figures xi

CHAPTER I

A. INTRODUCTION 1

B. SURVEY OF CURRENT LITERATURE 3

1. Formulation Factors and Manufacturing Technologies for Oral Controlled Release Dosage Forms: A Review 3

2. Propranolol Hydrochloride: A Review 43

3. Eudragit® Polymers: A Review 59

CHAPTER II

A. EXPERIMENTAL 65

1. Materials and Equipment 65

2. Preparation of Powder Mix 65
A. EXPERIMENTAL (CONT'D)

3. Preparation of Coating Solutions 65
4. Preparation of Beads 73
5. Determination of Propranolol Hydrochloride in the Beads 77
6. In Vitro Dissolution Studies 77
7. Preparation of Dissolution Media 78
8. Preparation of Propranolol Calibration Curves 78
9. Bioavailability Study 79
10. Study Design 85
11. Blood Sampling 87
12. Preparation of the Mobile Phase of the HPLC Assay 87
13. Apparatus and Conditions for Analysis 87
14. Preparation and Extraction of Standard Plasma Solutions 88

CHAPTER III

A. RESULTS AND DISCUSSION

1. Preparation of Controlled-Release Beads 90
2. Uniformity and Percent of Active Ingredient in the Beads 90
## A. RESULTS AND DISCUSSION (CONT'D)

<table>
<thead>
<tr>
<th>Topic</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>3. In Vitro Dissolution Results of Different Formulations</td>
<td>91</td>
</tr>
<tr>
<td>5. Influence of Percent Coating on Drug Release</td>
<td>110</td>
</tr>
<tr>
<td>6. Determination of Propranolol in Plasma by HPLC</td>
<td>113</td>
</tr>
<tr>
<td>7. Reproducibility (Precision) and Linearity</td>
<td>113</td>
</tr>
<tr>
<td>8. Recovery (Accuracy) of HPLC Assay</td>
<td>116</td>
</tr>
<tr>
<td>9. Bioavailability Measurements</td>
<td>122</td>
</tr>
<tr>
<td>10. Discussion on Area Under the Curve and Other Pharmacokinetic Parameters</td>
<td>125</td>
</tr>
</tbody>
</table>

## CHAPTER IV

### SUMMARY AND CONCLUSIONS

## CHAPTER V

### LIST OF REFERENCES
Dedicated to Sami, Anju and Shaheen
who paid for my endeavor very dearly.
ACKNOWLEDGEMENTS

I wish to express my sincere thanks to the chairman of the thesis committee, Dr. Sanford Bolton for his suggestions and guidance during my research work. I would also like to express my sincere gratitude to Dr. W.L. McKenzie, under whose guidance I have conducted a major portion of my work at Wallace Laboratories. I also like to thank Vector Laboratories, Marion, Iowa for use of their facilities and Centrifugal Granulator.

In addition Rohm Pharma, Germany provided financial assistance to rent equipment needed during different phases of the work and I like to extend my sincere gratitude to Peter Tiedman, Rohm Pharma, who watched its progress with keen interest.

I further like to thank Dr. Albert S. Belmonte, Dr. C.I. Jarowski, and Dr. Robert Nash for their invaluable help and guidance during the course of this work.

I also like to acknowledge the help of Ms. Wendy Sabo and Dr. David DeLong in the bioavailability study.

Finally I like to thank my wife who typed the thesis and whose encouragement made completion of my Ph.D program possible.
<table>
<thead>
<tr>
<th>Table</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Methacrylic Acid Co-Polymers</td>
<td>61</td>
</tr>
<tr>
<td>2. Methacrylate Ester Co-Polymers</td>
<td>62</td>
</tr>
<tr>
<td>3. Methacrylate Aminoester Co-Polymers</td>
<td>64</td>
</tr>
<tr>
<td>4. Materials used in the Investigation</td>
<td>66</td>
</tr>
<tr>
<td>5. Equipment used in the Investigation</td>
<td>68</td>
</tr>
<tr>
<td>6. Anti-Adherent/Plasticizer portion of Coating Formulation</td>
<td>70</td>
</tr>
<tr>
<td>7. Various Formulations of Eudragit® Lacquer Suspensions</td>
<td>71</td>
</tr>
<tr>
<td>8. Formulation of Binder Solution.</td>
<td>72</td>
</tr>
<tr>
<td>9. CF Granulating/Coating Trial Parameters (Optimized)</td>
<td>75</td>
</tr>
<tr>
<td>10. Summary of Coating Trials</td>
<td>76</td>
</tr>
<tr>
<td>11. Absorbance Values of Propranolol Hydrochloride in Different Media</td>
<td>80</td>
</tr>
<tr>
<td>12. Weight and Age of Dogs Used in the Bioavailability Study</td>
<td>86</td>
</tr>
<tr>
<td>13. Percent of Propranolol Hydrochloride in the Uncoated Beads</td>
<td>92</td>
</tr>
<tr>
<td>14. Quantity of Propranolol Hydrochloride in the Coated Beads</td>
<td>93</td>
</tr>
<tr>
<td>15. Cumulative Percent of Drug Release from Uncoated Beads and from</td>
<td>94</td>
</tr>
<tr>
<td>Formulation A in Deionized Water</td>
<td></td>
</tr>
</tbody>
</table>
Table

16. Cumulative Percent of Drug Release from Formulation B in Deionized Water 97
17. Cumulative Percent of Drug Release from Formulation C in Deionized Water 99
18. Cumulative Percent of Drug Release from Formulation D in Deionized Water 101
19. Cumulative Percent of Drug Release from Formulation E in Deionized Water 103
20. Cumulative Percent of Drug Release from Inderal LA® Capsules and Inderal® Immediate Release Tablets in Deionized Water 105
22. Propranolol Concentration Vs. Peak Area Ratio 117
23. Reproducibility Study of Propranolol Detection from Dog Plasma Matrix 119
24. Determination of the Extraction Efficiency from "Spiked" Dog Plasma Samples 121
25. Precision and Accuracy Determination of Propranolol Recovery from "Spiked" Dog Plasma-Statistical Treatment 123
26. Plasma Concentration of Propranolol in Dogs
Table

27. Plasma Concentration of Propranolol in Dogs after Oral Administration of Inderal® Immediate-Release Tablets 124

28. Plasma Concentration of Propranolol in Dogs after Oral Administration of Inderal LA® 160 mg Capsules 126

29. Summary of Pharmacokinetic Parameters 127

29. Summary of Pharmacokinetic Parameters 139
LIST OF FIGURES

Figure                                      Page
1. Typical Drug Level vs. Time Profiles      4
2. Schematic Drawing of the Motion Behavior in the Centrifugal Granulator 19
3. Manufacturing Steps Involved in Producing Spherical Beads using a Marumerizer 21
4. Basic Elements of the Wurster Coating Column 23
5. Manufacturing Flow Diagram for the Manufacture of Osmotic System Based Tablets 37
6. Cross Section of the Indomethacin (Osmosin®) Osmotic Dosage Form 38
7. Mechanism of Drug Release from a Matrix Tablet 40
8. Pre-Systemic "First Pass Effect" - Diagrammatic Representation 47
9. Metabolism of 14C Propranolol 49
10. Basic Elements of Centrifugal (CF) Granulator 74
11. Calibration Curve for Propranolol Hydrochloride in Methanol 81
12. Calibration Curve for Propranolol Hydrochloride in Water 82
13. Calibration Curve for Propranolol Hydrochloride in Simulated Gastric Fluid without Pepsin 83
14. Calibration Curve for Propranolol Hydrochloride
15. In Vitro Dissolution Profile of Propranolol Hydrochloride from Uncoated Beads and Formulation A in Deionized Water

16. In Vitro Dissolution Profile of Propranolol Hydrochloride from Formulation B in Deionized Water

17. In Vitro Dissolution Profile of Propranolol Hydrochloride from Formulation C in Deionized Water

18. In Vitro Dissolution Profile of Propranolol Hydrochloride from Formulation D in Deionized Water

19. In Vitro Dissolution Profile of Propranolol Hydrochloride from Formulation E in Deionized Water

20. In Vitro Dissolution Profile of Propranolol Hydrochloride from Inderal LA® Capsules and Inderal® Immediate Release Tablets in Deionized Water

21. In Vitro Dissolution Profile Comparison of Inderal LA® and Formulation E Beads by the pH Change Method

22a. Influence of Eudragit® RS & RL Ratio on the Dissolution Profile of Propranolol with a 15% coating

22b. Influence of the Percent Coating on the Dissolution Profile of Propranolol in Coated Beads

23. Chromatograms of Blank Plasma and Various Concentrations (10 and 100 ng/ml) of Propranolol with the Internal Standard Desimipramine Added
Figure

24. (a)(b). Comparison of Chromatograms of Blank Plasma Vs. Plasma Obtained 1 Hour After Administration of the Controlled Release Formulation 115

25. Calibration Curve for the Propranolol Concentration Vs. Peak Area Ratio 118

26. Plasma Propranolol Concentration in Dog 1, following Oral Administration of Inderal® and Inderal LA® 128

27. Plasma Propranolol Concentration in Dog 2, following Oral Administration of Inderal LA® and Inderal® 129

28. Plasma Propranolol Concentration in Dog 3, following Oral Administration of Inderal Tablets and Formulation E 130

29. Plasma Propranolol Concentration in Dog 4, following Oral Administration of Inderal® Tablets and Formulation E 131

30. Plasma Propranolol Concentration in Dog 5, following Oral Administration of Formulation E and Inderal LA® 132

31. Plasma Propranolol Concentration in Dog 6, following Oral Administration of Formulation E and Inderal LA® 133
Figure

32. Average Plasma Propranolol Concentration in 4 Dogs after Oral Administration of Four 40 mg Immediate Release Inderal® Tablets 134

33. Average Plasma Propranolol Concentration in 4 Dogs after Oral Administration of Inderal LA® 160 mg Capsules 135

34. Average Plasma Propranolol Concentration in 4 Dogs after Oral Administration of Formulation E, 160 mg Controlled Release Beads 136

35. Comparative Plasma Drug Profiles of Different Dosage Forms Used in the Bioavailability Study 137
CHAPTER I

A. INTRODUCTION

In order to maintain therapeutic concentrations of drugs in the body over a prolonged period of time, sustained/controlled-release oral formulations are utilized (1). Several advantages are cited for this method of drug administration. Most of the currently available oral controlled-release formulations provide satisfactory blood level of 8–12 hours. Recently, a controlled release formulation of propranolol hydrochloride (Inderal LA®) has been approved for once daily dosing.

The purposes of this study are as follows:

1. To prepare a controlled release bead formulation showing an in vitro release pattern comparable to that of the commercial product.

2. To establish the experimental procedures and conditions for the preparation of the core and coated beads using a centrifugal granulator, which is versatile and commercially available.

3. To use Eudragit® polymers to obtain a diffusion controlled dosage form showing a zero-order release profile, if possible.

4. To study the in vitro release profile of propranolol hydrochloride from beads coated using various dispersions of Eudragit® polymers.
5. To compare the bioavailability of Inderal® 40 mg immediate-release tablets, Inderal LA®, 160 mg capsules and the controlled-release formulation developed in this study (160 mg) using an "incomplete randomized block crossover design" in 6 dogs.
B. SURVEY OF CURRENT LITERATURE

1. FORMULATION FACTORS AND MANUFACTURING TECHNOLOGIES FOR ORAL CONTROLLED-RELEASE DOSAGE FORMS: A REVIEW

Drugs are formulated in dosage forms to make dosing precise, reliable, safe and effective. In conventional dosage forms (e.g., tablets, capsules, liquids, ointments, injectables), the drug is combined with ingredients that preserve the drug, prevent contamination, facilitate manufacture and facilitate or retard dissolution after administration. These dosage forms usually produce therapeutic concentrations soon after administration. The concentration then declines gradually through the dosing interval until the next dose again causes drug concentration to rise. These conventional products are usually referred to as immediate-release forms.

One requirement of successful therapy is that the drug should be presented to its site of action in the appropriate quantity and for the required length of time. This objective can be realized by the proper understanding of the GI tract physiology, dosage form design and pharmacokinetics of the drug. Thus, the design concept of the dosage form to sustain or control the fluctuating levels of the drug in the body (plasma) was conceived. This fundamental concept is graphically illustrated in Figure 1.
Figure 1. Typical Drug Level Vs. Time Profile.

A) STANDARD ORAL DOSE  C) I.V. INJECTION
B) ORAL OVERDOSE  D) IDEAL CONTROLLED RELEASE DOSE
Curve D, a result of the administration of a sustained-release dosage form is considered to be ideal for most drugs.

In the last 3 decades, these products have been described by various names by pharmaceutical scientists throughout the world. A review of the literature reveals a baffling array of terms (1).

Examples:

- Continuous release
- Controlled release
- Delayed absorption
- Delayed release
- Depot action
- Extended action
- Gradual release
- Long acting
- Long lasting
- Long term release
- Programmed release
- Prolonged action
- Protracted release
- Slowly acting
- Slow release
- Spaced release
- Sustained action
- Sustained release
- Time coat
- Timed release

A number of definitions to distinguish between several of these terms has also emerged. They are:

1. **USP (PROPOSED)**

   **Modified-Release** - Those dosage forms for which the drug release characteristics of time course and/or location are chosen to accomplish therapeutic or physician/patient convenience objectives not offered by conventional dosage forms such as solutions, ointments or dissolving dosage forms.
Two types of modified-release dosage forms are recognized and defined:

**Extended-Release** - One that allows at least a two-fold reduction in dosing frequency as compared to conventional dosage forms.

**Delayed-Release** - One that releases a drug at a time other than promptly after administration.

2. **Sustained-Release** - Some predetermined fraction of the total dose is immediately released to the GI tract to establish a therapeutic level. The remaining fraction is then released as rapidly as is required to maintain the initial plasma concentration constant for some desired time period.

3. **Prolonged-Action** - Some predetermined fraction of the total dose is immediately released to the GI tract to establish a therapeutic level. The remaining fraction is then released at some rate which extends the length of time the pharmacological response could be maintained.

4. **Repeat-Action** - The equivalent of a single dose is released initially and then another single dose is released at a later time.
5. **Controlled-Release** - Any drug delivery system that achieves slow release of drug over an extended period of time. If the system successfully maintains constant drug levels in the plasma or tissues, it is a controlled-release system.

Several potential advantages have been assigned to the use of controlled drug delivery systems. They are:

- Minimize patient compliance failure
- Utilize less total drug
- Minimize or eliminate local side effects
- Minimize or eliminate systemic side effects
- Less potentiation or reduction in drug activity with chronic use
- Minimize drug accumulation with chronic dosing
- Improved efficiency in treatment
- Cure or control conditions more promptly
- Improved control of therapy, i.e., less fluctuation in drug level.

However, controlled-release preparations also have certain drawbacks (2). They are:

- Absorption of the active principle may be unexpectedly low and result in inadequate plasma concentrations. This is particularly likely to occur in patients with abnormal gastrointestinal motility.
The preparations are more complicated to manufacture and require more extensive quality control.

Sustained-release preparations may contain a larger dose of the drug than is usually administered at one time. If the rate of release of the active principle is unexpectedly high, a toxic reaction may be produced.

Controlled/Sustained-Release Theory

There are several models that could be employed in considering the theory governing the design of a sustained-release dosage form. The simplest model is:

It is assumed that the immediate dose is rapidly absorbed following oral administration with the first-order rate constant, $K_1$, being the absorption constant and that the zero-order release from the sustained-release compartment is rate-determining and equal to $K_0$. Thus the
Immediate-release compartment is designed to achieve a rapid therapeutic blood level and the sustained-release compartment is intended to maintain the level in accordance with the following equation:

\[
\text{Rate in}, \ K_d = K_2 \times C_D \times V_D = \text{Rate out}
\]

Where,
- \( K_2 \) = Rate constant for drug elimination
- \( C_D \) = Desired drug level
- \( V_D \) = Volume space in which drug has distributed

**FACTORS INFLUENCING THE DESIGN OF ORAL CONTROLLED-RELEASE DOSAGE FORMS.**

The various factors to be considered in the design of an oral controlled-release dosage form can be broadly divided into 2 groups:

- Physicochemical properties of the drug
- Biological factors

**Physicochemical properties**

- Dose size
- Aqueous solubility
- Partition coefficient
- Drug stability
- Protein binding
- Molecular size
- Charge and pKa
Dose Size

Single dose size of 0.5 g for the conventional dosage form is an upper limit for the controlled-release system, because an unacceptably large volume of drug would be required for the latter system (3).

Aqueous Solubility

Aqueous solubility of a drug exercises its control on the absorption process in two ways: 1) by its influence on the dissolution rate of a compound, which establishes the drug concentration in solution and hence the driving force for drug-membrane permeation (3) and 2) by its effect on the ability of the drug to penetrate membranes and tissue. Drugs with solubility less than 0.01 mg/ml show dissolution-limited availability and are inherently sustained (4). This parameter is utilized in preparing controlled-release dosage forms by converting soluble salts to slowly dissolving compounds. Drugs with very high aqueous solubilities are difficult to convert to slowly dissolving forms. High aqueous solubility also restricts the mechanism that can be used in the design of these dosage forms. Drugs with low solubility cannot be used for the diffusion-controlled release dosage form because of the small driving force for diffusion. Drugs exhibiting strong pH-dependent solubility characteristics in the physiological pH range would be poor candidates for oral controlled-release products.
Partition Coefficient

The optimum partition coefficient which shows maximum flux for many body tissues is regarded as 1000/1 in n-octanol/water (5), where n-octanol represents the oil phase. Drugs with high partition coefficients can persist in the body for a long time. The phenothiazines (6,7) possess a high coefficient and thus are poor candidates for a slow release system.

Drug Stability

Drugs degraded in the stomach show increased bioavailability in the controlled-release form (8). The bioavailability of drugs metabolized in the intestine is decreased with the controlled-release dosage form, because it is designed to stay for a longer time in the intestine. Propantheline (9) and probanthine (10) are examples of the latter.

Protein-Binding

Many drugs bind to plasma proteins and can serve as a depot for a drug thus producing a prolonged release (11).

Drug Molecular Size

The ability of a drug to diffuse through membranes, called diffusivity, can be influenced by its molecular size which in turn is dependent on the molecular weight.
Knowledge of diffusivity of a drug is crucial if a polymeric membrane is relied upon as the controlled-release mechanism. In general drugs with molecular weights greater than 750 will show slow diffusion. A diffusion coefficient of about $10^{-8}$ cm$^2$/sec is desired for intermediate molecular weight substances (150-400 mol.wt).

Charge and pKa

According to the pH-partition hypothesis the uncharged form of a drug will be preferentially absorbed. Since the charged (ionic) to uncharged ratio is usually related to pH, there can be a significant influence of formulation on the absorption of drugs.

The uncharged form of a drug shows low binding capacity to intestinal proteins. A charged form of a drug will show greater potential for binding to the intestinal protein or mucin and thereby cause decreased absorption or loss of drug.

The charge on a compound also plays a key role in diffusion through the polymeric membrane of a drug delivery system.

Biological Factors

- Absorption
- Distribution
- Metabolism
Absorption

In the case of a poorly absorbed drug, a controlled-release dosage form may inhibit absorption because of the slow drug release rate from the dosage form and/or gastrointestinal transit time. The lower limit on the absorption rate constant is 0.25 hr\(^{-1}\) assuming a GI transit time of 10-12 hours (8). Some drugs are absorbed by an active process. This is often a saturable process and occurs at a specific absorption site in the intestine, so the controlled-release dosage form has no demonstrable advantage (12,13). However, modern formulation technology has overcome this difficulty by formulating a dosage form in such a way that it is hydrodynamically balanced to be buoyant in the gastric fluid. The dosage form remains buoyant in the gastric fluid until substantially all of the medicament therein has been released (14).

Distribution

For the successful design of controlled-release dosage forms, information regarding its disposition in the body is vital. One of the key parameters is volume of distribution.
The apparent volume of distribution influences the concentration and amount of drug either circulating in the blood or target tissues and it can influence the elimination kinetics of the drug. This influence is frequently not predictable due to difficulties in interpreting the apparent volume of distribution. An extensive discussion on this topic is found in a series of papers by Kruger-Thiemer, et al. (15-17).

**Metabolism**

Metabolic alterations of a drug can occur in a variety of tissues, some of which are richer in enzymes than others. Metabolism of alprenolol during the passage through the intestinal wall was more complete with a controlled-release dosage form than a conventional dosage form (18). High concentration of dopa decarboxylase in the intestinal wall was found to decrease the bioavailability of levodopa in a sustained-release dosage form (19). A number of other drugs undergo first-pass hepatic elimination with reduced bioavailability for the controlled-release dosage form. Examples of such drugs are nitroglycerin (20) and propranolol (21).

**Duration of Action of the Drug**

The biological half-life and therefore the duration of action of a drug plays a key role in the selection of a drug
as a candidate for controlled-release dosage forms. Drugs with a very short half-life will require too large a dose for the controlled-release dosage form (22). Certain drugs with short half-lives; e.g., methylprednisolone (half-life 3.3 hours) and prednisone (half-life 1 hour) exhibit extended drug effects for more than 2 days even with their short half-lives (23,24). Such drugs in controlled-release dosage forms offer no advantage over immediate-release dosage forms except for the claim that reduced peak blood level associated with less severity of side effects. Drugs such as phenylbutazone (half-life 72 hours) have no need for sustained-release dosage forms. The long half-life of the drug is due to extensive plasma binding (25). However, there are commercially available controlled-release products with intrinsically long biological half-lives. Examples include meprobamate, chlordiazepoxide and diazepam.

An optimum half-life for designing a controlled-release dosage form is about 4 hours for a 12 hour release product. Examples of such drugs include phenylpropanolamine (26), propranolol (27) and procainamide (28).

Margin of Safety

Therapeutic Index is one of the criteria used to describe the margin of safety of a drug. It is defined as:

\[
\text{Therapeutic Index} = \frac{\text{Median Toxic Dose}}{\text{Median Effective Dose}}
\]

-15-
There is wide variation in the therapeutic index of various drugs. A drug is considered to be therapeutically safe if its therapeutic index exceeds 10. Drugs with narrow therapeutic indices require precise control over drug concentration and consequently, sustained and controlled release forms are desired for these drugs. Examples of such drugs include cardiac glycosides and antiarrhythmics (29). Additional considerations to be entertained in the development of a sustained or controlled release dosage form include role of the disease state which would benefit from a controlled release dosage form (30) and the influence of circadian rhythm in overall drug response. Certain drugs formulated in controlled release dosage form tend to show reduced side effects as seen in the case of potassium chloride (31) (Micro K® Extencaps by A.H. Robins).

**TYPES OF ORAL CONTROLLED RELEASE PREPARATIONS:**

The following classification of controlled release dosage forms is based on their method of manufacture and formulation technology used.

- Barrier-coated beads/granules
- Coated ion-exchange resins
- Low-density hydrocolloids
- Wax matrices
- Plastic matrices
Barrier-Coated Beads/Granules

Beads enclosed in a hard gelatin capsule is the most widely used oral controlled-release dosage form. There are 4 methods commercially used to prepare barrier coated beads.

1. Conventional Coating Pans

In this case inert sugar seeds (non-pareils) are discharged into a coating pan. The pan is set to roll at a specified revolution and the binder solution is sprayed on to the inert sugar seeds. The wetted seeds are dusted with drug or drug-excipient mixture, which now adheres to the inert seeds. This process is repeated until the beads are built up to the required potency. The beads are now coated with polymeric solutions or waxes to delay the drug release. This method is extensively used in the industry. This is a time-consuming variable process and drug loading on the beads is limited to a maximum of 50 percent of the total weight.

2. Centrifugal Granulator

A specially designed fluid bed called a centrifugal
force granulator (32) sold by Vector Corporation (Marion, Iowa) is a very useful device for the production of spherical beads or pellets. Glatt Air Techniques (Ramsey, New Jersey) also markets a similar centrifugal force granulator (33) for the manufacture of beads or pellets. The fluidizing/agglomerating portion of the unit is shown in Figure 2.

A specially designed rotor is inside of a large stationary cylinder (stator) and a bed of powders, granules or beads forms a fluidizing doughnut along the wall of the stator with a rope twisting like motion which is created by joint forces of centrifugal force ($Z$), rotating speed, gravity ($G$) and fluidization air directed through the slit ($W$). When binding or coating solution and powders are sprayed onto this fluidizing twisted doughnut ring of the bed, they mix and develop very quickly and uniformly into uniform beads.

The unit is capable of performing agglomeration, granulation and coating for any kind of powder. Nearly perfect spherical beads with sharp size distribution can be produced in a short processing time. Controllability of spray solution and powder along with quick product discharge contribute to the ease of manufacture using this unit. Drug loading can be up to 90 percent. Alternately non-pareil seeds can also be used as the start up material followed by continuous addition of binder solution and drug powder.
Figure 2. Schematic Drawing of the Motion Behavior in the Centrifugal Granulator.
Uniform beads with up to 70 percent drug loading can be accomplished (34).

3. Marumerizer (35)

The process of forming spheres using a marumerizer involves wet granulating the powder mix in a suitable mixer. The amount of water, solvents or other excipients used is dependent on the nature of the powder. The wetted mass is then fed into the extruder. The extruder comprises a single or double screw which feeds the moistened material into a radial screen or axial die, from which it is extruded through apertures of 0.5 mm to 15 mm in cylinders of 2 to 20 cm long. The marumerizer consists of a stationary vertical cylinder, open at the top, with smooth internal walls and a diameter of 30 to 100 cm. Within the base of this cylinder rotates a rough surfaced plate with its periphery 0.25 mm from the internal surface of the cylinder. The speed of rotation of the plate may be varied from 400 to 1600 rpm and the surface of the plate is filled with grooves intersecting at right angles 1 to 2 mm deep and 2 to 4 mm apart. Figure 3 provides the sequence of steps in producing a spherical pellet.

Damp cylindrical segments from the extruder are introduced into the marumerizer bowl from above as the extrudate falls onto the rotating plate, the segments break into cylindrical pellets, centrifugal and gravitational forces
Figure 3. Manufacturing Steps Involved in Producing Spherical Beads Using A Marumerizer. The Numbers Indicate the Order In Which the Process is Carried Out.

1. POWDER MIXER

2. KNEADER

3. XTRUDER

4. MARUMERIZER

Steps:

1. POWDER MIX
2. WET MIX
3. CYLINDRICAL PELLETS
4. SPHERICAL PELLETS
create a mechanically fluidized ring of particles which slowly rotates against the inside wall of the marumerizer. Collisions with the wall, friction plate and other particles result in the plastic deformation of each granule as the shape gradually changes from cylindrical to spherical.

The desired shape is time-dependent and achieved predictably and repeatedly in a very brief period called the "spheronizing" time. These spherical beads can be then coated with polymeric solutions to control drug release. Drug loading up to 90 percent is possible using this technique.

4. Air-Suspension Coating

The original air-suspension coating equipment was developed by Dale Wurster at the University of Wisconsin (36). The process of air suspension coating simultaneously applies and dries encapsulating materials onto particles supported by an upward moving air stream resulting in intimate contact between the particles being coated and the drying air. The basic unit is shown in Figure 4.

The movement of particles within the coating chamber is controlled by the size and distribution of perforations in the plate, producing a cyclic flow pattern into which the coating material is atomized. The moving particles cycle past the nozzle every four to six seconds, receiving an
Figure 4. Basic Elements of Wurster Coating Column.
increment of coating on each pass. The particles exhibit uniform build-up of coating as the run progresses.

In the Wurster process, drying condition is a function of the humidity and temperature, and flow volume of the processing air stream. The volume of the processing air is determined by the size, shape and density of the material being encapsulated; small density particles require less air flow than large dense particles. The temperature of the processing air is limited only by the sensitivity of the material being encapsulated or the coating itself. A number of polymeric materials can be applied to drug beads using aqueous or non-aqueous systems in the Wurster column. Some of the polymers useful in controlled release include ethylcellulose, methylcellulose, hydroxypropyl cellulose, cellulose acetate phthalate, hydroxypropyl methylcellulose, polyvinyl acetate, shellac and acrylic polymers.

**TYPES OF COATING AND MECHANISM OF DRUG RELEASE FROM VARIOUS TYPES OF BEADS.**

1. **Using a Water-Insoluble Polymer** (37)

   In this case a water-insoluble polymeric material encases a core of drug. In the presence of fluids, the drug will partition into membrane and exchange with the fluid surrounding the particle. As time goes on, additional drug will enter the polymer, diffuse to the periphery and exchange with the surrounding media.

   \[
   \text{Release rate} = ADK \frac{\Delta C}{L}
   \]

   -24-
**2. Diffusion Control of Drug Release by Solid Drug Dispersed in an Insoluble Matrix (38).**

An example is the methyl acrylate/methyl methacrylate plastic matrix containing a drug. Higuchi derived the relationship for various factors affecting drug release from a granular matrix in which diffusion occurs through a channel.
\[ Q = \left[ \frac{D\epsilon}{T} \left( 2A - \epsilon C_s \right) C_0 t \right]^{1/2} \]

- \( Q \) = Weight in grams of drug released per unit area of surface at time \( t \)
- \( D \) = Diffusion coefficient of drug in the release medium
- \( \epsilon \) = Porosity of the matrix
- \( C \) = Solubility of the drug in the release medium
- \( \gamma \) = Tortuosity of the matrix
- \( A \) = Concentration of drug in the matrix expressed as gm/ml

3. Another diffusional mechanism is the system where a Partially Soluble Membrane Encloses a Drug Core

Dissolution of part of the membrane allows for diffusion of the constrained drug through the pores in the polymer coat (39).
Release rate = $AD/\ell (C_1 - C_2)$

$C_1$ = Concentration of drug in the core
$C_2$ = Concentration of drug in the surrounding media
$A$ = Area
$D$ = Diffusion coefficient
$\ell$ = Diffusion path length (thickness of the coat)

An example is a polymer coating consisting of ethylcellulose and methylcellulose. The latter dissolves leaving the ethylcellulose coat behind.

4. **Dissolution Control of Drug Release via Drug-Impregnated Erosion.** (40)

Microencapsulated drug where the drug is uniformly distributed in the matrix and the coating is erodible.

Release rate = $K_0 4\pi R^2$

Where $K_0$ = Dissolution constant in mg/hr-cm$^2$
$R$ = Radius of eroding core
The above equation is based on spherical tablets or particles. Erosion of conventional flattened tablets is similar but there is a combination of various R terms to be considered where R depends on the axis being measured.

5. Enteric-Coated Beads (41)

Drug is incorporated into pellets of uniform size and are uniformly coated with an enteric polymer which does not dissolve in the acidic contents of the upper GI tract. The release rate of the drug is dependent upon the stomach emptying rate for the pellets. The stomach emptying rate for several hundred pellets is random with an overall pattern approaching a normal distribution. Another approach (42) utilizes different enteric polymers to achieve dissolution in the various pH conditions encountered in the different regions of the GI tract. Examples of polymers include:

<table>
<thead>
<tr>
<th>Polymer</th>
<th>pH of solubility</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cellulose acetate phthalate</td>
<td>5.5</td>
</tr>
<tr>
<td>Hydroxypropyl methylcellulose (hp 50)</td>
<td>4.8</td>
</tr>
<tr>
<td>phthalate (hp 55)</td>
<td>5.8</td>
</tr>
<tr>
<td>Carboxymethyl ethylcellulose</td>
<td>6.0</td>
</tr>
<tr>
<td>Eudragit® L</td>
<td>6.0</td>
</tr>
<tr>
<td>Eudragit® S</td>
<td>7.0</td>
</tr>
</tbody>
</table>
6. **Dissolution Control of Drug Release via Thickness and Dissolution Rate of the Membrane Barrier Coat** (43).

![Diagram](https://via.placeholder.com/150)

Selection of a desired coating thickness leads to a repeat-action dosage form.

Equation describing release: Drug is provided in pulsed dose fashion once the coat has dissolved. The time for the coat to dissolve can be calculated from the dissolution rate constant for the polymer and the coating thickness.

7. **Slow-Release Beads**

Slow release beads can be manufactured using non-pareil seeds coated with drug using conventional enteric polymer solution as binder and encased using waxes. These beads can be mixed with an immediate-release granulation and tableted (44). An example is Theo-Dur® tablets manufactured by Key Pharmaceuticals. Drug release from these beads is
controlled primarily by the dissolution rate of the polymer.

**Coated Ion-Exchange Resins**

The strasionic (Strasenburgh) principle involves administration of capsules containing salts of drugs with polystyrene sulfonic acid resin. This resin salt exchanges drug for ions as it passes through the gastrointestinal tract (45). For example, an amine drug might be exchanged as:

\[
\begin{align*}
\text{RS}_3^- & \quad \text{H}_3\text{N}^+ - \text{R}^+ \quad \text{X}^+ \quad \text{RSO}_3^- \quad \text{X} + \text{R'}\text{NH}_3^+ \\
\text{Amine Drug Resinate} \\
\text{Where} \quad \text{X}^+ & = \text{H}^+, \text{Na}^+, \text{K}^+, \text{etc, or} \\
\text{RSO}_3^- & \quad \text{H}_3\text{N}^- - \text{R'} \quad \text{Y}^- \quad \text{RSO}_3^- + \text{R'}\text{NH}_2^+\text{HY}
\end{align*}
\]

The rate of drug release is thus proportional to the concentration of ions present in the gastrointestinal tract. It was shown that the amount of ions remain fairly constant throughout the gastrointestinal tract. The constant release principle is based upon a relatively constant exchange rate. Successful utility of this technology is seen in the case of a controlled-release liquid formulation manufactured by Pennwalt Corp (46).

According to Pennwalt, coated ion-exchange technology can totally eliminate unpleasant drug taste when used in liquid formulation.
**Low-Density Hydrocolloids**

Such controlled release formulations comprise one or more medicaments in combination with a hydrocolloid so as to be hydrodynamically balanced. In contact with gastric fluid, the product has bulk density (specific gravity) less than one and therefore is buoyant in gastric fluid. Thus, the product is retained in the stomach during the time when substantially all of the medicaments are released (14,47).

Examples of polymers used in the formulation include sodium carboxymethylcellulose (high viscosity grade) hydroxypropyl methylcellulose and ethylcellulose.

Riboflavin, a poor candidate for controlled release using conventional techniques was formulated and tested in vivo to demonstrate claims of controlled release via floating in the stomach of the dosage form. Another controlled-released dosage form commercially marketed using this technology is Valrelease®.

**Wax Matrices**

The drug is incorporated into a tablet with insoluble materials of high molecular weight fats and waxes. The tablets do not disintegrate but instead maintain their relative geometric shape throughout the gastrointestinal tract. The drug release is due to surface erosion of the intact tablet. An initial immediate release dose may be pan coated onto the surface of the core sustained-release tablet.
Slow K®, a controlled-release formulation of potassium chloride utilizes this concept (48).

Procan SR®, a controlled-release formulation of procainamide also utilizes this concept (49).

A controlled-release tablet containing fluoride is another example (50).

**Plastic Matrices (51)**

The drug is combined with a plastic matrix and made into a tablet dosage form. As the tablet passes through the gastrointestinal tract, the drug is leached out by the biological fluids at a rate which is relatively independent of pH and enzymes. Thus the shell, excreted intact, has been depleted of most of its drug content.

An example is Theograd®, a sustained-release theophylline dosage form by Abbott.

**Osmotic Systems (52)**

One of the most advanced forms of novel GI drug delivery systems is the elementary osmotic pump. This concept was developed by Alza and it has resulted in many useful therapeutic applications. The osmotic pressure controlled drug delivery system is fabricated by coating a core reservoir of an osmotically active drug or a combination of osmotically inactive drug with an osmotically active salt. The coating is generally a biocompatible polymer; e.g., cellulose
acetate which can form a semipermeable shape retaining coating. A delivery orifice with a controlled diameter is drilled by a laser beam through the coating membrane for the release of drug solutes (53). The following are the advantages cited for this dosage form:

- Release rates are independent of the agent properties.
- Delivers both macromolecules and ionic species.
- Yield relatively high fluxes.
- Release rates are not dependent on environmental conditions.

The disadvantages of the dosage form are:

- Subject to dose dumping if membrane breaks.
- More expensive than coated tablets.
- Possible plugging of laser orifice which might result in the drug being not released.

The coating membrane is rigid and capable of maintaining the structural integrity of the drug delivery system during the time of drug release. It is permeable to the influx of gastrointestinal fluids but is impermeable to drug solutes. When the product is administered, the gastrointestinal fluid which is continuously imbibed through the semipermeable membrane into the drug reservoir compartment, quickly dissolves the osmotically active salt and creates an osmotic pressure gradient across the membrane. Under this osmotic pressure gradient, the drug solutes are continuously
dispensed through the delivery orifice, over a prolonged period of time, at a rate defined by the following relationship (54).

\[
\left(\frac{Q}{t}\right)_{z} = \frac{P_{w}A_{m}}{\delta_{m}} \left(\pi_{t} - \pi_{e}\right) S_{D}
\]

\[
\left(\frac{Q}{t}\right)_{z} = \text{Zero-order release rate}
\]
\[P_{w} = \text{Water permeability of the semipermeable membrane}
\]
\[A_{m} = \text{Surface area of the semipermeable membrane}
\]
\[\delta_{m} = \text{Thickness of the semipermeable membrane}
\]
\[\pi_{t} = \text{Osmotic pressure in the saturated solution of osmotically active salt in the system}
\]
\[\pi_{e} = \text{Osmotic pressure in the gastrointestinal tract}
\]
\[S_{D} = \text{Solubility of the drug}
\]

The dosage form delivers drug at a zero order rate until the concentration of the osmotically active salt in the system drops to the level below the saturation solubility. This non-zero-order release pattern is described by the following equation (55).

\[
\frac{dQ}{dt} = \frac{\left(\frac{Q}{t}\right)_{z}}{1 + \frac{\left(\frac{Q}{t}\right)_{z}}{S_{D} \cdot V_{t}} (t-t_{z})^{2}}
\]

Where

\[
\left(\frac{Q}{t}\right)_{z} = \text{Zero-order drug release rate}
\]
\[V_{t} = \text{Total volume inside the system}
\]
tz = Total time at which the system delivers the drug at zero-order rate

\( t \) = Total residence time

The thickness of the coating membrane can be varied to obtain differences in the duration of zero-order release rate. The external surface of the semi-permeable membrane can be further coated with a layer of bioerodible polymer; e.g., enteric coating to regulate the availability of gastrointestinal fluid for permeation through the semi-permeable membrane (55). The coating membrane can also be constructed from a laminate of two or more semipermeable membranes with differential permeability (56).

A further development is the design of a two compartment osmotic pressure system. The two compartments are separated by a movable partition. The osmotically active compartment imbibes fluid from the gastrointestinal tract to create an osmotic pressure on the partition. In turn the partition moves to force the drug reservoir compartment to reduce its volume and to release the drug solutes through the delivery orifice (57).

Many of the steps in the manufacturing process are carried out by conventional pharmaceutical operations. For example, the cores containing sodium indomethacin trihydrate are made by granulating all of the core ingredients. This is followed by the usual milling and drying steps and finally compressed into tablets on a high-speed rotary...
press. The semi-permeable membrane and color coating are applied with air suspension coating equipment. The coated systems are dried to reduce residual solvent levels and then drilled with a laser unit to form the exit port for drug release. The steps involved in manufacturing are shown in Figure 5. The first commercial product to be marketed using this technology was 'Osmosin' tablets by Alza for Merck & Co. A cross section of the indomethacin dosage form is shown in Figure 6.

The system is designed to deliver 75 mg of indomethacin, 70% of which is delivered at a rate of 7 mg/hr. The product delivers the drug for 10-12 hours (58). Excess drug is incorporated into the core because some drug will remain in the system when it ceases to function.

While performing remarkably well in standard in vitro and in vivo conditions, the product proved a failure in clinical use due to a high rate of gastrointestinal side effects associated with the dosage form. The product was withdrawn from the market and investigations are continuing to determine the reasons for these side effects. However there are a number of other drugs presently being tested in the osmotic system (59, 60).

Formation of Less Soluble Complexes (Durabond Principle)

Amine drugs form insoluble complexes with tannic acid. Examples of such complexed drugs are chlorpheniramine
Figure 5. Manufacturing Flow Diagram for the Manufacture of Osmotic Tablets.
Figure 6. Cross Sectional View of Osmosin,® (Indomethacin Osmotic Dosage Form)
tannate, ephedrine tannate, phenylephrine tannate and pseudoephedrine tannate (61). These tannate complexes are formulated into tablets using conventional techniques and ingredients. The Mallinckrodt Chemical Company refers to these long-acting oral dosage form which employ such complexes as Rynatan®, Nallertan®, Atratan® etc.

**Hydrophilic Gum Matrices** (62)

A matrix can be defined as a well mixed composite of ingredients fixed into a specific shape either by tableting or by placing the mix into a capsule. The mechanism of controlled-drug release is achieved by utilizing a water-soluble polymer. When placed in the dissolution media, a gelatinous layer is formed on the tablet surface. The gel that forms is an aggregate mass of polymer, drug and excipients experiencing varying degrees of hydration. This gelatinous layer controls the release of drug by the following mechanisms:

- Water-soluble drugs may become available by diffusion through the pseudo-gel layer.
- Drugs may be available by erosion of the gel layer regardless of the drug's solubility.
- A water-insoluble drug is released to the dissolution media strictly through erosion.

This concept is shown schematically in Figure 7.

The polymers used include hydroxypropyl methylcellulose
Figure 7. Mechanism of Drug Release from a Matrix Tablet.

DRY TABLET

INGESTION OF TABLET

INITIAL WETTING
Tablet surface wets, and METHOCOL polymer starts to partially hydrate, forming a gel layer. Initial burst of soluble drug from the external tablet is released.

EXPANSION OF GEL LAYER
Water permeates into the tablet increasing the thickness of the gel layer, and soluble drug diffuses out of gel layer.

TABLET EROSION
Outer layer becomes fully hydrated and is released into the gastric fluids. "Water" continues to permeate toward the tablet core.

SOLUBLE DRUG
...is released by diffusion from the gel layer and by exposure through tablet erosion.

INSOLUBLE DRUG
...is released by exposure through tablet erosion.
A distinct advantage of this technology is the simplicity in manufacturing; i.e., only conventional mixing, tableting or encapsulation steps are involved.

**Microencapsulation**

Microencapsulation, in the pharmaceutical sense, may be considered as a method of encasing small drug entities in individual protective coatings for a variety of reasons. These coatings may be designed to protect or aid in storage and handling or may be fabricated so that the encapsulated material is released at a predictable rate in order to control or prolong drug action. The release of a drug from a microcapsule may be dependent upon moisture, pH, diffusion barrier and the nature of the drug. This capability of making very small capsules provided a method of converting liquids, inks, solvents and other chemical solutions to free flowing solids.

A variety of methods have been developed in the last 3 decades to encapsulate solids and liquids. They are summarized below.

<table>
<thead>
<tr>
<th>Method</th>
<th>Materials Encapsulated</th>
<th>Size Range (um)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coacervation</td>
<td>solids &amp; liquids</td>
<td>2-5000</td>
</tr>
<tr>
<td>Polymerization</td>
<td>solids &amp; liquids</td>
<td>0.2-3000</td>
</tr>
<tr>
<td>Phase separation</td>
<td>solids &amp; liquids</td>
<td>2-5000</td>
</tr>
<tr>
<td>Electrostatic</td>
<td>solids &amp; liquids</td>
<td>2-3000</td>
</tr>
</tbody>
</table>
Major elements in a microencapsulation system include core, encapsulation material, and processes.

One of the most interesting microencapsulated products for controlled release is the dosage form developed by Eurand Corporation. The Diffucap® dosage forms, as they are called, release the drug by a diffusion mechanism (67). It is claimed that the Diffulac membrane of undisclosed composition becomes microporous in water and permits dissolution of the contents at ambient pH. The dissolved drug then diffuses through the pores over an 8 to 12 hour period.
PROPRANOLOL HYDROCHLORIDE: A REVIEW.

Chemistry (68)

The chemical name of propranolol is 1-(isopropylamino)-3-(1-naphthoxy)-2-propanol hydrochloride having a mol.wt. 295.8. The common name of Inderal® is the ICI registered trade name used in the U.S. and other 70 countries. The ICI registered trade name is Avlocardyl® in France; Deralin® in Israel; Dociton® in Germany; Inderalici® in Mexico and Sumial® in Spain.

The structure of propranolol is:

![Chemical Structure of Propranolol]

Propranolol was synthesized by Crowther and Smith in October 1962. A U.S patent was granted in 1967.

Propranolol hydrochloride is an off-white to white crystalline solid with little or no odor. It has a bitter taste and a maximum melting range of 1.5°C, melting beginning between 162.5°C and 165°C. Propranolol dissolves in water to the extent of 1 part in 20 at 20°C. The compound is stable for 2 years at 50°C but is
photosensitive at room temperature. Aqueous solutions are prone to oxidation, manifested by discoloration and opalescence. The pH of a 1% w/v solution is 5.0-6.0. The pKa of propranolol free base is 9.45. The partition ratio (chloroform/water) of propranolol free base is 3900/1.

Pharmacological Actions

Propranolol is a beta-adrenergic blocking agent. The principal effect of beta-adrenergic blockade is to reduce cardiac activity by diminishing or preventing beta-adrenergic stimulation. By reducing the rate and force of contraction of the heart, and decreasing the rate of conduction of impulses through the conducting system, the response of the heart to stress and exercise is reduced.

Propranolol is the most widely used therapeutic beta-blocking agent. Its value in the treatment of hypertension (69-70), angina pectoris (71-82), cardiac arrhythmias (83-84), and hypertrophic subaortic stenosis (85), and in the management of hyperthyroidism (86) is well established. Recently, it has been shown to be effective in the prophylaxis of migraine headache (87), the prevention of stage fright (88) and effective in the reduction of mortality in patients who have experienced a myocardial infarction (89).
Contraindications

Propranolol hydrochloride is contraindicated in cardio­
genic shock, sinus bradycardia, bronchial asthma, congestive heart failure unless the failure is secondary to a tachyar­
rhythmia treatable with propranolol hydrochloride.

Toxicity

The most common toxicity or side effects of propranolol are nausea, vomiting, diarrhea, fatigue and dizziness. Cardiovascular effects include bradycardia, congestive heart failure, heart block, hypotension, cold extremities, Raynaud's phenomenon and paraesthesia. Central nervous system effects include depression, hallucinations, and disturbances of sleep and vision. Bronchospasm may occur, particularly in susceptible individuals. Blood disorders and skin rashes may also occur. Other adverse effects reported include constipation, fluid retention and weight gain, muscle cramps and dry mouth. Side effects may be minimized by starting treatment with a small dose and gradually increasing, although serious reactions have been reported after small doses.

CLINICAL PHARMACOKINETICS

Absorption

The fate of intravenously and orally administered pro­
pranolol has been studied by J.W. Patterson, et al. (90)
using $^{14}$C labelled propranolol. Results of the study showed that after oral administration there is virtually complete absorption from the GI tract. However, systemic availability is low after oral administration due to the extensive "first pass" effect (91). D.G. Shand and R.E. Rangno (92) have shown that after oral administration of doses less than 30 mg, only trace amounts of the drugs were detected in the systemic circulation. With oral doses exceeding 40 mg, the area under the blood concentration/time curve was linearly related to dose.

**Distribution & Metabolism**

As a result of the anatomical arrangement of the portal circulation, the liver can remove the drug from the portal venous blood during its transfer from the gut to the systemic circulation. The drug is extensively metabolized by the liver enzymes before reaching the systemic circulation. This phenomenon is referred to as "first pass" effect. In contrast, when administered intravenously, the drug is available to the systemic circulation immediately before it reaches liver to undergo metabolism. Both of these concepts are shown in Figure 8.

The three major biological determinants of propranolol disposition are the activity of the drug metabolizing enzymes in the liver, hepatic blood flow and plasma drug binding (27). The hepatic uptake process is so great that
Figure 8. Presystemic "First Pass Effect". A Diagrammatic Representation of Intravenous and Oral Administration of Propranolol. The Shading Represents Drug Concentration and the Arrows Represent Route of Administration.
the hepatic extraction ratio for the drug is very large after intravenous administration of normal therapeutic doses. An hepatic extraction in excess of 90% has been demonstrated directly in the dog and by inference in man, as its clearance from the blood (about 1.2 l/min) approaches a value for hepatic blood flow (92). Very high hepatic extraction results after an I.V. dose with a drug possessing a half-life of two to three hours.

When propranolol is administered orally, the drug is extensively metabolized by the liver before it reaches systemic circulation. The fraction of the dose removed during presystemic hepatic elimination is equal to the hepatic extraction ratio, so that the fraction that passes into the systemic circulation is given by \((1-e)\). The greater the extraction ratio, the smaller will be the fraction of the dose that is available to produce systemic effects. This fraction relates to the bioavailability of the drug. Drugs with high extractions, like propranolol, can therefore never be fully bioavailable even though their alimentary absorption is complete.

Using \(^{14}\text{C}\) labelled propranolol, Bond (93) showed that propranolol formed at least two metabolites, naphthoxylactic acid and 4-hydroxypropranolol. The latter compound has been shown to possess beta-blocking properties with both intrinsic sympathomimetic activity and membrane-stabilizing activity. The metabolites are shown in Figure 9.
Figure 9. Metabolism of $^{14}\text{C}$ Propranolol.

4-Hydroxypropranolol.

Naphthoxylactic acid.
Elimination

After I.V. administration, propranolol clearance from the blood approaches a value for hepatic blood flow (about 1.2l/min). The apparent volume of distribution in blood is about 250 liters (27). The relationship between drug clearance ($C_l$), apparent volume of distribution ($V_d$) and half-life ($t_{1/2}$) is given by

$$C_l = V_d \times \frac{.693}{t_{1/2}}$$

Because of the very high hepatic extraction ratio of propranolol, its clearance is sensitive to alterations in hepatic blood flow (95). Since the beta-blocking effects of propranolol result in reduced cardiac output (96), hepatic blood flow is lowered during administration of this drug and hepatic elimination is reduced. Thus intravenously administered propranolol, by its pharmacologic action, affects its own clearance by decreasing delivery of drug to the liver.

The availability of small single oral doses of propranolol is very small due to the "first pass" effect. However, as the single oral dose is increased above about 30 mg, the avid removal process becomes saturated and hepatic extraction falls, resulting in a larger fraction of an oral dose reaching the systemic circulation and a longer half-life of three to six hours in normal subjects (92). Furthermore this avid hepatic metabolism remains saturated throughout the usual six hour dosage interval so that drug concentrations in the blood accumulate during chronic oral
administration (97). Finally when steady state is reached during continuous oral administration, drug concentrations are essentially proportional to dose, in contrast to the situation following single oral doses. However, even during chronic oral administration the hepatic extraction is still relatively high (0.5 to 0.8) so that only 20-50% of the dose reaches the systemic circulation.

Propranolol Half-Life and Duration of Action

In the case of beta-blockade with propranolol after intravenous administration, it was found that reduction in exercise heart rate is a function of the logarithm of the plasma concentration (96). Thus, this effect declines as a linear function of time as the plasma concentration declines exponentially (i.e., first-order). It is therefore to be expected that drug effect should decline less rapidly than plasma concentration when exercise tachycardia is used to judge efficacy. On the other hand, the efficacy of propranolol can be determined from the antagonism to isoproterenol-induced tachycardia. This antagonism is competitive and therefore can be overcome by increasing isoproterenol dosage, that is, the dose/response curve for isoproterenol is shifted to the right in parallel fashion by propranolol. Such an effect can be quantified by calculation of a dose ratio (DR) for isoproterenol. When beta-adrenergic blockade is defined by the dose ratio to isoproterenol (DR), then
log (DR-1) is a function of log plasma concentration (99). In this case, DR-1 theoretically falls in parallel with time.

Zacest and Koch-Weser (100) have shown that over the range of dose ratios usually achieved clinically, a plot of the dose ratio against log plasma concentration is essentially linear.

The half-life of propranolol in normal subjects depends on the route and duration of drug administration but is always short and rarely exceeds six hours. Accordingly, the recommended oral dosage interval was set at about six hours. Since occurrence of toxicity is not related to dosage it would seem possible to administer the drug less often to individual patients especially, when compliance is a problem. Investigators have recently found adequate antihypertensive effects with twice-daily propranolol administration (101-102).

Coltart, et al. (103) investigated the plasma levels of propranolol and its metabolites after propranolol therapy and according to their results neither the drug nor the metabolites were detectable as early as 12-24 hours postwithdrawal.

Effect of Disease

Propranolol half-life is known to be prolonged by a reduction in liver blood flow, decreased activity of the
hepatic enzymes and by reduced plasma drug binding. Patients with heart failure and liver disease should be expected to handle the drug abnormally. In patients with liver disease, propranolol half-life is variable. It may be relatively normal or prolonged to as much as 35 hours in cirrhotic patients with surgically induced portocaval anastomoses and reduced plasma drug binding (92). In addition, such patients will have a very high oral bioavailability of drugs such as propranolol since the presystemic hepatic elimination is bypassed by the portosystemic shunt.

In the presence of renal disease, half-life is relatively unaffected and in some cases is even shortened (104). The shortened half-life and higher plasma concentrations reported in renal failure probably reflect a reduced volume of distribution resulting from loss of muscle mass.

**Drug Concentration and Effect**

The most important clinical problem is that of the very great variation in propranolol dosage required in patients treated for the same condition. Some patients with angina and hypertension may require as much as 2000 mg daily, while some respond to as little as 40 mg.

The study by Coltart and Shand (98) showed that there was a straight line relationship between block of exercise
tachycardia and the log of plasma propranolol concentration
but the propranolol level associated with a given effect two
hours after a single oral dose was one-half that observed
after intravenous administration. A ready explanation of
this discrepancy is available from the data of Patterson, et
al. (90) who found that an active metabolite of propranolol,
4-hydroxypropranolol, can be detected in the plasma only
after oral administration. This metabolite is equipotent to
propranolol (94) and achieves approximately the same
circulating concentrations as the parent drug shortly after
an oral dose (90). The effects of the metabolite will add
to those of propranolol. The presence of an active
metabolite makes interpretation of plasma concentration of
the parent drug difficult. However, 4-hydroxypropranolol
has a shorter half-life than propranolol so that by the end
of a six hour dosage interval all of the effects of a single
dose of the drug can be accounted for by the parent compound
(105-106). In addition, during chronic oral administration,
propranolol accumulates in the plasma. As early as two
hours after the dose, most of the resultant effect can be
accounted for by propranolol itself. The contribution of
beta-adrenergic blockade by 4-hydroxypropranolol is minor.
This view is supported by the data of Bodem, et al. (99),
who found levels of at least 100 ng/ml were required for
maximal effect after chronic oral administration. This is
the same amount that is required after I.V. administration
in which no active metabolite can be detected in plasma.

Although there is a clear relationship between plasma propranolol concentration and effect in any given individual, there is some variation in individuals of the plasma level required to produce a given effect. George, et al. (107) found as much as a four-fold difference in normal subjects. Zacest and Koch-Weser (100) have described two populations of hypertensive patients, one of which required 2.5 times the propranolol concentration to achieve comparable isoproterenol antagonism during chronic oral administration. This is in spite of the fact that within each population the correlation between drug concentration and effect was excellent. The less-sensitive subjects also tended to show higher plasma levels with a given oral dose and it was suggested that they might produce less 4-hydroxypropranolol (100).

Variation in receptor sensitivity might also be a cause of the individual variation. George and Dollery (108) have shown that after I.V. administration in dogs, when no 4-hydroxypropranolol was present and plasma propranolol concentrations were comparable, those animals most sensitive to isoproterenol were also most sensitive to propranolol.

Another explanation for differences in response to a given plasma level of propranolol is variation in plasma drug-binding. Data obtained from cardiac tissue in vitro suggest that with propranolol, as with other drugs, only
the unbound fraction of drug has access to the receptor and thus active. In man the bulk, >90%, of propranolol in plasma is protein-bound and hence inactive. Yet both free and bound propranolol are measured by the plasma propranolol assay. Small differences in plasma binding can result in substantial variation in free drug concentration. In normal subjects the plasma binding of propranolol varies from 90% to 95% (97). The free or active drug will vary from 5% to 10% and the two-fold variation is a factor which might account for modest individual variation in the effectiveness of the given total drug concentration.

Animal studies have shown that propranolol can decrease the rate of rise of the cardiac action potential. This effect which has been described as nonspecific myocardial depression or "quinidine-like" activity is contributing to the antiarrhythmic effect of the drug clinically. However, evidence is available that these nonspecific effects do not contribute significantly to the therapeutic or adverse effects with propranolol in man. In vitro data indicates that 10,000 ng/ml are required to slow the rate of rise of the action potential of human papillary muscle (109). As plasma drug binding in vivo would lower the effective free concentrations by a factor of 10-20, it would appear that the quinidine-like effect requires concentrations two or three orders of magnitude higher than those producing beta-blockade. Such concentrations are unlikely to
occur in patients even with the largest doses employed clinically.

Supportive evidence is obtained from the use of the d-isomer of propranolol which is devoid of beta-blocking properties, yet it retains the nonspecific "quinidine-like" effects (109). Coltart, et al. (110) found that four patients who had responded to I.V. infusion of dl-propranolol with abolition of premature ventricular beats failed to respond to d-isomer. These effects were obtained even though higher plasma concentrations were achieved: e.g., 60-75 ng/ml with dl-propranolol compared with 180-310 ng/ml with d-propranolol. These findings conflict however with the results of Howitt, et al. (111) who reported that racemic and dextro-propranolol had approximately equivalent effects on supraventricular and ventricular ectopic beats and tachycardia. The reason for this discrepancy may be due to the differences in the etiology of the arrhythmias studied or the criteria by which effectiveness was assessed. Nevertheless, the overall results support the conclusion that propranolol is an antiarrhythmic drug of clinical importance by virtue of its beta-adrenergic blocking activity. Its nonspecific effects play no more than a minor part. A similar conclusion can be reached in other situations for which propranolol is used. Dextro-propranolol is not effective in angina or hypertension, (112-113) while beta-adrenergic
blockers without quinidine-like activity are effective. These conclusions also support the contention that the nonspecific cardiac depressant effects contribute little to precipitation of heart failure in patients.

Hypertension is another condition in which consideration of dose is important. Propranolol lowers both supine and standing pressure equally. Buhler, et al. (73) suggested that patients with initially high renin activity responded best to modest doses, average 240 mg daily. The antihypertensive effect was related to the reduction of plasma renin activity. However several other workers have failed to confirm that the hypotensive effects of the drug were associated with the fall of plasma renin activity (114). Consideration of all the available data suggests that propranolol may have two modes of action as an antihypertensive. One lowering FRA level and another acting on the central nervous system (115).

Based on an overview of all the published data, it appears that a plasma propranolol concentration of 100 ng/ml should confer a very high degree of blockade of cardiac receptors and will be essentially maximal for some patients. Significant beta-blockade is produced by lower propranolol levels which appear to be sufficient for therapeutic effects in many patients.
EUDRAGIT® POLYMERS: A REVIEW

Rohm Pharma, West Germany, markets a range of film coating polymers under the trade-name Eudragit®. These polymethacrylates are copolymers of methacrylic acid, aminomethacrylates and neutral esters of acrylic acid and methacrylic acid (116). These acrylic polymers possess characteristic properties of solubility and permeability in the digestive juices of the gastrointestinal tract, depending upon the content of acidic, basic and hydrophilic groups in the polymers. There is now an extensive range of different forms available, which makes possible the controlled release of active ingredient in practically all usual or conceivable oral dosage forms. Based on chemical structure, these polymers can be categorized into 3 groups.

Methacrylic Acid Co-Polymers

Polymethacrylate resins with designations L and S are used as enteric coatings because of their content of carboxylate groups, which make them insoluble in acids and pure water. They form salts with alkalies and dissolve at pH values over 5.5. These form polymeric films which are resistant to gastric juice but dissolve readily in intestinal fluids (117). Eudragit® S contains fewer carboxylate groups than Eudragit® L and it dissolves slowly at pH values above 7.
Films of methacrylic acid co-polymers are relatively brittle and are recommended by the manufacturer to be used with a plasticizer. The different methacrylic acid copolymers are shown in Table 1.

**Methacrylate Ester Co-Polymer**

The products in this group are neutral polymers and are insoluble in the entire physiological pH range. However, they possess a defined swelling capacity and permeability with respect to water and dissolved drugs, which are independent of pH. These polymers are therefore considered to be suitable for the manufacture of controlled-release dosage forms. The release of the active ingredient is controlled by the permeability of the polymer by either using one of the two types of lacquer, Eudragit® RL or Eudragit® RS or by mixing the two materials in any desired ratio. In addition hydrophilic substances can be added to alter the permeability of the films (118). The different methacrylate ester co-polymers are shown in Table 2.

**Methacrylate Aminoester Co-Polymer**

The introduction of amino-ester groups in polymethacrylates results in basic products which are insoluble in water. They dissolve by salt formation in acids, that is, below pH 4 (119). Co-polymers of methacrylate amino-esters are therefore soluble in gastric fluid but are resistant
Table I. Methacrylic Acid Co-Polymers

<table>
<thead>
<tr>
<th>Scientific name</th>
<th>$n_1 : n_2$</th>
<th>MW</th>
<th>$R_1$</th>
<th>$R_2$</th>
<th>Behavior in digestive juices</th>
<th>Eudragit ® type</th>
<th>Marketed form</th>
</tr>
</thead>
<tbody>
<tr>
<td>Poly(methacrylic acid, ethylacrylate)</td>
<td>1:1</td>
<td>250,000</td>
<td>H</td>
<td>$C_2H_5$</td>
<td>soluble pH &gt;5.5</td>
<td>L 30 D</td>
<td>30% aqueous dispersion</td>
</tr>
<tr>
<td>Poly(methacrylic acid, methylethacrylate)</td>
<td>1:1</td>
<td>135,000</td>
<td>$CH_3$</td>
<td>$CH_3$</td>
<td>soluble pH &gt;6.0</td>
<td>L 12.5</td>
<td>12.5% solution in isopropanol</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>L 100</td>
<td>powder</td>
</tr>
<tr>
<td>Poly(methacrylic acid, methylnitromethacrylate)</td>
<td>1:2</td>
<td>135,000</td>
<td>$CH_3$</td>
<td>$CH_3$</td>
<td>soluble pH &gt;7.0</td>
<td>S 12.5</td>
<td>12.5% solution in isopropanol</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>S 100</td>
<td>powder</td>
</tr>
</tbody>
</table>
Table 2. Methacrylate Ester Co—Polymers

![Chemical structure of methacrylate ester copolymers](image)

<table>
<thead>
<tr>
<th>Scientific Name</th>
<th>$n_1:n_2:n_3$</th>
<th>MW</th>
<th>Behavior in digestive juices</th>
<th>Eudragit® type</th>
<th>Marketed form</th>
</tr>
</thead>
<tbody>
<tr>
<td>Poly(ethylacrylate, methylnethylacrylate)</td>
<td>2:1</td>
<td>800,000</td>
<td>PERMEABLE</td>
<td>E 30 D</td>
<td>30% aqueous dispersion</td>
</tr>
<tr>
<td>Poly(ethylacrylate, methylnethylacrylate) trimethyl-ammonioethylmethacrylate chloride</td>
<td>1:2:0.2</td>
<td>150,000</td>
<td>STRONGLY PERMEABLE</td>
<td>RL 12.5</td>
<td>12.5% solution in isopropanol/acetone</td>
</tr>
<tr>
<td>$R = CH_2-CH_2-N^+(CH_3)_3Cl^-$</td>
<td></td>
<td></td>
<td></td>
<td>RL 100</td>
<td>granulate</td>
</tr>
<tr>
<td>Poly(ethylacrylate, methylnethylacrylate) trimethyl-ammonioethylmethacrylate chloride</td>
<td>1:2:0.1</td>
<td>150,000</td>
<td>WEAKLY PERMEABLE</td>
<td>RS 12.5</td>
<td>12.5% solution in isopropanol/acetone</td>
</tr>
<tr>
<td>$R = CH_2-CH_2-N^+(CH_3)_3Cl^-$</td>
<td></td>
<td></td>
<td></td>
<td>RS 100</td>
<td>granulate</td>
</tr>
</tbody>
</table>
for some time in saliva and therefore can be used for taste masking (120). In neutral and alkaline environments, films of these materials are insoluble but they swell considerably and become permeable.

These polymers are frequently used with pigments to produce colored film coatings for tablets. Plasticizers are not required for film formation. The different methacrylate amino-ester co-polymers are shown in Table 3.
Table 3. Methacrylate Aminoester Co-Polymers

<table>
<thead>
<tr>
<th>Scientific Name</th>
<th>$n_1:n_2:n_3$</th>
<th>MW</th>
<th>Behavior in Digestive Juices</th>
<th>Eudragit Type</th>
<th>Marketed Form</th>
</tr>
</thead>
<tbody>
<tr>
<td>Poly(butylmethacrylate, (2-dimethylaminoethyl) methacrylate, methylmethacrylate) $R = -\text{CH}_2\text{-CH}_2\text{-N(\text{CH}_3)_2}$</td>
<td>1:2:1</td>
<td>150,000</td>
<td>soluble pH &lt; 4</td>
<td>E 12.5</td>
<td>12.5% solution in isopropanol/acetone</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>permeable pH &gt; 4</td>
<td>E 100</td>
<td>granulate</td>
</tr>
</tbody>
</table>
CHAPTER II
EXPERIMENTAL

Materials and Equipment
The materials used in the study are shown in Table 4 and were used as received. The equipment used are shown in Table 5.

Preparation of Powder Mix
Propranolol hydrochloride was mixed with microcrystalline cellulose in a 6:4 ratio with a Hobart mixer. The mixing was continued at low speed for 15 minutes. The mixture was then milled using a Fitzmill set up with a 1A screen, impact forward. The milling operation was repeated two more times to break up any lumpy particles.

Preparation of Coating Solutions
An anti-adherent suspension using talc and magnesium stearate in isopropyl alcohol was prepared. A 33% w/v solution of Carbowax® was then added to serve as plasticizer for the lacquer. The formulation is shown in Table 6. The lacquer suspension formulations of Eudragit are shown in Table 7. The binder solution formulation used in preparing beads is shown in Table 8.
<table>
<thead>
<tr>
<th>Chemical</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Acetone&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Fisher Chemical Co, Fair Lawn, NJ</td>
</tr>
<tr>
<td>2. Acetic Acid&lt;sup&gt;b&lt;/sup&gt;</td>
<td>J.T. Baker Chemical Co, Phillipsburg, NJ</td>
</tr>
<tr>
<td>3. Acetonitrile&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Ruger Chemical Co, NJ</td>
</tr>
<tr>
<td>4. Carbowax® 8000&lt;sup&gt;c&lt;/sup&gt;</td>
<td>Private Source</td>
</tr>
<tr>
<td>5. Desimipramine&lt;sup&gt;d&lt;/sup&gt;</td>
<td>Pel Freeze Biologicals</td>
</tr>
<tr>
<td>6. Dog Plasma-Nonsterile&lt;sup&gt;e&lt;/sup&gt;</td>
<td>Rohm Pharma, Darmstadt, W.Germany</td>
</tr>
<tr>
<td>7. Eudragit® RS 12.5&lt;sup&gt;f&lt;/sup&gt;</td>
<td>Shin-Etsu Chemical Co, Japan</td>
</tr>
<tr>
<td>8. Eudragit® RL 12.5&lt;sup&gt;f&lt;/sup&gt;</td>
<td>ICI England</td>
</tr>
<tr>
<td>9. Ethanol&lt;sup&gt;a&lt;/sup&gt;</td>
<td>FMC Corporation, Princeton, NJ</td>
</tr>
<tr>
<td>10. Hydrochloric Acid&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>11. Hydroxypropyl Cellulose&lt;sup&gt;g&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>12. Isopropyl Alcohol&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup> Fisher Chemical Co, Fair Lawn, NJ
<sup>b</sup> J.T. Baker Chemical Co, Phillipsburg, NJ
<sup>c</sup> Ruger Chemical Co, NJ
<sup>d</sup> Private Source
<sup>e</sup> Pel Freeze Biologicals
<sup>f</sup> Rohm Pharma, Darmstadt, W.Germany
<sup>g</sup> Shin-Etsu Chemical Co, Japan
<sup>h</sup> Ayerst Laboratories, NY
<sup>i</sup> ICI England
<sup>j</sup> FMC Corporation, Princeton, NJ
Table 4. (Cont'd)

13. Inderal® Tablets, 40 mg
14. Inderal LA® Capsules
15. Methanol
16. Microcrystalline Cellulose
17. Magnesium Stearate
18. Non-Pareil Beads
19. Potassium Phosphate
20. Propranolol Hydrochloride
21. Sodium Hydroxide
22. Sodium Chloride
23. Sodium Carbonate
24. Sodium Metabisulfite
25. Talc

---

a. Fisher Chemical Co, Fair Lawn, NJ  
b. J.T.Baker Chemical Co, Phillipsburg, NJ  
c. Ruger Chemical Co, NJ  
d. Personal Source  
e. Pel Freeze Biologicals  
f. Rohm Pharma, Darmstadt, W.Germany  
g. Shin-Etsu Chemical Co, Japan  
h. Ayerst Laboratories, NY  
i. ICI England  
j. FMC corporation, Princeton, NJ  
k. Ingredient Technology Corporation, NJ
Table 5. **Equipment Used in the Study**

1. Lightning Model Mixer with 4 Blade Stirrer\(^a\)
2. Centrifugal Granulator Model CF 360\(^b\)
3. Sonic Bath\(^c\)
4. Centrifuge\(^d\)
5. Falcon Sterile Disposable Tubes\(^e\)
6. HPLC Column (Hibar Lichrosorb)\(^e\)
7. Membrane Filters 0.22 \(\mu\)m and 0.45 \(\mu\)m\(^e\)
8. Liquid Chromatograph Model 1084 B\(^f\)
9. USP Dissolution Apparatus\(^g\)

\(^a\) Mixing Equipment Co. Inc; Rochester, NY
\(^b\) Vector Corporation, Marion, Iowa
\(^c\) Fisher Chemicals, Fair Lawn, NJ
\(^d\) Model DPR 6000, IEC/Damon Industries, MA
\(^e\) American Scientific Products, Industrial Div, Edison, NJ
\(^f\) Hewlett-Packard, Avondale, PA
\(^g\) Van-Kel Industries, Chatham, NJ
Table 5. (Cont'd)

10. Beckman DU 7 Spectrophotometer\textsuperscript{h}
11. Fluorescence Spectrophotometer, Model FS 970\textsuperscript{i}
12. Hobart Mixer\textsuperscript{j}
13. Fitzmill\textsuperscript{k}
14. Drying Oven\textsuperscript{l}
15. Mettler Scientific Balance\textsuperscript{m}

\textsuperscript{h} Beckman Instruments, Fullerton, CA
\textsuperscript{i} Kratos Analytical, Ramsey NJ
\textsuperscript{j} Hobart Manufacturing Co. Troy, OH
\textsuperscript{k} Fitzpatrick Co. Elmhurst, IL
\textsuperscript{l} Precision Scientific Co. NY
\textsuperscript{m} Mettler Instrument Corp. Hightstown, NJ
<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Weight (g)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Talc, U.S.P</td>
<td>91</td>
</tr>
<tr>
<td>Magnesium Stearate, N.F</td>
<td>9</td>
</tr>
<tr>
<td>Carbowax 8000, N.F.(33% in Water)</td>
<td>20</td>
</tr>
<tr>
<td>Isopropyl Alcohol, U.S.P</td>
<td>700</td>
</tr>
<tr>
<td><strong>Total Weight</strong></td>
<td><strong>820</strong></td>
</tr>
<tr>
<td><strong>Percent Solid Level</strong></td>
<td><strong>13% w/w</strong></td>
</tr>
</tbody>
</table>

Table 6. Anti-Adherent/Plasticizer Portion of Coating Formulation
Table 7. Various Formulations of Eudragit® Lacquer Suspensions

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Coating Formulations</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>A</td>
</tr>
<tr>
<td>Eudragit® RL 12.5</td>
<td>768 (96.0)*</td>
</tr>
<tr>
<td>Eudragit® RS 12.5</td>
<td>768 (96.0)</td>
</tr>
<tr>
<td>Anti-Adherent/Plasticizer Suspension</td>
<td>90 (11.7)</td>
</tr>
<tr>
<td>Acetone</td>
<td>310</td>
</tr>
<tr>
<td>Isopropyl Alcohol</td>
<td>310</td>
</tr>
<tr>
<td>Total Weight</td>
<td>2246 (203.7)</td>
</tr>
<tr>
<td>Percent Solid Level</td>
<td>9.07% w/w</td>
</tr>
<tr>
<td>Eudragit® RS:RL Ratio</td>
<td>50:50</td>
</tr>
</tbody>
</table>

* Values in Parenthesis Indicates Actual Solid Level in Grams
Table 8. Formulation of Binder Solution

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Quantity (g)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydroxypropyl Cellulose. LF</td>
<td>100</td>
</tr>
<tr>
<td>Ethanol, U.S.P.</td>
<td>900</td>
</tr>
</tbody>
</table>
Preparation of Beads

A Vector/Freund CF granulator, Model CF 360, was used for spheronizing the powder mix. A schematic view of the unit is shown in Figure 10. In this trial 750 grams of the non-pareil seeds, 25-30 mesh, was used as the seed material.

A quantity of 2 kg powder mix containing propranolol hydrochloride was charged into the hopper of the powder feed system. The rotor speed was set at 180 rpm. The binder solution was slowly sprayed onto the non-pareil seeds at a rate of 20 ml/min. After one minute the powder feeding device was activated at a setting of "60". The inlet and exhaust temperatures were set at 35°C and 27°C, respectively. A total of 76 minutes was necessary to apply the 1.5 kg powder mix in which 1.52 L of binder solution was applied.

The spheronized batch was screened to remove fines and agglomerates and dried in an oven at 40°C for 2 hours. One half (0.5) kg beads were then charged into the CF granulator for coating. Operating conditions remained the same except that the powder feeding mechanism was shut off. Five such coating trials were performed. The coating solution was kept stirred during the entire coating period. Table 9 shows the optimized coating trial parameters and Table 10 gives a summary of different coating trials.
Figure 10. Basic Elements of CF-Granulator.
Table 9. CF Granulating/Coating Trial Parameters (Optimized)

<p>| | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Trial Machine</td>
<td>CF-360 EX</td>
<td>6. Rotor Rotation</td>
</tr>
<tr>
<td>2. Core Volume</td>
<td>750 G*</td>
<td>7. Slit Air Volume</td>
</tr>
<tr>
<td>3. Spray Gun</td>
<td>A T</td>
<td>8. Slit Air Temp.</td>
</tr>
<tr>
<td>4. Spray Air Pressure</td>
<td>0.6 kg/cm²</td>
<td>9. Dispersion Temperature</td>
</tr>
</tbody>
</table>

* Core volume was 0.5 kg during coating trials.
Table 10. Summary of Coating Trials

<table>
<thead>
<tr>
<th></th>
<th>Formulation A</th>
<th>Formulation B</th>
<th>Formulation C</th>
<th>Formulation D</th>
<th>Formulation E</th>
</tr>
</thead>
<tbody>
<tr>
<td>Core Weight (g)</td>
<td>500</td>
<td>500</td>
<td>500</td>
<td>500</td>
<td>500</td>
</tr>
<tr>
<td>Coating Formulation</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>sprayed</td>
<td>A</td>
<td>B</td>
<td>C</td>
<td>C</td>
<td>C</td>
</tr>
<tr>
<td>Spray Rate (ml/min)</td>
<td>20</td>
<td>20</td>
<td>20</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td>Quantity Sprayed (g)</td>
<td>830</td>
<td>931</td>
<td>661</td>
<td>990</td>
<td>1190</td>
</tr>
<tr>
<td>Approx. Percent</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coating Applied</td>
<td>15</td>
<td>15</td>
<td>10</td>
<td>15</td>
<td>18</td>
</tr>
<tr>
<td>Total Spray Time (min)</td>
<td>37</td>
<td>43</td>
<td>31</td>
<td>52</td>
<td>64</td>
</tr>
<tr>
<td>Additional Talc</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Added (g)</td>
<td>8</td>
<td>8</td>
<td>6</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Final Yield (g)</td>
<td>571</td>
<td>570</td>
<td>548</td>
<td>572</td>
<td>587</td>
</tr>
</tbody>
</table>
Determination of Propranolol Hydrochloride in the Beads

In order to measure the percent of propranolol hydrochloride in the beads, methanol was used as the extraction medium. Triplicate samples of 100 mg uncoated or coated beads were placed in 100 ml volumetric flasks containing methanol. The suspension was then stirred vigorously to allow propranolol to dissolve from the beads. Numerous aliquots from all flasks were assayed for propranolol until no further increase in concentration was found. The amount of propranolol in the beads was determined using the standard curve shown in Figure 11.

In Vitro Dissolution Studies

The dissolution test for the coated beads was done with the USP basket assembly with a round bottom 1 l flask at a rotation speed of 50 rpm (121). The dissolution medium of 900 ml was kept at temperature of 37°C ± 0.5°C. The water in the tank surrounding the dissolution apparatus was kept at 37°C by a temperature controller and circulator. The concentration of propranolol in the dissolution medium was determined by a UV spectrophotometer (122) after appropriate sampling and dilution.

Procedure
Preparation of Dissolution Media

Deionized Water obtained from the laboratory was degassed using a sonic bath and then used in the dissolution study.

Simulated Gastric Fluid (without Pepsin)

<table>
<thead>
<tr>
<th>Component</th>
<th>Quantity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium Chloride</td>
<td>2.0 grams</td>
</tr>
<tr>
<td>Hydrochloric Acid (concentrated)</td>
<td>7.0 ml</td>
</tr>
<tr>
<td>Purified Water, q.s. to</td>
<td>1000 ml</td>
</tr>
</tbody>
</table>

The sodium chloride was added to the hydrochloric acid and enough water was added to make up the volume to the mark using 1 l volumetric flask. The pH of this solution was determined using a pH meter and found to be 1.2.

Simulated Intestinal Fluid (without Pancreatin)

<table>
<thead>
<tr>
<th>Component</th>
<th>Quantity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monobasic Potassium Phosphate (KH₂PO₄)</td>
<td>6.8 gms</td>
</tr>
<tr>
<td>0.2 N Sodium Hydroxide</td>
<td>190 ml</td>
</tr>
<tr>
<td>Purified water, q.s. to</td>
<td>1000 ml</td>
</tr>
</tbody>
</table>

Monobasic potassium phosphate was dissolved in 250 ml of water and 190 ml of 0.2 N sodium hydroxide was added. With continued mixing, purified water was added to the 1 liter mark.

Preparation of Propranolol Calibration Curves
Calibration curves were prepared in methanol, water, simulated gastric fluid and simulated intestinal fluid using the following concentrations of propranolol: 10, 20, 30, 40 and 50 mcg/ml. Beers Law plots were determined from solutions prepared on three different days. Figure 11 was used to quantitate propranolol in the beads and the other curves were used to determine the concentration of propranolol in the dissolution media at the different sampling times. The mean calibration data of propranolol hydrochloride in different media along with the regression coefficients are presented in Table 11. The mean values were used to prepare the calibration curves shown in Figures 11, 12, 13 and 14.

Sampling Procedure

The solution in the dissolution apparatus was allowed to equilibrate at a temperature of 37°C. Dissolution testing was performed on 6 immediate release tablets and sampling was at 15 minute intervals up to 1 hour. In the case of Inderal LA® and the controlled release formulations prepared in the study, sampling was performed at 0.5 hour and 1 hour followed by every hour for varying periods of time depending on the release pattern.

Bioavailability Study

Six male beagle dogs, weighing an average of 10.5 kg
Table 11. Absorbance Values of Propranolol Hydrochloride in Different Media

<table>
<thead>
<tr>
<th>CONCENTRATION (mcg/ml)</th>
<th>Water</th>
<th>SGF</th>
<th>SIF</th>
<th>Methanol</th>
</tr>
</thead>
<tbody>
<tr>
<td>10.00</td>
<td>0.210</td>
<td>0.198</td>
<td>0.198</td>
<td>0.200</td>
</tr>
<tr>
<td>20.00</td>
<td>0.408</td>
<td>0.399</td>
<td>0.390</td>
<td>0.401</td>
</tr>
<tr>
<td>30.00</td>
<td>0.609</td>
<td>0.579</td>
<td>0.590</td>
<td>0.608</td>
</tr>
<tr>
<td>40.00</td>
<td>0.805</td>
<td>0.769</td>
<td>0.810</td>
<td>0.811</td>
</tr>
<tr>
<td>50.00</td>
<td>1.004</td>
<td>0.960</td>
<td>0.990</td>
<td>1.016</td>
</tr>
</tbody>
</table>

\( \lambda_{\text{max}} \) (nm)

<table>
<thead>
<tr>
<th></th>
<th>290</th>
<th>289</th>
<th>289.5</th>
<th>290</th>
</tr>
</thead>
<tbody>
<tr>
<td>Slope</td>
<td>0.0198</td>
<td>0.0188</td>
<td>0.0200</td>
<td>0.0204</td>
</tr>
<tr>
<td>Intercept</td>
<td>0.0054</td>
<td>0.0102</td>
<td>0.0152</td>
<td>-0.0056</td>
</tr>
<tr>
<td>Correlation Coefficient</td>
<td>0.9999</td>
<td>0.9999</td>
<td>0.9999</td>
<td>0.9996</td>
</tr>
</tbody>
</table>

\( ^a \) Mean of three determinations.

\( ^b \) Linear regression of absorbance against concentration.
Figure 11. Calibration Curve for Propranolol Hydrochloride in Methanol.
Figure 12. Calibration Curve for Propranolol Hydrochloride in Deionized Water.
Figure 13. Calibration Curve for Propranolol Hydrochloride in Simulated Gastric Fluid (without Pepsin).
Figure 14. Calibration Curve for Propranolol Hydrochloride in Simulated Intestinal Fluid.
were used. The individual weights and ages of dogs are shown in Table 12. Prior to drug dosing the dogs were fasted overnight. Water was not withheld from the dogs during the study. Each dog was housed in a separate metabolism cage. The dogs were fed four hours after the drug was given.

Study Design

A "balanced incomplete randomized block crossover" design was used for the study. The study was performed on six dogs as follows:

1st dosing. A B A C B C (day 1)
2nd dosing. B A C A C B (day 8)

Where

A = 40 mg Inderal® tablets, Ayerst Laboratories, administered at 0, 6, 12 and 18 hours;
B = 160 mg Inderal LA®, ICI, England. One capsule administered in the morning;
C = 160 mg propranolol hydrochloride controlled-release bead formulation prepared in this study. One capsule containing 160 mg (Formulation E) propranolol administered in the morning.

A one week washout period is allowed between each dosing.
Table 12. Weight and Age of Dogs used in the Bioavailability Study

<table>
<thead>
<tr>
<th>Dog Number</th>
<th>Weight (Kg)</th>
<th>Age at Time of Experiment (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>10.0</td>
<td>582</td>
</tr>
<tr>
<td>2</td>
<td>12.0</td>
<td>582</td>
</tr>
<tr>
<td>3</td>
<td>10.9</td>
<td>569</td>
</tr>
<tr>
<td>4</td>
<td>10.9</td>
<td>586</td>
</tr>
<tr>
<td>5</td>
<td>9.8</td>
<td>580</td>
</tr>
<tr>
<td>6</td>
<td>9.6</td>
<td>585</td>
</tr>
</tbody>
</table>

Mean = 10.5
Mean = 580.7
**Blood Sampling**

Indwelling heparinized catheters were not used for blood sampling due to their reported effects on propranolol binding (123). Blood samples (10 ml) were collected by direct venipuncture at 0, 0.5, 1, 2, 4, 8, 14, 20, 24 and 30 hours.

Blood samples were placed in heparinized, disposable tubes, American Scientific Products, catalog number 2063. Plasma was separated by centrifugation, 1500 g for 10 min, and immediately frozen. Plasma samples were stored at -20°C until analyzed.

**Preparation of the Mobile Phase of the HPLC Assay**

A 0.03 M solution of acetate buffer was prepared. Glacial acetic acid, 1.8 ml was added to 1 l of water, the pH was adjusted to 5.5 ± 0.2 with 6 N sodium hydroxide and the solution was filtered through a 0.22 μm membrane filter. The mobile phase was prepared by mixing 65 parts of methanol with 35 parts of 0.03 M acetate buffer. This solution was filtered through a 0.45 μm filter and then degassed before use in an ultrasonic bath.

**Apparatus and Conditions for Analysis**

A Hewlett-Packard Model 1084 B liquid chromatograph, a Schoeffel Model FS 970 fluorescence spectrophotometer, a Hibar Lichrosorb CN (10 μm, 4.6 X 250 mm) column, American
Scientific Products catalog number C 5484 - 14 and an HP 3357 laboratory automation system (Hewlett-Packard, Avondale, PA) were used.

The mobile phase flow rate was 1.5 ml/min and the column temperature was 55°C. The spectrophotometer was set at 285 nm (excitation) and 405 nm (emission). The slit openings both for excitation and for emission were 5 nm.

Preparation and Extraction of Standard Plasma Solutions

Stock solutions of both propranolol and desimipramine were prepared in methanol to yield a concentration of 1 mg/ml. Working solutions of propranolol were made by diluting the propranolol stock solutions with methanol. A working solution of desimipramine was made by diluting the desimipramine stock solution with acetonitrile. All solutions were stored at -20°C.

Plasma standards of 10, 25, 50 and 100 ng of propranolol per ml of plasma were prepared at the time of analysis as follows: Exact volumes (100 μl) of working solutions of propranolol in test tubes were evaporated to dryness under a gentle stream of nitrogen. To each tube was then added 1 ml of blank dog plasma. The tube was then vortex-mixed for 1 minute. To each tube was added 1 ml of the internal standard solution (500 ng/ml desimipramine in acetonitrile) and 0.2 gram of sodium chloride and sodium
carbonate mixture (4:1). Samples were then vortexed for 30 sec and centrifuged at 2000 g for 5 min at 4°C. Thirty (30) microliters of the clean upper layer was directly injected into the chromatograph.
CHAPTER III
RESULTS AND DISCUSSION

Preparation of Controlled-Release Beads

Preparation of controlled-release beads required two steps. The first step involved the manufacture of core beads. The second step involved coating of the beads using Eudragit® suspensions. Both operations were accomplished in the centrifugal granulator. A mixture of propranolol with microcrystalline cellulose was prepared and this mixture was made to adhere to non-pareil sugar seeds to obtain a commercially viable product. Initial runs using a mixture of propranolol/microcrystalline cellulose ran into difficulties due to lumpy particles in the mixture. Subsequent batches used triple-milled propranolol/microcrystalline cellulose mixture which abated this problem. Product loss was negligible using this unit and discharge was easy. In the final optimized run, the agglomerated bead portion was less than 1 percent of the product and the amount of fines was also less than 1 percent.

Operating conditions for bead coating was the same as for spheronizing operation except that the powder feeding mechanism was shut off.

Uniformity and Percent of Active Ingredient in the Beads

After spheronization, the uncoated beads were dried in
an oven at 40°C for 2 hours and five random samples were drawn for analyzing propranolol potency and uniformity of beads. Propranolol was extracted using methanol and assayed spectrophotometrically. Results are shown in Table 13 for uncoated beads. Results indicate that with a % CV of 1.4, the powder mixture was uniformly coated onto the non-pareil beads. Table 14 gives the amount of propranolol in the coated beads. Quantitation of the amount of propranolol hydrochloride was necessary to determine the percent of propranolol released during the dissolution study.

In Vitro Dissolution Results of Different Formulations

The in vitro release patterns of propranolol from the beads coated with different coating dispersions along with commercially available Inderal LA® and Inderal® 40 mg tablets were studied using the USP XX dissolution test procedure described in the experimental section. The amount of beads was adjusted so that each dissolution sample contained approximately 160 mg propranolol. Table 15 and Figure 15 show the dissolution profile of beads coated using a 50:50 mixture of Eudragit® RS and RL (Formulation A) as compared to uncoated beads. It was found that the uncoated beads released the entire drug in one hour, while coated beads sustained the drug release up to 3 hours, although no zero-order release profile was seen. For instance, 54 percent of the drug was released from the coated beads in
Table 13. Percent of Propranolol HCL in the Uncoated Beads

<table>
<thead>
<tr>
<th>Sample Number</th>
<th>% Propranolol Hydrochloride</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>38.1</td>
</tr>
<tr>
<td>2</td>
<td>39.2</td>
</tr>
<tr>
<td>3</td>
<td>38.6</td>
</tr>
<tr>
<td>4</td>
<td>39.3</td>
</tr>
<tr>
<td>5</td>
<td>39.4</td>
</tr>
</tbody>
</table>

\[ \bar{X} = 38.9 \]
\[ \pm SD = 0.6 \]
\[ \% CV = 1.4 \]
Table 14. Quantity of Propranolol HCL in the Coated Beads

<table>
<thead>
<tr>
<th>Trial Number</th>
<th>Mg/100 Mg. Beads</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>32.0</td>
</tr>
<tr>
<td>2</td>
<td>33.5</td>
</tr>
<tr>
<td>3</td>
<td>36.1</td>
</tr>
<tr>
<td>4</td>
<td>32.5</td>
</tr>
</tbody>
</table>

\[ \bar{X} = 33.5 \]
\[ \pm SD = 1.8 \]
\[ \% CV = 5.5 \]
Table 15. Cumulative Percent of Drug Release—Uncoated Beads and Coated Beads from Formulation A (Eudragit® RS&RL, 50:50) - 15% Coating

<table>
<thead>
<tr>
<th>Time (Hour)</th>
<th>Uncoated</th>
<th>Formulation A</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5</td>
<td>84.0 (7.6)</td>
<td>18.4 (7.9)</td>
</tr>
<tr>
<td>1.0</td>
<td>97.8 (3.4)</td>
<td>54.0 (5.4)</td>
</tr>
<tr>
<td>2.0</td>
<td>98.4 (1.7)</td>
<td>87.0 (3.7)</td>
</tr>
<tr>
<td>3.0</td>
<td>97.2 (1.0)</td>
<td>99.1 (2.8)</td>
</tr>
<tr>
<td>4.0</td>
<td>97.9 (1.0)</td>
<td>98.9 (2.4)</td>
</tr>
<tr>
<td>12.0</td>
<td>97.5 (1.1)</td>
<td>98.5 (2.1)</td>
</tr>
</tbody>
</table>

\(^a\) Each reading is the mean of six samples.

\(^b\) Values in parenthesis indicate the percent coefficient of variation.
Figure 15. *In Vitro* Dissolution Profile of Propranolol Hydrochloride from Uncoated Beads and Formulation A.
one hour. The remaining drug was released within the next 2 hours.

Table 16 and Figure 16 shows the dissolution profile of propranolol beads coated with mixture of Eudragit® RS & RL (Formulation B) in deionized water. Drug release was sustained for up to 6 hours although no zero-order pattern was seen.

Table 17 and Figure 17 show the dissolution profile of propranolol beads coated with mixture of Eudragit® RS and RL (Formulation C). However, in this case only 10% by weight of coating was applied. Drug release showed apparent zero-order release up to 3 hours and 81 percent of the drug was also released. Drug release continued at a much slower rate for up to 8 hours.

Table 18 and Figure 18 show the dissolution profile of propranolol beads coated with Eudragit® RS & RL (Formulation D). Up to 15% coating was applied on to the beads. A zero-order release profile was seen up to 6 hours. However 85 percent of the drug was also released.

Table 19 and Figure 19 show the dissolution profile of propranolol beads in water from formulation E where 18% of the coating was applied. The dissolution profile showed a zero-order release up to 11 hours and 98.2% of the drug was released.

Table 20 and Figure 20 show the dissolution behavior of Inderal LA® capsules (160 mg) and 40 mg immediate-release
<table>
<thead>
<tr>
<th>Time (Hour)</th>
<th>Cumulative Percent Released$^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5</td>
<td>13.0 (14.2)</td>
</tr>
<tr>
<td>1.0</td>
<td>28.4 (9.4)</td>
</tr>
<tr>
<td>2.0</td>
<td>58.0 (5.3)</td>
</tr>
<tr>
<td>3.0</td>
<td>76.0 (6.0)</td>
</tr>
<tr>
<td>4.0</td>
<td>85.0 (3.8)</td>
</tr>
<tr>
<td>5.0</td>
<td>92.0 (2.9)</td>
</tr>
<tr>
<td>6.0</td>
<td>97.0 (2.4)</td>
</tr>
<tr>
<td>7.0</td>
<td>97.2 (1.9)</td>
</tr>
<tr>
<td>8.0</td>
<td>97.0 (1.8)</td>
</tr>
<tr>
<td>12.0</td>
<td>97.0 (1.9)</td>
</tr>
</tbody>
</table>

$^a$ Each reading is the mean of six samples.

$^b$ Values in parenthesis indicate the percent coefficient of variation.
Figure 16. In Vitro Dissolution Profile of Propranolol Hydrochloride from Formulation B in Deionized Water.
Table 17. Cumulative Percent of Drug Release—Coated Beads from Formulation C (Eudragit® RS & RL, 90:10)-10% Coating\textsuperscript{a}

<table>
<thead>
<tr>
<th>Time (Hour)</th>
<th>Cumulative Percent Released\textsuperscript{b}</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5</td>
<td>14.0 (15.7)</td>
</tr>
<tr>
<td>1.0</td>
<td>32.0 (9.0)</td>
</tr>
<tr>
<td>2.0</td>
<td>62.0 (6.6)</td>
</tr>
<tr>
<td>3.0</td>
<td>81.0 (3.3)</td>
</tr>
<tr>
<td>4.0</td>
<td>89.0 (3.2)</td>
</tr>
<tr>
<td>5.0</td>
<td>94.0 (2.6)</td>
</tr>
<tr>
<td>6.0</td>
<td>97.0 (2.1)</td>
</tr>
<tr>
<td>7.0</td>
<td>97.8 (2.3)</td>
</tr>
<tr>
<td>8.0</td>
<td>98.4 (1.8)</td>
</tr>
<tr>
<td>12.0</td>
<td>98.2 (1.7)</td>
</tr>
</tbody>
</table>

\textsuperscript{a} Each reading is the mean of six samples.

\textsuperscript{b} Values in parenthesis indicate the percent coefficient of variation.
Figure 17. In Vitro Dissolution Profile of Propranolol Hydrochloride from Formulation C in Deionized Water.
Table 18. Cumulative Percent of Drug Release - Coated Beads from Formulation D (Eudragit® RS®RL, 90:10) - 15% Coating

<table>
<thead>
<tr>
<th>Time (Hour)</th>
<th>Cumulative Percent Released&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5</td>
<td>9.0 ( 5.6 )</td>
</tr>
<tr>
<td>1.0</td>
<td>19.0 ( 5.5 )</td>
</tr>
<tr>
<td>2.0</td>
<td>36.0 ( 4.0 )</td>
</tr>
<tr>
<td>3.0</td>
<td>51.4 ( 3.8 )</td>
</tr>
<tr>
<td>4.0</td>
<td>63.2 ( 3.5 )</td>
</tr>
<tr>
<td>5.0</td>
<td>74.1 ( 3.3 )</td>
</tr>
<tr>
<td>6.0</td>
<td>85.0 ( 3.1 )</td>
</tr>
<tr>
<td>7.0</td>
<td>94.0 ( 2.8 )</td>
</tr>
<tr>
<td>8.0</td>
<td>97.2 ( 2.3 )</td>
</tr>
<tr>
<td>9.0</td>
<td>97.0 ( 2.0 )</td>
</tr>
<tr>
<td>10.0</td>
<td>97.0 ( 1.2 )</td>
</tr>
<tr>
<td>11.0</td>
<td>96.8 ( 1.0 )</td>
</tr>
<tr>
<td>12.0</td>
<td>97.1 ( 0.93)</td>
</tr>
<tr>
<td>24.0</td>
<td>97.0 ( 0.97)</td>
</tr>
</tbody>
</table>

<sup>a</sup> Each reading is the mean of six samples.

<sup>b</sup> Values in parenthesis indicate the percent coefficient of variation.
Figure 18. In Vitro Dissolution Profile of Propranolol Hydrochloride from Formulation D in Deionized Water.
Table 19. Cumulative Percent of Drug Release - Coated Beads from Formulation E (Eudragit® RS&RL, 90:10) - 18% Coating\textsuperscript{a}

<table>
<thead>
<tr>
<th>Time (Hours)</th>
<th>Cumulative Percent Released\textsuperscript{b}</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5</td>
<td>4.4 (10.4)</td>
</tr>
<tr>
<td>1.0</td>
<td>10.2 (12.1)</td>
</tr>
<tr>
<td>2.0</td>
<td>22.7 (8.4)</td>
</tr>
<tr>
<td>3.0</td>
<td>34.6 (6.7)</td>
</tr>
<tr>
<td>4.0</td>
<td>46.8 (4.3)</td>
</tr>
<tr>
<td>5.0</td>
<td>57.0 (5.8)</td>
</tr>
<tr>
<td>6.0</td>
<td>68.4 (3.9)</td>
</tr>
<tr>
<td>7.0</td>
<td>77.0 (3.6)</td>
</tr>
<tr>
<td>8.0</td>
<td>84.0 (2.9)</td>
</tr>
<tr>
<td>9.0</td>
<td>89.0 (2.7)</td>
</tr>
<tr>
<td>10.0</td>
<td>93.4 (3.2)</td>
</tr>
<tr>
<td>11.0</td>
<td>98.0 (2.4)</td>
</tr>
<tr>
<td>24.0</td>
<td>100.4 (1.8)</td>
</tr>
</tbody>
</table>

\textsuperscript{a} Each reading is the mean of six samples.  
\textsuperscript{b} Values in parenthesis indicate the percent coefficient of variation.
Figure 19. *In Vitro* Dissolution Profile of Propranolol Hydrochloride from Formulation E in Deionized Water.
Table 20. Cumulative Percent of Drug Release. Inderal LA® Capsules and Inderal® Immediate Releases Tablets

<table>
<thead>
<tr>
<th>Time (Hour)</th>
<th>Cumulative Percent Released&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Inderal LA® 160 mg</td>
</tr>
<tr>
<td>0.25</td>
<td>46.0 (6.1)</td>
</tr>
<tr>
<td>0.50</td>
<td>4.8 (9.6)</td>
</tr>
<tr>
<td>0.75</td>
<td>---</td>
</tr>
<tr>
<td>1.0</td>
<td>11.1 (11.4)</td>
</tr>
<tr>
<td>2.0</td>
<td>24.2 (10.8)</td>
</tr>
<tr>
<td>3.0</td>
<td>32.4 (8.0)</td>
</tr>
<tr>
<td>4.0</td>
<td>41.0 (8.9)</td>
</tr>
<tr>
<td>5.0</td>
<td>50.6 (7.2)</td>
</tr>
<tr>
<td>6.0</td>
<td>57.4 (6.2)</td>
</tr>
<tr>
<td>7.0</td>
<td>63.9 (5.4)</td>
</tr>
<tr>
<td>8.0</td>
<td>70.2 (4.6)</td>
</tr>
<tr>
<td>9.0</td>
<td>76.1 (4.2)</td>
</tr>
<tr>
<td>10.0</td>
<td>80.4 (4.2)</td>
</tr>
<tr>
<td>11.0</td>
<td>83.7 (3.8)</td>
</tr>
<tr>
<td>12.0</td>
<td>86.2 (3.1)</td>
</tr>
<tr>
<td>24.0</td>
<td>94.5 (1.6)</td>
</tr>
</tbody>
</table>

<sup>a</sup> Each reading is the mean of six samples.

<sup>b</sup> Values in parenthesis indicate the percent coefficient of variation.
Figure 20. *In Vitro* Dissolution Profile of Propranolol Hydrochloride from Inderal LA® and Inderal® Immediate-Release Tablets in Deionized Water.
Inderal® tablets. Complete dissolution of the immediate release dosage form occurred in one hour while the controlled release dosage form showed extended-release. However, only 86.2% of the drug was released in 12 hours and at the end of 24 hours, 94.5% of the drug was released.

Table 21 and Figure 21 show comparisons of dissolution profiles of Inderal LA® and Formulation E. The pH of the medium was kept at 1.2 for the initial 2 hours and at the end of the second hour the medium was changed to 7.5 using simulated intestinal fluid. The drug release profile was found to be unaffected by the change of pH and compared to dissolution behavior in deionized water.

Since bead-type oral dosage forms can reside in the GI tract for a period of 4-12 hours, an oral controlled-release dosage form which delivers drug over a 12 hour period is unsuitable as a controlled-release dosage form (124). However, new technologies such as hydrodynamically balanced dosage forms which might float in the gastric contents and can deliver drug over 12 hour period are emerging (52). Since the bead formulated may be subjected to the variability of the GI tract, no attempt was made to prolong the release of the drug over 12 hours. Formulation E, which showed drug release up to 12 hours was therefore used in the bioavailability study.
Table 21. Cumulative Percent of Drug Release by the pH Change Method

<table>
<thead>
<tr>
<th>Time (Hours)</th>
<th>pH</th>
<th>Inderal LA®</th>
<th>Formulation E</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5</td>
<td>1.2</td>
<td>4.7 (9.4)</td>
<td>5.1 (8.8)</td>
</tr>
<tr>
<td>1.0</td>
<td>1.2</td>
<td>10.4 (12.6)</td>
<td>11.0 (11.1)</td>
</tr>
<tr>
<td>2.0</td>
<td>1.2</td>
<td>21.1 (7.2)</td>
<td>22.1 (7.6)</td>
</tr>
<tr>
<td>3.0</td>
<td>7.5</td>
<td>34.6 (7.8)</td>
<td>34.2 (6.1)</td>
</tr>
<tr>
<td>4.0</td>
<td>7.5</td>
<td>45.2 (7.1)</td>
<td>45.4 (4.3)</td>
</tr>
<tr>
<td>5.0</td>
<td>7.5</td>
<td>56.1 (6.2)</td>
<td>57.1 (3.8)</td>
</tr>
<tr>
<td>6.0</td>
<td>7.5</td>
<td>62.3 (4.6)</td>
<td>64.3 (2.9)</td>
</tr>
<tr>
<td>7.0</td>
<td>7.5</td>
<td>67.1 (3.9)</td>
<td>73.9 (2.4)</td>
</tr>
<tr>
<td>8.0</td>
<td>7.5</td>
<td>71.8 (3.7)</td>
<td>82.6 (2.7)</td>
</tr>
<tr>
<td>9.0</td>
<td>7.5</td>
<td>75.2 (2.9)</td>
<td>89.6 (1.9)</td>
</tr>
<tr>
<td>10.0</td>
<td>7.5</td>
<td>78.1 (2.9)</td>
<td>94.1 (1.6)</td>
</tr>
<tr>
<td>11.0</td>
<td>7.5</td>
<td>82.5 (2.6)</td>
<td>96.8 (1.8)</td>
</tr>
<tr>
<td>12.0</td>
<td>7.5</td>
<td>86.1 (2.2)</td>
<td>97.8 (1.5)</td>
</tr>
<tr>
<td>24.0</td>
<td>7.5</td>
<td>100.2 (1.4)</td>
<td>99.8 (1.5)</td>
</tr>
</tbody>
</table>

a Each reading is the mean of six samples.

b Values in parenthesis indicate the percent coefficient of variation.
Figure 21. *In Vitro* Dissolution Profile Comparison of Inderal LA® and Formulation E Beads Using pH Change Method.
Influence of Eudragit® RS & RL Ratio on Propranolol Release

Eudragit® RS is a poorly permeable polymer, while Eudragit® RL is a readily permeable polymer. Three combinations of these polymers were evaluated for in vitro drug release using propranolol as the model drug.

Formulation A, which was coated with a 50:50 mixture, showed sustained drug release up to 3 hours. Formulation B was a 75:25 mixture (RS:RL) and the drug release extended up to 8 hours. Formulation D was a 90:10 mixture (RS:RL) and the drug release extended up to 8 hours. Comparative dissolution profiles of the three formulations are shown in Figure 22a. All these formulations are coated to a 15% weight gain.

Influence of Percent Coating on Drug Release

Coating dispersion C, containing Eudragit® RS:RL in 90:10 ratio was evaluated for the influence of percent coating on drug release. Formulation C, which was coated with the dispersion to a 10% weight gain showed apparent zero-order release up to 3 hours, while 15% weight gain showed up to 6 hours. At an 18% coating the beads released drug for a period of 11 hours. Figure 22b shows the comparative drug-release profiles of the 3 dosage forms. As the percent coating increases, the sustained-release profile is more prolonged. This is due to the increased
Figure 22a. Influence of Eudragit® RS & RL Ratio on Dissolution Profile of Propranolol Hydrochloride — At 15% Coating.
Figure 22b. Influence of Percent Coating on Dissolution Profile of Propranolol Hydrochloride from the Coated Beads.
quantity of Eudragit® RS which is poorly permeable.

Determination of Propranolol in Plasma by HPLC

Under the conditions described in the experimental section, propranolol had a mean retention time of 4.88 ± 0.20 minutes for all samples and for the internal standard, desimipramine, it was 5.72 ± 0.20 minutes. Figure 23 illustrates chromatograms of propranolol and desipramine in plasma at various concentrations of propranolol. No interfering peaks occurred at the time corresponding to the retention time for propranolol or desimipramine. From this it can be seen that the extraction procedure allowed for good resolution of propranolol and desimipramine while separating out interfering plasma compounds. Figure 24 (a) and (b) provides chromatograms of blank plasma obtained from dog number 4 previous to dosing, with the internal standard, desimipramine added and plasma sample drawn 1 hour after a 160 mg controlled-release formulation (Formulation E) was administered. The propranolol peak corresponds to a plasma concentration of 11 ng/ml. As seen from this figure, no interfering peaks occurred at the time corresponding to the retention time for propranolol or desimipramine. Thus the method is simple and accurate.

Reproducibility (Precision) and Linearity

The peak area ratio, determined by taking the peak area
Figure 23. Chromatograms of Blank Plasma and Various Concentrations (10, 100 ng/ml) of Propranolol Hydrochloride with the Internal Standard, Desimipramine Added.

Peak 1 = Propranolol
Peak 2 = Desimipramine

A = Blank Plasma Sample, with Desimipramine Added

B = Plasma Sample with 10 ng/ml Propranolol with Desimipramine Added

C = Plasma Sample with 100 ng/ml Propranolol with Desimipramine Added
Figure 24. Comparison of Blank Plasma Versus Plasma Obtained One Hour After Administration of the Controlled Release Dosage Form Manufactured in the Study.

Peak 1 = Propranolol
Peak 2 = Desipramine

A = Blank Plasma, from Dog #4 with Desipramine Added
B = Plasma Sample obtained 1 Hour after Dosing 160 mg Controlled Release Formulation E
response of propranolol and divided by the internal standard peak area response, versus concentration of propranolol in plasma was linear as shown in Table 22, also shown in Figure 25. This linearity extended over the whole range of the calibration curve from 10 to 100 ng of propranolol per milliliter of plasma. The results of the reproducibility studies are shown in Table 23. The reproducibility studies on replicates containing 10 ng of propranolol per plasma sample yielded a percent coefficient of variation of 2.73 and 6.23, 2.03 and 0.78 percent for 25, 50 and 100 ng propranolol respectively. These studies verify the precision of the HPLC assay for the detection of propranolol in plasma samples.

Recovery (Accuracy) of HPLC Assay

The efficiency of the extraction procedure was determined by evaluating the recovery of propranolol from "spiked" dog plasma standard samples. The plasma samples were extracted as outlined in the extraction procedure except that the internal standard, desipramine, was not added until after the propranolol was extracted and separated from the plasma. The extraction efficiency was determined as the percent of drug recovered. Data is shown in Table 24. The mean recovery of propranolol, as compared to standard, was $100.96 \pm 2.11$ with percent coefficient variation of 2.0.
Table 22. Propranolol Concentration Vs. Peak Area Ratio Extracted from Dog Plasma Matrix

<table>
<thead>
<tr>
<th>Concentration (ng/ml)</th>
<th>Peak Area Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0.0000</td>
</tr>
<tr>
<td>10</td>
<td>0.0440</td>
</tr>
<tr>
<td>25</td>
<td>0.1098</td>
</tr>
<tr>
<td>50</td>
<td>0.2073</td>
</tr>
<tr>
<td>100</td>
<td>0.4144</td>
</tr>
</tbody>
</table>

Correlation = 0.9999
Slope = 0.0041
Intercept = 0.0042
Figure 25. Calibration Curve for Propranolol Hydrochloride Concentration Vs. Peak Area Ratio.
Table 23. Reproducibility Study of Propranolol Detection from Dog Plasma Matrix

### A. Five Samples Containing 10 ng/ml of Propranolol

<table>
<thead>
<tr>
<th>Sample Number</th>
<th>Peak Area Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.0448</td>
</tr>
<tr>
<td>2</td>
<td>0.0444</td>
</tr>
<tr>
<td>3</td>
<td>0.0448</td>
</tr>
<tr>
<td>4</td>
<td>0.0440</td>
</tr>
<tr>
<td>5</td>
<td>0.0419</td>
</tr>
</tbody>
</table>

Mean = 0.0440
\(\pm SD = 0.0012\)
\% CV = 2.73

### B. Five Samples Containing 25 ng/ml of Propranolol

<table>
<thead>
<tr>
<th>Sample Number</th>
<th>Peak Area Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.1163</td>
</tr>
<tr>
<td>2</td>
<td>0.1049</td>
</tr>
<tr>
<td>3</td>
<td>0.1129</td>
</tr>
<tr>
<td>4</td>
<td>0.1144</td>
</tr>
<tr>
<td>5</td>
<td>0.1003</td>
</tr>
</tbody>
</table>

Mean = 0.1098
\(\pm SD = 0.0068\)
\% CV = 6.23
Table 23 continued,

C. Five Samples Containing 50 ng/ml of Propranolol

<table>
<thead>
<tr>
<th>Sample Number</th>
<th>Peak Area Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.2016</td>
</tr>
<tr>
<td>2</td>
<td>0.2124</td>
</tr>
<tr>
<td>3</td>
<td>0.2047</td>
</tr>
<tr>
<td>4</td>
<td>0.2085</td>
</tr>
<tr>
<td>5</td>
<td>0.2091</td>
</tr>
</tbody>
</table>

Mean = 0.2073
±SD = 0.0042
% CV = 2.03

D. Five Samples Containing 100 ng/ml of Propranolol

<table>
<thead>
<tr>
<th>Sample Number</th>
<th>Peak Area Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.4183</td>
</tr>
<tr>
<td>2</td>
<td>0.4104</td>
</tr>
<tr>
<td>3</td>
<td>0.4133</td>
</tr>
<tr>
<td>4</td>
<td>0.4129</td>
</tr>
<tr>
<td>5</td>
<td>0.4170</td>
</tr>
</tbody>
</table>

Mean = 0.4144
±SD = 0.0032
% CV = 0.78
Table 24. The Extraction Efficiency from "Spiked" Dog Plasma Samples

<table>
<thead>
<tr>
<th>Concentration (ng/ml)</th>
<th>Determined</th>
<th>Percent Recovered</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>10</td>
<td>10.0584</td>
<td>100.58</td>
</tr>
<tr>
<td>25</td>
<td>26.0064</td>
<td>104.03</td>
</tr>
<tr>
<td>50</td>
<td>49.6581</td>
<td>99.32</td>
</tr>
<tr>
<td>100</td>
<td>99.8983</td>
<td>99.90</td>
</tr>
</tbody>
</table>

Mean % recovery = 100.96

±SD = 2.11

% CV = 2.02
Precision and accuracy of the extraction procedure was statistically estimated and data are shown in Table 25. Total error percentage varied between 1.67 and 17.3, the latter for the 25 ng/ml sample. A total error percentage value of less than 20 percent is excellent while up to 50 percent is acceptable.

Bioavailability Measurements

In order for a formulation to be meaningful, it is necessary that the bioavailability of the formulation be measured. In the present study, blood level data was obtained for Inderal LA® 160 mg, Inderal® immediate release tablets, 40 mg, and a 160 mg controlled release formulation developed in this study. Each dosage form was administered to 4 dogs in an "incomplete randomized block design" as described in the experimental section. Table 26 shows blood level data obtained for 40 mg Inderal® tablets (administered at 6 hour intervals) in four dogs. Review of the data shows that plasma levels varied widely. This has also been previously reported by others (125). This variability in plasma levels of propranolol is due to individual differences in the metabolism and elimination of the drug. Mean values show initial higher values and a decline in plasma level as time progressed. This is probably due to tissue uptake of propranolol as time progresses. The coefficient of variation of average plasma
Table 25. Precision and Accuracy Determination of Propranolol Recovery from "Spiked" Dog Plasma—Statistical Treatment

<table>
<thead>
<tr>
<th>Standard Concentration (ng/ml)</th>
<th>Determined</th>
<th>Standard Deviation</th>
<th>Relative SD (%)</th>
<th>Mean Error</th>
<th>Relative Mean Error(%)</th>
<th>Total Error(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>10.25,10.25</td>
<td>0.2938</td>
<td>2.92</td>
<td>0.0584</td>
<td>0.58</td>
<td>6.46</td>
</tr>
<tr>
<td></td>
<td>10.16,10.06</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>9.55</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>25</td>
<td>27.59,26.76</td>
<td>1.6599</td>
<td>6.38</td>
<td>1.0064</td>
<td>3.87</td>
<td>17.3</td>
</tr>
<tr>
<td></td>
<td>24.81,27.13,23.72</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>50</td>
<td>48.29,49.03</td>
<td>1.0124</td>
<td>2.04</td>
<td>-.3418</td>
<td>0.69</td>
<td>4.73</td>
</tr>
<tr>
<td></td>
<td>50.90,49.97</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>50.10</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>100</td>
<td>100.865,99.63</td>
<td>0.7831</td>
<td>0.78</td>
<td>-.1016</td>
<td>0.1</td>
<td>1.67</td>
</tr>
<tr>
<td></td>
<td>99.53,98.93</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>100.54</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time (Hour)</td>
<td>Dog#</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>Mean</td>
</tr>
<tr>
<td>------------</td>
<td>------</td>
<td>----</td>
<td>----</td>
<td>----</td>
<td>----</td>
<td>------</td>
</tr>
<tr>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>0.5</td>
<td>66.2</td>
<td>18.1</td>
<td>110.0</td>
<td>126.7</td>
<td>80.2</td>
<td>48.7</td>
</tr>
<tr>
<td>1</td>
<td>49.00</td>
<td>45.5</td>
<td>39.8</td>
<td>117.2</td>
<td>62.9</td>
<td>36.4</td>
</tr>
<tr>
<td>2</td>
<td>34.6</td>
<td>28.0</td>
<td>29.1</td>
<td>84.0</td>
<td>43.9</td>
<td>26.9</td>
</tr>
<tr>
<td>4</td>
<td>2.5</td>
<td>9.0</td>
<td>12.3</td>
<td>31.0</td>
<td>13.7</td>
<td>12.2</td>
</tr>
<tr>
<td>8</td>
<td>16.0</td>
<td>48.7</td>
<td>28.4</td>
<td>75.0</td>
<td>42.0</td>
<td>25.8</td>
</tr>
<tr>
<td>14</td>
<td>37.0</td>
<td>79.2</td>
<td>65.1</td>
<td>94.0</td>
<td>68.8</td>
<td>24.3</td>
</tr>
<tr>
<td>20</td>
<td>20.2</td>
<td>25.1</td>
<td>55.3</td>
<td>62.0</td>
<td>40.7</td>
<td>21.1</td>
</tr>
<tr>
<td>24</td>
<td>2.4</td>
<td>12.8</td>
<td>4.5</td>
<td>20.0</td>
<td>9.9</td>
<td>8.1</td>
</tr>
<tr>
<td>30</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>4.0</td>
<td>1.0</td>
<td>2.0</td>
</tr>
</tbody>
</table>
values from the four dogs varied between 200 and 35. However, the CV of 200 was seen at the 30th hour when virtually no drug was detected in the plasma of 3 dogs and can be considered an outlier.

Table 27 show the plasma values from 4 dogs after administration of Inderal LA®. Variability in plasma drug levels is shown by the percent coefficient of variation which ranged from 20 to 89.

Table 28 show the plasma values from 4 dogs after administration of controlled-release Formulation E prepared in the study. Results indicate that the formulation showed comparable blood levels and no dose dumping. A percent coefficient variation value of 198 at the 24th hour is an outlier since only one dog showed a blood level value at this interval. The percent coefficient of variation at other intervals ranged from 25 to 82.

Figures 26 to 31 show blood level data obtained in each dog for various formulations. Figures 32 to 34 show average plasma levels of each dosage form obtained from 4 dogs. Figure 35 show comparative plasma drug profiles of the different dosage forms used in the bioavailability study.

Discussion on The Area Under the Curve and Other Pharmacokinetic Parameters

The area under the curve was calculated using the
Table 27. Plasma Concentration of Propranolol in Dogs After Oral Administration of Inderal LA®, 160 mg Capsules

<table>
<thead>
<tr>
<th>Time (Hour)</th>
<th>Dog# 1</th>
<th>2</th>
<th>5</th>
<th>6</th>
<th>Mean</th>
<th>±S.D</th>
<th>% CV</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0</td>
<td>0</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>0.5</td>
<td>0.0</td>
<td>4.0</td>
<td>6.7</td>
<td>12.2</td>
<td>5.7</td>
<td>5.1</td>
<td>89.4</td>
</tr>
<tr>
<td>1</td>
<td>2.7</td>
<td>8.1</td>
<td>7.6</td>
<td>15.2</td>
<td>8.4</td>
<td>5.1</td>
<td>61.2</td>
</tr>
<tr>
<td>2</td>
<td>4.8</td>
<td>22.0</td>
<td>25.8</td>
<td>11.0</td>
<td>15.9</td>
<td>9.7</td>
<td>61.0</td>
</tr>
<tr>
<td>4</td>
<td>7.1</td>
<td>24.0</td>
<td>20.0</td>
<td>14.0</td>
<td>16.3</td>
<td>7.4</td>
<td>45.2</td>
</tr>
<tr>
<td>8</td>
<td>28.0</td>
<td>18.0</td>
<td>19.5</td>
<td>24.5</td>
<td>22.6</td>
<td>4.7</td>
<td>20.6</td>
</tr>
<tr>
<td>14</td>
<td>18.0</td>
<td>10.0</td>
<td>14.0</td>
<td>14.0</td>
<td>14.0</td>
<td>3.3</td>
<td>23.3</td>
</tr>
<tr>
<td>20</td>
<td>4.0</td>
<td>6.0</td>
<td>0.0</td>
<td>3.5</td>
<td>3.4</td>
<td>2.5</td>
<td>82.8</td>
</tr>
<tr>
<td>24</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>30</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Time (Hour)</td>
<td>Dog#</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
<td>Mean</td>
<td>±S.D</td>
</tr>
<tr>
<td>------------</td>
<td>------</td>
<td>-----</td>
<td>-----</td>
<td>-----</td>
<td>-----</td>
<td>------</td>
<td>------</td>
</tr>
<tr>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>0.5</td>
<td>0</td>
<td>4.0</td>
<td>4.0</td>
<td>1.5</td>
<td>2.4</td>
<td>2.0</td>
<td>82.8</td>
</tr>
<tr>
<td>1</td>
<td>4.0</td>
<td>11.0</td>
<td>8.4</td>
<td>12.1</td>
<td>8.9</td>
<td>3.6</td>
<td>40.5</td>
</tr>
<tr>
<td>2</td>
<td>10.0</td>
<td>30.0</td>
<td>8.4</td>
<td>16.1</td>
<td>16.1</td>
<td>9.8</td>
<td>60.9</td>
</tr>
<tr>
<td>4</td>
<td>18.0</td>
<td>10.0</td>
<td>14.2</td>
<td>12.0</td>
<td>13.6</td>
<td>3.4</td>
<td>25.3</td>
</tr>
<tr>
<td>8</td>
<td>33.5</td>
<td>21.3</td>
<td>26.1</td>
<td>18.0</td>
<td>24.7</td>
<td>6.7</td>
<td>27.2</td>
</tr>
<tr>
<td>14</td>
<td>23.4</td>
<td>12.5</td>
<td>23.0</td>
<td>29.5</td>
<td>22.1</td>
<td>7.1</td>
<td>31.9</td>
</tr>
<tr>
<td>20</td>
<td>3.0</td>
<td>4.5</td>
<td>3.1</td>
<td>6.0</td>
<td>4.2</td>
<td>1.4</td>
<td>33.7</td>
</tr>
<tr>
<td>24</td>
<td>2.3</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.6</td>
<td>1.2</td>
<td>198.3</td>
</tr>
<tr>
<td>30</td>
<td>0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>
Figure 26. Plasma Drug Levels of Propranolol in DOG 1 Following Oral Administration.

Key: ● 40mg Inderal® tablets administered 4 times daily at 6 hour intervals (DAY 1)
▲ 160mg controlled release capsule, Inderal LA® (DAY 8)
Figure 27. Plasma Drug Levels of Propranolol in DOG 2 Following Oral Administration.

Key: 
- ● 40mg Inderal® tablets administered 4 times daily at 6 hour intervals (DAY 8)
- ▲ 160mg controlled release capsule Inderal LA® (DAY 1)
Figure 28. Plasma Drug Levels of Propranolol in DOG 3 Following Oral Administration.

Key:
- ● 40mg Inderal® tablets administered 4 times daily at 6 hour intervals (DAY 1)
- ■ 160mg controlled-release capsule, formulation E. (DAY 8)
Figure 29. Plasma Drug Levels of Propranolol in DOG 4 Following Oral Administration.

Key:
- • 40mg Inderal® tablets administered 4 times daily at 6 hour intervals (DAY 8)
- ■ 160mg controlled-release capsule, formulation E (DAY 1)
Figure 30. Plasma Drug Levels of Propranolol in DOG 5 Following Oral Administration.

Key:
- ■ 160mg controlled release capsule, formulation E. (DAY 8)
- ▲ 160mg controlled-release formulation, Inderal LA® (DAY 1)
Figure 31. Plasma Drug Levels of Propranolol in DOG 6 Following Oral Administration.

Key:
- ■ 160mg controlled release capsule, formulation E (DAY 1)
- ▲ 160mg controlled release formulation, Inderal LA® (DAY 8)
Figure 32. Mean Plasma Drug Levels of Propranolol After Administration of 40 mg Immediate-Release Inderal® tablets (40 mg at 0, 6, 12, and 18 hours). Error Bars Indicate one Standard Deviation. N = 4
Figure 33. Mean Plasma Drug Levels of Propranolol After Administration of 160 mg Inderal LA®. Error Bars Indicate one Standard Deviation. N = 4
Figure 34. Mean Plasma Drug Levels of Propranolol After Administration of 160 mg Controlled-Release Bead Formulation E. Error Bars Indicate one Standard Deviation. N = 4
Figure 35. Comparative Plasma Drug Profiles of Dosage Forms Used in the Bioavailability Study.

Key

■ Inderal®, 40 mg x 4 immediate-release.
△ Formulation E, 160 mg.
● Inderal LA®, 160 mg.
trapezoidal rule from the average plasma values for each dosage form in the 4 dogs. In the case of 40 mg Inderal® immediate release tablets, the equivalence of 160 mg is calculated by multiplying the area under the curve obtained for 40 mg by four times. This was necessary to avoid any discrepancies contributed by subsequent dosing of the animal with the drug. The area under the curve for one 40 mg dosage form after the fourth hour was calculated using the relationship:

\[ \frac{C_i}{K} \]

Where \( C_i \) is the plasma concentration at the 4th hour and \( K \) is the elimination rate constant.

Area under the curve was calculated for both the controlled-release formulations up to 30 hours. Data is summarized in Table 29. On a percent basis comparison to immediate release dosage form, Inderal LA® was found to be 38.22%, and Formulation E 45.59% bioavailable. In the case of Inderal® tablets peak concentration occurred in 30 minutes after administration, while in the case of both controlled-release formulations the peak concentration time occurred at the 8th hour.
Table 29. Summary of Pharmacokinetic Parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Inderal® Tablets</th>
<th>Inderal LA®</th>
<th>Formulation E</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC (ng/hr.ml)</td>
<td>773.4*</td>
<td>295.6</td>
<td>352.6</td>
</tr>
<tr>
<td>AUC Percent of Inderal tablets (ng/hr.ml)</td>
<td>100</td>
<td>38.2</td>
<td>45.5</td>
</tr>
<tr>
<td>C&lt;sub&gt;peak&lt;/sub&gt; (ng/ml)</td>
<td>80.2</td>
<td>22.6</td>
<td>24.7</td>
</tr>
<tr>
<td>t&lt;sub&gt;peak&lt;/sub&gt; (hour)</td>
<td>0.5</td>
<td>8.0</td>
<td>8.0</td>
</tr>
</tbody>
</table>

* Corrected to 160 mg propranolol.
SUMMARY AND CONCLUSIONS

1. A simple and rapid procedure for the preparation of controlled release beads is accomplished using a commercially available centrifugal granulator and Eudragit® RS & Eudragit® RL polymers. Propranolol hydrochloride, a highly water-soluble drug is used to illustrate the feasibility of the process. Both bead formation and coating were accomplished in the same unit.

2. The formulation used in the bioavailability study showed an in vitro controlled drug release profile. Zero-order was observed for up to 11 hours and approximately 98 percent of the drug was released. In vivo data showed no dose dumping and a sustained blood level indicating that the product releases drug slowly in the GI tract.

3. The in vitro dissolution test data using various ratios of Eudragit® RS & RL polymers established that increasing Eudragit® RS in the coating formulation results in prolonged drug release.
4. Increasing the amount of coating prolongs the dissolution profile. A 90:10 combination of Eudragit® RS:RL resulted in release rates which were dependent on the amount of coating applied. Ten (10) to 18% coating were evaluated.

5. An HPLC assay used in the study was found to be precise, accurate and reproducible for detecting propranolol in dog plasma.

6. The inter- and intra-subject variability was high when propranolol immediate release tablets were administered. Both Inderal LA® and Formulation E showed reduced variability in plasma levels.

7. The formulation developed in the study showed higher area under the curve indicating that the formulation is equivalent and/or superior to the commercially available formulation.
CHAPTER V
LIST OF REFERENCES


Research Conference, University of Wisconsin, Madison. (June 6-10, 1983)


34. C.F. Granulator, Technical bulletin. Vector Corporation, Marion, Iowa.


37. Vincent Hon-leung Lee and J.R. Robinson, Chapter 3, p. 141 in Reference 1


43. Vincent Hon Leung Lee and J.R. Robinson, Chapter 3, p. 152 in Reference 1


49. NDA # 87-510, Summary Basis of Approval Obtained Through FOI (1980)


53. U.S. Patent # 4,036,227 Assigned to Alza Corporation


55. U.S. Patent # 4,096,238 Assigned to Alza Corporation

56. U.S. Patent # 4,058,122 Assigned to Alza Corporation

57. G.B. Patent # 1,551,898


-147-

60. U.S. Patent # 4,439,199 Assigned to Alza Corporation


63. U.S. Patent # 3,065,143 Assigned to Merrel Dow Pharmaceuticals

64. U.S. Patent # 3,870,790 Assigned to Forest Laboratories

65. U.S. Patent # 4,226,849 Assigned to Forest Laboratories


68. Chemical and Physical Properties of Propranolol Hydrochloride. Information from Ayerst Laboratories


72. L. Hansson, R. Malmcrona, R. Olander et al, "Propranolol in
Hypertension", Report on 158 Patients Treated up to One Year. Klin Wochenschr; 50, 364-369 (1972)


82. U. Thadani, J.O. Parker, "Propranolol in the Treatment of Angina Pectoris; Comparison of Duration of Action in Acute and Sustained Oral Therapy", Circulation; 59, 571-579 (1979)


100. R. Zacest, J. Koch-weser, "Relation of Propranolol Plasma Level to Beta-blockade During Oral Therapy", Pharmacology; 7, 178 (1972)


102. G. Berglund, O. Anderson, L. Hansson, R. Olander

D.C. Harrison, "Determination of the Safe Period for Withdrawal of Propranolol Therapy", Circulation; 48, suppl. iv (1973)


106. C.R. Cleaveland, D.G. Shand, "Effect of Route of


117. Rohm Pharma Data Sheet (Info L/S-I/e)

118. Rohm Pharma Data Sheet (Info RL/RS-4/e)

119. Rohm Pharma Data Sheets (Info ED-2/e)

120. Rohm Pharma Data Sheet (Info E-2/e)


122. Information from Ayerst Laboratories Titled, "Analytical Control and Quality Standards for Propranolol Hydrochloride"


VITA

Muhammed Majeed was born September 25, 1948 in Quilon, India. His elementary and secondary education were completed in Quilon, India and he graduated from Craven, L.M.S. High School in March 1965.

Upon graduation from high school, he entered Kerala University where he spent 2 years majoring in general sciences followed by 4 years in pharmacy. While at Kerala University, he was general secretary, pharmacy student's association from its inception. He was graduated from Kerala University, College of Pharmacy in 1973 with a Bachelor of Science degree in pharmacy. Upon graduation, he taught for a year at the College of Pharmacy.

Mr. Majeed emigrated to the United States in early 1974 and joined Arnold & Marie Schwartz College of Pharmacy in 1977 to obtain his Master's degree in Industrial Pharmacy. He was conferred his degree in 1980 after completion of course work and thesis titled "Microencapsulation of Theophylline as a Sustained-Release Product".

He joined St. John's University in September 1980 to obtain his Doctor of Philosophy degree. His studies were under the guidance of Professor Sanford Bolton. Mr. Majeed is a naturalized U.S. Citizen. His previous professional affiliations include Standard Pharmacal, Pfizer, Inc and Carter-Wallace. Currently he is Manager, Pharmaceutical R&D for PACO Laboratories, Lakewood, N.J.