Formulation of Oral Dosage Forms by Three Dimensional Printing

by

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Bachelor of Science, Mechanical Engineering
Michigan Technological University, 1995

Submitted to the Department of Materials Science and Engineering in
Partial Fulfillment of the Requirements for the Degree of

MASTER OF SCIENCE
in Materials Science and Engineering

at the
MASSACHUSETTS INSTITUTE OF TECHNOLOGY

February 1998

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ABSTRACT

Pharmaceutical grade materials were used in the fabrication of fast-release and extended-release oral dosage forms. Tablets were processed by employing a method of solid freeform fabrication known as three dimensional printing™ (3DPTM). A microcrystalline cellulose powder was used in combination with pH-dependent and permeable polymeric binder solutions. Release studies in acidic media were performed using both dye and drug (antihistamine) as actives. Deposition was performed by micropipette into concept devices. It was concluded that printing parameters could be used to control the microstructure and release behavior.

The performance of a drop-on-demand inkjet printing system was evaluated to be highly accurate, and the system was used in the fabrication of model oral dosage forms. Tablets were constructed with a permeable polymer as binder. Mechanical tests showed that the tablets were comparable to industry references for both strength and friability. A USP dissolution method involving an acid and buffer stage was used for extended-release studies. Release by diffusion was found to depend on device porosity level and drug distribution as defined during fabrication.

Thesis Supervisor: Michael J. Cima
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ACKNOWLEDGEMENTS

First and foremost, I would like to thank my advisor, Professor Michael Cima, for all of his encouragement and advice, and without whom none of this would be possible. I didn’t know what I was getting into when I began the research, but it turned out to be an intellectually stimulating and fascinating endeavor. I’ll admit I was skeptical from the beginning, and was equally astonished that it all worked out. You never know until you try. And try.

The rest of the CPRL staff deserves a lot of credit for helping me accomplish what I did. Thanks to Lenny Rigione and John Centorino for keeping everything in shape around the lab. Thanks to Barbara Layne for taking care of the business. Spending money would not be so easy without you.

Special thanks to Ben Wu for keeping me company those late nights when proposals were due. You’ve given almost as much to this project as I did. Stampede lives on, but bring the shovel.

Thanks to the Therics guys, Bill Rowe and Bugra G., who always kept our spirits up around here. It was always good to see the lighter side of things. Thanks to all the rest of the CPRLers, particularly the 3DP group, who made serving time more tolerable.

Thanks to members of TCC for the spiritual development and prayer, without which I could not have kept my sanity. I owe deep gratitude to the CF gang, you all know who you are. I always looked forward to Friday nights, even though I was dead beat for many of them. You’ve all made my time at MIT very memorable.

Thanks to my family for being supportive and always giving me a retreat place when I needed a break. Thanks for the care, too.

And last but not least, thanks to St. Anthony for always looking upon me and to our Heavenly Father, to whom all this work is dedicated.

See, the science came, just like I promised!
1. INTRODUCTION

1.1 BACKGROUND

Many drugs are suggested to be delivered in a controlled fashion to provide the most effective treatment. A number of techniques can be used to control the delivery of drugs which are administered orally. Tablets and capsules are among the more popular modes and are ideal for targeted and extended release applications. Timed release of secondary drugs may also be included in the formulation strategy, and this is where conventional manufacturing methods often fall short. A solid freeform fabrication method, known as three dimensional printing™ (3DPTM), was proposed as an alternative method for the processing of oral dosage forms. 3DP has also participated in the fabrication of tissue engineering scaffolds and drug delivery devices. Two methods of controlled fluid delivery, continuous-jet and drop-on-demand, give 3DPTM its unique capabilities of being able to control microstructure, a critical factor in the aforementioned applications. The microstructure, in cooperation with the drug placement, governs the release characteristics of drug delivery devices.

1.2 ORAL DOSAGE FORM TECHNOLOGY

Many different methods can be used to deliver drugs to a patient; the most popular are injections, patches, inhalants, implants, ointments, and oral dosage forms. Oral dosage forms (ODFs) are often used because of their convenience and delivery flexibility. ODFs are most effective with drugs which need to be delivered within a 24-hour time period and which can be absorbed directly through the digestive tract into the circulatory system. Some forms deliver their entire contents immediately, and others deliver their contents slowly, and gradually pass through the entire gastrointestinal tract. Numerous methods have been developed to control the time or rate at which drugs are released, and most involve either degradable or permeable materials.

1.2.1 Controlled release

It is often found that the effectiveness of a drug is maximized if it is delivered at a certain time and rate in the gastrointestinal tract. Two general strategies relying on either targeted or extended release can be considered when planning the delivery of drugs for
optimal effect. Targeted release can be used when the drug should be delivered after a certain period of time within the GI tract. Extended release, also referred to as sustained release, can be used when the duration and rate of delivery are important. The two methods can be combined to obtain dual-release properties. Delivery of drugs from oral dosage forms is a daunting proposition because of the wide range of conditions throughout the digestive system. Conditions range from hostile acidic conditions to mildly basic conditions. Pharmacologists can take advantage of these varying conditions in planning controlled release strategies of the dosage to the patient.

The digestive system anatomy is shown in Figure 1.1. The travel path of an oral dosage form begins with ingestion where it is briefly exposed to salivary enzymes in the oral cavity. It proceeds to the stomach where it is exposed to gastric conditions for about one hour depending on food mobility. The conditions vary depending on content but are usually acidic in the range of pH 1 to 4. Immediate relief formulations typically release their contents at this point. The next stage is the intestinal tract where conditions are neutral to slightly basic with a pH of 5 to 7 for eight to twelve hours. Extended release dosage applications deliver in this time frame.
The concept of controlling the release of drugs has resulted in a proliferation of the types of oral dosage forms on the market. A number of delivery methods can be employed, including tablets, capsules, gelatin, or liquid forms. The optimal method depends on the drugs used and the type of delivery desired. Solid forms allow for the most versatility in delivery options. Many materials having varying levels of solubility and permeability under specific conditions can be used to obtain desired release characteristics. The inclusion of one or more of these materials into a single dosage form can provide for targeted and/or sustained release formulations.

One of the most challenging issues with manufacturing oral dosage forms lies in the formulation development process. Advances in drug combinatorial chemistry have resulted in an explosion of the number of drugs available for combating an ailment. Frequently more
than one drug needs to be included in the formulation to minimize side effects or to optimize effectiveness. The timing of the release of the secondary drugs is often key to their efficacy, further complicating the formulation process. Developing methods to control the release of multiple drugs is a priority in the research of oral dosage form technology.

1.2.2 Pellets and capsules

The introduction of pelletization technology into the pharmaceutical industry has enabled a great amount of flexibility in the formulation of oral dosage forms. A pellet is a small component which contains a fraction of the total dosage and many can be inserted into either capsule, gel, or tablet forms to deliver the appropriate dosage. Pellets of several different release properties could be manufactured and combined into a single dosage form to generate elaborate drug delivery responses. Each drug is completely isolated inside the pellets to minimize compatibility concerns. The use of pelletization techniques has been limited for two reasons. First, it is difficult to introduce the correct quantity into each dosage form in the manufacturing process. Second, consumers have become aware of the tampering concerns which can arise with capsule forms.

1.2.3 Tablets

Tablets are a popular medium of drug delivery for their simplicity and ease of manufacturing. Formulation of modern tablets has become increasingly complex to generate tablets with specific release characteristics. A large number of components can be considered such as binders, fillers, lubricants, disintegrants, surfactants, pH adjusters, release modifiers, and glidants. The proper ratio of each is critical and makes formulation an arduous process. Conventional tableting methods require large amounts of materials which can make formulation development a costly and time-consuming procedure.

A major advancement in tablet formulation technology was the development of coatings. Coatings can be applied to oral dosage forms to enhance taste or to influence release properties, and may be either soluble or permeable under given conditions. A soluble coating can be used for targeted release applications. The coating thickness and degradation rate determines the lag time until the onset of release. An enteric coating, used to target delivery in the intestinal tract, retains its integrity under acidic conditions but becomes soluble.
under pH > 5 conditions. The other type of coating is pH-independent and permeable and is commonly used for extended release applications. The thickness of this coating is capable of regulating the drug release rate by a diffusion mechanism. Both soluble and permeable coatings can be used within the same dosage form to obtain a large degree of control over release characteristics.

Tablets are ideal for simple delivery applications but are not always practical when potent or multiple drugs are involved. The drugs are processed in solid form are mixed with the base powder and pressed into tablet form. This usually results in a uniform distribution of drug and is limited to zero-order release kinetics. The tablet may not be homogeneous or contain the proper dosage when working with very small quantities of potent drugs, resulting in poor performance. Tableting techniques are also incapable of implementing timed release of multiple drugs. Multiple drugs also cannot be processed into tablet forms if there is a chance they will react with each other.

A method of processing oral dosage forms using solid freeform fabrication (SFF) was sought to overcome the limitations of conventional methods. SFF methods are expected to be able to deliver highly precise quantities of drugs to localized regions within the forms. They will also be able to process multiple materials and specify the microstructure to produce a wide range release properties.

1.3 THREE DIMENSIONAL PRINTING™ OVERVIEW

Three dimensional printing™ (3DPTM) is one of a number of solid freeform fabrication (SFF) techniques in which parts can be constructed directly from CAD files. Most SFF methods, including 3DPTM, employ a successive layering technique to generate three-dimensional parts from two-dimensional patterns. Patterns are created by selectively placing liquid binder with a nozzle onto a thin powder substrate. A broad spectrum of engineering materials can be used in the process, including metals, ceramics, polymers, and hydrogels. 3DPTM has the unique capability of being able to process traditional pharmaceutical materials (powders and binders), making it an ideal choice for the fabrication of oral dosage forms.
1.3.1 Process outline

The 3DP™ process is described in detail elsewhere. A brief synopsis is provided in this section. The 3DP™ machine is composed of three orthogonal axes of motion: fast axis, slow axis, and vertical piston axis. The three axes move independently to construct a part layer by layer. A simplified diagram of the process is shown in Figure 1.2.

The process begins with the piston at full height less the thickness of the first layer. A thin layer of powder is spread on the piston plate with the assistance of spread rails. Binder fluid is passed under pressure through a small nozzle affixed to the fast axis carriage. The carriage is rastered back and forth while stepping along the slow axis to deposit binder. The binder acts as a glue to the individual powder particles, to form a two-dimensional pattern. Binder can be selectively placed using masks, charge-and-deflection, or drop-on-demand printing techniques. The piston is lowered, the next layer of powder is spread, and the process is repeated until the full height of the part is achieved. The powder bed is allowed to dry and the excess unbound powder is removed to expose the finished product.

Figure 1.2: Schematic of the 3DP™ processing steps
1.3.2 Fluid delivery

Two general methods can be used to deliver fluids in three dimensional printing\textsuperscript{TM}: continuous-jet and drop-on-demand. Both methods are described in detail by Heinzel.\textsuperscript{6} A continuous-jet (CJ) printhead is traditionally used in the manufacturing of parts with 3DP\textsuperscript{TM}. A constant flow of binder is delivered through a nozzle under pressure using this system. Continuous-jet print heads are available in a range of sizes and can be used with a wide variety of fluids including organic solvents and ceramic slurries. They may be used with a mask over the powder bed, or they can be combined with a charge-and-deflection system to control binder placement. The charge-and-deflection system, shown in Figure 1.3, is composed of a nozzle, piezoelectric transducer, charging cell, deflection cell, and catcher.\textsuperscript{7} Fluid flow is established through the CJ nozzle and the piezoelectric transducer is activated to stimulate droplet breakoff. An electric potential is applied to the charging cell to selectively deliver an electrostatic charge to individual droplets. A constant voltage is applied to the deflection cell, and the charged droplets are deflected to the catcher while the uncharged droplets pass through to the powder bed. The unused fluid can usually be recycled but must be discarded if contamination is a concern. Charge-and-deflection is a powerful tool for selective binder placement but it is restricted to fluids which can be charged, limiting the use of many organic solvents.

![Diagram of Continuous-jet charge-and-deflection system](image)

**Figure 1.3: Continuous-jet charge-and-deflection system**
Drop-on-demand (DOD) printing is an alternative method of fluid delivery in 3DPTM which has been investigated. DOD printing is much more efficient than CJ printing for depositing small quantities of fluid because droplets are generated only upon request by applying electrical impulses. DOD systems are capable of delivering a range of mass flow rates by simply changing the pulse frequency. Their maximum rate, however, is lower than that for continuous-jet delivery because they must form discrete individual droplets and restore the liquid meniscus to its neutral position for optimal performance.

1.4 THREE DIMENSIONAL PRINTING™ OF BIOMATERIALS

A number of FDA approved biomaterials, including polyethylene oxide and polylactic acid, have demonstrated processing potential with 3DPTM. Design and fabrication of resorbable polymeric medical devices for tissue engineering applications, drug delivery devices, and oral dosage forms have been a major focus of 3DPTM biomaterials research.

1.4.1 Tissue engineering

3DPTM has been used to engineer scaffolds for tissue regeneration applications. The critical parameters of these devices is the level of porosity and microarchitecture for cell growth. These variables can be controlled by varying the printing parameters or using leachable materials in the matrix powder. Another important factor of tissue engineering scaffolds is the degradation rate of the matrix which depends on the polymer used and device microstructure.

The resulting porous matrix is seeded with cells, and under appropriate conditions the cells will proliferate to populate the scaffolding. The cells are allowed to differentiate and mature, and eventually an artificial tissue will be generated which is suitable for implantation. The scaffolding degrades over time and is eventually completely replaced with living tissue. This tissue engineering approach has been investigated for applications in liver, bone, and vascular grafts. An example of proposed bone regenerative devices are shown in Figure 1.4. The hydroxyapatite devices can be implanted into a bone defect to facilitate the healing process.
1.4.2 Drug delivery devices

The construction of drug delivery devices (DDDs) using 3DPTM has also been investigated as an integral part of the biomaterials program. A common objective of manufacturing DDDs is to obtain particular release characteristics by altering the microstructure of the device. A small quantity of drug can be placed in the interior of the device during the fabrication process, and its release will depend on its concentration and location within the device.

Release from DDDs may be modeled by either erosion or diffusion mechanisms. Release is assumed to occur via erosion when a relatively soluble device is placed into solution. Degradation of the device exposes the active, releasing it into the solution. This mechanism of degradation as related to 3DPTM was studied by Wu at the Massachusetts Institute of Technology. Wu demonstrated that release of dyes can be controlled from mini reservoirs of devices composed of water soluble poly(ethylene oxide) and insoluble polycaprolactone. Sections of the devices degraded at different rates upon exposure to dissolution media, releasing the dyes. The microstructure and dye placement within the devices were varied to explain a two-dimensional erosion mechanism of release.

Release by diffusion occurs in three steps when an insoluble but permeable device is placed into solution. First, the solution penetrates the matrix by diffusion. Next, the polymer swells, enhancing the diffusivity of the drug. Finally, the drug molecules diffuse into the solution media. The kinetics of drug release depend on the porosity, permeability, and
thickness of the polymer and the diffusion coefficient of the drug. An example DDD which releases by diffusion is an implantable device constructed of PLGA and polycaprolactone. The devices, shown in Figure 1.5, were designed to deliver 17-deacetylnoregestimate, a steroidal contraceptive, over a predefined period. The release was to be controlled by the thickness of erosion and barrier layers to alter lag time and diffusion rate. The devices were expected to have a 6 month active releasing life, after which they become dormant and can either be removed or left in place.

Figure 1.5: Implantable drug delivery devices as contraceptives

1.4.3 Oral dosage forms

It was suggested that 3DPTM could be used to produce oral dosage forms which exhibit more flexible release patterns than those produced by conventional tableting methods. Local composition, microstructure, and spatial positioning of drug can each be controlled to allow a large amount of flexibility in the formulation process. 3DPTM would be able to include multiple pH-dependent regions within the same dosage form to provide targeted and extended release behavior. It is also capable of working with multiple drugs in the formulation because each could be completely isolated. It could greatly simplify the formulation procedure by being able to work with smaller quantities of drug at a time and with a faster turnaround time.
Fewer variations of material formulas would also need to be investigated because many
parameters can be controlled during the processing itself.

1.5 OBJECTIVES
Criteria were set with several objectives in mind to confirm the feasibility of the above
proposal. The first objective was to verify that pharmaceutical materials can be processed
reliably and efficiently by three dimensional printing™. The materials should also exhibit
pH-dependent behavior and be appropriate for physiological controlled release applications.
Release profiles of the devices should be reproducible to meet industry standards and should
be easily controlled by adjusting the material compositions and microstructure. It should also
be shown that precise dosage delivery can be achieved. The final objective was to show that
the mechanical properties of the devices were comparable to current forms.

1.6 ORGANIZATION AND SCOPE OF THIS STUDY
The first step described in Chapter 2 was to define the device strategy by selecting
materials and designing the devices for simplified testing and modeling. Chapter 3 follows
the device design with fabrication of prototype devices to confirm the efficacy of the materials
selection. The chapter also proposes a model of the release mechanisms. Chapter 4 describes
the implementation of the drop-on-demand fluid delivery system which enables highly precise
dosages to be delivered into the tablets. The evaluation and optimization of this system are
discussed in detail. Chapter 5 combines all elements of Chapters 2 through 4 with the
fabrication of model oral dosage forms. The details of the construction process are discussed,
and more analysis is performed on the release mechanisms to describe the relation of printing
parameters and microstructure to the release kinetics. Conclusions are made regarding
important discoveries and observations, and future work is recommended in Chapter 6. A
suggested general strategy for the development of custom formulations is also provided in the
chapter.
2. CONCEPT DEVELOPMENT

2.1 INTRODUCTION

A number of options were available for consideration in the development of concept devices. Selecting the proper materials for use in the fabrication of oral dosage forms, as in all three dimensional printing™ programs, was critical for the success of this project. Release properties were defined to guide the materials selection process. A testing protocol was developed to rapidly screen the potential material combinations for those which looked promising. Materials were chosen which are used as traditional pharmaceutical excipients and binders. They were suitable for controlled release applications due to their pH-dependent or permeability properties.

Parameters were defined which would set definitive limits on the processing conditions for estimating binder and drug loading potential. The dependence of these parameters on both the mechanical and release properties are to be analyzed in future studies. The physical shape of the devices was defined to be similar to current dosage forms and to enable simplified modeling of the release behavior.

2.2 MATERIALS SELECTION

The selection of materials was the first concern in developing concept devices. The materials were to be selected from industrial pharmaceutical materials and should preferably exhibit pH-dependent properties. The constructed devices should be capable of delivering drug on a practical time scale and also be sufficiently strong to resist frying and fracture during shipping and handling.

A wide range of pharmaceutical grade materials was available for investigation. The powder excipient, binder, and active phase each needed to be selected carefully to obtain desirable properties. Purification and decontamination steps were avoided by considering only natural or biocompatible materials. Both inert and soluble powders were considered for use as excipient matrix materials. Several materials classes, including polymers and polysaccharides, were examined as binder system components.
2.2.1 Materials testing protocol

It was not possible to thoroughly investigate each of the material combinations for use in this oral dosage form study. A simple testing sequence was developed to select attractive material combinations and to minimize the number of steps to finding the optimum printing parameter range for maximum strength and best feature size. The protocol was performed on each material system before proceeding with in-depth analysis. It includes selecting a powder and binder combination and characterizing their interaction with zero-dimensional to three-dimensional tests to model actual 3DPTM processing conditions. The protocol concludes with optimization of the printing parameter range before promoting it to a three dimensional printingTM program.

2.2.1.1 Spread test

The powder spread test is the first step in evaluating a material system for use with 3DPTM. Thin layers of about 150 μm are spread on the piston plate simulating a typical build sequence to determine if there are any moisture or electrostatic problems that hinder the process. If a powder is difficult to spread it cannot be easily incorporated into the 3DPTM process. Additional processing of the powder such as milling or drying may, however, yield better properties, and should be considered before rejecting the powder material.

2.2.1.2 Binder solution analysis

Pure solvents are sometimes used but often are not adequate for use alone as a binder for the powder system. Polymeric or particulate solutions may be used to improve the binding strength. The addition of solutes alters the rheology of the solution and may cause viscosity and nozzle clogging problems. It should be verified that the solution will pass through the filter, usually a 7 μm porous sintered stainless steel (Nupro SS-2TF2-7), and nozzle for a reasonable time (> 1 hour). Binder flow rate should be sufficiently high (between 0.9 and 1.5 cc/min for 45 μm nozzles) and constant (<5% deviation) before continuing with analysis. Other filtering options, such as PTFE discs or steel meshes, may be tested if flow cannot be sustained. Larger nozzles may be used to provide adequate flow rate.
2.2.1.3 Drop test

The drop test is the first test of binder and powder interaction and is the most efficient method of eliminating powder/binder combinations. The binder must both wet the powder and provide mechanical or chemical bonding to be used in 3DPTM. A powder candidate is spread into a thick layer (3 mm) and a single drop of binder solution is deposited using a 10 μl pipette. A larger drop of 20 μl may be used depending on the viscosity and adherence of the solution to the pipette tip. If the solvent is not recommended for use with a Pipetteman®, a glass capillary tube of the appropriate size is used instead. The drop should be released from a height as close as possible to the powder bed without contact to minimize ballistic effects. The binder is allowed to dry and the drop primitive is recovered. A typical primitive is about 3 mm in diameter and 1 mm thick and should remain intact after being squeezed with tweezers to verify its strength.

The drop test is also useful to observe powder wettability of the binder. The drop should be absorbed into the powder bed within a few seconds. A powder/binder combination may be inappropriate for 3DPTM if the binder does not wet the powder bed. Furthermore, the binder should not have such a high affinity for the powder that it wicks extensively. This will result in poor feature size and lower strength. The powder should also be dense enough for the drop to remain at the surface and not fall deep into the powder bed. The powder may be milled to densify it or the solution made more viscous to compensate for this effect.

2.2.1.4 Line test

The line test is the first step in using the three dimensional printer in the materials selection procedure. The line test, a one-dimensional model of the 3DPTM process, is the most effective method for choosing between various powder/binder systems which appeared promising based upon the drop tests. A properly performed line test as described below will give a good estimate of binder strength and wicking.

Binder flow is established through the nozzle to obtain a steady mass rate. Single lines of binder are drawn at varying speeds (150 cm/s, 110 cm/s, 70 cm/s, and 40 cm/s) onto a 3 mm deep powder bed. The lines are recovered from the bed and their strength and size evaluated qualitatively after the binder has dried. The sizes can be estimated with an optical microscope photograph or SEM image, and their dependence on print speed can be plotted.
Lines using various binders and speeds can be compared against one another to select the combination with the best strength and dimensions. Ideal lines should have enough mechanical integrity to be removed from the 8 cm long powder bed in one piece and should be relatively thin (<0.4 mm). A thick line indicates binder bleeding and will likely be poor in strength.

Potential warpage concerns are first revealed with the line test. Warpage is believed to depend on the rate and direction of solvent evaporation. This phenomenon is not easily controlled, but it is possible to minimize its effects. The use of binders which evaporate slower, such as replacing methylene chloride with chloroform, have been shown to reduce warpage in many materials. Parts can also be printed with thin sacrificial ribs to reduce warpage problems.

The line test is also used to assess whether the powder bed is subject to ballistic damage by the impact of the droplet stream. Powders with high ballistic damage are poor candidates for the 3DPTM process because they will have poor surface finish and resolution, and they will have low density and strength.

2.2.1.5 Ribbon test

The ribbon test indicates how well individual lines can be stitched together to form a single layer. It models the 3DPTM process of printing a layer and allows the studying of line pairing and bleeding phenomena. A ribbon test is prepared identical to a line test with an 8 cm long and 3 mm thick powder bed. A series of adjacent lines are printed with a draw speed of 150 cm/s and line spacings of 50, 100, 150, and 200 µm each over 1 cm wide regions. The variation of spacing will reveal the sensitivity of the material properties to printing conditions. The thickness of the ribbons can be measured and recorded to give data comparable to the line test.

Desirable ribbon properties are good mechanical strength and low warpage upon drying. The double-print method of overlaying two staggered ribbons may be used if warpage occurs. Binder wicking problems are revealed with the ribbon test. A binder with high wicking potential will result in a ribbon over 1 mm thick even at high line spacing. This is an indication that the resolution will be poor in any 3DPTM part and the binder should not be used
where tolerances need to be tightly controlled. The ribbon test can also be used to study surface smoothness and resistance to chaffing.

2.2.1.6 Bar test

The bar test is the final procedure which can be used to confirm and optimize a material combination for printing. It progresses one step further than the ribbon test by stacking layer upon layer to closely model the actual three dimensional printing™ process. It is usually performed only after a material passes the drop, line, and ribbon tests. The bar test is the best tool for characterizing the powder/binder system and optimizing printing parameters such as line spacing and layer thickness to maximize strength, density, and resolution, and to minimize warpage.

The bar test begins by spreading a thin layer of powder (about 200 μm) on the build plate. Next, lines are printed at 150 cm/s for line spacings of 50, 100, and 150 μm over 5 mm regions. The following layers are constructed at between 150 and 200 μm thicknesses up to a 5 mm height. The result will be bars of different saturation levels, and strength or warpage problems may become evident in some bars. Binder saturation levels can be reduced by increasing line spacing if warpage is significant. Double-printing can also be performed by first printing a layer of increased line spacing and repeating the layer staggered over the first. This will give the solvent time to evaporate and should reduce the tendency to warp. The velocity or line spacings can be reduced and the test repeated if strength is low. The layer thickness should be reduced and the test repeated if the bars are found to delaminate easily.

SEM images can be taken of the bar cross sections to examine interlayer bonding and density. Note that a fracture surface or cut may not always be representative of the actual material since it may have been damaged in the process. Mechanical strength tests such as bending or tensile tests may also be performed on the bars to obtain a quantitative value of the bonding strength. Finally, the porosity can be measured with mercury porosymmetry or a comparable method. The bar test concludes the materials selection and evaluation protocol.

2.2.2 Powder and binder

A wide variety of classes of materials were considered as powder and binder combinations. The choices are listed in Table 2.1. Both inert and water or alcohol soluble
base powders which are commonly used in the tableting industry were studied for use as matrix materials. Polysaccharides and polymers which were found to have potentially interesting pH-dependent properties were investigated for use as binders. Each powder and binder combination were subjected to the testing protocol as described in Section 2.2.1 to evaluate their potential for 3DPTM processing. The results of the drop tests are shown in Table 2.2.

Table 2.1: Available materials for fabricating ODFs

<table>
<thead>
<tr>
<th>Powders</th>
<th>microcrystalline cellulose (Avicel® PH formulas)*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>hydroxypropyl methylcellulose (HPMC)</td>
</tr>
<tr>
<td></td>
<td>gelatin (Knox®)</td>
</tr>
<tr>
<td></td>
<td>methacrylic ester copolymers (Eudragit®)</td>
</tr>
<tr>
<td></td>
<td>methacrylic acid copolymers (Eudragit®)</td>
</tr>
<tr>
<td></td>
<td>polysaccharides</td>
</tr>
<tr>
<td></td>
<td>arabinogalactan</td>
</tr>
<tr>
<td></td>
<td>starch</td>
</tr>
<tr>
<td></td>
<td>lactose</td>
</tr>
<tr>
<td>Binders</td>
<td>methacrylic ester copolymers*</td>
</tr>
<tr>
<td></td>
<td>methacrylic acid copolymers*</td>
</tr>
<tr>
<td></td>
<td>polysaccharides</td>
</tr>
<tr>
<td></td>
<td>aqueous dispersions</td>
</tr>
<tr>
<td>Solvents</td>
<td>water</td>
</tr>
<tr>
<td></td>
<td>alcohols*</td>
</tr>
<tr>
<td></td>
<td>water/alcohol mixture</td>
</tr>
<tr>
<td></td>
<td>acetone*</td>
</tr>
</tbody>
</table>

* selected material
Table 2.2: Summary of results from drop tests

<table>
<thead>
<tr>
<th>Powders</th>
<th>PH 101</th>
<th>PH 105</th>
<th>PH 113</th>
<th>PH 301</th>
<th>HPMC</th>
<th>Starch 1500</th>
<th>lactose monohydrate NF</th>
<th>lactose NF</th>
<th>lactose USP</th>
<th>lactose 100M</th>
<th>Eudragit RL PO</th>
<th>Eudragit RS PO</th>
<th>Arabinogalactan PC-05315-U</th>
<th>(AG1)</th>
<th>Arabinogalactan F-N0595-F (AG2)</th>
<th>Arabinogalactan L-N0595-1</th>
<th>Knox blended powder</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eudragit RL 30D *</td>
<td>1</td>
<td>1.5</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eudragit NE 30D *</td>
<td>+</td>
<td>+.5</td>
<td>+</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Eudragit L30 D-55 *</td>
<td>+</td>
<td>+.5</td>
<td>+</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Eudragit RS 30D *</td>
<td>+</td>
<td>+.5</td>
<td>+</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Aquacoat ECD-30 *</td>
<td>2</td>
<td>2.5</td>
<td>2</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>20% Eudragit E100 crystals in ethanol</td>
<td>+</td>
<td>+.5</td>
<td>+</td>
<td>3</td>
<td>+ 2</td>
<td>+.5</td>
<td>+    +    1    1    +    +   +,4</td>
<td>+,4</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>10% Eudragit E100 crystals in ethanol</td>
<td>2</td>
<td>3</td>
<td>2</td>
<td>2</td>
<td>2.5</td>
<td>2.5</td>
<td>2    2    2    1    2    1    3.4</td>
<td>2.4</td>
<td>+</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;10% Eudragit RS PO in ethanol</td>
<td>2</td>
<td>3</td>
<td>2</td>
<td>2</td>
<td>2.5</td>
<td>2.5</td>
<td>2    1    1    2    3.4</td>
<td>+,4</td>
<td>+</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>20% Eudragit RL PO in ethanol</td>
<td>+</td>
<td>+.5</td>
<td>+</td>
<td>3</td>
<td>+ 2</td>
<td>+.5</td>
<td>+    +    1    1    +    +   2.4</td>
<td>+,4</td>
<td>+</td>
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<td></td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>40% AG1 in water*</td>
<td>3</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>+.5</td>
<td>+    +    1    1    +    +   1    1    3.4</td>
<td>3.4</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>40% AG2 in water</td>
<td>3</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>+.5</td>
<td>+</td>
<td>+    +    1    1    1    1    1    1    3.4</td>
<td>3.4</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>40% AG3 in water</td>
<td>3</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>+.5</td>
<td>+</td>
<td>+    +    1    1    1    1    1    1    3.4</td>
<td>3.4</td>
<td>+</td>
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</tr>
<tr>
<td>ethanol</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2.5</td>
<td>1    1    2    3.4</td>
<td>3.4</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>40% AG1 in 75% water/ 25% ethanol</td>
<td>+</td>
<td>1</td>
<td>+.5</td>
<td>+</td>
<td>+ 2</td>
<td>+.5</td>
<td>+    +    1    1    1    1    1    1    3.4</td>
<td>3.4</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>20% AG1 in 75% water/ 25% ethanol</td>
<td>2</td>
<td>1</td>
<td>2.5</td>
<td>+.5</td>
<td>+ 1</td>
<td>+.5</td>
<td>+    +    1    1    1    1    1    1    3.4</td>
<td>3.4</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
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<td></td>
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<td></td>
</tr>
</tbody>
</table>

1. poor wetting
2. poor strength
3. poor hardness
4. powder bed sets up after time
5. difficult to spread powder
+ good hardness and strength
* cannot print without clogging printer nozzle

The high solubility of the polysaccharides allowed them to be considered as either powder excipients or as components in binder solutions. The polysaccharide powders were eliminated, however, because of either poor wetting, strength, or feature size with the various binders and solvents. A 40% aqueous arabinogalactan binder solution provided good strength when deposited onto microcrystalline cellulose or polysaccharide powder beds. The solution was eliminated from the choices, however, because it yielded too high a degradation rate for this study.

The Avicel® formulas exhibited superior strength and feature size when used with polymeric binders. Avicel formulas are inert microcrystalline cellulose powders provided by
FMC Corporation, and are commonly used as excipients in the tableting industry. They are insoluble in most solvents and are available in a range of powder sizes, densities, and moisture contents. PH101 and PH301 were chosen for the ODF fabrication studies. PH101 has a bulk density of 0.28 g/cc and an observed packing fraction of 26%. PH301 is slightly more dense at 0.38 g/cc and has a packing fraction of 40%. Both powders have an average particle size of 50 µm and are moderately flowable, making them good candidates for use in 3DPTM.

The Eudragit® polymers (Rohm Pharma Polymers, ) RL, RS, and E100 formulations were selected for use as binder components. They are approved pharmaceutical materials which are commonly used as tablet coatings and binders. RL and RS are ammonio-methacrylic acid copolymers type A and type B (USP/NF), respectively, which contain ammonium groups to make them permeable to water. The RL formula has a higher fraction of ammonio groups, making it more permeable. Both polymers are available in particulate or aqueous dispersion forms and have an average molecular weight of 150,000. Their chemical structure is given below in Figure 2.1. They can be used in powder form with alcohol or acetone based binders, but they cannot be used with aqueous based binders due to hydrophobic effects. The polymers can be dissolved up to 20% (w/w) in acetone for use as a binder system.

Eudragit E100 (Rohm) was chosen for use as binder for its pH-dependent properties. It is a cationic copolymer based on dimethylaminooethyl methacrylate and neutral methacrylic esters and is soluble in gastric fluid (pH < 5), and is expandable and permeable in pH > 5. It can be applied as a readily disintegratable tablet coating for immediate relief formulations. It is available in granular form, and its solubility in ethyl alcohol is over 20% (w/w). Its average molecular weight is 150,000, and its chemical formula is given below in Figure 2.1.
2.2.3 Active selection

A large number of active ingredients were available for consideration in this study and are listed in Table 2.3. The active is to be placed within the oral dosage form as a second liquid phase in a subsequent step following the deposition of binder. Void space restrictions limit the amount of active which can be deposited into the matrix, so the active should be relatively potent. The active should be easy to detect when it is released from the tablet, preferably by UV-vis spectrophotometry. It should also be easy to deposit using drop-on-demand methods to obtain highly accurate dosage delivery.

Table 2.3: Active phases for deposition into ODFs

<table>
<thead>
<tr>
<th>Active</th>
</tr>
</thead>
<tbody>
<tr>
<td>amaranth dye*</td>
</tr>
<tr>
<td>black ink</td>
</tr>
<tr>
<td>chlorpheniramine maleate*</td>
</tr>
<tr>
<td>nifedipine</td>
</tr>
<tr>
<td>verapamil</td>
</tr>
<tr>
<td>diltiazem</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>* selected active</td>
</tr>
</tbody>
</table>

Amaranth dye and chlorpheniramine maleate were chosen for use in the oral dosage forms. Amaranth dye was selected because it is highly visible and can be deposited easily by micropipette into the devices. It was initially used in the devices to model the placement of the drug and for studying deposition characteristics. Chlorpheniramine maleate (C_{16}H_{19}ClN_{2}·C_{4}H_{4}O_{4}) is an antihistamine used in allergy medicines and is typically delivered.
in dosages as low as 2 mg and high as 40 mg. Immediate relief dosages are generally between 2 and 4 mg, and extended release dosages typically contain between 8 and 16 mg (Physicians’ Desk Reference 48th ed, 1994). It can be deposited in alcohol or aqueous media and is soluble up to 200 mg/cc.

2.3 PROCESSING BOUNDARIES

The 3DPTM process involves deposition of liquids, therefore, it was important to determine limiting parameters for defining saturation level which could be tolerated. It is important to note that a tradeoff exists between binder saturation level and resolution. Increasing the binder content will generally yield better mechanical properties but resolution may be compromised. Calculations should also be made to determine the maximum amount of drug solution which can be deposited into the devices during the fabrication procedure.

2.3.1 Binder content

The amount of binder deposited into the powder must be optimized to achieve the necessary strength and feature size. A larger amount of binder will provide greater strength and resistance to friability at the expense of resolution. Line spacing, print velocity, or layer thickness can be changed to vary the level of binder in the devices. Each parameter has a slightly different effect on the resulting microstructure and should be chosen using the testing protocol as a guideline.

A term often used to quantify the amount of binder loading is “binder per unit line length,” β. β, shown in Equation 2-1, is a quantitative way of representing the binder content and is described by Borland.12 The level of binder is critical in determining the final part strength, surface finish, and feature size. It has units of area and is measured as the volume of liquid binder deposited into a unit line as printed. Part properties are frequently described in relation to β.

\[ \beta = \frac{F}{V \rho_b}, \text{ where} \]

**Equation 2-1**

- \( F \) = binder flow rate in g/sec
- \( V \) = velocity of print head in cm/sec
- \( \rho_b \) = density of binder solution in g/cm³
\( \beta \) is utilized in another common term, percent binder saturation, \( \phi_b \), which more accurately characterizes the bleeding of solution in the powder. It is defined as the fraction of volume of binder deposited to the volume available in the powder, and its calculation is shown in Equation 2-2. Note that the packing density of the powder is included in this parameter. Percent saturation values assume that the time scale of evaporation is slower than the time to print adjacent lines.

\[
\phi_b = \frac{\text{vol deposited}}{\text{vol available}} = \frac{\beta}{\Delta x \cdot \Delta z \cdot f}, \text{ where}
\]

\( \beta \) is defined in Equation 2-1

**Equation 2-2**

\[
\begin{align*}
\Delta x &= \text{line spacing in cm} \\
\Delta z &= \text{layer thickness in cm} \\
f &= \text{packing fraction of powder}
\end{align*}
\]

Saturation level is particularly important in determining the maximum amount of binder in a printed part. 100% saturation indicates that the entire void space is filled with liquid during printing. A saturation level higher than this is considered supersaturated and is likely to yield poor resolution and dimensional tolerances because of binder bleeding. The saturation level may be increased by using rapidly evaporating solvents or by allowing the solvent to evaporate between printing passes. More space will be available for the next pass of binder if the solvent has been partially removed. It may take a significant amount of time to dry, however, depending on the vapor pressure. The drying process may be accelerated by applying heat, but care must be taken not to alter the material chemistry.

Binder fraction, \( \Omega \), defines the fraction of void space which contains polymer after solvent removal, and is directly proportional to binder saturation. The calculation of binder fraction is shown in Equation 2-3. The maximum value is unity when all void space is filled with polymer. High binder fractions are generally difficult to achieve, in practice, because of solubility limitations. Only a small fraction of solid will remain following solvent removal.
\[ \Omega = \frac{\text{vol polymer}}{\text{vol available}} = \frac{\theta_b f_p \rho_b}{\rho_p}, \]

where \( \theta_b \) is defined in Equation 2-2.

\[ f_p = \text{mass fraction of polymer in solution} \]

\[ \rho_p = \text{density of polymer} \ (\approx 1) \]

\[ \rho_b = \text{density of binder solution} \]

Equation 2-3

The percent volume polymer (PVP), \( \theta_p \), is another parameter related to binder saturation. It is defined as the volume fraction of polymer present within the final dried specimen, and its calculation is shown in Equation 2-4 below. This parameter will be used to characterize the devices in this study.

\[ \theta_p = \frac{F f_p}{V \Delta x \Delta z \rho_p} \times 100\% \]

Equation 2-4

The parameters are defined in the equations above. The maximum \( \theta_p \) is, ideally, equal to the complement of the powder packing fraction. The typical value is significantly less, however, because the polymer is deposited as a solution and space will remain following solvent evaporation. The polymer density was approximated as 1.0 g/cm\(^3\) to simplify \( \theta_p \) analysis.

2.3.2 Active content

The maximum amount of dye or drug solution which can be deposited into a device also needs to be considered when determining processing boundaries. The amount is limited to the void space, or porosity, which remains following binder deposition and solvent removal. Equation 2-5 shows the calculation for the remaining porosity. This parameter can be placed into Equation 2-6 to determine the saturation level of active solution, \( \phi_a \). The solution will tend to bleed if the saturation level is above 100\%. Supersaturation should be avoided when possible because release properties cannot be predicted if bleeding is excessive. The solvent in the powder bed from the binder pass should be allowed to dry before depositing the drug to maximize loading potential. Drug loading can be increased by allowing the solvent time to dry between multiple depositions. Saturation calculations should be performed prior to constructing any devices to assure that the amount of loading is within a reasonable dosage.
Concept Development

\[ \text{porosity} = 1 - \frac{\text{vol occupied}}{\text{total vol}} = (1 - f)(1 - \Omega), \] where

**Equation 2-5**

\( \Omega \) is defined in Equation 2-3

\( f = \) packing fraction of powder

\[ \phi = \frac{\text{vol deposited}}{\text{vol available}} = \frac{\phi_b \cdot f}{(1 - \text{porosity})}, \] where

**Equation 2-6**

\( \phi_b \) is defined in Equation 2-2

porosity is defined in Equation 2-5

\( f = \) packing fraction of powder

2.4 **DIMENSIONS**

The initial prototype devices were designed to be equivalent to typical tablets in size and shape for comparison purposes. Tablets were constructed in the shape of right circular cylinders and are represented in Figure 2.1 below. The outer diameter was 9 mm and the height was 5 mm. A single releasing phase located in the central region, 4 mm in diameter by 2 mm, was included to simplify modeling of release characteristics.

Figure 2.2: Prototype tablet design

2.5 **CONCLUSION**

A protocol was defined to simplify the evaluation of potential pharmaceutical material combinations for fabricating oral dosage forms. Eudragit\textsuperscript{®} polymers were found to provide the best properties when used in combination with Avicel\textsuperscript{®} powder. The selected materials possess properties for application in controlled release formulations. The boundaries for processing the materials were calculated to verify the upper limits for binder and drug loading.
Tablets were designed to be comparable to conventional forms and to accommodate the properties of the above materials. The devices will release either by erosion over short periods or diffusion over longer periods of time. The tablets include a single releasing phase in the center which may contain either a dye or drug for monitoring release.
3. CONCEPT DEMONSTRATION

3.1 INTRODUCTION

The use of pharmaceutical materials in the three dimensional printing™ process was a scientific front which had never been explored. A pilot study was performed to assess the general feasibility of processing the materials into oral dosage forms. The devices needed to possess sufficient mechanical strength, and they needed to be capable of containing drug and releasing it under controlled conditions. It also needed to be shown that the devices could release in the time frame under physiologic conditions.

The effect of materials and the associated microstructure was examined for their influence on release properties. The first series of experiments involved constructing devices with a degradable polymer, Eudragit® E100. Release of both dye and drug were studied under varying processing conditions, including isostatic pressing. A final series of experiments combined both E100 and a nondegradable polymer, Eudragit® RS, to construct a device which produced both immediate and extended release properties.

3.2 DEFINITION OF TERMS

Parameters were defined to characterize the dissolution properties of the degradable tablets. A logistic fit, given in Equation 3-1, was selected as the optimal curve to model the release profile. The fit accommodates a lag phase, releasing phase, and terminal phase. The logistic curve, furthermore, is also more flexible in the curvature at the beginning and end of release compared to a sigmoidal curve. An example release profile and curve fit are shown in Figure 3.1. The parameter $t_{50}$ defines the time at which half the dosage has released, and the slope at this point indicates the release rate. The equation for determining release rate is shown in Equation 3-2. Lag time is defined as $t_5$, or the time at which 5% has released. $A_1$ and $A_2$ define the minimum and maximum values, respectively, for the curve fit. The minimum is constrained to zero. The total dissolution time, $t_{95}$, is defined as the point which 95% of release has occurred.
Chapter 3

Equation 3-1

\[ y = \frac{A_1 - A_2}{1 + \left( \frac{t}{t_{50}} \right)^p} + A_2, \]

where

- \( A_1 \) = initial Y value (= 0)
- \( A_2 \) = final Y value
- \( t_{50} \) = time at 50% release
- \( p \) = power

Example release curve

Figure 3.1: Definition of release kinetic terms

Equation 3-2

\[ \text{release rate} = \left. \frac{dy}{dt} \right|_{t=t_{50}} = \frac{A_2 p}{4t_{50}} \]

Bleeding of the drug solution during deposition makes it difficult to precisely predict the final location of drug within the devices. Dosage distributions can be distinguished by combining the above parameters into a single parameter called the release coefficient, \( \gamma \). \( \gamma \) is defined as the fraction of total dissolution time during which release occurs, denoted by 5% to 95% release, and its calculation is shown in Equation 3-3. A large release coefficient indicates that the dosage is diffusely spread in the tablet, and a low coefficient indicates a concentrated, highly localized dosage. The validity of \( \gamma \) depends on several assumptions. The first assumption is that the binder density within the dosage region is equal to that of the device bulk. Phase separation due to thermodynamic incompatibility may cause irregularities.
in binder or drug distribution. It must also be assumed that there are no binder-drug chemical reactions, and that the degradation rate is constant throughout the life of the device.

**Equation 3-3**

\[
\gamma = 1 - \frac{t_5}{t_{95}} = 1 - 0.00277^{p^{-1}}
\]

Figure 3.2 shows the effect of changing either dosage distribution or percent volume polymer, \(\theta_p\), (Equation 2-4) on the release kinetics for devices following an erosion mechanism of release. The total degradation time should be independent of dosage distribution but should increase with binder saturation. The lag time will increase when either the dosage is concentrated more towards the center of the device or the binder saturation level is increased. \(\gamma\) should depend only on dosage distribution and remain constant with changes in binder saturation. For example, if half the volume of a device contains dosage, then release is expected to occur over approximately half the total dissolution time regardless of binder saturation levels, assuming constant erosion rate. The final parameter, not shown on the figure, is the release rate, which will decrease with increasing binder saturation.

**Ideal release kinetics**

![Figure 3.2: Ideal release kinetics as based on dosage distribution and polymer content, via erosion mechanism](image)

Figure 3.2: Ideal release kinetics as based on dosage distribution and polymer content, via erosion mechanism
3.3 **Prototype Dye Tablets**

The pilot study began with the fabrication of prototype dye tablets in an attempt to meet the proposed objectives. Materials were selected which would provide release under low-pH conditions. A primary objective was to show that the release kinetics could be altered by controlling the microstructure with printing parameters. The study was concluded by evaluating the efficacy of the micropipette dye deposition method.

### 3.3.1 Materials and methods

An initial round of tablets was constructed which contained amaranth dye in the central regions of the devices. The powder excipient used was Avicel® PH101, and the binder was a 20% (w/w) Eudragit® E100 ethanol solution. A Diconix® orifice plate print head was used to deliver the binder. The nozzle diameter was 74 μm, and the average mass flow rate was 1.4 g/min.

It is generally suggested to begin printing onto a base powder bed rather than the metal substrate for several reasons. The first few powder layers often cannot be uniformly spread, resulting in flaws in the bottom of the part. Printing on the metal substrate also causes the first few layers to be more dense. Furthermore, the parts are easily damaged upon removal. A strategy of printing sacrificial anchoring legs was adopted to overcome the above difficulties. The devices were affixed to the legs, and the legs could be easily removed after the parts had dried. A pictorial representation of the printing strategy is shown in Figure 3.3. Legs 2 mm high were created by drawing lines with binder at 80 cm/s using 250 μm thick powder layers.

![Figure 3.3: Print method using sacrificial anchoring legs](image-url)
The next step was to construct the body of the dosage forms attached to the legs. The parameters used during printing are summarized in Table 3.1. Layer thickness was reduced to 175 μm for the fabrication of the devices. A mask with a two-dimensional array of 5/16” holes was placed over the powder layer to deposit the binder into circular forms. The nozzle was rastered along the fast axis at a velocity of 150 cm/s over the mask. Line spacing along the slow axis was varied to produce tablets of four different binder saturation levels. The 75 and 100 μm line spacing devices included the double-printing technique by allowing the first binder pass to dry and following up with a second pass staggered over the first.

**Table 3.1: Parameters for printing prototype dye tablets**

<table>
<thead>
<tr>
<th>Dye tablets</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Powder</td>
<td>PH101</td>
</tr>
<tr>
<td>Binder</td>
<td>20% (w/w) E100 in ethanol</td>
</tr>
<tr>
<td>Active</td>
<td>5 μl amaranth dye solution</td>
</tr>
<tr>
<td>Print velocity</td>
<td>150 cm/s</td>
</tr>
<tr>
<td>Line spacing</td>
<td>75(2X), 100(2X), 125, 150 μm</td>
</tr>
<tr>
<td>Layer thickness</td>
<td>175 μm</td>
</tr>
<tr>
<td>Binder flow rate</td>
<td>1.4 g/min</td>
</tr>
</tbody>
</table>

Note: 2X indicates double-print method

Eleven layers of circles were constructed before depositing dye. 5 μL of amaranth dye was placed into the center of each device with a micropipette after printing layer 12. It was assumed that the dye would absorb into the device to produce a symmetrical distribution. The dye did not wet the printed powder because of the contact angle. It was allowed to dry a half hour and the layer was reprinted to rewet the powder bed before spreading the next layer of powder. An additional eight layers of circles were constructed as above to cap the devices. The printing parameters and associated tablet properties are listed in Table 3.2. Saturation level, $\phi_b$, is calculated as described in Equation 2-2. Percent volume polymer, $\theta_p$, is calculated by assuming that the polymer has a density near 1 g/cc using Equation 2-4. Final porosity is calculated with Equation 2-5.
Table 3.2: Properties of amaranth dye tablets

<table>
<thead>
<tr>
<th>Line spacing (μm)</th>
<th>$\phi_b$</th>
<th>$\theta_b$</th>
<th>Porosity</th>
</tr>
</thead>
<tbody>
<tr>
<td>75</td>
<td>190%</td>
<td>19.8%</td>
<td>0.55</td>
</tr>
<tr>
<td>100</td>
<td>145%</td>
<td>14.8%</td>
<td>0.60</td>
</tr>
<tr>
<td>125</td>
<td>115%</td>
<td>11.9%</td>
<td>0.63</td>
</tr>
<tr>
<td>150</td>
<td>95%</td>
<td>9.9%</td>
<td>0.65</td>
</tr>
</tbody>
</table>

The plate of tablets was dried overnight in a nitrogen glove box and was subsequently placed for 48 hours in a vacuum oven to complete solvent removal. A photograph of the resulting devices can be seen in Figure 3.4. The cross section confirmed that the dye was localized in the center of the devices.

![Figure 3.4: Prototype dye tablets](image)

3.3.2 Mechanical properties

A qualitative evaluation of tablet mechanical properties revealed that the strength was relatively poor. Further inspection revealed that the tablets were moderately friable. The cause of this was believed to be due to the high porosity and low polymer content (below 15% by mass). The tablets with higher binder content were stronger and less friable. Improving mechanical strength was a concern to be addressed in subsequent investigations.

3.3.3 Dissolution

Evaluation of the tablet degradation characteristics was the next step of analysis. A room temperature pH 2 $\text{H}_2\text{SO}_4$ solution was prepared as the dissolution medium. Three devices of each saturation level were individually placed into 20 cc scintillation vials (1-inch
diameter) of solution and were agitated with a RotoMix™ shaker. The shaker produced a horizontal circular motion of 1-inch amplitude at a frequency of about 100 Hz. It was assumed that sink conditions were approximated. 3 cc samples of the dissolution medium were taken and replaced with fresh solution when dye release was observed.

The solution samples were centrifuged in 15 ml polypropylene centrifuge tubes to remove powder sediment and analyzed with uv-vis spectrophotometry (Beckman Instruments) to determine the dye concentration. Lambert-Beer relationship (Equation 3-4) was used to calculate concentration from absorbance (523 μm) and the measured extinction coefficient (3297 cc/g). Integration of concentration over time yielded the total amount of active released. The release profile is depicted in Figure 3.5.

\[
C = \frac{A_v}{\varepsilon_v}, \text{ where}
\]

**Equation 3-4**

\[
C = \text{concentration of sample in g/cc}
\]

\[
A_v = \text{absorbance measured at wavelength } v
\]

\[
\varepsilon_v = \text{extinction coefficient at wavelength } v \text{ in cc/g}
\]

![Dye release from prototype tablets](image)

**Figure 3.5: Release from prototype dye tablets**

The kinetics data describing Figure 3.5, including lag time and release rate, are displayed in Figure 3.6. It can be seen that the devices which contained a higher saturation
level exhibited a significantly longer lag time and possessed a much lower degradation rate. There appears to be a linear relation of release kinetics above the 100% saturation level.

![Release kinetics of dye tablets](image)

**Figure 3.6: Dye release kinetics**

The release coefficient was also calculated to study how the dye was distributed throughout the tablets. Table 3.3 shows that the more highly saturated devices exhibited proportionately shorter release phases relative to their total dissolution times (lower $\gamma$), suggesting a more highly concentrated dye placement. This is a reasonable observation if it is assumed that the contact angle of the aqueous dye solution was high enough to prevent wetting of the printed powder bed. The devices with less binder may have allowed more penetration of dye solution than the devices with more binder.

**Table 3.3: Release coefficients of prototype dye tablets**

<table>
<thead>
<tr>
<th>$\theta_0$</th>
<th>Release coefficient, $\gamma$</th>
</tr>
</thead>
<tbody>
<tr>
<td>19.8%</td>
<td>0.42</td>
</tr>
<tr>
<td>14.8%</td>
<td>0.37</td>
</tr>
<tr>
<td>11.9%</td>
<td>0.25</td>
</tr>
<tr>
<td>9.9%</td>
<td>0.27</td>
</tr>
</tbody>
</table>

Several observations were made regarding the results of this pilot study with dye. The release profiles agreed with a logistic fit as predicted. It can also be seen that there was a
slight variation between the total amounts released, and this can be attributed to the difficulty in generating consistent droplet sizes with the micropipette. It was also found that, despite the pipetting inaccuracy, release kinetics were relatively reproducible between devices.

This pilot study demonstrated that oral dosage forms could be processed using conventional pharmaceutical grade materials with 3DPTM. The devices exhibited characteristics which were similar to conventional ODFs, and were shown to have predictable release characteristics which depended upon printing parameters. The mechanical strength needed improvement but was sufficient for prompting a deeper level of study into the project.

3.4 MONOPHASIC DRUG DEVICES

The next goal was to demonstrate that biological actives could be deposited into the device matrix to release in the same manner as the dye tablets. Reproducing the results would show that changes could be made in the active formula with only minor redesign considerations. It was also desired to develop a fundamental working model of the mechanism which governs release kinetics.

3.4.1 Construction

Prototype drug devices were constructed with similar printing parameters as the dye devices. Parameters were adjusted slightly to further optimize the printing procedure and are summarized in Table 3.4. The layer height was slightly increased to accommodate swelling during printing. A description of the bulk properties of the final devices is provided in Table 3.5.

A 20% (w/w) chlorpheniramine maleate water/ethanol (4:1) mixture was prepared as the deposition medium. Four increments of 5 μL solution were deposited by micropipette into the centers of the devices at layer 12 to deliver a total dosage of approximately 3.4 mg. This dosage is the equivalent of a short-term relief dosage. The solution, due to the ethanol content, wetted the printed powder bed better than the dye solution. Bleeding was observed as a result of the saturation levels and was more pronounced in the more highly saturated devices. 5 μL of amaranth dye was also deposited into the devices to act as a visual indicator.
Table 3.4: Printing parameters for monophasic drug tablets

<table>
<thead>
<tr>
<th>Drug tablets</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Powder</td>
<td>PH101</td>
</tr>
<tr>
<td>Binder</td>
<td>20% (w/w) E100 in ethanol</td>
</tr>
<tr>
<td>Active</td>
<td>20 µl 20% chlorpheniramine solution (3.4 mg)</td>
</tr>
<tr>
<td>Print velocity</td>
<td>150 cm/s</td>
</tr>
<tr>
<td>Line spacing</td>
<td>75(2X), 100, 125, 150 µm</td>
</tr>
<tr>
<td>Layer thickness</td>
<td>200 µm</td>
</tr>
<tr>
<td>Binder flow rate</td>
<td>1.4 g/min</td>
</tr>
</tbody>
</table>

Table 3.5: Properties of drug devices

<table>
<thead>
<tr>
<th>Line spacing (µm)</th>
<th>Binder saturation</th>
<th>θ_p</th>
<th>Porosity</th>
</tr>
</thead>
<tbody>
<tr>
<td>75</td>
<td>165%</td>
<td>17.9%</td>
<td>57%</td>
</tr>
<tr>
<td>100</td>
<td>125%</td>
<td>13.4%</td>
<td>62%</td>
</tr>
<tr>
<td>125</td>
<td>100%</td>
<td>10.7%</td>
<td>64%</td>
</tr>
<tr>
<td>150</td>
<td>85%</td>
<td>8.9%</td>
<td>66%</td>
</tr>
</tbody>
</table>

3.4.2 Dissolution

A slightly different assay method was used for the dissolution of the drug tablets. A larger fraction of water was sampled and replaced to better approximate sink conditions. The devices were placed in 10 cc of pH 2 solution and shaken. 5 cc samples were taken upon observation of the dye and replaced with fresh solution. Samples were centrifuged and analyzed with UV-vis spectroscopy. The absorbance was measured at 261 nm with an extinction coefficient of 13.2 cc/mg. The release data is compiled in Figure 3.7 and the associated kinetic data is shown in Figure 3.8. The data confirmed that a total of 3.4 mg of drug was released from the devices. Note that there is a large variation between the total amount released due to the inaccuracy of the micropipette deposition method. The overall degradation trends were similar to the dye tablets with minor differences. A reduced dissolution time was observed for the drug tablets. The reason for this is uncertain, but a possible explanation may be a phase interaction between the drug solution and the binder which caused an increase in binder solubility.
Drug release from prototype devices

Figure 3.7: Release of chlorpheniramine maleate from prototype tablets

Kinetics of drug release

Figure 3.8: Drug release kinetics from prototype tablets

Table 3.6 shows the release coefficients for these devices. There was only a slight variation with binder saturation, which indicates that the drug distribution was relatively
constant between the devices. The slight increase with polymer content may indicate that the drug was more disperse and bled to a higher degree during deposition.

Table 3.6: Prototype drug tablet release coefficients

<table>
<thead>
<tr>
<th>θ_n</th>
<th>Release coefficient, γ</th>
</tr>
</thead>
<tbody>
<tr>
<td>17.9%</td>
<td>0.51</td>
</tr>
<tr>
<td>13.4%</td>
<td>0.46</td>
</tr>
<tr>
<td>10.7%</td>
<td>0.34</td>
</tr>
<tr>
<td>8.9%</td>
<td>0.32</td>
</tr>
</tbody>
</table>

3.4.3 Microstructure

The microstructure of the drug tablets was examined to gain insight into the degradation kinetics. It needed to be confirmed that the devices were, in fact, homogeneous throughout their internal structure and that no alteration was made with the deposition of drug. A longitudinal cross section of a tablet was made and microstructural analysis was performed on both the perimeter and the central drug-loaded regions. The results are shown in the SEM micrographs of Figure 3.9. A significant difference cannot be seen between the two regions, therefore, it cannot be concluded that a microstructural alteration was responsible for the accelerated degradation kinetics.

![Figure 3.9: Photomicrograph of prototype drug devices, 8.9% polymer](drug-free_perimeter.png) ![Figure 3.9: Photomicrograph of prototype drug devices, 8.9% polymer](drug-containing_center.png)

The microstructure of the tablets was also studied to explain the mechanism of release. It appeared that the level of binder content was directly related to the rate of degradation. Figure 3.10 shows a SEM micrograph taken at the center of the most highly saturated drug
device. The device appears to be significantly more dense than the device shown in Figure 3.9. The reduction in void space is evidence of the polymer content increase from 9% to 18%.

Figure 3.10: Drug-containing center, 17.9% polymer

These prototype drug devices confirmed that biological actives can be used in the dosage forms in the same manner as dye with minimal adjustments. Their release properties were shown to follow the same trends as the dye tablets. Microstructural analysis also confirmed the proposed degradation mechanism.

3.4.4 Cold isostatic pressing

The porosity is believed to be the limiting factor which determines the release kinetics of drug devices. 3DP™ allows a high level of control over the microstructure and porosity of a device, but the final structures are still relatively porous. The dependence of porosity on tablet performance was examined by isostatically pressing drug tablets (Section 3.4.1) at 30,000 psi in a HIP (High Pressure Equipment Co, Inc. Erie, PA). A comparison between the pressed form and the nonpressed form is shown in Figure 3.11. The mechanical properties and surface finish of the pressed tablets were found to be significantly improved. Calculations showed that the density was near the theoretical density of the excipient powder, 1.6 g/cm³, indicating that porosity was almost completely eliminated.
The influence of pressing on degradation properties was also studied. Three tablets of each saturation level were subjected to dissolution in pH 2 as described above and release was measured with UV-vis. The release data is shown in Figure 3.12.

The associated release kinetics are shown in Figure 3.13. It can be seen that both the lag time and release rate have been greatly increased. There also appears to be a transition region at 100% binder saturation (10.7% volume polymer) where increasing saturation did not greatly effect the release kinetics. The reason for this is unclear, but a possible explanation may involve the degree of excipient powder coating with binder as follows. The particles may
not have been fully coated with polymer when the binder saturation was below 100% because the solution localized at the particle contact regions. Pressing the tablet reduced the porosity, but the uncoated particle area inevitably became a target for fast swelling and water imbibition. On the other hand, complete particle coating is established when binder saturation levels are above 100%. Polymer precipitation most likely occurs at localized regions, however, producing a nonuniform coating thickness. The thinnest coating point determines the erosion rate because swelling occurs rapidly once the coating has been penetrated. Increasing the binder saturation would not, in this case, change the erosion kinetics because of this nonuniformity. The lack of porosity, furthermore, restricts the dissolution to the surface.

**Figure 3.13: Release kinetics of pressed tablets**

The release coefficient was evaluated for the pressed tablets, and the results are shown in Table 3.7. The small variance, between 0.76 and 0.70, indicates that the behavior follows more closely the ideal case where polymer content does not change the drug distribution. These tablets should have exhibited the same trends as the unpressed tablets, suggesting there may be density variations throughout the tablet caused by pressing which modify release kinetics.
Table 3.7: Isostatically pressed drug tablet release coefficients

<table>
<thead>
<tr>
<th>$\theta_p$</th>
<th>Release coefficient, $\gamma$</th>
</tr>
</thead>
<tbody>
<tr>
<td>17.9%</td>
<td>0.76</td>
</tr>
<tr>
<td>13.4%</td>
<td>0.71</td>
</tr>
<tr>
<td>10.7%</td>
<td>0.71</td>
</tr>
<tr>
<td>8.9%</td>
<td>0.70</td>
</tr>
</tbody>
</table>

The microstructure of the pressed tablets was analyzed to confirm the density of the devices and is shown in Figure 3.14. The analysis showed that the external shell of the device is highly dense and contains very little void space. There appears to be a structural transition into the drug-containing region, however. The drug region looks slightly less dense and would be expected to yield accelerated degradation kinetics. This was not observed in dissolution studies, however.

Isostatic pressing was found to be a viable post-processing method for modifying the release characteristics of dosage forms. It is capable of forming fully dense structures and significantly retards degradation kinetics and produces better mechanical properties.

3.5 Dual-Phasic Drug Devices

The final stage of the concept demonstration was to show that complex release patterns could be obtained with 3DPTM processing. A rapid release, as well as sustained
release, drug formulation was developed and integrated into a single tablet. This was accomplished by using two different binders to create two distinct regions within one tablet. One half of the tablet was composed of the same binder as the prototype drug device (Section 3.4) to degrade in acid conditions. The other half of the tablet was constructed with a binder which did not degrade but was permeable to water for release by diffusion. A small amount of drug was placed within each region to study release characteristics.

3.5.1 Construction

The print method of Section 3.4 was used to construct these drug devices. Table 3.7 summarizes the parameters used in the process. The binder used for the rapidly degrading region was 20% (w/w) E100 ethanol solution. Ten layers were constructed with this binder as the bottom portion of the device. 20% (w/w) Eudragit® RS PO, a highly permeable polymer, in acetone was used as the binder for the top portion of the device to simulate long-term drug delivery.

<table>
<thead>
<tr>
<th>E100 region</th>
<th>RS region</th>
</tr>
</thead>
<tbody>
<tr>
<td>Powder</td>
<td>PH101</td>
</tr>
<tr>
<td>Binder</td>
<td>20% (w/w) E100 in ethanol</td>
</tr>
<tr>
<td>Active</td>
<td>10 μL 30% antihistamine (6 mg)</td>
</tr>
<tr>
<td>Print velocity</td>
<td>150 cm/s</td>
</tr>
<tr>
<td>Line spacing</td>
<td>125 μm</td>
</tr>
<tr>
<td>Layer thickness</td>
<td>200 μm</td>
</tr>
</tbody>
</table>

All devices were printed at 100% binder saturation level (10.7% volume polymer). 30% w/w ethanol drug solution was deposited in the centers of both regions of some devices but in only one of the regions of other devices. Controls were also created which contained no drug.
3.5.2 Dissolution
The devices were subjected to dissolution conditions as described above and the release is plotted in Figure 3.16. The devices yielded release data as anticipated with an immediate release from the region containing the E100 polymer, and an extended release over several hours from the RS region. This dual release technique has practical applications in the pharmaceutical industry by providing a tablet with an immediate dosage delivery in addition to an extended release.

![Drug release from dual-phasic tablets](image)

**Figure 3.16: Drug release from dual-phasic tablets**

3.6 Analysis of Mechanisms
Both mechanical properties and release characteristics were observed to depend on the amount of polymer binder deposited into the devices. Several models are proposed to explain the phenomena observed with these pilot studies.

3.6.1 Adhesive bonding
It was believed that the low polymer level was responsible for the poor mechanical properties. Increasing the polymer content was found to moderately increase the strength. Binder saturation concerns, however, limited the amount of binder which could be deposited. An understanding of the bonding mechanism provided an alternative method for increasing
strength. These devices relied on an adhesive mechanism of bonding which is generally weaker than a particle dissolution and re-precipitation mechanism. Failure usually occurs at the weak polymer-particle interface, as opposed to fracture of the polymer neck. The strength could be increased by using a powder with a higher packing fraction to increase the surface area of bonding. The increase in density would result in a decrease in tolerable binder saturation levels, however. The strength gained by the increased surface area should more than compensate for the strength lost due to the reduction in polymer content. The reduction in void space also decreased the amount of drug which could be contained in the device.

3.6.2 Release via erosion

Release occurred by an erosion mechanism for devices using Eudragit E100 binder. This sequence of events is summarized in Figure 3.17. The first stage of dissolution involved water imbibition and swelling. The matrix was highly porous and both the polymer and the excipient absorbed water, leading to net water uptake into the device. The presence of water allowed for swelling and dissolution of the polymer, resulting in rapid degradation and drug release. The time scale of diffusion was found to be relatively large compared to the time scale of erosion in these devices. Devices placed in water swelled but no release was observed over a period of several hours.

![Figure 3.17: Strategy for dosage release by erosion](image)

3.6.3 Release via diffusion

The other mechanism, release by diffusion, was observed with devices containing Eudragit RS as binder. This mechanism is composed of a sequence of three events occurs which are depicted in Figure 3.18. Imbibition is always the first stage and is followed by swelling and drug diffusion out of the device.
Release by diffusion can occur by either of two means. The first assumes the drug was located within the pore space at the surface of the polymer and is most applicable when the polymer is very dry prior to drug deposition. The immediate consequences of this mechanism are a higher rate of release because the drug must only diffuse through the pores into the dissolution media. The second means of release assumes the drug is homogeneously distributed within the polymer network and is more probable when the drug is deposited prior to binder solvent removal. An extra step for release is added onto the first method by requiring the drug to diffuse through the polymer before reaching the pore space. The net result is a reduction in the overall release kinetics. The permeability of the polymer and size of the drug molecule will both play an important role in determining the diffusion rate into the pore space. Swelling of the polymer must also be considered as another factor in the model.

3.7 CONCLUSIONS

This pilot study confirmed that pharmaceutical materials can potentially be used for the manufacturing of oral dosage forms by three dimensional printing™. It also provided some insight into the mechanisms of release. It was found that many parameters controlled the release properties, but materials chemistry, microstructure and dosage distribution were the dominating factors. The microstructure can be controlled with either materials selection, printing parameters, post-processing steps, or processing conditions.

The dye and drug devices produced encouraging results, but two critical issues remained which needed to be addressed in future studies. The part strength needed to be improved by either developing new printing techniques or by selecting new materials. The devices also sometimes behaved unpredictably, and this is believed to be due to the inaccuracy of the micropipette deposition method. A new method of drug deposition needed to be considered to improve the accuracy of the process. Using a drop-on-demand (DOD) fluid...
delivery system would allow for much more precise dosage delivery and would also allow for an increased level of automation which would be attractive to pharmaceutical manufacturers.
4. DROP-ON-DEMAND IMPLEMENTATION

4.1 INTRODUCTION

DOD is an attractive method of fluid delivery for ODFs because it is capable of delivering very precise, small amounts of fluid. It can handle multiple fluids and simultaneously deposit them accurately into defined regions. Figure 4.1 shows a representation of the potential of using DOD to control the dosage distribution within the device compared to conventional and micropipette methods.

![Drug placement with conventional methods](image1)
![Drug placement using 3DP and micropipette](image2)
![Drug placement using multiple-fluid DOD technology](image3)

Figure 4.1: Comparison of oral dosage form processing methods

Several criteria needed to be considered in determining whether DOD is a feasible method of fluid delivery in 3DPTM. First, it should be capable of functioning with a range of fluid types which vary in solvent, solute content, and viscosity. The system must also be accurate and reproducible in the droplet generation. Finally, it should be able to deliver a reasonable mass flow rate as required by the application.

The CJ system as described in Chapter 1 is ideal for use with biomaterials because it is very easy to control the level of binder saturation and device porosity. CJ printing is inefficient, however, for depositing small amounts of liquids such as those containing costly drugs. Integrating DOD with CJ printing would allow one to take full advantage of both systems. Either DOD can be used as a stand-alone method of fluid delivery to replace CJ printing, or it can be used as a supplementary system to deposit biological actives.

DOD was developed over a decade ago primarily for use in inkjet printers. Inkjet printers function very reliably and, because of their performance capabilities, are excellent candidates for use as a fluid delivery system for 3DPTM. A Hewlett Packard DeskJet 400™ was investigated for its potential to be used in 3DPTM. The single-chamber DOD cartridge
Drop-on-Demand Implementation (HP51626A) has a capacity of about 25 cc and is shown in Figure 4.2. Multiple-chamber cartridges for color printing were also available but were not used in this study.

![Drop-on-demand cartridge](image)

**Figure 4.2: Drop-on-demand cartridge**

### 4.2 CHARACTERIZATION

The components of the inkjet system are the fluid reservoir, silicon substrate, thin-film resistor, firing chamber, and orifice plate. The orifice plate, shown in Figure 4.3, contains an array of 56 nozzles in two staggered rows, of which 50 can be fired. The nozzles have an external diameter of 50.7 μm. The array of nozzles is 4.5 mm in length with a resolution of 150 DPI. They are divided into four electrically isolated banks of 13 (two nozzles are inactive). Several indexing holes are also present to assist in plate alignment with the firing chamber during assembly.
Figure 4.3: External view of orifice plate

The firing chamber, illustrated in Figure 4.4, lies adjacent to the orifice plate. EDS was used to determine the composition of the relevant chamber components. A tantalum resistor is patterned on a silicon substrate and forms the “floor” of the chamber. The resistor is about $32\Omega$ and is connected to the external electrical connector plate by a tantalum/aluminum lead which is also patterned on the silicon substrate. The “walls” of the chamber are constructed with a polymeric material. An electrical signal is carried through the lead to heat the tantalum resistor. The heat is quickly transferred to the liquid between the resistor and the orifice, resulting in vaporization and bubble generation. A droplet is ejected, and the liquid is replenished from the main reservoir by capillary driven flow.
4.3 FLUID COMPATIBILITY

A fluid must meet several chemical and physical qualifications for use with the DOD system. The plastic case must be resistant to swelling and cracking from the solvent. Water and alcohols have been successfully used with the HP cartridge but strong organic solvents such as acetone or chloroform cannot be used. Other criteria involve the physical properties of the fluid. The fluid will drip excessively through the nozzles if the contact angle or viscosity is too low, making reliable printing difficult. A pure solvent may be acceptable to print with, but the addition of solutes may alter the properties enough to render it unusable. Either no droplets will be ejected or they may be generated unreliably if the viscosity is too high.

4.4 CARTRIDGE PREPARATION

Preparing an ink cartridge for use with other fluids is a relatively simple procedure. The first step is to drain the ink from the cartridge by punching a hole in the top. The cartridge is rinsed thoroughly and allowed to dry. The bubbler device on the bottom panel is plugged to control leakage, and the cartridge is carefully filled through the top with replacement solution. The cartridge is placed in a vacuum to remove air from the nozzle reservoir, and the top hole is sealed with hot glue. The cartridge may drip from the nozzles for a short period of time until a negative pressure is developed inside to retain the fluid.
Some fluids may, however, leak excessively or may never stop leaking, in which case they cannot be used. The cartridge may be used as normal once the fluid has stabilized.

4.5 Signal Generation

A method of controlling the droplet generation needed to be pursued for studying nozzle performance. A number of factors are responsible for reliable droplet generation. The ejection of a droplet from the nozzle follows complex fluid mechanics which depend on the fluid characteristics, electrical signal, and nozzle configuration. The return of the meniscus to its neutral position in the nozzle is important in optimizing system performance. Changing one of the parameters will likely alter the breakoff characteristics of the droplet, reducing performance. It was assumed that the manufacturer had optimized the performance for the ink system, and that changes of liquid would alter the performance. A way to control pulse generation was, therefore, needed to modulate output if necessary.

A custom circuit was constructed to produce a finite number of droplets under controlled conditions. The signals generated by the HP printer for firing a nozzle were examined as a starting point for the design of the circuit. A Tektronix TDS-210 digital oscilloscope was used to observe the voltage across the nozzle when fired. The waveform is shown in Figure 4.7. The voltage applied to the nozzle was 17V, the pulse width was about 2.3 μs, and the operating frequency was 5 kHz.

![Figure 4.5: Trace of voltage across firing nozzle. Amplitude: 17V, width: 2.3 μs](image)
A test circuit was constructed to reproduce the above waveform. Components used in the circuit are the cartridge and carriage mating plate, nozzle selector, power source, pulse generator, and power MOSFET. A LabView® VI (virtual instrument) was written to control a data acquisition (DAQ) board (National Instruments AT-MIO-E2) to generate the signal pulse. The relevant pulse parameters were voltage amplitude, frequency, and pulse width. A gate signal supplied by a MM2000 controller (Newport Corp, Irvine, CA) was used to enable or disable the pulse train. The power for the nozzle was supplied by a Fluke high voltage power supply, and the current was gated by a power MOSFET (NSC 451N). The nozzle was modeled as a resistor. The functional circuit diagram is depicted in Figure 4.6 below. Activation of the MOSFET by the DAQ pulse allows current to flow by becoming conductive, and the net effect is application of a voltage across the nozzle.

![Figure 4.6: Wiring of DOD test circuit](image)

The above circuit was attached to the print cartridge. Pulses were generated using the observed HP parameters and the resulting nozzle waveform is depicted in Figure 4.7. The signal was comparable to the HP waveform of Figure 4.5, so it was assumed that the droplets generated were similar to those of the HP printer.
4.6 PERFORMANCE EVALUATION

Inkjet systems have proven very reliable for printing ink onto paper, but it needed to be confirmed that a range of materials could be reliably printed for application in 3DPTM. The sensitivity of droplet output with the electrical signal parameters was measured to assess reliability. Assumptions were made in approximating droplet size: 1) the droplets are uniform in size and none are skipped, and 2) each droplet contains the same concentration as the liquid reservoir.

The procedure for determining droplet size began by releasing a given number of droplets into a cuvette with water. UV-vis spectrophotometry was performed (Beckman Instruments) on the sample to measure the solute concentration. The assumed droplet size was calculated with the following equation:

\[
\text{Equation 4-1}
\]

\[
\begin{align*}
\nu_{\text{drop}} &= \frac{m_{\text{drop}}}{C} = \frac{4}{3} \pi r^3 \\
D_{\text{drop}} &= \sqrt[3]{\frac{6 \cdot m_{\text{drop}}}{\pi C}}
\end{align*}
\]

where
- \(m_{\text{drop}}\) = mass per droplet (mg)
- \(C\) = solute concentration (mg/cc)
- \(\nu_{\text{drop}}\) = droplet volume (cc)
- \(D_{\text{drop}}\) = droplet diameter (cm)

Figure 4.7: Voltage across nozzle using test circuit. Amplitude: 17V, width: 2.3 μs
The droplet output was expected to depend on three circuit parameters: pulse width, pulse voltage, and frequency. An additional fourth variable, operation time, was considered for evaluating transient variances in output. Experiments were performed to assess the robustness of the system in relation to each of these parameters using both ink and drug solutions.

4.6.1 Study with ink

The performance of the DOD system using the native ink system was evaluated and optimized, and the results were used as a control for studies with other fluid media. The ink formula is aqueous-based and has a viscosity slightly higher than that of water (1.5 cp at a shear rate of 100 sec\(^{-1}\)). Spectroscopic data shows that the ink absorbs at a wavelength of 572 nm with an extinction coefficient of 875 ml/ml.

4.6.1.1 Frequency

It was necessary to first determine the functional range of frequencies for the nozzles. The inkjet printer was observed to normally operate at a frequency of 5 kHz. The nozzles were found to be capable of functioning as low as 10 Hz, and the upper limit was found to be 30 kHz, in which case no output was observed.

A range of frequencies were chosen to analyze the effect on droplet output. Figure 4.8 shows that the droplet size remained relatively constant up to the operating frequency of 5 kHz. Beyond this frequency the droplets either were reduced in size or were periodically missed. The data also indicated that higher frequencies yielded higher mass flow rates, although precision was compromised and nozzle reliability was uncertain. The recommended operating frequency for printing with ink was chosen to be 5 kHz.
The fluid delivery capacity of the DOD system was compared against that of continuous-jet printing using the above data. A single DOD nozzle, operating at the maximum rate of 30 kHz, is capable of delivering up to 75 μl per minute. That rate is adequate for very small scale operations, but for manufacturing level operations one nozzle may be insufficient. The mass flow rate can be increased to 2 ml per minute if all 50 DOD nozzles are recruited at the suggested 5 kHz, greatly increasing processing speed and retaining reliability. This output level is competitive with that of continuous-jet printing. The impressive flow rate and accuracy which can be achieved with DOD demonstrates that it has potential for supplementing or replacing some CJ and/or charge-and-deflection systems.

4.6.1.2 Transient response

The transient response of the system was analyzed to determine how long it took the nozzle output to stabilize. Droplets were generated at multiple frequencies for different durations for this test. The voltage was set to 19V and the pulse width was fixed at 2.3 μs. Frequencies of 1, 3, and 5 kHz were used to generate 1000, 3000, and 5000 droplet quantities. The output solution concentration was measured and a droplet size calibration chart was generated as shown in Figure 4.9. The system appeared to approach steady state conditions.
after 5000 drops had been administered. It can also be seen that higher frequencies produced slightly smaller droplet sizes. 5 kHz, the optimal frequency as determined previously, appeared to produce the most stable droplet size when activated for various durations.

**Transient Droplet Characteristics**

![Graph showing transient characteristics of ink droplet generation](image)

**Figure 4.9: Transient characteristics of ink droplet generation**

4.6.1.3 Voltage

The next step in the circuit characterization procedure was to determine the performance response to voltage changes. The HP circuitry was observed to generate a 17 volt signal. It was found that a minimum of 17 volts was required to emit a droplet, and a maximum of 25 volts could be applied without damaging the nozzle. A sequence of tests within this voltage range were performed to see the effect on droplet output. Table 4.1 shows that the droplet size did not vary significantly with voltage changes. Higher voltages, however, exhibited a higher deviation of sizes. The optimum to be used in the test circuit was selected to be 17 volts.
### Table 4.1: Voltage influence on droplet size

<table>
<thead>
<tr>
<th>Voltage</th>
<th>Droplet size (µm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>17</td>
<td>66.7 ± 0.40</td>
</tr>
<tr>
<td>19</td>
<td>66.1 ± 1.00</td>
</tr>
<tr>
<td>21</td>
<td>67.3 ± 0.45</td>
</tr>
<tr>
<td>23</td>
<td>67.1 ± 0.69</td>
</tr>
<tr>
<td>25</td>
<td>68.1 ± 1.14</td>
</tr>
</tbody>
</table>

#### 4.6.1.4 Pulse width

The final parameter to be investigated was the pulse width. The minimum width for droplet generation was found to be 2.2 µs and the maximum was around 6 µs. It was found that the droplet size did not vary significantly within this range. The pulse width was, therefore, chosen to match the HP signal of 2.3 µs for use in this study.

The results of the above studies show that the pulse frequency is the dominating factor in determining system performance. Number of drops, voltage, and pulse width all have minor effects when the frequency is used as 5 kHz. Table 4.2 summarizes the pulse parameters selected for optimum performance. These parameters will be used throughout the remainder of the DOD investigation.

### Table 4.2: Parameters optimized for ink

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Voltage</td>
<td>17V</td>
</tr>
<tr>
<td>Frequency</td>
<td>5 kHz</td>
</tr>
<tr>
<td>Pulse width</td>
<td>2.3 µs</td>
</tr>
</tbody>
</table>

#### 4.6.2 Study with drug solution

The DOD system was proven to operate reliably when used with its native ink system. The performance of the DOD system with drug solution was evaluated. An aqueous solution containing 20% chlorpheniramine maleate (antihistamine) provided by Therics, Inc (Princeton, NJ) was prepared and deposited into a clean HP 51626A cartridge. Spectroscopic data showed absorbance at 261 nm with an extinction coefficient of 15 cc/mg in DI H2O.

A droplet calibration procedure was performed with the drug solution at various frequencies and durations of operation. Nozzles were activated for 1, 2, and 3 seconds at frequencies of 1, 3, and 5 kHz into silica cuvettes containing 3 cc water. UV-vis spectroscopy was performed...
on the samples, and the resulting data is shown in Figure 4.10. A good correlation between nozzle runtime and amount deposited was observed. This confirmed that a specific quantity of drug can be deposited by simply activating the nozzles for a specified time, making it applicable for dosage delivery.

![Dosage calibration for drug](image)

<table>
<thead>
<tr>
<th>Activation Time (sec)</th>
<th>0</th>
<th>0.5</th>
<th>1.0</th>
<th>1.5</th>
<th>2.0</th>
<th>2.5</th>
<th>3.0</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 kHz</td>
<td>0</td>
<td>5000</td>
<td>10000</td>
<td>15000</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 kHz</td>
<td>0</td>
<td>3000</td>
<td>6000</td>
<td>9000</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5 kHz</td>
<td>0</td>
<td>1000</td>
<td>2000</td>
<td>3000</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Figure 4.10: Calibration curve for DOD printing of 20% chlorpheniramine maleate**

The final goal of DOD evaluation was to show that reproducible results can be obtained with a range of fluid types. Table 4.3 below shows that the droplet size is relatively constant between ink and 20% antihistamine solution. The number of drops also appears to have little effect on the droplet output. These results suggest that executing the parameter optimization sequence with drug solution should yield comparable results to the ink data. Note that these conclusions are made for these two materials systems only, and a more exhaustive analysis which includes a larger sampling of fluids needs to be performed before making a more general statement.
Table 4.3: Droplet sizes of ink vs. drug for varying dosages

<table>
<thead>
<tr>
<th>Drops</th>
<th>Ink (μm)</th>
<th>Drug (μm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5000</td>
<td>63.05 ± 0.24</td>
<td>63.49 ± 0.08</td>
</tr>
<tr>
<td>10000</td>
<td>62.08 ± 0.21</td>
<td>63.44 ± 0.12</td>
</tr>
<tr>
<td>15000</td>
<td>63.62 ± 0.30</td>
<td>63.36 ± 0.17</td>
</tr>
</tbody>
</table>

4.6.3 Reliability

During the course of sampling the above data it was found that the reliability of the nozzles was questionable. A nozzle generally behaved reliably when a single stream of droplets was desired. When rapid cyclic activation of the nozzles were requested, however, they failed catastrophically after a several cycles. The reason for this remains to be determined. The original HP circuitry has proven much more reliable and has much more sophisticated multiple nozzle control, so it was adopted as the DOD system for future investigations.

4.7 COMBINING WITH CONTINUOUS JET

The combination of 3DPTM and DOD technology can address two important technical issues in the fabrication of multi-composition parts: reproducible deposition of small quantities of fluid, and accurate control over spatial positioning. It was concluded that single-nozzle printing was not a feasible option for implementing DOD in 3DPTM because of the limited mass rate and reliability concerns. Relying on the HP printer hardware to generate droplets by using currently available software drivers was chosen as the best alternative to overcome the limitations. The print head would be capable of using up to 50 nozzles for a single 4.5 mm wide pass.

The least invasive way to incorporate the DOD system with the existing continuous-jet system was to mount it directly to the slow axis. The frame of a HP DeskJet 400™ series printer was modified and attached to a bracket on the slow axis parallel to the fast axis. The resulting setup resembles that shown in Figure 4.11. The slow axis can be incremented the proper distance to align the two axes so that the printed area will overlap. A configuration of this nature allows simultaneous use of both the CJ and DOD axes for rapid part fabrication.
A standard drawing program can be used to construct the shapes to be printed. The Windows® DeskJet printer driver is used to control the motion of the DOD axis independently and generate the droplet signals. The current design requires manual advancement of the slow axis for each print pass, limiting the usable width to 4.5 mm. Future models will automatically increment the slow axis by translating input from paper feed signals to increase the print range.

4.8 CALIBRATION OF DOD

The first step after affixing the DOD printer to the slow axis was to calibrate it for dosage delivery. Tests were performed to show that it could reproducibly deliver precise amounts of fluid. A single circle 4 mm in diameter was drawn on CorelDRAW!®. The circle was printed onto plain paper to confirm its size. A linear array of 8 circles was printed into polystyrene cuvettes filled with 2 cc water to test the spatial accuracy of delivery. The 8 samples were averaged for each of three trials to verify reproducibility. The same tests were repeated with amaranth dye and 20% chlorpheniramine maleate solution. Figure 4.12 shows that the delivery is relatively reproducible between multiple trials and the three fluids.
data supports the conclusion that the droplet output is relatively insensitive to fluid changes for the aqueous media tested.

**Fluid delivery accuracy using DOD**
Amount deposited into 4mm circular region

![Graph showing fluid delivery accuracy using DOD](image)

Figure 4.12: Comparison between ink, dye, and drug dosage into solid circular region

The above data allows the droplet density to be determined by using previously determined droplet sizes. The density can be calculated to be 310 DPI based on a drop size of 63 μm. This is within 5% of the manufacturer-stated 300 DPI printer resolution. Knowing the droplet density and droplet sizes allows one to predict the dosage delivery into any shape or region.

4.9 CONCLUSIONS

DOD technology was investigated for its feasibility of being incorporated with 3DP™ processing of oral dosage forms. It will allow for a high level of control over both quantity and spatial distribution of fluid media within the dosage forms, and has proven to be compatible with a variety of fluids. Cartridges which contain multiple reservoirs could be used for processing several drugs which must be isolated. The very small scale that DOD handles (120 pl) also makes it an ideal method for depositing very potent drugs.

A number of factors were studied for their relation to droplet generation. Frequency was found to be the main variable governing droplet output performance. Output appeared to
depend relatively little on liquid used. Results were observed to be very reproducible for the data.

Investigation eventually shifted to using the native HP printer hardware and software for technical reasons. The printer was mounted to the 3DPTM machine to allow combined use of CJ and DOD systems, completing the implementation and evaluation procedure. The drop-on-demand system has been approved for use in the fabrication of oral dosage forms.
5. MODEL ORAL DOSAGE FORMS

5.1 INTRODUCTION
The main objective of this follow-up study was to incorporate DOD printing techniques, as described in Chapter 4, into the processing of oral dosage forms to obtain more precise dosage delivery. Construction methods similar to those of Chapter 3 were followed to fabricate tablets which exhibited either immediate or extended relief characteristics. A standard USP dissolution method was adopted for the testing of extended release tablets. Mechanical tests were performed on the tablets to evaluate strength and friability. Microstructural analysis was performed to study its effect on release and dependence on dissolution.

5.2 IMMEDIATE RELIEF TABLETS
The first round of tablets were intended to model immediate relief formulations and were constructed similar to the prototype tablets using continuous-jet for binder delivery and drop-on-demand (DOD) for deposition of dye. The first objective was to improve upon the mechanical properties of the prototype tablets. A second objective was to use DOD methods to more precisely control the placement of dye. The dependence of printing parameters on the release properties was studied and compared to the prototype tablet results.

5.2.1 Construction
A different powder was used in an effort to improve the mechanical properties. Minimal changes were made in the materials chemistry to maintain similarity between these and the prototype devices. Avicel® PH301 was chosen to replace the PH101 powder for its higher packing density. Increasing the density was expected to provide better mechanical properties by reducing pore volume and enhancing surface area for adhesive bonding.

A 45 µm diameter wire bonding tool, referred to as a CJ BoaJet™ nozzle, was used to deposit a 20% (w/w) E100 ethanol solution. Devices of three differing saturation levels were constructed by varying line spacing. Table 5.1 summarizes the parameters used for construction, and Table 5.2 lists the resulting physical properties. The double-print method was exercised on the 200% saturated devices to control bleeding.
Table 5.1: Parameters for DOD printed dye tablets

<table>
<thead>
<tr>
<th>Dye tablets</th>
</tr>
</thead>
<tbody>
<tr>
<td>Powder</td>
</tr>
<tr>
<td>Binder</td>
</tr>
<tr>
<td>Active</td>
</tr>
<tr>
<td>Print velocity</td>
</tr>
<tr>
<td>Line spacing</td>
</tr>
<tr>
<td>Layer thickness</td>
</tr>
<tr>
<td>Mass rate</td>
</tr>
</tbody>
</table>

Table 5.2: Physical properties of DOD dye tablets

<table>
<thead>
<tr>
<th>Line spacing (μm)</th>
<th>Saturation level</th>
<th>θ_p</th>
<th>Porosity</th>
</tr>
</thead>
<tbody>
<tr>
<td>70</td>
<td>200%</td>
<td>16.7%</td>
<td>0.43</td>
</tr>
<tr>
<td>100</td>
<td>140%</td>
<td>11.7%</td>
<td>0.48</td>
</tr>
<tr>
<td>130</td>
<td>110%</td>
<td>9.0%</td>
<td>0.51</td>
</tr>
</tbody>
</table>

Figure 5.1 shows a representation of the sequence used to construct the tablets. Anchoring legs were used to affix the devices to the build plate as described in Chapter 3. Masks were used for print the first six layers. A heat lamp was applied at alternating layers for one minute to enhance drying. CorelDRAW!® was used to construct a linear horizontal array of 4 mm diameter filled circles spaced 0.5”. The circles were first printed onto a transparency overlaid on the printed powder. Alignment was performed visually by indexing the slow axis and shifting the circles left or right on the drawing screen until they printed centered on the transparency. The transparency was removed and the circles were printed into the powder substrate. The spacing between the nozzle and bed was about 1.5 mm to minimize overspray. Seven passes of circles were printed into each device on layers 7 through 14. A total of 12.5 μl of dye was delivered according to a calibration of 0.223 μl per circle. It was assumed that the dye was distributed uniformly throughout the printed region and that it penetrated exactly one layer during deposition. It was also assumed that the dye was not drawn into previous or subsequent layers by capillary forces.
Chapter 5

Model Oral Dosage Forms

Figure 5.1: 6+8+6 method of construction with CJ and DOD

Little bleeding was observed in the devices during dye deposition. Figure 5.2 shows a photograph of the actual powder bed as printed. It can be seen that some regions are slightly off center, but this was not expected to significantly influence results. The devices were topped off with another six layers of powder and binder and were allowed to dry in vacuum.

Figure 5.2: Representation of powder bed after dye deposition with DOD

5.2.2 Mechanical properties

The strength of the tablets was found to be noticebly better than the prototype tablets. The more dense powder also appeared to provide better resistance to frying than the more porous powder. The objective of achieving improved mechanical properties while making minimal changes in materials formulations was, therefore, achieved.
5.2.3 Dissolution

Two tablets of each saturation were individually placed into 20 cc of room temperature pH 2 solution in scintillation vials. The samples were placed on a RotoMix shaker™ and aliquots were taken at 10 minute intervals by transferring the tablet into fresh solution. Centrifugation was performed on the samples and absorbance was measured for amaranth dye at 523 nm with spectrophotometry using polystyrene cuvettes.

The release profiles of devices of differing saturations is shown in Figure 5.3, and the corresponding kinetic data is shown in Figure 5.4. The results of these tablets were found to be significantly different from those of the prototype dye tablets. The lag times for release ranged from 12 to 35 minutes as compared to the 17 to 145 minute range for the prototype tablets. There also was not as large a spread for the peak release rates, with a factor of only 1.3 compared to 3.1 between the least and highest saturated devices.

![Amaranth release from DOD tablets](image)

Figure 5.3: Dye release from tablets using DOD
Model Oral Dosage Forms

The mechanism of tablet erosion can clearly be followed by observations at different time points. Figure 5.5 shows the tablets at various stages of dissolution. The appearance of dye at 20 minutes corresponds to the onset of the release phase.

A discrepancy between the amount of dye released and expected amount deposited was observed. The only explanation which can be given is the polymer had absorbed some of the dye and did not release it back into the solution. Red particles were, in fact, observed in the dissolution media and were lost during the centrifugation step. These devices contained dye in a much larger region than the prototype devices, therefore, there was much more opportunity for the dye to interact with the binder.
The release coefficients for the data are summarized in Table 3.6. The large $\gamma$ confirms that the dye was distributed throughout a much larger region of the device than the prototype tablets where $\gamma$ was as low as 0.32. Release was observed to consume a large portion of the dissolution cycle. It can also be seen that there is a decreasing trend for the coefficients which can be attributed to increases in contact angle of the dye solution with binder.

Table 5.3: DOD dye tablet release coefficients

<table>
<thead>
<tr>
<th>Binder saturation</th>
<th>Release coefficient, $\gamma$</th>
</tr>
</thead>
<tbody>
<tr>
<td>110%</td>
<td>0.72</td>
</tr>
<tr>
<td>140%</td>
<td>0.67</td>
</tr>
<tr>
<td>200%</td>
<td>0.57</td>
</tr>
</tbody>
</table>

These dye devices successfully showed that DOD methods can be used to deposit actives during the formulation process with 3DPTM. They were also shown to have much improved mechanical properties over the initial prototype devices. The release kinetics were found to depend on binder content, although not as dramatically as the prototype devices.

5.3 Extended-Release Tablets

The next series of devices were constructed to model tablets for use in extended-release applications. They incorporated a permeable polymer as a binder to regulate the diffusion of the drug over a long period of time. It was expected that varying the amount of polymer deposited during fabrication would correspondingly alter the release kinetics by changing the porosity. The devices would absorb water, expand, and release according to a diffusion mechanism. Mechanical tests were also performed on the tablets to obtain quantitative data on strength.

5.3.1 Construction

Tablets were constructed in a manner similar to those of the dye devices in Section 5.2.1. Device physical properties were the same as those in Table 5.2. The low permeability polymer, Eudragit® RL PO was used as the binder in acetone to control release. Drug solution was deposited in replacement of dye using DOD. Three rounds of six passes were made with the cartridge to deliver a total of 1.41 $\mu$l for each round. Recall that each pass delivered 0.235
μl according to the calibration of Figure 4.12. This resulted in a total 5.45 mg of drug delivered uniformly over the eight layers of deposition.

**Table 5.4: Parameters for DOD printing RL extended release tablets**

<table>
<thead>
<tr>
<th>Drug tablets</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Powder</td>
<td>Avicel PH301</td>
</tr>
<tr>
<td>Binder</td>
<td>20% (w/w) Eudragit RL PO in acetone</td>
</tr>
<tr>
<td>Active</td>
<td>33.8 μl 20% aqueous chlorpheniramine maleate (5.4 mg)</td>
</tr>
<tr>
<td>Print velocity</td>
<td>105 cm/s</td>
</tr>
<tr>
<td>Line spacing</td>
<td>70(2X), 100, 130 μm</td>
</tr>
<tr>
<td>Layer thickness</td>
<td>200 μm</td>
</tr>
<tr>
<td>Binder flow rate</td>
<td>0.85 g/min</td>
</tr>
</tbody>
</table>

5.3.2 Mechanical properties

Qualitative evaluation showed the undissolved tablets to contain exceptional mechanical strength. Hardness and friability tests were performed to obtain values for strength, and the results were compared with typical dosage forms.

5.3.2.1 Strength test

The tablets were first subjected to a fracture strength test. This test, although not a standardized test, provides an estimate of the compressive strength. A VanKel (Edison, NJ) VK200 Tablet Hardness Tester was used to obtain the data. A tablet is laid flat and centered between the jaws and is compressed until it fractures. The load at fracture is returned in kiloponds (kp). A kilopond is a metric unit of force measurement with 1 kp being equivalent to 9.807 N.

Strength data was obtained for six devices of each binder saturation level, and the results are shown in Figure 5.6. Tablets were tested at 0°, 45°, and 90° from the fast axis direction, but results did not appear to depend on orientation, suggesting the properties were isotropic. Fracture occurred on a plane normal to the compressive stress in all cases. The strength values are comparable to those of ordinary over-the-counter tablets. It can also be seen that a linear relationship exists between binder fraction and strength.
5.3.2.2 Friability test

The friability test was the second mechanical test performed on the tablets. The USP protocol <1216> was followed for tablet friability. This routine calls for tumbling the tablets in a 285 mm diameter, 39 mm deep drum at 25 rpm for 100 revolutions. Twenty tablets with an average mass of 135 mg were included in this test. The tablets were weighed before and after the test. The mass loss was recorded to be 1.05%, within the acceptable limit of 1% according to the specifications.

5.3.3 USP dissolution

A USP dissolution protocol <711> was followed for extended-release capsules using Type 2 specifications under the chlorpheniramine maleate monograph. The delayed-release article, Method B, <724> dissolution was used as reference. A Logan Instruments Corp. D-800 dissolution testing apparatus (Somerset, NJ) was used to perform the assay, and a schematic is shown in Figure 5.7. The protocol called for a paddle stirrer to be rotated at 50 rpm for the duration of the test. 900 ml of solution equilibrated at 37°C was used as the dissolution medium. Six vessels were run simultaneously with one containing 5.4 mg chlorpheniramine maleate as a standard. A peristaltic pump (Gilson Medical Electronics,
France) was used to continuously pump the dissolution medium through flow cells (Beckman Instruments).

**Figure 5.7: USP dissolution apparatus**

The tablets were enclosed in wire cages to sink them and were subjected to two stages of dissolution as described in the protocol. The first stage was a 0.1 N hydrochloric acid solution for one hour to simulate gastric conditions. The second stage entailed a pH 7.5 NaOH monobasic potassium phosphate buffered solution for six hours to simulate intestinal conditions.

Absorbance readings were taken at 15 minute intervals using an eight-cell translating sample holder. The data was collected and plotted as percent released relative to the standard solution. The output is shown in Figure 5.8. The figure also outlines the release specifications as called for by the USP for extended-release capsules.
Extended release tablets

Figure 5.8: Drug release from devices containing Eudragit RL binder, varying binder levels

A logistic curve fit (Equation 3-1) was applied to quantitatively model the release data. $A_1$ was constrained to zero, and $A_2$ was fit to be the maximum release. Table 5.5 shows the parameters which were obtained for the average curve fits. The lag time, $t_5$, was determined by solving for the time at which the release was 5%, and the release rate was taken as the slope at 50% release. The total release time, $t_{95}$, was taken at 95% release. Note that the release coefficient, $\gamma$, did not vary significantly for these tablets, suggesting that the dosage distribution was relatively uniform between the differing saturations.
Table 5.5: Logistic curve fit parameters for extended release tablets

<table>
<thead>
<tr>
<th>Parameter</th>
<th>$\theta_p = 16.7%$</th>
<th>$\theta_p = 11.7%$</th>
<th>$\theta_p = 9.0%$</th>
</tr>
</thead>
<tbody>
<tr>
<td>$A_1$</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>$A_2$</td>
<td>104.4</td>
<td>98.4</td>
<td>98.1</td>
</tr>
<tr>
<td>$t_{50}$ (hr)</td>
<td>3.79</td>
<td>2.32</td>
<td>1.46</td>
</tr>
<tr>
<td>$t_5$ (hr)</td>
<td>2.14</td>
<td>2.63</td>
<td>2.85</td>
</tr>
<tr>
<td>$t_{s0}$ (%/hr)</td>
<td>0.94</td>
<td>0.76</td>
<td>0.52</td>
</tr>
<tr>
<td>rate_{s0} (%/hr)</td>
<td>15</td>
<td>28</td>
<td>48</td>
</tr>
<tr>
<td>$t_{95}$</td>
<td>15</td>
<td>7</td>
<td>4</td>
</tr>
<tr>
<td>$\gamma$</td>
<td>0.94</td>
<td>0.89</td>
<td>0.87</td>
</tr>
</tbody>
</table>

Figure 5.9 summarizes the kinetic data for the tablets. Similar trends as discovered previously for the dye tablets were observed, with higher polymer contents exhibiting reduced overall kinetics. The lag time does not appear to vary greatly between the devices, but a small dependence can be seen. The lag times are relatively short, suggesting that the drug bled to a large degree in the devices. The high $\gamma$ values support this assumption, with release occurring during 94% of the total dissolution time.

![Kinetics of extended release](image)

Figure 5.9: Extended release tablet kinetics
Examination of the tablets immediately following dissolution revealed them to be relatively weak in strength. They were spongy in nature due to their water content, and they had a pulpy consistency. Little effort was required to crush or dissect them. It cannot be speculated whether they would remain intact while traveling through the gastrointestinal tract. The tablets regained much of their strength upon drying but did not reach their initial values. Polymer degradation was most likely responsible for strength loss.

The rates of release were within a reasonable time frame, and the total released, $A_2$, was very close to the predicted dosage delivered by DOD. It was noted that none of the devices met the USP specifications for extended-release capsules. The devices were not designed to conform to the behavior of capsules, however. Capsules are intended to deliver a portion of their dosage immediately and slowly release the remainder. Several methods could be adopted to obtain this method of delivery. A low saturation region could be incorporated in the device to provide the initial fast release, and an additional high saturation region could provide a slow rate of release. Multiple pH-dependent materials could also be incorporated into a single device as in Chapter 3. It is expected that only a few iterations would be needed to create devices which conform to the specifications.

5.3.4 Release mechanism

It was assumed that the devices released by a diffusion mechanism. Two assumptions were made in analyzing the data: 1) the porosity was related to binder saturation as estimated (Table 5.2), and 2) the drug was distributed uniformly and identically between all the devices. The sequence of events for release includes water imbibition, swelling, and diffusion through the polymer and pores. The exact time scale of each phase cannot be predicted from this study. It is difficult to determine conclusively from this data whether the imbibition occurred first, followed by swelling and diffusion or whether they were simultaneous processes.

Several indicators suggest that imbibition was the limiting factor in release for these tablets. If the tablets were not attached to sinkers, the highest porosity devices sank within the first hour, and the least porous sank after many hours. The appearance of bubbles at the tablet surface over the duration of the experiment also indicated that air was being slowly displaced from the porous matrix. The release is, thus, concluded to be limited by water imbibition.
5.3.5 Microstructural analysis

The devices were analyzed to understand the relation of their release properties to the microstructure. A device of each saturation level was longitudinally sectioned and reserved for analysis. Devices were recovered from dissolution studies and were sectioned in the same manner. SEM micrographs were taken of the drug regions before and after dissolution and the results are shown in Figure 5.10. There appears to be a difference in porosity between the devices before dissolution. The microstructures are nearly indiscernible, however, after being subjected to seven hours of dissolution conditions. The devices of 0.28 binder fraction underwent the largest structural change, and this was evidenced by their loss of mechanical properties. The devices were observed to be relatively brittle after dissolution and drying. The devices of 0.15 binder fraction did not appear to undergo as significant a loss in strength.
Another interesting phenomenon was found during examination of a transverse cross section of an undissolved device. A gradient in microstructure can be seen between the center of the device to the exterior of the device and is shown in Figure 5.11. The left view is a low-magnification view of the entire span, and the right views are magnified views of the edge and central drug regions. It can be clearly seen that the central region which contains drug is more dense than the edge portion which contains no drug.
5.4 CONCLUSIONS

These devices confirmed that drop-on-demand (DOD) delivery techniques can be used in the fabrication of oral dosage forms. Using DOD allowed a much higher level of control over the micropipette method to generate more reproducible dosages and dosage distributions. Dye devices which released according to an erosion mechanism were found to release in the same method as the prototype devices. Release kinetics of degradable devices depended linearly on the binder saturation as determined by the printing parameters.

Drug devices were also constructed to release according to a diffusion mechanism by using a polymer binder which was permeable. The amount of polymer controlled the porosity and imbibition rate and, hence, the release rate. The tablets also showed an improvement in
mechanical properties to be comparable to current forms on the market. A microstructural
difference was observed between devices of different binder contents, supporting the
imbibition and diffusion model of release. The mechanical properties were found to degrade
from dissolution, and microstructural analysis revealed a reduced level of binding.
6. DISCUSSION AND FUTURE WORK

6.1 INTRODUCTION

This project began by developing a strategy which would be used to guide the research progress. Goals were to obtain release which would be compatible with both immediate and extended-release formulations. The materials used, Eudragit® polymers and Avicel® powder, were found to possess properties favorable for 3DPTM processing. The dye and drug concept devices constructed with these materials showed that release properties were dependent on the processing parameters. Release was observed to be in the vicinity of controlled release applications. It was also found that the porosity was a main factor in the release mechanisms by both erosion and diffusion.

A final round of devices was fabricated which incorporated knowledge gained from the previous studies to address several issues. It was demonstrated that DOD could be used to reliably deposit a very precise quantity of liquid, and that its performance was relatively consistent between changes of liquid media. The accuracy of drug deposition was greatly improved over micropipette methods by using the newly-developed DOD technology. Mechanical properties were also greatly improved and were deemed comparable to dosage forms on the market. Microstructural analysis revealed that devices of higher binder fractions were significantly more dense. The difference in porosity was used to explain the diffusion mechanism of release.

6.2 ODF FORMULATION STRATEGY

The following sections discuss how the information presented can be applied to develop formulations which meet particular release criteria. A device is also proposed as the objective of future studies.

6.2.1 Procedural guidelines

The strategy for developing an oral dosage form involves three fundamental stages: materials selection, optimization, and dosage distribution. It is generally preferable, but not required, to proceed in the stated order. A high level of control can be exercised over either
Discussion and Future Work

The first stage includes selection of the materials. The materials chemistries should be chosen which will provide desired characteristics under specific conditions. Soluble and/or permeable materials can be used to obtain particular targeted and/or extended-release objectives. Enteric materials can be selected if resistance to gastric conditions is required. Multiple materials may also be used within the same device as needed. The selected materials should be subjected to the testing protocol in Chapter 2 to confirm that they can be used in the 3DPTM process.

The next stage is optimization of processing parameters in order to control the microstructure. Printing parameters should be optimized for obtaining the best mechanical properties without sacrificing resolution. In general, the polymer content in the binder solution should be maximized to give sufficient strength, and provide release properties in the range of interest. Higher polymer content will increase strength but will tend to retard release kinetics. If a high polymer content must be used for strength reasons but release is found to be too slow, one should consider the option of changing the dosage placement as below.

The last stage of ODF development utilizes the processing parameters and properties of the materials selected to determine the optimum dosage placement within the device. The evolution of drop-on-demand has enabled a high level of control over dosage distribution with the ability to deposit gradients. Knowledge of the degradation rates and diffusion coefficients can be used to approximate the time scale of release using models. The data can also help to determine whether the dosage should be concentrated or diffusely distributed, or whether it should be located near the exterior or interior of the device.

6.2.2 Device proposal

The above outline can be used to design ODFs which contain multiple regions, each with unique releasing properties, to generate complex release profiles. The components of a proposed device are shown in Figure 6.1, and its operation is depicted in Figure 6.2. The functionality of this device is similar to that of a capsule with a soluble exterior coating containing sub-components for individual targeted or extended-release. The exterior shell
degrades following ingestion, releasing the mini reservoirs, which deliver their contents at the proper location by either degradation or by diffusion. The soluble matrix may be composed of a binder which degrades under either aqueous or acid conditions such as Eudragit® E100 formula. The subcomponents may include binder with either enteric properties such as Eudragit L100 or with permeable properties such as Eudragit RL/RS.

![Figure 6.1: Cross-section of proposed oral dosage form manufactured by 3DP™](image)

![Figure 6.2: Function of proposed multi-component ODF](image)

### 6.3 Future Work

A number of issues arose during this study which are worthy of further consideration for improving the feasibility of the proposed devices. Improvements in the printing technology itself will lend a large advancement in the fabrication of drug delivery devices. New materials investigations will also continue to play a large role in the successful strategy for ODF development. These two issues should be coupled with a more in-depth analysis of modeling the release properties as related to materials and microstructure. This will allow a better prediction of the behavior of the devices to minimize the number of iterations in a design sequence. Finally, all of the above suggestions should be taken in light of the limitations which are inherent to the process itself prior to engaging in rigorous investigations.
6.3.1 Technology and materials

A number of technological improvements in printing technology need to be made before the devices as described above can be practical. A method of printing without masks would greatly enhance the resolution and features which can be constructed within a dosage form. It is conceivable that continuous-jet charge-and-deflection systems can use the polymeric solutions to more efficiently place binder. The solvents used, ethanol and acetone, should be compatible with this system with the only potential concern being the ability to break off droplets. The binder has been found to be too viscous for use with the current drop-on-demand systems.

Other improvements in printing technology involve increasing the polymer concentration of existing binders. The solutions used in this study were not near the solubility limits of the polymers due to viscosity limitations. Changes in filtering systems and using larger nozzles may potentially allow the use of more concentrated solutions to obtain better binding properties and resolution.

Further advancements in drop-on-demand technology would also be an important step in the project. The ability to process multiple drugs simultaneously has not yet been investigated, but it can be foreseen that a potential obstacle may be controlling multiple nozzles. Using colors to designate drug reservoirs on a pattern would be the most logical solution to this. Expanding the useful materials range for DOD is also worthy of further investigation. Only a limited number of solvents have been successfully used, and many are rejected because of viscosity or contact angle reasons. Finding ways to increase the fluid handling capabilities by using foam sponges or applying a better vacuum to retain fluid may allow the use of a wider variety of solutions.

Methods of increasing the drug concentration in solution should also be studied. Drugs are deposited as a liquid phase, and the level of drug loading directly depends on the amount which can be placed in solution. Many drugs are only slightly soluble in the solvents which are compatible with DOD. Current methods of deposition have been limited to dosages around 10 mg. Using different techniques, such as printing suspensions, may enable an increase in the drug loading potential.
Investigation of new material systems should also be an integral part of project development. This study has only scratched the surface in examining potential materials for oral dosage forms. Analysis of enteric materials has not yet been performed, and this may be a possible solution to including a lag time into the dosage forms. Mixing materials is another area which can also be explored.

6.3.2 Modeling

Developing suitable models for the release process should also be a priority in the development process. Predicting the behavior with models will allow for a minimization in the number of iterations for obtaining a particular release profile. Models can be developed to predict the stages of imbibition, swelling, and diffusion or degradation mechanisms as related to the 3DPTM processing parameters. Each of these stages will be dependent upon the materials properties and the processing conditions.

Modeling of the drug distribution within the device should also be pursued. The exact degree the drug solution bleeds during deposition is expected to be a function of the saturation level, contact angle, and porosity. How the drug interacts with the polymer also deserves attention. Knowing the time scale of binder solvent removal and thermodynamics may facilitate the determination of whether the drug is localized at the polymer surface, is homogeneously mixed with the polymer, or whether it phase separates.

6.4 PROCESSING LIMITATIONS

Advances in printing strategy are anticipated to be made to overcome many obstacles, but the limitations inherent to the 3DPTM process should be kept in perspective. Several of the more important issues have already been discussed and will be addressed in future investigations. Issues concerning the processing limitations of the materials are summarized below.

A number of processing limitations must be considered in the formulation process. The 3DPTM process uses powders and liquids, therefore, materials properties and solubilities will most likely be the limiting factors. Resolution depends on the powder size and has an upper limit of two particle diameters. Typical lines and walls constructed with the process
are on the order of 350 μm in thickness. The resolution will ultimately limit the number of features which can be incorporated into a dosage form of a given size. The dosage which the devices can contain will also be dependent on the amount of void space which remains following binder deposition. The process may prove feasible only for very potent drugs when wall space and drug solubility are taken into consideration. The surface finish may be another processing limitation which depends on the powder size and packing.

6.5 CONCLUDING REMARKS

The results of this project were very encouraging, but bringing the technology to the real world remains a separate issue. The practicality of these devices needs to be considered before they can be introduced to the market. 3DPTM will most likely never be a practical alternative for manufacturing over-the-counter medication. Rather, it is more likely to be used in niche markets where low quantity and highly specific formulations need to be administered. Capsule technology is probably the main competitor for these ODFs, but they are not practical for manufacturing at very small scales.

The cost-to-benefit ratio of using 3DPTM to manufacture oral dosage forms also needs to be considered. The production rate of current 3DPTM machines is inherently limited, making the manufacturing expense a large fraction of product cost. It is anticipated that the simplicity of the formulation process will compensate for this. The small scale at which it is capable of working allows for rapid formulation to yield large savings in both time and cost of product development.
BIBLIOGRAPHY