The Development of a Thin-Film Rollforming Process for Pharmaceutical Continuous Manufacturing

by

Ryan Slaughter

Submitted to the Department of Mechanical Engineering
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ABSTRACT

In this thesis, a continuous rollforming process for the folding of thin-films was proposed and studied as a key step in the continuous manufacturing of pharmaceutical tablets. HPMC and PEG based polymeric thin-films were considered for this application. An experimental apparatus was designed and developed to test the folding of thin-films. The experimental apparatus was designed in a modular fashion to facilitate testing of various process parameters. Analysis was carried out for the folding operations, based on which two folding strategies were proposed – (i) without scoring and (ii) with scoring. The first strategy relies on elastic deformation of the thin-films, whereas the later depends on localized, plastic deformation caused by the scoring geometry. From the experiments on folding we identified three regimes of process operation namely: insufficient scoring, appropriate scoring, and excessive scoring. The implications of different levels of scoring were observed and understood carefully for the scoring and folding operation. Practical guidelines were developed for carrying out folding successfully and the scope of future work was discussed.

Thesis Supervisor: Jung-Hoon Chun
Title: Professor of Mechanical Engineering

0.1 Acknowledgments

To begin, I would like to thank my advisor, Professor Jung-Hoon Chun, who allowed me the incredible opportunity to work in his research lab and provided me with indispensable supervision and guidance throughout the past few years. Without his personal support, concern, and truly extraordinary patience, I could not have completed this work. Thank you.

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Finally, I must express my overwhelming gratitude and love for my Mom, Dad, family, and dear friends who, despite my best efforts, have remained with me always, sustaining an unwavering love that continues to illuminate my life with meaning and purpose.

I regretfully apologize to the numerous family members, friends, and past teachers that I did not mention specifically for their support of my efforts–but please know that I appreciate you all and find it truly remarkable that I have been able to forge so many fulfilling relationships with such a wonderful and diverse group of people.

Thank you all.

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Chapter 1

Introduction

1.1 Importance of Continuous Manufacturing in Pharmaceutical Production

Manufacturing process design and implementation in the pharmaceutical industry is rapidly evolving from batch processing methods to more efficient continuous processing protocols under certain circumstances. It may seem surprising that the pharmaceutical industry has not developed continuous methods for product design, given the industry's maturity and fiscal strengths, but the traditional tablet is a commonly accepted drug delivery vehicle.

The global pharmaceutical industry is slow to shift from the traditional batch tablet design, because current methodology offers precise dosing, ease of handling, and a long shelf life [?]. However, examining some of the advantages of continuous sub-process development in comparison to similar batch-based methods can offer a viable solution to the conventional and complicated chain of solid powder batch formation.

The manufacturing of tablets involves two sub-processes: an upstream process, where chemical production is the focus, and a downstream process , where mechanical forming is the focus.

The primary output of the upstream chemical processes is the Active Pharmaceutical Ingredient (API). The upstream process is the collection of chemical reactions necessary to produce the API, which is the real drug component of a tablet. Medically value-added

API is compounded with raw chemical materials, which have no pharmaceutical effect, throughout the chemical synthesis process and then subsequently purified via crystallization. Tablets are formed at the downstream process by annexing adducts, such as excipients and solvents, to the APIs. An excipient is a pharmaceutically inert substance that acts as a carrier of APIs. Excipients are comprised of dilutents for size and volume control, disintegrating agents for absorption in the body, binders for adhesion, glidants for lubrication, stabilizers for shelf-life control, etc. The bulk and surface characteristics of the API solid powder are homogenized by the granulation and milling processes. This improves powder flowability of the transfer process and makes tablet compaction and binding easier. Thereafter, API powder is blended with excipient powder and then compacted at the tablet press to become the final solid tablet dosage form.

This complicated chain of batch operations has been the convention of the pharmaceutical industry since the late 19th century. However, this conventional methodology has intrinsic problems, specifically in the area of solid powder handling. Homogeneous mixing of API powder with excipient powder is difficult to accomplish during the blending process. Inefficiency in the blending protocol can lead to a non-uniform distribution of API content and density in the tablets. Moreover, the batch-based tablet manufacturing process is expensive, inefficient and has a longer production time in comparison to other processes in highly competitive industries, primarily because material flow is not continuous between its sub-operations. In addition to these factors, it is difficult to maintain flexible control on output volume when considering unpredicatable fluctuations in market demand, and when a new drug is developed, a batch-based manufacturing process requires excessive time and expense for the re-design and scale-up of the required manufacturing facility.

The batch-based tablet manufacturing process has been used in pharmaceutical factories on a global scale for over one hundred years, because until now, pharmaceutical companies have made enough profits on new drug designs to offset the problems associated with the downstream processing of the drugs. However, as the industry has continued to mature and grow in competitiveness, it has become more difficult and costly to discover and develop patent-protectable blockbuster drugs, such as those required to treat the ailments of hypertension, diabetes, heartburn, and high cholesterol medicines [?]. Hence, there is an

imminent push toward more efficient, timely, and cost-effective manufacturing processes in the pharmaceutical industry. Furthermore, competition in the generic drug market is quickly ramping up, because of rising companies in developing countries. Once a new drug patent expires, virtually any pharmaceutical company can develop a generic version of it. Only companies with the ability to produce the same drug at a lower cost will survive in this highly competitive industry, and for this reason, a more efficient manufacturing process is becoming increasingly important.

Thus, pharmaceutical companies are actively seeking more efficient and cost-effective methods of manufacturing their drugs. Motivated by these concerns, a research project has been launched at the Novartis-MIT Center for Continuous Manufacturing (CCM) with the aim of converting the conventional batch-based tablet manufacturing process into a continuous one. This research has the potential to change the pharmaceutical manufacturing paradigm by solving the problems originating from batch-processed and powder-based tablets. A continuous tablet manufacturing process can be realized by replacing solid powder handling with co-processing of APIs and excipients in a liquid-phase solution. Blending of APIs, excipients, and solvents in the liquid-phase improves homogeneity of blends. A continuous tablet manufacturing process can be accomplished by avoiding granulation operations, which are an essential part of solid powder handling, and the primary cause of discontinuous material flow. The continuous tablet manufacturing process has the following advantages as compared with the conventional batch-based manufacturing process: (a) uniform and rapid blending of API and excipients, (b) cost-saving, (c) fast production speed and high yield, (d) real-time quality inspection, (e) fast market introduction of new drugs (f) flexible output control and (g) easy automation.

When tablets are manufactured via liquid-phase solution of APIs, excipients, and solvents, one of the challenging issues is drying, that is, how to remove adequate amounts of solvents rapidly. In the general drying process, such as hot plate or hot air drying, the surface is dried and solidified first and then acts as a barrier obstructing solvent mass transfer. Because of this negatively compounding effect, it is difficult to get rid of solvents remaining in the inner part of the material. Solvent casting of thin films is one strategy to solve this potential drying challenge, since the process enlarges the surface area and reduces the

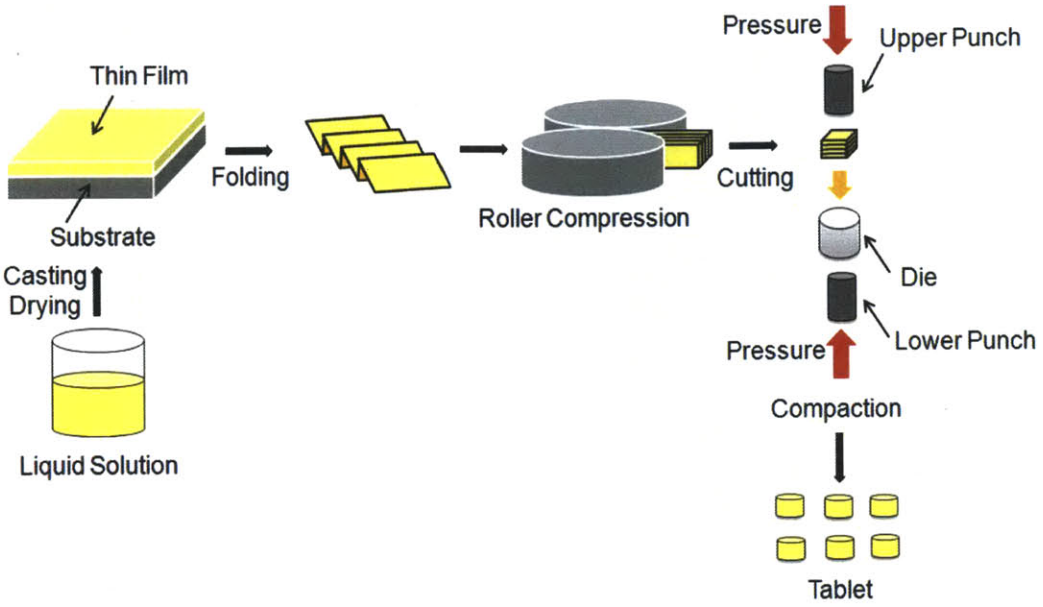

Figure 1-1: Thin-film tableting process overview.

required solvent diffusion length, so that solvent evaporation may occur more quickly and completely. Polymer films have not previously been investigated for buccal delivery [?], but clearly, solvent-cast thin films hold great promise for the continuous process manufacturing of tablets.

A folding operation is a potential candidate for producing tablets from the solvent-cast thin films. Thin-film sheets, which are cast on to a non-sticking substrate from the homogeneous liquid solution of APIs, excipients, and solvents, may be formed into accordion-like folds by this process. The folded thin-films could then be further treated, utilizing roller compression, cutting, and final shape compaction, to become tablets as shown Figure reffig:processoverview. These tablets will satisfy the requirements listed in Table 1.1 [?, ?, ?, ?].

1.2 Thin-Film Preparation

The thin-films were prepared by solvent casting using a casting apparatus. The key ingredients of the chemical formulation for film making are as follows:

Table 1.1: Key properties for pharmaceutical tablets

Mechanical Properties:	Hardness, Friability
Release Profile:	Disintegration, Dissolution Rate
Uniformity Content:	Density, Shape, Surface Uniformity
Stability:	Mechanical, Thermodynamic, Chemical Stability
General:	Appearance Biconvex Shape

(a) Active Pharmaceutical Ingredient (API) – the real drug substance for the medication,

(b) Excipient – a pharmacologically inactive substance used as a carrier for API,

(c) Plasticizer – a pharmacologically inactive substance that plays a key role in altering the mechanical properties and bonding behaviors of the films,

(d) Solvent – to aid in dissolving and mixing of the API, Excipient and Plasticizer to form a homogeneous solution. Note that the API, Excipient, Plasticizer and Solvent must all be compatible while in the solution.

In this thesis, we worked with placebo formulations, that is, thin-films without any active drug substance, to ameliorate any potential handling or safety issues. The placebo films were carefully formulated and processed to have mechanical properties similar to those of an API-based formulation.

In this study, we have employed hydroxypropyl methylcellulose, HPMC e3 and e15, as the primary excipients and used polyethylene glycol, PEG-400, as a plasticizer. Distilled water and ethanol were used as solvents.

The thin-film making procedure was performed as described below:

(a) The properly measured amounts of base polymer and excipient are dissolved in

Ethanol,

(b) To the above solution, water and PEG-400 are added,

(c) API is finally added.

The solution is stirred for approximately 24 hours, thereby ensuring homogenous mixing. After solution is prepared and mixed it is allowed to stand alone for several hours to allow for settling. It is then degassed in a vacuum chamber in order to remove gas bubbles that would negatively impact the resulting thin-film. Figure 1-2 shows prepared solution.

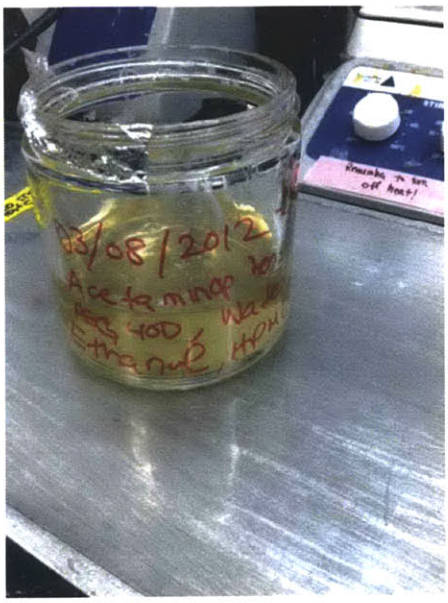

Figure 1-2: Example of a chemical formulation for thin-film preparation.

Preparation of thin-films was carried out using a casting apparatus comprised of an adjustable-height knife, to control the film thickness, and a stainless steel plate with a thin polyester sheet placed on top, as shown in Figure 1-3. The polyester sheet acts as a non-sticking substrate for the film solution. With the polyester sheet attached on the stainless steel plate, the placebo solution was poured over and the knife was dragged across to uniformly spread the solution and form a thin liquid film. The knife height was set to $95\mu m$ above the surface and was carefully controlled for this set of experiments, as the

initial film thickness directly affects the drying time and depth, and thus largely influences the resulting thin-film mechanical properties and final thickness. These hand-cast films were then used for testing and experiments.

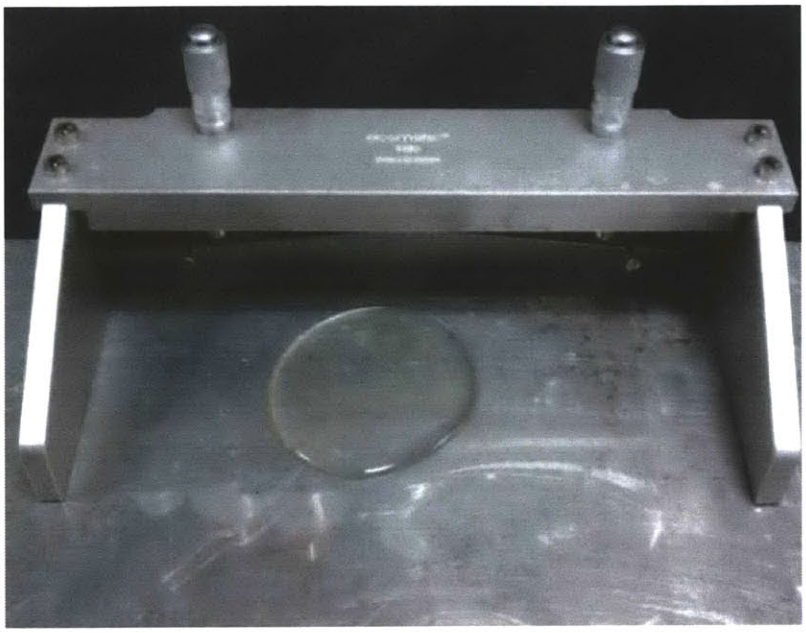

Figure 1-3: Example of solution casting for thin-film making.

For the sake of completeness, the chemical formulas of PEG and HPMC are shown in Figures 1-4 and 1-5.

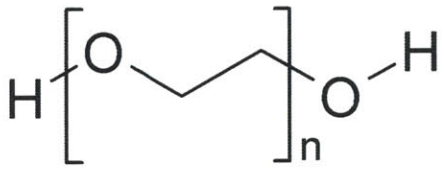

Figure 1-4: Chemical formula of PEG.

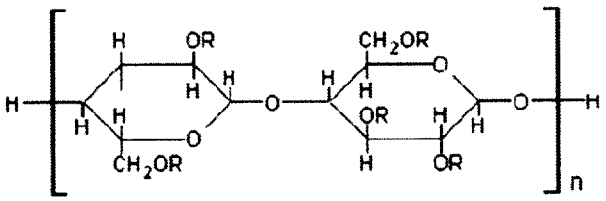

Figure 1-5: Chemical formula of HPMC.

1.3 Rollforming as a Pharmaceutical Manufacturing Process

Rollforming is a continuous processing method utilized for the mass production of many ubiquitous sheet-based products [?]. The sheet material is often a steel or aluminum alloy, but if the roll stand is designed accordingly, plastics and other materials can be processed as well. Two examples of typical rollforming stands are shown in Figures 1-6 and 1-7, continuously shaping the input metal from a flat sheet to a corrugated, U-like shape. Due to the diversity of materials used and the desired geometries of the final product, rollforming stands come in a large variety of shapes, sizes, and designs. For this thesis, an experimental rollforming apparatus was designed and fabricated to allow initial testing for a pharmaceutical thin-film based tabletting process.

It should be noted, that while designing the experimental apparatus, it was also informative to examine and review other closely related machines and operations that involve similar mechanical folding and deformation, such as the method for manufacturing of corrugated cardboard [?], the sheet folding device in [?], and the method for forming pleats in a sheet-like material [?].

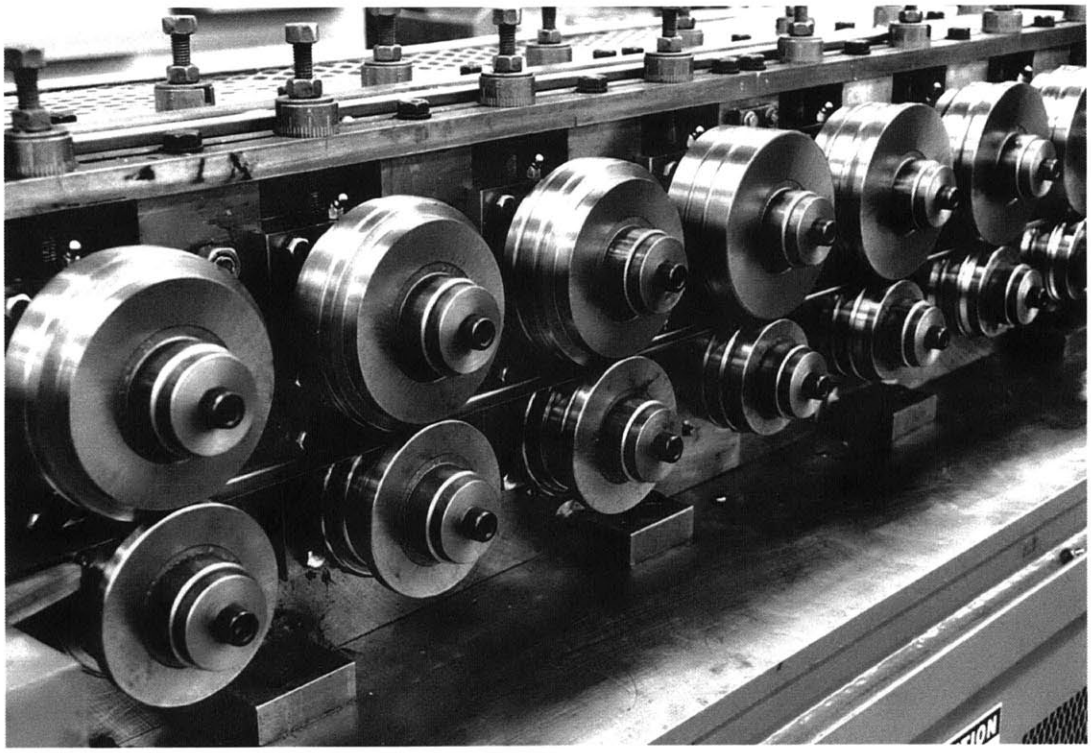

Figure 1-6: A rollformed metal sheet gradually bends and stretches as it follows the cantilevered rollers. [?]

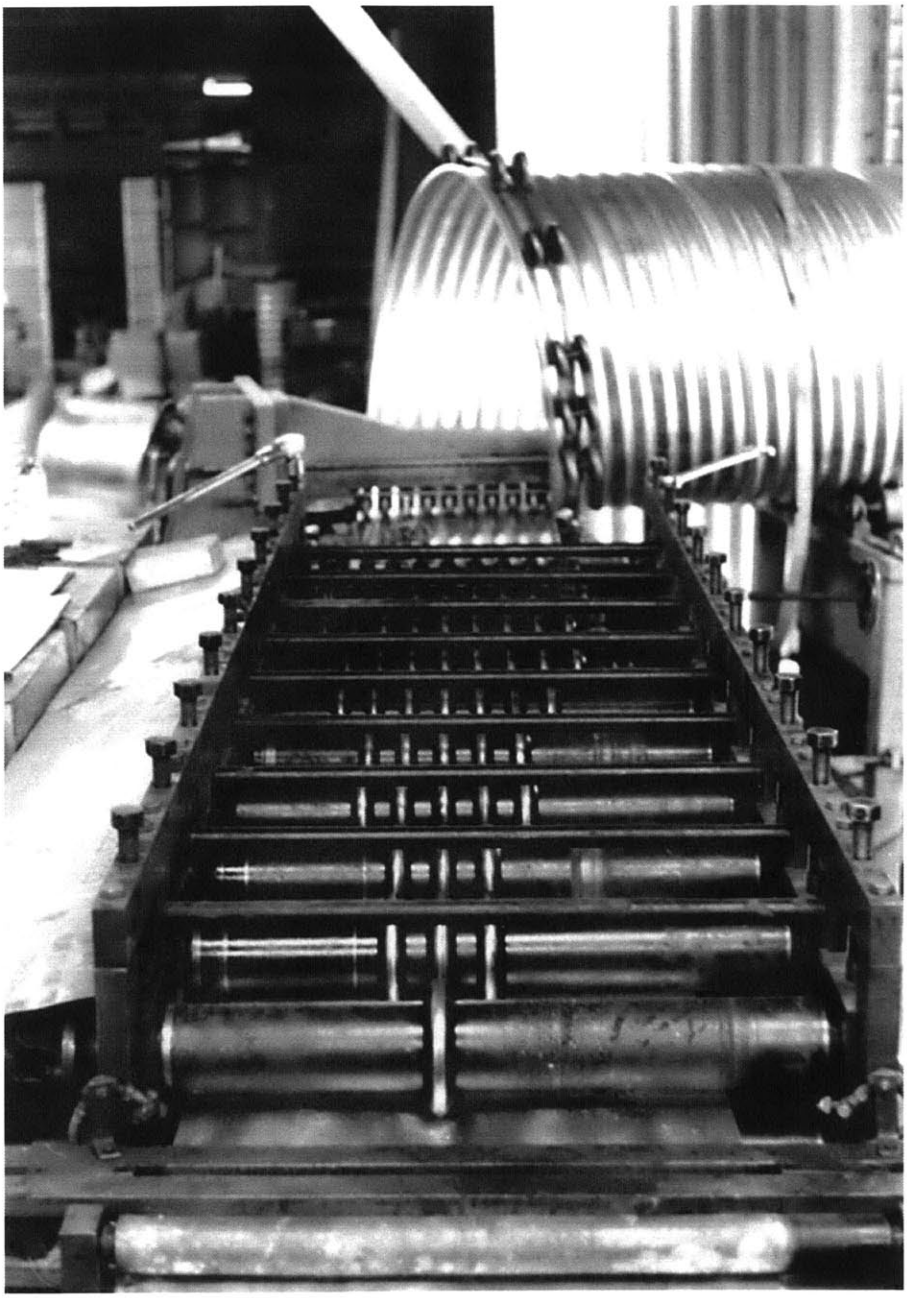

Figure 1-7: Traditional rollforming of sheet metal. [**?**]

1.4 Organization

The remainder of the thesis is organized as follows. In Chapter 2, we introduce the roll-forming process and carry out useful analysis of the folding operation. In Chapter 3 we propose and develop an experimental apparatus that is capable of completing several folding operations on the placebo thin-film and preparing it for subsequent processing steps. Here, key design issues, along with machine components are discussed in detail. In Chapter 4, we present the results and discussions based on the experiments performed. Finally, conclusions are drawn and the scope of future work is presented in Chapter 5.

Chapter 2

Analysis of Rollforming Processes

2.1 Rolling and Folding

2.1.1 Rollforming of Polymeric Thin-Films

In the past, significant research has been carried out on the design of the roll stands and roll schedules for use in the rollforming of various materials and output geometries. Several useful analytical and empirical models have been created and documented [?]. Some interesting studies on rollforming can be found in the following research: a wide-panel forming process to replace conventional rollforming [?]; cold rollforming of a U-channel made of high strength steel [?]; effect of interstand tension on roll load, torque and workpiece, deformation in the rod rolling process [?]; prediction of the wear profile of a roll groove in rod rolling [?]; prediction of the wear profile of a roll groove in rod rolling using an incremental form of wear model [?]; prediction of the surface profile and area of the exit cross section of workpiece in round-oval-round pass sequence [?]; new approach for prediction of roll force in rod rolling [?], a parametric study on forming length in roll forming [?]; cold-roll forming of smaller-diameter pipes with pre-notches [?]. For an overview on modeling details used in commonly employed rollforming processes the reader is referred to the following studies: [?], [?], [?], [?]. However, many of the typical models simplify the necessary analysis by assuming that the input material, often a metal, may be adequately modeled as a rigid-plastic material. In the case of many rollformed products, this fundamental as-

sumption is reasonable, given the material properties, sheet thicknesses, roll bending radii, and desired final geometries of the application at hand. Many of the modeling assumptions and techniques are not valid in the case of the polymeric thin-films, roll schedule, and final output material geometry that are the focus of the current research. When the prototypical thin-film studied in this research undergoes the roll schedule displayed in Figure 2-1, the thin-film remains entirely in the elastic regime until it passes through the final, vertical traction stand, where the layers are pulled through and compressed as the bend radii approaches zero. It is possible to fold thin-films using this primarily elastic folding method, however, by locally compressing and plastically deforming the thin-film along desired lines prior to passing it through the fold stands, the engineering challenge of folding may be simplified.

By incorporating specially designed discs with precise scoring features, the desired local plastic deformation may be achieved simply and effectively within the described roll-forming apparatus.

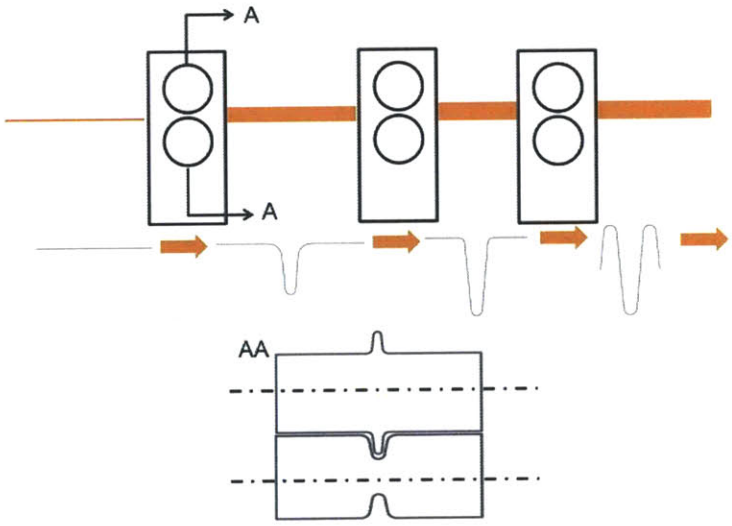

Figure 2-1: Sheet folding by rollforming process schematic.

2.1.2 Effect of Scoring on Folding Process

The effects of scoring may be better understood by modeling a single fold of the thin-film rollforming process as a Euler-Bernoulli beam with a deep notch.

Figure 2-2 depicts a simplified schematic of a single fold of a scored film being roll-formed. In the schematic M is the moment transmitted through both Sections 1 and 2, H is the thin-film thickness, d is the scored ligament thickness, and h is the depth of the section under consideration.

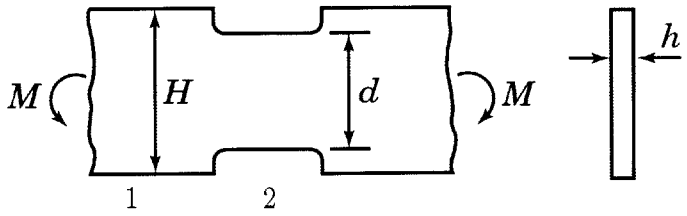

Figure 2-2: Simplified Euler bending model.

If the film is modeled as a Euler-Bernoulli beam undergoing a pure bending moment then

$$M = M_1 = M_2 \tag{2.1}$$

For such beam sections, M may be calculated as

$$M = \frac{EI}{R} \tag{2.2}$$

where E is the modulus of elasticity, I is the second moment of inertia, and R is the resulting bend radius of the initially straight beam. Substituting in the geometry of the two sections

$$M_1 = \frac{E}{R_1}\frac{hH^3}{12} \tag{2.3}$$

and

$$M_2 = \frac{E}{R_2}\frac{hd^3}{12} \tag{2.4}$$

Combining and simplifying Equations 2.3 and 2.3 results in

$$\frac{R_2}{R_1} = \left(\frac{d}{H}\right)^3 \tag{2.5}$$

If beam curvature, κ, is considered rather than beam radius, R, where

$$R = \frac{1}{\kappa} \tag{2.6}$$

it may be concluded that

$$\frac{\kappa_1}{\kappa_2} = \left(\frac{d}{H}\right)^3 \tag{2.7}$$

This cubic dependence of $\frac{\kappa_1}{\kappa_2}$, the non-scored to scored section curvature ratio, on $\frac{d}{H}$, the scored ligament thickness to total thickness ratio, highlights the dramatic effect of scoring on the relative bending stiffness and resulting curvature of the two sections. As shown in Figure 2-3, as $\frac{d}{H} \to 0$, $\frac{\kappa_1}{\kappa_2} \to \infty$. Assuming that the thin-film thickness, H, is held nearly constant, and the prescribed scoring depth, h_s, is sufficiently large, yet does not cut through the sheet, a highly localized and predictable bend, or fold, will be produced.

2.1.3 Local Yielding

Scoring and the resulting geometry change produce a two-fold effect that facilitates folding by locally reducing the bending stiffness and inducing a stress concentration that increases the stress endured by the scored section, which leads to increased yielding and bending springback reduction. Given system and input imperfection, both of these effects may contribute to more precise and consistent folding. Using the information from Figures 2-4 and 2-5 [?] along with an estimate of the thin-film geometry and material properties, we may calculate and plot the resulting non-dimensionalized stresses shown in Figure 2-6.

In Figure 2-6 where $\frac{d}{H}$ is approximately equal to 0.83 the nominal stress of the sheet is approximately equal to the yield stress of the material. As $\frac{d}{H}$ is reduced the nominal stress continues to increase well above the yield stress, aiding in springback reduction along the scoreline. Thus, for the given set of parameters, it would be prudent to operate with a scoring depth deeper than $0.17H$, to induce localized yielding to aid in springback

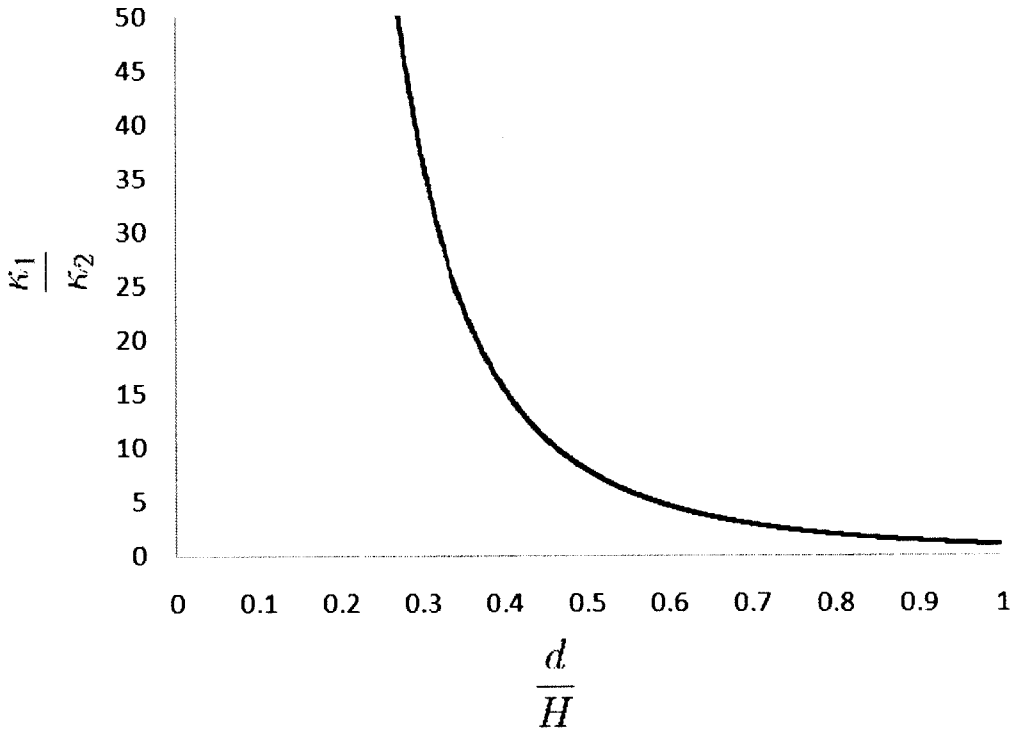

Figure 2-3: Euler beam bending model dimensionless ligament thickness vs. curvature ratio.

reduction.

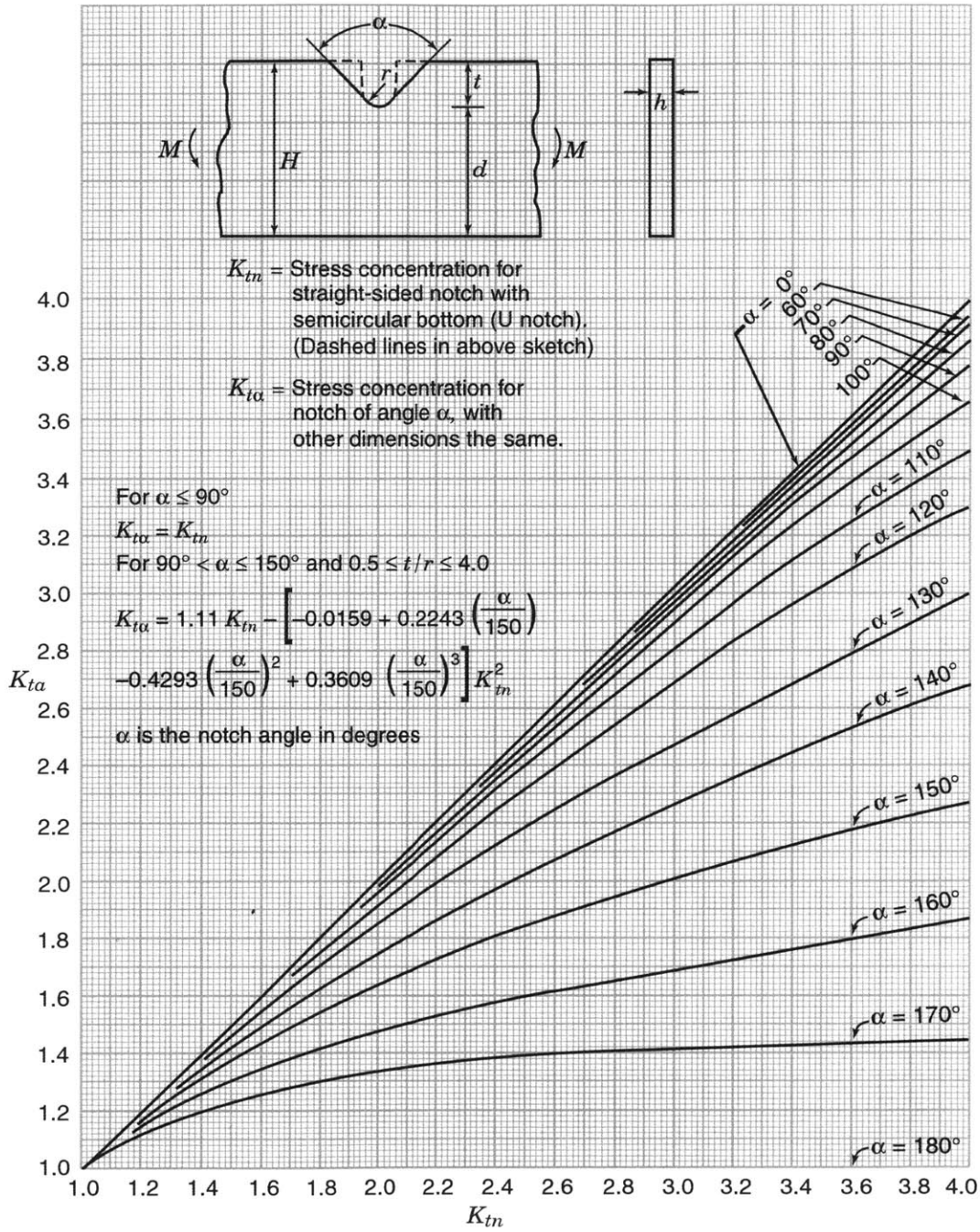

Figure 2-4: Effect of notch angle on stress concentration factors for a thin beam element in bending with a v-shaped notch on one side. [**?**]

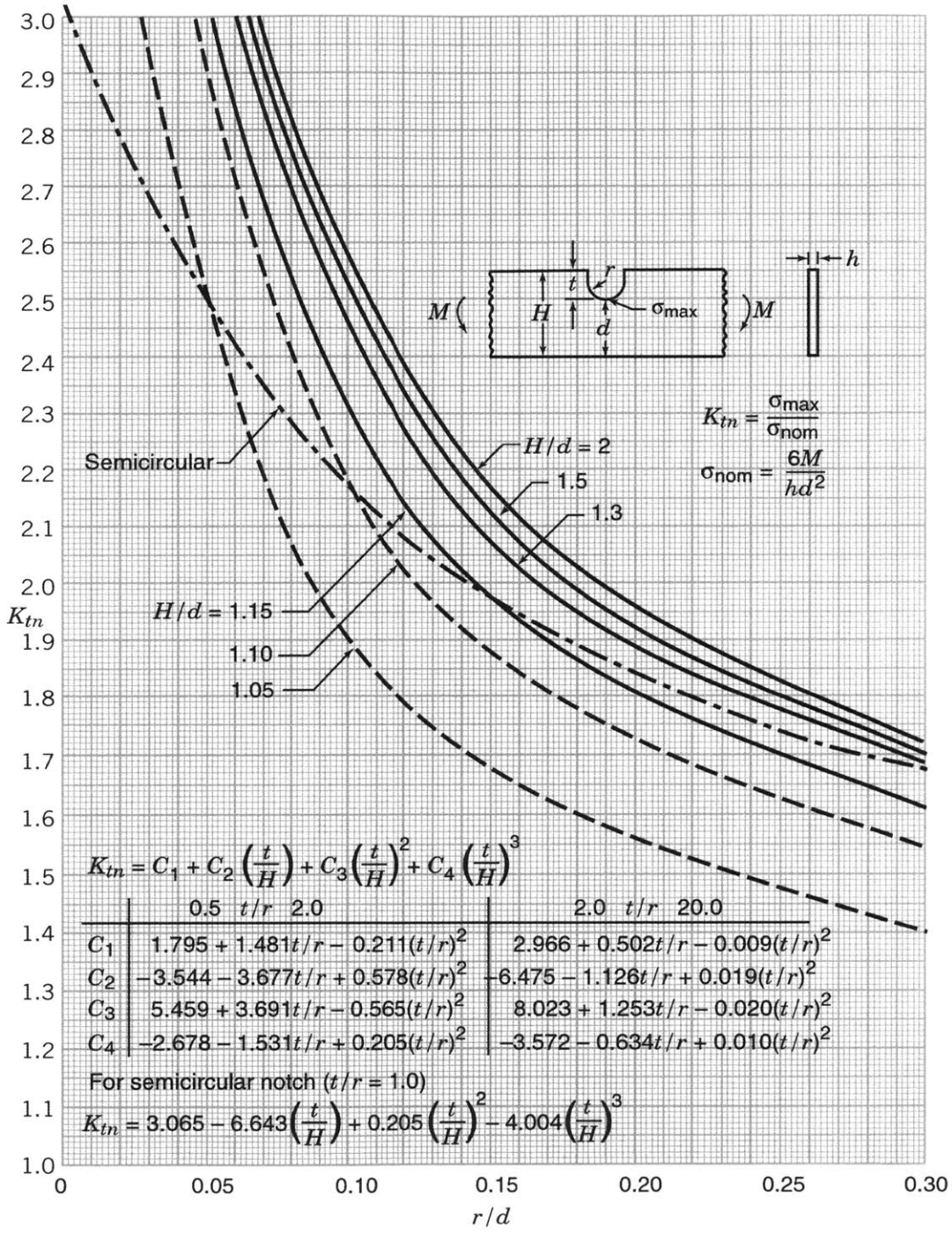

Figure 2-5: Bending of a thin beam element with a notch on one side. [?]

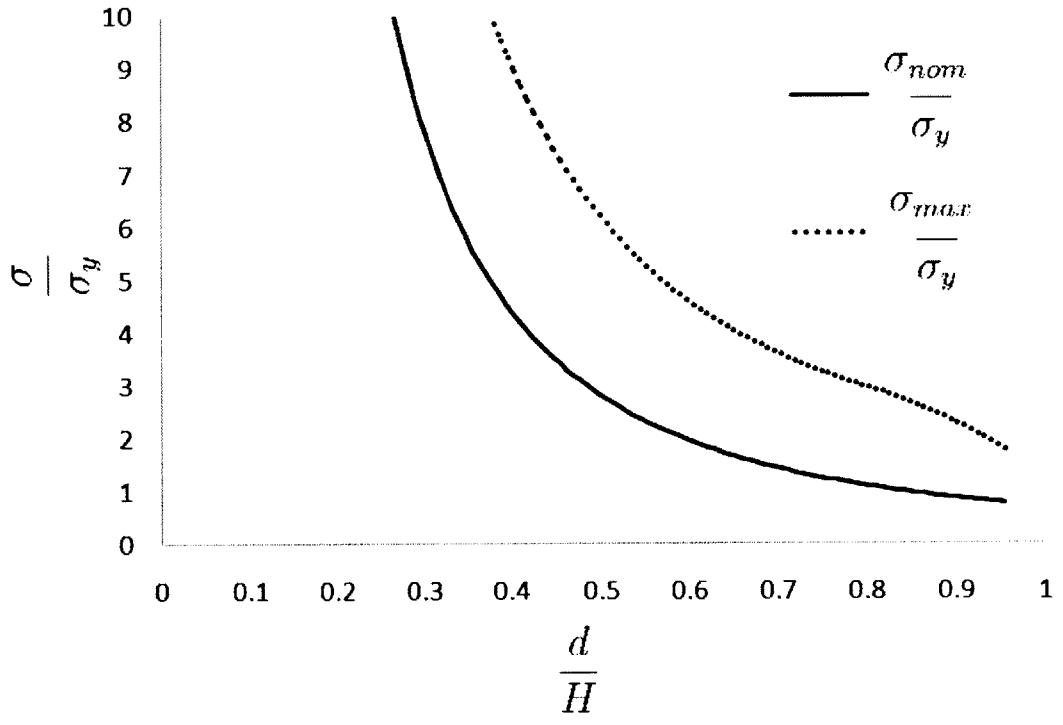

Figure 2-6: Dimensionless ligament thickness vs. dimensionless stress, based on stress concentration analysis for $E = 150MPa$, $\sigma_y = 12MPa$, $r = 11\mu m$, $H = 132\mu m$.

Chapter 3

Design of the Experimental Apparatus

In this chapter, we discuss the design and development the rollforming machine for the proposed folding operation. The central idea for the design is to take in a flat, thin-film and gradually achieve sequential folds through rollforming stands. To begin the section we shall discuss the mechanical properties of the thin-films that were used in this work and guided the sizing of the experimental apparatus.

3.1 Mechanical Characterization of the Thin-Films

As mentioned previously, placebo films have been used in this study. The mechanical characteristics of these films were employed for the development of the forming process using the design guidelines and rationale discussed in Chapter 2.

Figure 3-1 shows the universal mechanical tester on which experiments were carried out for this study. Figure 3-2 shows the stress-strain curve of the placebo film. A strain rate of 1 mm/mm-min was used during experimentation. From the figure, it is clear that the placebo film exhibits fairly distinct elastic and plastic regimes and a large elongation at break.

The initial design of the experimental apparatus was performed based on the properties of the given placebo film and after some preliminary testing, fine-tuning of the apparatus was achieved.

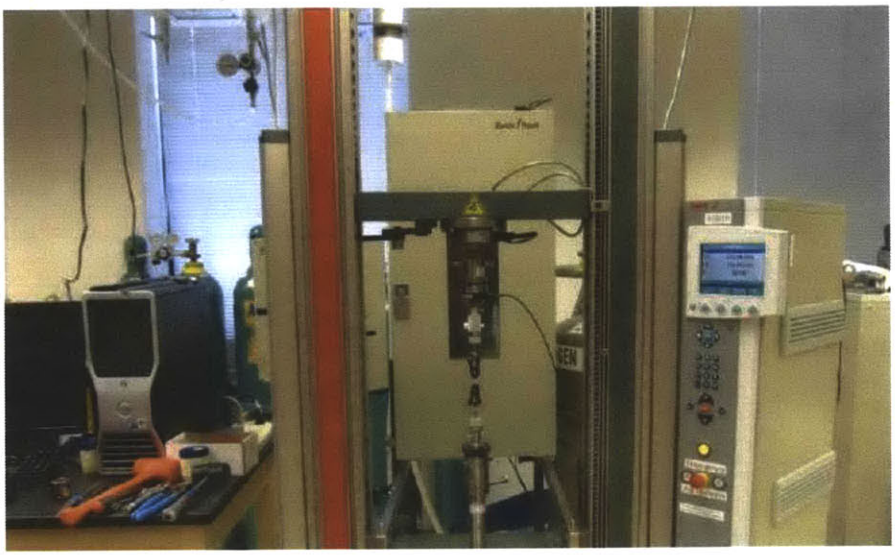

Figure 3-1: Zwick universal tester used for thin-film material property characterization.

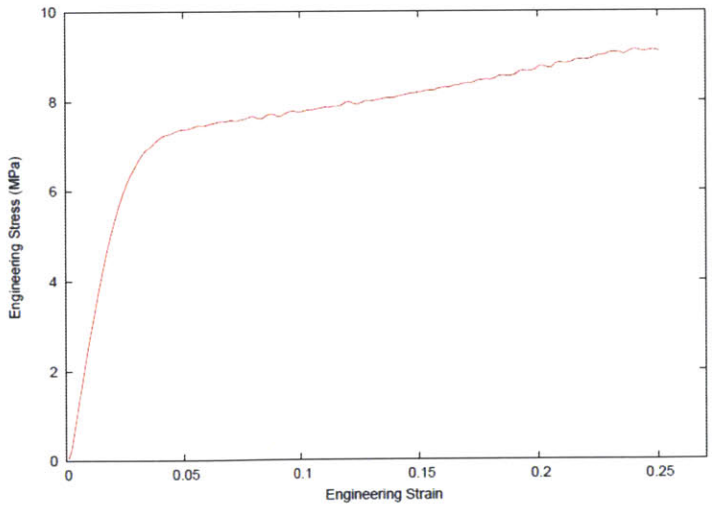

Figure 3-2: Characteristic stress-strain curve for placebo thin-film.

3.2 Functional Requirements

The goal of developing the experimental apparatus was to carry out studies on the folding operation. The main functional requirements for this setup are:

1. Accept and align the thin-film at the entrance roll stand.
2. Gradually fold the thin-film without tearing or excessive wrinkling.
3. Gather the folded thin-film together for subsequent processing.

3.3 Machine Components

The main components of the experimental apparatus necessary to achieve the aforementioned functional requirements are:

1. **Entrance Rollers**: The purpose of the entrance rollers is to take in and guide the thin-film into the folding section, as shown in Figure 3-3.

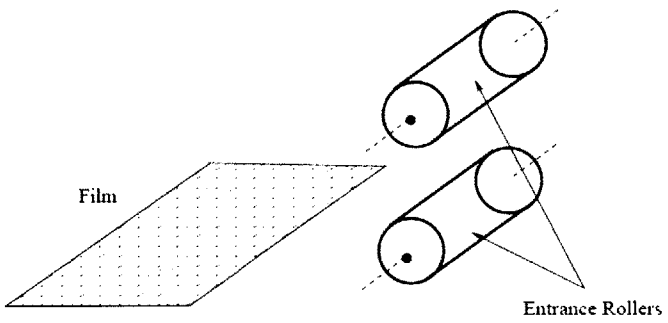

Figure 3-3: Entrance rollers to the rollforming station.

2. **Folding Discs**: The folding discs are key to the folding process. As the film passes through the folding rollers, the sheet is deformed and folds are created. Any scoring features are also machined onto these same discs. Figures 3-4 and 3-5 show the folding disc sub-assembly required to make one and three folds respectively. The folding discs are mounted on a shaft and kept in position using precision spacers. An illustration of a folding unit is shown in Figure 3-6.

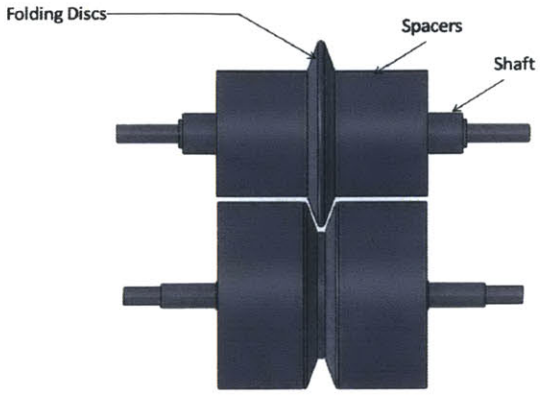

Figure 3-4: Folding rollers for 1-fold stand.

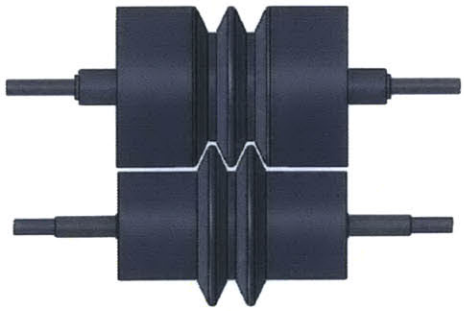

Figure 3-5: Folding rollers for 3-fold stand.

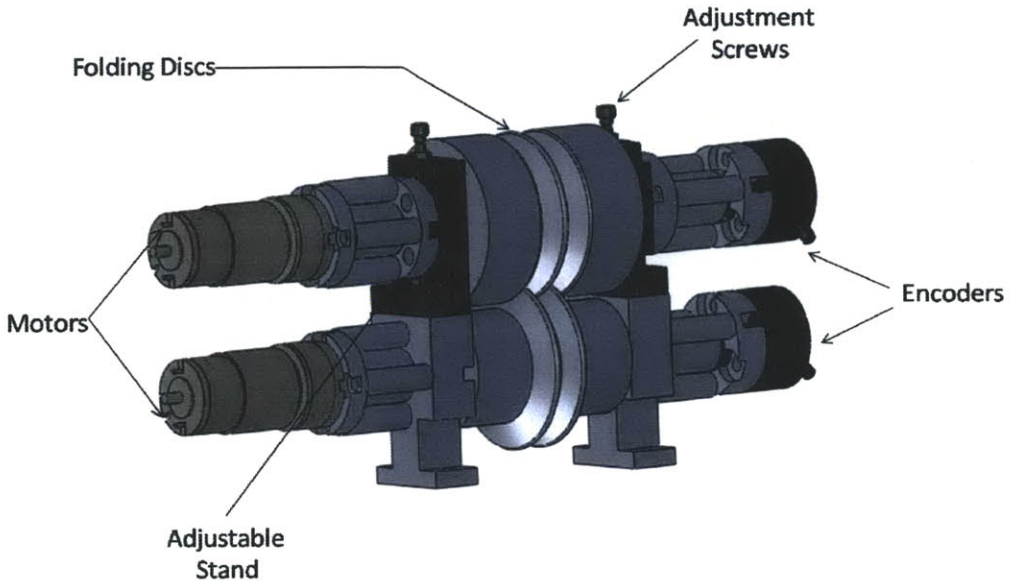

Figure 3-6: CAD model of a rollforming fold stand.

3. **Shafts**: These shafts carry the discs and spacers used for folding and are driven by a feedback controlled motor. The shafts are mounted on an adjustable stand with bearings. A top and bottom pair of shafts are used on a single folding unit.

4. **Adjustable Translation Stage and Micrometer**: The goal of the adjustable translation stage and micrometer is to precisely raise and lower the top shaft assembly so that the depth of the scoreline may be carefully controlled.

5. **Adjustable Translation Stage and Micrometer**:

   The lower fold roller assembly (shaft, spacers, discs, etc.) is held between a pair of ball bearings that are press fit into aluminum bases, while the upper fold roller assembly is held by a pair of ball bearings press fit into an aluminum plate mounted on two translation stages. This setup, along with dual screw micrometers

   allows for precise control of the vertical distance between the shaft axes. Controlling this distance is critical for the scoring and folding process. The film entrance rollers use this same overall assembly structure, but large flat tensioning discs are put onto the shaft, instead of the folding discs and spacers.

6. **Motors and Drive**: For each folding stand, a DC motor (M32P0721YBGT3) with a gear reduction was selected. A schematic illustration of the DC-motor, its drive and controller are shown in Figure 3-7. For the final traction rollers, a servomotor (AKM63K-VBCNR-00) and drive (AKD-P012-NAAN-000) were selected. More details on the electronics employed in this study can be found in [?].

7. **Traction Rollers**: As the folded thin-film exits out of the folding section, vertical traction rollers are needed to provide the necessary force to pull the film through for subsequent processing. Figure 3-8 shows the traction rollers and stand assembly.

8. **Encoders**: The encoders are present to provide closed-loop feedback control for the folding motors.

The thin-film is guided into the folding section through the entrance rollers. It is gradually folded as it is driven by the individually controlled fold stands and pulled through by the final traction stand.

The folding stands were designed to have a high degree of modular flexibility in order to enable precise control and quick changeover between the folding disc geometries. By altering and substituting these discs, we could more easily control the folding process parameters and fine tune the operation.

The pharmaceutical thin-film enters through a flat tension roller, then is gradually folded as it is driven by the individually controlled fold stands and pulled through by the final vertical traction stand. The folding station was designed to have a high degree of modular flexibility in order to enable precise control and quick changeover of the folding process parameters.

Each fold stand is comprised of a top and bottom shaft with folding discs and spacers. The shafts' motion is coupled through spur gears, which are driven by a shared DC servomotor, allowing independent control of the thin-film feed velocity between one fold stand to the next.

Finally, material properties of key machine components are listed in Table 3.1

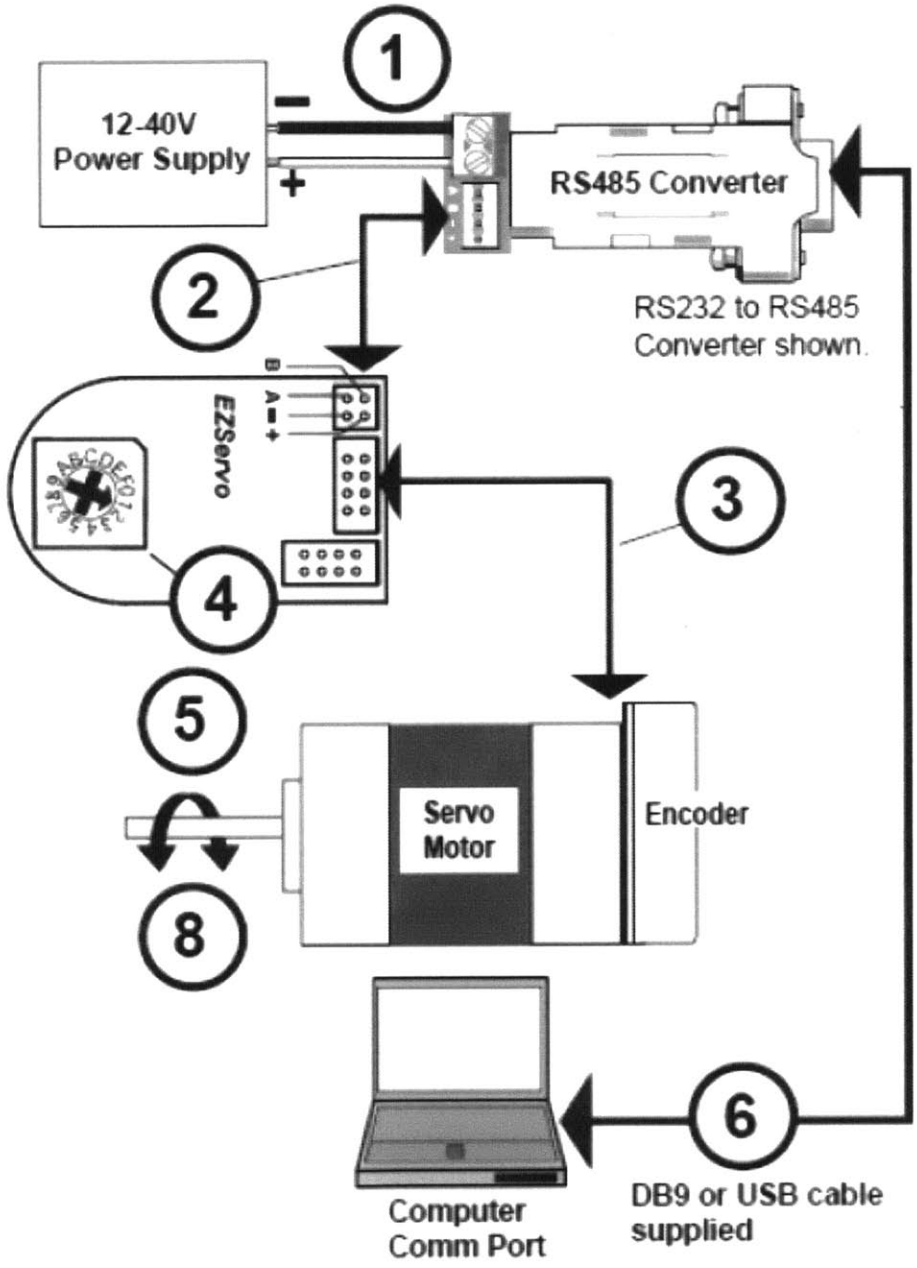

Figure 3-7: Folding stand electric motor and drive schematic.

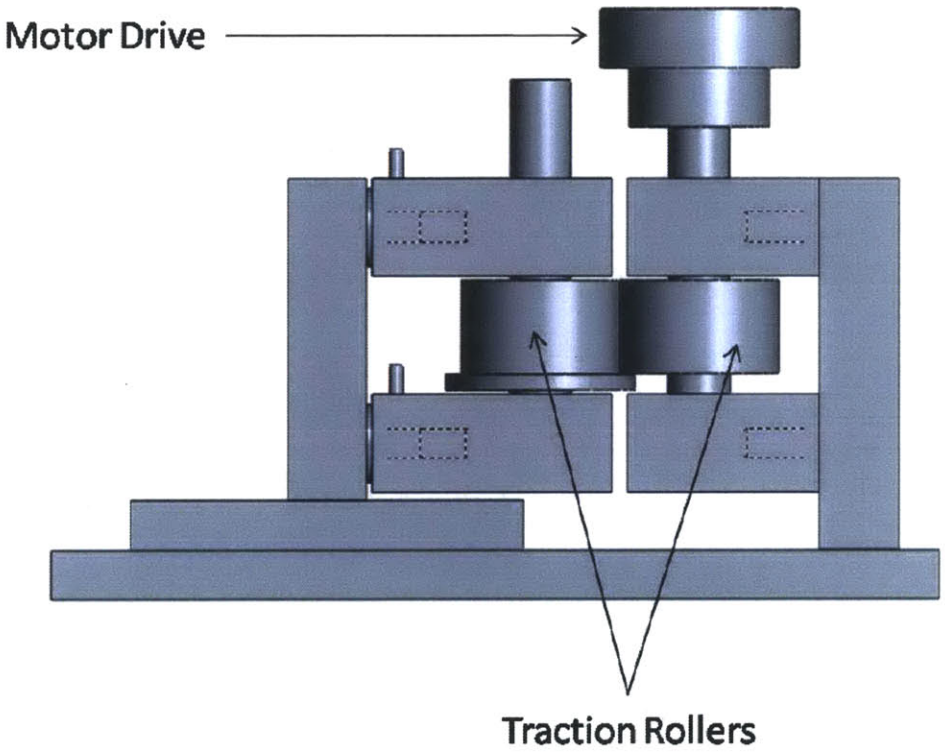

Figure 3-8: CAD model of the rollforming final traction stand.

Table 3.1: Material list for machine components.

Folding Stands	6061-T6 Al
Spacers	6061-T6 Al
Folding Discs	303 machineable stainless steel
Entry Rollers	303 machineable stainless steel
Shafts	Hardened 1566 steel
Traction Stand	303 machineable stainless steel

Chapter 4

Experimental Results

In the previous chapter, we discussed the design and implementation of the experimental apparatus used in the testing and development of a continuous rollforming process in order to fold placebo thin-films. In this chapter, we will report and discuss the findings of the performed experiments.

Broadly speaking, we have considered folding of films (i) without scoring and (ii) with scoring. Here, scoring implies that local plastic deformation occurs along desired lines in an effort to facilitate folding.

The degree of scoring is largely controlled by the profile and position of the folding disc. Figures 4-2 and 4-3 show the disc profiles that would be employed for folding without and with scoring, respectively. In the case in which folding is attempted without scoring, the key parameter for the disc is contact radius R. In the case of folding with scoring, the defining scoring geometry, h_s and θ , has a profound impact on the process.

The effect of scoring on the thin-film can be understood from Figure 4-4. In this figure:

1. H is the thickness of the film.
2. h_s is depth of the score.
3. w is the width of the score.
4. θ is the defining angle for the score.

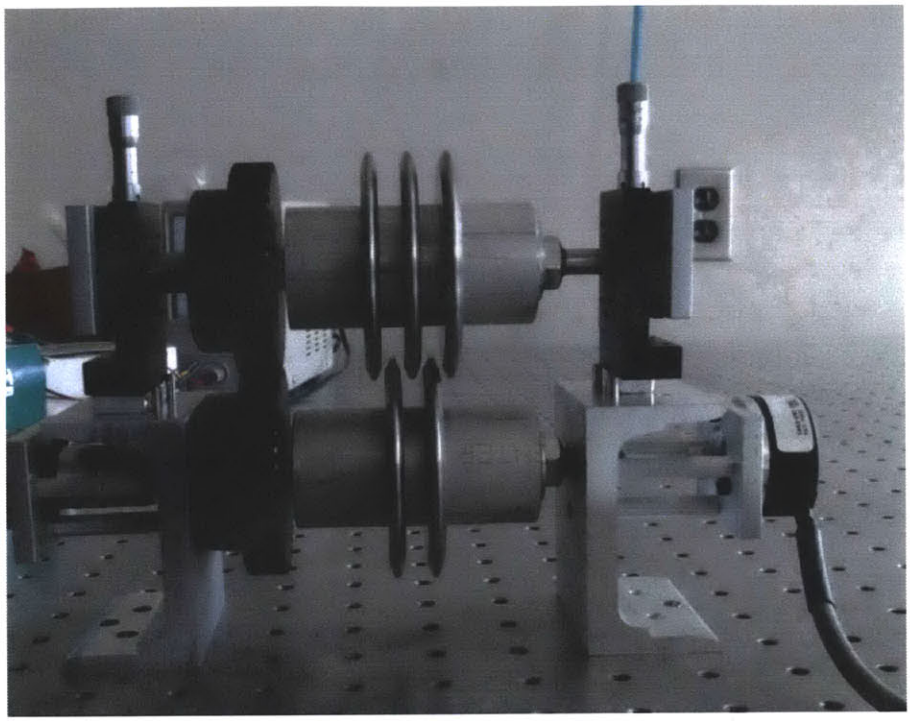

Figure 4-1: Rollforming folding stand unit.

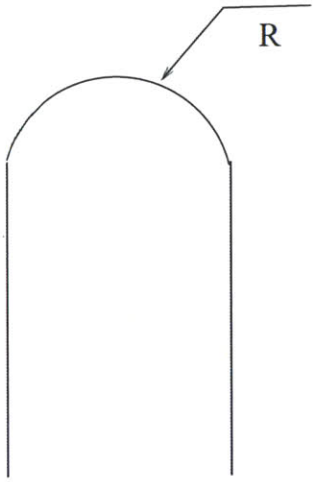

Figure 4-2: Folding disc profile without scoring feature.

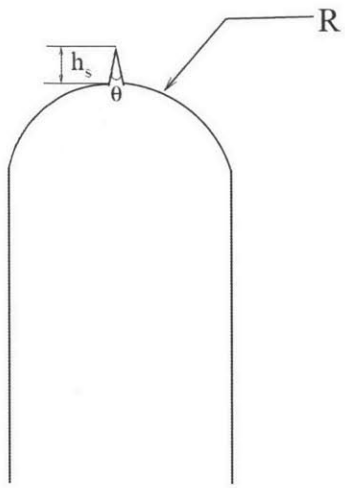

Figure 4-3: Folding disc profile with scoring feature. Not to scale.

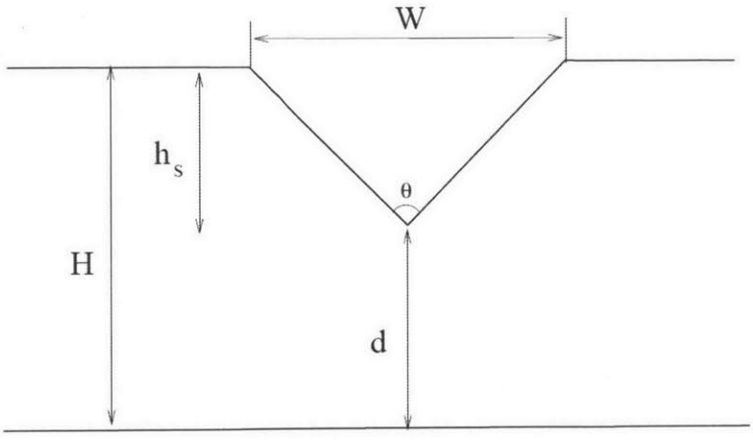

Figure 4-4: Film geometry along scoreline.

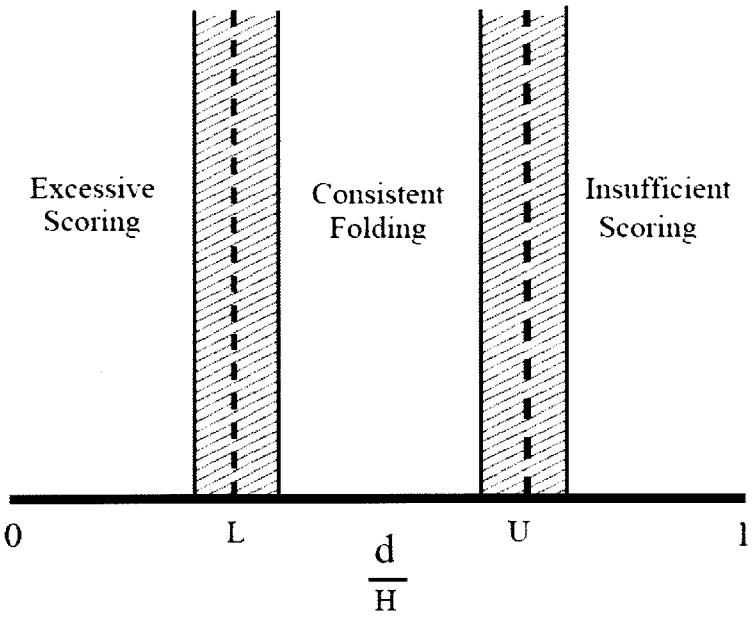

Figure 4-5: Folding regime identified for scoring.

Based on the preliminary calculations and experiments, a useful scoring geometry was identified. More importantly, we have identified that folding operations can largely be divided into three operating regions when considering the use of scoring. These operating regions are represented in Figure 4-5 and are primarily governed by the ratio $\frac{d}{H}$ and their associated errors. When $\frac{d}{H} = 0$, it is observed that excessive scoring has occured, resulting in a cutting or tearing failure along the desired fold line. Tearing makes material handling more difficult and is undesirable for the current folding apparatus. If $\frac{d}{H} = 1$ it may be concluded that no scoring has occured and subsequently no clear fold line is developed. Without having a distinct line which prescribed folding may follow, the thin-film is more likely to have alignment issues, drifting and folding in an undesirable manner. These process errors stem from system inaccuracy and the input material's thickness and material property variation. In a particular region enclosed by the lower limit, L, and upper limit, U, an acceptable and useful level of scoring was achieved that resulted in more consistent folding. Figure 4-5 shows the discussed folding regimes. The operating limits are shaded to denote the process uncertainty near those regions. L and U may be estimated as

$$L = \frac{\varepsilon_d + \varepsilon_H}{H} \tag{4.1}$$

and

$$U = 1 - \frac{\varepsilon_d + \varepsilon_H}{H} \tag{4.2}$$

where ε_d is the scoring depth error, largely due to the radial runout of the shaft-disc assembly, and ε_H is the thin-film thickness error. Thus, the scoring process should be set such that

$$L < \frac{d}{H} < U \tag{4.3}$$

Due to the complexity of the process, the stated value of U is an initial upperbound estimate that should be determined further through experiment. Because of this, experiments were ran nearer to the lower operating limit.

For the current process $\varepsilon_d \doteq 38\mu m$ and $\varepsilon_H \doteq 15\mu m$. Given that $H = 132\mu m$, the recommended operating window was somewhat small, but with proper control of the scoring depth, successful folding was achieved.

4.1 Folding Experiments

As discussed in the previous section, folding may be executed with or without using a scoring operation. In this study, we have attempted both strategies, and our resultant findings broaden our understanding of the issues associated with the folding operation.

Folding without scoring:

In this approach, we used the discussed experimental apparatus, assembled with folding discs without scoring features in an effort to achieve simple folds. The following issues were encountered during tests ran with the non-scoring strategy:

1. Difficulty feeding the thin-film into the entrance folding stand due to misalignment and slipping.

Figure 4-6: Experimental apparatus assembled with non-scoring discs, view 1

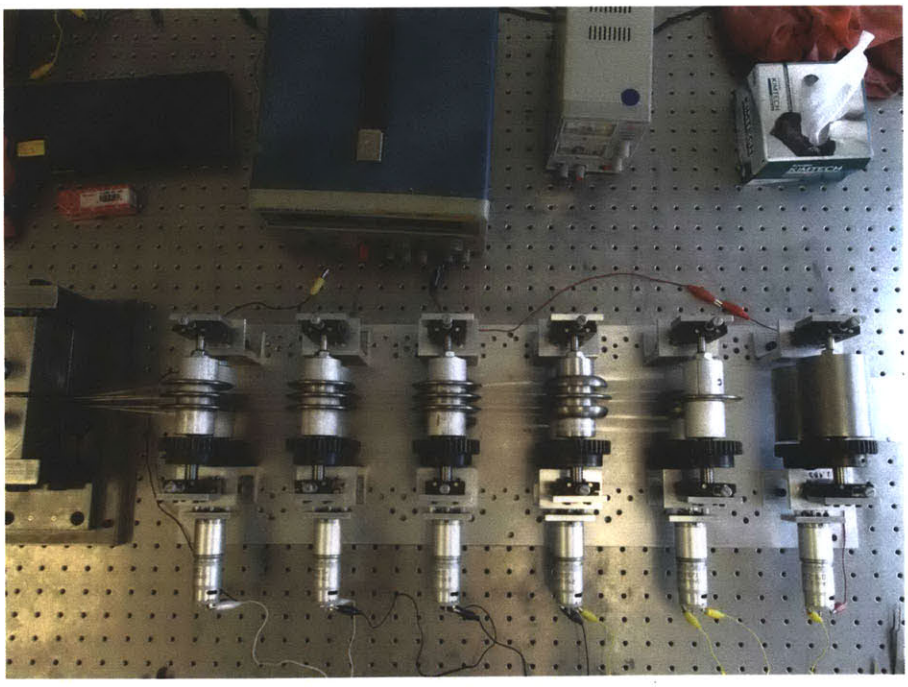

Figure 4-7: Experimental apparatus assembled with non-scoring discs, view 2

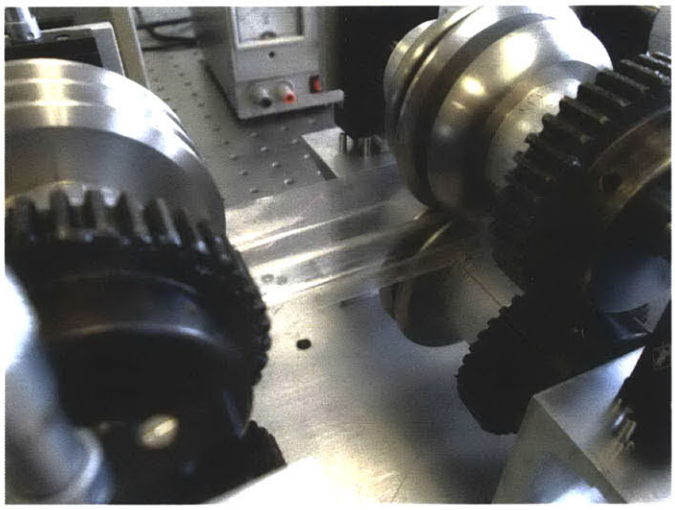

Figure 4-8: Thin-film undergoing folding process without scoring.

2. Difficulty maintaining the alignment of the thin-film while passing through the folding stands due to drifting.

We were able to achieve folding without scoring and results are shown in Figures 4-6 and 4-7, however the process was difficult to control due to the aforementioned issues.

Folding with scoring:

In this approach, we first scored the thin-film, then sought to create folds. Figures 4-11 and 4-10 show the scored and folded thin-film entering the traction rollers. The following observations were made during these operations:

1. Scoring of the thin-film developed a distinct line for folding and facilitated alignment control.

2. Due to the thin-film thickness variation, it was sometimes difficult to precisely control the depth of the score.

The scoring process was tested at varying depths and it was found that at lower depths, incomplete scoring would lead to inconsistent folding, often leading the thin-film to drift and bind the system. In contrast, sufficient scoring led to more a more consistent folding process. The resulting folded thin-films are shown in Figures 4-12 and 4-13. Microscopic images of thin-films with several scoring depths are shown shown in Figures 4-14 and 4-15.

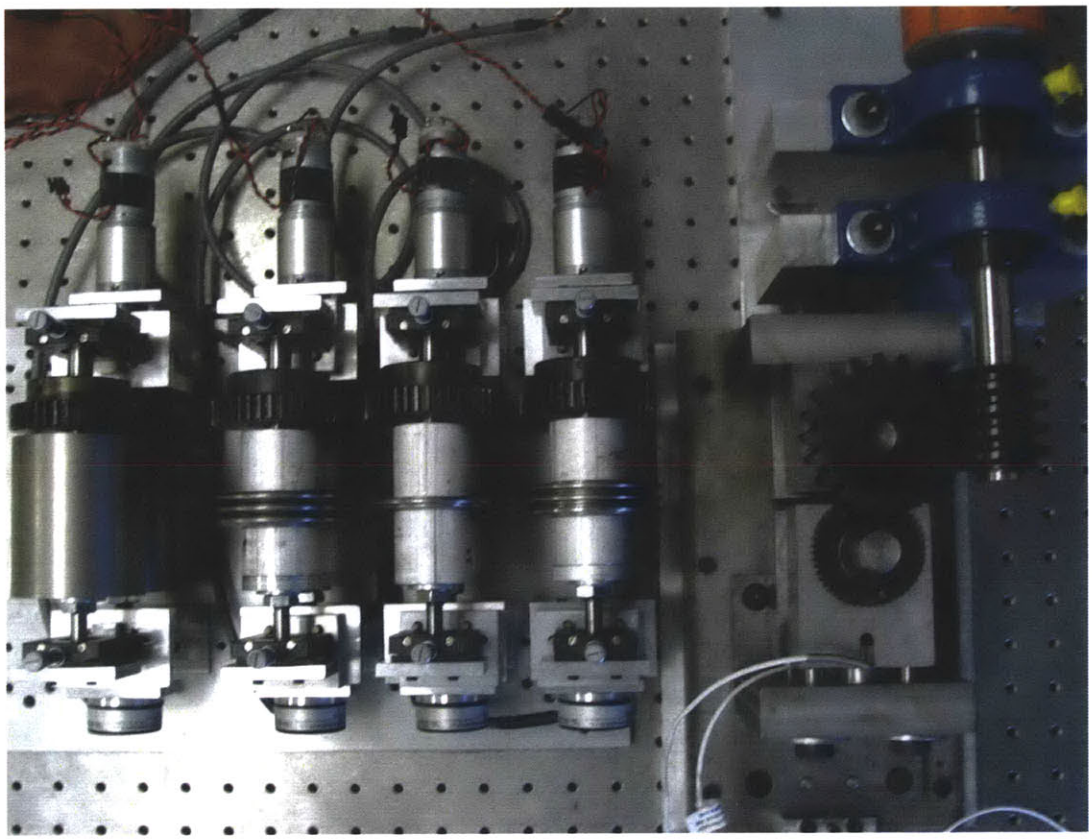

Figure 4-9: Experimental apparatus assembled with scoring discs, view 1

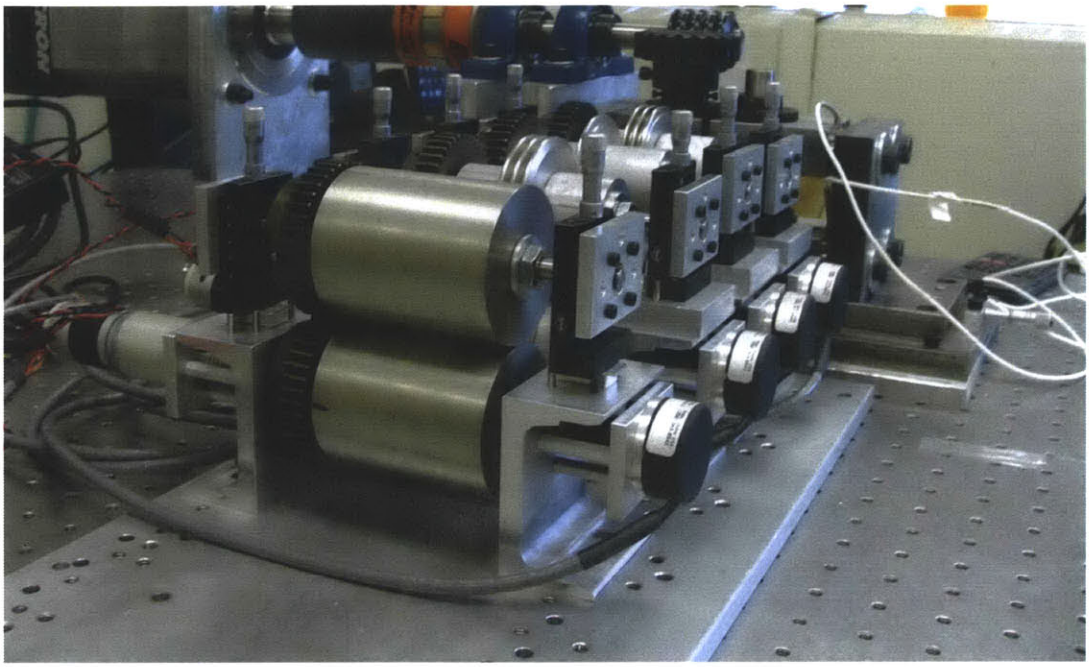

Figure 4-10: Experimental apparatus assembled with scoring discs, view 2

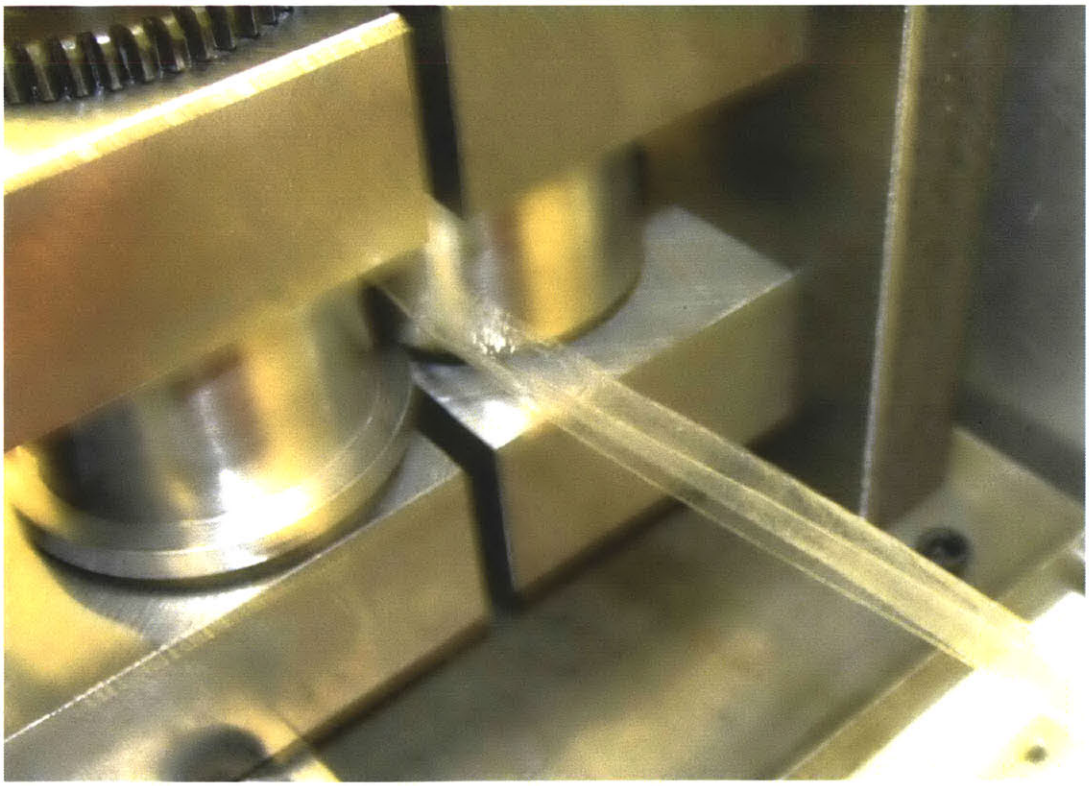

Figure 4-11: Scored thin-film exiting final traction rollers.

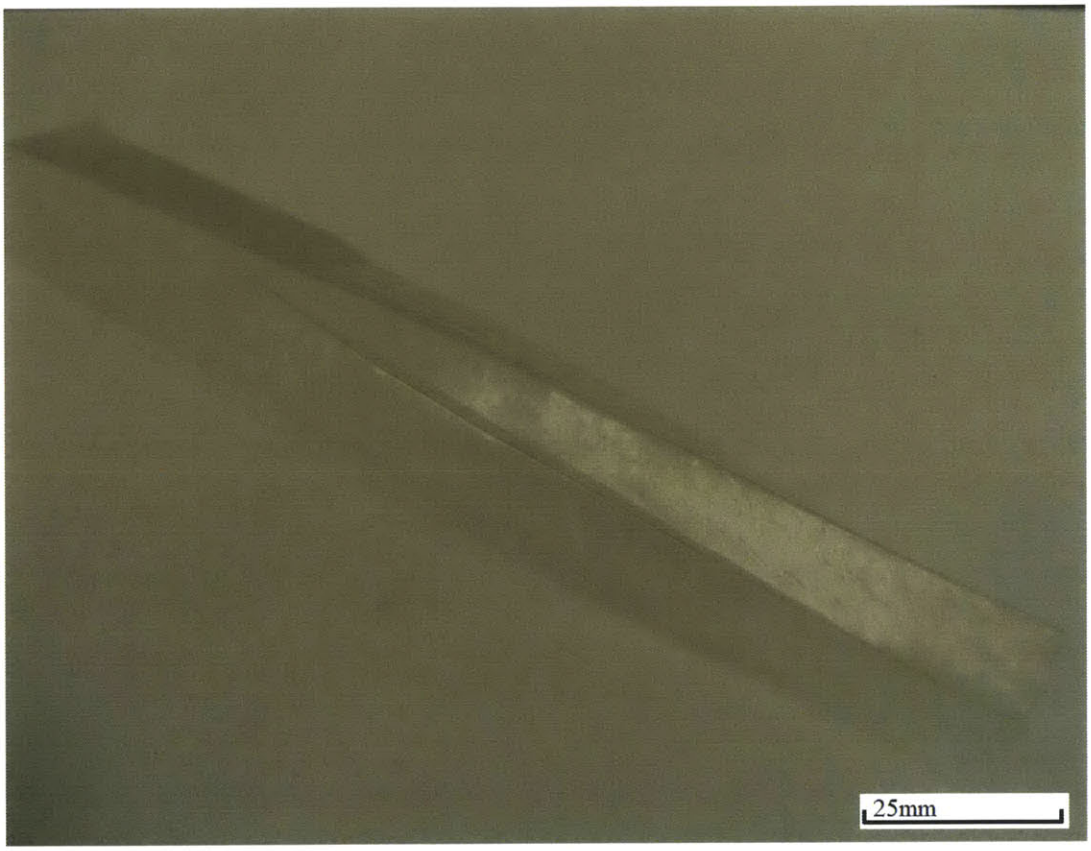

Figure 4-12: Folding with partial scoring and drifting defects.

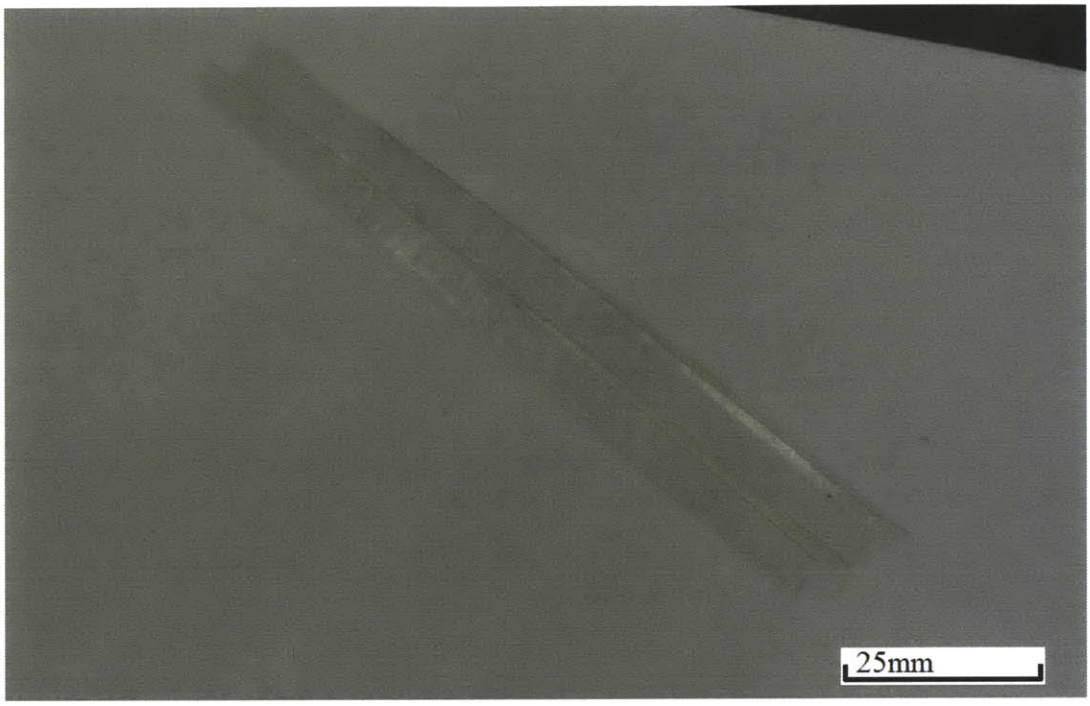

Figure 4-13: Scored thin-film output specimen.

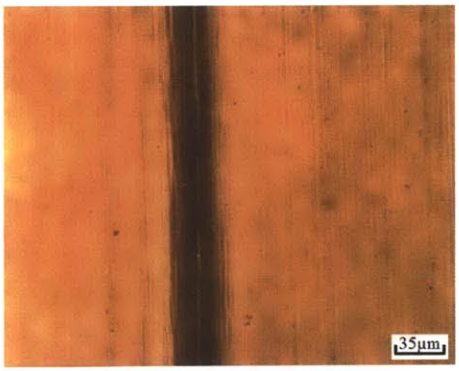

Figure 4-14: Microscopic image of scoreline with $w = 69.8\mu m$, $d_s = 34.9\mu m$.

Figure 4-15: Microscopic image of scoreline with $w = 33.3\mu m$, $d_s = 16.7\mu m$.

The experimental apparatus developed in this study was used to investigate thin-film folding with and without the use of a scoring operation. Folding could be achieved using either strategy with appropriate process parameters, although scoring appears to have made the process more robust to the current system and input imperfections. From these preliminary tests, several useful observations were noted, but more analysis and testing is required to more fully determine the operating range for either strategy in order to produce a higher number of folds with greater consistency.

Chapter 5

Conclusions and Future Work

Rollforming processes have been widely employed in the past for a variety of applications. In this work, we sought to leverage this past knowledge base and undertook the task of developing a rollforming folding strategy for the continuous manufacturing of pharmaceutical thin-films. The focus of this thesis was to investigate the steps of folding in detail for the overall strategy of liquid solvent casting, folding, bonding and shaping of thin-films in a continous tableting operation.

First, existing rollforming processes were analyzed and theoretical investigations were carried out on the bending, or folding, of a notched, or scored, specimen. This was done in light of the fact that notches facilitate the bending of an element and increase the endured stress. The overall folding operation depended upon the thin-film material properties, loading conditions and the dimensions of the score. These elements provided the guidelines for later development of a scoring strategy for folding.

An experimental apparatus was designed and assembled to test and further develop the process for folding thin-films. The apparatus consisted of a film-feeding module, followed by a set of rollforming stations to carry out folding, and traction rollers to provide the necessary forward drive for the thin-films. Mechanical characterization of the thin-films was performed and the properties were found useful in the design of the setup. The flexibility and modularity of the setup allowed for the convenient interchange of the parts.

Two folding strategies were proposed: (a) folding without scoring and (b) folding with scoring. In folding without scoring, the goal was to operate within the elastic regime of the

thin-film without causing significant plastic deformation. Whereas in folding with scoring, local plastic deformation was introduced to form creases to initiate and guide the process. Both strategies were found to be successful with certain advantages and disadvantages to each.

In folding without scoring, input misaligment and system inaccuracy, namely assembly run-out, were major issues that negatively affected the process. The key challenge in scoring is to achieve an appropriate penetration depth, without cutting through the material. Overall, the folding operation can be categorized into three regimes: (i) negligible or no scoring (ii) sufficient scoring, and (iii) excessive scoring or tearing. The middle regime of sufficient scoring is desirable so that consistent folding without failure may be achieved.

In future work, both strategies could be explored for a larger number of folds. Regarding the experimental apparatus, a more accurate assembly and controls process is recommended, along with improved process control in solvent casting. The experimental thin-films had a thickness of approximately $132 \pm 15 \mu m$. This variation in thickness, combined with the machine assembly error during operation, resulted in a varying score depth and thus hindered the goal of uniform scoring and folding. This non-uniformity affected the local stiffness near the fold, leading to inconsistent and often negative results. A more uniform thin-film thickness would likely have a profound impact in enabling a more consistent folding process.

In the future, more thorough estimates and modeling techniques could be employed to devise a more appropriate and detailed model for thin-film rollforming. The findings made in this study should guide the development of future processes and machines for use in continuous thin-film tableting.

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