DEVELOPMENT AND CHARACTERIZATION OF ALBUTEROL SULFATE LOADED TRANSDERMAL PATCHES WITH HME COUPLED FDM 3D PRINTING

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DEVELOPMENT AND CHARACTERIZATION OF ALBUTEROL SULFATE LOADED TRANSDERMAL PATCHES WITH HME COUPLED FDM 3D PRINTING

A Thesis
presented in partial fulfilment of requirements
for the degree of Master of Science
in the Department of Pharmaceutics and Drug Delivery
The University of Mississippi

Bhavana Chivukula
December 2021
ABSTRACT

Albuterol sulfate is a short-acting selective Beta 2 Adrenergic agonist. It is used to treat and prevent bronchospasm associated with asthma, bronchitis, and other breathing disorders. It is known to show extensive first pass metabolism and it requires frequent dosing which makes it difficult for patients to comply. To avoid these problems, transdermal route of delivery of Salbutamol was explored. Traditional methods of preparation of transdermal drug delivery systems involve the use of solvents and have multiple processing steps. To avoid the usage of solvents and decrease the processing steps, HME Coupled FDM 3D printing can be used. Different polymers such as Polyox WSR N-80, Eudragit RSPO, Kollidon VA64, Parteck MXP Polyvinyl Alcohol, Kollidon 12PF, Polyox WSR 301, Affinisol 100 LV were used in combination with the drug to extrude filaments with 11mm Twin Screw Extruder and then printed into patches with Prusa ik MK3 FDM 3D printer. The patches were characterized for their thermal behaviour with Differential Scanning Calorimetry (DSC), for drug content, weight variation, thickness, folding endurance, patch burst strength with Texture Analyser (TA), moisture content, in-vitro drug release in Vertical Franz Diffusion cells. Patches with drug release of 99.8± 0.2 (mean± SD) at 24 hours were formulated.
DEDICATION

This work is dedicated to all the women who made me

Mrs. Aruna Chivukula,

Mrs. Ch. Annapurna Visalakshi, Late Mrs. Kamakoti Chivukula, Dr. Latha Chaturvedula,

Dr. Kumari Chivukula, Late Mrs. Rajeswari, Late Ms. Bharati.

You walked so that I could run.
LIST OF ABBREVIATIONS

DSC- Differential Scanning Calorimetry
3D- Three Dimensional
ERSPO- Eudragit RSPO
FDM- Fused Deposition Modelling.
HME- Hot Melt Extrusion
IUPAC- International Union of Pure and Applied Chemistry
PBS- Phosphate Buffer Saline
PEO- Poly Ethylene Oxide
PVA- Poly Vinyl Alcohol
RPM- Revolutions Per Minute
SBT- Salbutamol
SD- Standard Deviation
TA- Texture Analyser
TDDS- Transdermal Drug Delivery Systems
Tg- Glass transition Temperature
UV- Ultra Violet
WHO- World Health Organization.
ACKNOWLEDGMENTS

I would like to thank my advisor Dr. Michael A. Repka for his guidance and support. I express my heartfelt gratitude to my committee members Dr. Walter G. Chambliss and Dr. Eman Ashour for their valuable time and expertise.

I would like to extend my heartfelt thanks to Dr. Suresh Bandari for their valuable inputs without which this project would not have come through.

I would like to acknowledge my colleagues Sagar Narala, Soo Yeon Chung and Deeksha Reddy Jakka for their support and help during the experiments. I profusely thank my friends Deeksha Reddy Jakka, Soo Yeon Chung and Priyanka Srinivasan for their encouragement and moral support throughout. And I thank all of the members of the department of Pharmaceutics and Drug Delivery for helping me in this journey.

Last but not the least, I would like to thank my dearest Father, Mother and darling Brother and Grandparents for their unconditional love, never ending support and encouragement. I am forever indebted to you all.
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CHAPTER I. INTRODUCTION

Asthma is a chronic inflammatory disease of the respiratory system, characterized by hyperresponsiveness of tracheobronchial smooth muscles to various stimuli. Along with narrowing of air tubes, it is often accompanied by increased mucus secretion, mucus plugging and mucosal edema.

It is a long-term condition and it plagues both adults and children. There are common triggers involved in the clinical expression of asthma. These can vary from person to person. Some of them include, dust, smoke, viral infections, fumes, weather changes, pollen, animal fur/feathers, strong perfumes etc.

According to WHO, asthma is often under-diagnosed and under-treated, in low and middle income countries. People with untreated asthma face challenges like sleep disturbances, tiredness during the day and poor concentration decreasing the quality of life.\[14][15][16].

Albuterol sulfate is a short-acting selective Beta 2 Adrenergic agonist. It is used to treat and prevent bronchospasm associated with asthma, bronchitis, and other breathing disorders. Albuterol sulfate has higher specificity for pulmonary beta receptors in comparison to Beta 1-adrenergic receptors. Albuterol sulfate is one of the most commonly prescribed drugs for asthma. Albuterol sulfate is available in the following dosage forms and strengths: Aerosol metered-dose albuterol inhaler (90 mcg (base)/ actuation, equivalent to 108 mcg albuterol sulfate), Powder metered-dose albuterol inhaler (90 mcg (base)/actuation, equivalent to 108 mcg albuterol sulfate), Tablet- 2 mg, 4 mg, Tablet (extended release)- 4 mg, 8 mg, Nebulizer solution- 0.083%, 0.5%, 1.25 mg/ 3 ml, 0.63 mg/3 ml, Syrup- 2 mg/5 ml. The dosing considerations for asthma maintenance- should be given as
follows: Nebulizer solution: 2.5 mg 2/3 times / day and 1.25-5 mg every 4-8 hours as needed for quick relief, Aerosol metered-dose inhaler: 180 mcg (2 puffs) inhaled orally every 4-6 hours, not exceeding 12 inhalations/ 24 hours, Powder metered-dose inhaler: 180 mcg (2 puffs) inhaled orally every 4-6 hours, not to exceed 12 inhalations/ 24 hours, one inhalation (90 mcg) every 4 hours maybe sufficient in some patients, Tablet and syrup 2-4 mg orally every 6-8 hours: not to exceed 32 mg/day, extended release: 8 mg orally every 12 hours not to exceed 32 mg/day. Albuterol sulfate undergoes extensive first-pass metabolism. Systemic bioavailability is 50%. It requires frequent administration by the oral route. The strengths available for the inhalation route requires dosing every 4-6 hours for relief. More frequent administration is not recommended. In order for the drug to be bioavailable, proper inhalation technique is required which varies every time from patient to patient. The performance can differ based on the type of device. Transdermal drug delivery offers advantages compared to oral, injectable and inhaler options, such as:

- Improved systemic bioavailability due to avoidance of first pass metabolism by the liver and digestive system (comparison with oral route).
- The controlled constant drug delivery profile
- Frequency of dosing can be decreased, longer duration of action with single application which increases patient compliance (comparison with oral and inhalation route).
- Undesirable side effects can be reversed just by removing the patch (comparison with injectable route).

**Section 1.1 Transdermal Drug Delivery System**

TDDS offers effective drug delivery, which is painless and easy to use. A transdermal patch
involves the application of the formulation onto intact and healthy skin where the drug penetrates through several layers of skin into the systemic circulation. The patch consists of components such as, a liner (protection to the patch in storage), drug reservoir (which consists of the drug), release membrane, adhesive and clear backing (to protect the patch from outside contamination). The drug can be in a single layer/ multi-layer incorporated into adhesive, it can be separate as a reservoir or the drug can be in a semisolid matrix. There are several studies in which transdermal patches of Albuterol sulfate were attempted to evade the first-pass metabolism and avoid continuous drug administration Albuterol sulfate can be safely delivered through the skin with the help of TDDS. [27] – [30], [41], [44].

FIGURE A

FIGURE B

FIGURE 1.1 Figure A- Matrix type transdermal system, Figure B- Reservoir type transdermal system- Source FDA Transdermal and Topical Delivery Systems DRAFT GUIDANCE. [32].
Section 1.2 Physiology of Skin:

The human skin is the second largest organ that is the outermost covering of the body. The skin has several layers histologically divided into the epidermis, the dermis, and the hypodermis.

The epidermis is waterproof and serves as a barrier to infection. There is a non-viable and viable epidermis. The non-viable part of the epidermis is the stratum corneum. The viable epidermis is made of several sublayers including stratum basale (basal cell layer), stratum spinosum (prickle cell layer), stratum granulosum (granular cell layer), and stratum lucidum (clear layer).

The dermis has a rich supply of blood vessels, sebaceous glands, sweat glands, and hair follicles. The dermis has sublayers such as the papillary layer, reticular layer.

The hypodermis or subcutis is an elastic layer and includes a large number of fat cells. The thickness of this layer varies from body region to body region and person to person.

The main route of permeation of the drug is through the stratum corneum (horny layer), around its cells called corneocytes. The corneocytes size depends upon the site of the body which regulates the permeation. [30][31]

Section 1.3 Routes of drug penetration through the skin:

The trans-epidermal pathway/route of drug penetration is divided into two types

- The transcellular route, where the drug passes through the cytoplasm of corneocytes and the lipid arrangement of the stratum corneum. Water-soluble molecules are largely transported in this route.

- The intercellular route, where the drug passes through endogenous lipid within the stratum corneum.

A molecule must partition and diffuse through several lipid lamellae and keratinocytes which is not very favorable for many drugs. In the case of transdermal patches, the absorption occurs
through a slow process of diffusion driven concentration gradient, requiring for the drug to be kept in continuous contact with the skin for a considerable time.\textsuperscript{30} \textsuperscript{31}

Section 1.4 Drug Profile and Pre-Formulation Parameters of Albuterol sulfate for Transdermal route of delivery:

- Albuterol sulfate
- IUPAC Name: 4-[2-(tert-butylamino)-1-hydroxyethyl]-2-(hydroxymethyl)phenol; sulfuric acid
- Molecular Formula: C\textsubscript{26}H\textsubscript{44}N\textsubscript{2}O\textsubscript{10}S
- Molecular weight: 576.7\textsuperscript{33}
- Log P: 0.11\textsuperscript{41}

![Figure 1.2 Structure of Albuterol and Albuterol sulfate Source Pubchem \textsuperscript{33}]

Section 1.5 Hot-Melt Extrusion coupled with FDM 3D printing:

For the preparation of transdermal patches hot melt extrusion coupled FDM 3D printing can be explored because:
• Hot melt extrusion maybe used to disperse the drug in a given matrix at molecular level.
• 3D printing of the filaments can help with the personalization of the patch in terms of shape, size, pattern etc.
• It is a versatile, safe and user friendly technique with a wide range of commercial machines with high to low budget ranges.

**Mechanism of Hot Melt Extrusion:**

HME is a continuous process where the drug is mixed with carriers in solid form, to which heat and pressure is applied to melt or soften materials through an orifice to produce filaments of uniform shape and density. The extruder is the main component of HME which has some basic elements assembled like the extrusion barrel, rotating screws in the barrel with rotating screws, die and motor. The extruder also contains heaters that provide heat for the melting or softening of materials. The rotating screws can provide shear stress, intense mixing of the materials. The heat and the mixing causes the materials to melt and the screws convey the material down the barrel. This extruder is controlled through a central electrical control. Some of the processing parameters that can be controlled are screw speed in revolutions per minute (RPM), feed rate, temperature along the barrel and die and the vacuum level for devolatilization.

**Mechanism of Fused Deposition Modelling:**

In FDM 3D printing the drug loaded filaments are fed into the printer which are then melted and softened and extruded out of the printer head onto the build plate as many layers each of which is fused together. These layers cool down and solidify and other layers are added on top of it until the printing is finished. [35][36].

Objective: The aim of this study was to prepare albuterol sulfate loaded transdermal patches by HME coupled FDM 3D printing, to decrease dosing frequency and overcome the problem of first pass metabolism.
### CHAPTER II MATERIALS AND METHODS

#### Section 2.1 MATERIALS AND INSTRUMENTS

Table 2.1: List of Materials

<table>
<thead>
<tr>
<th>S.No</th>
<th>Materials</th>
<th>Chemical name of the polymers</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Salbutamol sulfate (albuterol sulfate)</td>
<td>Poly(2-ethylhexyl methacrylate-copolymer trimethylamine methacrylate)</td>
<td>Sheerji Pharma, India.</td>
</tr>
<tr>
<td>2</td>
<td>PolyoxWSR N-80 (PEO WSR N-80)</td>
<td>Poly(ethylene oxide) mw. 200,000.</td>
<td>Colorcon, USA.</td>
</tr>
<tr>
<td>3</td>
<td>Kollidon VA64</td>
<td>Copovidone, VP/VAc copolymer 60/40</td>
<td>BASF, Germany.</td>
</tr>
<tr>
<td>4</td>
<td>ParteckMXP</td>
<td>Poly vinyl alcohol</td>
<td>Millipore Sigma, Germany.</td>
</tr>
<tr>
<td>5</td>
<td>Eudragit RSPO</td>
<td>Poly(ethyl acrylate-co-methyl methacrylate-co-trimethylammonioethyl methacrylate chloride) 1:2:0.1</td>
<td>Evonik Nutrition and care, Germany</td>
</tr>
<tr>
<td>6</td>
<td>Kollidon 12PF</td>
<td>Povidone(e), polyvidone, soluble</td>
<td>BASF, Germany</td>
</tr>
<tr>
<td></td>
<td>Polymers</td>
<td>Description</td>
<td>Supplier</td>
</tr>
<tr>
<td>---</td>
<td>--------------------------</td>
<td>------------------------------------------</td>
<td>-----------------------------------</td>
</tr>
<tr>
<td>7</td>
<td>Polyox WSR 301 (PEO WSR 301)</td>
<td>Poly (ethylene oxide) mw 4,000,000.</td>
<td>Dupont, Germany.</td>
</tr>
<tr>
<td>8</td>
<td>Affinisol 100LV</td>
<td>HPMC HME</td>
<td>Dupont, Germany.</td>
</tr>
<tr>
<td>9</td>
<td>Methanol</td>
<td></td>
<td>Fisher Scientific, USA.</td>
</tr>
<tr>
<td>10</td>
<td>PBS10X Solution</td>
<td>Phosphate buffer saline</td>
<td>VWR, Germany</td>
</tr>
</tbody>
</table>

**Instruments:**

For Hot Melt Extrusion: 11 mm Twin Screw Extruder, Thermo Scientific, USA.

For FDM 3D printing: Prusa i3 MK3 Printer, Czech Republic.

For DSC: TA Instruments, USA.

For Three point bend test: Texture Analyzer TAXT2i with TA-92N Three point bend rig, with a testing knife, Stable Microsystems/Texture Technologies Corporation, UK.

For spectrophotometric analysis: Thermo Scientific Genesys UV Visible Spectrophotometer, USA.

For Burst Strength: Texture Analyzer TA XT2i with TA 8 Ball Probe and TA-108s5 Small Film Extensibility Rig, Stable Microsystems/Texture Technologies Corporation, UK.

For In vitro Drug Release: Vertical Franz Diffusion Cells with a volume of 5 ml and contact area 0.64 cm² Logan Instruments Corp, USA.

**Section 2.2 METHODS:** [27]-[29] [38]-[40]

**2.2.1 Preparation of hot melt extrudates:**

The polymers and drug of batch size 30 g were hand mixed and sieved through 30 mesh to get a
uniform mixture without lumps. The drug polymer mixture was placed in a container (filled to 3/4 of the container) and placed in a laboratory size V-Blender for 15-20 minutes (based on the polymer flowability) to get a uniform mixture. The blend was extruded through an 11 mm Twin Screw Extruder (Thermo Scientific, USA.) with a 1.5 mm diameter die.

Table 2.2 Composition of Formulations

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>AFFINISOL 100LV + SBT 95:5</td>
</tr>
<tr>
<td>F2</td>
<td>AFFINISOL 100LV + SBT 90:10</td>
</tr>
<tr>
<td>F3</td>
<td>PEO WSR N-80 + SBT 95:5</td>
</tr>
<tr>
<td>F4</td>
<td>KOLLIDON VA64 + SBT 95:5</td>
</tr>
<tr>
<td>F5</td>
<td>EUDRAGIT RSPO + SBT 90:10</td>
</tr>
<tr>
<td>F6</td>
<td>KOLLIDON 12PF + SBT 90:10</td>
</tr>
<tr>
<td>F7</td>
<td>PEO WSR 301 + SBT 90:10</td>
</tr>
<tr>
<td>F8</td>
<td>PVA + SBT 90:10</td>
</tr>
<tr>
<td>F9</td>
<td>PEO WSR N-80 + KOLLIDON VA64 + SBT 80:10:10</td>
</tr>
<tr>
<td>F10</td>
<td>PEO WSR N-80 + KOLLIDON VA64 + SBT 60:30:10</td>
</tr>
<tr>
<td>F11</td>
<td>PEO WSR N-80 + EUDRAGIT RSPO + SBT 85:5:10</td>
</tr>
<tr>
<td>F12</td>
<td>PEO WSR N-80 + EUDRAGIT RSPO + SBT 80:10:10</td>
</tr>
<tr>
<td>F13</td>
<td>PEO WSR N-80 + EUDRAGIT RSPO + SBT 60:30:10</td>
</tr>
<tr>
<td>F14</td>
<td>PEO WSR N-80 + EUDRAGIT RSPO + SBT 30:60:10</td>
</tr>
<tr>
<td>F15</td>
<td>KOLLIDON 12PF + PEO WSR N-80 + SBT 60:30:10</td>
</tr>
</tbody>
</table>

FIGURE 2.1 Screw Configuration used to prepare the filaments Source European journal of Pharmaceutical sciences [37]
2.2.2 FDM 3D Printing of the hot melt extrudates:

The patch was designed in TinkerCAD (USA) and the filaments were printed in a Prusa i3 MK3 printer (Czech Republic), with the Ultimaker Cura (Netherlands) software. The filaments which were of thickness ranging from 1.5-1.7 mm were loaded into the printer and printed with the parameters listed below.

Table 2.3 Parameters set in the FDM 3D Printer.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patch shape</td>
<td>Circular</td>
</tr>
<tr>
<td>Dimensions</td>
<td>20 x 20 mm diameter, thickness 0.2 mm.</td>
</tr>
<tr>
<td>Profile</td>
<td>Fine 0.2 mm</td>
</tr>
<tr>
<td>Layer height</td>
<td>0.1 mm or 0.2 mm</td>
</tr>
<tr>
<td>Wall thickness</td>
<td>0.8 mm</td>
</tr>
<tr>
<td>Wall line count</td>
<td>2</td>
</tr>
<tr>
<td>Top bottom layers and thickness</td>
<td>1-2 layers, 0.1-0.2mm</td>
</tr>
<tr>
<td>Infill Density</td>
<td>100.0%</td>
</tr>
<tr>
<td>Infill Pattern</td>
<td>Zig Zag</td>
</tr>
<tr>
<td>Printing temperature</td>
<td>180.0 °C</td>
</tr>
<tr>
<td>Build Plate temperature</td>
<td>50.0-60 °C</td>
</tr>
<tr>
<td>Print speed</td>
<td>60.0 mm/S</td>
</tr>
</tbody>
</table>

The dimensions were chosen to achieve a patch weight of 50mg with 5mg drug load. (It is reported that a 5 mg drug load would help with the flux rate to obtain steady state serum concentration enough to improve the symptoms of asthma.)\textsuperscript{41,46}
Section 2.3 EVALUATION METHODS: [27]-[29],[38],[40]

The extruded filaments were tested for printability with three point bend test. The prepared patches were evaluated for thermal characterization (DSC), Drug content, Weight variation, Thickness, Folding endurance, Patch Burst strength, Moisture Content, In-vitro drug release.

2.3.1 Thermal Characterization by differential scanning calorimetry (DSC):

The characteristic peaks of the drug and the polymer from the extruded filaments and patches and the polymer-drug blend (physical mixture) is measured using Differential Scanning Calorimetry (TA Instruments, USA). The materials were placed in aluminum pans and heated to 230 °C at a rate of 10 °C/min and the thermograms were recorded.

2.3.2 Three Point Bend Test:

The strength of the filaments (required to print through the FDM 3D printer) was tested by Texture Analyzer TAXT2i with TA-92N three point bend rig, with a testing knife, Stable Microsystems/Texture Technologies Corporation, UK. Six filaments of length 6 cm were placed individually on the testing rig and the testing knife was lowered until the filament broke. The samples were acceptable if the time taken to break the filaments is more than 1 second.

2.3.3 Percent drug content:

The percent drug content in the filaments and patches were determined by using UV-Visible Spectrophotometry (Thermo Scientific Genesys UV Visible Spectrophotometer, USA). The filaments and patches were weighed and completely dissolved (no visible particles or agglomerations) in 50 ml of water: methanol (1:1) mixture for 24 hours and sonicated for two hours. The solution was filtered through a 0.45 um filter. The mixture was appropriately diluted (Dilution factor 100) and measured at 226 nm spectrophotometrically. A calibration curve was constructed with 0.5, 1, 2.5, 5, 10, 25, 50, 100 ug/ml dilutions made from 1000 ug/ml prior to this
with the drug dissolved in water:methanol (1:1).

PERCENT DRUG CONTENT = Amount of Drug*100/Dose

2.3.4 Weight variation:
Six patches were tested for weight variation and the mean standard deviation was reported.

2.3.5 Thickness:
Six patches were tested for variation in thickness by placing them in between glass slides and the thickness of the setup was measured with Vernier calipers and the mean standard deviation.

2.3.6 Folding endurance:
Six patches were tested for their strength and endurance to fold by repeatedly folding the patches in the same place until the patch was completely broken into pieces.

2.3.7 Patch burst strength:
The burst strength (kg/cm²) of a patch is the force required to break a patch, which is an indicator of its strength. It was measured in the Texture analyzer Texture Analyzer TA XT2i with TA 8 Ball Probe and TA-108s5 Small Film Extensibility Rig, (Stable Microsystems/Texture Technologies Corporation, UK.), using a ball probe. The patch was placed in the rig and the test was performed.
Table 2.4 Parameters set in the T.A.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Measure force in compression.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mode</td>
<td>Return to start</td>
</tr>
<tr>
<td>Option</td>
<td>Pre-test speed 2 mm/s</td>
</tr>
<tr>
<td>Test speed</td>
<td>1 mm/s</td>
</tr>
<tr>
<td>Post-test speed</td>
<td>10 mm/s</td>
</tr>
<tr>
<td>Target mode</td>
<td>Distance</td>
</tr>
<tr>
<td>Distance</td>
<td>5 mm</td>
</tr>
<tr>
<td>Trigger type</td>
<td>Auto</td>
</tr>
<tr>
<td>Trigger force</td>
<td>5 g</td>
</tr>
<tr>
<td>Stop plot at</td>
<td>Target position</td>
</tr>
<tr>
<td>Tare mode</td>
<td>Auto</td>
</tr>
</tbody>
</table>

2.3.8 Percent moisture content:

Six patches were weighed and placed in a desiccator with AlCl3 Crystals for 24 hours and checked for difference in weight.

Percent moisture content = \[ \frac{\text{Initial weight} - \text{Final Weight}}{\text{Initial weight}} \] *100

2.3.9 In-vitro drug release:

In-vitro drug release of the patches was tested by using the Franz diffusion cell apparatus (Vertical Franz Diffusion Cells with a volume of 5 ml and contact area 0.64 cm² Logan Instruments Corp, USA). The cells were prepared by washing with methanol and water (1:1) mixture and set aside to dry. The prepared patches were placed on the donor chamber and clamped down to the cell body in which the receptor medium of Phosphate Buffer Saline 7.4 (5 ml) was maintained at 32±0.5 °C. Samples were withdrawn from the sample port at 15 min, 30 min, 45 min, 60 min, 90 min, 120
min, 180 min, 240 min, 360 min, 480 min and 24 hours. The number of samples for each type of patch was 3. The withdrawn samples were diluted appropriately with the PBS and measured in UV Spectrophotometer at 226 nm. The membrane used was a Nylon membrane of pore size 0.22 μm. The amount of drug release at each time point was calculated from the linear equation of a calibration curve constructed with appropriate dilutions with PBS. (i.e., 1, 2.5, 5, 10, 25, 50, 100, 200, 500 ug/ml from 1000 ug/ml) The percent drug release was calculated based on the starting amount of the drug.
### CHAPTER III RESULTS AND DISCUSSION

Table 3.1 Polymer Selection Criteria, Extrusion Conditions, Printability, Filament properties (by visual observation), Patch Nature.

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Selection criteria for polymers</th>
<th>Temperature and extrusion conditions.</th>
<th>Filament properties Printability.</th>
<th>Patch nature</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>Suitable for HME, Lower Tg, extended release, no use of plasticizer.[1][2][3]</td>
<td>Temp: Zone 2: 25°C Zone 3-8: 150 °C Die: 170 °C Screw speed: 50-70 rpm.</td>
<td>Hard, No printability, Time</td>
<td>-</td>
</tr>
<tr>
<td>F2</td>
<td>Same as above.</td>
<td>Temp: Zone2 25°C Zone3-8 150°C Die 170°C Screw speed 50rpm</td>
<td>Hard, difficult to extrude. No printability</td>
<td>-</td>
</tr>
<tr>
<td>F3</td>
<td>Film former, extended release, transdermal application, low Tg.[4][10][11]</td>
<td>Temp: Zone 2:25°C Zone3-8 125°C Die 130°C Screw speed 50rpm</td>
<td>Soft, breakable, Printable.</td>
<td>Breakable</td>
</tr>
<tr>
<td>F4</td>
<td>Film former, extended release, transdermal application [5][6]</td>
<td>Temp: Zone2 25°C Zone3-8 165°C Die 165°C Screw speed 20 rpm</td>
<td>No filaments could be extruded, very sticky and hard. No printability.</td>
<td>-</td>
</tr>
<tr>
<td>F5</td>
<td>Transdermal application, extended release[7][8]</td>
<td>Temp: Zone2 25 °C Zone3-8 180°C Die 190°C Screw speed 30 rpm</td>
<td>Hard and brittle filaments. No printability.</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Description</td>
<td>Temperature Details</td>
<td>Characteristics</td>
<td></td>
</tr>
<tr>
<td>---</td>
<td>-----------------------------------------------------------------------------</td>
<td>-----------------------------------------------------------</td>
<td>-----------------------------</td>
<td>---</td>
</tr>
<tr>
<td>F7</td>
<td>Film former, extended release, transdermal application, low Tg.[^4][^11]</td>
<td>Zone 2: 25°C, Zone 3: 8-160°C, Die: 160°C, Screw speed: 50 rpm</td>
<td>Hard filaments, Not printable.</td>
<td>-</td>
</tr>
<tr>
<td>F8</td>
<td>Film former, transdermal application[^12][^13]</td>
<td>Zone 2: 25°C, Zone 3: 8-125°C, Die: 130°C, Screw speed: 20 rpm</td>
<td>Flexible, Not printable.</td>
<td>-</td>
</tr>
<tr>
<td>F9</td>
<td>Combination for stronger filaments/films, extended release</td>
<td>Zone 2: 25°C, Zone 3: 8-125°C, Die: 125°C, Screw speed: 50 rpm</td>
<td>Flexible, Printable</td>
<td>Flexible</td>
</tr>
<tr>
<td>F12</td>
<td>Combination for stronger filaments/films, extended release</td>
<td>Zone 2: 25°C, Zone 3: 8-135°C, Die: 135°C, Screw speed: 50 rpm</td>
<td>Flexible, printable</td>
<td>Flexible</td>
</tr>
<tr>
<td>F13</td>
<td>Combination for stronger filaments/films, extended release</td>
<td>Zone 2: 25°C, Zone 3: 8-135°C, Die: 135°C, Screw speed: 50 rpm</td>
<td>Flexible, printable</td>
<td>Flexible</td>
</tr>
<tr>
<td></td>
<td>Combination for Stronger filaments/films, extended release</td>
<td>Temp: Zone2 25 °C Zone3-8 180°C Die 190°C Screw speed 10rpm</td>
<td>Hard, Brittle, not printable</td>
<td></td>
</tr>
<tr>
<td>----</td>
<td>----------------------------------------------------------</td>
<td>-------------------------------------------------------------</td>
<td>------------------------------</td>
<td>----</td>
</tr>
<tr>
<td>F14</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>F15</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### 3.1 Breakdown of the extrusion and printing results:

Several polymers were screened for hot melt extrusion coupled with FDM 3D printing. The combinations of different polymers and the ratio of the drug were selected based on the extrusion temperature, flexibility of the filaments and later the printability of the filament. Hot Melt Extrusion temperature was desired to be no more than 180 °C to avoid discoloration and softening of the filaments as well as die swelling. The hardness, softness and brittleness described above were visually observed.

The filaments needed to be flexible enough to be fed through the print head in the FDM 3D printer. Temperature higher than 180 °C in the printing was causing clogging of the products (turning from off-white to yellow colour) in the nozzle, which may be indicative of some level of degradation or changes in the composition of the drug and the polymer. And it is undesirable for transdermal applications to be unattractive in color as it will not be acceptable by the patients.

Three combinations that were successful in giving flexible patches for further testing were F9, F12, F13. They are combinations of PEO WSR N-80, Eudragit RSPO and PEO WSR N-80, Kollidon VA64. Increase in the concentrations of Eudragit RSPO or Kollidon VA64 caused the filaments and patches to be brittle. The flexibility was also affected by the drug concentration, as higher concentration of Salbutamol sulphate made the filaments soft, which were not suitable for
printing. The major component in these three formulations is PEO WSR N-80, due to which the filaments were flexible and printable enough. Pure PEO WSR N-80 and the drug combination gave filaments that clogged up the printer nozzle due to its low degradation temperature, hence Kollidon VA64 and Eudragit RSPO were chosen to give the filaments flexibility.

*Polyox WSR N-80 (PEO WSR N-80):*

PEO WSR N-80 is a synthetic polymer obtained by the catalyst of an ethylene oxide monomer. PEO WSR N-80 has a molecular weight of 200 kDa. The polymer is known to show pronounced degradation after 150 °C. It is semi crystalline and is flexible for choosing extrusion temperature due to its glass transition, melting and decomposition temperatures. It has low toxicity in all routes, no skin irritation was reported. It is used as a rate controlling polymer suitable for hotmelt extrusion due to its thermoplastic nature along with good flow and low glass transition temperature. [4]

![FIGURE 3.1 Example of a printed patch of F13.](image)

**3.2 Three point bend test:**

Table 3.2 Three point bend test of the filaments that gave acceptable patches.

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Time in seconds (mean ± SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F9</td>
<td>1.5 ± 0.2</td>
</tr>
<tr>
<td>F12</td>
<td>1.9 ± 0.9</td>
</tr>
<tr>
<td>F13</td>
<td>1.3 ± 0.4</td>
</tr>
</tbody>
</table>
The filaments were broken after 1 second, which was taken as an indicator that they were flexible enough to be printed without breaking and clogging the nozzle of the printer.

3.2 Thermal Characterization (DSC thermograms):

![DSC Thermogram of Albuterol sulfate](image)

*FIGURE 3.2 DSC Thermogram of Albuterol sulfate*
FIGURE 3.3 DSC Thermogram of PEO WSR N-80

Enthalpy (normalized): 169.05 J/g
Onset: x: 61.87 °C
Peak temperature: 69.38 °C
FIGURE 3.4 DSC Thermogram of Kollidon VA64

Enthalpy (normalized): 115.39 J/g
Onset x: 56.03 °C
Peak temperature: 98.91 °C
FIGURE 3.5 DSC Thermogram of Eudragit RSPO

Enthalpy (normalized): 4.1908 J/g
Onset x: 55.38 °C
Peak temperature: 61.05 °C
FIGURE 3.6 DSC Overlays of Drug, PEO, Physical Mixture, Filament and Patch of F9
FIGURE 3.7 DSC Overlays of Drug, PEO N80, Physical Mixture, Filament and Patch of F12
FIGURE 3.8 DSC Overlays of Drug, PEO, Physical Mixture, Filament and Patch of F13

The characteristic peaks of the drug and the polymers were measured as shown in Figure 3.8 the DSC Thermogram overlays of the Physical mixture, Filament and the Patch. Figure 3.8 showed that the peak height of the drug decreased from the physical mixture to filament to patch indicating the change of the physical state of the drug. These changes may be due to the hot melt extrusion temperature and temperature used in 3D printing. The peaks of Kollidon VA 64 and Eudragit RSPO were not sharp and well defined due to their semi-crystalline and amorphous natures respectively (Figure 3.4 and 3.5).
3.3 Percent drug content:

![CALIBRATION CURVE](image)

FIGURE 3.9 Calibration Curve for Albuterol sulfate Content in water : methanol (1:1)

Table 3.3 Albuterol sulfate Content of Filaments and Patches.

<table>
<thead>
<tr>
<th>Formulation No.</th>
<th>% Drug Content Filament (mean±SD)</th>
<th>% Drug Content Patch (mean±SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F9</td>
<td>98.5±0.57</td>
<td>94.3±0.71</td>
</tr>
<tr>
<td>F12</td>
<td>96.3±1.65</td>
<td>92.0±1.80</td>
</tr>
<tr>
<td>F13</td>
<td>98.9±0.25</td>
<td>97.9±0.36</td>
</tr>
</tbody>
</table>
There is a slight decrease in the Albuterol sulfate content from filament to patch, which may be due to the effect of temperature from 3D printing. The percent drug content was also reflective of the type of mixing of the physical mixture, where over mixing (more than 15 minutes in the v-blender) caused significant differences between each sample (either patch or filament) which may be due to the drug being denser than the polymers, causing the drug to separate from the mixture.

### 3.4 Weight variation, thickness, folding endurance, percent moisture content:

Table 3.4 Weight variation, thickness, folding endurance, percent moisture content of patches.

<table>
<thead>
<tr>
<th>Formulation no.</th>
<th>Weight variation (mg) (mean±sd)</th>
<th>Thickness (mm) (mean±sd)</th>
<th>Folding Endurance (no.of folds)</th>
<th>Percent moisture content (%) (mean±sd)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F9</td>
<td>50.7 ± 0.08</td>
<td>0.21 ± 0.002</td>
<td>78 - 80</td>
<td>0.32 ± 0.21</td>
</tr>
<tr>
<td>F12</td>
<td>50.9 ± 1.11</td>
<td>0.22 ± 0.010</td>
<td>66-68</td>
<td>0.24 ± 0.21</td>
</tr>
<tr>
<td>F13</td>
<td>51.1 ± 0.05</td>
<td>0.23 ± 0.010</td>
<td>170-175</td>
<td>0.24 ± 0.21</td>
</tr>
</tbody>
</table>

All of the samples showed low standard deviation and less variability in between each sample for weight variation, thickness and folding endurance. The difference in weight variation was decreased by changing the parameters on the 3D printer suitably as well as avoiding overloading the Print head which gave uniform thickness and less weight variation. In regards to moisture
content, there was no significant difference in the weight of the patches after 24 hours, which may be indicative of less moisture content in the patches.

3.5 Burst strength:

Table 3.5 Patch Burst Strength

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Burst Strength kg/cm² (mean±sd)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F9</td>
<td>4.55 ± 0.18</td>
</tr>
<tr>
<td>F12</td>
<td>4.51 ± 0.10</td>
</tr>
<tr>
<td>F13</td>
<td>3.88 ± 0.30</td>
</tr>
</tbody>
</table>

Increase in Eudragit RSPO ratio from 10 to 30 in the formulation decreased the patch burst strength. Eudragit RSPO is known to make patches and films slightly more brittle.
3.6 In-vitro drug release:

FIGURE 3.10 Calibration Curve for In-vitro Albuterol sulfate Release in PBS 7.4.

Cumulative Percent Release of the patches:

When the patches were placed in the donor cell, it was observed that the F 9 and F 12 patches were rapidly dissolving in the receptor fluid. For F 9 the cumulative drug release was 99.22 ± 0.28 (mean ± SD) at 3 hours and saturation was seen and for F 12 the cumulative drug release was 99.38 ± 0.16 (mean ± SD) at 6 hours, followed by saturation. But for the F 13 patches, the cumulative drug release was 75.7 ± 1.5 % (mean ± SD) was at 8 hours and at 24 hours the cumulative release was 99.8 ± 0.2 (mean ± SD). As Kollidon VA 64 is a rapid release polymer it is showing faster release and increase in Eudragit RSPO ratio is increasing the delay in the release of the drug from the formulation because it is a delayed release polymer.
CONCLUSION:
Several polymer-albuterol sulfate combinations have been screened for extrudability from HME and for printability in FDM 3D Printing for the preparation of transdermal patches. The combinations of PEO WSR N-80, Kollidon VA64 and PEO WSR N-80, Eudragit RSPO gave the most flexible patches. Patches with the highest Eudragit RSPO concentration gave more of an extended release profile whereas the patches with Kollidon VA64 gave faster release. The patches with high Eudragit RSPO would be more suitable to fulfil the objective of preparing extended release albuterol sulfate transdermal patches.

FUTURE STUDIES:
Patch adhesive preparation, compatibility studies.
Ex-vivo permeation studies to assess the permeability and the flux of albuterol sulfate from the matrix, permeation enhancement strategy development.
BIBLIOGRAPHY


VITA

Born in 1997 in Pondicherry, India, BHAVANA CHIVUKULA completed her Bachelor of Pharmacy in Tiruchanoor India. She has completed training in Pharmaceutical manufacturing, analytical method development etc. She also attended several conferences and was an active member of the UM- AAPS Student Chapter 2021. She plans to pursue a job in a Pharmaceutical industry for a few years to strengthen her foundation as a Formulation Scientist and then pursue higher education.