World Journal of Pharmaceutical Science and Research
www.wjpsronline.com
Research Article
ISSN: 2583-6579
SJIF Impact Factor: 3.454
Year - 2023
Volume: 2; Issue: 6
Page: 54-78

DEVELOPMENT OF ORAL DISPERSIBLE TABLETS (ODT) WITH A COMBINATION OF ACTIVE SUBSTANCES WITH HIGH AND LOW SOLUBILITY

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Article Received: 29 September 2023 || Article Revised: 17 October 2023 || Article Accepted: 10 November 2023

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ABSTRACT

Chlorhexidine HCl and Lidocaine HCl with antiseptic and analgesic effect of diseases that cause sore throat and irritation it is used in the symptomatic treatment. The aim of this study is to develop a lozenge product with a combination of active ingredients with high and low solubility contained in low amounts in the formulation, technology transfer processes were carried out. During the trial production, the development studies of Chlorhexidine HCl and Lidocaine HCl raw materials, which are present in low amounts in the formulation, with different production methods were described in detail.

KEYWORDS: Chlorhexidine HCI Lozenge, Lidocaine HCI Lozenge, Dry Granulation, Wet Granulation, Spray Granulation and Technology Transfer.

1. INTRODUCTION

Generic drug or supplement product development processes in solid dosage forms consist of 4 basic methods. We can generally describe these processes as dry mixing, dry granulation, wet granulation and spray granulation. Dry mix production method is the easiest and cheapest production method. The raw materials supplied are produced within the determined processes. It is turned into the final mixture. Development studies with the dry mix method are ongoing; tablet fluidity problem in the final mixture before printing and content uniformity during chemical analysis problems may be encountered. In order to overcome such problems encountered during product development, the production method we call granulation is used.

Granulation is the granulation of powder particles with the help of a binder or mechanical force by combining them into solid, dry aggregates. Mostly tablet although they are intermediate products in the manufacture of capsules or capsules, granules are not the finished product. As a dosage form, for example; effervescent granules, coated granules, granules resistant to the stomach environment, It can be used as modified granules to granulation each powder component in the formulation is homogeneously ıt starts after mixing and is obtained after the granulation process. The granules produced can be packaged as a dosage form or used for tablet printing or it can also be used for capsule preparation. The benefits of the granulation process are as follows:

- Segregation of components in the powder mixture ıt prevents.
- It provides a uniform particle shape and diameter distribution.
- It provides improvement in the flow properties of the mixture.
- It improves the printing properties of the mixture and improves adhesion to the punch surface and reduces the tendency for capping.
- Both compressibility (consolidation) and compressibility, as well as handling and the mixture should be clustered to be more convenient for storage. increases its density.
- It reduces the risk of cross-contamination by reducing pollination and increases employee safety.
- Hygroscopic materials stick to a cake when stored in powder form. The granulation process reduces this possibility because although they absorb moisture, the granules retain their fluidity.

Granulation methods can be classified into two main groups:

1.1. Dry Granulation

Powder particles are turned into aggregates by applying high pressure. Two methods are used for this purpose:

- After pressing the powder mixture into briquette tablets, these tablets are broken and then sieved to form granules (slugging).
- Granule formation (roller compaction) is obtained by compressing the powder mixture between rotating rollers and forming compact structures in the form of strips and sieving them.

These methods are used when printing cannot be corrected by wet granulation and when the materials are sensitive to moisture and heat.

Dry granulation equipment and general information are given as follows[1]

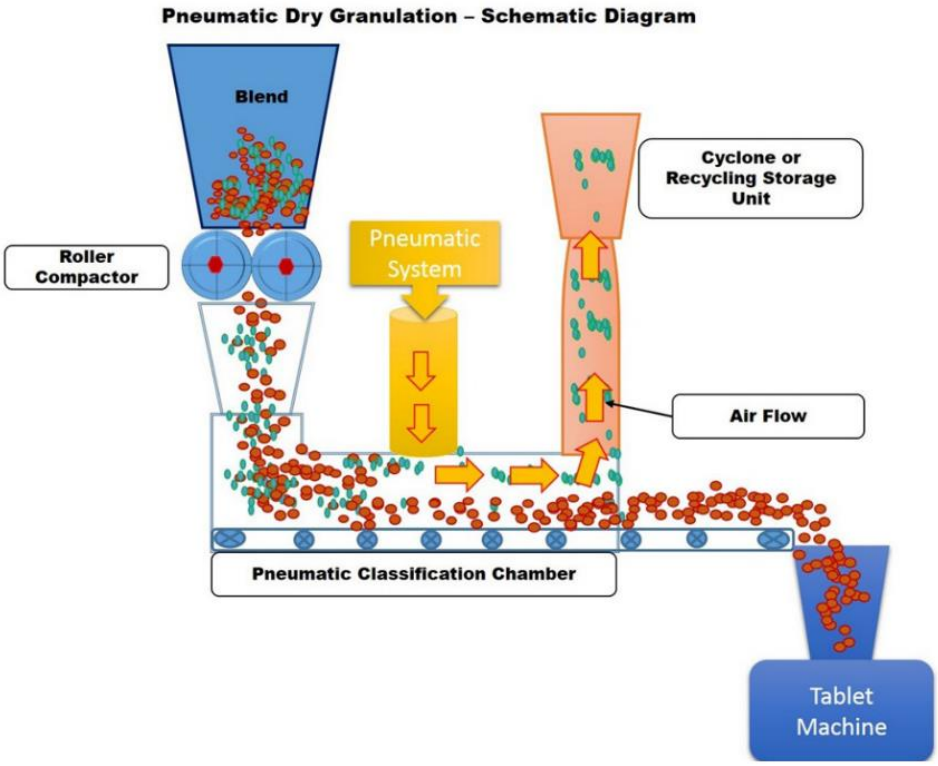


Figure 1: Stages of Dry Granulation Formations.[1]

1.2. Wet Granulation

This method involves turning the powder mixture into a wet mass by adding a liquid. If these liquid, binding substances are added to the solid, powder mixture (as internal binder).

It can be added alone or as a solution or paste containing the binding agent (as an external binder). The resulting wet mass is sieved and dried, and then granules are obtained by sifting again. In wet granulation, high-speed, blade mixers and granulators are used to prepare the wet mass.

With the fluidized bed device, all processes can be carried out in the same system without the need to transfer mass from one device to another. The granulation method and the equipment used ensure adequate liquid distribution and the time and labor required to form a sticky mass significantly affects the intergranular and intragranular porosity.

The quality of tablets depends mainly on the physicochemical properties of the powder or granules from which they are formed. With product validation within the scope of GMP (Good Manufacturing Practices), it is necessary to identify and monitor critical process variables related to the granulation process and use quantitative measurements to ensure that the granulation process is repeatable and under control. In this respect, the factors that need to be examined in granules are as follows[1]:

Mechanism of granule formation factors affecting granule diameter and the effects of granule diameter on processing and dosage form effects on.

Measurement and interpretation of granule diameter distribution;

- Determination of granule shape and surface area
- Granule density and compressibility
- Granule mechanical resistance and brittleness
- Electrostatic properties of granules
- Flow characteristics of granules
- Printability of granules
- Moisture determination of granules

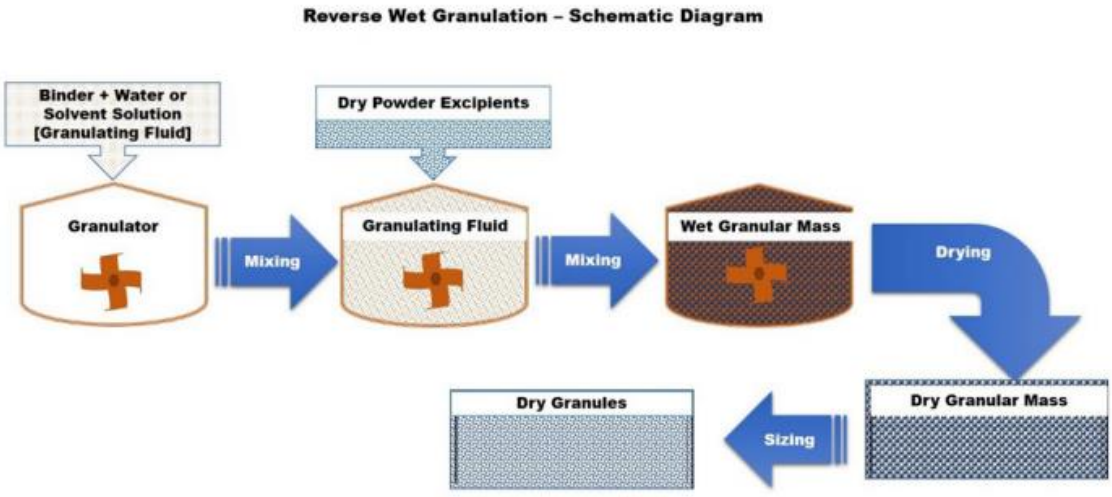


Figure 2: Stages of Wet Granulation Formations[1]

1.3. Spray Granulation in Fluid Bed Dryer

The manufacture of pharmaceutical dosage forms is a complex multi-step process involving many unit operations. Granulation, one of the key operations, is a size-enhancing process where small particles are aggregated into larger masses, either in liquid or solid form, with the help of an added binder. The resulting product is called granules and often has the desired size and microstructural characteristics. The granules are polydisperse and typically vary in size from 0.1 to 3 mm[2] In most cases, granules are intermediate products and are then used to make tablets or capsules. The active ingredient may first be granulated and then mixed with other excipients before the tablet is compressed or the capsule is filled. Alternatively, the active ingredient can be granulated with most or all of the excipients. The granules can also be coated later and filled into capsules.[3] Granules are preferred over fine powders because granulated powders resist segregation, flow better and ensure that the granules flow well through slides and hoppers into tablet molds without significant weight change. Dust is reduced, which minimizes material loss and the dangers of using toxic substances. The increase in bulk density of powders after granulation facilitates storage and transportation. Also, compact properties and appearance of granulated powders are better compared to finely ground powders.[4] Granules are easier to compress and make stronger tablets because of the well distributed links in the granular structure.

In this granulation method, a bed of powder particles supported on top of a liquid distribution plate is made to behave like a liquid by passing a liquid, usually air, with a flow rate exceeding a critical value. The phenomenon where the properties of that liquid are transferred to the layer of solid particles by passing the liquid through it at a speed that brings the solid layer to the most relaxed state possible just before it changes to the liquid state is called fluidization.[5] A fluid bed processor has several main components (Figure 3). These include the control system, air handling unit, product chamber, air expansion chamber, exhaust filters, exhaust fan, air distribution plate, spray nozzle, and finally the binding fluid distribution system.[6] During granulation, the powder particles circulate in the product chamber and create a continuous flow of particles through the dedicated spray granulation zone. In the spray granulation zone, a fine atomized liquid is typically sprayed and deposited on top of the fluidized bed particles. The wetting of the particles leads to the formation of granules. Partial drying of the wetted particles under the influence of air in the fluidized bed occurs continuously during granulation. After injecting the required amount of binder, the granules are quickly dried in a stream of hot air, and complete drying is often achieved. There are several different spray court systems available for use in a fluidized bed processor. These include hydraulic, ultrasonic and air spray/dual fluid nozzles. The most popular is the two-fluid nozzle system, where the binding fluid is sprayed with compressed air, because it can operate at very low fluid flow rates[7] and allows control of droplet size regardless of flow rate. Although the effect of spray drying is more pronounced with this type of nozzle, this is not a major problem when using water-based granulating fluids. Fluidized bed granulation processes can be further classified by the direction of the spray nozzle. Orientation determines not only the spray pattern of the binder liquid, but also the collision of the sprayed droplets and their subsequent spread to the powder particles. Consequently, it affects the properties of the formed granules.

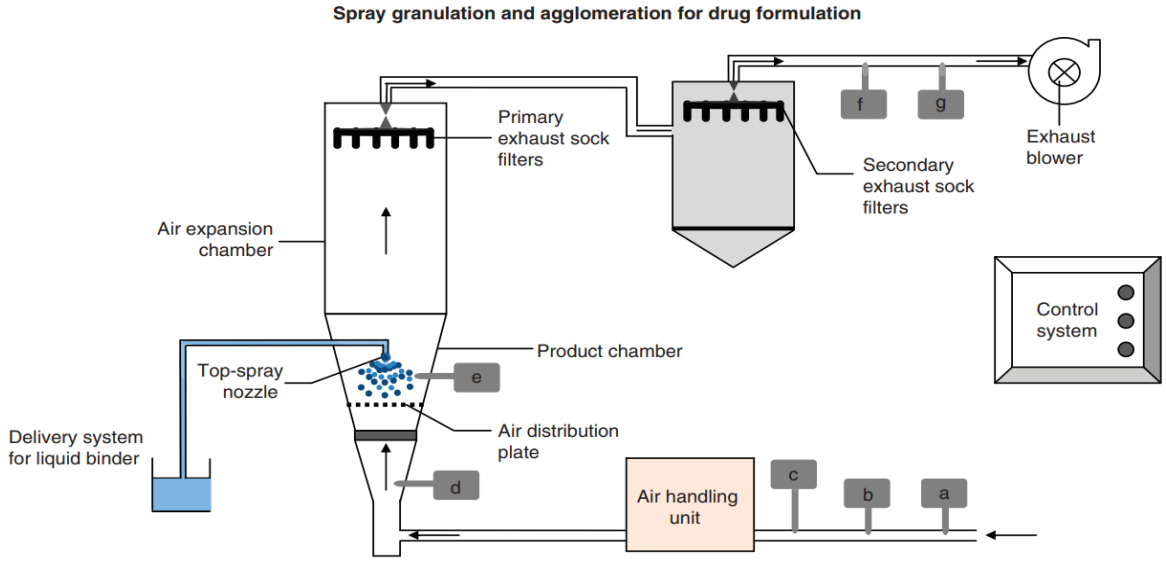


Figure 3: Fluid Bed Dryer.

1.4. Different Spray Directions Include

1.4.1. Top-Spray

Overspray granulation is one of the best known and most studied fluidized bed granulation methods since the 1960s.[8] As shown in Figure 4A, a spray nozzle is placed at the top of the production chamber and the leach liquid is sprayed onto the suspended solids with a countercurrent air flow. Granules produced by top-spray granulation are characterized by low bulk density and porous surfaces that promote the absorption of liquid into the interstices of the granules, which promotes their dispersion and disintegration.[9]

1.4.2. Tangential Atomization

The tangential atomization technique was designed to produce denser granules than is normally possible with fluidized bed granulation.[10] The spray is placed on the side of the product chamber and immersed in the powder bed during processing (Figure 4B). This rotary plate granulator, more commonly known as rotary processing, combines the efficiency of centrifugal, high-intensity mixing with fluid bed drying.[11] The rotating plate of the granulator creates a centrifugal force that forces the particles to the wall of the processing chamber at the edge of the production chamber. The fluidized bed air directed through the slot creates a vertical force that lifts the particles up before gravitational force causes the particles to fall down onto the disk.[12] Since the formed granules are spherical, denser and less porous than granules made by surface spraying technique, rotary processing is suitable for the production of coating granules.[13]

1.4.3. Bottom Spray

In this configuration, the spray is placed in the center of the air distribution plate at the bottom of the production chamber (Figure 4C). A distribution column is often installed, the presence of which controls fluidization and particle flow into the spray granulation zone.[14] The binding fluid is sprayed in the same direction as the air flow. It was mostly used for coating and less for granulation[15], but there were few reports of its use in pharmaceutical granulation in the 1990s.[16,17] However, there is still interest among some researchers[18,19] in using the bottom prayer technique for granulation. This granulation technique has also been given a new impetus by the development of advanced bottom spray processors in recent years.[20]

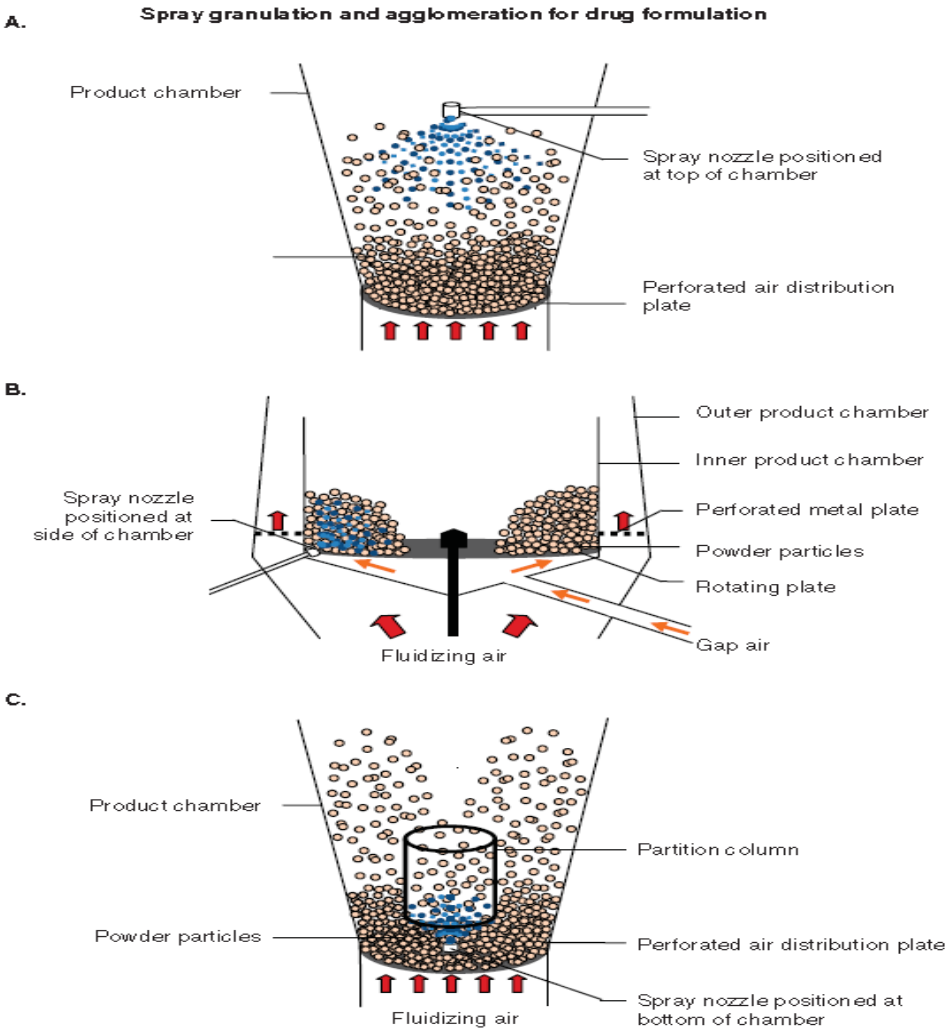


Figure 4: Schematic diagrams of (A) top spray granulator, (B) tangential spray granulator: two-chamber rotary processor, and (C) bottom spray granulator. The arrows indicate the direction of the air flow. [21]

1.5. Determination of Scale-Up Parameters of Products Produced By Wet and Spray Granulation Production Method

1.5.1. High Shear Mixer

1.5.1.1. Determination of High Shear Mixer Occupancy Rate (Mass / Volume)

In the products produced by wet granulation production method; the mass / volume of the product produced on a laboratory scale the scale should be equal to the mass/volume in the magnification study.

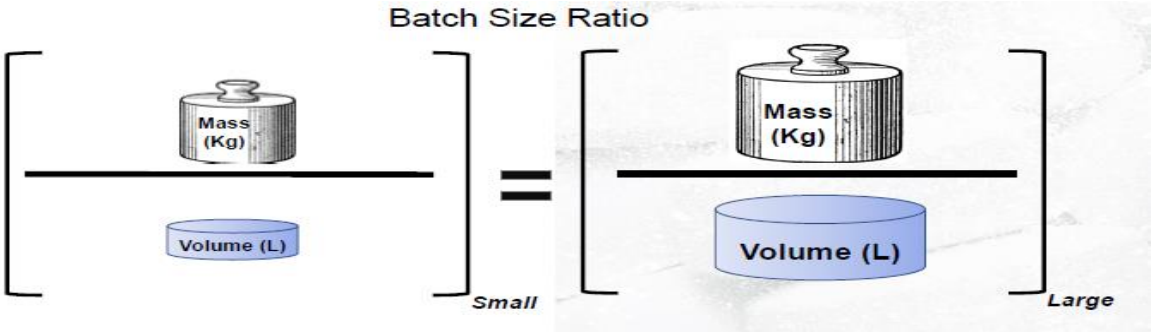


Figure 5: High Shear Mixer Occupancy Rate.

1.5.1.2. Determination of High Shear Mixer Spray Rate (Spray Rate / Product Mass)

In the products produced by wet granulation production method; Spraying volume / mass of the product produced on a laboratory scale the Spraying volume/mass in the scale-up study should be equal.

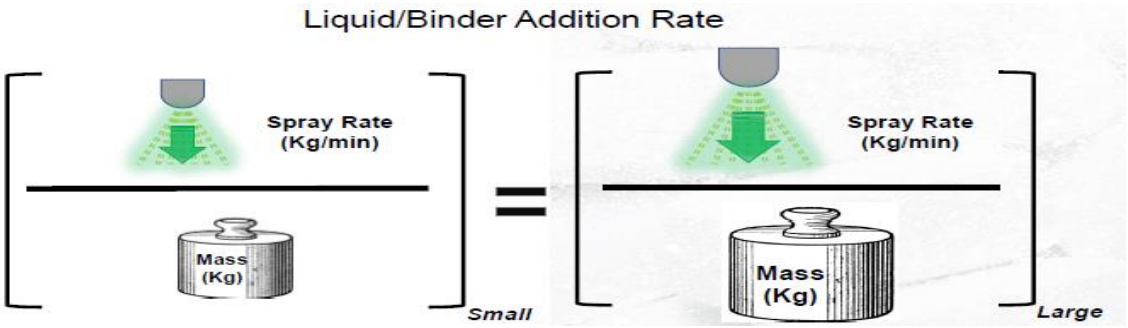


Figure 6: High Shear Mixer Spray Rate.

1.5.1.3. Determination of High Shear Mixer Impeller Speed

The following formula is used to determine the impeller velocity in scale up studies.

Froude : $FR = n^2.d /g$

n : Impeller Speed $[T^{-1}]$

d : Impeller Diameter [L]

g : Grabitational Constant $[LT^{-2}]$

$\mathbf{Fr_s} = n_s^2 d_5 / g$ $\mathbf{Fr_1} = n_1^2 d_1 / g$

Setting both equal to each other and solving for n_1

$\mathbf{n_1} = [n_s^2 d_s / d_1]^{0,5}$

1.5.2. Fluid Bed Dryer

In R&D, fluidized bed granulation requires a Decently long time to develop a robust process that yields acceptable product. In scaling up to commercial production, the same quality and results are expected with minimal improvement in the production scale. This is not always the case if the critical parameters are not Deciphered well on the R&D scale. The following are the theoretical scaling applications commonly used for fluidized bed granulation.

$\frac{\pi}{3}$ (R2 + r2 + Rr π)

1.5.2.1. Truncated Cone Volume Calculation

In Fluid Bed technology, the truncated cone formula is used to calculate the volume of the product to be sprayed or dried. R is calculated by the following formula as the semi-diameter of the base circle of the truncated cone, r is the semi-diameter of the ceiling circle and h is the height of the cone.

1.5.2.2 Inlet Air Volume Calculation

In order to maintain the fluidization rate in the lower grid (or air distribution plate), the air volume is scaled using the cross-sectional area of the hopper lower grids as follows

The area of the bottom screens is calculated

$A = \pi r^2$

A_1 = The Lower Screen Area of Unit 1 (m_2) :

A_2 = The Lower Screen Area of Unit 2 (m_2) :

AV_1 = Air Volume of Unit $_1$ (CFM) :

AV_2 = Air Volume of Unit $_2$ (CFM) :

1.5.2.3. Inlet Air Temperature Calculation

If the equipment temperatures can reach the same values, the inlet air temperature should be at the same values in large and small scale fluid bed dryers.

1.5.2.4. Spray Rate Calculation

In order to reproduce the product quality characteristics obtained in product development, it is necessary to reproduce the relative evaporation rates and dehumidification rates of the product at scale. Since it is recommended to keep the inlet temperature constant during scaling, the evaporation capacity is determined only by the increase in air volume. Therefore, the spraying speed needs to be increased to the same ratio as the air volume in order to maintain relative evaporation rates and moisture profiles.

1.5.2.5. Calculating the Atomization Rate

The droplet size is inversely proportional to the atomization air flow rate and directly proportional to the spraying speed. Therefore, as the spraying speed increases, the droplet size increases. Atomization The droplet size decreases as the air flow increases. Therefore, in scale-up, the spraying must be increased proportionally to the spraying speed with the air flow in order to keep the droplet size the same.

1.5.2.6. Product Temperature

In scale up operations, Product Temperature is a dependent variable affected by the following parameters. For this reason, when the following calculations are made correctly, it will be observed that the product temperature reaches the desired values.

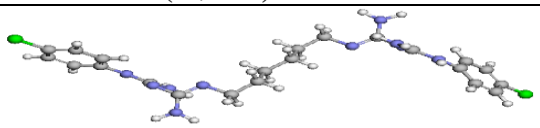
- Inlet Temperature
- Air Volume
- Atomization Rate
- Spray Rate

1.6. Chemical Characteristics of Chlorhexidine HCI

Chlorhexidine HCI is a broad spectrum antimicrobial biguanide used as a local antiseptic and in the treatment of inflammatory dental diseases caused by microorganisms in dentistry.[22] It is one of the most common skin and mucosal antiseptics used today. The molecule itself is a cationic biguanide consisting of two 4-chlorophenyl rings and two biguanide groups linked to a central hexamethylene chain.[23] Topical chlorhexidine for disinfection as well as dental mouthwashes. It is effective against many pathogens, including bacteria, yeast and viruses.[22,23,24]

Chlorhexidine is used as an ingredient of bacteriostatic and bactericidal by the activity of membrane disruption in a general purpose skin general skin cleansers, surgical scrub, germicidal hand rinses and animal disinfection products. It is used as a topical anti-infective for mucous membranes and as a preservative for eye drops. Chlorhexidine is also used as an antiseptic ingredient used in mouthwash to prevent oral plaque, oral bacteria and in treating gingivitis.

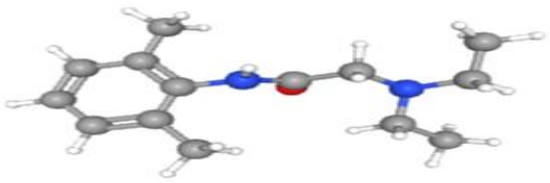
Table 1: Physical, Chemical and characteristic Properties of Chlorhexidine HCI.

Physical, Chemical and Characteristics of Chlorhexidine HCI	
Appereance	A white or almost white, crystalline powder
Solubility	Very slightly soluble in water, slightly soluble in propylene glycol, very slightly soluble in ethanol (96,00 %)
Structural Formula	
BCS Class	It is in Class II Drugs Category. (Low Solubility, High Permeability)
Chemical Formula	578.37 g/mol
Melting Point	$C_{22}H_{30}CI_2N_{10}.2HCI$
Storage Conditions	256 ^{0}C to 259 ^{0}C
CAS Number	Store in tightly closed containers.
Indication Information	Chlorhexidine is available over the counter in various formulations (eg, solution, sponge, cloth, cotton swabs) as a local antiseptic prior to surgery and/or medical procedures.[24,25,26,27] Prescription only dental preparations include mouthwashes designed to treat gingivitis[23] and slowly release a "chip" inserted into periodontal pockets designed to reduce pocket depth in adult patients with periodontitis as an adjunct to dental scaling and root planning.[28]

1.7. Chemical Characteristics of Lidocaine HCI

Lidocaine, also known as lignocaine and sold under the brand name Xylocaine, among others, is an aminoamide-type local anesthetic. It is also used to treat ventricular tachycardia.[29,30] When lidocaine is used for local anesthesia or nerve block, it usually starts working within minutes and lasts for half an hour to three hours.[30,31] Lidocaine mixtures can also be applied directly to the skin or mucous membranes to numb the area.[30] It is often used mixed with a small amount of adrenaline (epinephrine) to prolong its local effect and reduce bleeding.[30]

Table 2: Physical, Chemical and Characteristic Properties of Lidocaine HCI.

Physical, Chemical and Characteristics of Lidocaine HCI	
Apperance	White or almost white, crystalline powder
Solubility	Very soluble in water and Ethanol 96%, Soluble in Chloroform, Insoluble in ether
Structural Formula	
BCS Class	It is in Class III Drugs Category. (High Solubility, Low Permeability) [32]
Monecular Formula	270.80 g/mol
Chemical Formula	$C_{14}H_{23}CIN_2O$
Melting Point	74 ^{0}C to 79 ^{0}C
Storage Conditions	Store in tightly closed containers.
CAS Number	73-78-9
Indication Information	Lidocaine is an amide anesthetic indicated for local or regional anesthesia by infiltration techniques such as percutaneous injection and intravenous regional anesthesia by peripheral nerve block techniques such as brachial plexus and intercostal and central nervous system techniques such as lumbar and caudal epidural blocks. [33,34]

2. EXPERIMENTAL

2.1. Material and Method

Chlorhexidin HCI and Lidocaine HCI active substance was procured by (UNILAB, SWATI) The excipient which are used as respectively; Parteck SI 150 (MERCK), Parteck SI 1400 (MERCK), Citric Acid Anhydrous F6000 (JUNGBUNZLAUER), Lemon Flavour (SHARP) and Magnesium Stearate (PETER GREVEN) supplied. All raw materials used suitable for European Pharmacopoeia.

2.2. Tablet Formulation Trial and Scale Up Studies

Trial studies have been conducted to develop a chewable tablet formulation with Chlorhexidine HCI and Lidocaine HCI. The formulation table of the trial studies is given in detail below.

Table 3: Table of Formulation Trials.

Ingredients	Function	Trial 1 (mg/tb)	Trial 2 (mg/tb)	Trial 3 (mg/tb)	Trial 4 (mg/tb)	Scale Up Study (mg/tb)
Chlorhexidine HCI	Active Substance	5,000	5,000	5,000	5,000	5,000
Lidocaine HCI	Active Substance	1,000	1,000	1,000	1,000	1,000
Parteck SI 150	Filler	-	*	*	*	*
Parteck SI 400	Filler	*	-	-	-	-
Citric Acid Anhydrous	pH Agent	*	*	*	*	*
Magnesium Stearate	Lubricant	*	*	*	*	*
Lemon Flavour	Aromatizan	*	*	*	*	*
TOTAL		**1800.00**	**1800.00**	**1800.00**	**1800.00**	**1800.00**

* Raw materials used in the formulation of the experiments

- Raw materials not found in the trials.

Trial 1 Production Method (Batch Size: 1000 Tablets)

1. Weighing Stage

Raw materials are weighed in accordance with the production formula.

2. Sieving and Mixing Stage

Chlorhexidine HCL and Lidocaine HCl are sieved through a 400 micron sieve and subjected to the mixing process.

3. Sieving and Mixing Stage

The mixing process is applied by adding Parteck 400 sifted through a 630 micron sieve to the powder mixture.

4. Mixing Stage

Citric Acid and Lemon Flavor are added to the mixture and subjected to the mixing process.

5. Final Mixing Stage

Magnesium Stearate is sifted through a 420 micron sieve and added to the mixture and subjected to the final mixing process.

6. Tablet Compression

The final mixture is subjected to the tablet printing process in accordance with the specifications, so that it is 1800 mg/tb ± 5% (1710 mg – 1890 mg)

Trial-1 Result

The tablet that was subjected to tablet pressing was analyzed for uniformity of dosage unit and it was observed that Lidocaine HCl uniformity of dosage unit was out of limits (Average Value: 91.170 %) (The results are shared in the table below). Since the amount of lidocaine was not homogeneous, it was decided to try the wet granulation method.

Table 4: Trial 1 Uniformity of Dosage Unit Results(Lidocaine HCl).

Test	Specifications	Sample Information	Result
Uniformity of Dosage Unit Lidocaine HCI	1 mg /tablet ± %5 (0,950 mg/tb -1,05 mg/tb) Acceptance value (AV) should meet the requirements. Not more than 2 of the individual masses deviate from the average mass by more 5.00 % and none deviates by more than 10.00 %	**1. Sample**	0.165 mg/tb
		2. Sample	0.585 mg/tb
		3. Sample	1.232 mg/tb
		4. Sample	0.356 mg/tb
		5. Sample	1.348 mg/tb
		6. Sample	0.345 mg/tb
		7. Sample	0.632 mg/tb
		8. Sample	0.473 mg/tb
		9. Sample	1.034 mg/tb
		10. Sample	0.870 mg/tb
Standard Deviation			**37.989**
Average Weight			**0.704 mg/tb**
AV (Average Value)			**91.174**

Trial 2 Production Method (Batch Size: 1000 Tablets)

1. Weighing Stage

Raw materials are weighed in accordance with the production formula.

2. Sieving and Mixing Stage

Chlorhexidine HCL and Lidocaine HCl are sieved through a 400 micron sieve and subjected to the mixing process.

3. Sieving and Mixing Stage

30,00 % Parteck SI 150 raw material is sifted through a 630 micron sieve and added to the mixture.

4. Sieving and Mixing Stage

30,00 % Parteck SI 150 raw material is sifted through a 630 micron sieve and added to the mixture.

5.Sieving and Mixing Stage

40,00 % Parteck SI 150 raw material is sifted through a 630 micron sieve and added to the mixture.

6. Compaction Stage

It is subjected to the compaction process in order to increase the fluidity of the resulting mixture.

7. Mixing Stage

Citric Acid and Lemon Flavor are added to the mixture and subjected to the mixing process.

8. Final Mixing Stage

Magnesium Stearate is sifted through a 420 micron sieve and added to the mixture and subjected to the final mixing process.

9. Tablet Compression

The final mixture is subjected to the tablet printing process in accordance with the specifications, so that it is 1800 mg/tb ± 5% (1710 mg – 1890 mg)

Trial-2 Result

The tablet that was subjected to tablet pressing was analyzed for uniformity of dosage unit and it was observed that Lidocaine HCl uniformity of dosage unit was out of limits (Average Value: 19.840 %) (The results are shared in the table below). Therefore, it was decided to conduct a wet granulation trial production.

Table 5: Trial 2 Uniformity of Dosage Unit Results(Lidocaine HCl).

Test	Specifications	Sample Information	Result
Uniformity of Dosage Unit Lidocaine HCI	1 mg /tablet ± %5 (0,950 mg/tb -1,05 mg/tb) Acceptance value (AV) should meet the requirements. Not more than 2 of the individual masses deviate from the average mass by more 5.00 % and none deviates by more than 10.00 %	**1. Sample**	0.832 mg/tb
		2. Sample	0.953 mg/tb
		3. Sample	1.130 mg/tb
		4. Sample	0.866 mg/tb
		5. Sample	0.898 mg/tb
		6. Sample	0.945 mg/tb
		7. Sample	1.026 mg/tb
		8. Sample	0.951 mg/tb
		9. Sample	1.030 mg/tb
		10. Sample	0.988 mg/tb
Standard Deviation			**8.266**
Average Weight			**0.962 mg/tb**
AV (Average Value)			**19,840**

Trial 3 Production Method (Batch Size: 1000 Tablets)

1. Weighing Stage

Raw materials are weighed in accordance with the production formula.

2. Premix Stage

The Parteck Sl l50 is sieved through a 630 micron sieve and loaded into the granulator.

3. Preparation of Granulation Solution Stage

Lidocaine HCl is dissolved under the mixture into pure water. Citric Acid Anhydrous is added to the mixture and mixed until dissolved. Finally, Chlorhexidine HCl is added to the mixture and it is expected to be dispersed.

Note: Since the amounts of active substances in the formulation are very small, the active substances have been added to the mixture in order to ensure homogeneous distribution.

4. Wet Granulation

It is granulated with Parteck Sl 150 granulation solution taken into the granulator.

5. Wet Sieving

The resulting mixture is subjected to the wet sieving process.

6. Drying

Wet granules are added to the Fluid Bed Dryer and subjected to the drying process.

7. Sieving

The dried granules are sieved through the ossulator type sieve.

8. Final Mixing Stage

Magnesium Stearate is sifted through a 420 micron sieve and added to the mixture and subjected to the final mixing process.

9. Tablet Compression

The final mixture is subjected to the tablet printing process in accordance with the specifications, so that it is 1800 mg/tb ± 5% (1710 mg – 1890 mg)

Trial-3 Result

No abnormalities were encountered during the tablet compression process. When the chemical analysis results of the samples were evaluated, it was understood that both active substances were not in a homogeneous structure. Therefore,

it was decided to try the spray granulation production method again. The content uniformity analysis results of the two active ingredients are as follows.

Table 6: Trial 3 Uniformity of Dosage Unit Results (Lidocaine HCl).

Test	Specifications	Sample Information	Result
Uniformity of Dosage Unit Lidocaine HCI	1 mg /tablet ± %5 (0,950 mg/tb -1,05 mg/tb) Acceptance value (AV) should meet the requirements. Not more than 2 of the individual masses deviate from the average mass by more 5.00 % and none deviates by more than 10.00 %	**1. Sample**	0.970 mg/tb
		2. Sample	0.953 mg/tb
		3. Sample	1.042 mg/tb
		4. Sample	1.031 mg/tb
		5. Sample	0.812 mg/tb
		6. Sample	0.951 mg/tb
		7. Sample	1.054 mg/tb
		8. Sample	1.025 mg/tb
		9. Sample	1.031 mg/tb
		10. Sample	0.999 mg/tb
Standard Deviation			**6.87**
Average Weight			**0.987 mg/tb**
AV (Average Value)			**16.495**

Table 6: Trial 3 Uniformity of Dosage Unit Results(Chlorhexidine HCl).

Test	Specifications	Sample Information	Result
Uniformity Of Dosage Unit Chlorhexidine HCl	5 mg /tablet ± %5 (4.750 mg/tb -5.250 mg/tb) Acceptance value (AV) should meet the requirements. Not more than 2 of the individual masses deviate from the average mass by more 5.00 % and none deviates by more than 10.00 %	**1. Sample**	5.150 mg/tb
		2. Sample	5.242 mg/tb
		3. Sample	4.886 mg/tb
		4. Sample	4.950 mg/tb
		5. Sample	5.051 mg/tb
		6. Sample	4.510 mg/tb
		7. Sample	6.390 mg/tb
		8. Sample	4.875 mg/tb
		9. Sample	4.652 mg/tb
		10. Sample	5.084 mg/tb
Standard Deviation			**9.701**
Average Weight			**5.079 mg/tb**
AV (Average Value)			**23.282**

Trial 4 Production Method (Batch Size: 1000 Tablets)

1. Weighing Stage

Raw materials are weighed in accordance with the production formula.

2. Premix Stage

The Parteck Sl l50 is sieved through a 630 micron sieve and loaded into the fluid bed dryer.

3. Preparation of Granulation Solution Stage

Lidocaine HCl is dissolved under the mixture into pure water. Citric Acid Anhydrous is added to the mixture and mixed until dissolved. Finally, Chlorhexidine HCl is added to the mixture and it is expected to be dispersed.

Note: Since Chlorhexidine HCl does not dissolve in Pure Water, the final granulation solution was sieved through a 0.420 micron sieve in order not to clog the spray gun.

4. Spray Granulation

It is granulated with Parteck Sl 150 granulation solution taken into the fluid bed dryer.

5. Drying

The resulting granules are subjected to the drying process.

6. Sieving

The dried granules are sieved through the ossulator type sieve.

7. Final Mixing Stage

Magnesium Stearate is sifted through a 420 micron sieve and added to the mixture and subjected to the final mixing process.

8. Tablet Compression

The final mixture is subjected to the tablet printing process in accordance with the specifications, so that it is 1800 mg/tb ± 5% (1710 mg – 1890 mg)

Trial-4 Result

No unusual situation was encountered during the tablet printing process of the samples produced by spray granulation. When the chemical analysis results are evaluated, it is understood that both active substances are within the specification limits. It is planned to carry out the scale-up study after the stability processes. Detailed results of chemical analyzes are as follows.

Table 7: Trial 4 Finished Product Analysis Results.

Test	Specification	Results
Appearance	White to off-white colored round flat tablets with beveled edge; speckles are acceptable.	Visual
Identification Chlorhexidine HCl Lidocaine HCl	Retention times of main peaks which are obtained from sample and standard solutions chromatograms should be similar.	Complies
Water content	NMT 3.00 %	0.515 %
Disintegration	NMT 30 minutes.	11 minutes
Uniformity Of Dosage Units	Acceptance value (AV) should meet the requirements. Not more than 2 of the individual masses deviate from the average mass by more 5.0% and none deviates by more than 10.0%	Complies
Assay Chlorhexidine HCl Lidocaine HCl	 5.0 mg/tb ± 5.0% (4.75– 5.50 mg/tb) 1.0 mg/tb ± 5.0% (0.95– 1.15 mg/tb)	 5.302 mg/tb 1.031 mg/tb
Related Substances Chlorhexidine HCl Unknown Impurity Total Impurities **Lidocaine HCl** Impurity A Impurity H Unknown Impuritiy Total Impurities	 NMT 3.0% NMT 5.0% NMT 0.20% NMT 1.0% NMT 1.0% NMT 2.0%	 0.210 % 0.382 % Not Detected Not Detected Not Detected Not Detected

Table 8: Trial 4 Uniformity of Dosage Unit Results(Lidocaine HCl).

Test	Specifications	Sample Information	Result
Uniformity of Dosage Unit Lidocaine HCl	1 mg /tablet ± %5 (0,950 mg/tb -1,05 mg/tb) Acceptance value (AV) should meet the requirements. Not more than 2 of the individual masses deviate from the average mass by more 5.00 % and none	**1. Sample**	1.005 mg/tb
		2. Sample	1.002 mg/tb
		3. Sample	0.988 mg/tb
		4. Sample	1.042 mg/tb
		5. Sample	0.975 mg/tb
		6. Sample	0.992 mg/tb
		7. Sample	1.019 mg/tb
		8. Sample	0.995 mg/tb

	deviates by more than 10.00 %	**9. Sample**	1.033 mg/tb
		10. Sample	0.985 mg/tb
Standard Deviation			**2.049**
Average Weight			**1.003 mg/tb**
AV (Average Value)			**4.916**

Table 9: Trial 4 Uniformity of Dosage Unit Results(Chlorhexidine HCl).

Test	Specifications	Sample Information	Result
Uniformity of Dosage Unit Chlorhexidine HCl	5 mg /tablet ± %5 (4.750 mg/tb -5.250 mg/tb) Acceptance value (AV) should meet the requirements. Not more than 2 of the individual masses deviate from the average mass by more 5.00 % and none deviates by more than 10.00 %	**1. Sample**	5.200 mg/tb
		2. Sample	5.233 mg/tb
		3. Sample	5.085 mg/tb
		4. Sample	5.001 mg/tb
		5. Sample	4.882 mg/tb
		6. Sample	4.850 mg/tb
		7. Sample	5.119 mg/tb
		8. Sample	4.920 mg/tb
		9. Sample	4.983 mg/tb
		10. Sample	5.005 mg/tb
Standard Deviation			**2.458**
Average Weight			**5.028 mg/tb**
AV (Average Value)			**5.900**

2.3. Evaluation of the Flow Property

The flow characteristics of the final mixture obtained during product development studies are evaluated by Carr Index and Hausner Ratio. The flow characteristics for Trial-4 are evaluated below.

$$Carr's\ \text{Index} = \frac{Ptab - Pbulk}{Ptab} \times 100 \qquad Hausner\ \text{Rate} = \frac{Ptab}{Pbulk}$$

Table 10: Carr Index and Hausner Ratio Results Evaluation Table.

Flow Properties	Carr's Index (%)	Hausner Rate
Excellent	5-15	1,05-1,18
Good	12-16	1,14-1,19
Appropriate	18-21	1,22-1,27
Weak	23-35	1,30-1,54
Very Weak	33-38	1,49-1,61
Extremely Weak	>40	>1,67

Bulk Density ($\mathbf{p}_{bulk}$): 0.50 (g/ml) Tapped Density ($\mathbf{p}_{tap.}$): 0.58 (g/ml)

Carr's Index: $\frac{0.58 - 0.50}{0.58} * 100 = 13.79$ Hausner Ratio (HR): $\frac{0.58}{0.50} = 1.16$

As indicated in the above formula and tables, both the Carr's index value is between 5-15 (13.79) and the Hausner Ratio (HR) is between 1.05 -1.18 (1.16) indicating that the dust flow is good.

Table 11: Trial 4 Disintegration Time Results Table.

Dispersion Time in a Pure Water Environment at 37 ± 2°C *Spesification : NMT 15 minutes*	
Disintegration	**Trial 4 Disintegration Time**
1st Tablet	11 minutes 30 seconds
2nd Tablet	11 minutes 35 seconds
3rd Tablet	11 minutes 20 seconds
4th Tablet	11 minutes 45 seconds
5th Tablet	11 minutes 36 seconds
6th Tablet	11 minutes 08 seconds

Table 12: Trial 4 Long Term Stability Results.

Trial-4 Long Term Stability **Stability Test Condition : 25°C ± 2°C – 60 % RH ± 5**								
Tests	**Spesifications**	**The Beginning of Stability**	**3rd Month**	**6th Month**	**9th Month**	**12th Month**	**18th Month**	**24th Month**
Appereance	White to off-white colored round flat tablets with beveled edge; speckles are acceptable.	Appropriate	Appropriate	Appropriate	Appropriate	Appropriate	Appropriate	Appropriate
Identification ***Chlorhexidine HCl*** ***Lidocaine HCl***	Retention times of main peaks which are obtained from sample and standard solutions chromatograms should be similar.	Appropriate	Appropriate	Appropriate	Appropriate	Appropriate	Appropriate	Appropriate
Water Content	NMT 3.00 %	0.515 %	0.781 %	1.253 %	1.481 %	1.756 %	2.150 %	2.490 %
Disintegration	NMT 30 minutes.	11 minutes	11 minutes	11 minutes	11 minutes	10 minutes	10 minutes	10 minutes
Assay Chlorhexidine HCl Lidocaine HCl	 5.0 mg/tb ± 10.0% (4.50– 5.50 mg/tb) 1.0 mg/tb 10.0% (0.95– 1.15 mg/tb)	 5.302 mg/tb 1.031 mg/tb	 5.255 mg/tb 1.008 mg/tb	 5.218 mg/tb 1.015 mg/tb	 5.115 mg/tb 0.995 mg/tb	 5.055 mg/tb 1.060 mg/tb	 4.998 mg/tb 0.972 mg/tb	 4.981 mg/tb 0.960 mg/tb
Related Substances **Chlorhexidine HCl** Unknown Impurity Total Impurities **Lidocaine HCl** Impurity A Impurity H Unknown Impurity Total Impurities	 NMT 3.00% NMT 5.0% NMT 0.200 % NMT 1.000 % NMT 1.000 % NMT 2.000 %	 0.210 % 0.382 % Not Detected Not Detected Not Detected Not Detected	 0.360 % 0.425 % Not Detected 0.056 % Not Detected 0.081 %	 0.820 % 1.050 % 0.005 % 0.204 % Not Detected 0.672 %	 1.251 % 1.382 % Not Detected 0.507 % Not Detected 0.850 %	 1.592 % 1.650 % 0.020 % 0.618 % 0.136 % 1.275 %	 1.843 % 2.895 % 0.045 % 0.618 % 0.336 % 1.275 %	 2.508 % 3.066 % 0.118 % 0.981 % 0.757 % 1.599 %

Table 13: Trial 4 Accelerated Term Stability Results.

Trial-4 Accelerated Stability **Stability Test Condition : 40°C ± 2°C – 75 % RH ± 5**				
Tests	**Spesifications**	**The Beginning of Stability**	**3rd Month**	**6th Month**
Appereance	White to off-white colored round flat tablets with beveled edge; speckles are acceptable.	Appropriate	Appropriate	Appropriate
Identification Chlorhexidine HCl Lidocaine HCl	Retention times of main peaks which are obtained from sample and standard solutions chromatograms should be similar.	Appropriate	Appropriate	Appropriate
Water Content	NMT 3.00 %	0.515 %	1.570 %	2.752 %
Disintegration	NMT 30 minutes.	11 minutes	10 minutes	10 minutes
Assay Chlorhexidine HCl Lidocaine HCl	 5.0 mg/tb ± 10.0% (4.50– 5.50 mg/tb) 1.0 mg/tb 10.0% (0.95– 1.15 mg/tb)	 5.302 mg/tb 1.031 mg/tb	 5.205 mg/tb 0.985 mg/tb	 4.721 mg/tb 0.957 mg/tb
Related Substances Chlorhexidine HCl Unknown Impurity Total Impurities **Lidocaine HCl** Impurity A Impurity H Unknown Impurity Total Impurities	 NMT 3.00% NMT 5.0% NMT 0.200 % NMT 1.000 % NMT 1.000 % NMT 2.000 %	 0.210 % 0.382 % Not Detected Not Detected Not Detected Not Detected	 1.843 % 2.595 % 0.105 % 0.640 % 0.507 % 1.517 %	 2.508 % 3.258 % 0.184 % 0.990 % 0.904 % 1.950 %

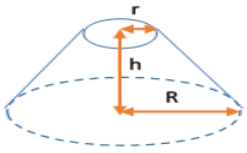
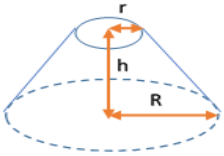
2.4. Scale Up Study (Batch Size: 100.000 Tablets)

The scale-up study is planned to be 100 times larger than laboratory-scale production. The obtained samples were placed in long-term stability (25°C ± 2°C/60 ± 5% RH) and accelerated stability (40°C ± 2°C/75 ± 5% RH) and monitored.

2.5. Determining the Parameters of the Scale Up Study

The parameters to be used during all scale-up studies were determined using the conversion factors in the literature research section of the article. The equipment information of our laboratory Scale and large scale fluid bed dryers is as follows.

Table 14: Determination of the Volumes of Fluidized Bed Dryers Used in the Studies.

Small Fluid Bed Dryer Volume	**Scale Up Fluid Bed Dryer Volume**
	
R: 15 cm	**R:** 90 cm
r : 10 cm	**r :** 60 cm
h: 40 cm	**h:** 120 cm
Volume = $\frac{3,14}{3}$ x40 (15x15+10x10+15x10) **Small Fluid Bed Dryer Volume =** 19,8 ~20 Liter	**Volume =** $\frac{3,14}{3}$ x 120 (60x60+90x90+60x90) **Scale Up Fluid Bed Dryer Volume** = 196,3 ~200 Liter

2.5.1. Calculating Inlet Air Volume

In the scale up study, the inlet air temperature was calculated as follows.

Table 15: Determination of the Inlet Air Volume.

Formulas	Small Fluid Bed Dryer	Scale Up Fluid Bed Dryer
A = Lower Display Area (m^2)	3,14 x 0,1 x 0,1 = 0,0314 m^2	3,14 x 0,6 x 0,6 = 1,13 m^2
r = Bottom Screen Radius (m)	10 cm = 0,1 m	60 cm = 0,6 m
$AV_2 = AV_1 A_2 / A_1$	AV_2 = 2142 x 0,03 / 1,13 = 80682 CFM	
$AV_2 = AV_1 A_2 / A_1$	AV_2 = 2142 x 0,03 / 1,13 = **80682 CFM** = 80682 CFM / 0,028 = **2259 m^3/h**	

***** Taken as 1 m^3/h = 0.028 CFM

2.5.2. Inlet Air Temperature Calculation

If equipment temperatures can reach the same values, the inlet air temperature should be the same in large and small scale fluid bed dryers.

2.5.3. Spray Rate Calculation

In the scale up study, the spray rate calculation was calculated as follows.

Table 16: Determination of the Spray Rate.

Formulas	Small Fluid Bed Dryer	Scale Up Fluid Bed Dryer
SR_2 = Spray Rate Of Unit 2 (rpm)	-	-
AV_2 = Air volume of unit 2 (CFM)	-	80682 CFM
SR_1 = Spray Rate Of Unit 1 (rpm)	12 rpm	-
AV_1 = Air volume of unit 1 (CFM)	2142 CFM	-
($SR_2 = SR_1 AV_2 / AV_1$)	**SR_2 = 12 x 80682 / 2142 = 452 rpm**	

2.5.4. Calculating Atomization Pressure

In the scale up study, the atomization pressure calculation was calculated as follows.

Table 17: Determination of the Atomization Pressure.

Formulas	Small Fluid Bed Dryer	Scale Up Fluid Bed Dryer
SR_2 = Spray Rate Of Unit 2 (rpm)	-	452 rpm
AAV_2 = Atomizing Air Volume Of Unit 2 (CFM)	-	-
SR_1 = Spray Rate Of Unit 1 (rpm)	60 rpm	-
AAV_1 = Atomizing Air Volume Of Unit 1 (CFM)	2142 CFM	-
$AAV_2 = AAV_1 SR_2 / SR_1$	AAV_2 = 2142 x 452 /60 = 16136,4 CFM = 16136,4 / 0,028 = **576,30 m^3/h**	

2.5.5. Calculating Product Temperature

In scale up operations, Product Temperature is a dependent variable affected by the following parameters. For this reason, when the following calculations are made correctly, it will be observed that the product temperature reaches the desired values.

- Inlet Temperature
- Air Volume
- Atomization Rate
- Spray Rate

As a result of the calculations, the spray granulation parameters were calculated as follows and used in the scale-up study.

Table 17: Comparative Spray Granulation Parameters Table.

Comparative Spray Granulation Parameters		
Parameters	**(Small Fluid Bed Dryer) 1000 Tablets**	**(Scale Up Fluid Bed Dryer) 100.000 Tablets**
Inlet Air Amount	2142 m^3/h	2259 m^3/h
Inlet Air Temperature	40 °C	40 °C
Shaking Period	5 Second	5 Second
Spray Pump Speed	12 rpm	452 rpm
Outlet Air Temperature	25 ± 5°C	25 ± 5°C
Product Tempature	26 ± 2°C	26 ± 2°C
Time	1.30 hours	1.30 hours

Table 18: Comparative Drying Parameters Table.

Comparative Drying Parameters		
Parameters	**(Small Fluid Bed Dryer) 1000 Tablets**	**(Scale Up Fluid Bed Dryer) 100.000 Tablets**
Inlet Air Amount	2142 m^3/h	2259 m^3/h
Inlet Air Temperature	60 °C	60 °C
Shaking Period	5 Second	5 Second
Spray Pump Speed	Closed	Closed
Outlet Air Temperature	50 ± 5°C	50 ± 5°C
Product Tempature	45 ± 2°C	45 ± 2°C
Time	45 minutes	45 minutes

Scale Up Production Method

1. Weighing Stage

Raw materials are weighed in accordance with the production formula.

2. Premix Stage

The Parteck Sl l50 is sieved through a 630 micron sieve and loaded into the fluid bed dryer.

3. Preparation of Granulation Solution Stage

Lidocaine HCl is dissolved under the mixture into pure water. Citric Acid Anhydrous is added to the mixture and mixed until dissolved. Finally, Chlorhexidine HCl is added to the mixture and it is expected to be dispersed.

Note: Since Chlorhexidine HCl does not dissolve in Pure Water, the final granulation solution was sieved through a 0.420 micron sieve in order not to clog the spray gun.

4. Spray Granulation

It is granulated with Parteck Sl 150 granulation solution taken into the fluid bed dryer.

5. Drying

The resulting granules are subjected to the drying process.

6. Sieving

The dried granules are sieved through the ossulator type sieve.

7. Final Mixing Stage

Magnesium Stearate is sifted through a 420 micron sieve and added to the mixture and subjected to the final mixing process.

8. Tablet Compression

The final mixture is subjected to the tablet printing process in accordance with the specifications, so that it is 1800 mg/tb ± 5% (1710 mg – 1890 mg).

Scale Up Study Finished Product Analysis Results

Table 19: Scale Up Study Finished Product Analysis Results.

Test	Specification	Scale Up Study Results
Appearance	White to off-white colored round flat tablets with beveled edge; speckles are acceptable.	Visual
Identification Chlorhexidine HCl Lidocaine HCl	Retention times of main peaks which are obtained from sample and standard solutions chromatograms should be similar.	Complies
Water content	NMT 3.00 %	0.621 %
Disintegration	NMT 30 minutes.	11 minutes
Uniformity Of Dosage Units	Acceptance value (AV) should meet the requirements. Not more than 2 of the individual masses deviate from the average mass by more 5.0% and none deviates by more than 10.0%	Complies
Assay Chlorhexidine HCl Lidocaine HCl	 5.000 mg/tb ± 5.0 % (4.75– 5.50 mg/tb) 1.000 mg/tb ± 5.0 % (0.95– 1.15 mg/tb)	 5.085 mg/tb 1.072 mg/tb
Related Substances **Chlorhexidine HCl** Unknown Impurity Total Impurities **Lidocaine HCl** Impurity A Impurity H Unknown Impurity Total Impurities	 NMT 3.0% NMT 5.0% NMT 0.20% NMT 1.0% NMT 1.0% NMT 2.0%	 0.150 % 0.426 % Not Detected 0.042 % Not Detected 0.075 %

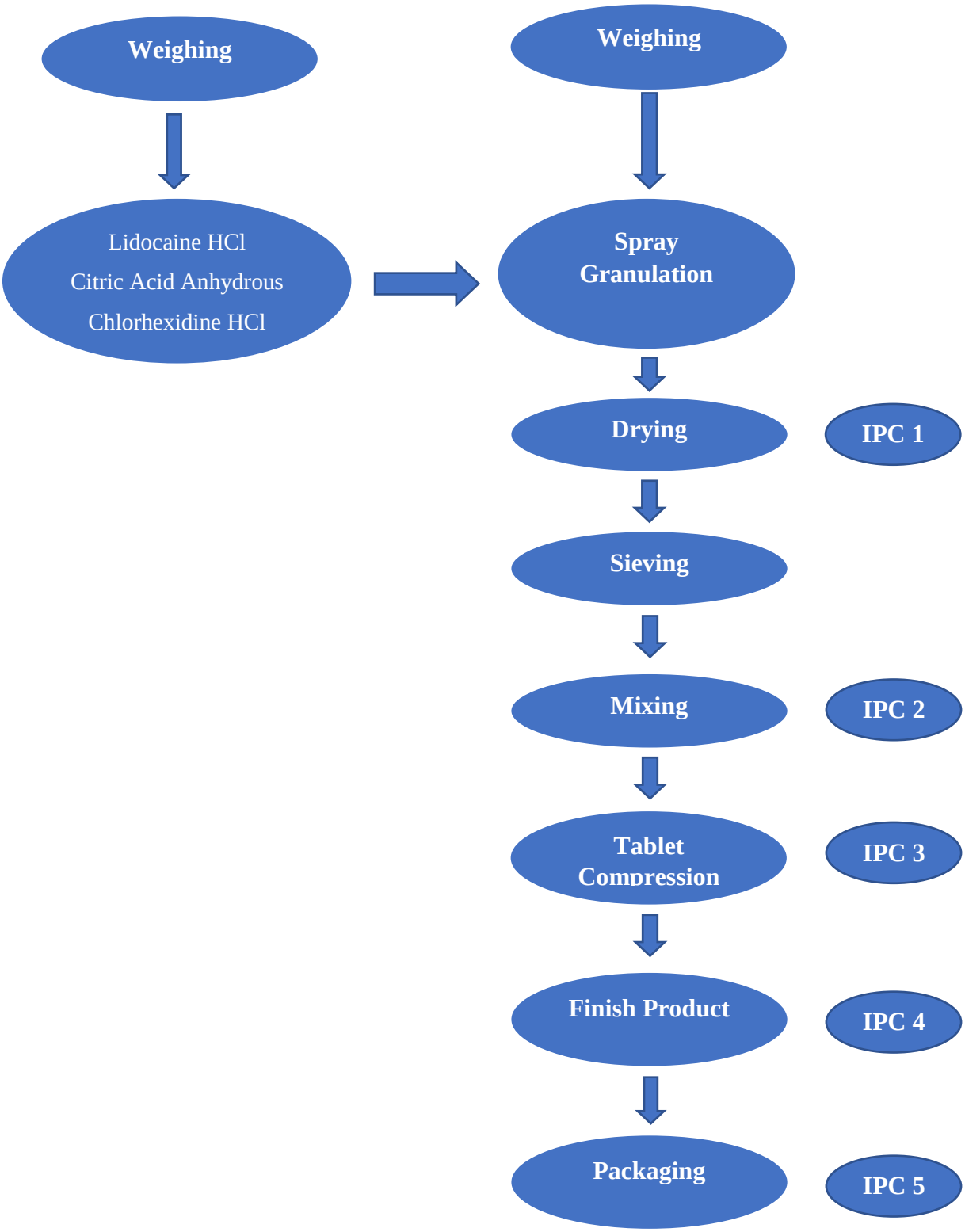
Table 20: Scale Up Study Long Term Stability Results.

Scale Up Study Long Term Stability **Stability Test Condition : 25°C ± 2°C – 60 % RH ± 5**								
Tests	**Spesifications**	**The Beginning Of Stability**	**3rd Month**	**6th Month**	**9th Month**	**12th Month**	**18th Month**	**24th Month**
Appereance	White to off-white colored round flat tablets with beveled edge; speckles are acceptable.	Appropriate	Appropriate	Appropriate	Appropriate	Appropriate	Appropriate	Appropriate
Identification ***Chlorhexidine HCl*** ***Lidocaine HCl***	Retention times of main peaks which are obtained from sample and standard solutions chromatograms should be similar.	Appropriate	Appropriate	Appropriate	Appropriate	Appropriate	Appropriate	Appropriate
Water Content	NMT 3.00 %	0.621 %	0.951 %	1.429 %	1.675 %	2.050 %	2.360 %	2.652 %
Disintegration	NMT 30 minutes.	11 minutes	11 minutes	11 minutes	11 minutes	10 minutes	10 minutes	10 minutes
Assay Chlorhexidine HCl Lidocaine HCl	 5.0 mg/tb ± 10.0% (4.50– 5.50 mg/tb) 1.0 mg/tb 10.0% (0.95– 1.15 mg/tb)	 5.085 mg/tb 1.072 mg/tb	 5.081 mg/tb 1.008 mg/tb	 5.016 mg/tb 1.015 mg/tb	 5.002 mg/tb 0.995 mg/tb	 4.992 mg/tb 1.060 mg/tb	 4.855 mg/tb 0.972 mg/tb	 4.810 mg/tb 0.960 mg/tb
Related Substances **Chlorhexidine HCl** Unknown Impurity Total Impurities **Lidocaine HCl** Impurity A Impurity H Unknown Impurity Total Impurities	 NMT 3.00% NMT 5.0% NMT 0.200 % NMT 1.000 % NMT 1.000 % NMT 2.000 %	 0.150 % 0.426 % Not Detected 0.042 % Not Detected 0.075 %	 0.540 % 0.725 % 0.015 % 0.080 % 0.015 % 0.081 %	 1.504 % 1.650 % 0.088 % 0.208 % 0.081 % 0.501 %	 1.500 % 1.882 % 0.105 % 0.359 % 0.375 % 1.050 %	 1.995 % 2.250 % 0.115 % 0.720 % 0.605 % 1.475 %	 2.182 % 2.495 % 0.135 % 0.818 % 0.336 % 2.106 %	 2.428 % 2.753 % 0.148 % 0.902 % 0.757 % 2.210 %

Table 21: Scale up Study Accelerated Term Stability Results.

Scale Up Study Accelerated Stability **Stability Test Condition : 40°C ± 2°C – 75 % RH ± 5**				
Tests	**Spesifications**	**The Beginning of Stability**	**3rd Month**	**6th Month**
Appereance	White to off-white colored round flat tablets with beveled edge; speckles are acceptable.	Appropriate	Appropriate	Appropriate
Identification ***Chlorhexidine HCl*** ***Lidocaine HCl***	Retention times of main peaks which are obtained from sample and standard solutions chromatograms should be similar.	Appropriate	Appropriate	Appropriate
Water Content	NMT 3.00 %	0.621 %	1.771 %	2.850 %
Disintegration	NMT 30 minutes.	11 minutes	10 minutes	10 minutes
Assay Chlorhexidine HCl Lidocaine HCl	 5.0 mg/tb ± 10.0% (4.50– 5.50 mg/tb) 1.0 mg/tb 10.0% (0.95– 1.15 mg/tb)	 5.085 mg/tb 1.072 mg/tb	 4.900 mg/tb 0.982 mg/tb	 4.685 mg/tb 0.968 mg/tb
Related Substances **Chlorhexidine HCl** Unknown Impurity Total Impurities **Lidocaine HCl** Impurity A Impurity H Unknown Impurity Total Impurities	 NMT 3.00% NMT 5.0% NMT 0.200 % NMT 1.000 % NMT 1.000 % NMT 2.000 %	 0.150 % 0.426 % Not Detected 0.042 % Not Detected 0.075 %	 1.352 % 1.950 % 0.150 % 0.267 % 0.349 % 0.968 %	 1.880 % 2.225 % 0.192 % 0.815 % 0.824 % 1.350 %

Production Flow Chart



3. CONCLUSION

To develop the lozenge product with the combination of active substances with high and low solubility contained in low amounts in the formulation, and technology transfer processes were carried out.

During the trial production, the development studies of Chlorhexidine HCl and Lidocaine HCl raw materials, which are present in low amounts in the formulation, were tried with different production methods and the spray granulation method was decided. The decided trial production has been followed throughout the stability and appropriate results have been obtained. With the appropriate results obtained, the product was made in commercial size and the stability suitability was checked in the same way. Stable product development has been completed with the spray granulation method, a combination of active substances with high and low solubility, when all the given has been collected.

ACKNOWLEDGEMENT

This article was sponsored by World Medicine Pharmaceutical Company. The authors are grateful to Rovshan Tagiyev, the founder and chairman of the World Medicine Pharmaceutial Company. I will not forget to share with you our valuable advisors and teammate in the realization of this study. I would like to thank, Technology Transfer and Product Development Manager Gökay GUN and R&D Director Erdinc BABUC.

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