"DEVELOPMENT & OPTIMIZATION OF THE FORMULATION AND PROCESS PARAMETERS FOR A LOW DOSE CHEWABLE TABLET"

A THESIS SUBMITTED TO

NIRMA UNIVERSITY

IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE DEGREE OF

MASTER OF PHARMACY

IN

PHARMACEUTICAL TECHNOLOGY AND BIOPHARMACEUTICS

BY

UTKARSH VYAS (11MPH115)
B. PHARM

UNDER THE GUIDANCE OF

DR. VIPAN DHALL –INDUSTRIAL GUIDE

Vice-president and Site Head, Piramal Pharmaceutical Development Services

Dr. TEJAL MEHTA – GUIDE

Professor and Head, Department Of Pharmaceutics and Pharmaceutical Technology

DEPARTMENT OF PHARMACEUTICS AND PHARMACEUTICAL TECHNOLOGY

INSTITUTE OF PHARMACY

NIRMA UNIVERSITY

AHMEDABAD-382481

GUJARAT, INDIA

MAY 2013

CERTIFICATE

This is to certify that the dissertation work entitled "Development & Optimization of the Formulation and Process Parameters for a Low Dose Chewable Tablet" submitted by Mr. Utkarsh Vyas with Regn. No. (11MPH115) in partial fulfillment for the award of Master of Pharmacy in "Pharmaceutics" is a bonafide research work carried out by the candidate at the Department of Pharmaceutics and Pharmaceutical Technology, Institute of Pharmacy, Nirma University under our guidance. This work is original and has not been submitted in part or full for any other degree or diploma to this or any other university or institution.

Industrial Guide

Dr. Vipan Dhall
Vice-president and Site Head,
Piramal Pharmaceutical
Development Services.

Academic Guide

Dr. Tejal Mehta
M. Pharm., Ph.D.
Professor & Head,
Department of Pharmaceutics &
Pharmaceutical Technology,
Institute of Pharmacy,
Nirma University.

Forwarded Through:

15.5.13

Prof. Manjunath Ghate
M. Pharm., Ph.D.
Director
Institute of Pharmacy,
Nirma University.

Date: 17 MAY, 2013

DECLARATION

I hereby declare that the dissertation entitled "Development & Optimization of the Formulation and Process Parameters for a Low Dose Chewable Tablet", is based on the original work carried out by me under the guidance of Dr. Vipan Dhall Vice-president and Site Head, Piramal Pharmaceutical Development Services and Dr. Tejal A. Mehta, Professor, Department of Pharmaceutics and Pharmaceutical Technology, Institute of Pharmacy, Nirma University. I also affirm that this work is original and has not been submitted in part or full for any other degree or diploma to this or any other university or institution.

MR. UTKARSH VYAS (11MPH115)
Department of Pharmaceutics and
Pharmaceutical Technology
Institute of Pharmacy
Nirma University
Sarkhej - Gandhinagar Highway
Ahmedabad-382481
Gujarat, India

Date: 17MAY, 2013

ACKNOLEDGEMENT

The joyness, satisfaction and euphoria that come along with successful completion of any work would be incomplete unless we mention the name of those people who made it possible whose constant guidance and encouragement served as a beam of light and crowed out efforts.

First of all, I am thankful to ***almighty (the supreme soul)*** *for always being with me and blessing me with good family, friends, teachers and well wishers and extend his helping hands to complete this project successfully. No research is ever the outcome of a single individual's efforts. This work is no exception. Some of the personalities known and unknown, which contributed to this project made it possible for me to present it in this format. I am extremely grateful to all of them.*

I am highly thankful to ***Dr. Manjunath Ghate*** *(Director, Institute of Pharmacy, Nirma University, Ahmedabad) for providing all necessary help and facility for my work and also for her constant support and encouragement.*

I express my warmest gratitude to my guide ***Dr. Vipan Dhall*** *(Vice-president and Site Head, Piramal Pharmaceutical Development Services) for his valuable guidance, keen interest, perennial inspiration and everlasting encouragement. It is with affection and reverence that I acknowledge my indebtness to him for outstanding dedication, often far beyond the call of duty.*

I would like to thank specially to ***Mr. Tejas shah****, Group Leader, Piramal Pharmaeutical Development Services, for providing all necessary help and facility for my work and also for his constant support and encouragement.*

I would like to thank ***Mr.Sudeep Sharma****, manager-HR,* ***Mr. Inder Gulati,*** *Group leader,* ***Mr. Vinay Patil****, Group leader,* ***Mr. Gunjan Vyas, Mr. Partha Saha and all Piramal Family*** *for their selfless support, co-operation and valuable suggestions.*

I express my warmest gratitude to my guide ***Dr. Tejal Mehta*** *(Professor, Dept of Pharmaceutics, Institute of Pharmacy, Nirma University) for her valuable guidance, keen interest, perennial inspiration and everlasting encouragement. It is with affection and reverence that I acknowledge my indebtness to her for outstanding dedication, often far beyond the call of*

duty. I am extremely indebted to her for motivational inspiration, kind expertise during the writing up of my thesis and the scientific attitude they have nurtured in me which will definitely stand in all my future endeavours.

I am extremely grateful to ***Dr. Shital Bariya, Dr. Renuka Mishra Dr. Mayur M Patel, Dr. Jigar N shah, Mr. Dhaivat Parikh,*** *Dept of Pharmaceutics, Institute of Pharmacy, Nirma University for their contious encouragement and everlasting support throughout the course of this dissertation work.*

I express my special thanks to ***Dr. Anuradha K. Gajjar****, Associate professor, Department of Medicinal Chemistry, Institute of Pharmacy, Nirma University, Dr****. Murali Badanthadka****, Associate Professor, I/C Head, Dept of Pharmacology, Institute of Pharmacy, Nirma University,* ***Dr. Priti J Mehta*** *Associate Professor, Head, Dept. of Pharmaceutical Analysis, Institute of Pharmacy, Nirma University for their constant moral support and kind cooperation.*

I owe special words of thank to ***Shailesh Bhai, Mukesh Patel and Shilpaben*** *for their precious help.*

Words are an inadequate medium to express my feelings and deep sense of gratitude to my beloved ***parents*** *who have always given me moral support & encouragement. Their prayers to God have made me achieve this milestone of my carrier. Their support and encouragement with their unending cheering have led to the successful completion of my research work.*

I am heartily thankful to all my classmates and friends especially ***Dhruvi, Zeal, Chintan , Dishant, Kashyap, Keyur, Mahima, Manali, Maulik, Nirav, Rashmi, Ronak, Sagar, Tora, Amit*** *for giving me constant support and help during my dissertation work. Words do not suffice to express my sincere and humble thanks to all my very special friends. I would like to thank my juniors* ***Chintan, Chitra, Darshi, Krunal, Mansi, Megha, Neha, Parth, Priyanka, Ronak, Ruchi, Rushi, Santur, Sapna, Tishir.***

I would like to thank specially to ***Mr. Gunjan Vyas*** *for his immense support and encouragement throughout the entire project. I am heartly thankful to my friends* ***Divij, Amisha, Doli, Samarth, Richa, Sahil, Meghal, Rina, Kaushal, Kashyup, Riddhi, Girish, Ronak, Pooja, Shikha, Barkat, Abrar*** *for giving me constant support.*

*I would also like to thank specially to my friends **Sanjana, Aditya, Jimmy, Gaurang, Neha, Disha, Pooja** for giving me constant support.*

Last, but not the least, I express my gratitude and apologize to anybody whose contributions, I could not mention in this page.

Date: 17/03/13

Utkarsh Vyas

Place: ***Institute of Pharmacy,***
Nirma University,
Ahmedabad.

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C. Abbreviations

Short Name	Abbreviation
IP	Indian Pharmacopoeia
BP	British Pharmacopoeia
USP	United States Pharmacopeia
USPNF	United States Pharmacopoeia National Formulary
UV	Ultra Violet
Calcarb	Calcium Carbonate with maltodextrin
°C	Degree Centigrade
Conc.	Concentration
Abs	Absorbance
µg	Microgram
ml	Milliliter
mg	Milligram
W/W	Weight By Weight
W/V	Weight By Volume
KN	Kilo Newton
Kp	Kilo pond
API	Active Pharmaceutical Ingredient

Development & Optimization of the Formulation and Process Parameters for a Low Dose Chewable Tablet

Vyas U.S. , Dhall V.[#] , Shah T.[#] , Mehta T.A.[+]

 # Piramal Pharmaceutical Development Services Pvt. Ltd

+ Institute of Pharmacy, Nirma University

Oral administration has been the most favourable route of drug delivery as 90% of all drugs used to produce systemic effects are administered by this route. Chewable tablet is one of the recent advances in oral dosage forms. They are intended to be chewed in the mouth prior to swallowing thus it gives ease of administration to children or to the elderly who may have difficulty in swallowing an intact tablet. PHL_158 is a BCS class I drug used in motion sickness. It is absorbed throughout the GI tract hence an ideal drug for preparation of chewable tablet. Chewable dosage form provides the advantage of taking the tablet without water and hence useful in motion sickness which commonly occurs during travelling. Chewable tablets were prepared by direct compression method using mannitol, xylitol, MCC and calcarb as diuents in different combinations and ratios using Korsch XL 100. Formulation had excellent mouth feel, no grittiness was observed and desirable taste was obtained but had poor flow property and segregation issues. So to improve flow property and reduce segregation tendency it was further optimized by dry granulation technique using roller compaction. Granulation is the process in which primary powder particles are made to adhere to form larger, multiparticle entities called granules. Powders are often granulated to improve their flow behaviour. Roller compaction is a widely used process for granulation to improve flow property and prevent segregation as the drug gets compacted into granules prior to compaction. Roller compaction was carried out by Alexanderwerk roller compactor by using Box-Behnken design to minimize the number of runs. Granules obtained from dry granulation using roller compaction process had good flow property and segregation tendency was not observed. Hence it can be concluded that process parameters like flow property and segregation tendency of blend can be improved by dry granulation process using roller compaction. Use of DOE helps in accurate optimization of formulation with minimum efforts, time and energy. Thus, this study proved the necessity of optimization of process parameters for low dose chewable tablet.

Chapter 1 Aim of Investigation

1.0 Aim of Investigation

The oral route of drug administration is the most common and favorable method for administrating drugs for systematic effects. Except in case of insulin therapy, the parenteral route is not widely used for self- administration of medication. Almost 90% of all drugs used to produce systemic effects are administered by oral route.

PHL_158 is an anti histaminic drug used in treatment of motion sickness. It competes with free histamine for binding at H1-receptor sites in the GI tract, uterus, large blood vessels, and bronchial muscle. It is also used as an anti allergic, in pruritus, in severe pain & in cough preparations.

Chewable tablets are intended to be chewed in the mouth prior to swallowing so ease of administration to children or to the elderly who may have difficulty in swallowing a intact tablet. It produces a light crunch when bitten and then dissolves quickly in the mouth and therefore can be taken without water. It gets disintegrated in the mouth itself so quicker onset of action is achieved. Chewable tablet have better stability and specific storage condition are not required and due to its cooling effect and pleasant taste it is consumer friendly.

PHL_158 is used in motion sickness which occurs during travelling. Hence, chewable tablets would provide the benefit of taking medicine without water. PHL_158 is well absorbed from GIT which is an ideal property for preparation of chewable tablets. Chewable tablet of PHL_158 was prepared by using four different diluents mannitol, xylitol, MCC and calcarb in different combinations and ratios by direct compression method. Mannitol and xylitol imparts good mouth feel while MCC was used for good flow and compressibility. Calcarb was used as an alternative to MCC to reduce the grittiness of formulation. Tablets were evaluated for flow property, segregation potential, compressibility, blend and content uniformity, friability, disintegration time, dissolution time, mouth feel, grittiness and taste. Batch having good mouth feel and no grittiness but

having poor flow property and segregation tendency were further optimized using roller compaction process using box behnken design by taking roll pressure, roll gap and fine screen granulator as independent factors. Chewable tablets obtained by roller compaction had better flow property and segregation tendency was not observed. Effect of roll pressure, roll gap and fine screen granulator were studied on parameters like bulk density, flowdex, FFc, cumulative % retained, main compression force, hardness and design space was created. The optimized batch was selected on basis of target product profile. Use of DOE helped in accurate optimization of formulation with minimum runs. Hence the aim of present investigation was to prepare chewable tablet of PHL_158 for better patient compliance than conventional dosage form by optimizing formulation and process parameters.

Chapter 2
Introduction

2.0 INTRODUCTION

The oral route of drug administration is the most important method of administrating drugs for systematic effects. Except in case of insulin therapy, the Parenteral route is not routinely used for self- administration of medication. At least 90% of all drugs used to produce systemic effects are administered by oral route.

Tablets provide with certain advantages over other oral dosage forms:

1. They are unit dosage form.
2. They are cost effective.
3. They are lightest and most compact of all oral dosage forms.
4. They are in general the easiest and cheapest to pack and ship.
5. Product identification is potentially the simplest and cheapest, requiring no additional processing steps when employing an embossed or monogrammed punch face.
6. They may provide the greatest ease of swallowing with the least tendency for "hang-up" above the stomach, especially when coated, provided that tablet disintegration is not excessively rapid.
7. Tablets are better suited to large-scale production than other unit oral dosage forms.
8. They have the best chemical, mechanical and microbiological stability of all the oral forms.

However there are certain disadvantages:

1. Some drugs resist compression into dense compacts, owing to their amorphous nature or flocculent, low-density character.
2. Drugs with poor wetting and slow dissolution properties maybe difficult to formulate and manufacture as a tablet.
3. Bitter tasting drugs, drugs with an objectionable odour, or drugs that are sensitive to oxygen or atmosphere moisture may require encapsulation or entrapment prior to compression, or the tablets may require coating. In such cases, the capsule may offer the best and lowest cost approach. [1]

Recent developments in dosage form technology are concentrating on presenting the patient with viable dosage alternatives which provide good palatability and ease of administration at the same time. This is especially valid when the preparation is to be administered to an infant or to an elderly

patient. In such cases, powders for reconstitution, suspensions, syrups, elixir solutions and chewable tablets are considered to be suitable alternatives which solve the above- mentioned problems in some cases and satisfy the needs of such patients**.** It is worth mentioning, though, that some patients still find inconvenience in taking the liquid dosage forms, in measuring the exact dose accurately or in carrying the package along while travelling. All the mentioned reasons make chewable tablets one of the excellent alternative choices as an easy method of drug administration for these patients. In fact, the FDA has invited pharmaceutical manufacturers to develop and produce proper dosage forms especially for paediatric patients. Until 1999, more than 60 chewable tablet medications were approved for patient use in the U.S.A. The list includes a wide range of medications such as analgesics, cold preparations, vitamins, anti-infectives, anti-convulsants and antacids. In this context, chewable tablets are known to be advantageous over liquid dosage forms in many aspects, such as higher palatability, better availability, stability, dose precisions, portability and ease of administration especially during travelling. [2]

2.1 Introduction to Chewable Tablets

These tablets are intended to disintegrate smoothly in mouth at a moderate rate either with or without actual chewing, characteristically chewable tablets have a smooth texture upon disintegration, are pleasant tasting and leave no bitter or unpleasant taste.

2.1.1 Potential advantages of chewable tablets

Chewable tablets are intended to be chewed in the mouth prior to swallowing and are not expected to be swallowed intact. The purpose of chewable tablet is to provide a unit dosage form of medication which can easily be administered to children or to the elderly who may have difficulty in swallowing a tablet intact.

Chewable tablets have some specific **advantages**

1. Effectiveness of the therapeutic agent is improved by the reduction in size that occurs during mastication of the tablet before swallowing.

2. Better bioavailability through bypassing disintegration (and perhaps increase dissolution).
3. Improved patient acceptance (especially paediatric) through pleasant taste.
4. Patient convenience; need no water for swallowing.
5. Possible to use as a substitute for liquid dosage forms where rapid onset of action is needed.
6. Absorption of drug is faster.
7. Product distinctiveness through marketing prospective.
8. The large size of the dosage form is difficult to swallow. In such case chewable tablet offers advantage over it.

   There are, of course, limitations to the use of chewable tablets. Bad tasting drugs and those having extremely high dosage levels present the formulator with significant obstacles to be overcome.

2.1.2 Organoleptic Factors

A. Taste and Flavour

Physiologically, taste is a sensory response resulting from a chemical stimulation of the taste buds on the tongue. There are four basic types of tastes; salty, sour, sweet, and bitter. Salty or sour tastes are derived from substances capable of ionizing in solution. Many organic medicinal compounds stimulate a bitter response even though they may not be capable of ionizing in an aqueous medium. Most saccharides, disaccharides, some aldehydes, and a few alcohols give a sweet taste. Substances incapable of producing a sensory stimulation of the buds are referred to as bland or tasteless.

The term flavour generally refers to a specific combined sensation of taste and smell (olfaction). For example, sugar has a sweet taste but no flavour, whereas honey has a sweet taste and a characteristic smell-the combination of the two being known as honey flavour.

B. Mouth-feel

The term mouth-feel is related to the type of sensation or touch that a tablet produces in the mouth upon chewing. As such, it has nothing to do with chemical stimulation of olfactory nerves or taste buds. However, for a formulation to be successful, the overall effect in the mouth is important.
In general, gritty (e. g., calcium carbonate) or gummy textures are undesirable, whereas a soothing and cooling sensation (e.g., xylitol) with smooth texture is preferred.

C. After Effects

The most common after effect of many compounds is aftertaste. For example, some iron salts leave a "rusty" aftertaste; saccharin in high amounts tends to leave a bitter aftertaste. Another common after effect is a numbing sensation of a portion of the whole surface of the tongue and mouth. Bitter antihistamines such as pyribenzamine hydrochloride is typical of this class of drug.

2.1.3 Formulation Techniques

Almost invariably, the formulation problem involves at least one of the following: undesirable taste, bad mouth- feel, or aftertaste. The desired product should prevent or minimize stimulation of the taste buds, contain a suitable flavour and sweetener, and achieve good mouth- feel and compressibility.

The following techniques are used to solve one or more of the above.

1. Coating by Wet Granulation
2. Microencapsulation
3. Solid Dispersions
4. Adsorbate Formation Techniques(Solvent Method and Melting Method)
5. Ion Exchange resins
6. Spray Congealing and Spray Coating
7. Formation of Different Salts or Derivatives
8. Use of Amino Acids and Protein Hydrolysates
9. Inclusion Complexes
10. Molecular Complexes

2.1.4 Evaluation of Chewable Tablets

Physical Evaluation

The physical evaluation involves the following:

1. Tablet physical appearance
2. Hardness
3. Friability
4. Disintegration
5. Dissolution

Chemical Evaluation

The Chemical evaluation involves the following:

1. Assay for drug content
2. Content Uniformity
3. In Vitro and In Vivo Evaluation

Organoleptic Evaluation

The Organoleptic evaluation involves the following:

1. Mouth feel
2. Grittiness
3. Taste

2.2 The Physiology and Psychology of taste

Taste sensation, can be expressed as a feeling by an individual when something is put into mouth in order to ascertain the wholesomeness of the component.

There are four fundamentals of taste

- Sweet and salty, mainly at the tip of the tongue
- Sour, at the side of the tongue
- Bitter at the back of the tongue

Fig.2.1 Human tongue with different taste zone

Human tongue contains 50-100 number onion shaped structures in, called as taste buds. Chemicals from foods or orally ingested medicaments are dissolved by saliva via taste pores. They either interact with surface proteins known as taste receptors or with pore-like proteins called ion channels. These interaction cause electrical changes within the taste cells that trigger them to send chemical signal translate into neurotransmission to the brain.

Salt and sour responses are of channel type responses, while sweet and bitter are surface protein response. Electrical responses, that send the signal to the brain, are result of varying concentration of charged atoms or ions within the taste cell. These cells normally posses net negative charge. Tastants alter this state by using varying means to increase concentration of positive ion within the taste cell. This depolarisation causes taste cells to release neurotransmitters, prompting neurons connected to the taste buds to send electrical messages to the brain. In the case of bitter taste, such as quinine, by binding to G-protein coupled receptors on the surface of the taste cell, prompts the protein subunits of alpha, beta, and the gamma to split and activate enzyme. This enzyme then converts the precursor within the cell into "second messenger". The second· messenger causes the release of calcium ions (Ca++) from endoplasmic reticulum of the taste cell. The resulting build-up of calcium ions cells leads to depolarization and neurotransmitter release. The signal gives a sense which is interpreted as a bitter taste.

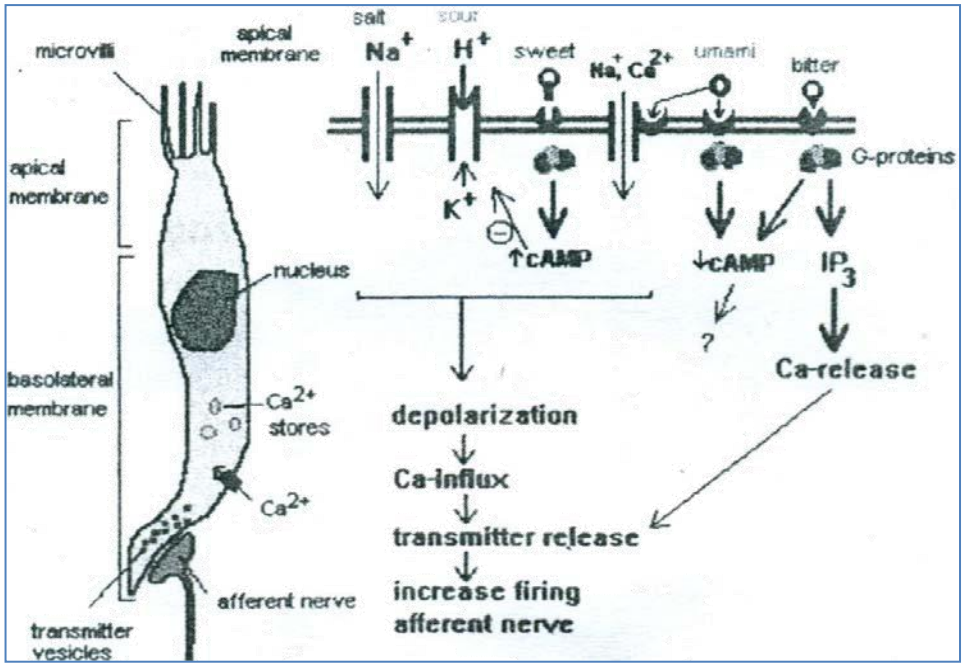


Fig: 2.2 Diagrammatic representation of taste sensation

Effective blocking of taste receptors can be accomplished by either coating the surface pore or competing with the channel themselves to reduce the net effect of bitter stimuli firing. Taste masking is defined as perceived reduction of an undesirable taste that would otherwise exist. Taste masking can be achieved using taste masking agents, specific flavour and sweeteners. Sweeteners are essential to complete the experience and produce a pleasant taste of the product.[3]

2.3 Introduction to Drug:

Table 2.1 Introduction to PHL_158

Drug	**PHL_158**
Water solubility	Freely soluble in water
Log P	4.4
Indications	PHL_158 is used as an antiemetic or to prevent motion sickness. It is used as an antiallergic, in pruritus, in severe pain & in cough preparations
Mechanism of action	PHL_158 is an H1-antagonist. It competes with free histamine for binding at H1-receptor sites in the GI tract, uterus, large blood vessels, and bronchial muscle
Absorption	On average, 88% of PHL_158 dose is absorbed after oral administration.
Half life	16-19 hours
Onset of action	20 mins after administration
Dose	12.5-50 mg

2.3.1 Marketed product of PHL_158

Table 2.2 Marketed product of Drug PHL_158

Sr. no	**Dosage Form & Route**	**Strength**	**Company**	**Indication**
1.	Injectable; Injection	25mg/ml, 50mg/ml	Teva Parenteral	Adjunct To Analgesics
2.	Suppository; Rectal	25mg, 50mg	G And W Labs	Nausea And Vomiting, Allergic Conditions
3.	Syrup; Oral	6.25mg/5ml	Wockhardt	Paediatric Cough Preparations
4.	Tablet; Oral	50mg	Sandoz	Motion Sickness

2.4 Introduction to Excipients:

- **MANNITOL**

1 Nonproprietary Names

BP: Mannitol

JP: D-Mannitol

PhEur: Mannitol

USP: Mannitol

2 Synonyms

Cordycepic acid; C*PharmMannidex; E421; Emprove; manna sugar; D-mannite; mannite; mannitolum; Mannogem; Pearlitol.

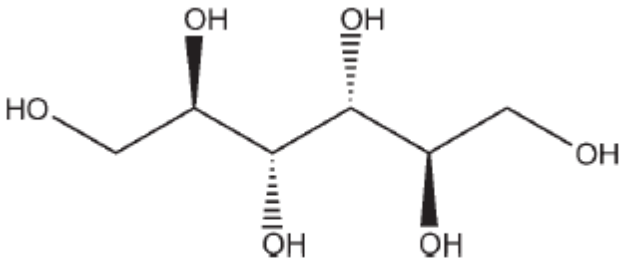
3 Chemical Name and CAS Registry Number

D-Mannitol [69-65-8]

4 Empirical Formula and Molecular Weight

C6H14O6 182.17

5 Structural Formula



6 Functional Category

Diluent; plasticizer; sweetening agent; tablet and capsule diluent; therapeutic agent; tonicity agent.

7 Applications in Pharmaceutical Formulation or Technology

Mannitol is widely used in pharmaceutical formulations and food products. In pharmaceutical preparations it is primarily used as a diluent (10–90% w/w) in tablet formulations, where it is of particular value since it is not hygroscopic and may thus be used with moisture-sensitive active ingredients. Mannitol may be used in direct-compression tablet applications, for which the granular and spray-dried forms are available, or in wet granulations.Granulations containing mannitol have the advantage of being dried easily. Specific tablet applications include antacid preparations, glyceryl trinitrate tablets, and vitamin preparations. Mannitol is commonly used as an excipient in the manufacture of chewable tablet formulations because of its negative heat of solution, sweetness, and 'mouthfeel'. In lyophilized preparations, mannitol (20–90% w/w) has been included as a carrier to produce a stiff, homogeneous cake that improves the appearance of the lyophilized plug in a vial. A pyrogen-free form is available specifically for this use. Mannitol has also been used to prevent thickening in aqueous antacid suspensions of aluminum hydroxide (<7% w/v). It has been suggested as a plasticizer in soft-gelatin capsules, as a component of sustained-release tablet formulations, and as a carrier in dry powder inhalers. It is also used as a diluent in rapidly dispersing oral dosage forms. It is used in food applications as a bulking agent. Therapeutically, mannitol administered parenterally is used as an osmotic diuretic, as a diagnostic agent for kidney function, as an adjunct in the treatment of acute renal failure, and as an agent to reduce intracranial pressure, treat cerebral edema, and reduce intraocular pressure. Given orally, mannitol is not absorbed significantly from the gastrointestinal tract, but in large doses it can cause osmotic diarrhea.

8 Description

Mannitol is D-mannitol. It is a hexahydric alcohol related to mannose and is isomeric with sorbitol. Mannitol occurs as a white, odorless, crystalline powder, or freeflowing granules. It has a sweet taste, approximately as sweet as glucose and half as sweet as

sucrose, and imparts a cooling sensation in the mouth. Microscopically, it appears as orthorhombic needles when crystallized from alcohol. Mannitol shows polymorphism.

9 Typical Properties

Density (bulk)

0.430 g/cm3 for powder;

0.7 g/cm3 for granules.

Density (tapped)

0.734 g/cm3 for powder;

0.8 g/cm3 for granules.

Density (true) 2.514 g/cm3

Dissociation constant pKa = 13.5 at 188C

Flash point <1508C

Flowability Powder is cohesive, granules are free flowing.

Heat of combustion 16.57 kJ/g (3.96 kcal/g)

Heat of solution _120.9 J/g (_28.9 cal/g) at 258C

Melting point 166–1688C

Osmolarity A 5.07% w/v aqueous solution is isoosmotic with serum.

10 Stability and Storage Conditions

Mannitol is stable in the dry state and in aqueous solutions. Solutions may be sterilized by filtration or by autoclaving and if necessary may be autoclaved repeatedly with no adverse physical or chemical effects. In solution, mannitol is not attacked by cold, dilute acids or alkalis, nor by atmospheric oxygen in the absence of catalysts. Mannitol does not undergo Maillard reactions. The bulk material should be stored in a well-closed container in a cool, dry place.

11 Incompatibilities

Mannitol solutions, 20% w/v or stronger, may be salted out by potassium chloride or sodium chloride. Precipitation has been reported to occur when a 25% w/v mannitol solution was allowed to contact plastic. Sodium cephapirin at 2 mg/mL and 30 mg/mL concentration is incompatible with 20% w/v aqueous mannitol solution. Mannitol is incompatible with xylitol infusion and may form complexes with some metals such as aluminum, copper, and

iron. Reducing sugar impurities in mannitol have been implicated in the oxidative degradation of a peptide in a lyophilized formation. Mannitol was found to reduce the oral bioavailability of cimetidine compared to sucrose.

12 Regulatory Status

GRAS listed. Accepted for use as a food additive in Europe. Included in the FDA Inactive Ingredients Database (IP, IM, IV, and SC injections; infusions; buccal, oral and sublingual tablets, powders and capsules; ophthalmic preparations; topical solutions). Included in nonparenteral and parenteral medicines licensed in the UK. Included in the Canadian List of Acceptable Mon-medicinal Ingredients.

- **XYLITOL**

1 Nonproprietary Names

BP: Xylitol

JP: Xylitol

PhEur: Xylitol

USP-NF: Xylitol

2 Synonyms

E967; Klinit; meso-xylitol; xilitol; Xylifin; Xylisorb; xylit; Xylitab;

xylite; Xylitolo; xylitolum.

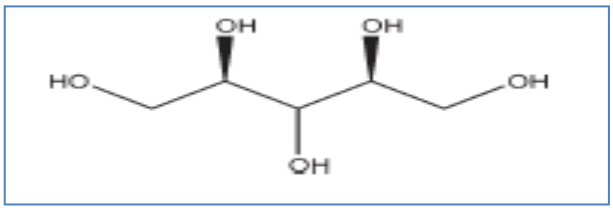
3 Chemical Name and CAS Registry Number

xylo-Pentane-1,2,3,4,5-pentol [87-99-0]

4 Empirical Formula and Molecular Weight

$C_5H_{12}O_5$ 152.15

5 Structural Formula



6 Functional Category

Coating agent; diluent; emollient; humectant; sweetening agent;
tablet and capsule diluent; tablet filler.

7 Applications in Pharmaceutical Formulation or Technology

Xylitol is used as a noncariogenic sweetening agent in a variety of pharmaceutical dosage forms, including tablets, syrups, and coatings. It is also widely used as an alternative to sucrose in foods and as a base for medicated confectionery. Xylitol is finding increasing application in chewing gum, mouthrinses, and toothpastes as an agent that decreases dental plaque and tooth decay (dental caries). Unlike sucrose, xylitol is not fermented into cariogenic acid end products and it has been shown to reduce dental caries by inhibiting the growth of cariogenic Streptococcus mutans bacteria. As xylitol has an equal sweetness intensity to sucrose, combined with a distinct cooling effect upon dissolution of the crystal, it is highly effective in enhancing the flavor of tablets and syrups and masking the unpleasant or bitter flavors associated with some pharmaceutical actives and excipients. In topical cosmetic and toiletry applications, xylitol is used primarily for its humectant and emollient properties, although it has also been reported to enhance product stability through a
combination of potentiation of preservatives and its own bacteriostatic and bactericidal properties. Granulates of xylitol are used as diluents in tablet formulations, where they

can provide chewable tablets with a desirable sweet taste and cooling sensation, without the 'chalky' texture experienced with some other tablet diluents. Xylitol solutions are employed in tablet-coating applications at concentrations in excess of 65% w/w.

8 Description

Xylitol occurs as a white, granular solid comprising crystalline, equidimensional particles having a mean diameter of about 0.4–0.6 mm. It is odorless, with a sweet taste that imparts a cooling sensation. Xylitol is also commercially available in powdered form, and several granular, directly compressible forms.

9 Stability and Storage Conditions

Xylitol is stable to heat but is marginally hygroscopic. Caramelization can occur only if it is heated for several minutes near its boiling point. Crystalline material is stable for at least 3 years if stored at less than 65% relative humidity and 258C. Milled and specialized granulated grades of xylitol have a tendency to cake and should therefore be used within 9 to 12 months. Aqueous xylitol solutions have been reported to be stable, even on prolonged heating and storage. Since xylitol is not utilized by most microorganisms products made with xylitol are usually safe from fermentation and microbial spoilage. Xylitol should be stored in a well-closed container in a cool, dry place.

10 Incompatibilities

Xylitol is incompatible with oxidizing agents.

11 Regulatory Status

GRAS listed. Approved for use as a food additive in over 70 countries worldwide, including Europe, the USA and Japan. Included in the FDA Inactive Ingredients Database (oral solution, chewing gum). Included in nonparenteral medicines licensed in the UK and USA. Included in the Canadian List of Acceptable Nonmedicinal Ingredients.

- **AVICEL PH-101**

1 Nonproprietary Names

BP: Microcrystalline Cellulose

JP: Microcrystalline Cellulose

PhEur: Cellulose, Microcrystalline

USP-NF: Microcrystalline Cellulose

2 Synonyms

Avicel PH; Cellets; Celex; cellulose gel; hellulosum microcristallinum; Celphere; Ceolus KG; crystalline cellulose; E460; Emcocel; Ethispheres; Fibrocel; MCC Sanaq; Pharmacel; Tabulose; Vivapur.

3 Chemical Name and CAS Registry Number

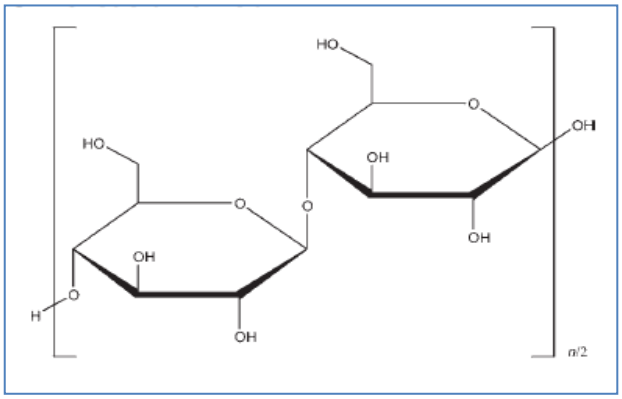
Cellulose [9004-34-6]

4 Empirical Formula and Molecular Weight

(C6H10O5)n _36 000

where n _ 220.

5 Structural Formula



6 Functional Category

Adsorbent; suspending agent; tablet and capsule diluent; tablet disintegrant.

7 Applications in Pharmaceutical Formulation or Technology

Microcrystalline cellulose is widely used in pharmaceuticals, primarily as a binder/diluent in oral tablet and capsule formulations where it is used in both wet-granulation and direct-compression processes. In addition to its use as a binder/diluent, microcrystalline cellulose also has some lubricant and disintegrant properties that make it useful in tableting.

8 Description

Microcrystalline cellulose is a purified, partially depolymerised cellulose that occurs as a white, odorless, tasteless, crystalline powder composed of porous particles. It is commercially available in different particle sizes and moisture grades that have different properties and applications.

9 Stability and Storage Conditions

Microcrystalline cellulose is a stable though hygroscopic material. The bulk material should be stored in a well-closed container in a cool, dry place.

10 Incompatibilities

Microcrystalline cellulose is incompatible with strong oxidizing agents.

11 Regulatory Status

GRAS listed. Accepted for use as a food additive in Europe. Included in the FDA Inactive Ingredients Database (inhalations; oral capsules, powders, suspensions, syrups, and tablets; topical and vaginal preparations). Included in nonparenteral medicines licensed in the UK. Included in the Canadian List of Acceptable Nonmedicinal Ingredients.

- **CROSCARMELLOSE SODIUM(AC-DI-SOL)**

1 Nonproprietary Names

BP: Croscarmellose Sodium

JP: Croscarmellose Sodium

PhEur: Croscarmellose Sodium

USP-NF: Croscarmellose Sodium

2 Synonyms

Ac-Di-Sol; carmellosum natricum conexum; crosslinked carboxymethylcellulose sodium; Explocel; modified cellulose gum; Nymcel ZSX; Pharmacel XL; Primellose; Solutab; Vivasol.

3 Chemical Name and CAS Registry Number

Cellulose, carboxymethyl ether, sodium salt, crosslinked [74811-65-7]

4 Functional Category

Tablet and capsule disintegrant.

5 Applications in Pharmaceutical Formulation or Technology

Croscarmellose sodium is used in oral pharmaceutical formulations as a disintegrant for capsules, tablets, and granules. In tablet formulations, croscarmellose sodium may be used in

both direct-compression and wet-granulation processes. When used in wet granulations, the croscarmellose sodium should be added in both the wet and dry stages of the process (intra- and extragranularly) so that the wicking and swelling ability of the disintegrant is best utilized. Croscarmellose sodium at concentrations up to 5% w/w may be used as a tablet disintegrant, although normally 2% w/w is used in tablets prepared by direct compression and 3% w/w in tablets prepared by a wet-granulation process.

6 Description

Croscarmellose sodium occurs as an odorless, white or grayishwhite Powder

7 Typical Properties

Acidity/alkalinity pH = 5.0–7.0 in aqueous dispersions.

Bonding index 0.0456

Brittle fracture index 0.1000

Density (bulk) 0.529 g/cm3 for Ac-Di-Sol

8 Stability and Storage Conditions

Croscarmellose sodium is a stable though hygroscopic material. A model tablet formulation prepared by direct compression, with croscarmellose sodium as a disintegrant, showed no significant difference in drug dissolution after storage at 308C for 14 months.Croscarmellose sodium should be stored in a well-closed container in a cool, dry place.

9 Incompatibilities

The efficacy of disintegrants, such as croscarmellose sodium, may be slightly reduced in tablet formulations prepared by either the wet-granulation or direct-compression process that contain hygroscopic excipients such as sorbitol. Croscarmellose sodium is not compatible with strong acids or with soluble salts of iron and some other metals such as aluminum,

mercury, and zinc.

10 Regulatory Status

Included in the FDA Inactive Ingredients Database (oral capsules, granules, sublingual tablets, and tablets). Included in nonparenteral medicines licensed in the UK. Included in the Canadian List of Acceptable Non-medicinal Ingredients.[4]

2.5 Introduction to Granulation:

In the pharmaceutical industry, the preferred tablet production method is direct tableting. Until the late 1950s the vast majority of tablets produced in the world were manufactured by a process requiring granulation of the powdered constituents prior to tableting. However, it is often necessary to improve the material's compaction and flow properties in order to obtain uniform die-filling and to produce tablets of adequate quality. These properties are commonly enhanced by converting fine powders into larger agglomerates by the process of granulation [5].

Granulation is the process in which primary powder particles are made to adhere to form larger, multiparticle entities called granules. Granulation normally commences after initial dry mixing of the necessary powdered ingredients so that a uniform distribution of each ingredient through the mix is achieved. After granulation the granules will either be packed (when used as a dosage form), or they may be mixed with other excipients prior to tablet compaction or capsule filling [6].

The granulation process of size enlargement used within the pharmaceutical industry has its roots in ancient times. The practice of delivering medicinal powder by hand rolling into a pill by using honey or sugar has been used for centuries. It is still the practice to deliver the botanical and herbal extract in homeopathic and ayurvedic branches of medicine, which are still practiced in India along with allopathic medicine. The term ‘‘granulated’’ material is derived from the Latin word ‘‘granulatum,’’ meaning grained. The granulated material can be obtained by direct size enlargement of primary particles, or size reduction from dry compacted material. In modern times, granulation technology has been widely used by a wide range of industries, such as coal, mining, and agrochemical. These industries employ agglomeration techniques to reduce dust, provide ease of handling, and enhance the material's ultimate utility [7].

The term ‘‘granulated’’ material is derived from the Latin word ‘‘granulatum,’’ meaning grained. The granulated material can be obtained by direct size enlargement of primary particles, or size reduction from dry compacted material. The classical granulation process using either wet or dry methods is employed in the process industries. Pharmaceutical granulation process is used for tablet and sometimes capsule dosage forms; however, in some applications the process is used to produce spherical granules

for the modified release indications or to prepare granules as sprinkles to be used by pediatric patients [7].

2.5.1 Reasons for granulation [6][7]:

(a) To prevent segregation of the constituents of the powder mix:

Segregation (or demixing) is due primarily to differences in the size or density of the components of the mix, the smaller and/or denser particles concentrating at the base of a container with the larger and/or less dense ones above them. An ideal granulation will contain all the constituents of the mix in the correct proportion in each granule, and segregation of the ingredients will not occur (Fig. 2.3). It is also important to control the particle size distribution of the granules because, although the individual components may not segregate, if there is a wide size distribution the granules themselves may segregate. If this occurs in the hoppers of sachet filling machines, capsule-filling machines or tablet machines, products with large weight variations will result. This is because these machines fill by volume rather than weight, and if different regions in the hopper contain granules of different sizes (and hence bulk density), a given volume in each region will contain a different weight of granules. This will lead to an unacceptable distribution of the drug content within the batch of finished product, even though the drug is evenly distributed, weight per weight, through the granules.

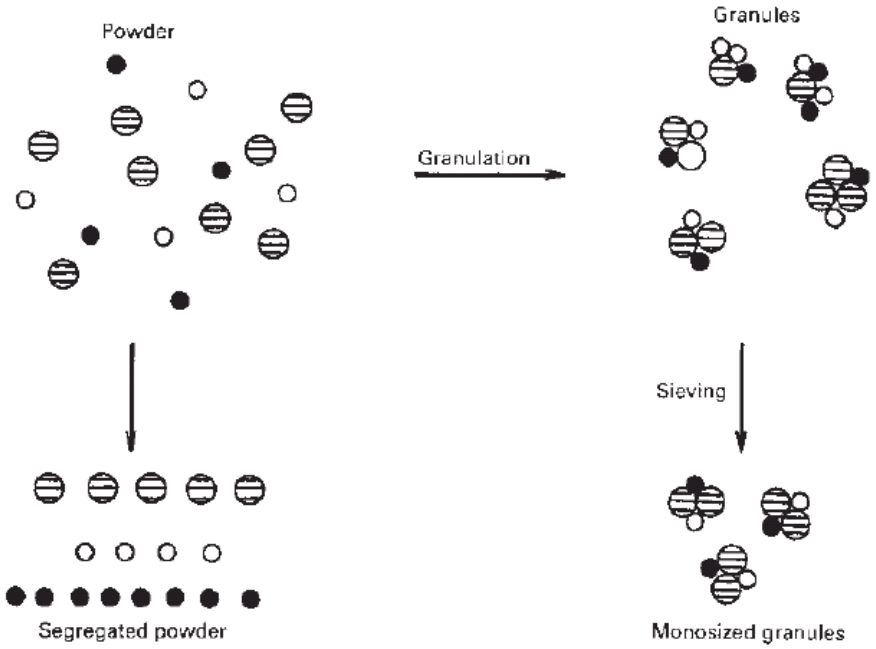


Figure 2.3 Granulation to Prevent Segregation

(b) To improve the flow properties of the mix:

Many powders, because of their small size, irregular shape or surface characteristics, are cohesive and do not flow well. Poor flow will often result in a wide weight variation within the final product owing to variable fill of tablet dies etc. Granules produced from such a cohesive system will be larger and more isodiametric, both factors contributing to improved flow properties.

(c) To improve the compaction characteristics of the mix:

Some powders are difficult to compact even if a readily compactable adhesive is included in the mix, but granules of the same formulation are often more easily compacted and produce stronger tablets. This is associated with the distribution of the adhesive within the granule and is a function of the method employed to produce the granule. Often solute migration occurring during the post granulation drying stage results in a binder-rich outer layer to the granules. This in turn leads to direct binder–binder bonding, which assists the consolidation of weakly bonding materials.

(d) The granulation of toxic materials will reduce the hazard associated with the generation of toxic dust that may arise when handling powders. Suitable precautions must be taken to ensure that such dust is not a hazard during the granulation process. Thus granules should be non-friable and have a suitable mechanical strength.

(e) Materials which are slightly hygroscopic may adhere and form a cake if stored as a powder. Granulation may reduce this hazard, as the granules will be able to absorb some moisture and yet retain their flowability because of their size.

(f) Granules, being denser than the parent powder mix, occupy less volume per unit weight. They are therefore more convenient for storage or shipment.

(g) Other reasons:

- To increase the uniformity of drug distribution in the product.
- To densify the material.
- To enhance the flow rates and rate uniformity.
- To facilitate metering or volumetric dispensing.
- To reduce dust.
- To improve the appearance of the product.

Granulation methods can be divided into two types: wet methods, which use a liquid in the process, and *dry* methods in which no liquid is used.

2.5.2. Wet Granulation (Involving Wet Massing)

Wet granulation involves the massing of a mix of dry primary powder particles using a granulating fluid. The fluid contains a solvent which must be volatile so that it can be

removed by drying, and be non-toxic. Typical liquids include water, ethanol and isopropanol, either alone or in combination. The granulation liquid may be used alone or, more usually, as a solvent containing a dissolved adhesive (also referred to as a binder or binding agent) which is used to ensure particle adhesion once the granule is dry. Water is commonly used for economical and ecological reasons. Its disadvantages as a solvent are that it may adversely affect drug stability, causing hydrolysis of susceptible products, and it needs a longer drying time than do organic solvents. This increases the length of the process and again may affect stability because of the extended exposure to heat [6]. Different operations and processes are involved in wet granulation process. The most important ones, which can affect the tablets of the resulting granulation, are: (see figure 2.4) [10].

- Preparation of the powder mixture with screening and mixing
- Spraying with solution to the appropriate wetness
- Drying the solid - liquid mixture
- Milling the dry granulate to proper particle size

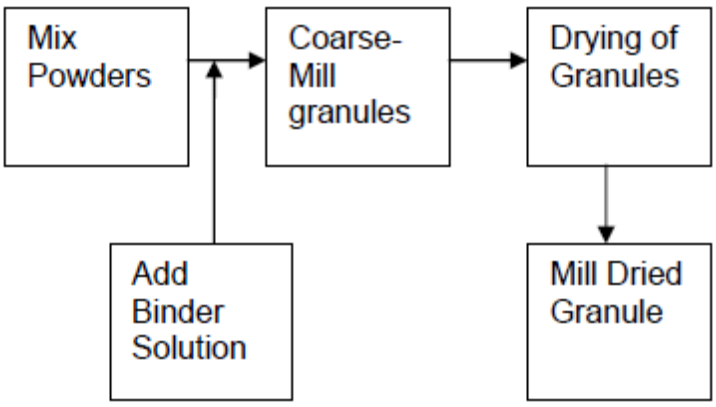


Figure 2.4 Flow Sheet of Granule production

2.5.3. Dry Granulation

In the dry methods of granulation, the primary powder particles are aggregated under high pressure. There are two main processes. Either a large tablet (known as a 'slug') is produced in a heavy-duty tabletting press (a process known as 'slugging') or the powder is squeezed between two rollers to produce a sheet of material ('roller compaction'). In both cases these intermediate products are broken using a suitable milling technique to produce granular material, which is usually sieved to separate the desired size fraction. The unused fine material may be reworked to avoid waste. This dry method may be used for drugs that do not compress well after wet granulation, or those which are sensitive to moisture [6]. Slugging is also called as a pre-compression process for the formation of extra large tablets (slugs), usually of variable weight, due to poor flow of the drug powder. The resulting slugs are subsequently broken down into granules, which are recompressed to obtain the final tablets. The procedure is applicable to the dry granulation of hydrolysable drugs, such as aspirin, which are not amenable to wet granulation [8].

Amongst the main drawing cards dry granulation is its simplicity and being a continuous process with a considerably larger throughput than wet granulation. However, dry granulation has been associated with technical challenges regarding the flowability of the granulate and its recompactibility, which means that until now wet granulation has been chosen in approximately 70% of cases despite the higher cost and lower efficiency ratios achieve [11] . Recent advances in formulation technologies have led to a shift from traditional wet granulation to dry granulation manufacturing processes in the development of solid oral dosage forms. This change has come about largely because of process expedition, easy handling, and time and cost savings; the wet granulation process requires multiple steps that involve agglomeration (granulation), drying, sieving, particle size reduction, and blending [12]. Dry granulation is suitable for medium and high-dose drugs and is particularly applicable for active pharmaceutical ingredients (APIs) that are heat and moisture sensitive [13].

2.5.4 Mechanisms of granule formation

In the dry methods, particle adhesion takes place because of applied pressure. A compact or sheet is produced which is larger than the granule size required, and therefore the required size can be attained by milling and sieving. In wet granulation methods, liquid

added to dry powders has to be distributed through the powder by the mechanical agitation created in the granulator. The particles adhere to each other because of liquid films, and further agitation and/or liquid addition causes more particles to adhere. The precise mechanism by which a dry powder is transformed into a bed of granules varies for each type of granulation equipment, but the mechanism discussed below serves as a useful broad generalization of the process. The proposed granulation mechanism can be divided into three stages.

Nucleation

Granulation starts with particle–particle contact and adhesion due to liquid bridges. A number of particles will join to form the pendular state illustrated in Figure 2.5**.** Further agitation densifies the pendular bodies to form the capillary state, and these bodies act as nuclei for further granule growth.

Transition

Nuclei can grow in two possible ways: either single particles can be added to the nuclei by pendular bridges, or two or more nuclei may combine. The combined nuclei will be reshaped by the agitation of the bed. This stage is characterized by the presence of a large number of small granules with a fairly wide size distribution. Providing that this distribution is not excessively large, this is a suitable end-point for granules used in capsule and tablet manufacture, as relatively small granules will produce a uniform tablet die or capsule fill. Larger granules may give rise to problems in small-diameter dies owing to bridging across the die and uneven fill.

Ball growth

Further granule growth produces large, spherical granules and the mean particle size of the granulating system will increase with time. If agitation is continued, granule coalescence will continue and produce an unusable, overmassed system, although this is dependent upon the amount of liquid added and the properties of the material being granulated. Although ball growth produces granules that may be too large for

pharmaceutical purposes, some degree of ball growth will occur in planetary mixers and it is an essential feature of some spheronizing equipment.

The four possible mechanisms of ball growth are illustrated in Figure 2.5.

Coalescence Two or more granules join to form a larger granule.

Breakage Granules break into fragments which adhere to other granules, forming a layer of material over the surviving granule.

Abrasion *transfer* Agitation of the granule bed leads to the attrition of material from granules.This abraded material adheres to other granules, increasing their size.

Layering When a second batch of powder mix is added to a bed of granules the powder will adhere to the granules, forming a layer over the surface and increasing the granule size. This mechanism is only relevant to the production of layered granules using spheronizing equipment.

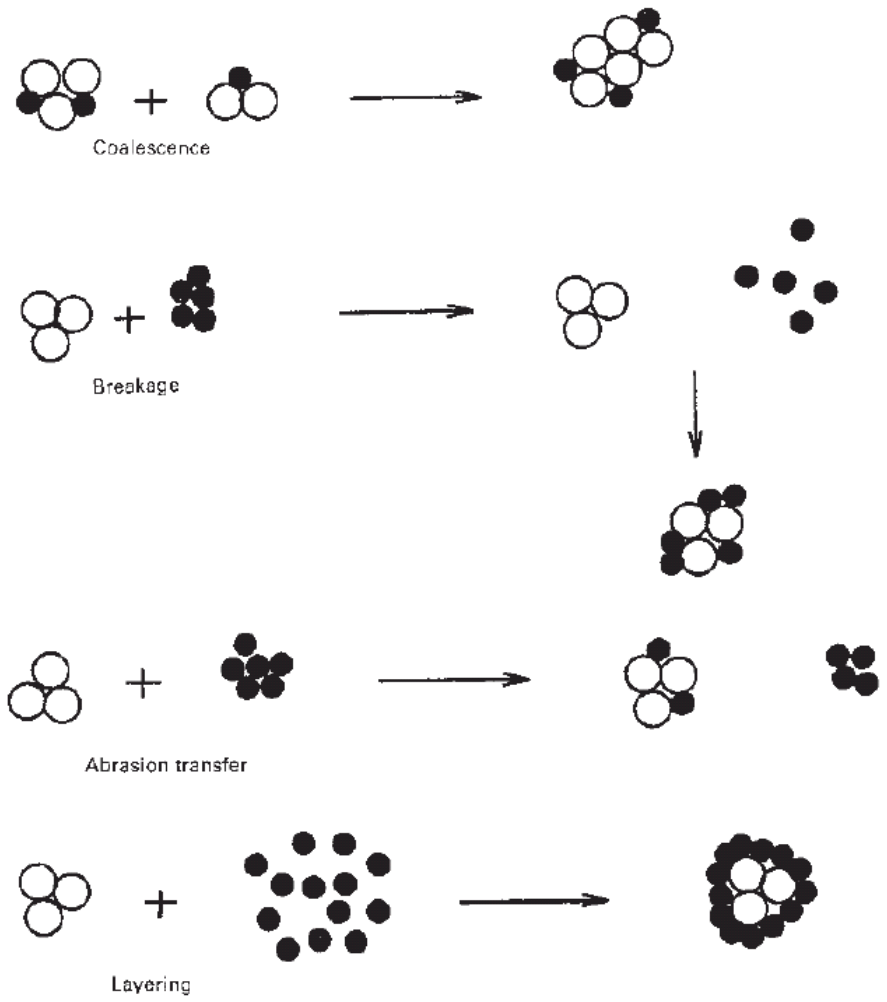


Figure 2.5 Mechanisms of ball growth during granulation

There will be some degree of overlap between these stages and it will be very difficult to identify a given stage by inspection of the granulating system. For end-product uniformity it is desirable to finish every batch of a formulation at the same stage, and this may be a major problem in pharmaceutical production. Using the slower processes, such as the planetary mixer, there is usually sufficient time to stop the process before over massing occurs With faster granulation equipment the duration of granulation can only be used as a control parameter when the formulation is such that granule growth is slow and takes place at a fairly uniform rate. In many cases, however, the transition from a non-granulated to an overmassed system is very rapid, and monitoring equipment is necessary to stop the granulation at a predetermined point, known as granulation end-point control.

2.5.5. Introduction to Dry granulation:

Dry granulation operations do not use moisture or heat to process powders into densified granules. The pharmaceutical industry employs two methods of dry granulation: slugging and roller compaction. Little has been written about pharmaceutical dry granulation technology. Its contemporary use in the industry is 50–60 years, beginning in the late 1940s. However, its popularity has risen in the last 15 years in parallel with the increased research on new efficacious active pharmaceutical ingredients (API) in the pharmaceutical industry. A number of these new API cannot be processed so easily using wet granulation and drying processing steps, because of their chemical fragility and sensitivity. Therefore, this pushes the need for the use of dry granulation processing techniques to advance new API in the 21st century. Briefly, in dry pharmaceutical granulation processing, the powder particles are aggregated under high pressure, typically a pressure of 30–70 bar. Particulate matter can be aggregated when compressed at high pressure because of bonding forces developed by the direct contact between the solid surfaces. The high pressure serves to improve the contact area between the surfaces and thus the overall bonding strength. Sometimes a binding agent is needed to provide additional bonding strength. In the pharmaceutical industry, dry granulation processing in the 1950s–1970s favored a process called slugging. This process design consisted of feeding powder into a large compression machine, such as a Stokes D3 type compression machine, where the powder was compressed into large tablets or slugs, typically in the order of 1 in. diameter with a tablet gauge of about 0.25 in. The tablet slugs were subsequently milled by a separate sizing machine to an appropriate particle size distribution, and further processed into pharmaceutical capsules, powder for oral suspensions, sachets, or tablet dosage forms. The slugging process is still used today by only a few manufacturing firms that have old pharmaceutical formulation processes. If a tablet press is used for the compaction process, the term slugging is used. But since particles with a small particle size do not flow well into the die of a tablet press, the results are weight differences from one tablet (slug) to another. This in turn causes large fluctuations in the forces applied onto the individual slugs, with translates in variations of the slug's mechanical strength. Therefore, the properties of these granulates obtained by milling the slugs cannot be controlled well either. This is one of the main reasons

why slugging is hardly used any more as a dry granulation method. Today, modern pharmaceutical formulation processes introduced into the Americas, Western Europe, Australia, and parts of Asia do not use this kind of dry granulation equipment in newly developed formulations. The slugging process is a relic of the past in modern pharmaceutical technology; roller compaction is the key technology to future dry granulation processing. The slugging process is externally influenced by raw material feed properties such as powder cohesiveness, density, flow characteristics, and powder particle size distribution. The slugging machine's design characteristics such as machine type, feed hopper, feed frame, die diameter, tooling features, compression speed, and slugging pressure also influence the slugging process and the final product properties. In general, the key processing operational aspect of slugging is to maintain a uniform powder fill weight into the dies during the dynamics of the slugging process. This assures the best chance to manufacture uniform powder slugs and, ultimately, uniform densified granules. The compression– slugging setup is a key essential to maximizing the slugging throughput and minimizing the hopper feed-frame and die powder flow problems associated with the process. Slugging compression is normally performed at 4–6 tons hydraulic pressure, at a rate of 10–30 turret revolutions per minute. The specific machine tonnage, turret speed, and roll dwell time required for the process are dependent on the powder blend's physical properties, the tooling configuration, machine parts, and ultimately the slug specifications. Typical slugging machine output ranges from 30 to 50 kg/hr and the machines are not instrumented with modern devices to control their performance. The disadvantages with the slugging technology in the pharmaceutical industry are:

- Single batch processing
- Excessive air and sound pollution
- Frequent maintenance changeover
- Increased use of storage containers
- Poor process control
- Increased needs of manufacturing space
- Poor economies of scale
- Increase of logistics
- Low manufacturing throughput per hour

- More energy and time required to produce 1 kg of slugs than 1 kg of roller compact

Unlike the slugging process technology, roller compaction technology is well suited for dry granulation agglomeration in the era of modern development of active pharmaceutical ingredients in pharmaceutical plants [14].

2.6 Introduction To Korsch Xl 100:

The KORSCH XL100 is an innovative tablet press for product development, scale-up, and clinical batch production. The XL100 offers a new standard in GMP, extreme accessibility to the compression zone, an exchangeable turret for maximum flexibility, and a combination of quick-disconnects and smooths surfaces that permit fast cleaning and changeover. The machine is extremely robust and rugged, offering a pre compression capability of 10 kN, and a main compression capability of 60 kN, contained in a unique structural design that eliminates vibration to the head piece and base frame. Every technical detail of the XL 100 has been meticulously developed for operator convenience and operational excellence. From the special steel for the turret and die table, to the precision toothed belt for the main drive, the XL 100 offers production scale performance in a development scale machine.

Features of Korsch XL100:

- Small Scale.
- Exchangeable Turret Capability 12/10/8 EU or TSM Tools.
- 10 kN Precompression Force.
- 60 kN Main Compression Force.
- 120 RPM Press Speed Capability.
- Fully Instrumented.
- Fully Portable.
- Large Touch Screen Flush Mounted for Ergonomic Operation.
- PharmaResearch® and PharmaControl® Upgrade Possible.

The XL 100 Pro permits the execution of full compaction studies with limited material quantities. The XL100 may be fully instrumented for the measurement of precompression force, main compression force, ejection force (segmented cam), and scrape off force, to permit product development parameters to be evaluated and stored. KORSCH offers the PharmaResearch®, a Windows based data acquisition system that permits storage, analysis, and export of compression and ejection force data. In combination with PharmaControl® 3 press force control or PharmaResearch®, the XL100 Pro offers a fully integrated solution for expedited product development and clinical batch production.

PharmaResearch® Comprehensive Data Acquisition and Analysis

PharmaResearch® is a Windows-based system that offers data acquisition and analysis for press force and punch displacement data. The system displays press force waveforms in real time and permits on-demand data collection. The system can collect data locally or write the data to a networked SQL server for centralized data storage and analysis. The system can work with the following tablet press instrumentation:

✓ Precompression Force
✓ Main Compression Force
✓ Ejection Force
✓ Scrape-Off Force
✓ Die-Wall Force
✓ Punch Displacement

The data analysis is automatic and provides a statistical assessment of:

✓ Peak Force
✓ Area Under The Force-Time Curve
✓ Contact Time
✓ Rate of Force Application
✓ Rate of Force Decay

2.7 Introduction to Roller Compaction:

The increasing scale of manufacturing pharmaceutical products worldwide, the need for high processing rates, together with increased levels of good manufacturing practices, necessitate controlled dry granulation processes with as few processing steps as possible. This has been accomplished by instrumenting roller compactors to automate and control the mechanical process. Roller compaction technology plays a very important role in providing competitive cost control, safety, and quality products in the pharmaceutical industry [14].

The aims of roll compaction/dry granulation are an improved handling of the powders due to a larger particle size and a better flowability. Dust problems are minimized or avoided and the die filling during tableting is improved. Also, this is achievable by increasing the bulk density because less air will escape during tableting process. Sometimes the capping of tablets might also be reduced. Roll compaction/dry granulation can be used, if the drug or the excipient is poorly flowing or sensitive to heat or moisture. It can also be used for densification of powders prior to encapsulation [15].

Compaction Theory:

The process of dry granulation relies on interparticulate bond formation. Granule bond formation is characterized in different stages, which usually occur in the following order:

1. Particle rearrangement
2. Particle deformation
3. Particle fragmentation
4. Particle bonding.

Particle rearrangement occurs initially as powder particles begin filling void spaces. Air begins to leave the powder blend's interstitial spaces, and particles begin to move closer together. This action increases the powder blend's density. Particle shape and size are key factors in the rearrangement process. Spherical particles will tend to move less than particles of other shapes because of their close initial packing to one another.

Particle deformation occurs as compression forces are increased. This deformation increases the points of contact between particles where bonding occurs and is described as plastic deformation.

Particle fragmentation follows as the next bonding stage. This occurs at increased compression force levels. At this stage, particle fracturing creates multiple new surface sites, additional contact points, and potential bonding sites. Particle bonding occurs when plastic deformation and fragmentation occur. It is generally accepted that bonding takes place at the molecular level, and that this is due to the effect of van der Waals forces.

When powder granules undergo an applied force or stress, a stress force is released from the granules. The granules attempt to return to their original shape or form; this is described as elastic deformation. A deformation that does not totally recover after the stress is released is a plastic deformation. Elastic and plastic deformations can occur simultaneously, but one effect usually predominates.

Parrott identified three theories of compression bonding: mechanical, intermolecular, and liquid-surface film. Mechanical bonding purports that individual particles undergo elastic, plastic, and brittle deformation. Bonding of this nature occurs because particle surfaces intertwine, forming mechanical bonds. Intermolecular theory identifies that there are some unsatisfied surface ions that have a potential need to bond to one another. Under pressure, intermolecular forces become pushed together close enough so that van der Waals forces can act to consolidate particles. The liquid surface film theory identifies that bonding occurs because of the existence of a thin liquid film. The thin liquid film is generated from pressure induced by the energy of compression. This mechanism acts as a bonding agent promoting mechanical strength and an enlarged particle [16].

2.7.1 Mechanisms of Roll Compaction

The principle of compaction is based on equipment design and operating parameters that influence the starting material in a manner to produce an optimum compact. The space between two rolls, where different mechanisms occurs, is generally divided in three regions (see figure 2.3) [15]:

1. Slip region (feeding zone) – this zone is characterized with particles slipping at the roll surface and at the same time rearrangement and de-aeration can occur. The effectiveness of the slip region is related to wall friction and interparticle friction of the feed (14). The speed of the material is lower than the peripheral speed of the rolls.

2. Nip region (compaction zone) – in the nip region, the material is trapped between two rolls and is moving at the same speed as the roll surface. This forces the material through

the region of the maximum pressure where the particles deform plastically and/or break. The limit between feeding and compaction zones is the nip angle α. This angle is directly affected by the roll diameter and established in a line through the rolls' centers to a point on both roll where the powder starts to move at the same speed as the roll (see figure 2.6). To achieve acceptable compaction, the nip angle should be sufficiently large. It is about 12° and material characteristics, as particle size and density, can have influence on this value.

3. Extrusion region (release zone) – when the roll gap starts to increase, the compacted ribbon exhibits relaxation as it is released from the rolls.

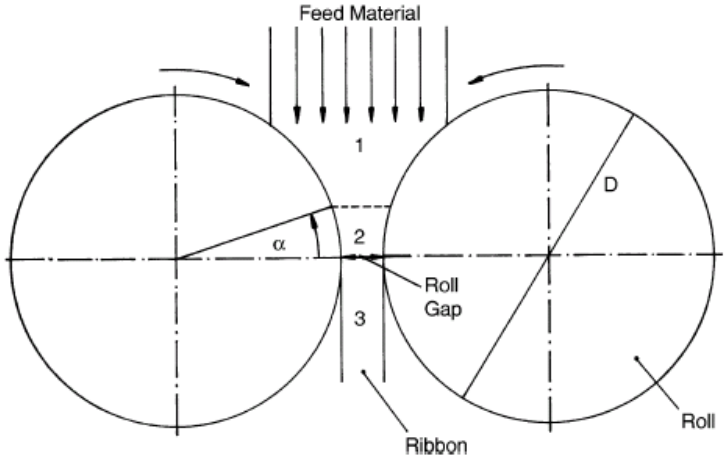


Figure 2.6 Roll compactor and different zones: 1, feed zone; 2, compaction zone; 3, extrusion zone.

Equation 1 is developed for the linear variation of compact thickness at a specific roll diameter [14]

$$e_1 = D\,\frac{d0}{((d1-d0))(1-\cos[\![\alpha]\!])} \qquad (1)$$

Where e_1 is compact thickness, D is roll diameter, d0 is material density at angle α and d1 is compact density. According to equation 1 it can be concluded that if the same compact thickness is required with different roller diameters, the density of the compacts would be greater with the larger diameter rollers.

Only few suppliers of roll compactors are established in the pharmaceutical field. The machine design differs between suppliers (Fig. 2.7) [11].

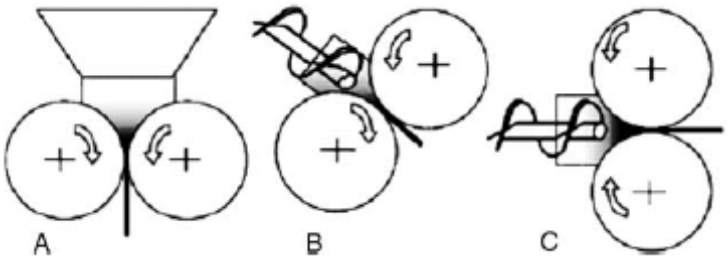


Figure 2.7 Configuration of roll compactors [11]

However, important improvements were implemented by different suppliers during the last decades. The suppliers provide machines in different sizes. Furthermore, the process control depends to a certain extent on the layout of the equipment. For example, if the two rolls are fixed, the compaction force will greatly vary with the fluctuating mass flow. In the case of one movable roll the compaction force can be kept constant by changing the gap width in case of fluctuating mass flow. Another important factor is the roll diameter. Since the nip angle is independent from the roll diameter, a higher roll diameter will result in a higher densification at a constant gap width. Therefore, some machine suppliers only offer machines with the same roll diameter but varying roll width, whereas other suppliers offer machines with different roll diameters.

Model of Roll Compaction Process

Theoretical analysis of the operation of roll-type pressing machines has first been proposed by Johanson in 1965. It was based on understanding the behavior of the material within roll press which involves the interaction between the particles of the material itself as well as the interaction between the material and roll surface. According to Johanson [15] roller compaction involves the continuous shear deformation of the material into a solid mass. The material is assumed to be isotropic, frictional, cohesive and compressible.

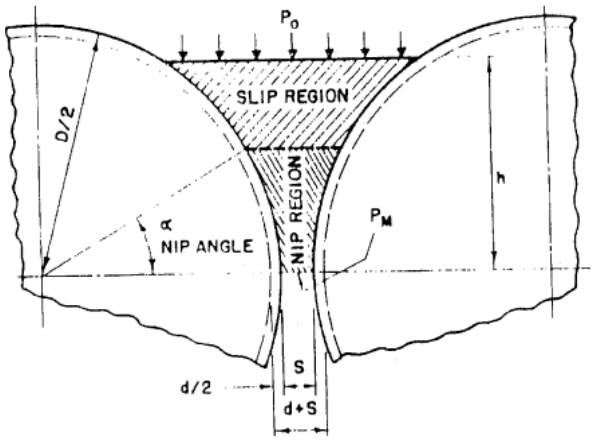


Figure 2.8 Front view of compactor rolls in horizontal plane.

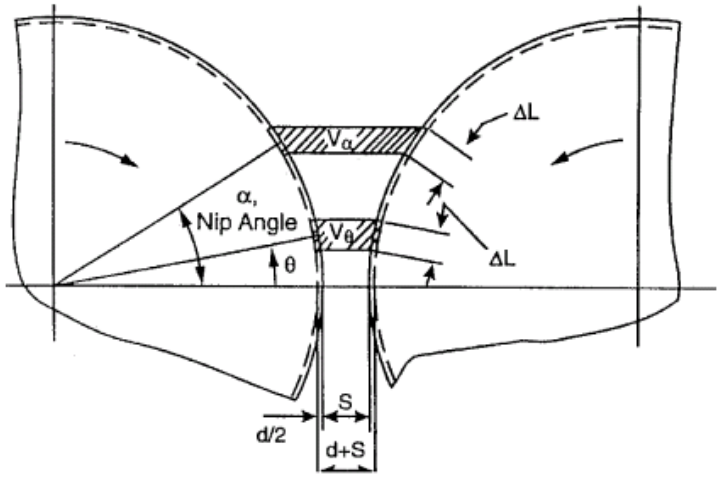


Figure 2.9 Front view of compactor rolls, depicting nip angle.

In Figure 7, P_0 = horizontal pressure between rolls, θ = angular position of roll bite, α= nip angle, 2d=roll diameter D, h= height above the roll center line at which feed pressure P_0 is applied, Pm= horizontal pressure at θ=0, S=roll gap, ΔL=arc-length segments, V_α =material trapped in volume space described by arc-lengths, V_θ =compressed volume space described by arc-lengths, γ_α and γ_θ respective powder bulk densities in volume spaces V_α and V_θ, and K=a material property constant for a given moisture content, temperature and time of compaction. Johanson stated that the pressure σ_θ at any $\theta < \alpha$ can be determined as a function of the pressure σ_α, at $\theta = \alpha$, by the pressure–density relationship. It was understood that, for increasing pressures, log density was a linear function of log pressure.

Two zones are considered in this approach [20]:

- $\alpha < \theta < \theta h$: slip zones, the rolls moves faster than the powder

- $\theta = \alpha$: the powder sticks to the rolls V powder = V roll

- $0 < \theta < \alpha$: densification takes place

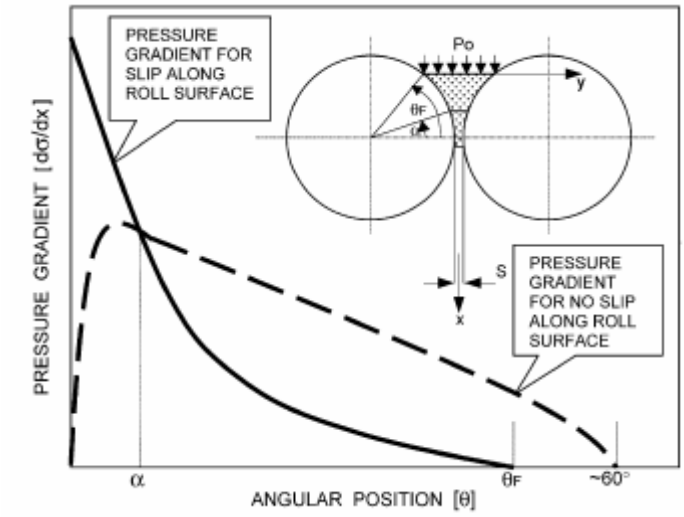


Figure 2.10 Vertical pressure gradient vs. angular position in roll bite (comparison of different methods)

To determine the nip angle two equations are considered, as it is shown in Figure 9. Determination of the pressure distribution above the nip region was based on the continuous plane-strain deformation and assuming the slip along the roll surface in the slip region, pressure gradient (dσ/dx) is given by the following equation 2.

$$\frac{d\sigma}{dx} = \frac{4\left(\frac{\pi}{2} - \theta - \vartheta\right)\tan\delta}{D/2[1 + \frac{S}{D} - \cos\theta][\cot(A-\mu) - \cot(A+\mu)]} \qquad (2)$$

Where θ is the angular position of the surface of a roll, such that θ = 0 corresponds to the minimum gap, ν acute angle, δ angle of internal friction, μ friction coefficient, and parameter A is given by:

$$A = \frac{\theta + \vartheta + \left(\frac{\pi}{2}\right)}{2} \qquad (3)$$

A typical dσ/dx function is shown by the solid line in Figure 2.10.

In the nip region no slip occurs along the rolls surface and all material trapped between the rolls at the position of nip angle must be compressed into a compact with a thickness equal to the roll gap. In this case, where slip does not occur, pressure gradient (dσ/dx) is given by equation 4.

$$\frac{d\sigma}{dx} = \frac{K\sigma 0(2\cos\theta - 1 - S/D)\tan\theta}{D/2[\frac{d}{D} + (1 + \frac{S}{D} - \cos\theta)\ \cos\theta]} \qquad (4)$$

This function is illustrated by the dashed line in Figure 9. According to Johanson [19] at the nip angle α (equation 5) the pressure gradient in the slip and nip regions are equal

$$\left(\frac{d\sigma}{dx}\right) slip = \left(\frac{d\sigma}{dx}\right) nip \qquad (5)$$

The intersection point of two curves (see figure 9.) gives the angles of nip α.

In general, the nip angle strongly depends on the material compressibility factor K, material flow properties, angle of internal friction, angle of wall friction. Dependence on the roll diameter and roll gap is almost negligible, especially when dimensionless roll gap S/D is less than 1 [17] [19] [20]

Equipment

The successful roll compaction of a powder depends on the matching powder properties, especially its compressibility and flowability, and to both the design and operating conditions of the compactor [20]. In the pharmaceutical field only a few producer of roll compactors are established. Although the general layout of the machines looks alike, there are some features that differ from compactor to compactor. These lead to a type classification:

Roll assembly: rolls can be mounted in a horizontal, inclined and vertical position (see figure 10).

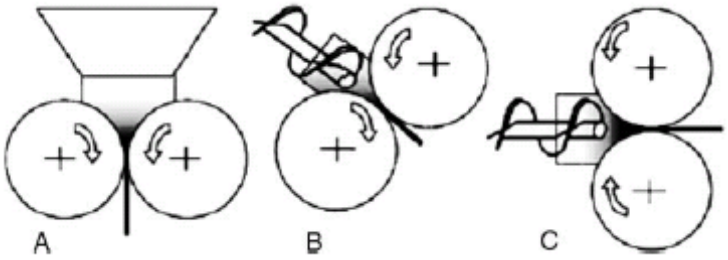


Figure 2.11 Configuration of roll compactors [15]

Horizontal position of rolls is a characteristic for Fitzpatrick Company, Bepex, Komarek (A), inclined for Gerteis (B) and Vertical for Alexanderwerk (C) [15]

The position of the rolls is mainly a manner of design and therefore it only plays minor role. However, the vertical assembly might induce that the nip angles in upper and lower roll differ. This can happen because the direction of force by friction and force of gravity is completely different for the two rolls. If nip angle is quite small the powder might stay in place, showing an increase in temperature, giving reason for concerning a thermal degradation of the material. When vertically assembled rolls are used differences in nip angles should be taken in to account.

- Fixed vs. movable rolls: according to gap system two type of roller compactors exist. One in which the distance between the rolls is constant during the process of powder densification and one in which this distance can be changed. In the first case gap size cannot be varied during the process of compaction. Ribbons which are produced have the same geometrical dimensions, but porosity can be changed with the fluctuating mass flow [15]. Compactors with variable gap system have one fixed and one moveable roll. The consolidating force on the material between two rolls is supplied by hydraulic units (see fig 2.12). This unit acts upon the floating roll which can move horizontally depending on feeding rate and applied pressure [20].

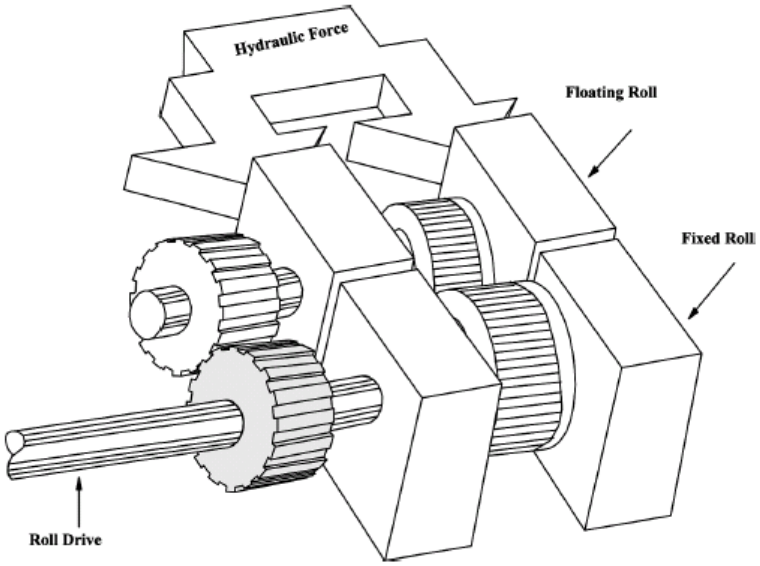


Figure 2.12 Fixed and floating roll pair.

- **Roll surface**: Roll surface has an effect on the efficiency and production rate in the powder compaction. According to powder properties different roll surface can be used: smooth, knurled and pocket design (see fig 2.13)

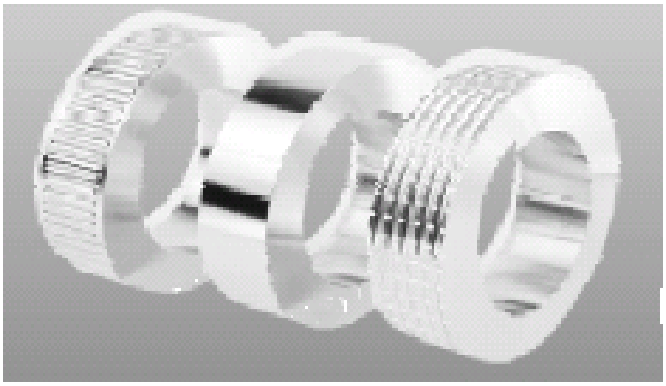


Figure 2.13 Various roll surfaces for compaction

-Feeding system: three different ways of feeding material into to the compactor exist, gravity transport, single screw feeder and double screw feeder (see figure 2.14). It must achieve a uniform and continuous flow of material in order to fill the nip between the rolls correctly and sufficiently, so that the formed compacts are not heterogeneous. When powder is dense and free flowing gravity feeder can be used, but for most powders, which are lightweight and do not fly freely single or double screw feeder is required. During

feeding, vacuum deaeration can be applied to remove air from a powder with low bulk density.

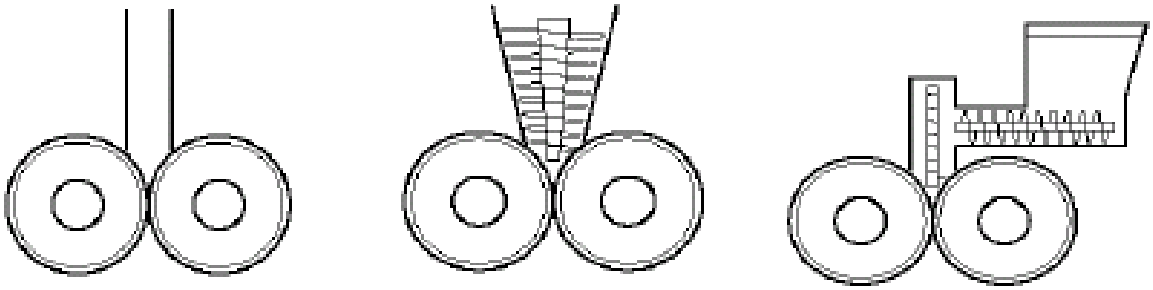


Figure 2.14 Different feeding system: a) gravity feeder, b) single screw feeder, c) double screw feeder

Process Parameters

Compaction in a roll press is more complicated than it looks at the first sight. Efficiency of roller compaction is based on the equipment design and operating parameters. The main process variables which can affect compaction are:

- **Compaction pressure:** if pressure is too low there is no compaction, but in the same time if it is too high over compaction will occur.

-Speed of feeding screw (vertical vs. horizontal): speed of vertical and horizontal screw should be optimized otherwise feeding is not continuous and compaction is not homogeneous.

- **Roll speed** affects the compaction by determining the dwell time that material should spend in the nip region which has an impact on the ability of the product to deaereate prior to passing between two rolls.

-Roll gap is the distance between the rolls at their closest point. This is the critical parameter of compaction and one that needs to be stabilized by the process parameters mentioned above. It is in a function of pressure applied to the rolls and the amount of material that is passed between them.

Formulation parameters:

The influence of formulation parameters on the properties of a product cannot be ignored. However, the influence of physical properties of a material, such as particle size and porosity, on its compactibility using roller compaction technique has not been extensively studied. Most of the studies carried out were those to investigate the influence of the physical properties of starting materials employed for manufacturing techniques other than roller compaction. In most cases, roller compaction preceded tabletting. Thus, properties of the resultant tablets were of interest. Only a few studies had been carried out to investigate the properties of flakes produced and their relationship with the resultant granule and tablet properties.

-Effects of size and porosity of particles:

McKenna and McCafferty [64] found that smaller particle size of a plastic deforming material, Sta-Rx 1500 and a fragmenting material, lactose, resulted in tablets of higher tensile strength. However, the tensile strength of microcrystalline cellulose (MCC) tablet appeared to be independent of primary particle size. Binary mixtures of different particle size fractions of α-lactose monohydrate had been investigated [65] The authors found that tablet crushing strength and tablet specific surface area of various binary mixtures were lower than the values obtained by linear interpolation of tablets compressed from single sieve fractions. The lowest specific surface area and crushing strength were obtained by compacts produced with 40% fine fractions.

-Effect of intrinsic nature of material:

Scientists demonstrated that different roller compaction parameters were required for lactose 200M and maize starch to obtain granules with optimal properties. Lactose, a fragmenting material, required a high roller speed: horizontal screw speed ratio while maize starch, a plastic deforming material, performed better with a low roller speed: horizontal screw speed ratio [47] Crystalline lactose monohydrate is the most widely used diluent for tablet formulation. It is also referred to as lactose, hydrous lactose or regular lactose. It is usually supplied in powder form (ground) for use as a filler for tablet manufacture, often by the wet granulation technique. For use in direct compression, coarse, regular grade or

sieved crystalline fractions of α-lactose monohydrate, particularly the 100-mesh grade, is used because of their better flowability.

Advantages [14]

- Simplifies processing
- Uses less raw materials
- Facilitates powder flow
- Eliminates water-induced degradants
- Uses minimal energy to operate
- Improves process cycle time
- Requires less man-hours to operate
- Prevents particle segregation
- Improves drug dosage weight control
- Facilitates continuous manufacturing
- Reproduces consistent particle density
- Improves content uniformity
- Produces good tablet and capsule disintegration
- Does not require explosion proof room/ equipment
- Eliminates aqueous and solvent granulating
- Produces a dry product that is process scalable

Disadvantages:

- Weakening or disruption of the crystal lattice
- Production of fines
- Loss of reworkability

Since granulating solvent is not used during dry granulation, solution or solution mediated phase transformations are eliminated, thus the probability of phase transitions with this granulation unit operation is reduced. However, the applied mechanical stresses during processing may lead to phase transformation via the solid-state or melt mechanisms [22].

Process Parameters

Besides the type and design of mill, the most important factors which can affect the quality of particles are: feed rate, screen size and rotor speed.

- **Feed rate** controls amount of material that enter to the mill and can control overfeeding or underfeeding. Although, either phenomenon should be avoided, overfeeding is relatively more harmful. When amount of material which is fed is bigger than amount which is discharged it stays in the milling chamber and it leads to greater size reduction, over loads the motor and reduced capacity of the mill [24]. In general, the feed rate should be equal to the rate of discharge.

- **Screen**, located directly under the blade, prevents particles to leave the chamber until they are at least the same size as the screen holes. The screen size doesn't necessarily define the particle size of the final product. Depending on rotor speed, particles find various dimension and shape of angle at which they approach the screen. The higher rotor speed will influence the smaller angle under which particles hits the screen. This means that particles will pass through the smaller hole in the screen (see figure 2.15), leading to smaller particle size of the final product. The thickness of the screen has influence on the particle size as well. The thicker the screen, the smaller particle can pass the screen (see figure 2.16)

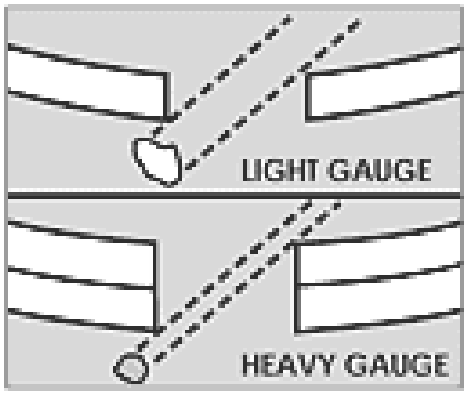


Figure 2.15 Influence of the screen thickness to particle size

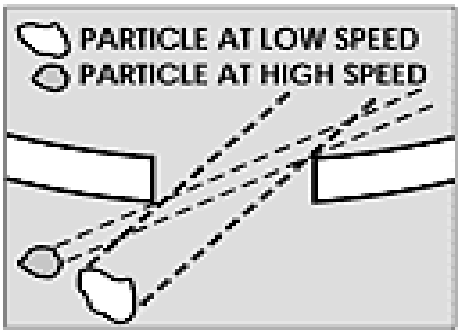


Figure 2.16 Influence of the rotor speed to particle size

- **Rotor speed** directly affects the particle size range. If all the other variables are the constant, faster rotor speed induces the smaller particle size.

As all processes, milling has some advantages and disadvantages, which should be considered before starting with size reduction of the material.

2.8 Introduction to Milling

The final product of the roller compaction – ribbons, must be subsequently broken to the required particle size. In general, the milling or size reduction is the mechanical process of reducing of the size of particles or aggregates. To initiate reduction of particle size external forces should be applied [23].

The milling is affected by a variety of factors and has a direct influence on the quality of the final product. The selection of equipment which should be used for this process is determined by the properties of feed material and specification of the product.

Classification of Mills

The most convenient classification of size reduction equipment is according to the way in which forces are applied; impact, shear attrition and shear-compression [24].

Table 2.1 Characteristic of Different Types of Mill

Mechanism of Acting	Example	Particle size
Impact	Hammer mill	Medium to fine
Shear	Extruder and hand screen	Coarse

Attrition	Attrition Oscillating granulator	Coarse to medium
Shear-compression	Comil	Medium to coarse

The type of mill can affect the shape of the granules and throughput, and shape of the granules affect the flow properties.

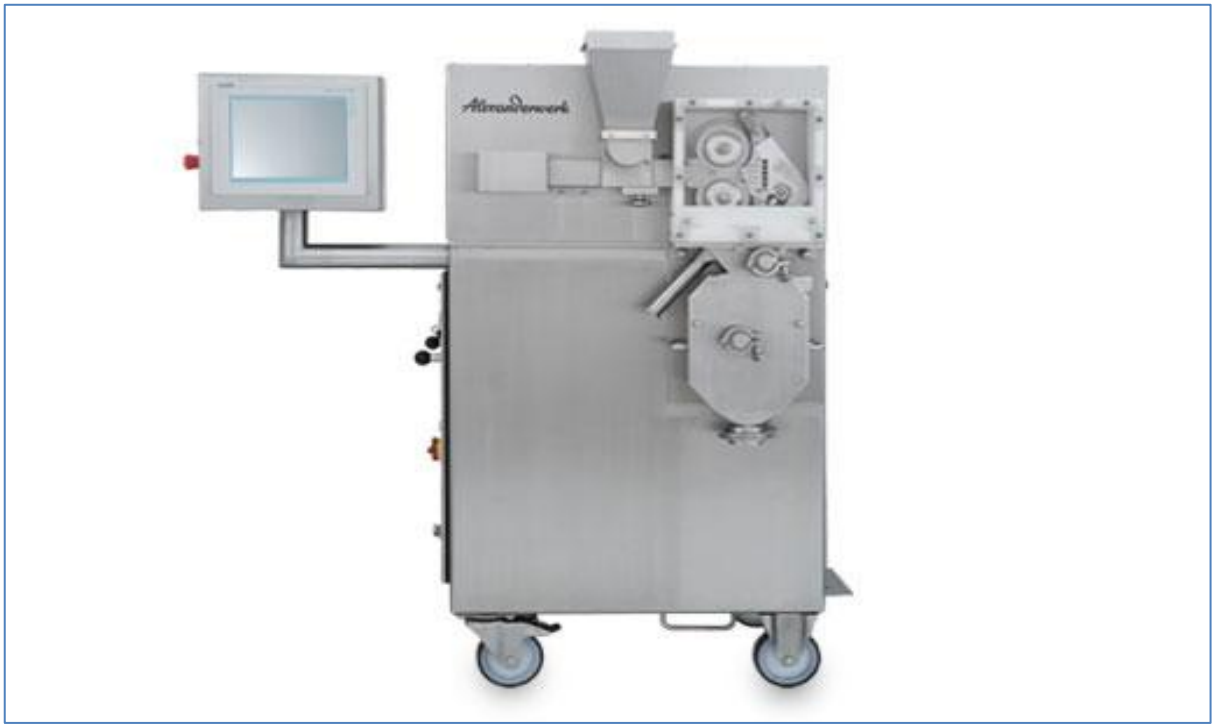
An impact mill produces sharp and irregular granule where flowability sometimes may be a problem, whereas granules produced by attrition mill are more spherical.

Fig 2.17 Mill Sieve

Table 2.2 Advantages and disadvantages of milling

Advantages	**Disadvantages**
-Increase of surface area (increase dissolution and bioavailability)	-Change in polymorphic form
-Enhance content uniformity (increase number of particles per unit weight)	-Possible degradation of the drug
-Improve flowability (irregular shape of the material)	
-Control particle size distribution	

2.9 INTRODUCTION TO ROLLER COMPACTOR (Alexanderwerk)



The Alexanderwerk Automated Control System is designed to provide optimum process control with excellent operator interface and data monitoring. The system includes a Programmable Logic Controller which is connected to an Operator Interface Station. The operator is able to view all of the instrument measurements and machine status information in picture form on the control monitor. Features of the Alexanderwerk Automated Control System include:

- Operator Interface
- On-Line Help and Diagnostic Functions
- Restricted Access of Various Functions
- Maintenance Screen
- Calibration Screen
- Roll Gap Control
- Programmable Recipes
- Historical Trending
- Report Generation
- Alarm Management

• Optional XL Reporter for Data Parameter Logging, Facilitating 21CFR Part II Compliance

2.10 Introduction to Tablets

As it is explained in the beginning, tablets can be produced from a mixture of a powder, or aggregated particles of a powder (granules). Whatever method is used, the resulting tablets should have certain properties. Tablets have to be enough strong and resistant to abrasion during manufacturing, packaging and use, but in the same time, active material from tablets must be bioavailable. Bioavailability can be monitored by dissolution and disintegration test [26]. In order to achieve these characteristics, active pharmaceutical ingredient is blended with different ingredients having specific functions. The homogeneity of the powder mixture is essential to improve both mechanical and medicinal properties of the tablets.

Although, tablets exist in different forms, the way in which they are produced is in general the same [27].
When a force is applied on a powder bed, a lot of mechanisms become involved in transformation of the powder into a porous, coherent compact called tablet.

According to Nyström [28] five mechanisms are involved in the powder compaction:
1. Particle rearrangement
2. Elastic deformation of particles
3. Plastic deformation of particles
4. Fragmentation of particles
5. Formation of interparticulate bonds

At the beginning of powder compaction, particles are rearranged, and reduction in volume occurs due to closer packing of powder. Depending on the packing characteristics of particles, at certain load no more rearrangement can take place.
As the pressure is increased, the initial particles change shape or deform and further compression leads to some type of deformation (see figure 2.18). When the load is removed, some particles are able to return to original shape (elastic deformation), whilst other ones are permanently deformed (plastic deformation). The force required to initiate

a plastic deformation is noted as yield stress [29]. Brittle particle undergo fragmentation, crashing of the original particles into smaller units. A single particle may pass through several of these stages during compaction [27] [30].

Some materials consolidate by a plastic deformation (microcrystalline cellulose, starch, sodium chloride), some by fragmentation (crystalline lactose, sucrose, Emcompress), but all materials posses both elastic and plastic component [28].

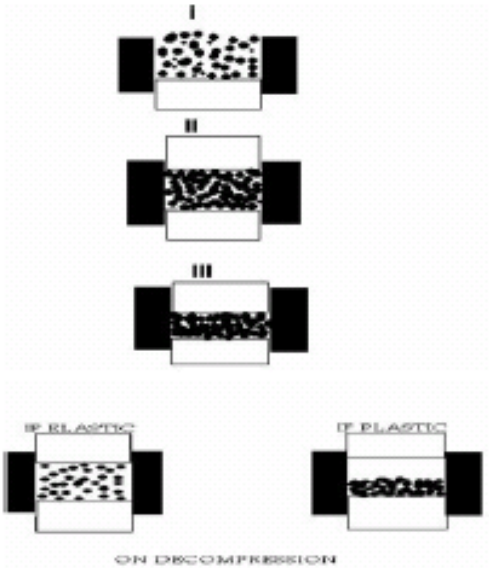


Figure 2.18 Stages involved in compression (I – III) and decompression

Compression Bonding Mechanisms

When particles get together, adhesive forces are developed, which are responsible for the strength of compacts after compression and compaction [10]

In compression of dry powders, dominating bonds of interparticular adhesion are [10] [28] :

- Solid bridges
- Distance attraction forces (intermolecular forces)
- Mechanical interlocking (between irregular shaped particles)

Solid bridges can be formed at the place where there is a particle-particle contact at an atomic level. Due to their structure, solid bridges seem to be relatively strong bonds and tablets containing this type of bonds can be related with prolonged disintegration time.

Intermolecular forces are all bonding forces which coordinate between surfaces separated with some distance and these forces are relatively weak. In this group are involved: Van der Waals forces, electrostatic forces and hydrogen bonding [28].

Material which is bonded with forces of mechanical interlocking has low strength and accelerated disintegration time, but for producing tablets it requires a high compression forces. This type of bonds induces the hooking and twisting of the packed material.

Mechanical interlocking and Van der Waals forces are the mechanisms which are included in the process of roller compaction so it could be expected that disintegration time of tablets produced by this method is fast.

Properties of Tableting Materials:

As it is previously explained materials could consolidate by different type of deformation. Materials which are undergoing extensively fragmentation during compaction creates a large number of interparticulate contacts point and relatively weak attraction force, which act over distance. However, even weak attraction force are formed, due to the large number of attractions zones relatively strong compacts could be formed. Less fragmenting materials form a less number of contact points between particles and only if strong attraction forces are created, strong compacts could be formed. Extensively plastic materials could develop a large number of attraction forces and form strong compacts. Due to compression behavior, both fragmenting and plastic behavior materials are considered as bond-forming compression mechanisms. The difference between two mechanisms is that fragmentation affects mainly the number of interparticulate bonding while plastic deformation affects mainly the bonding force of these bonds. This is due to fact that fragmenting material form a large number of bonds, while material with plastic deformation forms a strong attraction force as well.

Mechanical Properties of Tablets:

The characterization of compressibility and compactibility of the material has very important role in the tablet manufacturing. Compressibility is an ability of a powder to decrease in volume under pressure, and compactibility is the ability of the material to be compressed into a tablet of specified strength [32]. Since the first accurate compaction data were obtained, the use of compaction equations have played an important role to

relate the relationship between density or porosity of the compact, and the applied pressure [33] [34]. Many compaction techniques are used to characterize the consolidation behavior of pharmaceutical solids.

2.11 Introduction to Experimental Design

It is the methodology of how to conduct and plan experiments in order to extract the maximum amount of information in the fewest number of runs.

Types of Experimental Design

Choice of experiments depends on level of knowledge before experiments, resource available and objectives of the experiments

Discovering important process factors

- Placket-Burman
- Fractional Factorial

Estimating the effect and interaction of several factors

- Full Fractional
- Fractional Factorial
- Tiguchi

For optimization

- Central composite
- Simplex lattice
- D-optimal
- Box Behnken

Box-Behnken designs

The Box-Behnken design is an independent quadratic design in that it does not contain an surrounded factorial or fractional factorial design. In this design the treatment combinations are at the midpoints of edges of the process space and at the center. These designs are rotatable (or near rotatable) and require 3 levels of each factor.

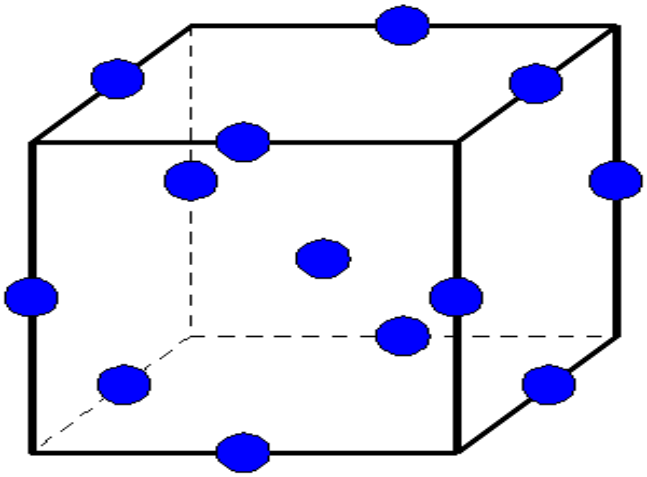


Fig 2.19 Box-Behnken Design

- Box-Behnken designs are response surface designs, specially made to require only 3 levels, coded as -1, 0, and +1.
- Box-Behnken designs are available for 3 to 10 factors. It is formed by combining two-level factorial designs with incomplete block designs.
- This procedure creates designs with desirable statistical properties but, most importantly, with only a fraction of the experimental trials required for a three-level factorial. Because there are only three levels, the quadratic model was found to be appropriate.
- In this design three factors were evaluated, each at three levels, and experiment design were carried out at all seventeen possible combinations.

Table 2.3 Box-Behnken Design

Box-Behnken			
Rep	***X*1**	***X*2**	***X*3**
1	-1	-1	0
1	+1	-1	0
1	-1	+1	0
1	+1	+1	0
1	-1	0	-1
1	+1	0	-1
1	-1	0	+1
1	+1	0	+1
1	0	-1	-1
1	0	+1	-1
1	0	-1	+1
1	0	+1	+1
3	0	0	0
Total Runs			15

Chapter 3
Literature review

3.0 LITERATURE REVIEW

3.1 Literature review for chewable tablet

T. Pongjanyakul et al disclosed that Amberlite 69 produced dextromethorphan resinates with a broader size distribution when compared to those prepared from DowexR50W. The release profiles of the resinates in simulated intestinal fluid, gastric juice and simulated gastric fluid showedsustained release characteristics.

T.Y. Puttewar et al disclosed that Ion exchange resin Indion 234 was selected because of high drug loading capacity. Drug–resin complex was prepared using batch method and effect of various processing parameters viz. drug–resin ratio, pH, temperature and drug concentration was studied to optimize the loading conditions. Maximum loading was obtained at drug–resin ratio 1:2, pH 5, temperature 50 °C and drug concentration 4 mg/ml. A successful taste masking of resinate was confirmed by time intensity method and also by taking drug release in 0.01 N hydrochloric acid and in simulated salivary fluid.

Ciara Agresti et al disclosed that DPH interacted with a-helical poly(glutamic acid) specifically to produce DPH/poly(glutamic acid) complexes, mostly spherical in shape with a diameter of around 1.0 lm. Other drugs with similar chemical structures as DPH, such as phenylephrine and pseudoephedrine, could not form complexes with poly(glutamic acid) or other polymers under the same conditions. Although DPH in DPH/poly(glutamic acid) complexes existed amorphously, it showed increased stability. In addition, DPH/poly(glutamic acid) complexes were not stable in neutral or weak acidic (pH > 5) environments and dissolved rapidly and completely. Therefore, DPH/poly(glutamic acid) complex may serve as a new formulation for taste masking and controlled DPH release in gastrointestinal tract.

Seong Hoon Jeong et al disclosed that Dextromethorphan HBr could be loaded up to the ratio of 3 (drug): 1 (resin), depending on the physicochemical properties of the resin. As the crosslinking ratio and particle size increased, the drug loading and release rate decreased due to the reduced effective diffusion coefficient and surface area.

Saikat Das et al disclosed that After acid activation & swell in water, resin & ciprofloxacin (proper ratio) stirred by magnetic stirrer for definite time, temperature &unbound drug in filtrate were estimated spectrophotometrically and high drug-loading efficiency was found.The molecular properties of drug complexes by DSC & FTIR study confirm the complexation of ciprofloxacin with Indion 234. The % drug release in pH 6.8 also confirms the masking of bitterness of ciprofloxacin.

Hiroyuki Suzuki et al disclosed that The Witocan® H tablet with 1% (w/w) saccharin plus 5% (w/w) Benecoat BMI-40 (Sc1-B5), and theWitocan® H/Witocan® 42/44 (92.5:7.5, w/w) mixture tablet with 1% (w/w) aspartame plus 5% (w/w) Benecoat BMI-40 suppressed bitterness and shows excellent sweetness.

3.2 Literature Review on Granulation:

Malcolm Summers et al mentioned that Granulation is the process in which primary powder particles are made to adhere to form larger, multiparticle entities called granules. Pharmaceutical granules typically have a size range between 0.2 and 4.0 mm, depending on their subsequent use. Granulation normally commences after initial dry mixing of the necessary powdered ingredients so that a uniform distribution of each ingredient through the mix is achieved. After granulation the granules will either be packed (when used as a dosage form), or they may be mixed with other excipients prior to tablet compaction or capsule filling. Scientists have described the different types of granulation process as well as mechanism of granulation.

Bryan J. Ennis mentioned that Granulation technology and size-enlargement processes have been used by a wide range of industries, from the pharmaceutical industry to fertilizer or detergent production to the mineral processing industries. Size enlargement generally encompasses a variety of unit operations or processing techniques dedicated to particle agglomeration. He described that an alternative approach to size enlargement is agglomeration by compression, or compaction, where the mixture of particulate matter is fed to a compression device which promotes agglomeration due to pressure. Ether continuous sheets of solid material or solid forms such as briquettes or tablets are produced. Compaction processes range from confined compression devices such as tableting to continuous devices such as roll presses, briqueting machines, and extrusion.

Ennis and Litster developed the rate processes contribute to granulation. These include wetting and nucleation, coalescence or growth, consolidation, and attrition or breakage. Wetting promotes nucleation of fine powders, or coating in the case of feed particle size in excess of drop size. Often wetting agents such as surfactants are carefully chosen to enhance poorly wetting feeds. In the coalescence or growth stage, partially wetted primary particles and larger nuclei coalesce to form granules composed of several particles. The term nucleation is typically applied to the initial coalescence of primary particles in the immediate vicinity of the larger wetting drop whereas the more general term of coalescence refers to the successful collision of two granules to form a new, larger granule. The nucleation process is strongly linked with the wetting stage. As granules grow, they are consolidated by compaction forces due to bed agitation. This consolidation stage controls internal granule voidage or granule porosity, and therefore end-use properties such as granule strength, hardness, or dissolution. Formed granules may be particularly susceptible to attrition if they are inherently weak or if flaws develop during drying.

Hans Leuenberger described the scale up in the field of granulation and drying. Today the production of pharmaceutical granules is still based on the batch concept. In the early stage of the development of a solid dosage form the batch size is small, e.g., for first clinical trials. In a later stage the size of the batch produced in the pharmaceutical production department may be up to a 100 times larger. Thus the scale-up process is an extremely important one. Unfortunately, in many cases the variety of the equipment involved does not facilitate the task of scale-up. During the scale-up process the quality of the granules may change. A change in granule size distribution, final moisture content, friability, compressibility, and compactibility of the granules may strongly influence the properties of the final tablet, such as tablet hardness, tablet friability, disintegration time, dissolution rate of the active substance, and aging of the tablet. In the following sections, the scale-up process is analyzed, taking into account mathematical considerations of scale-up theory, the search for scale-up invariants, the establishment of in-process control methods , as well as the design of a robust dosage form. In this respect new concepts such

as percolation theory play an important role. Finally, a new concept concerning a quasicontinuous production line of granules is presented. This concept permits the production of small-scale batches for clinical trials and of production batches using the same equipment. Thus scale-up problems can be avoided in an elegant and cost-efficient way.

3.3 literature review on roller compaction

Parrott E.L. identified three theories of compression bonding: mechanical, intermolecular, and liquid-surface film. Mechanical bonding purports that individual particles undergo elastic, plastic, and brittle deformation. Bonding of this nature occurs because particle surfaces intertwine, forming mechanical bonds. Intermolecular theory identifies that there are some unsatisfied surface ions that have a potential need to bond to one another. Under pressure, intermolecular forces become pushed together close enough so that van der Waals forces can act to consolidate particles. The liquid surface film theory identifies that bonding occurs because of the existence of a thin liquid film. The thin liquid film is generated from pressure induced by the energy of compression. This mechanism acts as a bonding agent promoting mechanical strength and an enlarged particle.

Dehont et al. provided a simplified approach to roller compaction theory . They described that powder granules move through stages in the feed area. The material is drawn into the gap by rubbing against the roll surfaces. The densification that occurs in this area is particle rearrangement. Dehont's team noted that nip angle varies according to the material characteristics of particle size and density and the angle is about 12˚. They defined the neutral angle, γ, which corresponds to the point where the pressure applied by the rollers is the greatest on the material. They also defined elastic deformation, δ, and that occurs after the compact begins leaving the compression roll area. They concluded that if the same flake thickness were obtained with different roller diameters, the flake density would be greater with larger-diameter rollers. This is due to the greater nip angle formed with the larger rolls allowing more material to be compacted.

R. W. Heckel considered the compaction of powders analogous to that of a firstorder chemical reaction. The pores were the reactant and the densification of the material the product. The proportionality between the change of the density with the pressure and the pore fraction was the process kinetics. Heckel explained mathematical constants that described the compaction behavior of a given powder and developed a mathematical relationship. The expression of density–pressure relationship permitted the determination of density values in the range of the pressures investigated. Heckel described mathematically that the curved region when plotting ln(1/1-D) vs. P is associated with powder densification. This occurred by a mechanism of individual particle movement in the absence of interparticle bonding. Heckel concluded that the densification represented by the linear region of the plot, ln(1/1-D) vs. P, occurred by plastic deformation of the compact after an appreciable amount of interparticle bonding had taken place. Heckel concluded that density–pressure data indicate that the rate of the change of density with pressure, any pressure, is proportional to the pore fraction in the compact at that pressure.

J. R. Johanson identified, through very comprehensive mathematical models and relationships, material properties, press dimensions, and operating conditions for roll compactors. In part, he explained that roller compaction involves a continuous shear deformation of the granules into a solid mass. To satisfy the theory's assumption, it was postulated that the material be iso-tropic, frictional, cohesive, and compressible. Johanson pointed out that no roller compactor theories at that time determined the angle of the nip and the bulk density at $\theta=\alpha$, except by actually rolling the granular solid in a roll press. He also provided a method to calculate the nip angle and the pressure distribution between the rolls. His calculations determined the pressure distribution above and in the nip area. He provided the technical rationale to calculate the nip pressures in the nip region. Johanson found that the nip angle does not depend on the magnitude of the roll force or the roll diameter. He demonstrated that the nip angle was affected very little by the geometry of the press or the cut grooves on the roll surface. It was mostly influenced by the nature of the materials that were compressed.

Peter Kleinebudde described that Roll compaction/dry granulation (RCDG) is an agglomeration process of growing importance. New machine generations and improvements in instrumentation and process control have resulted in an increasing number of pharmaceutical applications of RCDG. He illustrates the progress and the use of RCDG in the production of directly compressible excipients, the compaction of drugs and drug formulations, and the granulation of inorganic materials, the granulation of dry herbal material and the production of immediate/sustained release formulations. Dry granulation process by roll compaction has product as well as process advantages. In general, a major advantage of dry granulation over wet granulation is the absence of water or any organic solvents. Therefore, this methodology is especially attractive for drugs, which are moisture or heat sensitive. In addition, this process is environmentally friendly. Also the roll compaction technique provides an efficient and easily automated process. The process is easily scalable, which offers conceptual simplicity and low operational costs. However, compaction in a roll press is still not fully understood.

Leon Farber et al developed model that describes the relationship between rollercompaction conditions and tablet strength is proposed. The model assumes that compaction is cumulative during roller compaction and subsequent granule compaction, and compact strength (ribbon and tablet) is generated irreversibly as if strength is controlled by plastic deformation of primary particles only. Roller-compaction is treated as a compaction step where the macroscopic ribbon strength is subsequently destroyed in milling. This loss in strength is irreversible and tablets compressed from the resulting granulation are weaker than those compressed by direct compression at the same compression force. Roller-compacted ribbons were produced at a range of roll forces for three formulations and subsequently milled and compacted into tablets. Once the total compaction history is taken in account, the compaction behavior of the uncompacted blends and the roller-compacted granules ultimately follow a single master compaction curve—a unified compaction curve (UCC). The model successfully described the compaction behavior of DC grade starch and formulations of lactose monohydrate with 50% or more microcrystalline cellulose, and may be more generally applicable to systems containing significant proportions of any plastically deforming material, including MCC and starch.

Maja ˇSantla et al carried out study to investigate the influence of various powder agglomeration processes on tableting mixture flow and compaction properties. Four different granulation methods of the same model placebo formulation were tested at a semi-industrial scale and their properties were compared to those of the directly compressed mixture. The wet granulated mixtures had superior flow properties compared to other mixtures and showed better compressibility, measured by the Heckel and Walker models. This was attributed to work hardening due to the double particle processing and also to shorter contact times due to higher initial densities of dry granulated mixtures, allowing a shorter time for deformation. A strong linear correlation was established between the Heckel and Walker coefficients, which were further confirmed by the net energy results of force–displacement measurements. It was shown that the Walker model had slightly better discriminative power to differentiate tableting mixtures according to compressibility. The compactibility was considerably lower for the slugged mixture; however, the roller-compacted mixture produced tablets with unexpectedly high tensile strength. In conclusion, it is important to emphasize those general assumptions like higher porosity provides better compressibility or better compressibility gives better compactibility cannot be established for complex tableting mixtures.

A.V. Zinchuk et al developed method for simulation of the roller compaction process using a laboratory scale compaction simulator was developed. The simulation was evaluated using microcrystalline cellulose as model material and ribbon solid fraction and tensile strength as key ribbon properties. When compacted to the same solid fractions, real and simulated ribbons exhibited similar compression behavior and equivalent mechanical properties (tensile strengths). Thus, simulated and real ribbons are expected to result in equivalent granulations. Although the simulation cannot account for some roller compaction aspects (non homogeneous ribbon density and material bypass) it enables prediction of the effects that critical parameters such as roll speed, pressure and radius have on the properties of ribbons using a fraction of material required by conventional roller compaction equipment. Furthermore, constant ribbon solid fraction and/or tensile strength may be utilized as scale up and transfer factors for the roller compaction process. The improved material efficiency and product transfer methods could enable formulation of tablet dosage forms earlier in drug product development.

H. Lim et al carried out study with the purpose to assess the porosity variation of roller compacted ribbons made using different process parameters; in addition, the feasibility of using near-infrared chemical imaging (NIR-CI) to evaluate porosity variations was examined. Ribbons of neat microcrystalline cellulose were compacted using a range of roll pressures (RP), roll speeds (RS) and feed screw speeds (FSS). The ribbon porosity decreased as RP increased with the exception of ribbons produced by the combination of high RS and low FSS where increasing RP increases the porosity of the ribbons. Lower RS was found to produce ribbons with lower porosity and the porosity increases as the RS increased. Increased FSS will decrease ribbon porosity at higher RS while it slightly increase the ribbon porosity at lower RS. A simple linear regression model showed NIR-CI was able to predict the ribbon porosity with a correlation of 0.9258. NIR-CI is able to characterize differences in porosity as a function of position on the ribbon where regions with lower porosity show higher absorbance. Nevertheless, NIR-CI is able to show sinusoidal variation in intensities along the roller compacted ribbon among all settings studied.

Sabine Inghelbrecht et al Different types of microcrystalline cellulose (MCC) and blends of MCC, a mainly plastic deforming material and ibuprofen, used as a mainly fragmenting material were roller compacted. All MCC types, except Avicel® CE-15, produced excellent quality granules but the corresponding tablet mechanical strength was low. Addition of ibuprofen reduced the number of usable roller compactor parameter combinations. The presence of 25% ibuprofen had a negative influence on granule quality while the tablet mechanical strength improved. A further increase of the ibuprofen concentration yielded an acceptable granule quality and a high tablet mechanical strength due to the fragmentation and sintering properties of ibuprofen. It remained difficult to predict the influence of roller compactor pressure on the final tablet mechanical strength. Differences in MCC particle density influenced the dissolution rate more than the particle size. The presence of an additional dry binder did not improve granule strength and decreased the dissolution rate. The *t*90 release values of the 75% ibuprofen tablets were low for hydrophilic gum–MCC associations, Avicel® PH-301 and PH-302.

S. Patel et al. investigated the effect of roller compaction pressure on the bulk compaction of roller compacted ibuprofen using instrumented rotary tablet press. Three different roller pressures were utilized to prepare granules and Heckel analysis, Walker analysis, compressibility, and tabletability were performed to derive densification, deformation, course of volume reduction and bonding phenomenon of different pressure roller compacted granules. Nominal single granule fracture strength was obtained by micro tensile testing. Heckel analysis indicated that granules prepared using lower pressure during roller compaction showed lower yield strength. The reduction in tabletability was observed for higher pressure roller compacted granules. The reduction in tabletability supports the results of granule size enlargement theory. Apart from the granule size enlargement theory, the available fines and relative fragmentation during compaction is responsible for higher bonding strength and provide larger areas for true particle contact at constant porosity for lower pressure roller compacted granules. Overall bulk compaction parameters indicated that granules prepared by lower roller compaction pressure were advantageous in terms of tabletability and densification. Overall results suggested that densification during roller compaction affects the particle level properties of specific surface area, nominal fracture strength, and compaction behavior.

Paul J. Sheshkey et al. studied the Effects of roller compaction variables like roll and feed screw speeds and applied roll pressure; roll design, granulation technologies and concentration of HPMC polymer on the physical properties of and subsequent drug release from, a model controlled release drug formulation. The result showed that differences in roller compaction equipment variables and roll surface design had a relatively small effect on these properties; granulation methods had the greatest effect on crushing strength; and high levels of HPMC increased bulk and tap densities, decreased tablet crushing strength and increased time to release. None of the variables affected tablet friability. Roller compaction variables such as feed screw speed and roll speed have little effect on the physical properties of the tablets or their drug release profiles. Roll surface design had no measurable effect on particle size distribution, tablet friability, crushing strength or drug release. The granulation methods had varying effects on tablet properties and drug release. They mentioned that high HPMC level resulted in increased

bulk and tap densities, decreased tablet crushing strength. Polymer level did not affect tablet friability.

Franziska Freitag et al studied the effect of roll compaction/dry granulation on the particle and bulk material characteristics of different magnesium carbonates were evaluated. The flowability of all materials could be improved, even by the application of low specific compaction forces. The tablet properties made of powder and dry granulated magnesium carbonate were compared. Roll compaction/dry granulation resulted in a modified compactibility of the material and, consequently, tablets with reduced tensile strength. The higher relative tap density of the compacted material does not allow a densification to the same extent as the uncompacted powder. The degree of densification during tableting can be expressed as the ratio of the relative tablet density to the relative tap density of the feed material. Increasing the specific compaction forces resulted in higher apparent mean yield pressure, gained from Heckel plots, of all materials analysed. The partial loss of compactibility leads to the demand of low loads during roll compaction. Comparing the tablet properties of different magnesium carbonates reveals an obvious capping disposition. However, it depends on the type of magnesium carbonate, the specific compaction force and also on the tableting force applied.

Ervina Hadˇzovi´ et al investigated that Roller compaction is a dry granulation method which results in tablets with inferior tensile strength comparing to direct compaction. The effect of roller compaction on compressibility and compactibility of tablets prepared from Theophylline anhydrate powder, Theophylline anhydrate fine powder and Theophylline monohydrate was investigated by measuring tensile strength of tablets as well as calculating compressibility and compactibility parameters by Leuenberger equation. The tablets under the same conditions were prepared by direct compaction and roller compaction. The binary mixtures of Theophylline anhydrate powder, Theophylline anhydrate fine powder, Theophylline monohydrate and microcrystalline cellulose were prepared in order to determine the optimal ratio of active material and excipients which delivers a sufficient mechanical strength of tablets. Tensile strength of MCC tablets and compactibility parameters calculated by Leuenberger equation after roller compaction was significantly decreased, while THAP, THAFP and THMO tablets showed only a

minor reduction in compactibility and compressibility. Adding MCC to a mixture with Theophylline showed that the right choice and ratio of excipients can enable a sufficient mechanical strength of the tablets after roller compaction.

Shawn A. Mitchell et al enhanced the dissolution rate of poorly water-soluble drugs with hypromellose using a compaction process without the use of solvent or heat addition. Low viscosity hypromellose or low viscosity MC can be used to enhance dissolution of poorly water-soluble drugs through a compaction process. Compacted then milled dry mixtures of drug and hypromellose maintained intimate contact between hypromellose and drug particles during dissolution, enhancing drug dissolution relative to drug alone and also relative to loosely-mixed drug and hypromellose powders. Roller compaction and slugging were each successful in combining drug and polymer to improve drug dissolution rates. These compaction procedures produced drug: hypromellose agglomerates with dissolution rates approximately 9 times faster than drug alone for nifedipine and naproxen, and at least 5 times faster than drug alone for CBZ. Drug distribution *vs.* particle size in compacted agglomerates was remarkably similar for the three drugs tested. Thus, compacting hypromellose and drug appears to have potential in normalizing drug dissolution regardless of the particle size distribution of drug itself. This study demonstrated that by keeping poorly water-soluble drugs and hypromellose particles in close proximity, drug dissolution rates were enhanced. The compaction methods in this study may provide a lower cost, quicker, readily scalable alternative for poorly water-soluble drugs.

Chapter 4
Experimental work

4.0 EXPERIMENTAL WORK

4.1 Materials and Equipment Used

Table 4.1: Material Used

Ingredients	Category
PHL_158	Drug
Avicel PH102	Diluents
Xylitol	
Mannitol	
Calcarb (90% Calcium carbonate + 10% Maltodextrin)	
Hydroxy Propyl Cellulose (Klucel EXF)	Dry binder
Croscarmellose Sodium	Disintegrant
Magnesium Stearate	Lubricant
Silicon Dioxide	Glidant
Citric Acid	Flavour
Neo-Sucralose	Sweetner
Orange	Flavour
Orange	Colour

Table 4.2: Equipment Used

Equipments	Company name
Electronic Weighing Balance	Mettler Toledo, Mumbai, India
Moisture analyzer	Mettler Toledo HG63 Halogen, Mumbai, India
Sieve Shaker	Retsch GmbH, Germany
Roche Friabilator	Labindia FT020,Thane, India
Tap density tester	Labindia TD1025, Thane, India
USP dissolution apparatus-I	Labindia, Thane, India
Tablet Compression machine	Korsch, Silverwater, Australia.
UV Spectrophotometer	Shimadzu 1800, Shanghai, China.
Ultrasonicator bath	EIE Instruments Pvt ltd (India)
Disintegration apparatus USP	Labindia DT1000, Thane, India
Hardness Tester	Dr. Schleuniger Pharmatron 8M, Switzerland
Turbula Blender	WAB (Willy A.Bachofen AG Maschinenfabrik), Mahopac, New York.
16 station punching machine	Cadmach CMD4 (D tooling), Ahmedabad, India
Segregation tester	Jenike & Johanson INC, USA
Ring Shear Tester	Dr. Dietmar Schulze Wolfenbuttel, Germany
Flowdex	Retsch GmbH, Germany
Geopyc	Micromeritics, Germany
Quadro Co-mill	Quadro Engineering, Waterloo, Canada
Rotary Micro Riffler	Quantachrome Instruments, Florida, USA
Roller Compactor	Alexanderwerk, Shanghai, China

4.2 ESTIMATION OF PHL_158:

4.2.1 Standard curve of PHL_158 in 0.1 N HCl:

Preparation of stock solution:

10 mg of PHL_158 was accurately weighed and transferred into 100 ml volumetric flask. It was dissolved in 0.1 N HCl and volume was made up to the mark with 0.1 N HCl to get 100 µg/ml solution.

Preparation of Standard Curve:

A primary stock solution was prepared by weighing accurately 10 mg of PHL_158 on an electronic weighing balance**. The drug was transferred into 100 ml volumetric flask and then 25 ml of** 0.1 N HCl **was added and sonicated for 15 mins. The final volume was made up to 100 ml with** 0.1 N HCl **and was mixed well. A series of dilutions were prepared by withdrawing required amount of volume like 0.1, 0.2, 0.3, 0.4, 0.5, 0.6 ml and so on from stock solution (100 µg/ml) and were transferred to a 10 ml volumetric flask. The final volume was made up to 10 ml with** 0.1 N HCl **to get 1-14 µg/ml respectively.**

Table 4.3: Standard curve of PHL_158 in 0.1 N HCl

Conc(µg/ml)	Abs
0	0.000
1	0.098
2	0.155
3	0.224
4	0.285
5	0.390
6	0.448
7	0.520
8	0.584
9	0.651
10	0.720
11	0.810
12	0.880
13	0.930
14	0.980

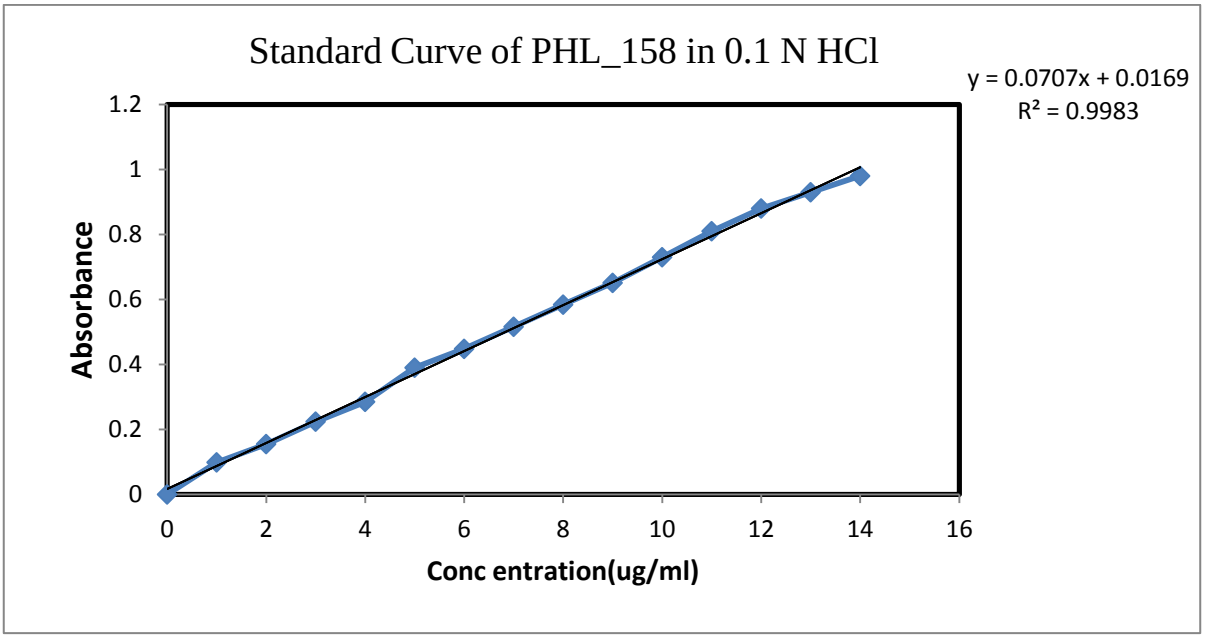


Fig 4.1 Standard Curve of PHL_158 in 0.1 N HCl

Regression Analysis

Table 4.4 Regression analysis for standard curve of PHL_158 in 0.1 N HCl

Regression parameter	Value
Correlation coefficient	0.9983
Slope	0.0707
Intercept	0.0169

4.3 Formulation Development

4.3.1 Preparation of chewable tablet by direct compression

Table 4.5 Formula for direct compression

Sr no.	Ingredients	Category	% Amount	Quantity
1	PHL_158	Drug	5	25 mg
2	MCC/ Xylitol/ Mannitol/ Calcarb	Diluents	82.5	412.5 mg
3	Hydroxy Propyl Cellulose (Klucel EXF)	Dry binder	5	25 mg
4	Croscarmellose Sodium	Disintegrant	3	15 mg
5	Magnesium Stearate	Lubricant	2	10 mg
6	Silicon Dioxide	Glidant	1	5 mg
7	Citric Acid	Flavour	1	5 mg
7	Neo-Sucralose	Sweetner	q.s	1.5 mg
8	Orange	Flavour	q.s	1 mg
9	Orange	Colour	q.s	q.s
TOTAL				**500 mg**

Procedure:

- Blending: All the ingredient except magnesium stearate, neo-sucralose & orange flavour were added into the turbula blender. Blending was done for 15mins at 30 rpm (450 revolutions).
- Co-milling: After blending, blend was passed through co-mill having 0.8 mm screen size at 1900 rpm.
- Lubrication: Lubrication was done by adding magnesium stearate and along with it neo-sucralose & orange flavour was added to the blend to ensure uniform mixing of sweetner & flavour. Lubrication was done using turbula blender for 5 mins at 30 rpm (150 revolutions).

- Compression: Compression was done using KORSCH XL100 tablet press. 12 mm round & flat punches of B-Type tooling were used. Compression speed was kept at 20 rpm. Targeted tablet weight was 500 mg and targeted hardness was 8-10 Kp.

4.3.1.1 Rationale of using Diluent Combination

Table 4.6 Characteristics of diluents

Diluent	Characteristic
MCC	Good compressibility
Mannitol & Xylitol	Cooling effect, sweet taste, non gritty & low calorie value
Calcarb	Alternative to MCC so as to decrease the grittiness and obtain desired compressibility as well as flow

4.3.1.2 Proposed Combination of Diluents

- Various combination of diluents were proposed by taking into consideration grittiness, compressibility & flowability of them. The detail of the proposed combination are below:
- MCC + Mannitol
- MCC + Xylitol
- MCC + Mannitol + Xylitol
- Calcarb + Mannitol
- Calcarb + Xylitol
- Calcarb + Mannitol + Xylitol

4.3.1.3 Optimization of formulation parameters

Table 4.7 Formula containing 40 % MCC & mannitol-xylitol in different ratio

Batch. No.	MCC (%)	Mannitol (%)	Xylitol (%)
A1	40	60	--
A2	40	--	60
A3	40	30	30

Table 4.8 Formula containing 10 % MCC & mannitol-xylitol in different ratio

Batch. No.	MCC (%)	Mannitol (%)	Xylitol (%)
B1	10	90	--
B2	10	--	90
B3	10	45	45

Table 4.9 Formula containing 10 % Calcarb & mannitol-xylitol in different ratio

Batch. No.	Calcarb (%)	Mannitol (%)	Xylitol (%)
C1	10	90	--
C2	10	--	90
C3	10	45	45

4.4 Evaluation parameters

4.4.1 Powder Characteristics

1. Moisture content: Weigh accurately 1.5 gm of powder sample & place it in the moisture analyzer disk. Keep the temperature at 105˚C for 5 mins. % Loss on drying observed should be less than 5.

2. Bulk Density: The bulk density of a powder may be described as the density of the powder 'as poured' into a measuring vessel. Bulk density was measured using Scott Volumeter Bulk Density Tester. Powder was poured from top of the instrument having 18# screen and it flows through 4 glass baffles and gets accumulated in the receiving cup of 25 ml. Weight of the powder was noted and bulk density was calculated.
   Bulk Density = Bulk Mass/Bulk Volume

3. Tapped Density: The bulk and tapped densities were measured into a 100 ml graduated measuring cylinder in Tap density tester. The tapped volume was noted after 250 taps followed by 500 taps if difference in volume is less than 2%. If difference is more than 2% then granules were subjected for 1250 taps to bring the difference in volume less than 2%.

4. Carr's Index & Hausner's Ratio: Carr's Index was determined by the following formula:-

   Carr's Index= ((Tapped density-Bulk density)/Tapped density) ×100

   Hausner's Ratio is a ratio of Tapped density and bulk density.

5. Flowdex: It is composed of a cylinder with the interchangeable discs with holes of various diameters at the bottom. The determination of fluidity is based on the capacity of the powder to fall freely by a hole in the disc. The hole is carefully charged by which a powder fall freely. If the hole is small, greater its flow. 60 grams are carefully charged in the cylindrical container. Tap the funnel slightly so that the powder is passing without compacting itself. After loading, wait approximately 30 seconds; release the lever and observe if the powder runs. Start with a disc of 16 mm for unknown powders. If the test is positive, repeat the process with smaller discs until the test is negative. If the powder does not run, repeat the test with discs with larger holes until the test is positive. Flowability can be measured from table 4.5 and 4.6.

Table 4.10 Measurement of Flowdex

Flowdex	
Disk#(mm)	**Flowdex(1000/Disk#)**
8	125
9	111
10	100
12	83
14	71
16	63
18	56
20	50

Table 4.11 Measurement of Flowability using Flowdex

Flowdex	**Flowability**
200 and above	Excellent
100 – 199	Good
50 – 99	Medium
Below 50	Poor

6. Ring shear tester: The Ring Shear Tester provides computer controlled The powder sample is contained in an annular shear cell. A vertical load is applied through an annular lid. To shear the sample, the shear cell rotates relative to the lid, and the torque necessary for shearing is measured. Usually, test requires around 20 minutes. FFc value was obtained at the end of the test which determines the flowability & cohesivity of the powder.

Table 4.12 Measurement of Flowability using Ring shear tester

Ring shear tester	
FFc value	**Powder property**
Less than 1	Not flowing
1 – 2	Very cohesive
2 – 4	Cohesive
4 – 10	Easy flowing
More than 10	Free-flowing

7. Angle of repose: It was calculated by keeping funnel at 2.5 cm above the flat surface and allowed the powder to pass through funnel. Radius of circle was measured which was created by powder.

   $\tan \Theta = h/r$

   Where;

   h= height of heap (2.5cm)

   r= radius of circle created by heap.

8. Blend uniformity: After completion of blending stage, 2X weight of the tablet was collected from top, middle & bottom of the blender and samples were analyzed for blend uniformity.

9. Segregation test: Forced Segregation was generated in the blend by segregation tester by applying air pressure to mimic the hopper flow. Initially the test was run at high flow & then at low flow for a run time of 240 sec.

10. Particle size distribution: 50 gm of blend was placed in the upper sieve of sieve shaker and then it was operated for 10 mins. Sieve shaker consist of different screen size sieves from top to bottom. At the end of the test the particles retained in different sieve was weighed and cumulative % retained was calculated.

4.4.2 Tablet Characteristics

- Compression forces: Main compression force & pre compression force were recorded online to check the compressibility of the blend. The lesser the compression force required, the better the compressibility of blend.
- Hardness: Hardness of tablet was evaluated by Dr. Schleuniger Pharmatron 8M hardness tester.
- Friability: 6.5 gm of tablet weight was taken for friability testing and placed in Roche Friabilator for 4 mins at 25 rpm.
- Disintegration time: 6 tablets were taken and disintegration test was performed in disintegration apparatus USP containing 900 ml water at 37˚C.
- Dissolution time: Dissolution test was performed in USP apparatus I at 100 rpm by using 0.01 N HCl. Samples were collected at different time points and analyzed using UV spectrophotometer.

4.4.3 Taste evaluation

- Methodology: Three volunteers of each gender were used to evaluate the taste of Chewable tablets
- The evaluation of taste was performed on healthy volunteers. Chewable tablet containing 25 mg of API was tested. Before each Chewable tablet administration, the volunteers were made to wash their mouth with 100 ml of distilled water. Then, Chewable tablet was chewed. Volunteers were informed to check the taste during chewing & the after test for 30 mins.
- Volunteers were informed to give points in the scale of 1-10.

Conclusion

- From the above formulation batches it can be concluded that Flow property of mannitol was good compared to xylitol. However cooling effect in mouth obtained was less & sticking was observed with mannitol when used in higher amount.
- Xylitol has excellent cooling effect but segregation tendency was observed when used in higher % amount & flow was poor.
- When xylitol was used in combination with mannitol it gave excellent cooling effect, segregation tendency was observed and flow was moderate.
- MCC when used in higher amount had grittiness issues.
- Calcarb can be used as an alternative to MCC to avoid grittiness & when there are issues of compatibility.
- Batch B3 was the optimized batch as it has highest cooling effect & no grittiness. There was no segregation tendency & no issues in direct compression.
- However MCC, mannitol and xylitol were used in combination which is not cost effective and compatibility issues may occur with different API.
- Batch B2 has poor flow property & segregation was highest. However it showed excellent mouth feel & grittiness was not observed.
- So in order to improve flow property & reduce segregation tendency, Dry granulation technique was applied on Batch B2 using roller compaction.

4.6 Preparation of chewable tablet by dry granulation

Objective of the study was to improve flow property & reduce segregation tendency of xylitol by dry granulation technique using roller compaction.

Table 4.29 Formula for dry granulation

Sr no.	Ingredients	Category	% Amount		Quantity(mg)	
1	PHL_158	Drug	5		25	
2	MCC	Diluents	10	82.5	41.25	412.5
3	Xylitol	Diluents	90		371.25	
4	Hydroxy Propyl Cellulose (Klucel EXF)	Dry binder	5		25 mg	
5	Croscarmellose Sodium	Disintegrant	3		15 mg	
6	Magnesium Stearate	Lubricant	2		10 mg	
7	Silicon Dioxide	Glidant	1		5 mg	
7	Citric Acid	Flavour	1		5 mg	
8	Neo-Sucralose	Sweetner	q.s		1.5 mg	
9	Orange	Flavour	q.s		1 mg	
10	Orange	Colour	q.s		q.s	
TOTAL					**500 mg**	

Procedure

- Croscarmellose sodium and Magnesium Stearate were divided into two equal proportion for intra-granular and extra-granular addition.
- Blending: All the ingredient except extra-granular croscarmellose sodium and extra-granular magnesium stearate were added into the turbula blender. Blending was done for 15mins at 30 rpm (450 revolutions).

- Co-milling: After blending, blend was passed through co-mill having 0.8 mm screen size at 1900 rpm.
- Roller compaction: roller compaction was performed at 3 different roll pressure, 3 different roll gaps and 3 different Fine granulator screen size.
- Lubrication: Lubrication was done by adding extra-granular croscarmellose sodium & extra-granular magnesium stearate to the blend. Lubrication was done using turbula blender for 5 mins at 30 rpm (150 revolutions).
- Compression: Compression was done using KORSCH XL100 tablet press. 12 mm round & flat punches of B-Type tooling were used. Compression speed was kept at 20 rpm. Targeted tablet weight was 500 mg and targeted hardness was 8-10 Kp.

4.6.1 Variables of Roller Compactor

Independent variables:

Based on prior knowledge & experimental work 3 factors which affects the roller compaction process significantly are:

Table 4.30 Factors affecting roller compaction process

Factors	Range
Roll pressure	40-70 Bar
Roll gap	2.0-2.8 mm
Granulator final screen	0.6 – 1.0 mm

❖ Constant parameters

- Surface of rolls was kept constant (Upper-Smooth & Lower-Knurled)
- Feed Screw speed, Roller unit speed, Fine granulator speed was kept constant.

❖ Statistical Analysis

Based on the range of three factors, runs were taken at three levels using box-behnken design.

Box-behnken design was selected as central points will be covered and a design space will be created

Dependent variables:

- Bulk density
- Tapped density
- FFc
- Flowdex
- Particle size distribution
- Main compression force
- Tablet Hardness

Table 4.31 Runs of Box-Behnken design in coded form

Factors / Runs	Roll Pressure (Bar)	Roll Gap (mm)	Granulator Screen Size (mm)
1	-1	-1	0
2	1	-1	0
3	-1	1	0
4	1	1	0
5	-1	0	-1
6	1	0	-1
7	-1	0	1
8	1	0	1
9	0	-1	-1
10	0	1	-1
11	0	-1	1
12	0	1	1
13	0	0	0
14	0	0	0
15	0	0	0

Table 4.32 Levels for Box-Behnken design

Factors / Levels	Roll Pressure (Bar)	Roll Gap (mm)	Granulator Screen Size (mm)
1	65	2.6	1.0
0	55	2.3	0.8
-1	45	2.0	0.6

Table 4.33 Runs of Box-Behnken design in actual values

Factors / Runs	Roll Pressure (Bar)	Roll Gap (mm)	Granulator Screen Size (mm)
1	45	2.0	0.8
2	65	2.0	0.8
3	45	2.6	0.8
4	65	2.6	0.8
5	45	2.3	0.6
6	65	2.3	0.6
7	45	2.3	1.0
8	65	2.3	1.0
9	55	2.0	0.6
10	55	2.6	0.6
11	55	2.0	1.0
12	55	2.6	1.0
13	55	2.3	0.8
14	55	2.3	0.8
15	55	2.3	0.8

4.6.2 Targeted product profile

- FFc (ring shear tester) - greater than 8
- Flowdex -10 or less than 10
- Cumulative % retained on 60# (granular portion) - greater than 40 %
- Hardness - greater than 8 kp
- RSD for Blend uniformity and Segregation test should be less than 5.
- % Assay should be within limits (95-110%)

Conclusion

- Flow property of Roller Compacted batch was improved wastly due to formation of granules compared to direct compression.
- Segregation tendency of directly compressed batch was not observed in roller compacted batch as drug is bounded within the granules.
- Content uniformity was obtained in roller compacted batch due to the granulation process.
- There was no issue in compression after roller compaction which shows that xylitol is elastic in nature and does not lose its elasticity after roller compaction.
- Dissolution profile was almost similar in both the process, i.e 85% of drug released in 15 mins. So it can be concluded that dry granulation process doesn't affect drug release.
- Good cooling effect was obtained with dry granulation and no grittiness was observed after roller compaction. Thus it can be concluded that roller compaction does not affect the taste characterization.

Chapter 5
Summary

5.0 SUMMARY

From all the route of administration, Oral administration has been the most common and favourable route for delivery of the drugs. PHL_158 is used in motion sickness which occurs during travelling. Hence, chewable tablets provided the benefit of taking medicine without water. PHL_158 is well absorbed from GIT which was ideal property for preparation of chewable tablet. Chewable tablet provides better patient compliance than conventional dosage forms.

In the current study, chewable tablets of PHL_158 were developed using four different diluents, mannitol, xylitol, MCC and calcarb in different combinations and ratios by direct compression method.

Flow property of mannitol was good compared to xylitol, however cooling effect in mouth obtained was less & sticking was observed with mannitol when used in higher amount.

Xylitol had excellent cooling effect but segregation tendency was observed when used in higher amount & flow was poor.

When xylitol was used in combination with mannitol it gave excellent cooling effect, segregation tendency was not observed and flow was moderate.

When MCC was used in higher amount grittiness issues were occurred.

Calcarb can be used as an alternative to MCC to avoid grittiness & when there are issues of compatibility.

Batch B3 was the optimized batch as it has highest cooling effect & no grittiness. There was no segregation tendency & no issues in direct compression. However MCC, mannitol and xylitol were used in combination which is not cost effective and compatibility issues may occur with different API.

Batch B2 has poor flow property & segregation was highest. However it showed excellent mouth feel & grittiness was not observed. So in order to improve flow property & reduce segregation tendency, Dry granulation technique was applied on Batch B2 using roller compaction.

Dry granulation technique was performed by Alexanderwerk roller compactor using box-behnken design taking roll pressure, roll gap and granulator screen size as independent variables and responses of dependent variables like bulk density, flowdex, FFc, cumulative % retained (60#), main compression force and avg. hardness were measured.

Targeted product profile was decided and according to it batch D5 was the optimized batch.

Flow property of optimized batch was improved vastly due to formation of granules compared to direct compression.

Segregation tendency of directly compressed batch was not observed in optimized batch as drug was found bounded within the granules. Content uniformity was obtained in optimized batch due to the granulation process.

There was no issue in compression after roller compaction which showed that xylitol is elastic in nature and does not lose its elasticity after roller compaction.

Dissolution profile was almost similar in direct compression and dry granulation method, i.e. 85% of drug released in 15 mins. So it can be concluded that dry granulation process doesn't affect drug release. However method of granulation influences flow property, compression and tableting behavior.

Good cooling effect was obtained with dry granulation and no grittiness was observed after roller compaction. Hence it was concluded that roller compaction did not affect the taste characterization.

Therefore the issue of flow and segregation tendency obtained in direct compression batches was rectified by dry granulation technique using roller compactor. Thus the study concluded that dry granulation using roller compaction helps in formulation of effective chewable tablet for a drug having low dose.

Chapter 6
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Chapter 7
Annexure

ANNEXURE I

Item No.:4
Project No.: **IEC/NU/III/IP/04**

CERTIFICATE

This is to certify that the Project entitled **"Development & Optimization of The Formulation and Process Parameters for a Low Dose Chewable Tablet"** submitted by **Prof. Tejal Mehta**, Institute of Pharmacy, Nirma University Ahmedabad, has been approved by the IEC, Nirma University.

Name of the Member Secretary

Dr. Sriram Seshadri
Member Secretary

7th May, 2013

Signature with Date

ANNEXURE II

Presented a poster in NIPICON-2013 on "Taste Masked Ion Exchange Based Combination Therapy for Preparation of Chewable Dosage Form" at Institute of Pharmacy, Nirma University on 19th January 2013.

ABSTRACT

Taste Masked Ion Exchange Based Combination Therapy for Preparation of Chewable Dosage Form

Vyas Utkarsh, Mehta Tejal

Department of pharmaceutics,

Institute of Pharmacy, Nirma University, Sarkhej-Gandhinagar highway, ahmedabad-382 481 (Gujarat) India

e- mail id: uv37_10@yahoo.com

Combination therapy has been used to obtain synergistic effect, improve compliance and decrease adverse effects. Combination of Dextromethorphan HBr and Diphenhydramine HCl were used for Anti tussive activity. Dextromethorphan HBr is an NMDA antagonist which suppresses the urge to cough and provide relief from dry, sticky coughs. Diphenhydramine HCl is an antihistamine which works by blocking the effects of histamine and dries secretions in the nose. Absorptivities of both drugs were found at 278 nm and 258 nm using UV spectrophotometer by Simultaneous Equation Method. These drugs exhibit bitter taste when administered orally. Therefore, suppression of the bitter taste has been an important part for development of dosage forms. Various techniques were tried and out of these ion exchange resins technique for taste masking was selected. Acid activation of resin was carried out before swelling. A mixture of drug, resin and water was stirred for definite time at constant temperature and speed. Dried residue of drug-resin complex was estimated spectrophotometrically and % drug loading efficiency was calculated. Bitterness of drug was optimized using different drug: resin ratios. The batch containing 1:5 drug: resin ratio shown complete taste masking and % drug loading was found to be 100%. The developed dosage form was found effective for development of chewable tablet dosage forms. Developed tablets were evaluated and all parameters were found within range.

"Taste Masked Ion Exchange Based Combination Therapy for Preparation of Chewable Dosage Form"

Vyas Utkarsh, Mehta Tejal
Department of Pharmaceutics, Institute of Pharmacy, Nirma University, S. G. highway, Ahmedabad-382481, Gujarat, India
e-mail address: uv37_10@yahoo.com

NIRMA UNIVERSITY
INSTITUTE OF PHARMACY

INTRODUCTION

- Dextromethorphan HBr is an NMDA antagonist which suppresses the urge to cough and provide relief from dry, sticky coughs.
- It is used for Temporary relief of coughs caused by minor throat and bronchial irritation that may occur with common colds, allergies, or inhaled irritants.
- Diphenhydramine HCl is an antihistamine which works by blocking the effects of histamine and dries secretions in the nose.
- It is used for relief of symptoms associated with the common cold (e.g., rhinorrhea, sneezing, cough).
- Fixed dose combination of these two agents was prepared for obtaining Anti -Tussive effect

RATIONALE

- The decongestants such as Dextromethorphan produce a narrowing of blood vessels. This leads to clearing of nasal congestion.
- Administration of Dextromethorphan is accompanied by histamine release. Histamine can cause severe nausea, vomiting, itching, sneezing, running nose, and watery eyes.
- To inhibit this side effect of Dextromethorphan, antihistamines are given in combination with Dextromethorphan.
- Antihistamines such as Diphenhydramine work by preventing the effects of histamine, which is produced by the body or by some external agents.

ADVANTAGES OF CHEWABLE TABLET

1) Not required to be swallowed so ease of administration, especially for paediatrics and geriatrics patient.
2) Complete disintegration in the mouth thus a rapid effect can be obtained.
3) No water is required after administration of drug
4) Unit dosage form
5) Ease of transportation
6) Improved stability
7) Less chances of microbial contamination

SIMULTANEOUS EQUATION METHOD

As Combination of Dextromethorphan HBr and Diphenhydramine HCl are not available in the market, determination of absorptivities of both drugs by Simultaneous Equation Method was carried out to find the concentration of both drugs which are released from the combinational dosage form.

Simultaneous Equation:

$Cx = A2\,ay1 - A1\,ay2 / ax2\,ay1 - ax1\,ay2$

$Cy = A1\,ax2 - A2\,ax1 / ay1\,ax2 - ay2\,ax1$

Where,

Cx= Concentration of Dextromethorphan HBr

Cy= Concentration of Diphenhydramine HCl

ax1= Absorptivity of Dextromethorphan HBr at 278 nm = 62.44 gm/100ml

ax2= Absorptivity of Dextromethorphan HBr at 258 nm = 18.48 gm/100ml

ay1= Absorptivity of Diphenhydramine HCl at 278 nm = 0.6355 gm/100ml

ay2= Absorptivity of Diphenhydramine HCl at 258 nm = 16.28 gm/100ml

A1=absorbance at λ1(278 nm)

TASTE MASKING OF DRUGS

Techniques:

IDEAL CHARACTERISTICS OF DRUGS FOR RESINATE PREPARATION

- Drug should have acidic or basic nature in their chemical structure
- Biological half life should be between 2-6 hrs
- The drug is to be absorbed from all part of GI tract
- Drug should be stable in gastric fluid.

RESIN ACTIVATION

- Accurately weighed Resin (100 mg), was placed on a whatman filter paper in a funnel, and was washed with Deionized water.
- Subsequently it was washed with 1 N HCl (50 ml) for Acid Activation.
- Then the resin was rewashed with deionized water again to reach neutral pH.
- These Activated resins are further used in complexation process.

PREPARATION OF DRUG-RESIN COMPLEX

Required Acid Activated Resins was taken in a beaker and 30 ml of deionized water was added to it and it was placed for swelling

↓

After completion of swelling time, drug was added to it and it was placed on a stirrer

↓

After completion of stirring time, the drug resin slurry was filtered using whatman filter paper

↓

These drug-resin complex obtained is washed with deionized water to remove H^+ ions

↓

Then the drug resin Complex is Placed for drying for 24 hrs

↓

Swelling time, Loading time and Drug-Resin Ratio was optimized.

OPTIMIZATION OF PROCESS PARAMETERS

Dextromethorphan HBr

1)Optimization of swelling time

Batch	Drug: Resin Ratio	Swelling Time (mins)	Stirring (loading) Time (mins)	Taste	% Drug Loading
A1	**1:2**	**30**	**150**	+	**50.80**
A2	1:2	60	150	+	50.57
A3	1:2	90	150	+	50.74

2)Optimization of Stirring (Loading) Time

Batch	Drug: Resin Ratio	Swelling Time (mins)	Stirring (loading) Time (mins)	Taste	% Drug Loading
A4	1:2	30	90	+	27.48
A5	1:2	30	120	+	37.63
A6	1:2	30	150	+	50.80
A7	1:2	30	180	+	67.35
A8	**1:2**	**30**	**210**	+	**78.49**
A9	1:2	30	240	+	78.40
A10	1:2	30	270	+	78.46

3)Optimization of Drug: Resin Ratio

Batch	Drug: Resin Ratio	Swelling Time (mins)	Stirring (loading) Time (mins)	Taste	% Drug Loading
A11	1:1	30	210	+	67
A12	1:2	30	210	+	79
A13	1:3	30	210	++	93
A14	1:4	30	210	++	96
A15	**1:5**	**30**	**210**	+++	**101**

Diphenhydramine HCl

1)Optimization of swelling time

Batch	Drug: Resin Ratio	Swelling Time (mins)	Stirring (loading) Time(mins)	Taste	% Drug Loading
B1	**1:2**	**30**	**150**	+	**74.49**
B2	1:2	60	150	+	74.33
B3	1:2	90	150	+	74.29

2)Optimization of Stirring (Loading) Time

Batch	Drug: Resin Ratio	Swelling Time (mins)	Stirring (loading) Time(mins)	Taste	% Drug Loading
B4	1:2	30	90	+	45.68
B5	1:2	30	120	+	57.15
B6	**1:2**	**30**	**150**	+	**74.00**
B7	1:2	30	180	+	74.04
B8	1:2	30	210	+	73.88

3)Optimization of Drug: Resin Ratio

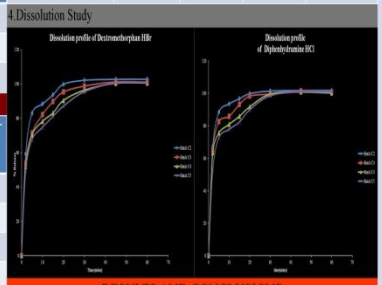
Batch	Drug: Resin Ratio	Swelling Time (mins)	Stirring (loading) Time(mins)	Taste	% Drug Loading
B9	1:1	30	150	+	60
B10	1:2	30	150	+	74
B11	1:3	30	150	+	83
B12	1:4	30	150	++	96
B13	**1:5**	**30**	**150**	+++	**100**

Note: + Bitter, ++ Slightly Bitter, +++ Acceptable

EVALUATION OF CHEWABLE TABLETS

Evaluation parameters	Batch C2 (Kyron T-314)	Batch C3 (SSG)	Batch C4 (Ac-di-Sol)	Batch C5 (No SDT)
1.Hardness	5.32 kps	4.95 kps	5.06 kps	5.65 kps
2.Friability	0.7	0.8	0.7	0.6
3.Disintegration time	44 sec	53 sec	58 sec	69 sec

4.Dissolution Study



RESULTS AND CONCLUSIONS

- From the above results it can be concluded that Drug: Resin Ratio of 1:5 and Swelling time of 30 minutes were found to be optimum for both drugs. Loading time of 210 minutes for Dextromethorphan HBr and 150 minutes Diphenhydramine HCl were found to be optimum.
- From the evaluation parameters of Chewable Tablets of BatchC4, BatchC5, BatchC6 & BatchC7 it can be concluded that Hardness(4-6 kps) and Fraibility(>1) of all batches are within the standard limits. Batch C2 containing Kyron T-314 showed least disintegration time . From the Dissolution study of all batches, 85% of Dextromethorphan HBr was released within 5 mins from Batch C2, within 10 mins from Batch C3 & within 20 mins from Batch C4 & Batch C5. 85% of Diphenhydramine HCl was released within 5 mins from Batch C2, within 10 mins from Batch C3, within 15 mins from Batch C4 & within 20 mins from Batch C5. So it can be concluded that Kyron T-314 is more suitable super-disintegrent for this Formulation.

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"This Poster has been presented at NIPiCON-2013 organized by Institute of Pharmacy, Nirma University, Ahmedabad"