PREFACE

This textbook of Pharmaceutical Technology and Industrial Pharmacy is designed to cover major basic Pharmaceutical Technology curriculum of 300 to 600 level undergraduate students and postgraduate students of pharmacy. In addition, all the areas covered by the contributing authors have been given an industrial approach to enable pharmacist that may wish to go into production to have comprehensive knowledge of the science and technology of drug production. Contributing authors were selected on the basis of competence and their contributions are masterpiece in the field of Pharmaceutical Technology and Industrial Pharmacy. Chapter 1 to 4 deals with solid dosage pharmaceuticals (tablets capsules and coated dosage forms), chapter 5 deals with oral sustained release dosage forms, chapter 6 deals with pharmaceutical suspensions and chapter 7 deals with parenteral products. Effervescent products, chewable tablets and medicated lozenges are discussed in chapter 8, while emulsions are discussed in chapter 9. Chapter 10 contains discussion on creams and ointments, instability of pharmaceutical products in the tropics and expiry date prediction are discussed in chapter 11 and relevant Industrial Pharmacy laws are presented in chapter 12. Chapter 13 deals with relevant pharmacokinetics.

We are particularly grateful to our many sources and publications which include: British Pharmacopoeia, The Pharmaceutical Codex, Remington's Pharmaceutical sciences and the numerous journal publications, bulletins and textbooks.

We have put together a simple yet detailed text that will be valuable to undergraduate, and postgraduate Pharmacy students, industrialists and practicing Pharmacists.

In as much as the editor takes responsibility for the quality of the articles by contributors, the contents and correctness of information are the responsibility of the contributing authors.

The editor is grateful to the contributors, to his wife **Akuzuo**, two kids **Chidera** and **Chiazam** and to **Chioma** for being around and useful when help was needed.

S.I. Ofoefule, PhD
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List of Contributors

S.I. Ofoefule, PhD, MPSN (Editor)
Department of Pharmaceutical Technology and Industrial Pharmacy,
University of Nigeria, Nsukka.

Amarauche Chukwu, PhD, MPSN, FPC. Pharm.
Department of Pharmaceutical Technology and Industrial Pharmacy,
University of Nigeria, Nsukka.

Ogbonna Okorie, M.Pharm, MPSN
Department of Pharmaceutical Technology and Industrial Pharmacy,
University of Nigeria, Nsukka.

CHAPTER 1

TABLET DOSAGE FORMS I

S. I. OFOEFULE, Ph. D.

CONTENTS:

GENERAL INTRODUCTION

The oral route of drug administration is the most important method of administering drugs for systemic effects. At least 90% of all drugs used to produce systemic effects are administered by oral route.

Compressed tablets are oral solid dosage forms containing active substance(s) with or without suitable diluents. They should be elegant having their own identity while being free of defects such as chips, cracks, discoloration, contamination etc. They should have the strength to withstand the rigor of mechanical shocks encountered during production, packaging, shipping and dispensing. They should have the chemical and physical stability to maintain their physical attributes over a period of time. Other requirements include: ability to release the medicinal agent(s) in the body in a predictable and reproducible manner and they should have a suitable chemical stability over time so as not to allow alteration of the medicinal agents.

The objective of the design and manufacture of compressed tablets is to deliver orally, the correct amount of drug in the proper form, at or over the proper time and in the desired location and to have its chemical integrity protected up to the point of ingestion.

Excipients which are inert substance may be added to the active ingredient of a tablet to increase its bulk and give those desirable properties lacking in the active ingredient alone.

Compressed tablets as a means of administering medicinal substances to patients have the following advantages

(I) The patient generally finds a tablet the simplest dosage form for self medication

(II) It is an accurate dosage form in which in most cases represents one dose. For scored tablets uniform division can be achieved by the patient to obtain a required dose.

(III) In terms of transportation, it is convenient for the manufacturer, the pharmacist and the patient.

TYPES OF TABLETS

I) Normal Release Tablets (Oral Tablets)

These are tablets that are swallowed, usually with a glass of water. They are meant to disintegrate in the GIT before the effective absorption of the drug can take place. They are generally referred to as uncoated tablets. Most uncoated normal release tablets disintegrate within 15 minutes. An example of oral tablets is paracetamol tablets.

II) Sublingual or Buccal Tablets

They are tablets whose contents are expected to be released in the oral cavity. They are usually small and flat. They are administered by placing them between the cheeks and the gum in the mouth. The active ingredient is released

and absorbed from the buccal cavity. They GIT is avoided and some drugs that are easily destroyed by enzymes in the GIT are administered by this route. An example of drug administered by this route is glyceryl trinitrate used in the treatment of angina pectoris.

III) Lozenges or Troches

These are tablets intended to be held in the mouth while they dissolve gradually so that the drug is in contact with the mouth and the throat for a prolonged period of time. Lozenges are used for the local effect of antiseptics, astringents and local anaesthetics. Lozenges do not contain disintegrants. Direct compressible sugars are usually applied as diluents for lozenges. An example of lozenges is dequialinium chloride.

IV) Chewable Tablets

These are designed to be broken down rapidly in the buccal cavity by the action of the teeth. Diluents which produce a cooling sensation in the mouth are suitable for their formulation. Mannitol which has negative heat of solution thereby producing cooling sensation in the mouth is a typical of diluents used in chewable tablets. They do not require incorporation of a disintegrant. They usually contain a flavoring agent. Some antacids are chewable tablets.

V) Effervescent Tablets

They dissolve in cold water with evolution of gas. They undergo rapid disintegration and increases palatability. They contain citric or tartaric acid and bicarbonates. They are formulated using a fusion method.

VI) Coated Tablets

These are tablets that are either coated with sugar to mask obnoxious taste or with polymers to protect them from environmental factors such as light, mechanical damage, aid product identification, enhance appearance or produce modified release of the incorporated drug.

VII) Vaginal Tablets

These are generally referred to as inserts. They are usually compressed into a pear shape. They are usually formulated with diluents which cause rapid release of the drug.

VIII) Implants

These are tablets or pellets that are implanted in the body by incision or by use of a Kearne implanter. They are usually implanted in the thigh. Hormones used in birth control are typical examples of tablets or pellets. Implants serve as a depot from which the hormone is released slowly over a prolonged period of time.

IX) Tablets for Miscellaneous use

These include dental cones which are used in the mouth. The cones are loosely packed in the socket after tooth extraction. It contains an antibacterial agent which prevents local proliferation of bacteria. There are tablets that are used in disinfections and those used for chemical sterilization of instruments. There is also reagent tablets that are used in diagnosis. A typical examples are acetest reagent tablets used to test ketonuria and ictotest reagent tablets used to test urinary bilirubin. Other types of tablets include prolonged release tablets, solution tablets and dispersible tablets.

TABLET COMPONENTS AND EXCIPIENTS

Tablets are generally composed of the following components

I) Active ingredient

II) Filler or Bulking agent

III) Binder or Granulating solution

IV) Disintegrants

V) Lubricants

VI) Glidants

VII) Colorants

VIII) Flavors/Sweetening agent

IX) Wetting agents

All these components may not be present in all tablet formula. For tablets formulated by wet granulation method, binding agents, disintegrants and lubricants must be present in addition to the active drug substance. All these tablet components will be discussed but more detailed discussion will be devoted to binding agents, disintegrants and lubricants.

Fillers/Bulking Agents

In tablet formulation, it is not feasible to make tablets weighing less than 70mg. Fillers are added in most tablet formulations to provide bulk in order to make tablets of practical size for compression. In some formulations such as low dose drugs, the filler can make up to 90% of the total tablet weight. High dose drugs such as chloroquine phosphate, paracetamol etc., may not need any filler when they are prepared by wet granulation. Fillers used in tableting should be chemically and physiologically inert and should be stable over long periods of storage. In addition, they should be compatible with a wide range of drugs and excipients. This is one of the major consideration in the choice of fillers. Their solubility is also very important as this will influence how the tablet disintegrates. There are many fillers available in commerce. It is only the fillers that are widely used in wet

granulation of tablets will be discussed. Fillers used in direct compression are discussed in details in chapter 2.

Lactose

The commercially available product for wet granulation is the α - lactose. It is available as a crystalline or spray-dried product. It is available in two particle size ranges, 200 – 225 mesh and 300 to 325 mesh. It is the most widely used fillers in wet granulation largely because of its low cost and compatibility with most drug substances and excipients. Furthermore, it has less tendency to cause browning of tablets. It can be combined with other fillers such as calcium phosphate, corn starch and Avicel (microcrystalline cellulose).

Sucrose

Sucrose is normally used in chewable tablets. The form available for wet granulation contains about 3% starch which has been included to prevent caking. Tablets prepared with sucrose tend to harden on storage. It is a reducing sugar and its use as a tablet diluent may pose problem to diabetic patients.

Other diluents used in wet granulation include mannitol, Dextrose, fructose, sorbitol, dicalcium phosphate, calcium sulphate, starch and cellulose.

Binders/Granulating Agents

Binders are usually polymeric materials which possess both cohesive and adhesive properties. Their presence is very crucial in wet granulated granules and tablets. They function by holding filler and drug particles together in agglomerates thereby converting them into granules which are free flowing. They are usually water soluble materials, though some are soluble only in alcohol or hydro-alcoholic solvents. They are usually added as mucilages. In some cases the dry powder can be distributed in the drug-filler blend and then water or

alcohol or water-alcohol mixture are added to form the binder solution in situ. Binders added in this way are know to produce not too strong a tablet. Uniform distribution and the amount of a binder employed in a granulation are critical. Insufficient binder tends to poor adhesion, capping and soft tablets. Excessive binder yields a slowly disintegrating and hard tablets. Furthermore, the presence of excessive binder in a formulation makes granulation and tableting extremely difficult. Seager *et al*[*] have given an excellent discussion on the role of the binder in granule structure and tableting.

Binders that are commonly used in tableting and their use levels are given in Table 1.

Binders	**Use level % w/v**	**Remark**
Starch	5 – 10	2 – 5% w/w
Acacia	10 – 20	
Sucrose	70 – 85	
Gelatin	10 – 20	1 – 3% w/w
Glucose	25 – 50	
Methylcellulose	5 – 10	
Ethylcellulose	5	in alcohol
Polyvinylpyrrolidone	5	in alcohol or water

Disintegrating Agents

Disintegrating agents are substances added to tablet formulations to facilitate the break-up of the tablets in the stomach. They function to counteract the effect of binders and the physical forces of compression used in forming the tablets. The stronger the binding agent used, the stronger will be the effect of the disintegrant in order to guarantee the release of

[*] Seager *et al* Int. J. Pharm. Tech & Prod. Mfg 1(1) 2 – 6 (1980)

the active ingredient in the GIT. There are three basic methods of incorporating disintegrants into tablet formulation – Intragranular, Extragranular and Intragranular-Extragranular incorporations. In Intragranular incorporation, the disintegrant is mixed with other excipients before the incorporation of the binder solution. Extragranular incorporation involves incorporating the disintegrant into the granules prior to the addition of lubricants. Intragranular-Extragranular incorporation involves mixing half or a portion of the disintegrants with the other excipients before the addition of the binder solution and the remainder is added to the granules before compression. Intragranular-Extragranular appear to be the best method of incorporation. Extragranularly added portion causes immediate disruption of the tablet into the previously compressed granules while the portion added intragranularly cause further erosion of the granules to the original powder particles.

Corn and potato starches have traditionally been employed as disintegrants. Starch is composed of two components – amylose and amylopectin. Amylose makes up to 20 – 30% of the content of starch grains. It is a straight chain fraction that is insoluble in cold water but absorbs a large amount of water and swells. The disintegrant properties of starch rests on the amylose fraction. Amylopectin is a branched chain compound and it makes up 70 – 80% of the starch grains and rapidly forms colloidal solution at room temperature. It is responsible for the binding properties of starch. Starch is used at a concentration of 5 – 10% w/w.

Apart from starch, there are now available new disintegrants that possess super disintegrant properties. These include:

a) Sodium Starch Glycolate

This is one of the modifications of starch aimed at improving its disintegration properties. It can be produced by chemical modification that involves carboxymethylation of starch grains. The presence of carboxymethyl groups makes

the starch more hydrophilic, but not completely water soluble. The process also causes a two to three fold increase in the size of the starch grains. It is used at a relatively low concentration and a minimum concentration of 4% is required for most formulations. Carboxymethyl starch or sodium starch glycolate is available commercially as Explotab and Primogel.

b) Cross-linked Sodium Carboxymethyl Cellulose

This is internally cross-linked carboxymethylcellulose fibres. The cross linking greatly reduces water solubility while still permitting the material to swell and absorb many times its weight in water without losing individual fibre integrity. It causes fast disintegration of tablets at low concentrations. It is used at a concentration of 1 – 3% (2% for direct compression and 3% for wet granulation). Its effectiveness at low concentration has been attributed to its fibrous nature, which allow intraparticulate wicking of water into tablet matrices by single fibres rather than by a continuum of many individual and more special particles. It is available commercially as Ac – Di – SOL.

Other disintegrants include cross-linked polyvinyl pyrrolidone, soy polysaccharide, purified cellulose (Solka Floc), methylcellulose, carboxymethylcellulose, alginic acid etc.

Mechanism of Disintegrant Action

The mechanism of disintegrant action varies from one disintegrant to the other. Many theories have been proposed to explain the mechanisms by which disintegrants exert their disintegrant action. These include: (i) Swelling (ii) Porosity and capillary action and (iii) Deformation. Each of these mechanism will be given a brief discussion.

I) Swelling

This is the mechanism by which the new super-disintegrants and polymeric gums cause the disintegration of tablets. They absorb water and swell with great force. By so doing they overcome the adhesiveness of other ingredients in

the tablet and cause the tablet to fall apart. Apart from the new super disintegrants (Explotab, Ac-Di-SOL) the polymeric gums used as disintegrant have the disadvantage of forming viscous plug thereby hindering further fluid penetration into the tablet. For these polymers, disintegration time increases with increase in their concentrations. There is always a minimum concentration at which they exert optimum disintegration action.

II) Porosity and Capillary Action

This is also known as wicking action. For water or fluid to enter into a compressed tablet and activate the disintegrant to bring about disintegration, there must be pores though which the fluid is imbibed. No tablet possesses a zero porosity in practice. Porosity is affected by compression force employed in compressing the tablet. Capillary action has been attributed to be responsible for the disintegrant action of starch. This is based on the finding that although aspirin tablets containing starch disintegrated in 15 sec, the starch grains were not swollen. However, a drop of dye solution placed on the tablet penetrated rapidly. It is now known that water can wick into tablets either as a result of pore capillarity or by sorption.

III) Deformation

This mechanism has been presented as a better explanation of the process by which starch exerts its disintegrant action. Starch grains are generally thought to be elastic, i.e. starch grains that are deformed under pressure tend to return to their original shape and size when the pressure is removed. It has been suggested that at certain compression pressure, that starch may undergo permanent deformation. These permanently deformed starch grains are rich in energy

and when these energy rich grains are exposed to water, this energy is released causing disintegration of the tablets. These energy rich starch grains swell more rapidly in water than undeformed granules.

For the purposes of research, it must be noted that tablets which consist primarily of highly water soluble drugs and excipients tend to dissolve rather than disintegrate even when traditional disintegrants are present. Consequently, highly water soluble high dose drugs may not be good candidates in the evaluation of disintegrant properties of potential disintegrants.

Lubricants, Glidants and Anti-adherants

Lubricants are substances added to tablet granulation to:

i) ease ejection of tablets from the die

ii) prevent sticking to punches and dies

iii) prevent excessive wear of punches and dies

Glidants on the other hand are substances that improve the fluidity of granulation. They act as ball bearing thereby facilitating the flow of granulations.

Anti-adherants prevent sticking of granules/tablets on the punch faces. A list, properties and use levels of commonly used lubricants in tableting are given in Table 2.

Lubricants are generally used in small quantities. They can cause serious problems in tablet formulations. When they are used at a low level concentration, filming, picking and capping as well as binding in the die cavity may occur. High levels may cause prolonged disintegration and dissolution. They tend to coat particle surfaces and interrupt bonding sites between drug and/or excipient surfaces causing a weakness in the tablet structure thereby decreasing tablet hardness.

Lubricants should be incorporated as fine powder into the granules to ensure proper coating of the granules. They are usually screened through a 200-mesh screen prior to incorporation.