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EVALUATION OF CHITIN METAL SILICATE CO PRECIPITATES
AS POTENTIAL MULTIFUNCTIONAL EXCIPIENTS IN TABLET
FORMULATIONS

By

Rana Hani Mohammed Ali Al-Shaikh Hamed

A thesis Submitted in
Partial Fulfillment of the
Requirements for the Degree of

Master of Science

at

Petra University

Faculty of pharmacy

Amman-Jordan

June 2009

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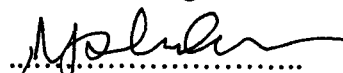


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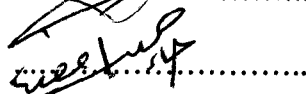
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Abstract

EVALUATION OF CHITIN METAL SILICATE CO PRECIPITATES AS POTENTIAL MULTIFUNCTIONAL EXCIPIENTS IN TABLET FORMULATIONS

By

Rana Hani Mohammed Ali Al-Shaikh Hamed

Petra University, 2009

Under the supervision of Prof. Mohammed Shubair and Dr. Faisal Al- Akayleh

Three novel chitin metal silicates (CMS) were prepared namely chitin calcium silicate (CCaS), chitin magnesium silicate (CMgS), and chitin aluminum silicate (CAIS).

These CMS were tested as multifunctional direct compression and wet-granulation excipients in the design of tablets containing ibuprofen (IBU), metronidazole (MET) and spironolactone (SPL) as models of low and high dose drugs.

Commercial tablets containing these drugs and tablets made using Avicel[®] 200; one of the most commonly and widely used commercial direct compression excipient; were studied for comparison purposes.

The pH of the media of preparation of these CMS co precipitates was measured to be: 10, 9, and 4 for CCaS, CMgS, and CAIS, respectively. CAIS was selected to test the effect of altering this pH from 4 to 7 or 8 and found to highly

affect its functionality with respect to hardness, disintegration time and dissolution rate.

The friability values for all the prepared tablets were below the maximum 1% USP tolerance limit. All CMS containing formulas showed crushing strength within the acceptable range (>40N). For all tested drugs, the CMS (prepared at their appropriate pH_s), 10, 9 and 4 for CCaS, CMgS and CAIS respectively) based tablets showed outstanding disintegration characteristics (disintegration time less than 60s) for tablets prepared by direct compression or wet granulation methods. The type of CMS was found not to affect the disintegration time and crushing strength of the tablets. Regarding the dissolution profiles, CMS tablets demonstrate superiority over the Avicel[®] 200 based tablets except for those with metronidazole which showed similar dissolution profile. In addition, they demonstrate faster dissolution profiles than Fleximex[®] and Dumazole[®] but slower than Aldactone[®].

Compressional properties of formulations were analyzed using density measurements and the compression equations of Heckel and Kawakita as assessment parameters. CMgS was selected as an example. All tested formulas gave plots with an initial curved region followed by a linear portion, which is typical of B-type materials; this indicates that the materials first underwent fragmentation, followed by plastic deformation. Formulas containing CMgS with ibuprofen, metronidazole or spironolactone showed lower yield values (Py) than CMgS alone which indicate faster onset and higher amount of plastic deformation. A linear relationship was found to exist between P/C (applied pressure/degree of volume reduction) and P (pressure) for all tested formulations (CMgS alone and CMgS with ibuprofen, metronidazole or spironolactone). The value of "1/b"; which represents the cohesive properties of powders, for CMgS alone is higher than those with drugs. The lower value of "1/b" of

CMgS in the presence of drugs is indicative of the reduction in cohesive forces. In other words, the presence of drugs increased the plastic deformation of CMgS under pressure. These results are in positive correlation with Heckel parameter (Py).

Differential scanning calorimetry (DSC) was used as a screening technique for assessing the compatibility of the model drugs with CMS employed in tablet formulations. On the basis of DSC results, CMS co precipitates were found to be chemically compatible with the tested drugs.

These results conclusively show that the prepared CMS co precipitates have the potential to be used as filler, binder, and disintegrant, all-in-one, in the design of tablets containing either a low or high dose drug by direct compression and wet-granulation methods.

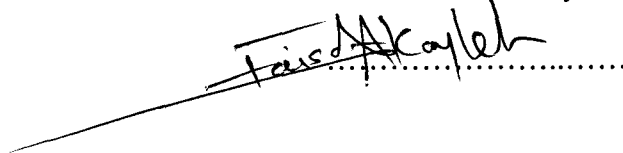
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To
My Family.....

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Rana, Jordan, June 2009

Rana Hani Mohammed Ali Al-Shaikh Hamed

Table of Contents

Contents	Page
TITLE PAGE	I
ABSTRACT	III
DEDICATION	VI
ACKNOWLEDGEMENTS	VII
TABLE OF CONTENT	IX
LIST OF FIGURES	XII
LIST OF TABLES	XV
ABBREVIATIONS	XVII
Chapter One: Introduction	
No.	Page
1	2
1.1	2
1.2	2
1.2.1	3
1.2.2	4
1.2.3	7
1.2.3.1	7
1.2.3.2	9
1.2.3.3	10
1.2.3.4	11
1.2.4	16
1.3	18
1.3.1	18
1.3.2	20
1.3.3	21
1.4	24
1.4.1	24
1.4.1.1	25
1.5	29
1.6	32
1.6.1	32
1.6.2	32
1.6.3	33
1.7	34

Contents		Page
Chapter Two: Experimental		
No.		Page
2	Materials and Methods	37
2.1	Materials	37
2.2	Methods	38
2.2.1	Preparation of Chitin- Ca, -Mg and -Al Silicate Co precipitates	38
2.2.2	Preparation of Chitin Al Silicate Co precipitates of pH7 and pH8	39
2.2.3	Preparation of Tablets by Direct Compression Method	39
2.2.4	Preparation of Tablets by Wet Granulation Method using Chitin Mg Silicate	39
2.2.5	Measurement of Tablets Friability	40
2.2.6	Measurement of Tablets Hardness and Thickness	42
2.2.7	Disintegration Test	42
2.2.8	Dissolution Test	42
2.3	Calibration Curves of Model Drugs	43
2.3.1	Calibration Curve of Ibuprofen	43
2.3.2	Calibration Curve of Metronidazole	43
2.3.3	Calibration Curve of Spironolactone	44
2.4	Tablets Compressibility Studies	44
2.4.1	Heckel Plot	44
2.4.2	Kawakita Plot	45
2.5	Differential Scanning Calorimetry (DSC) Study	46
2.6	Statistical Analysis	46
Chapter Three: Results and Discussion		
No.		Page
3	Results and Discussion	48
3.1	Preparation and Characterization of Tablets using a Single Tablet Excipient	48
3.1.1	Hardness , Thickness and Friability Studies	48
3.1.1.1	Effect of Excipient Type on Crushing Strength	50
3.1.1.2	Effect of the Method of Addition of Chitin Mg Silicate on the Crushing Strength	51
3.1.1.3	Effect of pH of the preparation media of Chitin Al Silicate on Crushing Strength	52

Contents		Page
3.1.1.4	Effect of different Drug / Chitin Metal Silicate Ratio on Crushing Strength	53
3.1.2	Disintegration Studies	54
3.1.2.1	Effect of Chitin Metal Silicate Type on Disintegration Time	54
3.1.2.2	Effect of the Method of Addition of Chitin Metal Silicate on Disintegration time	54
3.1.2.3	Effect of pH of the preparation media of Chitin Al Silicate on Disintegration time	54
3.1.2.4	Comparative Disintegration Time with commercial products and Avicel® 200 containing formulas	55
3.1.3	Calibration Curves of Model Drugs	57
3.1.4	Dissolution Studies	59
3.1.4.1	Effect of Chitin Metal Silicate Type on Drug Dissolution	59
3.1.4.2	Comparative Dissolution Profile Studies	61
3.1.4.3	Effect of pH of the preparation media of Chitin Metal Silicate on Drug Dissolution	64
3.1.4.4	Effect of different Drug / Chitin Metal Silicate Ratio on Drug Dissolution	65
3.1.4.5	Effect of the Method of Addition of Chitin Metal Silicate on Drug Dissolution	66
3.2	Compressibility Studies	68
3.2.1	Heckel Plot Results	68
3.2.2	Kawakita Plot Results	71
3.3	Compatibility Study	74
3.3.1	Differential Scanning Calorimetry (DSC)	74
Chapter Four: Conclusions		
4	Conclusions	82
Appendix		
References		

List of Figures

Figure No.		Page No.
Chapter One: Introduction		
1.1	Structure of cellulose	14
1.2	Structure of chitin	19
1.3	Structure of chitosan	19
1.4	Structure of ibuprofen	32
1.5	Structure of Metronidazole	32
1.6	Structure of spironolactone	33
Chapter Three: Results and Discussion		
3.1	Effect of Drug/CMS ratio on crushing strength	53
3.2	Disintegration test for ibuprofen tablets containing CCaS (chitin Ca silicate), CMgS (chitin Mg silicate), CAIS (chitin Al silicate), Avicel [®] 200 as fillers, and commercial product.	56
3.3	Disintegration test for metronidazole tablets containing CCaS (chitin Ca silicate), CMgS (chitin Mg silicate), CAIS (chitin Al silicate), Avicel [®] 200 as fillers, and commercial product.	56
3.4	Disintegration test for spironolactone tablets containing CCaS (chitin Ca silicate), CMgS (chitin Mg silicate), CAIS (chitin Al silicate), Avicel [®] 200 as fillers, and commercial product.	57
3.5	Calibration curve of ibuprofen.	57
3.6	Calibration curve of metronidazole.	58
3.7	Calibration curve of spironolactone.	58
3.8	Dissolution profile of ibuprofen released from Formula ID1 (chitin Ca silicate), Formula ID2 (chitin Mg silicate) and Formula ID5 (chitin Al silicate).	59
3.9	Dissolution profile of metronidazole released from Formula MD1 (chitin Ca silicate), Formula MD2 (chitin Mg silicate) and Formula MD3 (chitin Al silicate).	60
3.10	Dissolution profile of spironolactone released from Formula SD1 (chitin Ca silicate), Formula SD4 (chitin Mg silicate) and Formula SD10 (chitin Al silicate).	61
3.11	Dissolution profile ibuprofen of Formula ID1 (chitin Ca silicate), Formula I Avicel (Avicel [®] 200) as fillers, and commercial product.	62

Figure No.		Page No.
3.12	Dissolution profile metronidazole of Formula MD1 (chitin Ca silicate), Formula M Avicel (Avicel® 200) as fillers, and commercial product.	62
3.13	Dissolution profile spironolactone of Formula SD1 (chitin Ca silicate), Formula S Avicel (Avicel® 200) as fillers, and commercial product.	63
3.14	Dissolution profile ibuprofen of Formula ID4 (chitin Al silicate pH 7) and ID5 (chitin Al silicate pH 4).	64
3.15	Dissolution profile spironolactone of Formula SD8 (chitin Al silicate pH 8), SD9 (chitin Al silicate pH 7) and SD10 (chitin Al silicate pH 4).	65
3.16	Dissolution profile spironolactone from Formulas of different drug/chitin Mg silicate ratio; SD4 (1/11), Formula SD6 (1/4) and SD7 (1/1).	66
3.17	Dissolution profile of ibuprofen with chitin Mg silicate Formula ID2 (direct compression), Formula III (wet intra- granulation) and IE1 (wet extra-granulation).	66
3.18	Dissolution profile of metronidazole with chitin Mg silicate Formula MD2 (direct compression), Formula MI2 (wet intra- granulation) and ME2 (wet extra-granulation).	67
3.19	Heckel plot of chitin Mg silicate.	68
3.20	Heckel plot of formula ID2 (400mg ibuprofen with 300mg chitin Mg silicate).	69
3.21	Heckel plot of formula MD2 (500mg metronidazole with 300mg chitin Mg silicate).	69
3.22	Heckel plot of formula SD4 (25mg spironolactone with 275mg chitin Mg silicate).	70
3.23	Kawakita plot of chitin Mg silicate.	72
3.24	Kawakita plot of formula ID2 (400mg ibuprofen with 300mg chitin Mg silicate).	72
3.25	Kawakita plot of formula MD2 (500mg metronidazole with 300mg chitin Mg silicate).	73
3.26	Kawakita plot of formula SD4 (25mg spironolactone with 275mg chitin Mg silicate).	73
3.27	DSC of chitin Ca silicate, chitin Mg silicate and chitin Al silicate.	75

Figure		Page
No.		No.
3.28	Comparison between ibuprofen alone and ibuprofen with chitin calcium silicate (CCaS).	75
3.29	Comparison between ibuprofen alone and ibuprofen with chitin magnesium silicate (CMgS).	76
3.30	Comparison between ibuprofen alone and ibuprofen with chitin aluminum silicate (CAIS).	76
3.31	Comparison between metronidazole alone and metronidazole with chitin calcium silicate (CCaS).	77
3.32	Comparison between metronidazole alone and metronidazole with chitin magnesium silicate (CMgS).	77
3.33	Comparison between metronidazole alone and metronidazole with chitin aluminum silicate (CAIS).	78
3.34	Comparison between spironolactone alone and spironolactone with chitin calcium silicate (CCaS).	78
3.35	Comparison between spironolactone alone and spironolactone with chitin magnesium silicate (CMgS).	79
3.36	Comparison between spironolactone alone and spironolactone with chitin aluminum silicate (CAIS).	79

List of Tables

Table No.		Page No.
Chapter Two: Experimental		
2.1	Tablets compositions, weight, punch size used and formula number.	41
2.2	Dissolution conditions used for IBU, MET and SPI tablets.	43
2.3	Weight of each formula used to measure true density	44
Chapter Three: Results and Discussion		
3.1	Hardness, friability and disintegration time of the commercial as well as the formulated tablets.	49
3.2	Effect of the type of chitin metal silicate on crushing strength.	50
3.3	Effect of wet granulation method on crushing strength using chitin Mg silicate.	51
3.4	Effect of pH of chitin Al silicate on crushing strength.	52
3.5	Disintegration times of tablets containing chitin Al silicate prepared in different media of preparation.	55
3.6	Parameters obtained from Heckel plots for Formulas ID2, Formula MD2, Formula SD4, and chitin Mg silicate alone.	70
3.7	Parameters obtained from Kawakita plots for Formulas ID2, Formula MD2, Formula SD4, and chitin Mg silicate alone.	74
Appendix		
A 3.1	% Released of ibuprofen from Formula ID1, Formula ID2 and Formula ID5 which represent the three types of CMS; chitin Ca silicate, chitin Mg silicate and chitin Al silicate respectively.	84
A 3.2	% Released of metronidazole from Formula MD1, Formula MD2 and Formula MD3 which represent the three types of CMS; chitin Ca silicate, chitin Mg silicate and chitin Al silicate respectively.	84
A 3.3	% Released of spironolactone from Formula SD1, Formula SD4 and Formula SD10 which represent the three types of CMS; chitin Ca silicate, chitin Mg silicate and chitin Al silicate respectively.	85
A 3.4	% Released of ibuprofen of Formula ID1 (chitin Ca silicate), Formula I Avicel (Avicel [®] 200) as fillers, and commercial product.	85

Figure		Page
No.		No.
A 3.5	% Released of metronidazole of Formula MD1 (chitin Ca silicate), Formula M Avicel (Avicel [®] 200) as fillers, and commercial product.	86
A 3.6	% Released of spironolactone of Formula MD1 (chitin Ca silicate), Formula S Avicel (Avicel [®] 200) as fillers, and commercial product.	86
A 3.7	% Released of ibuprofen of Formula ID4 (chitin Al silicate pH 7) and ID5 (chitin Al silicate pH 4).	87
A 3.8	% Released of spironolactone of Formula SD8 (chitin Al silicate pH 8), Formula SD9 (chitin Al silicate pH 7) and SD10 (chitin Al silicate pH 4).	87
A 3.9	% Released of spironolactone of Formulas of different drug/chitin Mg silicate ratio SD4 (1/11), Formula SD6 (1/4) and SD7 (1/1).	88
A 3.10	% Released of ibuprofen from Formulas contains ibuprofen with chitin Mg silicate prepared in different method, Formula ID2 (direct compression) Formula III (wet intra- granulation) and IE1 (wet extra-granulation).	88
A 3.11	% Released of metronidazole from Formulas contains metronidazole with chitin Mg silicate prepared in different method, Formula MD2 (direct compression) Formula MI2 (wet intra- granulation) and ME2 (wet extra-granulation).	89
A 3.12	Heckel plot calculations chitin Mg silicate.	89
A 3.13	Heckel plot calculations of formula ID2 (400mg ibuprofen with 300mg chitin Mg silicate).	90
A 3.14	Heckel plot calculations of formula MD2 (500mg metronidazole with 300mg chitin Mg silicate).	90
A 3.15	Heckel plot calculations of formula SD4 (25mg spironolactone with 300mg chitin Mg silicate).	91
A 3.16	Heckel plot calculations of ibuprofen.	91
A 3.17	Kawakita plot calculations of chitin Mg silicate.	92
A 3.18	Kawakita plot calculations of formula ID2 (400mg ibuprofen with 300mg chitin Mg silicate).	92
A 3.19	Kawakita plot calculations of formula MD2 (500mg metronidazole with 300mg chitin Mg silicate).	93
A 3.20	Kawakita plot calculations of formula SD4 (25mg spironolactone with 300mg chitin Mg silicate).	93

Abbreviations

CMS	Chitin Metal Silicates
CCaS	Chitin Calcium Silicate
CMgS	Chitin Magnesium Silicate
CAIS	Chitin Aluminum Silicate
MFE	Multi-Functional Excipient
DSC	Differential Scanning Calorimetry
IBU	Ibuprofen
MET	Metronidazole
SPL	Spironolactone

Chapter 1

Introduction

Chapter 1

1. Introduction

1.1 Solid Dosage Form

A pharmaceutical dosage form is a preparation designed to make possible the administration of drug in measured or prescribed amounts, such as a tablet, capsule or injection. The route of administration is dependent on the dosage form of a given drug (Allen *et al*, 2005; Gad, 2008).

Solid dosage form is one of the most popular pharmaceutical dosage forms contain active and inactive ingredient(s), in which the drug present as prescribed amount, so it is more accurate, stable and easier to administer to patient, i.e. it is more convenient for administration (Medina and Kumar, 2006).

1.2 Pharmaceutical Tablets

Because oral administration of drugs is simple, convenient and safe, it is the most frequently used route. At least 90% of all drugs used to produce systemic effects are administered orally (Gohel *et al*, 2007a).

The European Pharmacopoeia (2002) defines tablets as solid preparations each containing a single dose of one or more active substances and usually obtained by compressing uniform volumes of particles. Tablets are intended for oral administration. Some are swallowed whole, some after being chewed, some are dissolved or dispersed in water before being administered and some are retained in the mouth where the active substance is liberated. Despite the long and continuing history of the development of new technologies for administration of drugs, the tablet form remains the most commonly used dosage form (Eup. P., 2002).

In addition, tablets are considered to be one of the most preferred dosage forms because of their ease of manufacturing, convenience in administration, accurate dosing and stability compared with oral liquids, and because they are more tamperproof than capsules. So their popularity is continuously increasing day by day (Lund, 1994; Winfield and Richards, 2004).

1.2.1 Classification of Tablets

Based on their drug-release characteristics, tablets can be classified into:

a- Immediate Release Tablets

In immediate release tablets the drug is intended to be released rapidly after administration, or the tablet is dissolved and administered as a solution. This is the most common type of tablets and includes: disintegrating, chewable, effervescent, lozenges, sublingual and buccal tablets (Goran, 2002).

b- Modified-Release Tablets

In contrast to conventional tablets or tablets for instant release, modified release tablets can provide a range of release patterns (extended, delayed or repeated release) resulting in deposition of the drug in varying positions within the gastrointestinal tract.

Several alternative terms are used to describe extended release systems, such as controlled release, prolonged release and sustained release. The release rate and/or time to release onset differ among the modified release tablet systems, but the main common objective is to control the release of the drug from the dosage form. The main mechanisms that can be controlled are the dissolution of the active substance and the diffusion of the dissolved drug within the tablet. There are several techniques available to accomplish this. A dissolution controlled release system can be obtained by covering the readily soluble drug particles and / or the tablets with slowly soluble

coatings. It is also possible to modify the structure of the active substance to reduce its solubility, resulting in a slower dissolution rate. The diffusion can be controlled by the addition of an insoluble membrane surrounding the drug particles or the tablets or by forming matrix tablets. In the latter, the active substance dissolves within the tablet and diffuses through the membrane or matrix. The drug can also be incorporated into an eroding matrix; the drug is then released as the matrix erodes and also by a diffusion process within the matrix (John and Chris, 2002).

1.2.2 Tablet Excipients

In tablet formulation, a range of excipient materials is normally required along with the active ingredient in order to give the tablet the desired properties. For example, the reproducibility and dose homogeneity of the tablets are dependent on the properties of the powder mass. The tablet should also be sufficiently strong to withstand handling, but should disintegrate after intake to facilitate drug release. The choice of excipients will affect all these properties (Goran, 2002). These pharmaceutically inactive ingredients include:

Diluents or fillers: which fill out the size of a tablet or capsule, making it practical to produce and convenient for the consumer to use by increasing the bulk volume of the formulation, the final product has the proper volume for patient handling. A good filler must be inert, compatible with the other components of the formulation, non-hygroscopic, soluble, relatively cheap, compactable, and preferably tasteless or pleasant tasting (as in chewable tablet). Examples of diluents are lactose, dicalcium phosphate dihydrate, sucrose, glucose, mannitol, sorbitol, calcium sulphate and others (Lachman *et al*, 1986).

Binder: A material with a high bonding ability can be used as a binder to increase the mechanical strength of the tablet. A binder is usually a ductile material

prone to undergo plastic (irreversible) deformation (Mattsson and Nyström, 2000). Typically, binders are polymeric materials, often with disordered solid state structures. Of special importance is the deformability of the peripheral parts (asperities and protrusions) of the binder particles (Nyström *et al*, 1993).

Thereby, this group of materials has the capacity of reducing interparticulate distances within the tablet, improving bond formation. If the entire bulk of the binder particles undergo extensive plastic deformation during compression, the interparticulate voids will, at least partly, be filled and the tablet porosity will decrease. This increases the contact area between the particles, which promotes the creation of interparticulate bonds and subsequently increases the tablet strength (Olsson *et al*, 1998).

However, the effect of the binder depends on both its own properties and those of the other compounds within the tablet (Mattsson and Nyström, 2000). A binder is often added to the granulation liquid during wet granulation to improve the cohesiveness and compactability of the powder particles, which assists formation of agglomerates or granules. It is commonly accepted that binders added in dissolved form, during a granulation process, is more effective than used in dry powder form during direct compression. Binders such as starches, gelatin acacia, sucrose, sodium alginate, polyvinyl pyrrolidone (PVP), carboxymethyl cellulose, hydroxypropyl methyl cellulose, ethyl cellulose,.... etc. (Goran, 2002).

Water and alcohol are not true binder, but because of their solvent power on certain materials (as lactose) they could be considered to be binder or granulating agents (Cormick, 2007; Lachman and Schwartz, 1989).

Glidants, antiadherents and lubricants: Glidants are added to increase the flowability of the powder mass, reduce interparticulate friction and improve powder

flow in the hopper shoe and die of the tableting machine. Antiadherents can be added to decrease sticking of the powder to the faces of the punches and the die walls during compaction, and lubricants are added to decrease friction between powder and die, facilitating ejection of the tablet from the die. However, addition of lubricants (here used as a collective term, also including glidants and antiadherents) can have negative effects on tablet strength, since the lubricant often reduces the creation of interparticular bonds. Further, lubricants can also slow the drug dissolution process by introducing hydrophobic films around drug and excipient particles (Westerberg and Nyström, 1991).

These negative effects are especially pronounced when long mixing times are required. Therefore, the amount of lubricants should be kept relatively low and the mixing procedure kept short, to avoid a homogenous distribution of lubricant throughout the powder mass.

Lubricants such as magnesium stearate, calcium stearate, stearic acid and talc (poor lubricant) are the most frequently used lubricants in tablets or hard gelatin capsules and others (Johansson, 1984).

Flavours, sweeteners and colourants: Flavours and sweeteners are primarily used to improve or mask the taste of the drug, with subsequent substantial improvement in patient compliance. Colouring tablets also has aesthetic value, and can improve tablet identification, especially when patients are taking a number of different tablets (Banker and Rhodes, 1990).

Disintegrants: Disintegrants are normally added to facilitate the rupture of bonds and subsequent disintegration of the tablets (El-Barghouthi *et al*, 2008). This will be discussed in detail in next section since it represents a measure part of the present work.

1.2.3 Tablet Disintegration

Disintegrants are usually added for the purpose of causing the compressed tablet to break up when placed in an aqueous medium, into smaller fragments, thereby facilitating dissolution and made the active ingredients ready for absorption in the digestive tract. The most conventionally used disintegrants are: corn starch, potato starch, and alginic acid. Other substances which swell in water can be used as disintegrants such as gelatin, sodium carboxy methyl cellulose, Avicel, and Bentonite (El-Barghouthi *et al*, 2008; Chang *et al*, 1998).

As day's passes, demand for faster disintegrating formulation is increased. So, pharmacist needs to formulate superdisintegrants which are effective at low concentration and have greater disintegrating efficiency than the conventional disintegrants. Most of these superdisintegrants have a critical drawback that they are hygroscopic therefore not used with moisture sensitive drugs (El-Barghouthi *et al*, 2008; Banker and Rhodes, 1990).

And these superdisintegrants act by swelling and due to swelling pressure exerted in the outer direction or radial direction, they cause tablet to burst or the accelerated absorption of water leading to an enormous increase in the volume of granules to promote disintegration. The most commercially used superdisintegrants are sodium starch glycolate (Primogel[®], Explotab[®]), cross linked polyvinyl pyrrolidone (Polyplasdone[®] XL) and cross linked sodium carboxy methyl cellulose (Ac-Di-Sol[®]) (Chang *et al*, 1998; Sworbrick and Boylan. 1990).

1.2.3.1 Mechanisms of Tablet Disintegration

Tablet break to primary particles by one or more of the following mechanisms:

1. Capillary Action

Disintegration by capillary action is always the first step. When the tablet is placed into suitable aqueous medium, the medium penetrates into the tablet and replaces the air adsorbed on the particles; this weakens the intermolecular bond and breaks the tablet into fine particles. Water uptake by tablet depends upon hydrophilicity of the drug and / or excipient and on tableting conditions. For these types of disintegrants maintenance of porous structure and low interfacial tension towards aqueous fluid is necessary which helps in disintegration by creating a hydrophilic network around the drug particles (Goran, 2002; Carter, 2002).

2. Swelling

The swelling of disintegrant particles is perhaps the most widely accepted mechanism of action for tablet disintegration. Primarily, this is because almost all disintegrants swell to some extent. A positive correlation was generally found between the rate of swelling and the tablet disintegration time. (Melia and Davis, 2007; Zhao and Augsburger, 2005).

3. Air Expansion

When disintegrants with exothermic properties gets wetted, localized stress is generated due to capillary air expansion, which helps in disintegration of tablet. This explanation, however, is limited to only a few types of disintegrants and can not describe the action of most modern disintegrating agents (Sharma, 2008).

4. Particle/Particle Repulsive Forces

Another mechanism of disintegration attempts to explain the swelling of tablet made with 'non-swelling' disintegrants. A particle repulsion theory based on the observation that non-swelling particle also cause disintegration of tablets. The electric

repulsive forces between particles are the mechanism of disintegration and water is required for it (Goran, 2002; Ferrari *et al*, 1996).

5. Deformation

During tablet compression, disintegrated particles get deformed and these deformed particles get into their normal structure when they come in contact with aqueous media or water. Occasionally, the swelling capacity of starch was improved when granules were extensively deformed during compression. This increase in size of the deformed particles produces a break up of the tablet. This may be a mechanism of starch and has only recently begun to be studied (Goran, 2002; Carter, 2002; Lowenthal, 1972).

6. Release of Gases

This group of disintegrants functions by producing gas, normally carbon dioxide, in contact with water. Such disintegrants are used in effervescent tablets and normally not in tablets that should be swallowed as a solid. The liberation of carbon dioxide is obtained by the decomposition of bicarbonate and carbonate salts in contact with acidic water. The acidic pH is accomplished by the incorporation of a weak acid in the formulation, such as citric acid or tartaric acid. (Goran, 2002; Gohel and Sumitra, 2002).

7. Enzymatic Reaction

Here, enzymes present in the body such as amylase, protease, cellulase, and invertase act as disintegrants. These enzymes destroy the binding action of binder and help in disintegration (Sharma, 2008).

1.2.3.2 Methods of Addition of Disintegrants

The method of addition of disintegrants is also a crucial part. Disintegrating agent can be added either prior to granulation (intragranular) or prior to compression

(after granulation i.e. extragranular) or at the both processing steps. Extragranular fraction of disintegrant (usually, 50% of total disintegrant required) facilitates break up of tablets to granules and the intragranular addition of disintegrants produces further erosion of the granules to fine particles (Goran, 2002; Adebayo *et al*, 2008).

1.2.3.3 Factors Affecting Disintegration

1. Effect of Fillers

The solubility and compression characteristics of fillers affect both the rate and the mechanism of disintegration of tablet. If soluble fillers are used then it may cause increase in viscosity of the penetrating fluid which tends to reduce effectiveness of strongly swelling disintegrating agents. As they are water soluble, they are likely to dissolve rather than disintegrate. However, insoluble diluents produce rapid disintegration with adequate amount of disintegrants. Chebli and cartilier proved that tablets made with spray dried lactose (water soluble filler) disintegrate more slowly due to its amorphous character and has no solid planes on which the disintegrating forces can be exerted than the tablet made with crystalline lactose monohydrate (Chebli and Cartilier, 1998; Johnson *et al*, 1991).

2. Effect of Binders

As binding capacity of the binder increases, disintegration time of tablet increases and this counteract the rapid disintegration. Even, the concentration of the binder can also affect the disintegration time of tablet (Akin-Ajani *et al*, 2005).

3. Effect of Lubricants

Mostly, lubricants are hydrophobic and are usually used in smaller amount than any other ingredient in the tablet formulation. When the mixture is mixed, lubricant particles may adhere to the surface of the other particles. This hydrophobic

coating inhibits the wetting and consequently tablet disintegration (Sheskey *et al*, 1995; Banker and Rhodes, 1990).

As lubricant has a strong negative effect on the water uptake, so it is important to optimize its concentration in the formulation (Late *et al*, 2009).

4. Effect of Surfactants

The addition of a surfactant into a tablet formulation appears to be attractive method of improve the drug release rate. The improved release rate is often associated with the effect of surfactant increasing the hydrophilicity of the dosage form thereby promoting drug dissolution. The findings of this investigation showed that the presence of surfactant influenced the tablet disintegration rate, producing a finer dispersion of disintegrated particles. It follows that the action of surfactant improving drug dissolution from tablets may be attributed to the action of surfactant producing fine disintegrated particles with correspondingly larger surface area for drug dissolution (Heng *et al*, 1990).

In general, the quantity of the pharmaceutical inactive ingredients used must be carefully regulated, since the tablet must disintegrate after administration to liberate the drug (Chebli and Cartilier, 1998).

1.2.3.4 Some Commercial Disintegrants and Superdisintegrants

Disintegrants and superdisintegrants used in tablets formulation include:

Cross-linked Polyvinyl Pyrrolidone (Cross Povidone)

The capillary activity of cross povidone for water is responsible for its tablet disintegration property. Cross-linked PVP as Polyplasdone[®]XL and Polyplasdone[®]XL10 has maximum moisture absorption and hydration capacity and can be considered for the selection of new disintegrant. They act by wicking, swelling and possibly some deformation recovery. They possess apparent binding property

resulting in low percent of tablet friability, provide rapid disintegration and improved dissolution where it is employed as disintegrant even in low concentration 0.5 to 5 percent. Polyplasdone®XL as disintegrating agent has small particle size distribution that imparts a smooth mouth feel to dissolve quickly (Kibbe, 2003; Gohel *et al*, 2007b; Bolhuis *et al*, 1997; Bussemer *et al*, 2003).

An acidic medium does not reduce the liquid uptake rate and capacity of cross povidone (El-Barghouthi *et al*, 2008).

Starch

Starch and its derivatives constitute an important class of tablet disintegrant and were rated among the top ten pharmaceutical ingredients by the International Joint Conference on excipients. They may be used as disintegrants, glidants or lubricants in powder form or as binders in the mucilaginous (paste) form. Corn and potato are the official starches most commonly employed in tablet production (Adebayo *et al*, 2008; Riley, 2008).

The mechanisms of starch action in tablet disintegration have been widely studied. Some of the popular mechanisms include creation of capillary microstructure through which liquid can penetrate tablets, evolution of heat of wetting and the expansion of entrapped air, swelling of disintegrant particles and force development. Generally, the intrinsic moisture sorption, hydration and swelling capacity have been recognized as providing qualitative assessments of potential disintegrating agents (Adebayo *et al*, 2008).

The typical concentration range of starch used in tablet formulation is up to 10% w/w (Goran, 2002).

Pregelatinized Starch

Pregelatinized starch which acts by irreversible swelling or even disruption of the starch granules, depending upon the severity of the treatment applied. Collapse of crystalline order associated with gelatinization within the starch granules is one of the most important irreversible changes (Rondaa and Roos, 2008).

Modified Starch

To have a high swelling properties and faster disintegration, starch is modified by carboxy methylation followed by cross-linking, which is available in market as cross-linked starch. One of them is sodium starch glycolate marketed as Explotab[®] or Primojel[®] (Edge *et al*, 2002).

Mechanism of action of this modified starches are rapid and extensive swelling with minimum gelling. The disintegration efficiency of sodium starch glycolate is unimpaired by the presence of hydrophobic excipients such as lubricants (El-Barghouthi *et al*, 2008; Gohel *et al*, 2007b).

Cellulose and its derivatives

Cellulose (figure 1.1) is reported to be effective as a disintegrant and has a high swellability with water and ruptures the tablets into small particles (El-Barghouthi *et al*, 2008).

One of cellulose derivative is sodium carboxy methylcellulose (NaCMC and carmellose sodium) has highly hydrophilic structure and is soluble in water. But when it is modified by internally cross-linking we get modified cross-linked cellulose i.e. cross-carmellose sodium which is nearly water insoluble due to cross-linking. It acts by swelling action which facilitated tablet disintegration. An acidic medium significantly reduces the liquid uptake rate and capacity of carmellose sodium (Gohel *et al*, 2007a).

Another cellulose derivative is calcium salt of carboxymethyl cellulose (CaCMC) finds the main use in tablet formulations where it is used as a binder, diluent and disintegrant. Although CaCMC is insoluble in water, it is an efficient disintegrant because it swells to several times of its original volume on contact with water (Porscha and Wittgren, 2005)

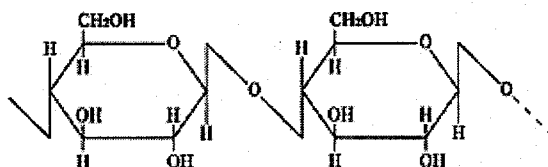


Figure 1.1 Structure of cellulose.

Microcrystalline Cellulose (MCC); (Avicel[®]) is a cellulose derivative that is currently the most commonly used direct compression excipient and primarily function as a binder/filler (Medina and Kumar, 2006; Ke *et al*, 2001).

MCC is obtained by chemical hydrolysis. It was currently commercially available in different grades. Studies show that different brands of MCC (Avicel[®] PH 101, 102, 103, 105, 112, 113, 200, 301, and 302) differ in their physical and mechanical properties and hence their performance as a tablet excipient. Various factors known to influence the physical and mechanical properties include the origin and nature of the cellulose source, methods of manufacturing, and processing variables employed during their manufacture (Medina and Kumar, 2007; Gohel, 2005).

Avicel[®] 200 with large particle size offers increased flowability with effect on compression characteristics. It can be used to reduce tablet weight variation and to

improve content uniformity. It is of higher lubricant sensitivity and lower carrier capacity (Gohel, 2005).

Alginates

Sodium alginate is a natural hydrophilic polysaccharide derived from seaweed. The ability of this polymer to rapidly form viscous solutions and gels on contact with aqueous media has been exploited by the pharmaceutical industry, in its wide application as a carrier in hydrophilic matrix controlled release oral dosage forms (Hodsdon *et al*, 1995).

Sodium alginate is the sodium salt of alginic acid. The pKa of alginic acid ranges between 3.4 and 4.4, depending on the type of alginate and the salts present in the mixture. Therefore, changes in pH over the region of pH 3 to 4, from more neutral pH values, influence polymer hydration and alginate gel rheology, due to the ready interconversion of carboxylate anions (sodium alginate) to free carboxyl groups (alginic acid), as the concentration of hydrogen ions increases. At neutral pH sodium alginate is soluble and hydrates to form viscous solutions, but below pH 3, alginic acid, water swellable but insoluble, is rapidly formed. Since the hydration characteristics of the polymer and the subsequent physical properties of the hydrated gel layer may critically influence drug release, any change in the properties of the hydrated surface layer caused by a change in pH, is likely to influence the performance of sodium alginate as a sustained release carrier (Hodsdon *et al*, 1995).

Ion-Exchange Resin

Ion exchange resin (Ambrelite[®] IPR-88) has highest water uptake capacity than other disintegrating agents like starch and sodium CMC. It has the tendency to adsorb certain drugs and usually used in concentration range of 0.5-5 % w/w (Jain, 2006).

Guar gum

Guar gum is a non-ionic polysaccharide. In pharmaceutical formulations, guar gum is used as a binder and disintegrant in solid dosage forms and as a suspending, thickening and stabilizing agent in liquid formulations. There are many reports of the use of guar gum for oral delivery of drugs (George and Abraham, 2007).

1.2.4 Tablet Manufacturing Methods

Manufacturing methods of tablets include:

1. Direct Compression

This method is limited for materials of special properties as free flowing crystals or granules and cohesive enough to bind under compression. These properties are applicable only to few crystalline materials, such as sodium chloride, potassium chloride, potassium bromide and aspirin in granular form. In addition to these crystalline materials, there are some diluents which can be compressed directly, such as microcrystalline cellulose (Avicel[®] 101, 102 and 200), microfine cellulose (Elcema G150 / G250[®]), Spray dried lactose, Anhydrous lactose, Dicalcium phosphate dihydrate (Emcompress[®]), Amylose V, Starch 1500 and Spray crystallized maltose-dextrose (Emdex[®]). Tablet production by direct compression involves only two operations in sequence, powder mixing and compression. The advantage of direct compression is primarily a reduced production cost, and as heat and water are not involved, product stability can be improved. Finally, drug dissolution might be faster from a tablet prepared by direct compression owing to fast tablet disintegration into primary drug particles. The disadvantages of direct compression are mainly technological. In order to handle a powder of acceptable flowability and bulk density, relatively large particles must be used which, firstly, may be difficult to mix to a high homogeneity, and secondly are prone to segregate. Moreover, a powder consisting

mainly of drug will be difficult to form into tablets if the drug itself has poor compressibility. Direct compression has been used mainly for two types of drug, firstly, relatively soluble drugs which can be processed as coarse particles (to ensure good flowability) and, secondly, relatively potent drugs which are present in a few milligrams in each tablet and can be mixed with relatively coarse excipient particles (Gohel, 2005; Remington, 2000; Phuriwat *et al*, 2004).

2. Granulation

Granulation is the process of collecting particles together by creating bonds between them. There are several different methods of granulation. The most popular, which is used by over 70% of formulation in tablet manufacture is wet granulation. Dry granulation (slugging) is another method of granulation (Goran, 2002).

a. Wet Granulation

Wet granulation is the most widely used method for preparation of tablets and considered to be the most important step in tableting technology. Wet granulation involves the massing of a mixture 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 (Goran, 2002; Jakob and Vibeke, 2006).

Water is commonly used for economical 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. The primary advantage of water is that it is non-flammable, which means that expensive safety precautions such as the use of flameproof equipment need not be taken. Organic solvents are used when water-sensitive drugs are processed, as an alternative to dry granulation, or when a rapid drying time is required (Goran, 2002; Jakob and Vibeke, 2006).

In the traditional wet granulation method the wet mass is forced through a sieve to produce wet granules which are then dried. A subsequent screening stage breaks agglomerates of granules to uniform size and shape (Goran, 2002; Jakob and Vibeke, 2006).

b. Dry Granulation (Slugging)

In the dry methods of granulation the primary powder particles are aggregated under high pressure. These are two main processes. Either a large tablet (known as a slug) is produced in a heavy-duty tableting 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 sieve to produce granular material of the desired size fraction. The unused fine material may be reworked to avoid waste. This dry method is usually used for drugs that are sensitive to moisture or drugs affected by heat on drying and when substances have sufficient cohesive properties. However, dry granulation method has disadvantages such as dust problems (so dust collector is needed) and loss of the materials (Goran, 2002; Soares *et al*, 2005).

1.3 Chitin and chitosan

1.3.1 Chemical Structure and Sources

Chitin ($C_8H_{13}O_5N$)_n is a long-chain polymer of a N-acetylglucosamine, a derivative of glucose, and it is found in many places throughout the natural world.

Chitin is the second most abundant polysaccharide in nature (after cellulose); the total production of chitin in earth annually is about 1 to 100 billion ton. It is tough, protective, semitransparent substance, primarily a nitrogen-containing polysaccharide, forming the main component of the cell walls of fungi, the exoskeletons of arthropods, such as crustaceans (like the crab, lobster and shrimp) and the insects, including ants, beetles and butterflies, the radula of mollusks and the beaks of the cephalopods, including squid and octopuses. Chitin has also proven useful for several medical and industrial purposes (Cauchie, 2002).

Chemically, chitin is closely related to chitosan. Chitosan is a product derived from N-deacetylation of chitin in the presence of hot alkali. It is also closely related to cellulose in that it is a long un-branched chain of glucose derivatives (Lópezl *et al*, 2008).

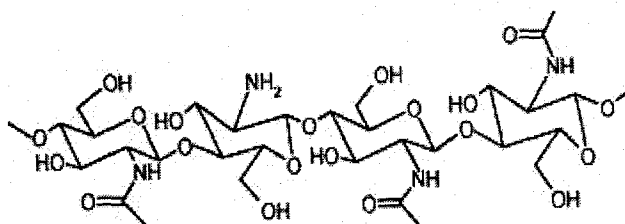


Figure 1.2 Structure of chitin.

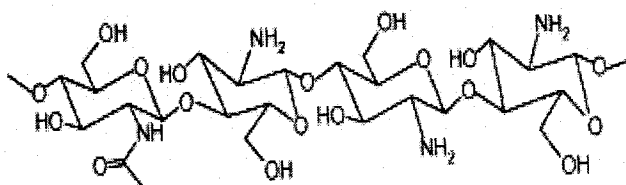


Figure 1.3 Structure of chitosan.

Chitin and chitosan (figure 1.2 and 1.3 respectively) are also known to exhibit polymorphism. The polymorphic forms of chitin differ in the packing and polarities of adjacent chains in successive sheets (Kurita, 2006).

Although the molecular structures of chitin and chitosan seem quite similar, the physical characteristics and the chemical reactions they undergo are often surprisingly distinct. Both polymers possess reactive hydroxyl and amino groups, but chitosan is usually less crystalline than chitin, which presumably makes chitosan more accessible to reagents. After heating, they decompose prior to melting, thus these polymers have no melting points. Probably the most striking difference between chitin and chitosan lies in their solubilities (Kurita, 2006; Burkhanova *et al*, 2000).

1.3.2 General Pharmaceutical Uses

Chitin and chitosan have the following general pharmaceutical uses:

- Diluents in direct compression of tablets.
- Binder in wet granulation
- Slow-release of drugs from tablets and granules
- Drug carrier in microparticle systems
- Films controlling drug release
- Preparation of hydrogels, agent for increasing viscosity in solutions.
- Wetting agent, and improvement of dissolution of poorly soluble drug substances
- Disintegrant
- Bioadhesive polymer
- Site-specific drug delivery (e.g. to the stomach or colon)
- Absorption enhancer (e.g. for nasal or oral drug delivery)
- Biodegradable polymer (implants, microparticles)

- Carrier in relation to vaccine delivery or gene therapy (Satpathy, 2008).

1.3.3 Uses of Chitin in the Preparation of Novel Superdisintegrant

Chitin is a highly hydrophobic and insoluble in water, but still can absorb water. This character gives chitin or its derivative a disintegration power so chitin play different roles in tablet formulations as an excipient for direct compression and as a disintegrant (Kurita, 2006; Majeti and. Kumar, 2000).

However, the substance has a bad flow and compression properties. The co-precipitation with silicon dioxide or related water-absorbent compounds provides the polymer with proper flow and compression properties, and increases the power of polymer for water absorption (Rashid *et al*, 2008).

When chitin or its derivatives utilizes a colloidal silicon dioxide, it has been found that the resultant excipient product surprisingly provides disintegration power which is substantially improved even in comparison to normal commercially available disintegrants. Another surprising effect is the powerful improvement in flow and compaction of the new co precipitate excipient compared to each component when taken alone (Rashid *et al*, 2008).

Some excipients, such as Avicel PH101[®] and Avicel PH102[®], demonstrate both properties, being disintegrants and binders. For a successful formulation, equilibrium between binder and disintegrant concentrations must be reached for the ingredient granules to be easily compressed, to form a tablet and finally disintegrate after reaching an aqueous medium (Chebli and Cartilier, 1998).

Recently, co precipitation of metal silicates onto chitin particles made by Rashid et al group has been given an enormous attention on the basis of its effective functionality as a pharmaceutical diluent, binder and superdisintegrant; multifunctional excipient (used in direct compression or granulation). Such new