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

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Major Supervisor	
Name	Signature
Prof. Mohammed Shubair	.....
Co- Supervisor	
Dr. Faisal Al-Akayleh	.....

Examination Committee	
Name	Signature
1. Prof. Mohammed Shubair	.....
2. Dr. Faisal Al-Akayleh	.....
3. Prof. Nasir Idkaidek	.....
4. Dr. Hatim Al-Khatib	.....

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 (CAlS).

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 CAlS, respectively. CAlS 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 CAlS 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.

Major Supervisor Signature

Prof. Mohammed Shúbair

Co- Supervisor Signature

Dr. Faisal Al- Akayleh

To

My Family…..

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Rana Hani Mohammed Ali Al-Shaikh Hamed

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Abbreviations

CMS	Chitin Metal Silicates
CCaS	Chitin Calcium Silicate
CMgS	Chitin Magnesium Silicate
CAlS	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