Evaluation of Pregelatinized Enset (*Ensete ventricosum*) Starch as a Tablet Disintegrant in Enteric Coated Acetyl Salicylic Acid Tablet

By

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List of Abbreviations

AAU	Addis Ababa University
API	Active Pharmaceutical Ingredient
ASA	Acetylsalicylic Acid
CAP	Cellulose acetate phthalate
CAT	Cellulose acetate trimellitate
Conc	Concentration
ES	Enset Starch
H	Hour
HCl	Hydrochloric acid
ICH	International Conference for Harmonization
MAE	Methacrylic acid ethyl acrylate copolymer
MCC	Microcrystalline cellulose
min	Minute
NSAID	Non-steroid anti-inflammatory drug
PG	Propylene glycol
PGES	Pregelatinized Enset Starch
PGS 1500	Pregelatinized starch 1500®
RH	Relative humidity
Rpm	Revolution per minute
SD	Standard deviation
SOP	School of Pharmacy
SSG	Sodium starch glycolate
UK	United Kingdom
USP	United States Pharmacopoeia
UV	Ultra violet

ABSTRACT

The process of aqueous coating of moisture labile drugs demands careful selection of tablet excipients, mainly disintegrants. Although the application of pregelatinized enset starch (PGES) as tablet disintegrant is well documented, its potential use as tablet disintegrant in the development of moisture labile drug for aqueous coating is not well studied. Therefore, the objective of this study is to assess its potential use as tablet disintegrant in the development of enteric coated acetylsalicylic acid (ASA) 81 mg tablet in comparison to other starch based disintegrants including native enset starch (ES), sodium starch glycolate (SSG) and pregelatinized starch 1500® (PGS 1500). ASA is a moisture-sensitive drug and can be hydrolyzed into acetic and salicylic acid when exposed to high humidity and elevated temperature. As the coating process will subject ASA tablets to both high temperature and humidity, it is important that the formulation exhibit minimum interaction with the aqueous coating solution.

The study began with the development of an optimum coating technique, which can offer the maximum mechanical and chemical stability and other pertinent tablet qualities but minimum exposure time to the coating solution to the tablet. Then, to investigate the effect of the type and quantity of the disintegrant on stability and other tablet attributes, twelve different ASA 81 mg tablet formulations, containing three different levels of the above four disintegrants, were directly compressed using microcrystalline cellulose (MCC) as a direct compression filler and talc as a lubricant and characterized. The tablets were then coated using enteric coating polymer Wangit L30D-55 (aqueous dispersion of methacrylic acid-ethyl acrylate copolymers) by conventional pan coating technique and were further characterized. Finally, the tablets were subjected to a three month accelerated stability study conditions and the stability of the tablets was assessed based on coat integrity, assay results and change in the level of free salicylic acid within the formulation.

The results of the study showed that the uncoated tablets had the desired attributes including tablet weight variation, friability, hardness, disintegration time and dissolution time results which were well within the acceptable limits of the USP 30-NF 25 (2007)

standards. Results of the three month accelerated stability study showed that tablets formulated with sodium starch glycolate were unstable and resulted in softening and sticking of the coat. Besides, there was a significant increase in free salicylic acid percentage and release of drug in the acidic stage. Unlike tablets formulated with sodium starch glycolate, tablets formulated with the pregelatinized starches, pregelatinized enset starch and starch 1500® as disintegrants maintained their appearance and the cumulative percent drug release in 0.1 N HCl and buffer stage. Percent free salicylic acid, assay results and other tablet attributes unchanged except tablet hardness, which was also within the acceptable limit. Tablets prepared with ES were stable but ES was inferior as tablet disintegrant. Therefore, pregelatinized enset starch can be used as a better alternative to sodium starch glycolate and as a replacement to pregelatinized starch 1500® as tablet disintegrant in those formulation that contain moisture susceptible drugs.

Key Words: Enset starch; Disintegrant; Stability; Enteric coated; Acetylsalicylic Acid; Pregelatinized starch, Sodium starch glycolate

1. INTRODUCTION

Formulation of a stable dosage form is essential for the patient's safety and drug efficacy. The presence of additives as well as storage conditions, which may affect the stability of drugs, has received considerable attention in the field of pharmaceutics (Omaimah and Raida, 2000). In the development of pharmaceutical dosage forms; one of the persistent challenges is assuring acceptable stability. While classically stability refers to the ability to withstand loss of a chemical due to decomposition, in the pharmaceutical world, the term "stability" more often refers to the storage time allowed before any degradation product in the dosage form achieves a sufficient level to represent a risk to the patient (Kenneth and Roger, 2005).

Chemically, ASA undergoes hydrolysis to degrade into salicylic acid and acetic acid, Figure 1.1. In a number of circumstances, the degradation of ASA has been studied in connection with the solid-state properties of the excipients. For example, in a study it was observed that the degradation of ASA was lower when formulated with microfine cellulose powders than its slightly more crystalline analogue, MCC (Mihranyan *et al.*, 2006). In another study, increasing the specific surface area of dicalcium phosphate dihydrate powders also increased the degradation of ASA in the dosage form (Landln *et al.*, 1995).

Many excipients used in the production of solid dosage forms contain some moisture, which may act both as a reagent and reaction medium. Water may be associated with the excipient in various ways including water of crystallization, tightly bound water of sorption (also known as non-freezing water), intermediately bound water of sorption, and free/bulk water (also known as freezing water). The energy needed to remove water differs substantially among the types, which, in turn, influences moisture's availability to induce hydrolysis (Heidarian *et al.*, 2006).

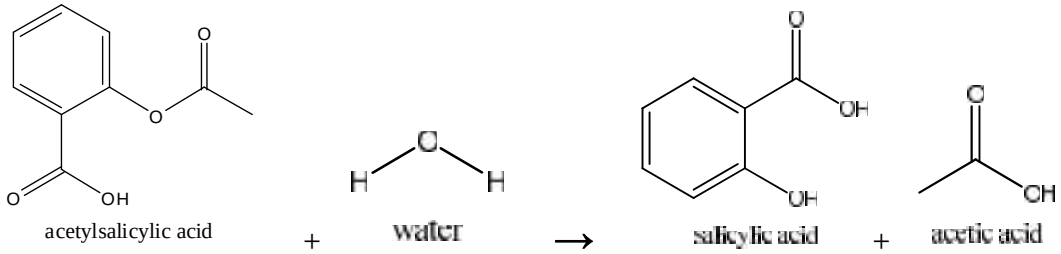

Figure 1.1: Hydrolysis of ASA (Heidarian *et al*., 2006)

1.1 Physicochemical properties of ASA

A. Pharmacological effect

ASA was first isolated in 1928 from willow bark by Johann Buchner; it is still clinically relevant drug (Oyeniyi and Itiola, 2012). ASA (also well known as aspirin), together with sodium salicylate, was the first non-steroid anti-inflammatory drug (NSAID) to be used in clinical practice in the early 20th century. ASA in particular is considered as the prototype NSAID (Goodman and Gilbert, 2007). It is a substituted phenyl ester that hydrolyses to salicylic acid and acetic acid upon exposure to moisture (Villari *et al.*, 1992).

In recent years, ASA has been prescribed for a host of indications. In addition to its uses as an analgesic, anti-inflammatory, and antipyretic agent, ASA now is indicated for use in the prevention and treatment of heart diseases and stroke. Further studies are under way investigating the potential use of ASA to bolster the immune system, treat cognitive decline, and lower the risk of colon and ovarian cancer. A low daily dose of, 75–81 mg, is commonly used in preventive ASA therapy (Yamazaki *et al.*, 2010).

ASA act by inhibiting the cyclooxygenase activity resulting in decrease synthesis of prostaglandin, leukotriene and thromboxane precursors which is the ubiquitous enzyme that catalyze the initial step in the synthesis of prostanoids. Historically, ASA has been regarded as a potential gastric irritant, and studies have shown that the incidence of gastric intestinal side effects may increase with regular use. Enteric coating of the

tablets, therefore, is desirable for preventing stomach upset or irritation in those taking daily ASA therapy (Batterman, 1958).

B. Pharmacokinetics of ASA

The pharmacological activity of ASA is mainly due to salicylic acid, a metabolite formed after hydrolysis. Alkaline urinary pH increases the renal clearance of salicylate thus plasma level of the salicylate reduced. Bioavailability of ASA is lower because of partial hydrolysis during absorption and "first-pass" effect in the liver (Borga *et al.*, 1976). Elimination half life: 4.7 to 9 h (average 6 h) and the half-life is dose-related. ASA, administered to normal volunteers reported to have a half-life of only 13 to 20 min (Done, 1960).

C. Physicochemical properties of ASA

ASA is slightly soluble in water, freely soluble in ethanol (96 per cent) and has a melting point of about 143 ^{o}C (BP, 2009). ASA is known to exist in different crystalline forms. Earlier reports on the polymorphism of ASA have revealed that the difference in the physicochemical properties of the drug could be due to the differences in crystal size and habit or due to crystal defects (Longuemard *et al*., 1998). ASA powder is also high hydro-labile and as such, judicious selection of both the pharmaceutical excipients and tableting method cannot be overemphasized. In order to ensure stability of ASA tablet, direct compression is mostly preferred method of production. Direct compression is the simplest and most economical method of producing pharmaceutical tablets, since it requires less processing steps than other techniques of tableting, such as wet granulation and roller compaction (Oyeniyi and Itiola, 2012).

1.2 Direct compression excipients

It is a remarkable fact that, in the new millennium, tablets still account for more than 80% of all dosage forms administered to man. The principal reasons for their continued popularity include their ease of manufacture, their convenience of dosing, and their stability compared with liquid and semi-solid presentations. One mode of tablet manufacture is that of direct compression of the active ingredient with other appropriate

excipients to form a tablet, normally for medium- to high-potency compounds where the drug content is less than 30% of the formulation. The advantages of direct compression are well-known, the most important being fewer processing stages and the elimination of heat and moisture effects (Khan and Rhodes, 1973).

Although the principles governing direct compression have been well known for many years, the technique has only recently become more established as a result of the introduction of excipients specifically designed for direct compression (Armstrong, 1986). These excipients are not only directly compressible themselves, but can also be mixed with a large proportion of drug substance with no significant deterioration in tablet quality (Armstrong, 1998).

Pharmaceutical excipients are substances other than the pharmacologically active drug or prodrug which are included in the manufacturing process or are contained in a finished pharmaceutical product dosage form. Although excipients are considered to be inert in therapeutic or biological actions, they should hinder unwanted phase transitions and ensure the required stability of the drug in the formulation during the manufacturing process and storage. The International Pharmaceutical Excipients Council (IPEC) has defined pharmaceutical excipients as any substance other than the active drug or prodrug which has been appropriately evaluated for safety and are included in a drug delivery system to either 1) aid processing of system during its manufacture, or 2) protect, support or enhance stability, bioavailability, or patient acceptability, or 3) assist in product identification, or 4) enhance any other attribute of the overall safety and effectiveness of the drug during storage or use (Davies *et al.*, 2004).

Excipients should play a key role in turning an unstable drug into an acceptable product. Fundamentally unstable drugs can be transformed into viable medicinal products by formulating with appropriate excipients that have some direct effect on the molecular integrity of the active pharmaceutical ingredient (API) (Crowley, 1999). It might be necessary to consider developing a formulation that compensates for any basic deficiencies in the stability of the drug substance. During product optimization,

excipients should be selected based on a variety of acceptance criteria. When developing successful formulation, it is important to understand the API, the excipients and the process, and in particular, their limitations (Davies, 2001).

Direct compression formulations can be developed with minimal numbers of excipients. Typically the minimum excipients needed are a diluent (filler-binder), a disintegrant and a lubricant. Additional components may include a glidant, a surfactant, pigments and stabilising agents. Commonly used excipients in these categories are listed in Table 1.1 (Rojas, 2013; Armstrong, 1986; Davis, 2001; Jivraj *et al.*, 2000; Lachman *et al.*, 1989; Wang *et al.*, 2010).

1.3 Pregelatinized enset starch

A. enset starch

Starches are widely employed as multipurpose excipients in various solid dosage forms, especially as diluents, disintegrants, and binding agents in tablet formulations due to their suitable physico-chemical properties as well as their relative cheapness and inertness. The versatility of starches implies a need to continue to develop new starch excipients with suitable properties to meet the special needs of drug formulators and the demands of novel formulations.

Enset starch is obtained from Ensete ventricosum (Welw.) Cheeseman, Musaceae. Ensete ventricosum (Welw.). Cheeseman belongs to the family Musaceae, and the genus enset. Enset looks like a large, thick, single-stemmed banana plant. Both enset and banana have an underground corm, a bundle of leaf sheaths that form the pseudostem, and large leaves. Enset, however, is usually larger than banana, with the plant up to 10 m tall and pseudostem up to one meter in diameter. Because of its resemblance to the banana plant, enset is often referred as "False Banana" as it does not bear edible fruit. Instead, it is used for the production of starchy foods. It was reported that enset starch demonstrated a number of similar physico-chemical properties and comparable binding and disintegrating properties in granulated tablet formulations with potato starch (Wondimu & Gebre-Mariam, 2010).

Table 1.1: Commonly used direct compression formulations excipients (Jivraj *et al.*, 2000).

Function	Common Examples
Diluent	Lactose monohydrate, anhydrous lactose, microcrystalline cellulose, partly pregelatinised starch, mannitol, dibasic calcium phosphat (anhydrous & dihydrate)
(Super)-disintegrant	Croscarmellose sodium, sodium starch glycolate, crospovidone,
Lubricant	Magnesium stearate, calcium stearate, sodium stearylfumarate, stearic acid
Glidant	Colloidal silicon dioxide, talc
Pigment	Aluminum lakes, iron oxides
Stabiliser	Buffers such as sodium carbonate and citric acid. Antioxidants such as butylatedhydroxyanisole and butylatedhydroxytoluene.
Surfactant	Sodium lauryl sulphate, polysorbates

Numerous studies revealed that enset starch has amylose content, granule size, X-ray diffraction pattern and gelatinization temperature which is comparable to potato starch. However, the swelling power and solubility properties are lower than that of potato starch. The granules of the enset starch are angular and elliptical in shape, different from potato starch. Enset starch demonstrated numerous pharmaceutical applications, including binder, disintegrant, super disintegrant, and gelling agent (Wondimu & Gebre-Mariam, 2010).

B. Modification of enset starch

Irrespective of modification process, modified starch has been reported to perform better during processing than native starch. By simple, cold, dilute acid hydrolysis of starch, a reduction effect on elastic and therefore gelling tendencies of starch is attained. This improves its use as disintegrant. Accordingly, defatting of starch was reported to lead to

better granular properties which resulted in good flowability, better disintegrant property and lower friability (Igwilo *et al*., 1996).

The cross-linked and acetylated form of enset starch showed its potential use as a novel drug delivery system (Wondimu *et al.,* 2014). Moreover, sodium starch glycolate prepared from enset starch demonstrated comparable disintegrant efficiency to that of Primojel® (sodium starch glycolate produced by carboxymethylation and cross-linking of potato starch) .This evidenced the potential candidacy of enset starch for modification, to replace the commercialized modified starches from overseas with local products (Gebre-Mariam & Schmidt, 1996a).

C. Pregelatinized starch

Pregelatinization of natural starches has been used to produce cold-water swellable forms with improved flowability. This process, which leads to irreversible granule swelling, loss of birefringence, and crystallinity, is usually done by heat treatment. Other methods such as solvent based processing, oxidation, hydrolysis and cross-linkage have also been used.

The process of gelatinization causes substantial changes in both the chemical and the physical nature of granular starch due to the rearrangement of intra- and intermolecular hydrogen bonding between the water and starch molecules resulting in the collapse or disruption of molecular orders within the starch granule. This results in irreversible changes in the starch properties. Evidence of the loss of an organized structure includes irreversible granule swelling, loss of bifringence and crystallinity (Odeku *et al.,* 2008).

The properties exhibited by starch during gelatinization are governed by several factors, including granule size and shape. When raw starch is heated in excess water, granules swell and lose their birefringence. After the granules are swollen to a maximum volume, they burst dispersing ‘‘starch substance’’ forming a colloidal dispersion in water. Studies also revealed that pregelatinized starches exhibited lower values of the Hausner’s ratio, suggesting better flowability than the native starches. The values of mean particle

diameter and particle density for the pregelatinized starch were, however, higher than those for the native starches (Alebiowu and Itiola, 2002; Odeku *et al*., 2008; Adedokun and Itiola, 2009).

Pregelatinized starches showed higher water absorption capacity, swelling ability, and percentage solubility than the native starches due to the disruption of associative bonds and amylose leaching out during gelatinization (Wootton and Bamunuarachchi, 1978; Alebiowu and Itiola, 2002; Adedokun and Itiola, 2009; Nakorn *et al*., 2009). Pérez-Sira and González-Parada (1997) reported that the apparent viscosity of pregelatinized starch suspensions showed a marked reduction with an increase in shear force; this denoted their pseudoplastic character. Compaction study revealed that pregelatinized starch underwent plastic deformation (Maarschalk *et al*., 1997).

D. Pregelatinized enset starch

Pregelatinized enset starch slurry prepared in cold water with reasonable viscosity can be considered as better binder/granulating agent compared to native enset starch paste that requires higher energy for efficient granulation and need longer time for drying due to its higher viscosity which incurs additional time and cost in the overall production. Granules prepared by using pregelatinized enset starch as granulating agent demonstrated comparable properties with the granules prepared using starch 1500®. This indicates that pregelatinized enset starch can be a potential tablet binder in wet granulation method (Wondimu & Gebre-Mariam, 2010).

1.4 Influence of excipients on the stability of ASA containing solid dosage forms

The pharmacopeial requirements for a pharmaceutical dosage form may be summarized in terms of safety, purity, efficacy and stability. Final pharmaceutical dosage form generally consists of an API combined with varying number of excipients. Because many new drug candidates exhibit poor solubility and stability, the function of excipients is to define a formulation that is physically and chemically stable, manufacturable, and bioavailable (Joshi, 2004). Pharmaceutical excipients may function as stability enhancers

and therefore they should protect, support, or enhance stability or bioavailability of drug product. However, excipients may initiate degradation of drug substances: functional groups or residues in excipients can have the propensity to interact with unstable API. (Crowley, 1999).

Thus, to develop a pharmaceutically acceptable, stable formulation, instabilities within the API or excipients must be explored and stabilized. By investigating the intrinsic stability of the drug, it is possible to advise on formulation approaches and indicate types of excipients, specific protective additives and packing which are likely to improve the integrity of the drug product (Morris *et al.,* 2001). Besides, each excipient must be shown to be compatible with the formulation and efficiently perform its desired function in the product (Jackson *et al.,* 2000).

ASA is a moisture-sensitive drug and can undergo hydrolysis into acetic and salicylic acid when exposed to high humidity and elevated temperatures. Particularly, during preparation of ASA enteric coated tablets, as the coating process involves exposing the tablet to both high temperatures and humidity and it is important to develop a formulation which is resistant to the coating process.

The degradation rate of ASA during storage at elevated conditions may be directly associated with the influence of formulation excipients due to their water adsorption characteristic. Hygroscopic excipients may also enhance drug stability by binding moisture, thus making the dosage form less susceptible to effects of moisture during manufacturing or storage. By controlling the coating conditions and selecting the excipient that is most resistant to moisture interaction it is possible to reduce the amount of adsorbed water and the degradation of moisture-labile drug (Mitrevej and Hollenbeck, 1983).

Mitrevej and Hollenbeck found that a hydrophilic field is generated around ASA crystals under high-humidity conditions and upon combining the ASA with certain hydrophilic disintegrants, condensation in the vicinity of the ASA crystal can occur (Mitrevej and

Hollenbeck, 1983). A study done by Faroongsarng and Peck showed that during aqueous film coating of ASA tablets, the depth of water penetration into the tablet core could be directly linked to the concentration and type of disintegrant used in the formulation (Faroongsarng and Peck, 1991).

Most pharmaceutical solid dosage formulations contain disintegrants. Modern disintegrants, often referred to as superdisintegrants, act by rapid uptake of water followed by rapid and, for some, enormous swelling up to 300 times excipient volume. Although superdisintegrants have demonstrated improved disintegration and dissolution functionality over traditional starch disintegrants, they can also be associated with tablet stability problems related to moisture uptake. Superdisintegrants function primarily by drawing large amounts of water into the tablet and simultaneously swelling. It is this great affinity for water that can impact the stability of moisture-sensitive materials under accelerated storage conditions. Cunningham *et al.* showed that in the formulation of direct-compression hydrochlorothiazide containing partially pregelatinized starch, partially pregelatinized starch performed as effectively as the superdisintegrants, and due to its low propensity for moisture uptake may afford superior moisture stability (Cunningham *et al*., 1999).

Inclusion of a high level of superdisintegrant in tablet formulations can affect the physical appearance of the final coated dosage form, such as the smoothness of the film. Superdisintegrant particles compressed into the surface of the tablet may get activated prematurely on contact with droplets of aqueous film coating solution resulting in very fast and excessive water penetration into the core and uneven surface of the coated product. Water penetration into the tablet core can lead to potential storage problems with formulations that contain moisture-sensitive materials. That is why the choice of disintegrant type in such formulations can have a significant effect on coated product stability (Thibert and Hancock, 1996).

1.5 Enteric coating

By definition, enteric coatings are those which remain intact in the stomach (and exhibit low permeability to gastric fluids), but break down readily once the dosage form reaches the small intestine, (Lachman *et al.*, 1989). This type of formulation either protects the stomach from potentially irritating drugs (e.g., ASA and certain steroids) or protects the drug from partial degradation in the acidic environment of the stomach (e. g., erythromycin). To obtain enteric coated tablets that meet the requirements (insoluble for 2 h at pH 1 and readily soluble at pH 6.8), the tablet cores should generally be coated with an amount of 3- 6 mg solids /cm^2 (Bühler, 2009).

The performance of enteric-coated dosage forms has often been open to question. Certainly much of the uncertainty can be related to the earlier common use of "natural" polymers (such as shellac) and simplistic coating procedures. The use of synthetic, predictable polymers and the adoption of modern processing technology should have done much to dispel these concerns. However, problems still exist today. Unfortunately, many of the factors that can dramatically affect the performance of enteric coatings have long gone unrecognized. Some of the important factors that can influence the behavior of enteric coatings include:

- The nature of the drug in the dosage form (for example, some drugs can greatly influence dissolution of the coating),
- The quantity of coating applied (application of excessive quantities of coating can substantially delay release of drug from the dosage form),
- The presence of imperfections in the coating (fissures or "pick" marks will destroy the integrity of the coating), and
- The dissolution pH of the polymer used in the coating.

The effect of *in vitro* test conditions (dissolution of the coating, and ultimate drug release, can be affected dramatically by the pH and ionic strength of the test solutions and the agitation rate) (Lachman *et al*., 1989).

Aqueous film coating systems are either solutions or dispersions, depending on the water solubility of the film former polymers. Film formation from the polymer solution occurs through a series of phases. When the polymer solution is applied to the surface of a tablet, cohesion forces form a bond between the coating polymer molecules (Banker, 1996).To obtain high cohesion, the cohesive strength of the polymer molecules must be relatively high and continuous surfaces of the film material must coalesce. Coalescence of adjacent polymer molecular layers or surfaces occurs through diffusion. When most of the water evaporates, the viscosity of the solution increases (gelation) and leaves the polymer chains in close proximity to each other and deposited over previous polymer layer. If there is adeguate cohesive attaraction between the molecules and sufficient diffusion and coalescence upon the more complete evaporation of the residual water, the individual polymer chains align themselves to form a cohesive film (Harris and Ghebre-Sellassie, 1997).

Film formation from dispersion occurs when polymeric particles coalesce to form a continuous film, making it a more complex mechanism compared to film formation from solution (Obara and McGinity, 1995). Several reports on mechanism of aqueous polymer dispersion film formation have been presented in the literature (Ortega, 1977;Yang and Ghebre- Sellassie, 1990).

1.5.1 Enteric coating polymers

Enteric coating polymer should resist dissolution at pH values below 4.0, but begin to dissolve at pH 5.0 or above, and become readily soluble at pH 7.0 in the GI tract. The coating must have low water permeability, compatibility with broad spectrum of drugs, and a low tendency to be hydrolyzed in a humid and high-temperature environment. In addition, the enteric coating system must be environmentally safe and acceptable (McGinity, 1997).

An ideal enteric coating material should possess the following attributes:

- Resistance to gastric fluids,

- Permeability to intestinal fluids,
- Compatible with most of the coating solution components and the drug substances,
- Stability alone and in the coating solutions i.e. the film should not change upon aging,
- Formation of a continuous film on the dosage form,
- Non-toxic and non-irritant,
- Low cost,
- Ease of application without specialized equipment, and
- Ability to be readily printed or to allow film to be applied to de bossed tablets.

A. Cellulose acetate trimellitate (CAT)

This cellulose derivative contains part of OH groups acetylated and part esterified with mellosic acid. It is practically insoluble in water and ethanol; soluble in acetone. Along with CAT diethyl phthalate triacetin can be used as plasticizer (Wise, 2000).

B. Cellulose acetate phthalate (CAP)

Cellulose acetate phthalate was synthesized in 1940 by Hiatt and was one of the first polymers used for its enteric coating properties. The CAP polymer exhibits rapid dissolution at pH > 6 and is relatively permeable to moisture and gastric juices. Due to its high moisture permeability, CAP is susceptible to hydrolytic decomposition. Phthalic and acetic acid molecules may get hydrolyzed during storage and significantly compromise the degree of enteric protection that the film coating provides. The addition of a plasticizing agent has been shown to improve the water resistance of CAP films. It is practically insoluble in water and ethanol; soluble in acetone. CAP concentrations in oral formulations are typically limited to 0.5-0.9% of the tablet core weight (Rowe, 2009).

C. Hydroxyl propyl methyl cellulose phthalate (HPMCP)

HPMCP is natural cellulose synthetically modified to produce partly methyl ethers, 2-hydroxy propyl ethers and phthalyl esters. It is typically used in oral pharmaceutical

formulations as enteric coating material for tablets, beads or granules. This polymer is characteristically insoluble in gastric fluid but is swellable and rapidly soluble in the upper part of the small intestine. It can be used as coating agents because it does not require the addition of plasticizer or other film formers to produce coatings for oral formulations (Rowe, 2009).

HPMCP is insoluble in dichloromethane, methanol, isopropanol, ethyl acetate and ethanol but demonstrates desired solubility in acetone, tetrahydrofuran, mixtures of dichloromethane and methanol, mixtures of dichloromethane and ethanol and mixtures of acetone and methanol. The insolubility of this polymer in single-solvent system makes it challenging to conduct simple drug-compatibility studies and spray drying applications. This polymer remains chemically and physically stable at room temperatures for several years but is susceptible to hydrolysis under elevated temperatures and humidity conditions (Rowe, 2009).

D. Hydroxyl propyl methyl cellulose acetate succinate

Hydroxyl propyl methyl cellulose acetate succinate is a synthetically modified mixture of acetic acid and monosuccinic acid esters of HPMC. It is available in three grades (L, M & H), which correspond to pH dependent release profiles of low pH (5), medium (5.5) and high (6.5) pH. This polymer is incompatible with acids, peroxides and other oxidizing materials and is practically insoluble in all organic solvents, but it can form a turbid viscous solution with the addition of acetone, or a mixture of ethanol and dichloromethane. It has a glass transition temperature ranging between 120°C -135°C (Rowe, 2009).

E. Polyvinyl acetate phthalate

Polyvinyl acetate phthalate is another enteric polymer commonly used to coat solid dosage forms. This polymer is structurally similar to CAP containing the dicarboxylicphthalic acid in a partially esterified form. Faster release of drug components occurs with this polymer because its dissolution occurs at a pH of

approximately 5.0. Due to its lower moisture permeability, it is relatively more stable to hydrolysis than CAP (McGinity, 1997).

F. Polymethacrylates

In the mid 1960s, Lehmann and Dreher developed copolymers of methyl methacrylate and ethyl acrylate as ester components with methacrylic acid for use as enteric polymers. These polymers are produced by an emulsion-polymerization process and are commercially available in several forms. The dissolution properties of these polymers are dependent on the content of carboxyl groups in the polymer (Lachman *et al.*, 1990). They are synthetic cationic and anionic polymers of dimethyl aminoethylmethacrylates, methacrylic acid and methacrylic acid esters in varying ratios (Rowe, 2009).

Polymethacrylates are primarily used in oral capsule and tablet formulations as film-coating agents. Depending on the type of polymer used, films of different solubility characteristics can be produced. It is soluble in gastric fluid below pH 5. In contrast, Eudragit L, S and FS types are used as enteric coating agents because they are resistant to gastric fluid (Rowe, 2009).

Different types of enteric coatings are soluble at different pH values: e.g. Eudragit L is soluble at pH > 6 whereas Eudragit S and FS are soluble at pH > 7. The S grade is generally used for coating tablets, while the flexible FS 30 D dispersion is preferred for coating particles. Eudragit L 30 D-55 is used as an enteric coating film former for solid-dosage forms. The coating is resistant to gastric juice but dissolves readily at above pH 5.5. Kollicoat MAE 100 P, Acryl-EZE and Acryl-EZE MP are also commercially available as redispersible powder forms, which are designed for enteric coating of tablets or beads. Eastacryl 30 D and Kollicoat MAE 30 DP are aqueous dispersions of methacrylic acid–ethyl acrylate copolymers. They are also used as enteric coatings for solid-dosage forms (Rowe, 2009).

The copolymer products Kollicoat® MAE 30 DP and Kollicoat® MAE 100 P based on methacrylic acid and ethylacrylate only dissolve at pH values of 5.5 and above, and are

used for enteric film-coatings for tablets, pellets, granules and capsules. Both the aqueous dispersion, Kollicoat® MAE 30 DP and the powder, Kollicoat® MAE 100 P can be processed easily in water, are impermeable to protons, ions and water, and have low hygroscopicity (Bühler, 2009).

The dissolution in water irrespective of the pH is identical for both Kollicoat® MAE grades. The powder Kollicoat® MAE 100P is partly neutralized. Therefore it is possible to produce the polymer dispersion for manufacturing by stirring this powder into water without the addition of any alkaline substance. A further advantage of Kollicoat® MAE 100P is that the dispersion obtained by this manner is more compatible with other excipients and less sensitive about shearing forces in comparison with the commercial dispersion Kollicoat® MAE 30DP, which is not partly neutralized. As the Kollicoat® MAE copolymer has a very low plasticity, always it is recommended to add a plasticizer like 1, 2-propylene glycol or triethyl citrate (Bühler, 2009). A comparission of cellulosic and acrylic enteric coating systems is given in Table 1.2. (McGinity, 1997).

1.5.2 Other enteric coating constituents and coating process parameters

Film coating prepared from pure polymers tends to be brittle and crack upon drying. The additions of plasticizers to the coating liquid decrease the intermolecular forces along the polymer chains by relieving molecular rigidity. Plasticizer molecules interpose themselves between the individual polymer chains, thus breaking down polymer-polymer interactions, making it easier for the polymer chains to move past each other. The plasticizer improves the flexibility and reduces the brittleness of the film coating and makes it more resistant to mechanical stress during the coating process. Typical plasticizers of aqueous film coating formulations are glycerol, propylene glycol, polyethylene glycol and triacetin (Johnson *et al*., 1991; Heinamaki *et al*., 1994; Heng *et al*., 1996).

A distinctive color is often used in film coating for tablet identification. Opacifiers, like titanium dioxide, iron oxides and other pigments with high refractive indices, can be

included in film coatings to protect light-sensitive drugs (Sakellariou and Rowe, 1995). Talc or colloidal silicon dioxide can be used to minimize tackiness between coated tablets.

Many quality aspects of the final coated product are greatly influenced by the combined effect of process parameter values used in aqueous film coating. Coating process parameters affect the spreading, penetration and drying (i.e. evaporation of water) of the coating liquid on the tablet surface and, subsequently, the surface roughness and the residual moisture of the coated tablets (Twitchell *et al*., 1995b; Obara and McGinity, 1995). Coating process parameters includes: air flow rate, absolute humidity of inlet air, spraying air pressure, flow rate of coating solution, pan air temperature and rotating speed of the pan.

Table 1.2: Comparison of enteric coating systems (McGinity, 1997)**.**

Type of system	CAP & CAT	HPMCP	Acrylic
Aqueous ***(+)***	Long history of use Flexible coating conditions Lower plasticizer conc. required Easily applied Easily cleaned Stable solution Thinnest film with enteric protection Least expensive Can accommodate more additives Colored dispersions available	Same as CAP and stable coating	Stable Lowest water permeation
(_)	May require subcoat High permeation of gastric fluid $MgCO_3$ required to enhance stability Talc to reduce gastric fluid permeation NH_3 odor Tackiness after coating Lake pigments must be milled	May require subcoat High permeation Discoloration on storage NH_3 odor Tackiness after coating Lake pigments must be milled	Usually subcoat required Odor, Monomers Higher coating wt. required Critical coating condition air outlet temp. window to spray-dry Bacterial growth Highest cost

Solvent (+)	Stable No heated inlet air required Low permeation of gastric fluid Fast spray time No subcoat required High Tg No water to intact with core Cost vs toxicity	Same as CAP and environmentally friendly (EtOH\water solvent)	Not applicable
(_)	Environmental concerns Solvent recovery		Not applicable

1.6. Objectives of the study

1.6.1. General objective

To formulate and characterize enteric coated ASA 81 mg tablet containing different disintegrants and to evaluate the effects of pregelatinized enset starch as tablet disintegrant on the stability of enteric coated ASA 81 mg tablet.

1.5.3 Specific objectives

- To formulate and characterize enteric coated ASA 81 mg tablets containing different type and concentration of disintegrants;
- To perform accelerated stability study for the coated tablets;
- To compare the stability profile of enteric coated ASA formulated by enset pregelatinized starch with ASA formulated by other starch based excipients as disintegrants;
- To analyze the effects of the type and concentration of the disintegrants used on the stability and other characteristics of the formulated enteric coated ASA tablets; and
- To suggest a suitable concentration and type of disintegrant to formulate stable enteric coated ASA tablet.

2. EXPERIMENTAL

2.1.Materials

ASA (yixing city xingyu, Jiangsu, China), Microcrystalline cellulose (JRS Pharma GmbH, Rosenberg, Germany), Wangit L30D-55 dispersion (Lianyungang Wantai, Jiangsu, China), Pregelatinized starch 1500® (Virchow, Hyderabad, India), Sodium starch glycolate & Talc (High Hope, Nanjing, China), Tri-sodium phosphate Hexahydrate (Fluka GmbH, Neu-Ulm, Germany), 1,2,propylene glycol (Horst G.F. Valtier GmbH, Hamburg, Germany), HPLC grade 1-heptane sulfonic acid sodium salt & Acitonitrile (Fisher Scientific, Loughborough, UK), Sodium acetate, Hydrochloric acid, Acetic acid glacial & Ethanol absolute anhydrous (Carlo Erba, Sabadell, Spain), Formic acid 85 % pure (BDH laboratory, England), were used as received. Native enset starch was donated by the Department of Pharmaceutics and Social Pharmacy, SOP, AAU, Addis Ababa, Ethiopia.

2.2. Methods

2.2.1. Preparation of pregelatinized enset starch

Pregelatinized enset starch was prepared according to Wondimu & Gebre-Mariam, 2010. Briefly, aqueous starch slurry (starch to water ratio of 1:2) was heated on a thermostated water bath (THERMOVISC®, Fungilab, Barcelona, Spain) at 62 ^{o}C with continuous stirring for 15 min. The resultant pregelatinized enset starch was spread on a stainless steel tray in the form of a thin layer (1–2 mm) and dried at 60 ^{o}C in an oven (Heraeus®, Kendro, Langenselbold, Germany) for 24 h. Then the dried mass was powdered using a coffee blender (Philips Saeco, Philips, Hong kong, China) and was passed through a fine sieve (100 µm) and stored in air tight plastic jars.

2.2.2. Construction of calibration curve

Two stock solutions containing 1 mg/ml of ASA in phosphate buffer (pH 6.8) and 0.1N HCl (pH 1) were prepared. From the stock solution, five (55, 50, 45, 40, 30 µg/ml) and six (100, 90, 80, 75, 70, 65 µg/ml) working concentrations were prepared, and their absorbance was read using a UV/Visible spectrophotometer (UV-1800, Shimadzu,

Kyoto, Japan) at 280 and 265 nm, for the acid and buffer systems, respectively. The corresponding mediums were used as blanks. Finally, the calibration curves and the corresponding correlation coefficients and equations describing the relationship between concentration and absorbance were obtained following Beer-Lambert's law.

2.2.3. Powder characterization

2.2.3.1. Drug-excipients compatibility study with Fourier Transform Infrared (FTIR) spectroscopy

FT-IR spectra's were recorded on a FTIR spectroscopy using KBr pellet technique using a Shimadzu FT-IR 84005 Spectrophotometer (Shimadzu, Tokyo, Japan) in the wavelength region of 4000 to 400 cm^{-1}. The procedure consisted of dispersing a sample (drug alone & mixture of drug and excipients) in KBr and the powder was compressed by mortar and pestle to form a transparent pellet. The pellet was placed in the light path and the spectrum was obtained.

2.2.3.2.Moisture content

The moisture content of the excipients was determined gravimetrically on a Mettler Toledo moisture analyzer (Mettler Toledo, Switzerland). Approximately, 1gm of sample was taken and placed uniformly onto the sample pan, and then the heating cycle was conducted with a maximum temperature of 162°C. The percentage of moisture content was read and an average was taken.

2.2.3.3.Angle of repose

Angle of repose (θ) was determined according to USP 30-NF 25 (2007). Briefly, accurately weighed amount of the powder (30 g) was allowed to flow through a 15 mm diameter stem less funnel, which was held 10cm above the surface of a graph paper. Then, the radius (r) and height (h) of the powder cone was measured and the angle of repose was calculated using Equation 2.1.

$$\text{Tan } \theta = h/r \qquad \text{Eq.2.1}$$

2.2.3.4.Bulk and tapped density

Both bulk and tapped densities were measured according to USP 30-NF 25 (2007) method I. Accordingly; 30 g of powder was introduced into a 250 ml measuring cylinder. And the initial reading was taken. Then the cylinder was tapped using a tap densitometer (STAV 2003, Gemini BV, Apeldoorn, Netherlands), that provides a fixed drop of 14 ± 2 mm at a nominal rate of 300 drops per minute, until no further change in the volume was noted (500 times) and the tapped volume was read. Finally, the bulk and tapped densities were calculated using Equations 2.2 & 2.3, respectively.

Bulk density = Weight of the powder/ Volume of the packing Eq. 2.2

Tapped density = Weight of the powder / Tapped volume of the packing Eq. 2.3

2.2.3.5.Compressibility Index and Hausner's ratio

Carr's Compressibility Index and Hausner's ratio of the powder blend were calculated using Equations 2.4 and 2.5.

Carr's index = (Tapped density – Bulk density) / Tapped density x 100 Eq. 2.4

Hausner's Ratio = Tapped density/ Bulk density Eq. 2.5

2.2.4. Tablet compression

Due to stability and simplicity reasons, direct compression method was chosen. Accordingly the ingredients (Table 2.1) were sieved through a 40# size mesh and were mixed using a laboratory scale multiblend mixer (MB005®, Pharmatech, Buckinghamshire, UK) for 15min. The dry blend was then compressed in a 16 station rotary compression machine (B_3B®, Manesty, Liverpool, England), fitted with 8 mm standard concave tooling and compression was made at a fixed die volume and the desired crushing strength was 50-100 Newton.

Table 2.1: Compositions of various enteric coated ASA 81 mg tablets used for the study.

Ingredients (mg)	**F_1**	**F_2**	**F_3**	**F_4**	**F_5**	**F_6**	**F_8**	**F_9**	**F_{10}**	**F_{11}**	**F_{12}**
ASA	81	81	81	81	81	81	81	81	81	81	81
Talc	3.9	3.9	3.9	3.9	3.9	3.9	3.9	3.9	3.9	3.9	3.9
MCC	38.6	35.4	32.1	42.5	38.6	34.7	35.4	32.1	38.6	35.4	32.1
PGS 1500	6.5	9.75	13	-	-	-	-	-	-	-	-
SSG	-	-	-	2.6	6.5	10.4	-	-	-	-	-
PGES	-	-	-	-	-	-	9.75	13	-	-	-
ES	-	-	-	-	-	-	-	-	6.5	9.75	13
Average weight	**130**	**130**	**130**	**130**	**130**	**130**	**130**	**130**	**130**	**130**	**130**

2.2.5. Enteric coating

2.2.5.1. Preparation of enteric coating solution

First 3 g of 1, 2- propylene glycol was mixed with 30.3 g deionized water. Then 66.7 g Wangit L30D-55 dispersion was added to the solution with continuous stirring for 30 min and the formed dispersion was passed through a 90 µm sieve. On dry weight basis 1, 2 propylene glycol contributes 15% of the coating film.

2.2.5.2.Enteric coating

Tablet coating was carried out in the 12-inch conventional pan (ERWEKA GmbH, Heusenstamm, Germany) equipped with a spray gun. The coating dispersion was delivered to the spray gun through a tube fed from a peristaltic pump. The pan load of ASA 81mg tablet was 200 g. Samples of tablets for performance testing were removed from the coating pan at increments from 8–10% theoretical coating weight gain. The coating process parameters were optimized to enhance the stability of ASA giving a better coating. Consequently, during coating the drum speed was set at 16 rpm with an average inlet and outlet air temperature of 50 and 40 ^{o}C, respectively. The coating process was carried out in 13 cycles where in each cycle the coating solution was sprayed for 1 min at rate of 8 g/min with a spray pressure of 2 bar followed by 9 min drying taking the total coating process to 2 h.

2.2.6. Tablet characterization

2.2.6.1.Tablet physical appearance

Twenty uncoated tablets were taken and visually inspected for any discoloration or physical change over a course of time. The procedure was repeated for the coated tablets.

2.2.6.2.Weight uniformity

To determine weight uniformity, ten tablets were separately weighed using an analytical balance (ae ADAM®, Danbury, USA) and the weight variation was calculated according to USP 30-NF 25 (2007).

2.2.6.3.Tablet hardness

The hardness of ten tablets was measured using a hardness tester (ERWEKA GmbH, Heusenstamm, Germany) and the average and standard deviation values were calculated.

2.2.6.4. Friability

Twenty tablets of known weight were placed in a friability tester (ERWEKA GmbH, Heusenstamm, Germany) and were rotated at 25 rpm for 4 min. Then, the tablets were sieved and weighed, and the percent loss in weight was calculated as friability.

2.2.6.5.Disintegration time

Tablet disintegration time was determined using a USP disintegration apparatus (ZT304, ERWEKA GmbH, Heusenstamm, Germany). One tablet was introduced into each tube of the basket rack assembly of the disintegration apparatus without disc and the disintegration time was determined in distilled water maintained at 37±2°C. For enteric coated tablets the test was carried out in a different disintegration media, for first two h in 0.1 N HCl followed by phosphate buffer (pH 6.8) until all tablets were disintegrated and the time was recorded.

2.2.6.6.*In vitro* dissolution study and drug release profile

USP dissolution type I apparatus (DT 700 H, ERWEKA GmbH, Heusenstamm, Germany) was used to conduct *in vitro* drug release study. During the study 500 ml of 0.05 M acetate buffer of pH 4.5 was used as a dissolution medium and release study was conducted for 30 minutes at 37 ± 0.5°C and 50 rpm. At the end of 30 min sample was withdrawn and the amount of ASA released was determined. For enteric coated tablets the method was slightly modified. Thus, the study was conducted first for 120 min in acidic media (1000 ml 0.1N HCl, pH=1) and then for 90 min in 1000 ml phosphate buffer (pH 6.8). The study was conducted at 100 rpm and 5 ml sample was withdrawn. For drug release profile five ml of aliquots of the dissolution medium were removed at 30, 45, 60 and 90 min. Equal amount of fresh medium kept at the same temperature was transferred into the dissolution vessel to keep the sink condition.

2.2.6.7.Determination of the level of free salicylic acid in ASA tablets

The amount of free salicylic acid within the ASA tablets was determined according to Heidarian *et al*, 2006. Consequently, the degradation of ASA in the samples was determined by measuring the absorbance of salicylic acid in 95% ethanol at 303 nm (E1% 1 cm at 303 nm = 262) as a function of time. For the analysis, 20 tablets were taken and finely powdered. An accurately weighed amount of the powder, equivalent to 50 mg of ASA, was transferred to a test tube and 25 ml 95% ethanol was added. The suspension was then vigorously shaken, centrifuged at 5000 rpm for 5 min and the supernatant was subsequently analyzed using a UV visible spectrophotometer.

2.2.6.8.Assay

Assay for enteric coated ASA 81 mg tablets was conducted according to the USP 30-NF 25 (2007) using HPLC system equipped with a UV-Vis detector at λ 280 nm (CLASS-VP^{TM}, Shimadzu, Kyoto, Japan). The chromatographic determination was carried out using a C_{18} HPLC column 4 mm x 30 cm (Beckman Coulter, California, USA) as a stationary phase, a system containing 2 g of sodium 1-heptanesulfonate dissolved in a mixture of 850 ml water and 150 ml of acetonitrile was used as a stationary phase at a flow rate of 2 ml/min and injection volume of 10 µl. The pH of the mobile phase was adjusted to 3.4 using glacial acetic acid as an acidifying agent.

For the assay, a 0.5 mg/ml standard ASA solution was prepared using USP ASA reference standard. Twenty tablets were finely powdered and a powder mass equivalent to 100 mg of ASA was weighed and transferred into a flask containing 20 ml of diluting solution (a mixture of acetonitrile and formic acid 99: 1) and glass beads. The suspension was then shaken for 10 min, centrifuged (and further diluted 1 to 10 using the diluting solution). Finally, the chromatograms of the standard and test solutions were recorded and the quantity (in mg) of ASA in the tablets was calculated according to Equation 2.6.

$$\text{mg of ASA in the tablet} = 200C\,(r_o/r_a) \qquad \text{Eq 2.6}$$

Where: C is the concentration, in mg per ml, of USP ASA RS in the standard solution; r_a & r_o are the heights of the ASA peaks in the test and standard solutions, respectively.

2.2.6.9.Accelerated stability study

For the stability study, enteric coated ASA 81 mg tablets were packed in a high-density polyethylene bottles (200 tablets/ bottle) and were placed in a stability chamber (Binder Gmbh, Tuttlingen, Germany) for three months at 40°C and & 75% RH. Determination of tablet properties was conducted at the zero and three month times and the results were compared.

2.2.6.10. Statistical analysis

Statistical analysis of the results obtained was carried out using a computer software SPSS® 16.0. Two way ANOVA ($p = 0.05$) was used to assess the differences between various formulations. Tukey-Kramer multiple comparison test was used to compare the difference between individual formulations. The results obtained are reported as mean of and standard deviation.

3. RESULTS AND DISCUSSION

3.1.Construction of calibration curve

Standard calibration curves for ASA were constructed separately in pH 6.8 phosphate buffer (Fig 3.1) and 0.1 N HCl (Fig 3.2). The equations describing the relationship are Y= 0.003X + 0.006 and Y= 0.006X + 0.01 (where Y is the absorbance and X is the concentration in µg/ml) in phosphate buffer and 0.1 N HCl with correlation coefficient values of 0.9993 and 0.9985, respectively.

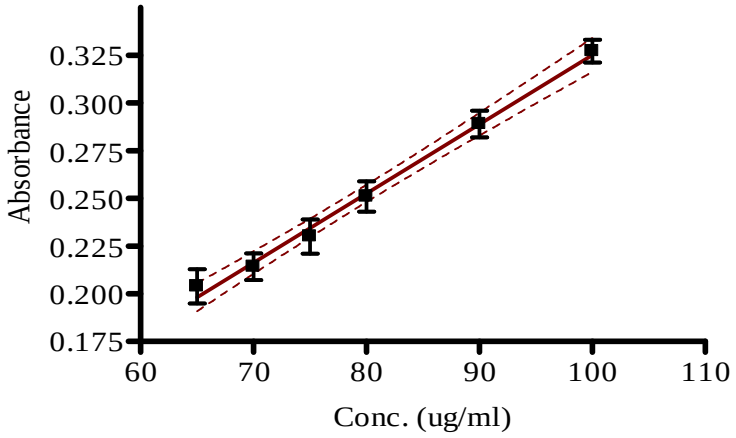

Figure 3.1: UV calibration curve of ASA in phosphate buffer (pH 6.8) obtained at 265 nm. The 95% confidence interval band is designated (r^2 = 0.9993).

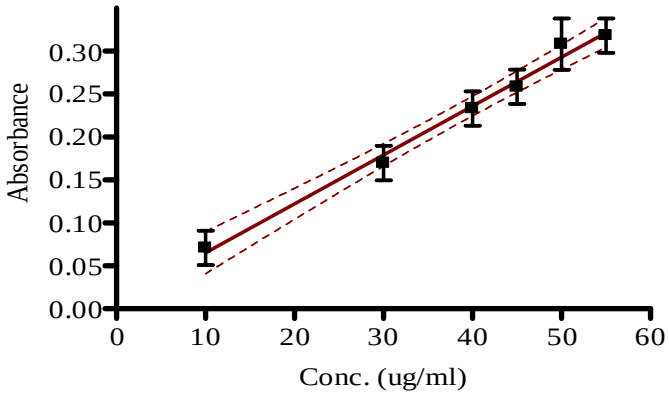

Figure 3.2: UV calibration curve of ASA in 0.1 N HCl obtained at 268 nm. 95% confidence bands are indicated in red (r^2= 0.9985).

3.2.Formulation development of ASA 81 mg enteric coated tablet

ASA is a moisture sensitive drug and hydrolyzed into acetic and salicylic acid when exposed to high humidity and elevated temperatures (Mitrevej and Hollenbeck, 1983). However, it has good compaction and flow properties and can be compressed directly (Lachman *et al.,* 1989): elimination of wet granulation step improves its stability. Likewise, in this experiment ASA 81 mg tablets were directly compressed using MCC as a direct compression filler and talc as a lubricant using sodium starch glycolate, pregelatinized starch 1500®, pregelatinized or native enset starch as a disintegrant set at three different levels, Table 2.1.

The ability and efficacy of enteric polymers in directing the drug to the target site is very critical due to the presence of wide range of pH values and enzymes in the gastrointestinal tract. Organic solvent based enteric coatings have long served this purpose but constrained due to economical and ecological prospects. The conversion of organic solvent based coating to aqueous solvent based coating makes the coating process more acceptable with environmental considerations (McGinity, 1997).

During the aqueous film coating process, Faroongsarng and Peck determined that depth of water penetration into the tablet core could be directly linked to the concentration and type of disintegrant used in the formulation (Faroongsarng and Peck, 1991). Inclusion of a high level of superdisintegrants in tablet formulations can affect the physical appearance of the final coated dosage form, such as the smoothness of the film. Superdisintegrant particles compressed into the surface of the tablet may get activated prematurely on contact with droplets of aqueous film coating solution resulting in very fast and excessive water penetration into the core and uneven surface of the coated product. Water penetration into the tablet core can lead to potential storage problems with formulations that contain moisture-sensitive materials. That is why the choice of disintegrant type in such formulations can have a significant effect on coated product stability (Thibert and Hancock, 1996).

Studies also revealed that pregelatinized starches exhibited lower values of the Hausner's ratio, suggesting better flowability than the native starches. The values of mean particle diameter and particle density for the pregelatinized starch were, however, higher than those for the native starches (Alebiowu and Itiola, 2002; Odeku *et al.*, 2008; Adedokun and Itiola, 2009). Pregelatinized starches showed higher water absorption capacity, swelling ability, and percentage solubility than the native starches due to the disruption of associative bonds and amylose leaching out during gelatinization (Wootton and Bamunuarachchi, 1978; Alebiowu and Itiola, 2002; Adedokun and Itiola, 2009; Nakorn *et al.*, 2009). Pérez-Sira and González-Parada (1997) reported that the apparent viscosity of pregelatinized starch suspensions showed a marked reduction with an increase in shear force; this denoted their pseudoplastic character. Compaction study revealed that pregelatinized starch underwent plastic deformation (Maarschalk *et al.*, 1997).

3.3.Pre-compression parameters:

Determination of moisture content, flow and other related properties

Measurement of angle of repose has been used to characterize the flow properties of powders and granules. It is a characteristic related to the interparticulate friction or resistance to movement between particles (USP 30-NF 25, 2007). Accordingly the angle of repose of the 12 formulations prepared was determined, Table 3.1. As can be seen in the Table, the angle of repose of all the formulations was in the range of 25.8° to 31.6° indicating that they exhibited good flow. The type and amount of disintegrants did not have significant effect on the value of angle of repose ($p > 0.05$) except in the case of formulations made with SSG, which has a relatively lower angle of repose.

Besides, in recent years the compressibility index and the closely related Hausner's ratio have become the simple, fast, and popular methods of predicting powder flow characteristics. Moreover, the compressibility index has been proposed as an indirect measure of bulk density, size and shape, surface area, moisture content, and cohesiveness of materials because all of these can influence the observed compressibility index (USP 30-NF 25, 2007). Thus, the compressibility index and Hausner's ratio values

of the various formulations obtained (Table 3.1) lie within the range of 13.9 to 23.1 and 1.15 to 1.30, respectively indicating that all the formulations exhibit good flow and compressibility properties regardless of the type and amount of disintegrants.

Table 3.1: Micrometrics properties of various ASA containing formulations (Mean ± SD).

Formulation	Angle of Repose (deg)	Carr's index (%)	Hausner's ratio
F_1	31.6 ± 0.85	21.4 ± 0.62	1.26 ± 0.01
F_2	31.3 ± 0.92	23.1 ± 0.59	1.30 ± 0.01
F_3	30.4 ± 0.67	17.9 ± 0.98	1.23 ± 0.02
F_4	25.8 ± 0.9	17 ± 0.67	1.22 ± 0.01
F_5	29.6 ± 0.55	14.3 ± 0.64	1.17 ± 0.006
F_6	26.7 ± 0.99	17.2 ± 0.59	1.20 ± 0.006
F_7	30.8 ± 0.47	13.9 ± 0.64	1.15 ± 0.01
F_8	28.5 ± 0.53	16.7 ± 0.96	1.2 ± 0.01
F_9	29.7 ± 0.5	18.6 ± 0.59	1.22 ± 0.01
F_{10}	31.3 ± 0.49	19 ± 0.96	1.22 ± 0.02
F_{11}	29.7 ± 0.72	17.9 ± 0.95	1.24 ± 0.01
F_{12}	31 ± 0.49	17 ± 0.59	1.32± 0.02

IR spectra of ASA and ASA mixed with each excipient are presented in Table 3.2. Pure ASA spectra showed characteristic peaks O-H stretch (from RCOOH) 1760 cm^{-1}, R-COOH group near 2900.7-2927.7 cm^{-1}, aromatic C=C peaks around 1458.0 cm^{-1} and C=O stretching (from RCOOH) near 1689.5 cm^{-1}. The above characteristic peaks

appear in the spectra of all Excipient- ASA mixture at the same wave number indicating no interaction between the drug and the excipients. The moisture content was determined for all excipients and loss on drying of all was found to be between 0.2% - 8.87%.

3.4.Characterization of uncoated ASA 81 mg tablets

As has been summarized under this section and stated under the methodology part, evaluation of most of the tablets characteristics were conducted according to USP 30-NF 25 (2007).

3.4.1. Tablets appearance and weight variation

Visual inspection of all the tablets showed no sign of initial physical instability: all the tablets were white in color. Besides, a tablet is designed to contain a specific amount of drug in a specific amount of tablet formula. To check whether the tablet contains a proper amount of drug, weight of tablet should be routinely measured. Accordingly, the tablets were examined for their uniformity of weight and the values (Table 3.3) showed that all the tablets comply with the limits set by the USP (generally ±10% for tablets weighing 130 mg or less, ±7.5% for tablet weighing more than 130 mg to 324 mg and ± 5% for tablet weighing more than 324 mg) (Remington, 2000) .

3.4.2. Tablet friability test

Tablets that are to be coated must possess some proper physical characteristics. The tablets roll in a coating pan and to tolerate the intense attrition of tablets striking other tablets or walls of the equipment, the tablets must be resistant to abrasion and chipping. Accordingly, the friability of the various formulations was determined (Table 3.3). All values were found to be well within the acceptable range (< 1). Besides, although the formulations formulated using PGS 1500 as disintegrant showed slightly higher values, analysis of the results showed that the type and amount of disintegrants did not have a significant effect on friability ($p > 0.05$).

Table 3. 2: FTIR Interpretation

Functional Groups	Wave Number (cm^{-1})						
	ASA	ASA + MCC	ASA + PGS 1500	ASA+ PGES	ASA + ES	ASA + SSG	ASA + Talc
R-COOH 2500-3000	2900.7-2927.7	2923.8	2912.3	2896.8	2920.0	2923.8	29820.0
C=C bend, Aromatic, 1500-1700	1458.0	1458.0	1458.0	1458.0	1458.0	1458.0	1458.0
O-H stretch (from RCOOH) 1760	1755.1	1755.1	1755.1	1755.1	1755.1	1754.3	1755.1
C=O stretching (from RCOOH) 1689	1689.5	1685.6	1685.6	1685.6	1685.6	1685.6	1685.6
C-O(acid Ester)	1188.0	1188.0	1188.0	1188.0	1188.0	1188.0	1188.0

Table 3.3: Physicochemical characteristics of the uncoated ASA 81 mg tablets (Mean ± SD).

Parameters	Formulation											
	F_1	F_2	F_3	F_4	F_5	F_6	F_7	F_8	F_9	F_{10}	F_{11}	F_{12}
Average weight (mg)	129.6 ±0.97	130.1 ±0.88	130.5 ±0.97	128.7 ±0.95	129.4 ±0.96	131 ±0.94	129.7 ±0.95	129.9 ±0.88	129 ±0.88	129.3 ±0.48	129.5 ±0.71	130.4 ±0.7
Friability (%)	0.19	0.49	0.74	0.27	0.12	0.08	0.04	0.23	0.16	0.15	0.04	0.18
Hardness (N)	74 ±0.39	66.9 ± .45	67.8 ± 0.4	82.9 ± .39	73.7 ± 0.4	65.8 ± .43	62.3 ± 0.6	52.6 ±0.7	47.8 ±0.29	67.5 ±0.42	65.6 ±0.39	62.8 ±0.42
Disintegration time (sec)	56.7 ± 0.3	50 ± 0	41.3 ± 0.4	47.7 ± 0.6	37.3 ± 0.6	32.7 ± 0.6	41.3 ± 0.6	27.7 ±0.58	29 ±1	59.7 ±0.58	31 ±1	23.7 ±0.6
Cumulative % drug released in 30 min	44.19 ±1.8	99.73 ±1.3	99.04 ±1.3	94.80 ±1.7	97.05 ±1.2	97.4 ±1.1	56.29 ±2	93.38 ±1.5	95.14 ±1.3	43.45 ±1.9	65.33 ±1.6	87.43 ±1.8

3.4.3. Tablet hardness

The hardness of the tablets is given in Table 3.3. As can be seen in the table, the hardness values lie within 47.8 N to 82.9 N suggesting that all the formulations possess good mechanical strength rendering them amenable for coating. Besides, the results showed that the type and amount of disintegrant have no significant effect on tablet hardness ($p > 0.05$), except in case of SSG where the tablets were relatively harder especially compared with those tablets formulated with PGES.

3.4.4. Disintegration time

There is two main mechanism proposed for disintegration. Disintegration takes place by the annihilation of the interparticle bonding (passive mechanism) and by the development of separating stress due to swelling of disintegrant by the fluid permeating into the tablet (active mechanism) (Ferrari *et al.*, 1996). Thus the disintegration times in Table 3.3. show that all the formulations disintegrated in less than 60 seconds. The results also showed that, although the difference was not statistically significant, among the four disintegrants used formulations prepared with SSG exhibited relatively shorter disintegration time especially considering that those groups of tablets have the highest tablet hardness. Besides, the results showed that disintegration time decreased significantly as the level of disintegrant increases ($p > 0.05$).

3.4.5. *In-vitro* dissolution study

All the 12 formulations were subjected to *in vitro* dissolution studies and the results obtained showed that depending upon the type and concentration of the disintegrant used the cumulative percent of ASA released in 30 min varied from 43.45% to 99.73% (Table 3.3). As can be seen in the table, the percentage of drug released was significantly lower when native starch was used as a disintegrant than the other disintegrants ($p < 0.05$). Besides, as the concentration of the disintegrants increases the percentage drug released increased significantly with the exception of SSG, where no significant difference in percentage drug released was observed with change in disintegrant concentration ($p < 0.05$).

3.5.Film coating solution

The film coating solution was optimized in such a way to improve adhesion of the coating to the core material, to decrease bridging of intagliations and to increase coating hardness. Wangit L 30 D-55 was selected as the coating polymer for study based on its efficiency and superior advantages over other coating polymers such as CAP, and HPMCP. Wangit L 30 D-55 can be processed easily in water, is impermeable to water and has low hygroscopicity (McGinity, 1997) and hence it improves the stability of ASA tablets.

To determine coating solution content and coating parameters like: Pan rpm, inlet temperature and exhaust temperature preliminary study was performed with two batches with different concentration of film forming polymer (15% & 20%). Consequently, concentration of film forming polymer was 20% and during coating the drum speed was set at 16 rpm with an average inlet and outlet air temperature of 50 and 40 °C, respectively. The coating process was carried out in 13 cycles where in each cycle the coating solution was sprayed for 1 min at rate of 8 gm/min with a spray pressure of 2 bar followed by 9 min drying taking the total coating process to 2 h.

3.6. Evaluation of ASA 81 mg coated tablets

3.6.1. Change in tablet weight

The various physicochemical attributes of the enteric coated tablets are shown in Table 3.4. As can be seen in the table all the formulation did not show any significant variation in tablet weight and dimension ($p > 0.05$).

The weight of coated tablet was found to be between 139.9 mg to 141.6 mg. The total weight gain after enteric coating was found to be between 8 % and 9.75%. Although it was not statistically significant, tablets formulated with sodium starch glycolate and pregelatinized enset starch at low concentrations showed higher weight gain than others ($p > 0.05$).

Table 3.4: Physicochemical properties of the formulated enteric coated ASA 81 mg tablets at zero month time (Mean ± SD).

Parameters	**F_1**	**F_2**	**F_3**	**F_4**	**F_5**	**F_6**	**F_7**	**F_8**	**F_9**	**F_{10}**	**F_{11}**	**F_{12}**
Average weight (mg)	140.3 ± 1.3	141.6 ±1.8	139.9 ± .99	140.7 ± 1.4	141 ±1.3	141.1 ± 1.4	140.4 ± 1.4	140.5 ± 1.4	140.4 ±0.97	140.4 ±1.17	141.2 ± .92	140.5 ± .97
Total weight gain (%)	9.75	8.6	8.75	9	8.53	8	9.75	8.5	9.5	8.75	9.43	8.5
Hardness (N)	138.8 ± .62	123.3 ± 0.6	123.1 ± .88	149.8 ± .95	131.4 ± .59	120.2 ± .92	105.8 ± 1.1	109.4 ± .69	50.1 ±0.8	97.9 ±1.6	122.6 ±0.71	116.1 ±0.67
Disintegration time (min in pH 6.8)	18 ± 0.87	15 ± 0.9	14 ± 1.1	17 ± 0.6	15 ± 0.9	17 ± 0.8	18 ± 0.5	14 ± 0.9	26 ± 0.6	26 ± 0.7	30 ± 0.86	35 ± 0.94
Cumulative drug release in phosphate buffer pH 6.8 (%)	99.2 ± 6.2	105.3 ± 4	107.2 ± 2.9	108.4 ± 3.5	108.9 ± 2.3	115.9 ± 2.7	78.5 ± 8	106.7 ± 5	101.8 ± 3	66.7 ± 5	85.2 ± 1.9	86 ± 2.1
Cumulative Drug release in 0.1 N HCl (%)	2.78 ± 1.1	5.6 ± 1.6	7.14 ± 1.6	7.48 ± 2	5.54 ± 3.2	6.13 ± 1.5	5.85 ± 2.3	5.41 ± 1.4	8.76 ± 2	7.46 ± 1.2	5 ± 0.6	5.57 ± 3

3.6.2. Tablet hardness and friability

As can be seen in Table 3.4, the tablet hardness value ranged from 50.1 to 149.8 N. Tablets formulated with pregelatinized enset starch at high concentration showed lowest hardness value than others but it was not statistically significant ($p > 0.05$).

3.6.3. Tablet disintegration time

The result of disintegration studies involving enteric coated tablets showed that all the tablets remained stable and acid resistant in 0.1 N HCl with no evidence of disintegration, cracking, or softening for two h. However, the tablets disintegrated in phosphate buffer (pH 6.8) between 14 to 35 min (Table 3.4). These values are acceptable as per the USP 30-NF 25 (2007) standards. The results in the Table also show that the disintegration time in phosphate buffer (pH 6.8) of tablets prepared using native enset starch as a disintegrant is significantly longer than tablets formulated using the other disintegrants ($p < 0.05$). However, the amount of disintegrant did not have significant effect in disintegration time of ASA in phosphate buffer (pH 6.8) ($p > 0.05$).

3.6.4. *In vitro* drug release and drug release profile

Cumulative drug release study

In vitro drug release of coated ASA tablets was determined according to the USP 30-NF 25 (2007) for delayed release ASA tablets. Accordingly, the cumulative percentage of ASA released in phosphate buffer (pH 6.8) after 90 min is depicted in Table 3.4. As can be seen in the Table, the percentage drug released was in the range of 66.7% to 115.9% and, like the disintegration time, the release of the drug from tablets formulated using ES and lower level of PGES as disintegrants was significantly lower than tablets formulated using the other disintegrants at all concentrations. Besides, the percent drug released, except F_7 and F_{10}, tablets formulated at lower levels of PGES and ES, respectively, all the tablets met the criteria set by the monograph: releasing more than 80 % of the drug in intestinal media at 90 min.

Moreover, significant difference in percentage drug released at low and high concentrations of disintegrant was observed ($p < 0.05$). Therefore, the amount of

disintegrant can affect the percentage drug released from enteric coated ASA 81 mg tablet.

On the other hand, as can be seen in Table 3.4, the percentage drug released in acidic medium was in the range of 2.78 % to 8.76%, which is also within the pharmacopeial limit: less than 10% drug release in acidic media (USP 30-NF 25, 2007).

Drug release profiles

Apart from the one point release study, the dissolution profiles of the formulations formulated at a selected level of the disintegrant (selection based on the concentration of the disintegrant that gave the best cumulative 90 min release), was obtained at 30, 45, 60 & 90 min, Figure 3.3. As can be seen in the Figure, the release profile of tablets formulated using native enset starch is significantly lower than tablets formulated using other disintegrants ($p < 0.05$). Although statistically insignificant, a faster dissolution rate was obtained with sodium starch glycolate & PGS 1500, than PGES, which may be associated with the rapid disintegration of the particles (Lachman *et al*., 1989).

3.6.5. Level of free salicylic acid

The percentage of free salicylic acid measured in each of the formulations is shown in Figure 3.4. The results in the Table showed that the percentage of free salicylic acid in all the formulations (0.97% to 2.2%) is within the USP (2007) limits for coated ASA tablets, which is less than 3%. Although, tablets formulated by PGES and native ES contain low levels of free salicylic acid than others and the values are not statistically significant ($p > 0.05$). Therefore, the type and amount of disintegrants did not affect the stability of enteric coated ASA 81 mg tablet at zero month time.

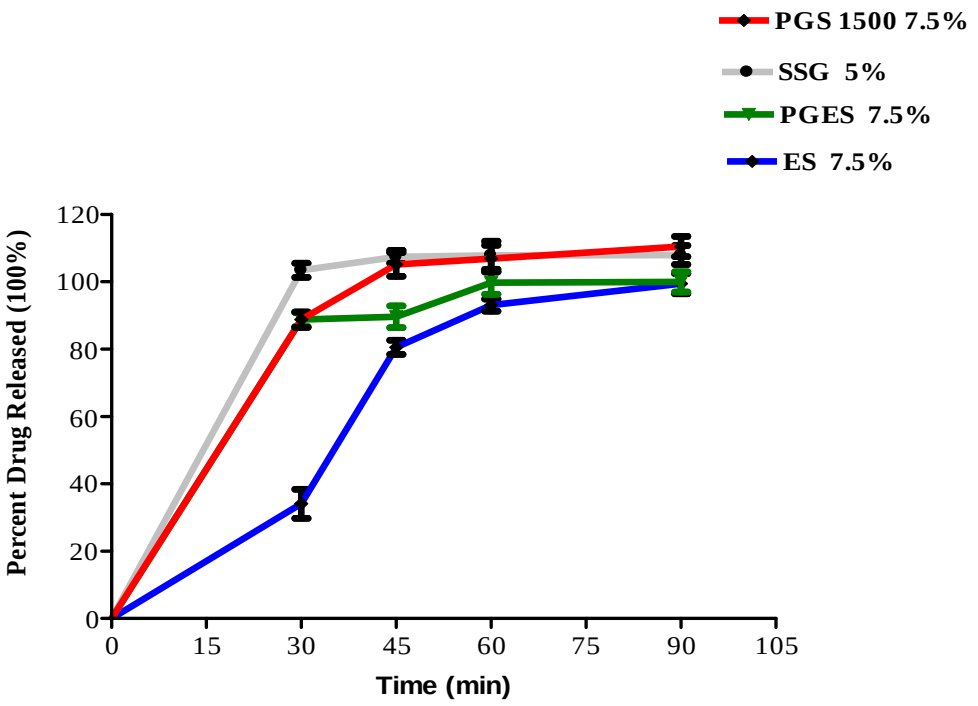

Figure 3.3: *In vitro* drug release profile in phosphate buffer pH 6.8 of enteric coated ASA 81 mg tablets formulated using various types of disintegrants.

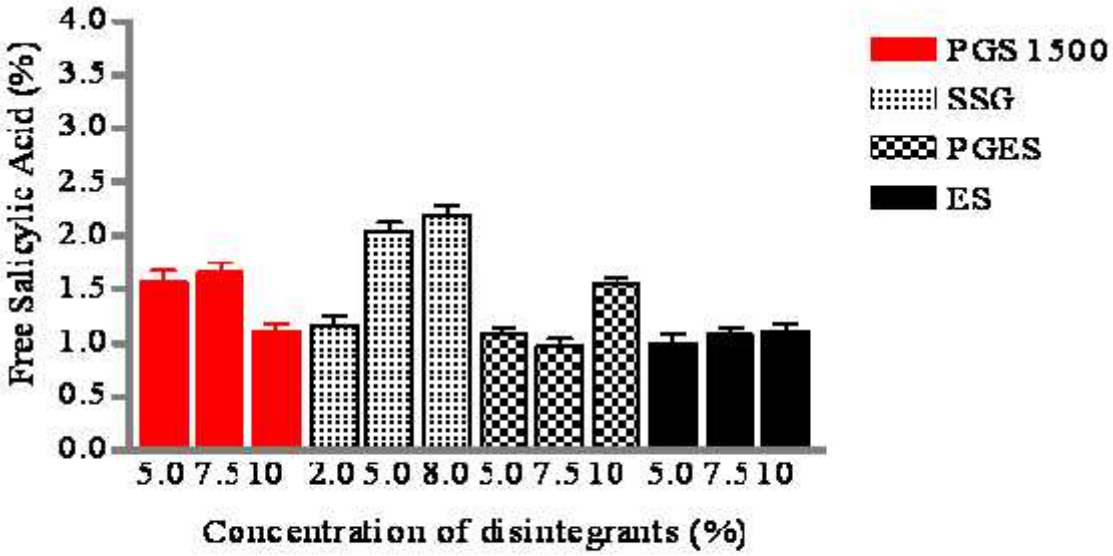

Figure 3.4: The zero time free salicylic acid content of ASA 81 mg enteric coated tablets formulated using different disintegrants at three concentration levels.

3.6.6. Assay

Assay for enteric coated 81 mg ASA was performed according to the USP (2007). The results obtained are shown in Figure 3.5 and are within USP (2007) limits (95- 105 %) for all formulations. Besides, there is no statistically significant difference between the formulations suggesting that the type and concentration of disintegrant have no significant effect on the stability of the drug at zero month time.

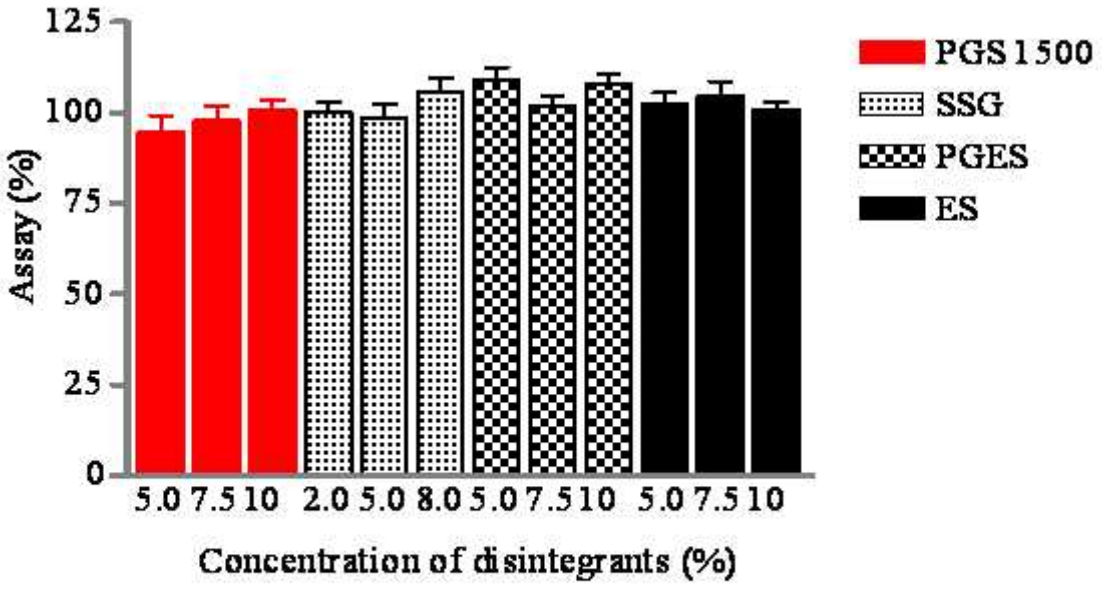

Figure 3.5: The zero time assay results of ASA 81 mg enteric coated tablets formulated using different disintegrants at three concentration levels

3.6.7. Accelerated stability study

Accelerated stability study was conducted for the enteric coated tablets. During the study the tablets were kept in a humidity chamber maintained at 40 ± 2 ºC and 75 ± 5 % RH.

3.6.7.1.Evaluation of tablet physicochemical properties

Analysis of the 3 months data revealed that tablets formulated using sodium starch glycolate as disintegrant exhibited softening of the film coating and sticking of the

tablets to one another, Figure 3.6. Whereas, with the other disintegrants employed, the film remained intact.

The results in Table 3.5 show that the tablets mechanical strength after exposure to accelerated temperature and humidity conditions decreased significantly for all the formulations ($p < 0.05$). As can be seen in the table, tablets formulated using sodium starch glycolate & pregelatinized enset starch at all concentration levels exhibited significantly lower mechanical strength than those tablets formulated using PGS 1500 & native ES ($p < 0.05$).

Pregelatinized starch 1500®7.5% Sodium starch glycolate 5%

Pregelatinized enset starch 7.5% Native enset starch 7.5%

Figure 3.6: Appearance of ASA 81 mg enteric coated tablets after three months of storage at 40 °C & 75% RH.

The disintegration times in phosphate buffer (pH 6.8) were found to be between 12 to 29 min, which complies with the USP (2007) standards and there was no significant difference among the formulations ($p > 0.05$), except for ES where they exhibited longer disintegration time. However, there was no significant difference in disintegration time in phosphate buffer at the initial time point and after three months ($p > 0.05$). Moreover, only those tablets formulated by pregelatinized enset starch and pregelatinized starch 1500® at all concentration levels remained intact and acid resistant with no evidence of disintegration, cracking, or softening in 0.1 N HCl for two h.

As can also be seen, the results in Tables 3.5, the cumulative percent drug release in acidic stage increased significantly after three months of storage at 40 °C and 75 % RH ($p < 0.05$). The results also show that the amount of disintegrant did not have significant effect on the cumulative percent drug released in 0.1 N HCl ($p > 0.05$). The amount of drug released for tablets formulated using pregelatinized enset starch and pregelatinized starch 1500® at all concentration level are significantly lower than those tablets formulated with sodium starch glycolate and native enset starch ($p < 0.05$). Consequently, only tablets formulated with pregelatinized enset starch and pregelatinized starch 1500® passed *in vitro* drug release test as the percentage drug released in acidic stage was within the USP (2007) limits of less than 10% drug release in acidic media.

The cumulative percent drug release in phosphate buffer (pH 6.8) is depicted in Table 3.5, which was in the range of 88.7 % to 101.7%. All the formulations met the release criteria set by the USP (2007), which demands release of more than 80 % of the drug in phosphate buffer of pH 6.8 with in 90 min. Besides, no significant difference in cumulative percent drug release was observed among the formulations indicating that both the type and amount of disintegrant used have no significant effect on drug release ($p > 0.05$).

Table 3.5: Physicochemical properties of the formulated enteric coated 81 mg ASA tablets after three months of storage in stability chamber at 40 °C & 75% RH.

Parameters	Formulation No.											
	F_1	**F_2**	**F_3**	**F_4**	**F_5**	**F_6**	**F_7**	**F_8**	**F_9**	**F_{10}**	**F_{11}**	**F_{12}**
Hardness (N)	52 ± 0.6	53 ± 0.3	50 ± 0.8	45 ± 0.4	42 ± 0.4	36 ± 0.5	46 ± 0.8	43 ± 0.6	38 ± 0.4	51 ±0.7	54 ± 0.6	55 ±0.7
Disintegration time (min) in phosphate buffer pH 6.8	14 ± 1.3	13 ± 1.8	12 ± 0.9	14 ± 1	15 ± 1.5	16 ± 1.2	14 ± 0.9	13 ± 1.4	25 ± 1.2	29 ± 1.6	28 ± 1.1	19 ± 1.3
Dissolution in 0.1 N HCl (%)	5.39 ± 0.5	8.26 ± 2.2	6.6 ± 1.3	25.5 ± 0.12	26.3 ± 0.5	25.9 ± 4.7	6.8 ± 1.4	6.2 ± 0.4	5.7 ± 1.7	33.9 ± 10.9	24.6 ± 1.2	24.4 ± 0.9
Cumulative drug release in phosphate buffer pH 6.8 (%)	99.3 ± 6.5	97 ± 1.8	95.3 ± 0.9	101.7 ± 8.1	99.7 ± 1.9	92.6 ± 1.5	100.3 ± 3.8	97.7 ± 3.2	97.2 ± 1.7	88.7 ± 2.2	97.3 ± 1.4	99 ± 1.2

3.6.7.2. Assay and determination of free salicylic acid

The percentage of free salicylic acid in each formulation after three months of storage is shown in Figure 3.7. As can clearly be seen in the figure, the percent free salicylic acid in the tablets formulated using sodium starch glycolate as disintegrant is relatively higher than the other formulations. Even SSG based formulations containing ≥ 5% of the disintegrant contain greater than 3% salicylic acid, which is out of USP (2007) limits for enteric coated ASA tablets. However, analysis of the results showed that tablets containing pregelatinized starch 1500® have the same stability as tablets containing pregelatinized and native enset starch ($p > 0.05$) and there was no significant increase in salicylic acid content upon storage under accelerated stability conditions for three months.

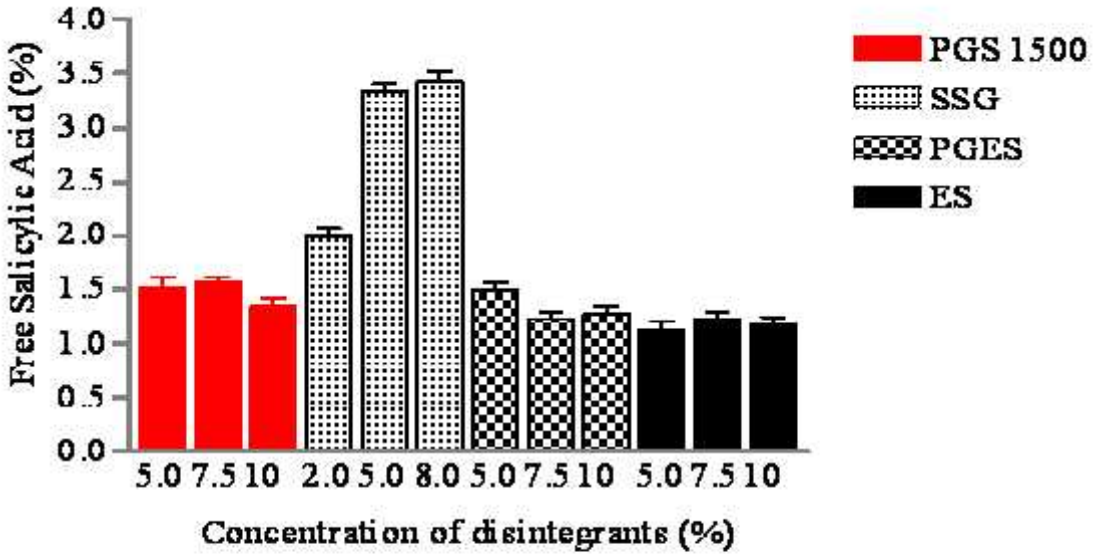

Figure 3.7: Free salicylic acid content of ASA 81 mg enteric coated tablets formulated using different disintegrants at three concentration levels after three months of storage at 40 °C & 75% RH.

The assay results obtained after three months of storage under accelerated stability study conditions are shown in Figure 3.8. As can be seen in the figure the percentage of ASA in tablets formulated using sodium starch glycolate at all three concentration levels was below 95%. However, there was no significant difference observed in assay among the formulations ($p > 0.05$).

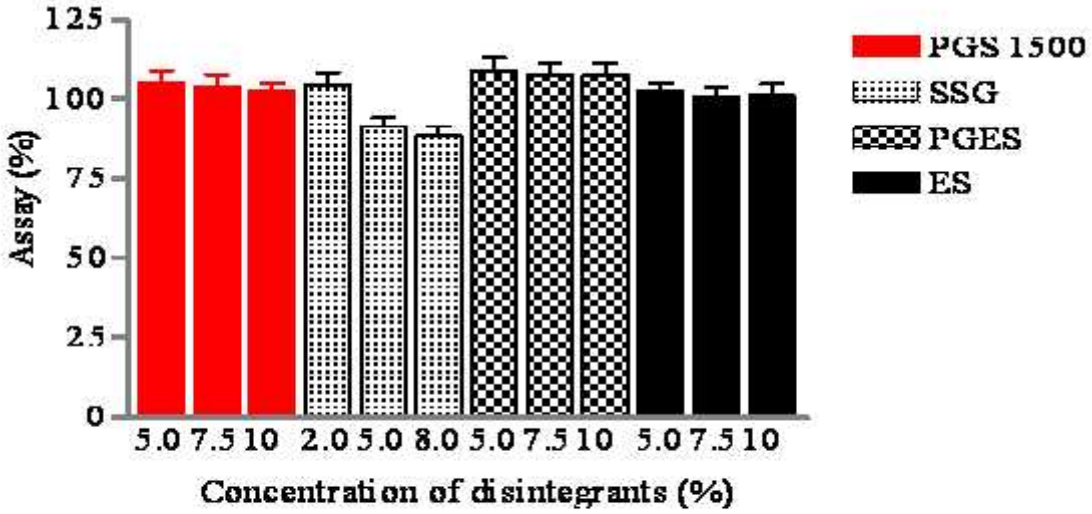

Figure 3.8: Assay result of the ASA 81 mg enteric coated tablets formulated using different disintegrants at three concentration levels after three months of storage at 40 °C & 75% RH.

Thus, generally tablets formulated using SSG as disintegrant were not stable, both physically and chemically. It might be due to the fact that superdisintegrant particles compressed into the surface of the tablet may get activated prematurely when in contact with droplets of aqueous film coating solution resulting in a very fast and excessive water penetration into the core and uneven surface of the coated product. A number of studies have also shown this. According to Thibert & Hancock, 1996, water penetration into the tablet core can lead to potential storage problems with formulations that contain moisture-sensitive materials (Thibert and Hancock, 1996). Cunningham *et al.,* (1999) also showed that in the formulation of direct-compression hydrochlorothiazide tablets,

partially pregelatinized starch performed as effectively as superdisintegrants, and due to its low propensity for moisture uptake may afford superior moisture stability (Cunningham *et al.*, 1999).

The qualities of tablets prepared with pregelatinized starches were also better than tablets prepared with native starch. This is most likely attributed to the water absorption and swelling ability of pregelatinized starch than the native starch. Nakorn *et al*., (2009) and others reported that pregelatinized starches showed higher water absorption capacity, swelling ability, and percentage solubility than the native starches due to the disruption of associative bonds and amylose leaching out during gelatinization (Nakorn *et al*., 2009).

4. CONCLUSION

To investigate the effect of the type and quantity of disintegrant on the stability and various other attributes of the tablets, twelve ASA 81 mg tablets were formulated by direct compression method. Tablet coating was carried out at a theoretical weight gain of 10 %, using Wangit L 30 D-55 polymer dispersion in water at 20% solid content and the tablets were subjected to a three month accelerated stability study conditions.

The results of accelerated stability study revealed that tablets formulated using sodium starch glycolate as a disintegrant have major stability problems. The integrity of the film coat was severely affected where softening of the coat and sticking of the tables was observed. Most importantly there was a significant increase in percent salicylic acid within the formulation, which was a consequence of hydrolysis of the drug. A significant increase in cumulative drug release in 0.1 N HCl was also observed, which can be associated with affected integrity of the polymer coat. In case of ES, although the salicylic acid and coat integrity were not observed, a significant reduction in percent drug release in phosphate buffer (pH 6.8) and a significant increase in drug release in 0.1N HCl were also observed.

On the contrary, the appearance, hardness, release in both acidic and buffer media, assay, and free salicylic acid content of tablets that were formulated using the pregelatinized starches remained unchanged.

Therefore, the findings of this study showed that type of disintegrant significantly affects the stability of enteric coated ASA 81 mg tablet. Although SSG gave tablets of good attributes, it is at the cost of stability of moisture labile drug. On the other hand tablets of desired quality and optimum stability were obtained using pregelatinized enset starch as disintegrant. All the advantages of SSG could be attained by using a relatively higher percentage of the starch as well. Its effect was also comparable to that of PGS 1500. But native ES is poor disintegrant with slight effect on drug stability.

5. SUGGESTIONS FOR FURTHER WORK

The results of this study suggest further investigation on the following directions:

- The effect of particle size distribution of pregelatinized enset starch on stability of moisture labile drugs, and
- The effect of packaging precautions such as desiccant packages or other specialized packaging materials on stability of moisture labile drugs formulated with pregelatinized enset starch as a disintegrant.

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