FORMULATION AND EVALUATION OF TABLETS MANUFACTURED FROM DODONAEA ANGUSTIFOLIA PLANT MATERIAL

EGIDE KAYITARE

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Supervisor: Prof. James A. Syce

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Egide Kayitare

KEYWORDS

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ABSTRACT

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E. KAYITARE

M. Pharm. thesis, School of Pharmacy, Department of Pharmaceutics, University of the Western Cape.

The liquid dosage form is the most frequently used form for traditional plant medicines. However, this dosage form is associated with many problems, e.g. physicochemical instability, microbial contamination, etc. which may be solved using a solid dosage form. This study investigates the formulation and manufacture of tablets containing two types of material prepared from the leaves of *Dodonaea angustifolia*.

The main goal of the present study was to formulate and produce tablets containing the same amount of plant material as found in the usual dose of *D. angustifolia* decoction. In addition, the suitability of using directly dried leaf powder and dried aqueous extract of the leaves, as raw material for the tablets, was compared. It was hypothesized that tablets with acceptable physical properties and containing 80% or more of plant material could be produced and that tablets containing dry leaf powder or dry plant extract would possess different properties.

Raw plant material in the form of dried leaf powder and dried aqueous extracts (Dry Extract 1 from wide leaf plant and Dry Extract 2 from narrow leaf plant) of *D. angustifolia* were prepared and their physical characteristics determined. Based on the latter, suitable excipients were selected and formulas containing the same amount of the plant material as found in a single decoction dose of *D. angustifolia* were elaborated. Thereafter, tablets containing these plant materials were manufactured

using the direct compression method and the physical properties of the manufactured tablets were assessed.

Results of the pre-formulation study indicated distinct differences in physical properties between the three plant materials. The dry leaf powder had a median particle size of 20μm compared to 200μm and 344μm for Dry Extracts 1 and 2, respectively. The dry leaf powder was significantly more soluble in ethanol than water (55.7±0.9 vs. 26.1±3%, t-test, p=0.05), while the extracts dissolved completely but required vigorous shaking. The compressibility of the dry powder was very good (11.9±0.5%), that of dry extract 2 good (15.9±2.8%) and that of Dry Extract 1 only passable (22.6±0.8%). All the powders showed poor flowability, but they had different potentials to pick up moisture. More importantly, the dry extracts became very cohesive and tended to dissolve in the absorbed moisture at relative humidity above 60%. The tablets containing the dry leaf powder and those containing Dry Extracts 1 and 2 required different formulas and different compression forces and displayed different physical properties. The final proportions of plant material per tablet were 85% for dry powder, 65% for dry extract 1 and 70% for dry extract 2. Finally, all the final tablets had acceptable physical properties. However, the tablets containing the dry extracts showed slow disintegration (27.6 and 29.6min for Dry Extracts 1 & 2, respectively, vs. 3.1min for dry powder) and low dissolution rate (38.6% and 60.2% at 45min for Extracts 1 and 2 vs. 92.7% for the dry powder).

We conclude that the different forms of raw material prepared from the leaves of *D. angustifolia* have different properties, but can be formulated and manufactured into directly compressed tablets. However, the form of raw material dictates whether the tablets can contain a high proportion (80% plus) of plant material and also influences the properties of the final tablets. Comparable results can be anticipated if materials from other parts of the plant and/or from other plants are to be used.

May 2001

DECLARATION

I declare that the thesis Formulation and Evaluation of The Tablets Manufactured From *Dodonaea Angustifolia* Plant Materials is my own work, that it has not been submitted before for any degree or examination in any other university, and that all the sources I have used or quoted have been indicated and acknowledged by complete references.

EGIDE KAYITARE MAY 2001

SIGNED:

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CHAPTER 1
INTRODUCTION

Medicinal plants have now been used for many centuries in many cultures and societies. Although their use is associated with some disadvantages, such as adverse effects resulting from the use of uncontrolled dosages, or the interaction with ordinary medicine when they are given together, the use of medicinal plants is expanding in many countries. Their use is even becoming popular in developed countries. The latter is mainly driven by the belief that what is natural is best. This trend is however further supported by the results of increasing investigations on several species of plants that have demonstrable therapeutic effects. These investigations have, however, essentially focused on the identification and evaluation of the biological activity to be found in the plant materials. The formulation and production of pharmaceutical dosage forms of plant material have seldom been the focus in such investigations.

In traditional medicine, decoction, tinctures, solutions, ointments and powders are the current favoured dosage forms used. Unfortunately, these dosage forms present a number of disadvantages, for example the doses are difficult to be standardized, the dosage form itself is not usually very stable, and, in addition, the liquids and ointments may be good media for the growth of fungi, molds, bacteria, etc. These problems may be resolved if the plant materials are formulated into an alternate more appropriate and stable dosage form.

Dodonaea angustifolia (*D. angustifolia)* is one of the medicinal plants used in traditional medicine. It is usually used in the form of a decoction made from freshly picked leaves and used as a remedy for fever. A decoction obtained from its dried leaves has also been shown to have analgesic and antipyretic effects in an animal model. It is unclear how stable the active ingredient(s) are in this traditional dosage form of this plant medicine. Also a lengthy preparation is required before

each dose is to be taken. Further, if evaluation of the effects of this plant is to be tested in humans a stable reproducible standardized dosage will be required.

Tablets are the oral dosage forms most frequently used in healthcare. They enjoy a popular acceptability among patients because they are typically easy to use, have a good stability, provide standardized doses and are generally inexpensive. The tablet dosage form of a medicinal plant such as *D. angustifolia* should provide the same advantages e.g. it offers a greater precision of dosage, stability of active drug, ability to withstand extended storage, and convenience of administration. But, because the active ingredients of the plant is not yet known, the tablets of *D. angustifolia* must contain the equivalent amount of active ingredient(s) found in the large number of leaves from which each dose of decoction is prepared. It should also be expected that the form of the plant raw material (e.g. whether fresh leaves, dried leaves or even an extract of the leaves) which are used to make such tablets of *D. angustifolia* need to be considered if the tablets are to be made.

The overall objective of this study was, consequently, to formulate and manufacture a tablet dosage form of *D. angustifolia* plant material. The specific aims were to formulate and produce tablets containing a maximum amount of plant material (80%) per tablet and to compare the suitability of using dried leaf powder and dry aqueous extract of the leaves as raw material. To realize these objectives the physical properties of the dried leaf powder and aqueous extract raw materials were to be characterized and used to select suitable excipients for the tablet formulations. From this information several formulations were to be elaborated and directly compressed tablets produced. Finally, the manufactured tablets were to be tested for physical properties such as: weight uniformity, hardness, friability, disintegration time and dissolution rate.

CHAPTER 2

LITERATURE REVIEW

2. 1 TRADITIONAL MEDICINAL PLANTS

The topic of traditional medicinal plants covers a vast area. In this section I will however focus on the importance and increasing trend of the use of the medicinal plants, warnings about the use of medicinal plants, and the possible contribution of the traditional healers in research on medicinal plants.

Traditional medicinal plants are important since they constitute our green heritage (Roberts, M., 1992). Medicinal plants were once a primary source of all the medicines in the world and they still continue to provide new remedies. Natural products and their derivatives represent more than 50% of all drugs used in the world in the clinical field (Van Wyk, B. E., 1997). Higher plants contribute no less than 25% to the total and the number of higher plants on this planet is estimated to be between 370,000 and 500,000 species. All higher plants elaborate chemicals that are potential of medicinal interest (Williamson, E., 1997). In South Africa, approximately 3,000 species of plant materials are known as medicines and some 350 species are commonly used as medicinal plants (Van Wyk, B. E., 1997). A large part of the day to day medicine is derived from plants and these are considered as something for the future not of the past. In fact, there is a growing interest in natural remedies and traditional medicines constitute a source of new commercial products (Van Wyk, B. E., 1997).

The use of medicinal plants is receiving great consideration in many countries. There is a world-wide "green" revolution which is mainly driven by the belief that herbal remedies are safer and less damaging to the human body than synthetic drugs (Williamson, E., 1997). For example, in the United States the number of users of traditional medicines has risen (Brevoort, P., 1996). The principal

reasons identified for this were that the consumers are interested in returning to a more natural life style and that the public continues to be dissatisfied with many aspects of modern health care which they perceive as being ineffective, expensive and with unwanted side effects. These factors contribute to the growth of herbal medicine in the United States (Brevoort, P., 1996) and probably also in other parts of the western world. For example, tons (75-80) of *Griffonia simplicifolia* seeds are exported each year to Germany from Ghana and large quantities of various medicinal plants are also exported to France from Senegal (Sofowora, A., 1996). Thus there is a world-wide increased use of plant medicines.

The use of plants for medicines has a long and honorable history, since at one time all drugs were obtained from natural sources. It is also linked to the initial development of the science of pharmacology, which used natural products to elucidate physiological processes and even to define them (Williamson, E., 1997). Hippocrates, known as the father of medicine (in 460 B.C) described herbal recipes, in the seventeenth century, Culpeper, herbalist, prescribed the hundreds of herbs to treat diseases and illness, the use of coca dates to the 16th century (Le Strange, in Sofowora A, 1982). The long historical development of herbal therapeutics in China, for example, has led to a remarkable array of standard or reference herbal formulations, which may be used to address specific clinical situations (Ergil, K. V., 1996). These Chinese herbal formulas are often prepared as water decoctions, but they may also be powdered and/or rendered into pills, pastes and tinctures.

Natural products derived from plants are the basis of many standard drugs used in modern medicine. Often these are so widely used that many laymen, and even some members of the medical profession, are unaware that they are of plant origin. Some examples of such drugs include; digoxin, hyoscine (scopolamine), theophylline, ergometrine, pilocarpine, quinine and atropine (Williamson, E., 1997 and Van Wyk, B. E., 1997).

The users of plant material medicines, however, have to be made aware that such medicines can cause damage and can provoke fatalities. Harmful effects could stem, on the one hand, from the nature of the plant and, on the other hand, from the uncontrolled doses and dosage forms used. In her book entitled "Indigenous healing plants ", (Roberts, M., 1992) advises that one never treat [oneself] or anyone else with herbal medicines without consulting a doctor, untold harm can be done if a dose and the plant are not correctly used and identified.

Many investigations have been done and are still being done on medicinal plants. Laboratories around the world are engaged in the screening of plants for biological activity of therapeutic potential. One major criterion by which, medicinal plants have been selected for such studies or investigations, is the claims made by traditional healers on the therapeutic usefulness of plants (Roberts, M., 1992 and Sofowora, A., 1996). For example, according to Sowofora "the current awareness of AIDS in Africa and development of screening programs for anti-HIV activity in plants should herald the screening of African plants claimed by the traditional practitioners to be used in treating AIDS-related symptoms". Indeed, each traditional healer has knowledge on a number of medicinal plants, which they use to treat their patients (Sofowora, A., 1996). In RSA, for example, there are an estimated 200,000 such indigenous traditional healers and up to 60% of South Africans consult them, usually in addition to using modern bio-medical services (Van Wyk, B. E., 1997). In other words, the traditional healers could also contribute to research on traditional medicinal plants and therefore their collaboration should be sought.

However, the service quality of traditional healers needs improvement. This is well illustrated by the observation of Evans which says that traditional healers
" observe their patient for symptoms and signs but do not perform a pathological examination because they lack the training in such techniques" (Evans, W. C.,

1996). In addition, the traditional healers probably do not have enough, and suitable, tools for the safe preparation and conservation of their medicines.
From the above considerations it is clear that the investigations of medicinal plants are the domain of traditional healers as well as the scientists.

The treatment provided by traditional healers include the use of religious invocations through divination, physical methods as well as the use of plant, animal and other natural materials (Sofowora, A., 1982). Analysis of the type of treatment offered by traditional medicine practitioners could basically provide information useful in the investigation on medicinal plants. Examination of the ways in which preparations are used in traditional medicine has lead to the following general observations (Williamson, E., 1997): (i) Plant remedies used for minor ailments owe their therapeutic benefits to their physicochemical properties, for example, the plant remedies used for fever rely on the presence of antipyretic principles. In such instances, where the clinical symptoms are self-evident, the treatment is clearly directed at alleviating the physical component of the illness. (ii) When plant preparations are used in the treatment of serious chronic illnesses for which the traditional healers usually do not have the necessary technology for accurate diagnosis, the underlying cause may simply be attributed to supernatural intervention. In such cases, the plant is therefore not used so much for its pharmacological properties but for its ritualistic significance (placebo effect) (Williamson, E., 1997). In other words, it must be accepted, up-front, that all plant medicines used by traditional healers do not have therapeutic effects.

Much of current scientific research on traditional plant medicines is focussed on the isolation and evaluation of the biological activity or therapeutic effects of these medicines. The study of the vehicle i.e. dosage form in which the traditional plant medicine is applied is receiving almost no attention.

2.2. ISSUES PERTINENT TO DOSAGE FORMS OF MEDICINAL PLANTS

Few studies have been done in this area, but the dosage forms most used in traditional medicine probably present some problems due to instability, non-standardized doses and vague directions for use and preparation.

Currently, plant medicaments used in traditional medicine are typically administered in the form of liquids (decoctions, tinctures, oil-mixtures), solids (powders, ointments), or gas (steam inhalation) (Evans, W. C., 1996).

According to Meyer, M.C., the liquid dosage forms have the pharmacological advantage of being absorbed directly after administration. However, the liquid and ointment dosage forms present a number of problems (Meyer, M. C., et al., 1984). Firstly, they can be good media for the growth of fungi, moulds and bacteria and, in this respect, decoctions may show significant deterioration within a few hours. Secondly, the extractive liquid preparations are prone to the formation of sediment upon standing. Infusion and decoctions are perhaps the worst offenders in this respect; the longer they stand, the worst they appear, especially if fungi and moulds develop (Burlage, H. M. and Rising, L. W., 1963).

A medicament must however at all times have a good physical, chemical and microbial quality, e.g. the active substance must be present having all the needed qualities at the time it is to be used by the patient (Polderman, J., 1977). In order to overcome the above-cited problems associated with the liquid forms an extemporaneous preparation could be used. But the latter involves considerable increased handling of the materials and, especially if prepared by the patient, preparation is under low hygienic conditions. If the active ingredients could be rendered into powder or dry extract form and supplied in hard gelatin capsule or in tablet dosage form, many of these problems could be remedied.

Another problem directly associated with the dosage forms of traditional medicine is the directions for use of the preparations. These medicines are frequently not supplied with clear unambiguous instructions and/or with a measuring device (e.g. medicine measure) so that they can be administered in strictly regulated doses based on the weight of plant material, volume of solvent and/or the time interval between doses (Evans, W. C., 1996). The preparation is usually issued with only vague instructions (Sofowora, A., 1982), e.g. the patient is advised to take tumblerful, a calabashful, or a teashellful of decoction from time to time (Williamson, E., 1997).

The method of preparation of traditional medicine dosage forms is also critical. Instructions on how to prepare and take the remedy is either given on the label or conveyed orally by the healers. The preparation methods include instruction on the amount of fresh or dry material to be used, the addition of appropriate volumes of solvents and the required additional activities (such as boiling for specified length of time or partial burning until achieving a desired color, etc). One advantage of the additional activities is that it can serve to neutralize certain toxins (Van Wyk, B. E., 1997).

The collective solution to the above issues may be the use of more appropriate unit dose forms of the plant medicine. Unit dose forms, particularly tablets and capsules, are convenient to carry due to their small bulk. The dose is closely controlled and the patient is not concerned with the measurement of the dose, but only with the number he/she must take. Because they are dry these products lend themselves to a high level of production, packing and storage, resulting in a good shelf-life (Shotton, E. and Ridgway, K., 1974).

The issue of making and using tablet unit dose forms of plant materials has thus far not been given appropriate attention. Through literature review, we can note that few investigations have been done in manufacturing of the tablets using plant material. The dosage form from plant materials presented in the pharmacopoeia

are the liquid dosage form viz. tinctures (B.P, 1980 and Martindale, 1977), decoction (USP XVII and Martindale 1977) and tea etc.

2. 3 TABLET DOSAGE FORM

The information provided in this section concern the tablet dosage form in general. It briefly covers the history of the tablet dosage form, the advantages and potential disadvantages of tablets and the challenges encountered in the formulation of the tablets, the physical properties of the tablet dosage form must comply with, viz. tablet size, shape appearance, hardness, friability, disintegration and dissolution profiles.

2.3.1 Introduction

Tablets are defined as unit dosage forms of solid medicaments which is prepared by compaction of powders, crystals, or granulate, with or without excipient, into a single solid body by means of punches in suitable dies (Racz, I., 1989). They belong to the group of oral dosage forms and the latter comprise the majority of drug products currently used in therapeutics (Lieberman, H.A. and Lachman, L., 1989).

Historically, the first dosage form made was a pill. Compressed tablets were introduced into pharmacy in the middle of the nineteenth century and their use has since grown so that they are now one of the most important vehicles for administering drugs (Shotton, E. and Ridgway, K., 1974).

Tablets, as a means of administering medicine, have a high level of acceptability with patients. The prime reasons for this includes easy accurate dosage, good physical and chemical stability, competitive unit production costs and elegant distinctive appearance (Marshall, K. and Rudnic, E. M., 1989). Accurate dosing can be obtained with tablets because the dose is simply defined by the number of tablets that needs to be taken on each occasion. Tablets are relatively stable particularly if they are protected from moisture (Shotton, E. and Ridgway, K.,

1974). In addition, they are conveniently made on a large scale with high degree of consistency. Potential disadvantages with tablets are the irritant effects on the gastro-intestinal mucosa caused by some tablets and the possibility of bio-availability problems caused by the fact that both disintegration (in most cases) and dissolution must take place before the drug contained in the tablet is available for absorption (Marshall, K. and Rudnic, E. M., 1989).

Although a simple tablet might be formed by the mere compaction of active materials in granular form, tablets must, in general, comply with some physical properties such as appropriate hardness, brittleness, rate of disintegration, rate of dissolution, etc. These characteristics are controlled or modified by the incorporation of excipients (Johnson, J. C., 1974). Size, shape and appearance also characterize tablets. The shape of the tablets is obtained by means of the punch faces. The size is determined by the amount of raw material incorporated into the tablet. Usually the appearance of the tablet dosage form does not have a large impact on the success of the particular product. However, good formulation and tablet processing will result in tablets that meet all the minimum elegance criteria. The appearance of tablets is evaluated by its color, texture, shape, size, and coating (when present) and any embossing characteristics. The appearance of the tablets can be an index of stability of the medicine. For example, drug-excipient interactions may, over time, change the appearance of the tablet. All these factors must be considered in the design of the tablet dosage form.

The design of the tablet usually involves a series of compromises on the part of the formulator, because producing the desired properties (for example, resistance to mechanical abrasion or friability; rapid disintegration and/or dissolution, etc) frequently involves competing objectives. In addition, it is important to remember the great paradox in pharmaceutical tabletting, viz. the need to manufacture a compact of sufficient mechanical strength which is able to withstand the rigors of processing and packaging, yet at the same time capable of reproducible breakdown on administration and releasing the drug (Marshall, K. and Rudnic, E.

M., 1989). The correct selection and balance of excipient materials for each active ingredient or combination of ingredients in a tablet formulation aims to achieve the desired response and to overcome some of the problems most frequently encountered in tablet manufacturing.

2.3.2 The formulation of the tablet dosage form

The formulation of tablets involves the consideration of the powders that have to be transformed into unit solid dosage form. The aim and the factors involved in tablet formulation are mentioned in this section to facilitate further understanding of the issues pertaining to the formulation of tablets containing plant material.

The purpose of the formulation of a tablet is to transform the active substance into real medicament. Formulation may be described as a process whereby the formulator ensures that the correct amount of drug is in the right form and is delivered at the proper time, at the proper rate and in the desired location, while having its chemical integrity protected until its use. Therefore, the route of administration is primarily chosen on the basis of the results of pharmacological tests, making allowance, if possible, for it to be convenient for the patient. Economical factors can also influence the choice of dosage form (e.g. cost of coated and uncoated tablets). In addition, the preference of customers, through their acceptability of the manufactured tablet, may sometimes influence tablet formulation (Polderman, J., 1977).

Formulation must also take full account of the intended production process that will be used to make the tablets and the production process has an important influence on the ultimate efficacy of the drug preparation (Devis, A. E., 1966). For instance, in the classical sense of drug formulation, there is a need for a drug product, which is able to provide rapid release, rapid effect and optimal therapy after administration. However, in certain disease states such as diabetes, hypertension, etc., it may be desirable to maintain drug concentration in the blood

for a prolonged period, possibly at a constant and therapeutically optimal level (Racz, I., 1989).

The consideration of several factors is involved in tablet formulation. Firstly, the characteristics of the raw material powder, especially physiochemical properties of the active ingredient, and the inter-relationship of the characteristics can, for instance, influence a range of formulation and processing factors (York, P., 1983). A fuller understanding of these characteristics is likely to lead to a more rational and predictive approach to formulation design and solid dose manufacture. Secondly, the physiological properties of the absorbing organ and other factors involved in pharmaceutical technology and methodology must be considered (Racz, I., 1989).

The formulation of a tablet is directed by the components of the drug dosage form, and these components can be grouped into active ingredient and excipients.

2.3.2.1 Active ingredient

The active ingredient is the compound in the tablet that is responsible for the biological effects. The impact that the active ingredient has in tablet formulation depends on its properties and the amount that is to be incorporated in the tablet.

In the case of the tablets, which contain a low percentage of active ingredients, the tableting properties (e.g. flow and compressibility) of the tablet formulation is primarily dictated by the tableting properties of the excipients. However, if the tablet formula contains a large proportion of active ingredient, as proposed in this study, the choice of excipients may be restricted. The tablet formulas can contain only minimal quantities of excipients and the latter must therefore be those able to perform their functions at relatively low levels. Tablets containing a high percentage of active ingredients may require granulation methods of manufacture in case the excipients, at the low levels at which they are included, cannot perform their desired function in the direct compression method (Lieberman, H. A., et al., 1989). Drugs or active ingredients that form a major proportion of the tablet will

impart many of their characteristics to the final tablet. For example if a drug does not compress easily, a soft tablet will result, while a brittle crystalline drug will yield a brittle tablet (Marshall, K. and Rudnic, E. M., 1989). The characteristics of the active ingredients used in this study are given in the section dealing with the pre-formulation study (section 4.2.2)

The processing treatment that the active ingredients receive depends upon the amount, and the physical and chemical properties of both the active drug substance and the excipients used and the method of tableting to be employed.

Bio-availability considerations are also taken into account in tablet formulation. Before drugs from tablets that are taken orally can effectively pass through the gastro-intestinal wall on their way to producing a systemic effect, they must be in solution i.e. the drug's dissolution is a prerequisite to effective drug absorption (Peck, G. E. et al., 1989). The various processes of tablet making, including the aggregation of the drug into granular particles, and the compaction of powder into a dense compact, are all factors, which mitigate against rapid drug dissolution and absorption in the gastro-intestinal tract. To overcome these problems caused by some of the properties of active ingredients and the tabletting process, the formulator uses the non-active ingredients or excipient(s).

2.3.2.2 Non-active ingredients

Excipients are mostly used in tablet formulation in order to obtain the desirable properties on the final tablet. The most frequently used excipients are listed and their roles in formulation discussed in this section.

Excipients are used in the compounding of the tablets in order to confer desirable properties on the final product. Almost all tablets will require the addition of non-active ingredients or excipients to produce satisfactory drug release, to achieve acceptable physical and chemical properties, and to facilitate their manufacture (Peck, G. E. et al., 1989). Polderman, J. suggests that it is extremely rare to find a

a drug system, which does not involve the use of excipients, because most of the active substances do not possess sufficient tableting properties (e.g. flowability and compressibility) (Polderman, J., 1977).

Although all non-active ingredients or excipients in tablets were previously defined as inert ingredients (Shotton, E. & Ridgway, K., 1974,), nowadays, an excipient is known as " any component, other than the active substances, intentionally added to the formulation of a dosage form" (Pharmacopoeia forum 1995). In fact, the excipients must be physiologically inert and chemically compatible with the active ingredient or with other components of the dosage form, but they can profoundly affect the properties of the final dosage form. For instance, the excipients used during drug compounding may significantly alter the absorption of the active ingredient.

The effect of the active ingredient may be altered by the amount of the non-active ingredient used. In such cases it is necessary to determine the concentration at which this occurs (Racz, I., 1989). Knowledge of the properties of all the additives and how they may affect the properties of the total formulation is thus necessary to provide guidelines in their selection. Many additives may also have secondary functions, which may or may not be beneficial for solid dosage form design, especially of oral dosage form. For example, some fillers or diluents may facilitate tablet dissolution, which is beneficial while others may impair dissolution.

The selection of non-active ingredients or excipients in tablet formulas is based on their possessing properties needed to provide a correct reproducible basic formulation and to produce tablets which are compatible with the manufacturer's specifications and on their acceptable cost (Renoux, R. et al., 1996). The non-active ingredients fall into six major categories: diluents, binders, lubricants, disintegrants, colorants, and sweeteners. These additives are usually classified according to the primary functions that they perform in the tablet. Therefore, the

non-active ingredients are classified based on their functions into two major categories (Peck, G. E. et al., 1989):

- those which affect the compressional characteristics of the tablet such as diluents, binders and adhesives, lubricants, anti-adherents, and glidants and
- those which affect the bio-pharmaceutical, chemical and physical stability and marketing considerations of tablets: disintegrants, colorants, flavorants and sweeteners (Peck, G. E. et al.,1989).

The common excipients most used in tablet formulation are:

2.3.2.2.1 Fillers or diluents

An increasing number of drugs are used in very low dosage. In order to produce tablets having a reasonable size, it is necessary to dilute such drugs with an inert material. Low cost and good tableting qualities are the primary criteria for the selection of diluents (Marshall, K. and Rudnic, E. M., 1989). Where small dosage levels of drugs are involved, a high level of diluent or filler is necessary. However, if the content of drug is large, little or no diluent will be required.

Because of their general ability to enhance the products' mechanical strength as well as their lack of toxicity, acceptable taste, and reasonable solubility profiles, carbohydrates (e.g. lactose and methylcellulose), are the most-widely used diluents (Peck et al., 1989). Some of the most important products are based on α-lactose (Marshall, K. and Rudnic, E. M., 1989).

2.3.2.2.2 Binders or adhesives

Binders and adhesives are added to tablet formulations in order to add cohesiveness to powders and to provide the necessary bonding properties to the powdered mixture, which under applied pressure, must form a cohesive mass or compact solid referred to as a tablet. The pharmaceutical binders are the major

class of excipients that are used to improve tablet formulation. In addition, they are added in the formulation to aid in the lubrication of the formulation. They do so by decreasing the adhesion of the formulation to the processing equipment and improving the flowability of the formulation thereby reducing the variability in weight and uniformity of the tablet dosage forms (Symecko, C. W. and Rhodes, C.T., 1995).

The primary criterion for choosing a binder is its compatibility with the other tablet components. Secondly, it must impart sufficient cohesion to the powders to allow normal processing (sizing, compression and packing), yet allow the tablet to disintegrate and the drug to dissolve after ingestion, releasing the active ingredients for absorption (Peck, G. E. et al., 1989).

2.3.2.2.3 Disintegrants

The disintegrating agents are the excipients added to the formulation in order to achieve a rapid disintegration of the tablet. The properties of the disintegrant must facilitate the break up of the tablet after administration. For example, tablets designed for rapid release of the drugs need to be so formulated that the effect of the drug is maximized. In other words, disintegration of such a tablet must allow the promotion of a rapid dissolution and subsequent absorption (Banker G. S., 1989), and the tablets that are to be swallowed must break up in the stomach or intestine in order to release the medicament, followed by absorption (Shotton E. and Ridgway, K., 1989).

Disintegrating agents can act by swelling, by particle deformations, or by electric repulsive forces. In the case where the surface of the active ingredient is hydrophobic, this may be rendered hydrophilic by the use of disintegrating agents such as surfactants (Racz, I, 1989). The characteristics (such as particle size and molecular structure) of the disintegrants, also influence the disintegration mechanisms of tablets (Marshall, K. and Rudnic, E. M., 1989).

Many disintegrants have also been shown to possess effective binder or adhesive properties. Starches are the most common disintegrating agents in use today. The activity of starches, as disintegrating agents, is attributed to intermolecular hydrogen bonding, which is formed during compression and suddenly released in the presence of excess moisture (Ingram, J. T. and Lowenthal, W., 1989). The starches show a great affinity for water through capillary action, resulting in the expansion and subsequent disintegration of the compressed tablets (Peck, G. E. et al., 1989). The derivatives of cellulose such as microcrystalline cellulose are also known to possess disintegrant properties and are commonly added in formulation (Blair, T. C. et al., 1990). Other disintegrants used are alginates, gums, surfactants, polyvinylpyrolidine (P.V.P), etc

2.3.2.2.4 Lubricants

Many substances adhere to the punch faces and the die wall during compression. The appearance of the tablet is spoiled and in addition it is very difficult in such cases to eject the tablet from the die. In order to overcome these difficulties lubricants are mixed with the powder. The primary function of the lubricant is to reduce the friction between the die wall and the tablet edge as the tablet is being ejected (Peck, G.E et al., 1989). On compression, the lubricant particles are rubbed across the punch faces and the die wall and prevent the powder from sticking (Shotton E. and Rudnic, K., 1974).

The lubricants possess anti-adherent or glidant properties. The glidants are added to the formulation in order to improve the flow properties of the materials to be fed to the die and sometimes to aid particle rearrangements within the die during the early stages of compression. Examples of such lubricants are starch and talc. The anti-adherents are used in the formulation when materials are found to have strong adhesive properties toward the metal of the punches and dies (Marshall, K. and Rudnic, E. M., 1989).

The disadvantage of adding lubricants to a granulation is that they can form a coat around the individual particles (granules) which remain more or less intact during compression. This coating may also extend to the tablet surface. The best lubricants are however hydrophobic (e.g. magnesium stearate) and in this case, then, the presence of the lubricant coating may cause an increase in disintegration time which can affect the dissolution rate (Peck, G. E. et al., 1989) of the tablet. The most common approach to overcome these problems is to substantially limit the length of time of lubricant blending, often reducing it to as little as 2 to 5 minutes when alkaline stearate lubricant is used. Another option is to abandon the use of the alkaline stearate lubricant (example magnesium stearate) and to use hydrogenated vegetable oil (Shangraw, R. F. et al., 1989). In such cases, however, a high concentration of lubricant is necessary because these agents are not such good lubricants.

2.3.2.2.5 Adsorbent

An adsorbent may be necessary where the formulations contain a hygroscopic ingredient, especially when the absorption of moisture leads to a cohesive powder that does not feed properly into the tablet press. Kaolin, bentonite, and fillers (e.g. starch) possess pronounced adsorbent qualities. However, in general they reduce the tablet's hardness and may be abrasive (Marshall, K. and Rudnic, E. M., 1989).

The above discussion focussed on the constituents of tablets. Tablet formulation however also goes hand in hand and interacts with the method used in the tabletting process; whether direct or compression after granulation. These methods of tableting are therefore considered below.

2.3.3 Direct compression

In the present study direct compression was proposed as the method to use in the tabletting process because of its advantages. The potential requirements and challenges of this method are therefore now discussed.

The term direct compression was long used to define the process through which single crystalline compounds are manipulated into a compact tablet without the addition of other substances (Renoux, R. et al., 1996). Nowadays the term is used to define the process by which tablets are compressed directly from powder blends of the active ingredient and excipients. In this process of tablet manufacturing there is no treatment of the powder blends by wet or dry granulation procedures (Shangraw, R. F., 1989). Except for spray-dried lactose, all the direct compression excipients currently in use were developed after 1962. By the beginning of the 1980s, the use of direct compression became more wide-spread due to the availability of machinery and direct compressible tablet vehicles, especially because the latter possessed both good fluidity and compressibility properties (Shangraw, R. F., 1989). The excipients most used are, for example, Avicel®, an effective dry binder/filler; Starch 1500®, a partially pre-gelatinized starch and a number of directly compressible sugars, sorbitols and mannitol products.

Direct compression has particular value because of the industrial manufacturing time it can save. While the cost of direct compressible raw material may be higher, the labor time, and energy cost saving realized by eliminating granulation, drying, and sizing of raw material may more than justify the increased material cost (Lieberman, H. A. et al., 1982).

Direct compression provides another significant advantage in terms of tablet quality, viz. its procedures do not involve moisture and heat, which are inherent in most of the wet granulation procedures. Furthermore, the use of direct compression also avoids the high compression pressures that are involved when producing tablets by slugging or roll compaction. The various steps encountered in the process of granulation and which can lead to innumerable tableting problems, are minimized when using the direct compression method.

Shangraw suggests that one of the least recognized advantages of direct compression is probably that of the optimization of tablet disintegration, i.e. the process in which each primary drug particle is liberated from the tablet mass and becomes available for dissolution (Shangraw, R. F., 1989). When tablets are made using the granulation (followed by compression) process, they disintegrate into agglomerates of small drug particles. While the individual small drug particles have a large surface area, the surface area of the agglomerate is reduced. Since increased surface area results in rapid drug dissolution, dissolution from the agglomerates is therefore slower. Also, in tablets made by direct compression each of the disintegrating agents are more likely to perform their functions optimally in the small primary particles compared to their situation in the agglomerates. If properly formulated the tablet made by direct compression should disintegrate rapidly to the primary particle states.

However, this technique of direct compression is problematic when the formulation contains a large amount of poorly compressible drugs (Renoux, R. et al., 1996). Few chemicals possess the flow, cohesion, and lubricating properties under pressure to make a solid compact possible and their number diminishes further if one considers only materials with therapeutic effects (Peck, G. E, et al., 1989). Such cases are usually encountered with micronized drugs, which lead to an increasing inter-particulate friction and decreasing powder fluidity, resulting in poor compressibility. Also, if and when compacts are formed from poorly compressible substances, a large compression force is required. This then result in tablets having a lengthy disintegration time, delayed drug release and possibly causing problems of dissolution of the active drugs.

Direct compression is, therefore, the method of choice in tablet manufacturing, when the process can be employed to produce a high quality finished product (Sangekar, S. A., 1972). However, direct compression should not be conceived as a simple modification of the granulation process for making tablets. It requires a

flow properties of the powder blends and the good effects of the formulation on the process of compression of the tablet (Herbert A., Lieberman et al., 1989).

2.3.4 Granulation

When direct compression is not possible, granulation is advised. Granulation is used in order to densify the fine powders into granules that have a better flowability and better compression capacity (Hervieu, H. and Dehont, F., 1994). In addition, the granulation method aims to prepare the uniform mixture and to improve the appearance of the tablet (Bandelin, F. J., 1989). Both dry granulation and wet granulation should be used, but the dry granulation process is preferable in formulation design when the wet granulation process may modify the original properties of the raw materials. Where the active drug or other formulation ingredients have inherent binding capacity, and particularly for moisture sensitive drugs, a dry granulation or pre-compression process is advised (Jenkins, W. A. and Osborn, K. R., 1993).

The granules may be considered as new raw material in terms of the density and particle size of the resulting granules. For example, Bolhuis G. K and Zuurman K., 1995) have shown that the effect of granulation of α-lactose and β-lactose by wet granulation improved the flow properties but decreased the compactibility of the powder. Riepma, K. A. et al. also found differences between primary properties, viz. granule size, and compactibility, of α-lactose monohydrate and roller dried β-lactose powder and granules (Riepma, K. A. et al., 1993).

The use of the slugging or double compression is suggested when granulation is needed for material which must not come into contact with water (Little, A., 1963). If rapid disintegration is required, slugging could provide the answer (Little, A., 1963). Slugging is a process used to make material more suitable for normal processing on a machine, in other words, to improve its flow and binding properties. The process consists of making as large and hard a tablet as possible

properties. The process consists of making as large and hard a tablet as possible and subsequently breaking it into granules. The latter are compressed finally into tablet.

2.3.5 Bonding mechanisms

In tablet processing, the particles of the powdered mixture bond with each other and form a unique solid body. The criteria for success of this process, are adequate bonding and no fracture (Hiestand, N. E., 1977). The factors involved are basically associated with the chemical structure and physical structure (e.g. amorphous and crystalline properties) of the particles of powder. When the powdered mixture is compressed into the die between the upper and lower punches, some events such as repacking of the powder particles occur. This repacking is an initial step, and is followed by a significant reduction in the volume of the material within the die (Pather, S. I., 1989).

To arrive at the solid body, consolidation of the powder mass occurs. Two primary consolidation mechanisms in pharmaceutical powders are plastic deformation and brittle fracture (Khossravi, D., 1999). The plastic deformation process entails the deformation of individual particles under high pressure, with subsequent flow and creep of the material under pressure to form a solid compact. Whereas in the brittle fraction process, the individual particles fracture into smaller particles and then form a compact within smaller volumes under the higher applied pressures.

The compression force to apply to produce the bonding of the particles of powder has an optimum range, which depends on the physicochemical properties of the powder. As the pressure on the particles or crystals increase in the die, the particles rearrange closer together to fill the inter-particle void spaces and the individual particles begin to deform elastically. This deformation continues until the elastic limit of the material is reached and at this stage the material begins to deform plastically, or fracture. Thereafter permanent deformation takes place by formation of the inter-particle bonds. In addition, the bonding mechanism is also a

result of the interlocking or non-uniformity of irregular shaped particles, and therefore depends on the structure of the surface of the particles, especially on the ability of particles to fit together (Symecko, C. W. and Rhodes, C. T., 1995). When most of the particles have irregular shapes, the area of contact between the particles may be limited. An increase in pressure exerted by the tabletting press tremendously increases the pressure at these points of contact. The particles may respond to this pressure by deforming elastically. In such cases, if the pressure is suddenly removed from the elastically deformed particles, the deformation is reversed and the particles return to their original shape. It is therefore necessary to exceed the elastic limit before bonds are formed in the tablet and the number of bonds formed are proportional to amount of pressure exerted by the punches (Lum, S. K. et al., 1988).

The effect of the punch velocity on compression also has an influence on the bonding process. For example, Achantan, A. S. et al. and Yang, L. et al. have determined the influence of punch velocity on compression, using polyethylene oxide powder (Achantan, A. S. et al., 1997) and (Yang, L. et al.,1996). They have shown that for the material that consolidates plastically, the extent of plastic deformation would be reduced if the time during which the material is held under load is shortened with an increase in punch velocity.

The above discussion on the factors involved in tablet making suggests that sufficient information on the ingredient(s) which the formulator uses, especially when the active ingredient has to be used for the first time, must be available in order to obtain a successful tablet. This falls in the realm of preformulation.

2.4 PREFORMULATION

2.4.1 Introduction

Preformulation is defined as a study that precedes product development (Racz, I., 1989). Prior to the development of the dosage forms such as tablets, capsules

etc, with a new drug candidate, it is essential that the physical and chemical properties of drugs are determined. The characterization of the physical and chemical properties of the raw material during preformulation study provides the important information that is required for the manufacturing method, as well as for the stability, the bio-pharmaceutical function and correct use of the final medicine (Nicolas et al., 1999). Thus, the results of the preformulation study may dictate many of the subsequent events and possible approaches in formulation development (Wells, J. I., 1988).

According to Wadke, D. A., preformulation aims to generate information that is useful for the formulator to develop the stable and bio-available dosage forms. This process is considered as a step and labour in that potential problems may be identified and solved at this stage (Wadke D. A., 1989). Carstensen, J. T. gives an example of the incompatibility exhibited by the drugs against the excipients. He adds that through a preformulation study, disasters could be prevented in advance (Carstensen, J. T., 1989). The preformulation study may also provide a rational basis for particular tablet design, such as one that has rapid disintegration and dissolution (Peck, G. E, et al., 1989).
The aspects that form the focus of the preformulation study are discussed below.

2.4.2 Organoleptic properties

Organoleptic properties refer the appearance, odour and taste of the substance. The colour, odour and taste of the new drug substance are determined in the preformulation study. The characterization of these properties is important because the colour or odour may constitute an indication of stability of some substances and/or they may influence the formulation (e.g. when they need to be masked, etc). The colour and odour may be described using descriptive terminology (Lieberman, H. A., 1989).

When the odour and colour is not required in the formulation, they should be suppressed in the tablet by using appropriate flavorants and or by coating the final

dosage form in order to promote the acceptability of the latter by the patient or allow for differentiation between drugs.

2.4.3 Particle size, shape, and surface area

Determination of shape and size of particles is very important in tablet formulation because several chemical and physical properties of the raw materials depend on the shape and particle size distribution. The shape and size of particles determine, in some instance, the pharmaceutical properties of the final drug substance (Lieberman, H. A. et al., 1989). The size of particles plays a big role in the homogeneity of the final dosage form. For an example, when there is a large difference between the size of active components and excipients, mutual demixing effects can occur making thorough mixing difficult or difficult to maintain during the subsequent processing step. Randomly distributed mixtures can only be achieved when the particles meet certain requirements for size, density, and form (Cartensen, J. T., 1993) and (Polderman, J., 1977). If the particles deviate significantly in particle size, they do not form homogeneous mixtures or these separate quickly; usually the smaller particles shift to a lower layer. As related by Marshall, K., The characteristics, e.g. disintegration and dissolution rate, of the final tablets also depend on the size and the shape of raw material. For example, the starch having grains of relatively large particle sizes is a more efficient disintegrant than that having finer particles (Marshall, K. et al., 1989).

The studies on particle size, shape, and surface area of the powder may indicate any flow problems that are likely to be encountered during further formulation and tablet processing. For instance, spherical particles flow well and thus enable good mixing, but they also de-mix easily. When particles have many sharp angles and projections, they cause poor flow, they may interlock and thus decrease the de-mixing potential. The physical interlocking of non-uniform irregularly shaped particles are also involved in bonding mechanisms which depend strictly on the structure of the surface of the particles and their ability to fit together (Symecko, C. W. et al., 1995). Therefore, both size and shape influence the flow, mixing

C. W. et al., 1995). Therefore, both size and shape influence the flow, mixing efficiency and compressibility of powders or granules (Lieberman, H. A. et al., 1989).

The influence which the shape and size of the particles has may be more completely understood if the mechanical properties (e.g. flowability and compressibility) of pharmaceutical powders or systems are considered. This provides the most systematic and rational approach to the formulation design of tablets, because the mechanical properties of the powder determine the success of the tablet processing (Hiestand, N. E., 1997).

2.4.4 Flowability

Flowability is a measure to determine how a solid material flows. When a powder needs to be handled, the assessment of its flow properties is of primary importance to the formulator. The particle size is one of the most important factors, which can affect the flow properties of powders (Wells, J. I., 1988). There is an optimum range of particle size distribution in which the particles have good flowability. For example, when powders contain large particles they do not flow well, however, when materials become too fine, undesirable properties such as electrostatic effects and other surface properties cause undue stickiness and lack of flowability. When the particles are below approximately 10μm, the powder becomes increasingly cohesive and tends to form agglomerates (Shotton, E and Ridgway, K., 1974). In addition, the flowability of powder may also be affected by density, shape of particles, electrostatic charge, and moisture content. Concerning the shape of particles, Carstensen, J. T. et al. suggested that the particles having a near spherical shape possess the best flowability (Carstensen, J. T., et al., 1977).

Powder or granulation that must be compressed must have a good flow to ensure efficient mixing and acceptable weight uniformity for the compressed tablet.

Whether the wet granulation or direct compression method is used, in the tablet operation the filling of the die is a volumetric process and the ability of powder to flow freely is very important. Thus, if a drug is identified to be poorly compressible at the preformulation stage, selection of the appropriate excipients is important in order to solve this problem. In some cases, drug powders may be pre-compressed or granulated for improving their flow properties (Wadke D. et al., 1989).

2.4.5 Density

In tablet preformulation the measurement of densities, i.e. bulk and tapped densities, constitute one of the means used to evaluate how powder flows. This is done by comparing the loose and tapped volumes of packed powder and the rate of packing down. Tapped density is a quick way to evaluate the flow properties of powders because there is relationship between the degree of the compaction and flow properties (Guerin, E. et al, 1999).

The results of a density study can indicate, on the one hand, how a powder is likely to behave when it is compressed. The substances with low bulk densities or which have a large difference between bulk and tapped density do not flow well and form a poor compact because of the incomplete contact between the particles. On the other hand, the indication of voidage, i.e. the volume of the air spaces between the particles, provided by a density study is an important indicator of the wettability and solubility of the powder and/ or the final tablet.

2.4.6 Solubility

The oral solid dosage forms administered for a systemic activity must dissolve in the gastro-intestinal fluids prior to their absorption. Thus, the poor solubility of drugs is generally an undesirable physical property, which may increase the drug's ability to irritate the gastro-intestinal tract because of the prolonged contact time with the mucosa (Alsaidam, S. M. et al., 1998).

When a compound is poorly soluble, the preformulation studies may include investigation of methods to improve solubilisation, for example the use of co-solvents such as alcohol or glycerol. The solubility studies may indicate that the drug could present bio-availability problems. For example, often drugs that have limited solubility (less10%), in the gastro-intestinal tract fluids, exhibit poor absorption. In tablet preformulation, the analysis of the solubility of the drug is important, because the choice of filler is often based on the solubility of the active drugs; for example, a soluble filler is preferable when active drug is insoluble and vice versa.

2.4.7 Hygroscopicity

A substance, which absorbs sufficient moisture from the atmosphere, can dissolve itself in that moisture. This requires that the saturated solution formed has a lower vapor pressure than the atmosphere. Materials unaffected by relative humidity (water available in the surrounding atmosphere) are termed non-hygroscopic, whereas the raw materials that are in dynamic equilibrium with water from the atmosphere are defined as hygroscopic (Wells, J. I., 1988). When considering hygroscopicity, two aspects to the concept are important, viz. the potential for moisture uptake and the rate with which the moisture is taken up (Carstensen, J. T., 1993).

The hygroscopicity of drug substances has an important role in tablet preformulation because, most often, the drugs are processed in a variety of environments, where the air may be more or less humid and where the humid day and a dry day are distinguished (Carstensen, J. T., 1993). The changes in the moisture level of hygroscopic material greatly influence many important parameters, including chemical stability and compactibility.

Moreover, many drug substances and excipients, particularly water soluble compounds, exhibit a tendency to absorb moisture. The presence and distribution of water depend on the chemical properties of the particulate material, its physical

properties such as particle size and porosity, and the ambient relative humidity. The latter determines the equilibrium moisture content and this may then influence the flow and compression characteristics of powders and the hardness of the final tablets. For example, the effect of moisture on the consolidation of the Emcompress® (dicalcium phosphate dihydrate) tablet has been examined and it was shown that increasing the moisture content of Emcompress® resulted in an increase in apparent tablet density, both under pressure during compression and in the final tablet after ejection.

The presence of water may exert a significant effect on the elastic properties of raw material and hence on quality of the tablet. Thus, where moisture can affect drug stability, the initial moisture level, as well as the tendency of the material to retain or pick up moisture, must be considered (Peck, G. E. et al., 1989). This is particularly applicable on dry aqueous extracts since most of them are known to be hygroscopic. If moisture is not a problem for drug stability, a certain level of moisture may be beneficial and assist consolidation by promoting inter-particulate lubrication and by increasing the plasticity of the brittle particles.

Thus, by careful control of humidity conditions during the compression process tablet quality may be optimized (Armstrong, N. A. et al., 1988). The drugs may be (and often are) moisture sensitive e.g. effervescent drugs, and dry extracts of plant materials, so that tablets of such materials need manufacturing under very low humidity conditions, and the final products must be protected against moisture.

2.5 *DODONAEA ANGUSTIFOLIA*

2.5.1 Description

D. angustifolia, also commonly called Sand Olive in English, Tsekatseki in Tswana, Mutuzwe in Zulu, Mkapwani in Swahili (Roberts, M., 1992), is a shrub

of about five meters in height, with pale green and shiny leaves having an elliptic form. The young parts of the leaf bases and inflorescences are sometimes slightly hairy. It has inconspicuous yellow-green flowers and bears small winged paper fruits (Van Wyk, B.E., 1997). The sand olive is often a multi-stemmed shrub planted as a hedge or windbreak.

2.5.2 Habitat

Dodonaea is a plant readily found in many types of areas. It grows well in areas with difficult climates, hot summers, bitterly cold winters or dry arid conditions and also grows amazingly quickly in open vegetation, from desert to low shrubby forest, on dry soil and often on the rocks of steep slopes (Roberts, M., 1992 and Palmer, E. et al., 1972).

2.5.3 Distribution

The *Dodonaea* is in the family of Sapindaceae (Van Wyk, B. E., 1997) and includes several species, the most current are the following:

- *Dodonaea viscosa var. Angustifolia,* a pantropical coastal species which is characterized by its broad leaves;
- *Dodoneaa angustifolia,* an inland species occuring throughout the tropics and subtropics and which is characterized by its narrow leaves;
- *Dodonaea elaeagonoides,* restricted to Florida and a part of Antilles;
- *Dodonaea polyandra*, restricted to Small Papua New Guinea, and
- *Dodonaea madagascariensis,* which is endemic to Madagascar (Leenhouts, P. W., 1983)

Dodonaea angustifolia and *Dodonaea viscosa. var. angustifolia* used in this study grows in the Orient , Indian sub-continent, in tropical Africa in the followed countries: Ghana, Congo Republic, Congo, Sudan, Egypt, Ethiopia, Uganda, Kenya, Tanzania, Mozambique, Malawi, Zimbabwe, Angola, and the Republic of South Africa (Leenhourts P.W., 1983). In South Africa, *D. angustifolia* is found in

the Southern Western Cape to Eastern Cape, Transvaal, Natal Zululand and the Orange Free State (Palmer, E. et al., 1972). Other members of the species *Dodonaea angustifolia* include *D. thunbergiana Radlk* and *D. thunbergiana Radlk. var.linearis sond.* Wherever *Dodonaea* is known it is commonly used as a medicinal plant.

2.5.4 Medicinal use and preparation

The Sand Olive has been used medicinally for many years for a great number of ailments and diseases. *Dodonaea* is best known for treatment of stomach disorders and fever (Roberts, M., 1992). Brewed decoction helps to bring down fever and a large quantity can be made and used to ease discomfort of heat rash, heat stroke and inflammation. Decoction is a liquid prepared by placing the plant in cold water, bringing it to boil, simmering for about 15 minutes or longer up to 1 hour and then allowing the mixture to stand for a further 15 minutes, usually the aqueous extract is the decanted or filtered part (Sowofora, A., 1982). In Ethiopia, *D. angustifolia* is among the medicinal plants assessed for antiviral activity against human immuno-deficiency HIV (Asres, K. et al., 2001).

In South Africa, *Dodonaea* is used in remedies for many diseases, particularly for stomach disorders and as febrifuge (Roberts, M., 1992). In Madagascar, the leaves are remedies for fever and sore throat. The preparation is made from fresh leaves and twigs, which are boiled in water, steeped and filtered.

2.5.5 Active ingredients

The *Dodonaea* leaf is said to contain alkaloids, glucosides, resins, flavonoids, tannin materials as well as saponins (Watt, J. M. et al., 1962). Generally, these compounds are all soluble in water. The plant also contains dodonic acid, hautriwaic acid (Van Wyk, B. E. et al., 1997). In 1982, Sachdev K. et al., isolated structurally related diterpenoids from several *Dodonaea* species. This included the following seven flavonoids:

- 5-hydroxy-3,6,7,4'-tetramethoxyflavone,

- 5,7,4'-trihydroxy-3,6-dimethoxyflavone,
- pinocembrin(5,7-dihydroxyflavone),
- santin(5,7-dihydroxy-3,6,4'-tetramethoxyflavone),
- aliarin (5,,7,4'-trihydroxy-3'(3-hydroxy-methylbutyl)-3,6-dimethoxyflavone),
- dulentin(5,4'-dihydroxy-3,6,7-trimethoxylavone,
- isorhamnentin 3-rhamnosylgalactoside

plus a new previously undiscovered one (5,7dihydroxy-3'(hydroxymethylbuthyl),3,6,4'tetramethoxy-flavone). The solubility of these compounds in aqueous medium is dependent on the presence of free hydroxyl group. (Sachdev, K. et al., 1983)

2.5.6 Pharmacological effects

Apart from anecdotal evidence very little is known about the pharmacological effects of *Dodonaea*. The antipyretic and analgesic properties of *Dodonaea* were investigated in a recent study by Amabeoku, G. et al. (2001), but the molecular mechanism responsible for this activity has not yet been identified. It is assumed that each of the principal compounds cited in section 2.5.5, especially the flavonoids, may potentially contribute to this activity or other activities of this plant. The flavonoids have several proven medicinal properties, such as their ability to strengthen veins and to decrease their permeability, they also have anti-inflammatory, anti-allergic and antibacterial effects (Van Wyk, B. E., 1997).

In traditional medicine, the decoction from *Dodonaea* is made from fresh leaves and twigs, which are boiled in water, steeped and filtered and a patient takes 1 cup, i.e. approximately 180ml, of decoction three times a day.

D. angustifolia is thus a medicinal plant well known and frequently used in various areas, but the dosage form in which it is used may suffer from most of the same problems (cited in section 2.2), associated with liquid dosage forms in general (Burlage, H. et al., 1963) and (Podelman, J., 1977). A unit solid dosage form could

overcome some of these problems. A unit solid dosage form may also be most valuable when the further verification of its pharmacological effects in vivo is attempted.

The tablet dosage form of *D. angustifolia* is proposed for this study. The tablet dosage form of a medicinal plant such as *D. angustifolia* should provide the same advantages of tablet dosage form associated to a greater precision of dosage, stability of active drug, an ability to withstand extended storage, and convenience of administration.

But, the fact that the tablets of *D. angustifolia* must contain the equivalent amount of active ingredient(s) as found in a number of leaves used in preparation of the decoction leads to two main problems which must be considered. Firstly, the tablet will contain a high amount of plant material, secondly, the different forms of plant raw material (viz. powder form dry leaves or any extract of the leaves) may have different properties, and both of these issues must be considered in tablet formulation.

CHAPTER 3
WORK PLAN

3.1 OBJECTIVES AND HYPOTHESES

The primary objective of this study was to produce a drug dosage form in which, the active ingredients of the plant, *D. angustifolia*, could be presented. The selected dosage form had to offer the best convenience for the patient and a greater stability of the active ingredient compared to the currently used dosage form (decoction). The tablet dosage form was proposed as a solution. Consequently, the secondary objective of this study was to formulate and manufacture a tablet dosage form containing the same amount of active ingredient as found in the single dose decoction prepared from *D. angustifolia* plant material. The third objective was to assess the suitability of using dried leaf powder vs. dry aqueous extract of the leaves of *D. angustifolia* in tablet formulation and manufacture.

It was hypothesized that tablets containing a large amount of *D. angustifolia* plant material (80% of plant material per tablet), but still complying with all the criteria set for a tablet dosage form (i.e. suitable hardness, friability, disintegration and dissolution) could be formulated and manufactured by the direct compression method. It was also hypothesized that the raw plant material obtained by direct powdering of dried leaves and by extraction of the leaves will have different properties which will require different formulation strategies.

3.2 STUDY APPROACH

In order to satisfy the above objectives the following activities had to be undertaken: the preparation of plant material, a preformulation study, the selection of excipients, the formulation of the tablet, the manufacturing of the tablet and the evaluation of the manufactured tablets.

3.2 .1 Preparation of plant material

The plant material, dry powder and dry extract were prepared from the leaves of *D. angustifolia.* The leaves were to be collected, dried at low temperature, ground and sieved and the dry extract prepared from aqueous decoction. Distilled water was to be used as solvent because a majority of active substances of the plant, for example alkaloids, flavonoids, tannins material, glucosides, etc were known to be soluble in water (Watt, J. M. and Breyer-Brardwijk, M.G., 1962).

3.2.2 The preformulation study

The role played by the characteristics of raw material had to be considered. Thus in the preformulation study, the physicochemical properties of the dry powder and dry extracts (raw material) viz. the density, flowability, shape and size of the particles, and moisture content were to be determined. Based on these determinations the suitability of the direct dry powder and dry extract obtained from the leaves of *D. angustifolia* for tablet formulation was to be assessed.

3.2.3 The selection of excipients

To manufacture tablets having good physical properties, which in turn basically is dependent on the properties of ingredients used in the tablet formulation, suitable excipients had to be selected. The selection of these excipients was to be directed by the results obtained in the preformulation study of the raw material. The selection would also focus on those excipients, which could perform their functions at low concentrations and were directly compressible.

3.2.4 The formulation of the tablet

The formula of the tablet had to contain *D. angustifolia* plant material, in the same amount of active ingredient equivalent as found in the decoction of *D. angustifolia*. This equivalent dose of active substance first had to be estimated. To determine the formula which allowed the incorporation of a maximum proportion of the active substance in the tablet, the approach to be followed was to start with a minimum number of excipients and a high proportion of active ingredients. Depending on

the performance of the product, the formulations were to be progressively adjusted (i.e. active substance decreased and excipients increased or changed) to obtain the desired end product.

3.2.5 The manufacture of the tablets (tabletting process)

To manufacture the tablets of the *D. angustifolia* plant material, it was decided to use the direct compression method because of its advantages. To arrive at the final compression conditions (i.e. compression force and tablet mass) preliminary evaluations of hardness and mass uniformity of the manufactured tablet was to be used as a guide.

3.2.6 The evaluation of the tablet

Finally, the manufactured tablets were to be evaluated for their properties, e.g. hardness, friability, disintegration and dissolution rate. The tablets manufactured from dry powder and the tablets manufactured using the dry extracts were to be compared based on these parameters.

CHAPTER 4

PREPARATION AND CHARACTERIZATION OF POWDER OF PLANT MATERIAL (PREFORMULATION STUDY)

In this chapter the materials, equipment and methods used to prepare and characterize the powder of *D. angustifolia*, as well as the results obtained, are discussed.

4.1 EQUIPMENT AND MATERIALS

The equipment and materials listed below were used in the preparation of the plant material, the preformulation study, and the evaluation of the tablets (chapter 5).

4.1.1 Equipment

Oven

Model Memmert 854 Schwabach, West Germany

Coffee Grinder

Model Kenwood Cg 100, Kenwood Ltd, Great Britain

Centrifuge

Model Heraeus Labofuge Ae, Heraeus Sepatech Gmgh, West Germany

-85°C Freezer

Lozone Cfc Freezer Model U855360, New Brunswick Scientific, USA

Savant Freeze Drying System consisting of

Refrigerated vapor Trap, Model SAVANT RVT4104, SAVANT, Instruments, Inc., Farmingole, NY, USA

Freeze drying chamber, Model FDC 906, and Digital Vacuum Gauge, Model DVG 50, Vacuumbrand GMBH + CO,West Germany

Freeze-Dryer

Model Virtis Freeze Mobile 72SL, The Virtis Company Gardner, New York, USA

Light Microscope

Nikon Monocular Model Sc, Japan

Stage Micrometer

Graticules Ltd, Tonibridge Kent, England.

Eyepiece Micrometer

Olympus, Japan.

Filtration System (SUPELCO) connected to

Vacuum pump, Medi- Pump

Model 1132-2, Thomas Industries, Inc., USA

The Lp16 Infrared Dryer

Mettler Toledo, Type PJ 300MB, Mettler-Toledo GmbH, Greifensee, Switzerland

Test Sieve Shaker

Endecott sieve shaker, E.F.L. 1MK11, Endecotts (test sieve) Ltd, London, England

Digital Hygrometer

E.T.I Ltd, Worthing, Sussex

Balance Scaltec SPB42

Model SPB71, Scattec Instruments, Heiligenstadt, Germany

4.1.2 Materials

The following raw materials were used in the formulation of the tablets.

Leaves of *D. angustifolia*

Starch1500®

Lot 510016, Colorcon LTD, England

α-Lactose monohydrate

UniLab® Lot 386 20 00, Saarchem Holpro Analytic (Pty) Ltd, Krugersdorp, South Africa

Tablettose®

Leochem (Pty) Ltd, Germany.

Magnesium stearate

Lot 412 39 00, UniLab® Saarchem Holpro Analytic (Pty) Ltd Krugersdorp, South Africa

4.2 PREPARATION OF THE PLANT MATERIAL

The plant materials from the leaves of *D. angustifolia* were prepared in the following manner.

4.2.1 The collection of the leaves and preparation of the powder

Dodonaea grows in different locations in South Africa, but the plant material used in this study was collected at Kirstenbosch National Botanical Garden (site

House12 NB) in Cape Town and Karoobot Garden in Worcester, both in the Western Province. The fresh leaves were collected in two different seasons: summer and winter of 2000, and from two species of Dodonaea, one having narrow leaves (collection number 198,114) and the other broad leaves (collection number 13 and number 104).

To prepare the dried leaf powder the collected leaves were first dried at a low temperature (30^0C) in the oven over 3 days. Thereafter the dry leaves were ground with a coffee grinder to obtain a fine powder. The latter served, firstly, as raw material in the tabletting processes and, secondly, as the raw material to prepare the dry extract. The dry leaf powder was further sieved to obtain a fine powder with more or less homogeneous particles. The powder to be used in the preparation of the extract was passed through a 850μm sieve. The use of this sieve provided a maximum amount of powder from the leaves, and, in addition, provided a sufficient surface area for the dissolution of the powder. To obtain the fine powder needed for tablet compression the plant material was passed through a 355μm sieve.

4.2.2 Preparation of the dry extract

Both *D. angustifolia* having narrow leaves (collection number 13, 114 in register) and *D. angustifolia* with broad leaves (collection number 198 and number 104 in register), were used in the preparation of the dry extract. Decoctions from powder were prepared by mixing the powder from the leaves of *D. angustifolia* with boiling water in the proportion of 1/40 (weight/volume), or 5g/200ml of boiling water, for a total contact time of 6 hours. Then the solution and marc were separated by centrifuging at 3000 rpm for 10 minutes. Thereafter, the decoction was poured into a bottle, frozen at -85^0C in the freezer and freeze-dried using either the Savant Freeze Drying System operating at -104^0C or the Virtis Freeze Mobile 72SL operating at -53^0C.

The dry extract was obtained after 3 days of freeze-drying and the dry extracts from the narrow leaves and broad leaves were designated **Dry Extract 1** and **Dry Extract 2**, respectively.

4.2.3 Results and Discussion

Pictures of the plant in its natural habitat (before collection) and the broad and narrow leaves are given in figures 1, 2 and 3.

Pictures of the sieved leaf powder and Dry Extracts 1 and 2 are given in figure 4.

Figure1: *D. angustifolia* in its natural habitat (Van Wyk, B. E., 1997.p.109)

Figure2: broad and narrow leaf of *D. angustigolia*

Figure 3: Dodonaea broad leaf

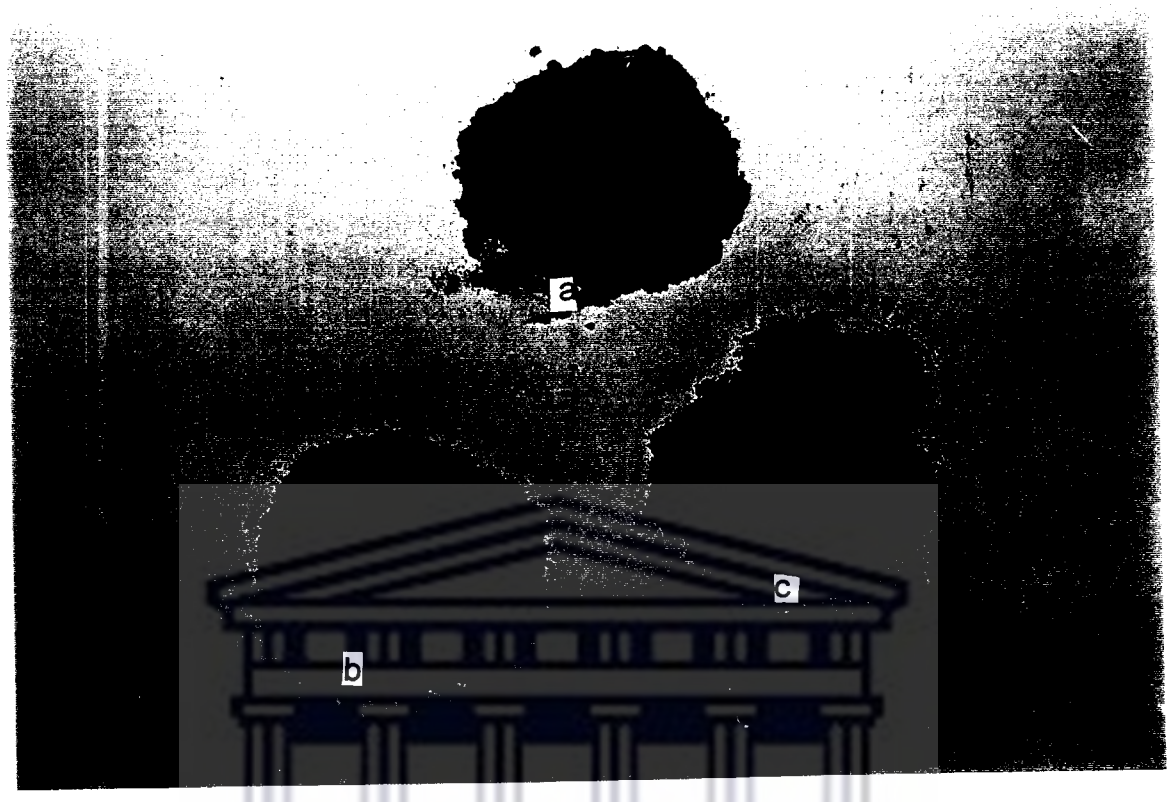


Figure 4: The Dry leaf powder (a), Dry Extract 1(b) and Dry Extract 2(c).

The yields obtained for the dry extracts from the powder are given in table 1.

Table1: Yield of dry extracts from dry powder

Collection Number in Register	Weight of dry powder (g)	Weight of dry extract (g)	Type of leaves	Season of collection	Yield (%)
114	87	19.37	Narrow	Winter	22.26
13	30	8.47	Broad	Summer	28.2
198	35	8.29	Narrow	Summer	23.6
104	175	50	Broad	Summer	28.5
200	40	9.12	Narrow	Winter	22.8

The plants with narrow leaves yielded slightly less extract compared to that obtained from the plants with broad leaves, strongly suggesting that the composition of the extracts might be different and/or would have different characteristics. The use of slightly different freeze-drying conditions (e.g. –54°C vs –105°C) was not responsible for this slight difference since collections number 104 and 200 were done under the same conditions. The few plant collections made do however not allow conclusions to be drawn on the effect that seasonal collection may have on the yield (but the issue could be explored in the future).

4.2. PREFORMULATION STUDY

4.2.1 Materials and methods

In this section I describe the methods used to determine the properties of the raw materials (dry leaf powder and both Dry Extracts 1 and 2) and present and discuss the results of these determinations.

4.2.1.1 Colour and odour

The colour of the powders prepared from the leaves of *D. angustifolia* was characterized by visual inspection with the naked eye. The dry sieved powder was pale green, the Dry Extract 1 bright-brown, and the Dry Extract 2 brown (see figures 3 and 4). The powders also had characteristic, but difficult to describe odours, which set them apart from other plant materials and from each other. For example, the dry extracts were less odorous than the dry leaf powder. Other physical characteristics were determined by the more measurable methods given below.

4.2.1.2 Density and compressibility index

The density of the raw material was determined on an apparatus (figure 5) having a variable speed motor and a platform on which a measuring cylinder could be clamped. When the motor was operating, a measuring cylinder attached to the

apparatus raised the platform gradually and smoothly to a maximum height. Further rotation of the cam caused the cylinder to drop about one centimeter due to the combined mass of the platform, the cylinder and its contents.

The following procedure was used.

Before determining the density of the powder, it was sieved in order to break up agglomerates. To determine the loose density, the powder was poured into a graduated cylinder via a large funnel, and the volume and the weight of the powder were measured. From the results loose density was calculated using equation 1. To measure the tapped density, the powders were similarly poured into the measuring cylinder, but now the volume of the powder was read (loose volume), before the measured cylinder containing a known mass of powder was placed on the mechanical tapping device. The latter was operated at a fixed number of taps (at 100rpm) until the powder bed volume had reached a minimum level (after 12.5 minutes). Now, the volume was read again (packed volume), and the tapped density was calculated using equation 2. The densities were determined using the following equations:

Loose (bulk) density = Weight of powder / loose volume **eq.1**

Tapped density = weight of powder / tapped volume **eq.2**

To calculate the index of compression or Carr's compressibility index (Wells, J. I., 1988) the following equation was used.

$$\text{Index Compressibility} = \frac{\text{packed density-loose density}}{\text{Packed density}} \times 100 \quad \text{eq.3}$$

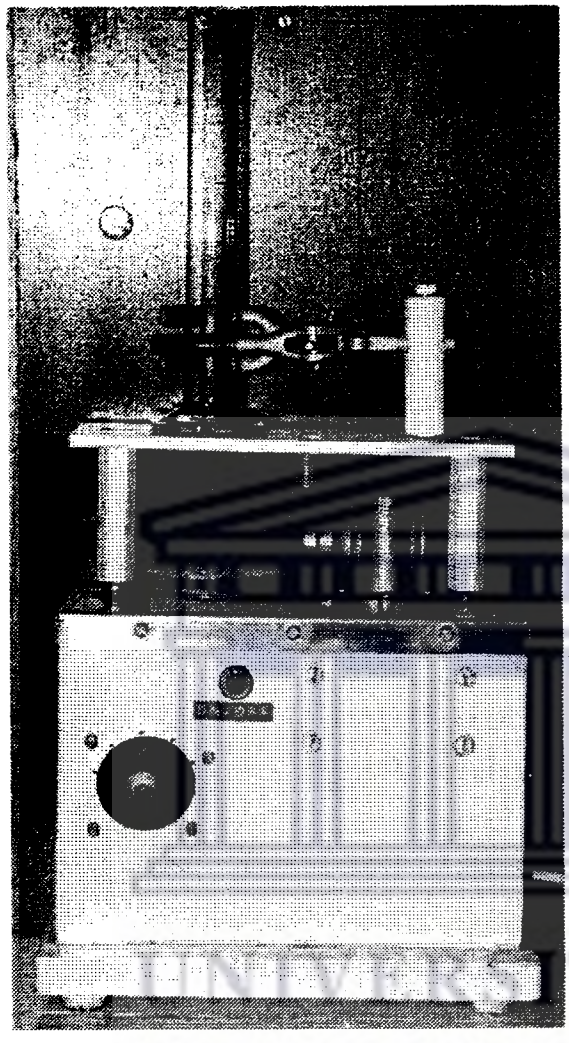


Figure 5: Apparatus for measuring tapped density.

4.2.1.3 Flowability

Normally, the flowability of powders is determined by measuring the angle of repose or by the recording balance pan method (Carstensen, J.T, 1993). In the present study, the flowability was determined by measuring the angle of repose using a glass funnel and by using a static method.

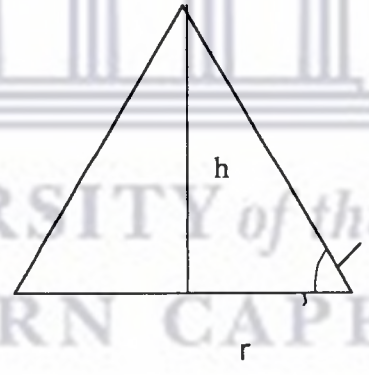
Firstly, the angle of repose was determined using the glass funnel method (A): In this method a glass funnel was filled with the powder while keeping the stem

opening of the funnel closed. Once all the powder was in the funnel, the blocked stem was opened allowing the powder to fall onto a piece of paper. The diameter and height of the heap of powder were measured and the angle was calculated using equations 4 and 5 given below. The disadvantage of this method was that the falling particles distorted the shape of the cone, hence the static method was preferred.

Secondly, the determination of angle of repose was done by the static method (B): In this method no particles fall onto the heap to distort it and a glass cylinder with both ends open was used. First, the cylinder was kept on a piece of white printing paper in the upright position and half-filled with the test powder. Then, the cylinder was swiftly and smoothly lifted leaving a cone of powder on the paper. The angle of repose was then calculated, as described above (method A), using the following equations.

$$\mathbf{Tan\theta = h/r} \qquad \text{eq.4}$$

$$\mathbf{\theta = arctan = tan^{-1}} \qquad \text{eq.5}$$



where Tanθ = tangent of angle, r = radius of base of the heap (cm) and h = height of heap (cm).

4.2.1.4 Size and shape of the particles

Two methods were used to determine the size and one to determine the shape of the particles of the plant material.

4.2.1.4.1 The sieve method

The degree of fineness of a powder can be expressed by reference to the number of the sieve through which it can pass (British Pharmacopoeia 1993), therefore the size of particles of plant material was determined in terms of the sieve number. Sieves having numbers of 500, 355, 180, 125 and 90 µm were successively assembled in an increasing order of mesh on a Test Sieve Shaker apparatus (Endecott sieve shaker, E.F.L. 1MK11). Ten gram of powder was poured onto the first top sieve and the system was shaken for 30 minutes. Thereafter fractions of the powder collected on each of the sieves (500, 355, 180, 125 and 90 µm sieve) were collected, weighed and the percentage of each fraction was determined. According to the British Pharmacopoeia, if no less than 95% by weight of powder passes through a sieve and no more than 40% by weight of powder passes through the next sieve, the powders can be described by the following terms as they pass through successive (500, 355, 180, 125 and 90 µm) sieves: coarse powder, moderately fine powder, fine powder, and very fine powder (British Pharmacopoeia 1993, Addendum 1996).

This method was complemented by the use of the microscopic method, which had the advantage of providing not only the size of particles, but also allowed the identification of the shape of particles of the plant materials.

4.2.1.4.2 Microscopic method

To determine the shape and size of the particles a light microscope (Nikon Monocular) with a micrometer (Graticules®), which had been accurately calibrated using a stage micrometer (the eyepiece OLYMPUS micrometer; 100 divisions = 1mm) was employed. First, slides of the powder were prepared by sprinkling a few milligrams onto a glass slide and placing it under the microscope. The slide was then viewed through the stage micrometer (in the eye piece) and 100 particles were randomly selected from various fields on the slide and measured. The dimensions of the particles were obtained by converting the eyepiece units to micrometer (µm) units using the appropriate calibration. The particle dimensions

were then recorded into appropriate size groups. If the particles were spherical, only one dimension i.e. diameter was measured. When the particles were not spherical, the length (L) and breadth (B) of the particles were also determined and the Heywood's ratio for elongation (N) calculated using the following equation (Pather, S. I., 1982):

$$N = L/B \qquad \text{eq. 6}$$

All the particles found in a random square were selected for measurement.

4.2.1.5 Solubility

The determination of the solubility of the plant material was intended to provide the information on the approximate solubility at 20°C (British Pharmacopoeia, 1980, Vol.I). Approximately, 30 mg of fine powder (which had been sieved through the 355µm sieve) was weighed and mixed with 1ml of water or alcohol. Thereafter the solution and the residue (marc) were separated using a filtration system (SUPELCO) connected to a vacuum pump. The vacuum filtration system process was continued until there was no change in the weight of the dry residue and the amount of dissolved powder was determined according to the following formula.

Amount dissolved = Weight of initial powder - weight of dry residue

4.2.1.6 Moisture content

To determine the moisture content, the Mettler TOLEDO LP16 Infrared dryer was used. This apparatus produces infrared radiation of wavelength 2µm to 3.5 µm, which heats the sample from the bottom and facilitates the evaporation of moisture. The apparatus includes a precision balance system which monitors the change in weight of the powder. The wet weight (initial mass) is set equal to 100%, and the apparatus automatically calculates the rate of moisture loss using equations 8 and 9. This method has the advantage of being rapid and is suitable

for all substances, which could decompose at the high temperatures used in ovens.

To determine the moisture content of the powders 1g of powdered plant material powder was subjected to the process and the moisture content values obtained from the machine. Several control substances e.g. starch, lactose, etc. were subjected to the same process.

Moisture content (%) = (moisture weight x 100)/ wet weight eq. 8

Moisture weight = Initial mass - Dry weight eq. 9

The percentage of humidity in environmental air was also determined using the DIGITAL HYGROMETER apparatus so that the humid and dry days mentioned by Carstensen in literature review section 2.4.7 (hygroscopicity) were distinguished.

4.2.2 Results and discussions

4.2.2.1 Densities and compressibility

The results of the determination of densities and index of compressibility are given in table 2and 3

Table2: Densities of powders of the raw plant material

	Loose density g/cm^3	Packed density g/ cm^3	Index of Compressibility (%) (i.e. Carr's index)	
			Samples	Average ± SD
Dry leaf powder	0.373	0.423	22.7	22.6 ± 0.8
	0.366	0.416	23.5	
	0.370	0.420	21.8	
Dry extract 1	0.136	0.18	11.9	11.9 ±0.05
	0.136	0.18	12	
	0.136	0.17	11.9	
Dry Extract 2	0.53	0.61	13.1	15.9 ±2.8
	0.52	0.64	18.7	
	0.52	0.62	16.1	

Table3: Densities of powders of some excipients used in present study

	Loose density g/cm^3	Packed density g/ cm^3	Index of Compressibility (%) (i.e. Carr's index)	
			Samples	Average ± SD
Lactose	0.49	0.66	24.7	24.7 ±0.05
	0.48	0.65	24.8	
	0.49	0.65	24.8	
Starch1500®	0.35	0.40	11.6	11.9 ±0.5
	0.35	0.39	11.7	
	0.35	0.40	12.6	
Tablettose®	063	0.71	11.2	12 ± 1.4
	0.61	0.71	14	
	0.61	0.70	12.8	
Emcocel 90M®	0.35	0.39	10.2	9.9 ± 0.2
	0.36	0.40	10.0	
	0.37	0.41	9.7	
Avicel PH101®	0.32	0.38	15.7	16.1 ± 0.4
	0.31	0.37	16.2	
	0.30	0.36	16.6	

According to Carr (1965) powders with a low Carr's index have better flowability and compressibilty. This relationship is more fully presented in Annexure1. From the above results it was seen that the dry powder had a very good index of compressibility (11.9 ± 0.05%), the Dry Extract 2 had a *good* index of compressibility (15.9 ± 2.8%), and the Dry Extract 1 had a passable index of compressibility (22.6 ± 0.8%). Although these results clearly suggested that all 3 forms of the plant raw material would present little problem as far as tabletting by direct compression was concerned, there were nevertheless distinct differences (ANOVA, p= 0.0007) in their compressibility properties which had to be kept in mind when the other excipients were selected.

4.2.2.2 Flowability of the powders

The results of the determination of flowability of the powders from *D. angustifolia* plant material are given in table 4.

Table 4: Flowability of the dry leaf powder (850μm sieved) from the leaves of *D. angustifolia*

Sample number	Height cm	Radius cm	Angle of repose (°)
1	2.2	3.12	35.1
2	2.4	3.25	36.4
3	2.3	3.0	37.4
Average ± S.D	2.3±0.1	3.12±0.1	36.3±1.1

Table5: Flowability of the dry leaf powder (355μm sieved) from the leaves of *D. angustifolia*

Sample number	Height gm	Radius gm	Angle of repose (°)
1	2.6	2.34	42
2	2.3	2.65	40.9
3	2.5	2.62	43.6
Average ± SD	2.5±0.1	2.53±0.2	42.1 ±1.3

Table6: Flowability of the Dry Extract1 from the leaves of *D. angustifolia*

Sample number	Height cm	Radius cm	Angle of repose (°)
1	2.5	2.95	40.27
2	2.8	2.43	41.03
3	2.3	2.8	39.4
Average ± SD	2.5 ±0.2	2.7 ±0.3	40.2 ±0.8

Table7: Flowability of the Dry extract 2 from the leaves of *D. angustifolia*

Sample number	Height cm	Radius cm	Angle of repose (°)
1	2.1	2.7	37.8
2	1.9	2.8	32.3
3	2.1	3	34.9
Average ± SD	2.0±0.1	2.8 ±0.2	35± 2.7

The flow properties of powder are estimated by the angle of repose. Wells, J. I. has established the relationship between the angle of repose and flow properties of powder (Wells, J. I., 1988) as shown in Annexure2. The powder that possesses the lower value of angle of repose has the better flow. The theoretical lower limit of the angle of repose is 25° (Wells, J. I., 1988). In addition, the angle of repose can be considered as an indication of cohesive behaviour of the powder i.e. "the larger the angle, the larger cohesive force" (Carstensen, J. T., 1993).

As indicated by the results above all the powders assessed in this study viz. dry powder, dry extract 1 and dry extract 2, showed poor flowability. Based on the terms used by Carstensen (Carstensen, J. T., 1993), both the dry powder and dry extract 1 were characterized as having poor flowability (42.1° ±1.3 ° and 40.2° ±0.8 °, respectively), while the dry extract 2 powder had a passable flowability (35° ± 2.7 °). The reduction of the particle size of the dry powder by sieving (from 855 to 355 um) clearly also did not improve the flowability of the powder; in contrast the effects of friction of the very fine particles were manifested. Several examples of such cohesive behaviour of small particles of powder can be found in the literature. For example, in a study done on furosemide it was shown that the milling process reduced the size of particles, but also increased the cohesion between the small particles of furosemide (De Villiers, M.

increased the cohesion between the small particles of furosemide (De Villiers, M. M. et al., 1995). In another example, drugs were micronized in order to improve their dissolution by ensuring the maximum surface area available for dissolution, but such drugs having small particles were often cohesive and stuck together forming agglomerates (De Villiers, M. M. et al., 1993). The moisture content also contributed to the poor flowability and agglomeration.

It was clear from these results, that the powder the study materials obtained from *D. angustifolia* did not have optimal flow properties and these needed to be improved upon in formulation step.

4.2.2.3 Size and shape of particles

The size of particles was obtained from sieving methods and microscopic method.

4.2.2.3.1.Results obtained from sieving methods

Sieving of the various dry powders presented the following results:

- 77% of the particles of the dry leaf powder passed through the180μm sieve and only 23 % particles of the powder passed through the 90μm sieve,

- 85% of the Starch B.P. powder passed through a 180μm sieve and only 15% of the particles of the same powder passed through a 90μm sieve.

- 95% of the particles of ∝-Lactose monohydrate powder passed through a 500μm sieve and 20% of the particles passed through the 355μm sieve.

According to British Pharmacopoeia 1993 definitions, both the dry leaf powder and the ∝-Lactose monohydrate powder could therefore be described as fine powders, while the starch B.P. powder was a very fine powder. Assessment by the sieving was more or less fast, but not as accurate and reproducible as the

microscopic method. In addition, the powders of the dry extracts could not be characterized by this method. They were hygroscopic and tended to stick to the sieve.

4.2.2.3.2 Results obtained from microscopic method

These results are given in Appendix 1.1, 1.2, 1.3 and are summarized in the graphs shown in figures 6, 7 and 8.

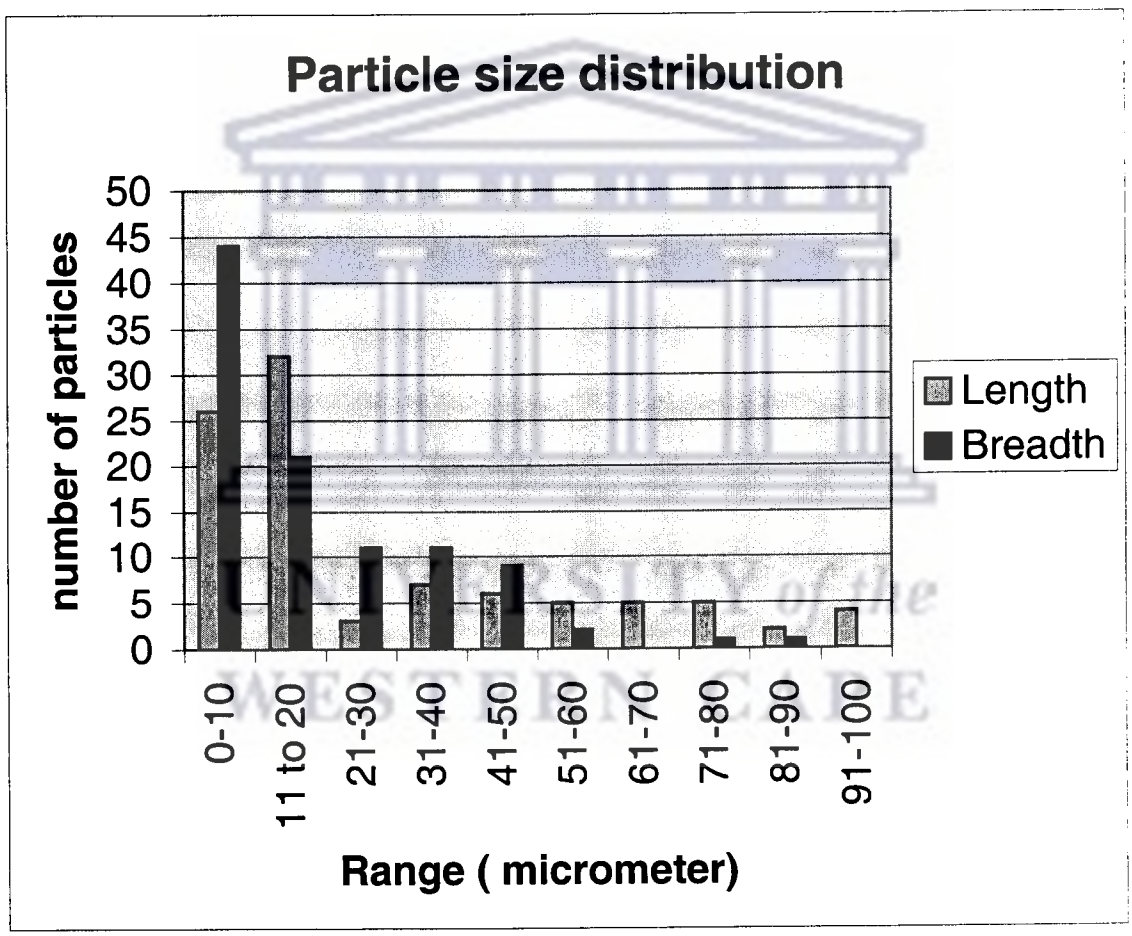


Figure 6: Graph of particle size distribution of the dry powder *(D. angustifolia)*.

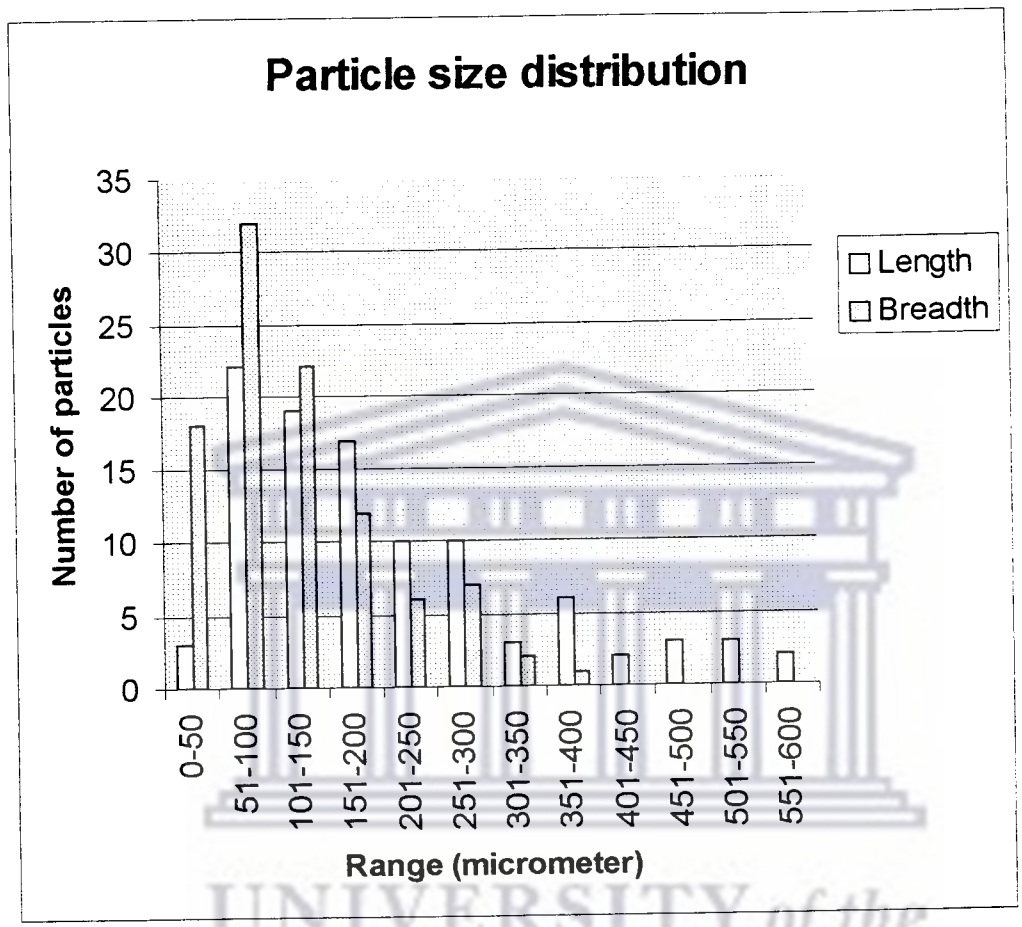


Figure7: Graph of particle size distribution of Dry Extract 1 *(D. angustifolia)*

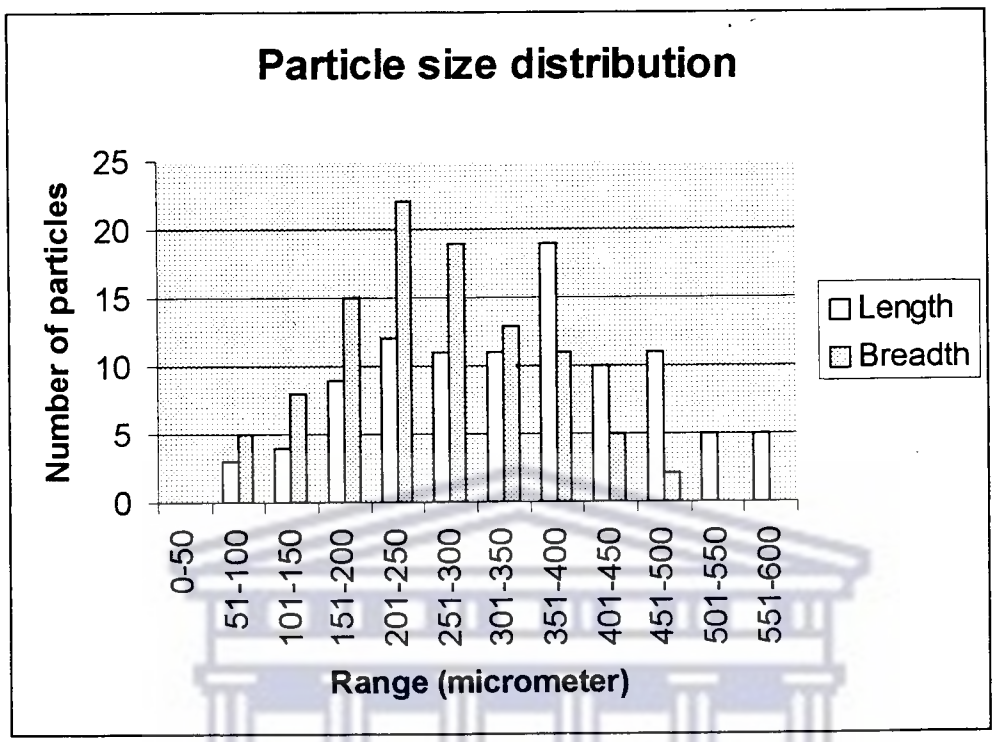


Figure8: Graph of particle size distribution of Dry Extract 2 *(D. angustifolia)*

The Heywood ratios for particles of each of the powders were also calculated using equation 7, and the results are given in appendix 1.1, 1.2 and 1.3 and are summarized in figure 9.

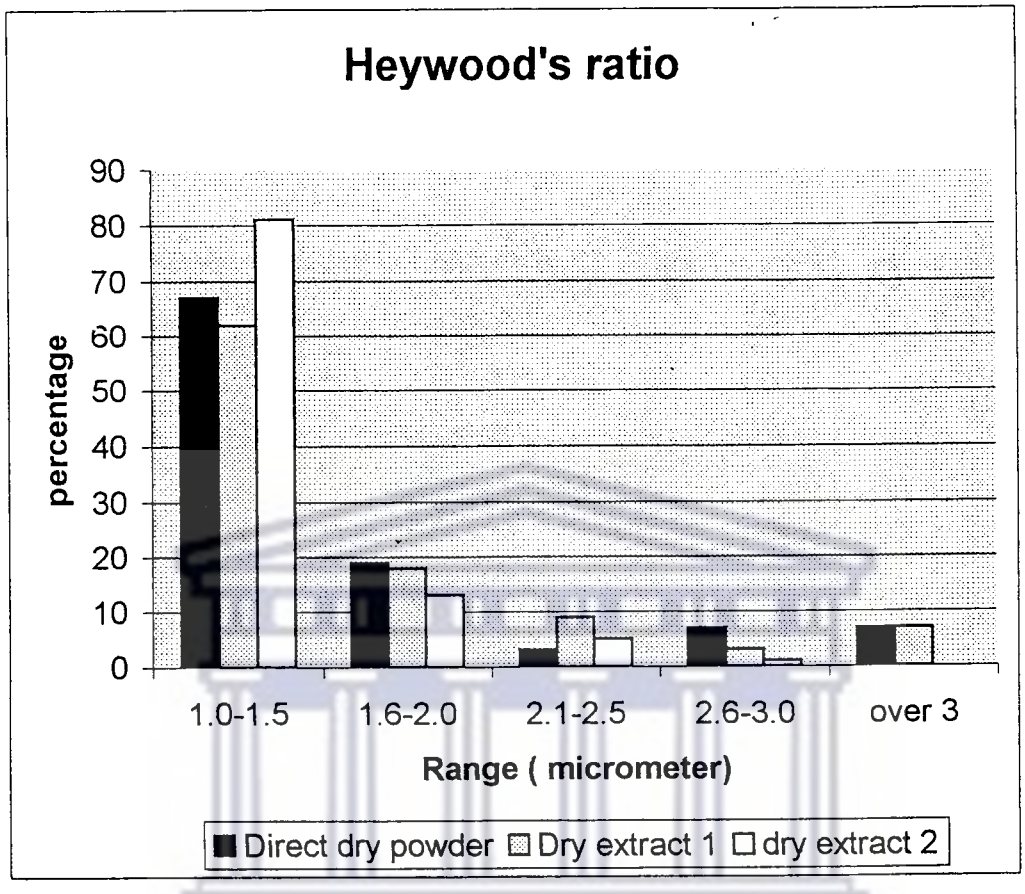


Figure 9: Heywood ratios (L/B) of the study powders of *D. angustifolia* leaves

L: length, B: Breadth

4.2.2.3.4 Discussion

In terms of length, at least 50% of the particles of dry leaf powder were between 5 and 30 µm in size and the median size was 20µm, while about 50% of the particles of Dry Extract 1, were between 50µm and 150µm with median size of the particle of 200µm, and the 50% of particles of Dry Extract 2 were between 200 and 350µm with median size equal to 344µm.

These results clearly indicated that there was a difference in particle shape and size between the dry leaf powder and extracts, as well as a difference between Extract 1 and Extract 2. These differences between the powders could be responsible for the differences observed in the flowability and compressibility behaviour of the dry powder, Dry Extract 1, and Dry Extract 2. Unless corrected in

the final formulation, these differences among the plant powder materials could ultimately lead to differences in the disintegration and dissolution rates of tablets manufactured from these materials (Hiestand, N. E., 1997).

The results obtained by microscopy, as well as the results from the Heywood ratio determinations, also indicated several differences between the particles of the dry powder, Dry Extract 1 and Dry Extract 2. Most of the particles of the dry leaf powder had a spherical shape, while the particles of Dry Extract 1 were more or less crystalline in appearance, and the particles of the Dry Extract 2 were more or less amorphous in appearance. In the compression step, these different shapes of the particles would be expected to have an impact on the mechanical properties, such as compressibility of the powder as well as on the bonding mechanisms between the particles (Symecko, C. W. et al., 1995). From these present results, and everything else being equal, it was expected that the dry leaf powder would be easier to compress.

4.2.2.3 Solubility

The results of the determination of the solubility of dry leaf powder of *D. angustifolia* are presented in tables 8 and 9.

Table 8: Solubility of dry leaf powder of *D. angustifolia* (broad leaves) in distilled water

Weight of initial Powder (mg)	Weight of Residue (mg)	Amount of dissolved powder (mg)	* Solubility (%)
29	19.9	9.1	31
29.9	23.1	6.8	22.7
29.9	21.8	8.1	27
27.6	19.9	7.7	27.8
29.4	22.9	7.1	22.1
30.4	23.3	7.1	23.3
Mean±SD: 29.3±0.9	21.5 ± 1.5	7.7 ± 0.8	26.1 ± 3

Table 9: Solubility of dry leaf powder of *D. angustifolia* (broad leaves) in ethanol (70%)

Weight of initial Powder (mg)	Weight of residue (mg)	Amount of dissolved Powder (mg)	* Solubility (%)
30.3	13.4	16.9	55.7
30.2	13.3	16.9	55.9
27.7	12.6	15.1	54.5
29.9	12.8	17.1	57.1
31.1	13.9	17.2	55.3
30.5	13.2	16.8	55.1
Mean ± SD: 30 ± 1.2	13.2 ± 0.5	16.6 ± 0.8	55.7 ± 0.9

* Solubility calculated from (amount dissolved / initial weight) x 100.

These results showed that the powder prepared from the *Dodonaea* leaves was significantly more soluble in alcohol than in water (55.7±0.9% vs. 26.1 ± 3%, student t-test, p = 0.05). This might suggest that alcohol would have been a better solvent to use for the preparation of the leaf extracts. However, alcohol was not used as the extraction solvent because almost all the pharmacologically active substances found in *D. angustifolia* plant material are known to be soluble in water (Watt, J. M. and Breyer-Brardwijk, 1962), In general, the free base of the alkaloid is soluble only in an organic solvent, but some of pseudo- and protoalkaloids are substantially soluble in water. In addition, the salts of alkaloids and quaternary alkaloids are normally highly soluble in water (Cordell, A. G., 1981). The flavonoids possessing a number of unsubstituted hydroxyl groups or sugar, are polar are moderately soluble in polar solvent like water but the presence of an attached sugar (commonly encountered) tends to render the flavonoid more soluble in water (Marakham, K. R.,1982). Furthermore, when used in traditional medicine *D. angustifolia* is in an aqueous dosage form (decoction). The alcoholic extract was also more distinctly green in colour, which suggested

that the additional compounds that were soluble in the alcohol probably included more of the compounds which should be not needed in present study. Therefore the use of water as a solvent provided a kind of improved selectivity in the extraction method.

The Dry Extracts 1 and 2, on the other hand showed, as expected, good solubility in both water and in alcohol. They dissolved at better than 1 part per 1 part of these solvents. However, the complete dissolution demanded a long and vigorous shaking, especially in the case of distilled water. This might have been due to the poor wettability property of the powder and might eventually be reflected in the dissolution profiles of the final tablets prepared from these powders.

4.2.2.4 Moisture content

The results of the assessment of the moisture content of plant material of *D. angustifolia* and some excipients used in this study are given in table 10.

Table10: Moisture content of tablet raw materials

Substance	Moisture content Mean ± S.D, (%) **
Dry leaf powder	8.27 ± 0.9
Dry Extract 1	9.75 ± 0.3
Dry Extract 2	1.2 ± 0.01
Starch BP	13.23 ± 0.2
Starch 1500®	11.67 ± 0.2
Emcocel 90M®	5.43 ± 0.2
Avicel PH 101®	5.7 ± 0.3
Mg stearate	2.74 ± 0.4
Tablettose®	3.9 ± 0.2
α-Lactose monohyd.	0.72 ± 0.6

** Moisture content was determined, on samples (n=3) of each substance, as described under section 4.2.1.5

The results showed that the powders used in this study had different potentials to take up moisture. Starch B.P. was able to take up as much as 13% moisture, while lactose and Dry Extract 2 only picked up around 1% moisture. The moisture content of Dry Extract 2 (1.2 ± 0.01%) was also significantly different (t-test, $p<0.0001$) to that of Dry Extract 1 (9.75 ± 0.3%), and the latter's moisture content was different (t-test, $p=0.0008$) to that of the dry leaf powder (8.27 ± 0.9 %). The results of the moisture content did however not reflect the hygroscopic characteristics of the substances. As stated in the literature review (section 2.4.7), the hygroscopicity of powder is more associated with the behaviour of the powder in the presence of moisture than with the amount of water it can take up. For example, the starches contained a high level of water in comparison with the dry extracts, however, the latter were more affected by the relative humidity (water available in the surrounding atmosphere) than the starch. For instance, at a relative humidity above 60% both of the dry extracts became very cohesive and even tended to dissolve in the absorbed moisture (this was visually observed and seen in changes in particles viewed under microscope). The dry leaf powder were however unaffected by changes in the relative humidity. The effect which moisture can have on a tablet is highly dependent on the initial moisture found in its ingredients, and in such cases closer control of the moisture content of the raw material powders is necessary to ensure an optimum stability of the final tablets (Fischer, M. et al., 1995). While the Dry Extract 1 and Dry Extract 2 had different moisture contents their hygroscopic behaviour could be expected to affect the final tablet integrity and performance and this had to be considered during the formulation and manufacture of tablets from these materials.

4.2.2.5 Conclusion

Three different samples of material were prepared from the leaves of *D. angustifolia* and the primary aim of this preformulation study was to determine the different physical characteristics viz. flowability, density, compressibility, moisture content, size and shape of particles of these materials in order to assess their

suitability for incorporation into directly compressed tablets having a high proportion of plant material. The following conclusions could be drawn from the results obtained.

Firstly, there were distinct differences(ANOVA, p= 0.0007) found in the compressibilities of the three forms of plant material and these had to be kept in mind when the other excipients were selected. However, it could be expected that all three forms of the plant raw material would still present little problem as far as tabletting by direct compression was concerned,

Secondly, all three powder forms of the study material did not have optimal flow properties and these needed to be improved upon in the formulation step.

Thirdly, there were also differences between the particle shape and size distributions for the dry leaf powder, Dry Extract 1 and Dry Extract 2. If everything else remained equal, it was expected that the dry leaf powder would be easier to compress. For the other two powders the need for binders was anticipated to improve their compressibility.

Fourthly, all three powders had satisfactory solubility characteristics in water and alcohol, except that their complete dissolution demanded a long and vigorous shaking process, especially in the case of distilled water. If this was due to the poor wettability of the powders it could eventually be reflected in the dissolution profiles of the final tablets prepared from these powders.

Fifthly, the 3 different powders of plant material had different capacities to absorb moisture, but the dry extracts were particularly hygroscopic at high humidity (above 60%) while the dry leaf powder was unaffected by changes in the relative humidity. Although the Dry Extracts 1 and 2 had different moisture contents their hygroscopic behaviour could be expected to affect the final tablet integrity and

performance and this had to be considered during the formulation and manufacture of tablets from these materials.

In this study, the plant material had to form a major proportion of the tablet, and it was expected that the plant material would impart many of its characteristics to the final tablet (Marshall, K. and Rudnic, E. M., 1989). Since, the plant material from the leaves of *D. angustifolia*, especially the dry extracts, showed poor flowability, the direct compression method would have been expected to be less easy, and in such cases the wet granulation could provide a solution, (Carstensen, J. T., 1993). However, the fact that the dry extracts were very sensitive to the presence of water (hygroscopic), made the wet granulation method not appropriate. Consequently, other strategies had to be considered in the following steps of tablet formulation and tablet manufacture.

CHAPTER 5

FORMULATION AND EVALUATION OF TRIAL-TABLETS

In this chapter the equipment, materials and methods used to formulate, manufacture and evaluate the tablets of dry leaf powder and leaf powder extract of *D. angustifolia*, as well as the results obtained, are discussed.

5.1 EQUIPMENT AND MATERIALS

In addition to some of the equipment and materials lists under 4.1 the following equipment and materials were also used.

Compress Machine

Type F3, Manesty Machine Ltd, Liverpool, England

Hardness Tester

Type Ptb 301 Erweka, Pharma Test, Hainburg, W. Germany

Friabilitator

Erweka-Apparatebau-GmbH, Heusentamm Kr.offenbach, Western Germany

Disintegrating Apparatus

Erweka-Apparatebau-GmbH, Heusentamm Kr.offenbach, Western Germany

Spectrophotometer

Hitachi Model U3200, Spectrophotometer Hitachi, Ltd, Tokyo, Japan

Dissolution Tester

Model 72RL Hanson, Hanson Research Corp., Bahama, U.S.A

Millipore Filter

Cameo 25 AS, DDA 02025So

MSI: Micro separation Inc., USA

The following raw materials were used in formulation of the tablets.

Emcocel M90®

Lot 958101, Penwest Pharmaceuticals Oy, England

Light Kaolin

Heyness Mathew Ltd, Observatory, R.S.A

5.2 FORMULATION OF THE TABLETS

The aim of the tablet formulation was to find a suitable formula which allowed the incorporation of the maximum amount of plant material of *D. angustifolia* in the tablet. This tablet had to comply with all the usual physical properties of tablets and to contain the equivalent amount of active ingredient as found in the number of leaves used in the preparation of decoction of *D. angustifolia*.

The formulation was basically dictated by the physicochemical properties of the raw material (e.g. flowability and compressibility). Because the dry leaf powder and dry extracts had different physical properties, different formulas were required, especially in terms of the proportion of plant material to be used in each tablet. The physical properties of the plant raw material (e.g. hygroscopicity) also dictated the selection of the excipients to be used in the tablet formulation.

In this section the determination of the amount of plant material per tablet and the selection of the excipients are discussed and the different tablet formulae presented.

5.2.1 Determination of amount of the plant raw material per tablet

From oral information provided by local Traditional healers on the dose of *Dodonaea* they recommended, an estimation of the amount of the plant material to incorporate in one tablet could be made. Generally, these healers recommended that the decoction of *D. Angustifolia* be prepared by pouring 3 liters of boiling water over leaf powder (12-15 g) derived from approximately weight of 1/2 bunch of dry leaves. After cooling and straining, the patient needs to take 1 cup, approximately 180 ml, of decoction three times a day.

Using this information the amount of dry leaf powder to incorporate into each tablet was estimated in the following manner. To prepare1000 ml of decoction, 4 -5 g of dry leaf powder were used. This meant that 180 ml contained 900mg of dry powder. Thus, in the tablet formulation the dosage was estimated to be 900 mg. But this was a very large mass for one tablet. Therefore it was decided to split this dose into two tablets each having 450 mg.

To determine the amount of dry extract to incorporate into each tablet the yield of extract (table1) obtained from 900mg of dry leaf powder was taken into consideration, i.e. the amount of dry extract to incorporate into one tablet = yield X 0.900g/ 100. For example, the yield of Dry Extract 1 was 22.7% and this meant that 100 g of dry leaf powder would provide 22.7 g of dry extract and that 0.900 g dry leaf powder would yield 0.204 g of Dry Extract 1 to be incorporated per tablet.

Based on the above calculations, it was decided to use 450 mg (900 mg/2) of dry leaf powder, 200 mg powder of Dry Extract 1 and 250 mg powder of Dry

Extract 2 as the amounts of plant material of *D. angustifolia* to be incorporated, separately, per tablet. The patient then needed to take these tablets three times a day to obtain the same daily dose as they would receive with the decoctions.

5.2.2 Selection of excipients

Various excipients were needed and selected in order to facilitate the tablet formulation and manufacture, and to overcome some of the poor properties of the three plant powders, especially the poor flowability, hygroscopicity and eventual slow dissolution of the tablets. Excipients possessing the properties of a disintegrant, binder, diluent and/or glidant were selected. To minimize the number of excipients, the selection focused on those excipients that were able to play more than one role in the tablet formulation. Another criterion of the selection procedure was that the excipients had to be directly compressible. The following excipients were considered and used in this study, for the reasons as explained below.

5.2.2.1 Starches

The first and most important excipient chosen for the tablets was starch.
Starch could serve as filler as well as disintegrant or binding agent. It is known that the disintegrating properties of starches are due to the induction of water uptake in the tablets and the varieties of starch containing large grains are preferable, because they tend to provide the optimum pore size distribution in tablets (Marshall, K. and Rudnic, E. M., 1989). Starches also have glidant properties, in particular the starches having the larger grain size.

Starch concentrations up to 10% are commonly used in tablet formulations, but higher concentrations of starch often result in loss of bonding properties (Marshall, K. and Rudnic, E. M., 1989). In the present study the proportion of starch used ranged between 6 and 17%.

From the variety of starches that are available three were used in this study, viz. Starch BP, Starch 1500® and Explotab® or Sodium starch glycolate. Starch 1500® is a starch modified by pregelatinization and is marketed for direct compression formulation (Wade, A. and Weller, P. J, 1994). It is free flowing, may be used as diluent, binder and disintegrating agent, swells rapidly in water (Peck, G. E. et al., 1989) and has a good compactibility. Explotab® or sodium glycolate is a product of carboxymethylation of starch, which changes the molecular structure of the starch so that there is substantial modification of the disintegration and dissolution properties of the starch (Rudnic, E.M et al.1985). Sodium starch glycolate improves the water uptake properties of the tablet by increasing its affinity for water. This property is particularly pronounced when, in the tablet formulation, the sodium starch glycolate is combined with microcrystalline cellulose, which hydrates in the presence of water (Wan, L.S.C et al., 1989). Thus, in the present study, the Explotab® was used in the tablet formulation to improve the disintegration and dissolution of the tablet by facilitating the entry of the water into the tablet. Explotab was used at low concentration (1-4%) (Wade, A. and Weller, P. J, 1994), because of its low compressibility.

5.2.2.2 Lactose

In general lactose is widely used as diluent in tablet formulation. This wide use of lactose is derived from its many advantages. For example, lactose displays a good stability in combination with most drugs whether used in hydrous or anhydrous form. Lactose formulations also show good drug release rates and tablets containing lactose generally show fast disintegration, good friability and low weight variation (Peck, G. E. et al., 1989).

Two lactose products were used in the present study, viz. α-lactose monohydrate and Tabletose®. Anhydrous α-lactose (100mesh) was selected because it presents good flow properties and it is directly compressible. However its compressibility is relatively low (Bolhuis, K. and Zuurman, K., 1995). Tablettose®

on the other hand is a hydrous lactose having the same disintegrating properties as α-lactose, but in which the binding properties are improved because the lactose particles are in a granulated form (Van Kamp, H. V. et al., 1986). The amount of Tablettose® used in the formulation ranged between 5 and 10%.

5.2.2.3 Microcrystalline cellulose

Microcrystalline cellulose is directly compressible and has the ability to function as both binder and disintegrant in the tablet formulae. It exhibits very good disintegrating properties by facilitating fast aqueous penetration of the tablet mass (Lerk, C. F. et al., 1979). The best disintegrating properties are observed when microcrystalline cellulose is present in the tablet at a level below 10%. Excessively high levels of microcrystalline cellulose can result in tablets having the tendency to stick to the tongue, due to the rapid capillary adsorption of the moisture in the mouth (Peck, G. E. et al., 1989). And at high concentration, the viscosity of microcrystalline cellulose in water can affect the dissolution rate of the tablet. Usually Avicel PH101® (powder) and Avicel PH102® (granular) are the microcrystalline cellulose products most frequently used because they produce tablets that have a good hardness and low friability (Peck, G. E. et al., 1989).

In the present study, Emcocel 90M® was however used. According to Williams, E. et al, Avicel® and Emcocel products should be directly substitutable for each other with Avicel PH101® being substitutable by Emcocel50M® and Avicel PH102® by Emcocel 90M® (Williams, E. et al., 1997 and Doelker, E. et al., 1987). The latter products have the size of particles (100 mesh) which favors a good flowability of the powder mass and improved disintegration of the tablet. Emcocel 90M® was used at the concentration 0.5 -1.5% (Wade, A. and Weller, P. J., 1994).

In summary, the following excipients were selected to be used in the tablet formulae as discussed above i.e. Starch BP, Starch 1500®, Explotab® (Sodium

starch glycolate), α-lactose monohydrate, Tabletose® and Emcocel 90M® as well as one which was discussed in section 2.3.2.2.4, viz. magnesium stearate.

5.2.3 Formulas of tablets

The purpose of the formulation process was to obtain a formula by which *D. angustifolia* plant material could be incorporated in the tablet dosage form. The latter had to contain the equivalent amount of plant material as found in the average number of leaves typically used to prepare the decoction dosage form of this traditional medicine. In addition a minimum of excipients were to be used.

The formulation process was tackled in the following order: first the formulation of tablets containing dry leaf powder, then formulation of tablets containing dry extract 1 and finally the formulation of tablets containing dry extract 2. In order to arrive at a formula which contained the maximum amount of plant material in the tablet, formulation was started with the minimum number and lowest amount of excipients possible. Tablets were then prepared from these formulae and evaluated for hardness and uniformity of mass. Depending on the results, the formulae were progressively improved by gradually increasing the number and amount of excipients. This, of course, resulted in an associated decrease in the proportion of plant material in the formula (e.g. see formula 1.a and 1.b). In some instances certain excipients were replaced by others (e.g. compare Formulas 1.b and 2.a), in another instance new excipients were added (e.g. compare Formulas 4 and 5.a).

5.2.3.1 The formulas containing the dry leaf powder

Five trial formulas (formula 1.a, 1.b, 2.a, 2.b, and 3) for the tablets containing dry leaf powder were elaborated and these are given in Tables 11, 12, 13, 14 and 15.

Table 11: Formula 1.a

	Weight for 1 tablet mg	Proportion (%)
Dry powder	450	90
Starch BP®	30	6
α-Lactose monohyd.	15	3
Emcocel 90M®	2	0.4
Mg Stearate	3	0.6
Total	500	100

Table 12: Formula1 .b

	Weight for 1 tablet mg	Proportion (%)
Dry powder	450	88.2
Starch BP®	40	7.8
α-Lactose monohyd.	15	3
Emcocel 90M®	2	0.4
Mg Stearate	3	0.6
Total	510	100

Table 13: Formula 2.a

	Weight for 1 tablet mg	Proportion (%)
Dry powder	450	84.9
Starch BP®	47.5	9
Tablettose®	26.5	5
Emcocel 90M®	2.5	0.4
Mg Stearate	3.5	0.7
Total	530	100

Table 14: Formula 2.b

	Weight for 1 tablet mg	Proportion (%)
Dry powder	450	84.9
Starch 1500®	47.5	9
Tablettose®.	26.5	5
Emcocel 90M®	2.5	0.4
Mg Stearate	3.5	0.7
Total	530	100

Table 15: Formula 3

	Weight for 1 tablet mg	Proportion (%)
Dry powder	450	85.5
Starch 1500®	47.5	9
Tablettose®	26.5	5
Emcocel 90M®	2.5	0.5
Total	526	100

All of these formulas contained more than 80% of dry leaf powder and only 3 to 4 excipients. The total powder mass ranged from 500 to 530 mg.

5.2.3.2 Formulas containing the dry extracts

Four trial formulas (formula 4, 5.a, 5.b, and 6) for tablets containing Dry Extract 1 and two formulas (formula 7 and 8) for Dry Extract 2 were elaborated and these are given in tables 16 to19 and 20 to 21, respectively.

Table 16: Formula 4

	Weight for 1 tablet mg	Proportion (%)
Dry extract1	200	70
Starch 1500®	49	17
Tablettose®	31	11
Emcocel 90M®	3	1
Mg stearate	3	1
Total	286	100

Table 17: Formula 5.a

	Weight for 1 tablet mg	Proportion (%)
Dry extract1	200	66
Starch 1500®	79	26
Tablettose®	18	6
Emcocel 90M®	1.5	0.5
Mg stearate	1.5	0.5
Kaolin	3	1
Total	303	100

Table 18: Formula 5.b

	Weight for 1 tablet mg	Proportion (%)
Dry extract1	200	65
Starch 1500®	68	22
Tablettose®	31	10
Emcocel 90M®	3	1
Mg stearate	3	1
Kaolin	3	1
Total	308	100

Table19: Formula 6

	Weight for 1 tablet mg	Proportion (%)
Dry extract1	200	65
Starch 1500®	68	22
Tablettose®	31	10
Emcocel 90M®	3	1
Mg stearate	3	1
Explotab®	3	1
Total	308	100

Table 20: Formula 7

	Weight for 1 tablet mg	Proportion (%)
Dry extract 2	250	70
Starch 1500®	53.5	15
Explotab®	14	4
Tablettose®	32	9
Emcocel 90M®	5.5	1.5
Mg stearate	2	0.5
Total	357	100

Table 21: Formula 8

	Weight for 1 tablet mg	Proportion (%)
Dry extract 2	250	80
Starch 1500®	31	10
Tablettose®	22	7
Explotab®	6	2
Emcocel 90M®	1.5	0.5
Mg stearate	1.5	0.5
Total	312	100

The first four formulas contained between 65 and 70% of powder of Dry Extract 1 and 4 to 5 excipients and the total tablet powder mass ranged from 286 to 308mg. The last two formulas contained 70% and 80% of the powder of Dry Extract 2 and 5 excipients each, while the total powder mass were 357mg and 312mg. The proportion of plant material that could be incorporated in the dry extract form was therefore less than that in the formulas of elaborated for the dry leaf powder form. The suitability of these formulas could however only be assessed after tablets

based on the formulas were manufactured and the tablets of these formulas were produced as indicated below.

5.3 MANUFACTURE OF THE TRIAL-TABLETS

Trial tablets based on the formulas given in section 5.2 were produced by mixing the required weighed amounts of each component substance and directly compressing it into tablets using a single punch compression machine. The tabletting process comprised the following steps: filling of the die, compression of the volume of powder between the upper and lower punches, and the ejection of the manufactured tablet.

Before proceeding to the final compression, trial runs were done to obtain the desired tablet weight by adjusting the filling volume of the die. The compression force to be applied for each formula was also determined in this preliminary compression experiment.

To obtain the final tablets the dry leaf powder formula mix was compressed using the dial setting on the Manesty F3 single punch tabletting press ranging between 40-45, while the range were between 25 and 30 to compress the mixture of powder containing Dry Extract 1 and 2. The compression force resulting from the latter setting was sufficient [*] when it was applied under conditions of low relative humidity. However the dry extracts were hygroscopic and the compressibility of their powder masses decreased when the humidity increased. When the atmosphere contained more than 60% relative humidity, the dry extracts exhibited a high cohesiveness and adhesion onto the punches. The addition of kaolin (formulas 5.a and 5.b) as absorbent did not solve the problem as long the relative humidity was above 60%. The tabletting process for the dry extracts was consequently only performed when the level of relative humidity in the atmosphere was less than 55%.

([*]: The Manesty F3 single punch press does not compress at any specific force. The force depends on the size of the tablet, it's weight, and the compressibility of the material.

The markings on the scale of the top punch are arbitrary markings that determine the distance the top punch moves down.)

Approximately 30 to 50 tablets were manufactured based on each of the formulas, and these trial tablets were evaluated for their physical properties as described below.

5.4 EVALUATION OF THE TRIAL-TABLETS

5.4.1 Methods

The physical properties viz. mass uniformity, hardness, friability, disintegration and dissolution rate of the trials tablets were evaluated as described below.

5.4.1.1 Mass uniformity

The test of uniformity of mass for uncoated tablets was performed as stated in the British Pharmacopoeia 1980. For each formula, twenty tablets were randomly chosen, each tablet individually weighed and the average weight, standard deviation and coefficient of variation calculated.

5.4.1.2 Hardness

The hardness of the tablets was assessed by measuring the maximum force needed to fracture the tablets (Monedero, M. C. et al., 1998) using an ERWEKA hardness tester.

5.4.1.3 Friability test

This test was designed to measure the breakdown of tablets due to rubbing, undershock or vibration. Ten tablets were dusted with a small brush to remove any powder and weighed (W1). Then the tablets were placed in the plexiglass drum of the apparatus (ERWEKA Friabilitator), which was operated at 25 rpm for 4 minutes. Thereafter, the tablets were removed from the drum, again dusted and weighed (W2), and the percentage of the mass lost determined using equation 11.

% mass lost = (W1-W2) / W1 X 100 eq.11

5.4.1.4 Disintegration test

The disintegration of the manufactured tablets was tested using the disintegrating apparatus described in the British Pharmacopoeia 1980. One tablet was placed in each of the five functional tubes of the apparatus. The disintegration medium was distilled water, kept at 37±1°C. The apparatus was operated for sixty minutes, the disintegration time for five tablets recorded individually and the mean values calculated. All the tablets that had good friability and hardness were subjected to this test.

5.4.1.5 Dissolution test

The amount of plant material dissolved from each manufactured tablet and the rate of dissolution was determined using the UV-Visible spectrophotometer. To determine the wavelength of maximum absorption, a diluted solution of plant material, ($0.01\%^{w}/_{v}$) was prepared and its absorption spectrum obtained over the wavelength range of 260 to 320nm.

The dissolution test was done using the Hanson Dissolution Tester with the paddles rotating at 100 rpm (Hanson, A. W., 1982) and distilled water as dissolution medium. The distilled water is recommended for tablets not specified in monographs (Hanson, A. W., 1982). Six tablets were taken and each placed in 900ml of the aqueous medium, de-aerated with helium and kept at 37 ± 1° C. Thereafter 5ml samples of solution were withdrawn with a glass syringe at 15 minute intervals. Each sample withdrawn was immediately replaced with equal volume of fresh dissolution medium. The samples were filtered through membrane filter and the absorbance of the filtrate determined in the spectrophotometer at the wavelength of maximum absorption (285.6nm).

The absorbance of each sample was converted to concentration with the aid of a standard curve of concentration versus absorbance. To obtain this standard

curve, the solutions containing amounts of powder equivalent to 25%$^{w}/_{v}$, 50% $^{w}/_{v}$, 75% $^{w}/_{v}$ and 100% $^{w}/_{v}$ of the powder of plant materials incorporated in one tablet were prepared by means of serial dilution in dissolution medium and the absorbance of each standard solution read at the wavelength of maximum absorption (285.6nm). A standard curve of concentration versus absorbance was plotted and the concentrations of the dissolution samples determined using the Graph Pad software (Prism2.01).

5.4.2 Results and discussion

Representative examples of tablets which were prepared are given in figure 6 and the results of the assessment of their physicochemical properties are given below

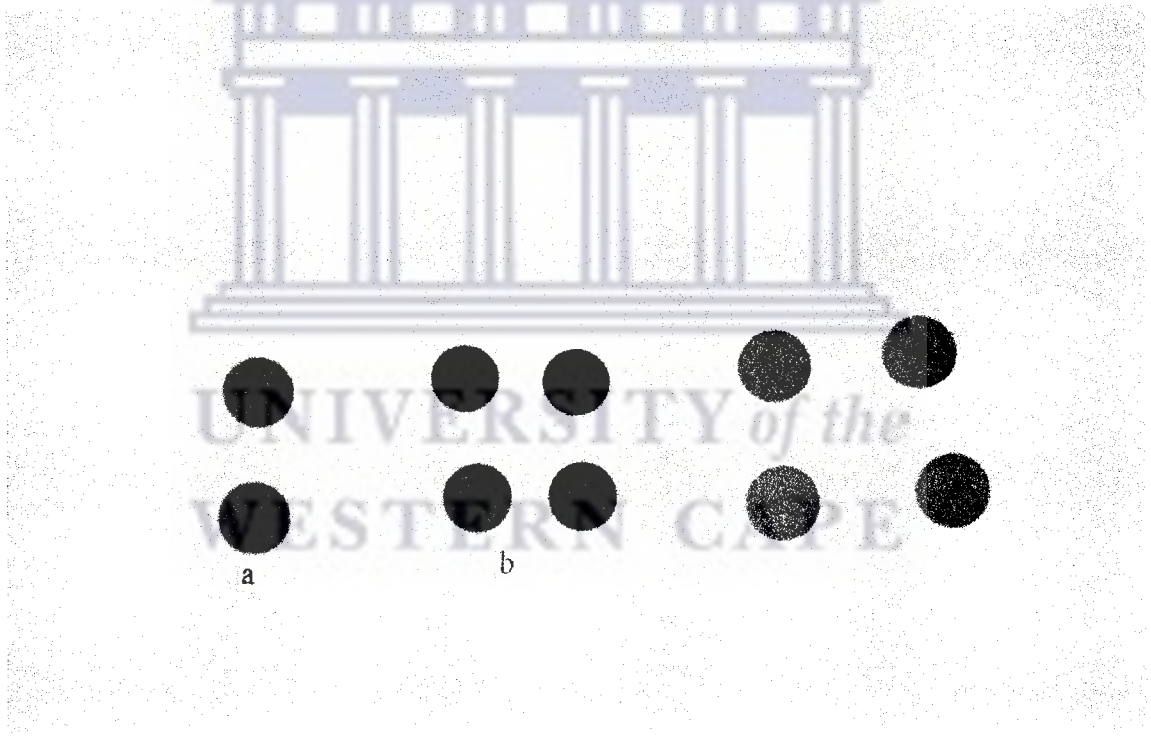


Figure 6: Tablets made from Dry Extract 1 (a), Dry Extract 2 (b) and from dry leaf powder (c).

5.4.2.1Mass uniformity

The results of this test are given in Tables 22 and 23.

Table 22: Mass of the tablets containing dry leaf powder

	Formula1.b	Formula2.a	Formula2.b	Formula3
Tablet	Weight (mg)	Weight (mg)	Weight (mg)	Weight (mg)
1	503	524	560	510
2	509	513	532	493
3	535	540	561	533
4	506	520	559	544
5	543	513	542	496
6	537	525	555	517
7	507	512	557	538
8	550	526	551	540
9	537	506	526	516
10	531	532	544	512
11	508	515	532	508
12	535	513	542	502
13	510	525	525	517
14	521	494	540	500
15	540	549	550	498
16	537	538	530	520
17	531	525	551	507
18	528	532	528	502
19	552	493	535	520
20	507	502	544	530
Mean	526	519	543	515
Std. dev.	3.5	14	11.9	15.2
C.V	0.6	2.6	2.2	2.9
Mean+5%	542	545	570	540
Mean-5%	500	493	516	489

Table 23: Mass of the tablets containing the Dry Extracts

	Formula5.a	Formula4	Formula6	Formula7	Formula8
Tablet	Weight (mg)	Weight (mg)	Weight (mg)	Weight (mg)	Weight (mg)
1	272	300	296	351	300
2	277	295	305	355	302
3	290	299	306	350	306
4	283	302	299	356	316
5	280	305	298	356	296
6	287	301	307	350	305
7	295	299	308	359	308
8	286	312	303	351	300
9	293	303	304	354	304
10	281	300	306	355	305
11	279	288	298	358	312
12	286	313	297	356	313
13	279	290	301	260	301
14	288	298	299	350	307
15	285	296	303	353	311
16	285	295	300	355	309
17	282	289	295	356	303
18	286	316	297	352	312
19	290	305	302	357	310
20	293	300	300	354	299
Mean	285	300	301	354	305
St.dev.	6.3	7.4	3.8	3	5.4
C.V	2.2	2.4	1.2	0.8	1.8
Mean+5%	299	315	316	371	320
Mean–5%	270.75	285	286	336	289

The final weights of the tablets essentially depended on the initial amount of plant raw material incorporated. Therefore the tablets manufactured with the dry leaf powder obviously had a higher mass (515 mg) than the tablets containing the dry extracts (354mg). The weights of the tablets also depended on the proportion of plant material incorporated per tablet, i.e. the mass increased when the percentage of plant material decreased, as shown by the mass of tablets made from formula 1.b vs. that from formula 3, and the mass of tablets obtained from formula 7 vs. that from formula 8. The deviation in mass of the tablets was however within the limits of the Pharmacopoeia; i.e. for each batch the mass of not more than two tablets deviated from the average weight by more than ± 5% of the average weight (B.P.1980, vol.II.). Also the coefficient of variation was low. All the formulas therefore resulted in tablets having acceptable uniformity of mass.

5.4.2.2 Hardness

The mean and standard deviation of the values of hardness measured on 4 randomly chosen tablets per formula batch are given in table 24. The small sample was due to the few tablets produced in each batch.

Table24: The hardness of the manufactured tablets

	Hardness of tablet (N) per Formula										
	Formula with dry leaf powder					Dry Extract 1				Dry Extract2	
Formula	1.a	1.b	2.a	2.b	3	4	5.a	5.b	6	7	8
Tablet 1	8	27	25	23	26	8	25	20	31	57	58
2	12	32	23	19	24	10	27	28	29	52	62
3	11	25	26	15	22	16	23	28	33	57	60
4	9	30	24	20	27	12	29	24	27	54	60
Average (Std. Dev)	10 (1.8)	28.5 (3.1)	24.5 (1.3)	19.2 (4)	25.8 2.2	11.5 (3.4)	26 (2.5)	25 (3)	30 (2.6)	55 (2.4)	60 (1.6)

The results showed that the tablets derived from the three different plant materials used in the present study differed strikingly in hardness. The final formula for tablets containing dry leaf powder (formula 3) provided tablets having a hardness of 25.8N. This was significantly (t-test, $p < 0.0001$) different from that obtained for tablets using the first formula (10N). This difference was, as anticipated, mainly due to the different amounts of the binder (Starch) used in the formulations (i.e. 6% in first formula vs. 9% in the final formula). In other words when the tablets based on formula 1.a was found to have unacceptable hardness, more binder was intentionally added (formulas 2 & 3) to solve the problem. The hardness of the tablets obtained from the formulas containing Dry Extract 1 ranged from 11.5N to 30N; again the increase in amount of the binder used (starch 1500), from 17% to 22%, was responsible for this result.

Finally, the hardness of tablets made from Dry Extract 2 was very high (55N and 60N), most likely because of the high proportion (15%) of binder used. However the crystalline appearance of the particles of Dry Extract 2 (mentioned in section 4.3.3.4), probably also contributed to this excessive hardness. Thus, for all the three forms of raw plant material, the hardness of the manufactured tablets increased with the increased amount of the binder used in the tablet formulation for each batch. The dry leaf powder however required a lower proportion of binder than the Dry Extracts.

The hardness of the tablets made from the different plant material also differed. The tablets obtained from the final formula containing dry leaf powder (formula 3) had a hardness of 25.8N, while the final formulas containing Dry Extract 1 and 2 (formula 6 and 7) provided tablets which had hardnesses equal to 25N and 55N, respectively. These differences between the tablets from different plant material were, most likely, due to the differences in the physical properties of the powder of the three forms *of D. angustifolia* plant material and the proportion of binder used in the formulation.

Although the pharmacopoeias do not specify a limit value for the hardness of tablets, tablets having a hardness of approximately 35N would be considered to be satisfactory because the higher hardness of the tablets could lead to slower disintegration and dissolution of the tablets (Achanta, A. S., 1997). Based on the above considerations, it can be concluded that the final formulas for all three forms of plant material resulted in the tablets having acceptable hardness, but tablets made from Dry Extract 2 (formula 7 & 8) may have slower disintegration and dissolution.

5.4.2.3 Friability

The aim of the friability test was to assess if the manufactured tablets had the physical ability to withstand the processes such as storage and transport which occur subsequent to tabletting (Wilson, K. and Potter, A., 1998).

The results of the friability tests conducted on 10 tablets per trial batch are given in Table 25.

Table 25: Friability (%) of tablet formulated with *D. angustifolia* plant material

	Formula containing										
	Dry leaf powder					Dry Extract 1				Dry Extract2	
	1.a	1.b	2.a	2.b	3	4	5	5.b	6	7	8
Friability (%)	5	2	0.9	1.1	0.8	5	1.2	1.5	0.8	0.95	0.98

The friability of the trial tablets was determined to evaluate the ability of tablets to be handled without chipping, cracking or breaking. Generally a formula is considered optimal when the friability of the tablets is less than 1%.

The final formula (formula 3) for tablets containing dry leaf powder allowed the manufacture of the tablets which had a friability of only 0.8%. This was

significantly different to that obtained for tablets based on the first formula (5%). As was the case in the hardness test, the friability of the tablets also depended on the proportion of binder used in the formulation (e.g. 6% of binder in the first formula vs. 9% of binder in the final formula). The friability of the tablets from Dry Extract 1 ranged between 5 and 0.8%, and the proportion of binder used ranged between 17% and 22%. The friability of the two batches of tablets containing Dry Extract 2 was 0.95% and 0.98% and the proportion of binder used was 15%.

It was noted that the friability of the tablets decreased with an increasing amount of the binder used in the formulation and with increasing hardness of the tablets. Consequently, the strategy adopted was to improve the friability by increasing the proportion of binder in the formulation for each plant material.

The friability and hardness of the manufactured tablets could also be improved by increasing the compression force, but this approach was not adopted because it was anticipated that a high compression force could provoke an undesirable increase in disintegration time and dissolution time of the tablets (Hanson, A. W., 1982).

Finally, the results obtained in this study suggest that the final formulas elaborated for the three forms of plant material of *D. angustifolia*, had allowed the manufacture of tablets with acceptable friabilities, viz. 0.8% for tablets containing dry leaf powder (in formula 3) and tablets containing Dry Extract 1 (in (formula 6), and 0.95% for the tablets containing Dry Extract 2 (formula 7).

5.4.2.4 Disintegration test

Tablets prepared from formulas 1.a, 1.b, 4 and 5.a did not have satisfactory hardness and friabilities and were therefore not subjected to the disintegration test. The results of the disintegration test performed on the tablets from the other formulas are presented in table 26.

Table 26: Disintegration times of the tablets containing *D. angustifolia* plant material.

Disintegration time of each of the 5 tablets (min)	Tablet Formula containing						
	Dry leaf powder			Dry Extract1		Dry Extract2	
	2.a	2.b	3	5.b	6	7	8
T1 (min)	4	2.5	3	35	26	28	34
T2 (min)	4	3	3	38	27	29	34.5
T3 (min)	6	4	3.5	40	27	29	35
T4 (min)	6	4	3.5	40	28	30	35
T5 (min)	7	5	4	41	30	32	36
Mean (min)	5.4	3.7	3.1	38	27.6	29.6	34.9
Std.dev.	(1.3)	(0.9)	(0.3)	(2.3)	(1.5)	(1.5)	(0.7)

The results showed that the tablets containing dry leaf powder disintegrated rapidly (between 3 and 5 min), while the tablets containing the dry extracts only disintegrated after a long time (i.e. 27.6min and 29.6min for the tablets containing Dry Extract 1 and 2, respectively). Usually the optimum disintegration time for a tablet is 30 min (Hanson, A. W., 1982). Renoux, R. et al. (1996) found the comparable results from the formula containing 50 % of active plant origin. This possessed relatively long disintegration times between 40 and 45 minutes.

In this study, it was also noted that the fast disintegration of the tablets containing dry leaf powder was accompanied by their breaking up and releasing the particles of the tablets into the disintegration medium. On the other hand the long disintegration of the tablets containing the Dry Extracts occurred without their breaking up; instead they dissolved during the disintegration process. Normally the process of disintegration of the tablets consists of water penetration into the tablet, swelling and finally break-up. The slow disintegration of the present tablets containing Dry Extract 1 and 2 was due to poor water penetration (Van Kamp, H.

V., 1986). In fact, the slow disintegration of these tablets was the consequence of the slow solubility of the dry extracts as was observed in the preformulation study.

Excipients with disintegrant properties were used in the formulation to improve the disintegration of the tablet. For example the addition of Explotab® (1%) in the formulation resulted in the reduction of disintegration time of the tablets containing Dry Extract 1 from 38 min to 27.6 min.

Comparison of the disintegration times of tablets from formula 7 vs. that from formula 8, and that from formula 5.b vs. formula 6 clearly showed that increasing the proportion of excipients having the disintegrating properties, viz. Starch1500® and Explotab®, α-Lactose monohydrate, Tablettose®, and Emcocel 90M®, per tablet resulted in a significant reduction (T-test, $p < 0.0001$) in the disintegration time (see table 27).

Table 27: The effect of proportion of disintegrants on the disintegration time of the tablets

	Disintegrant and proportion					Disintegra-
Formula	Starch 1500® (%)	Tablettose® (%)	Emcocel ® (%)	Explotab® (%)	Total (%)	tion time ± Std. Dev. (Min)
5.b	22	10	1		33	38 ± 2.3
6	22	10	1	1	34	27.6 ± 1.5
7	15	9	1.5	4	29.5	29.6 ± 1.5
8	10	7	0.5	2	19.5	34.9 ± 0.7

Because of the known influence which compression force has on disintegration time, in terms of porosity of the tablets (Lowenthal, W., 1972 and Rockosloh, K. et al., 1999) the powder mixes in this study were only compressed with moderate compression force.

In summary, even though the tablets containing the Dry Extracts disintegrated slowly, all the tablets from the final formulations had acceptable disintegration times; 3min for tablets formulated with dry leaf powder, 27.6 min for the tablets formulated with Dry Extract 1 and 29.6min for the tablets formulated with Dry Extract 2.

5.4.2.4 Dissolution test

The UV-Visible spectrophotometric scan/graph for the aqueous solutions of the *D. angustifolia* plant materials (dry leaf powder and dry extracts) indicated 2 peaks for maximum absorption (see figure10). The peak at wavelength 285.6 nm was selected to monitor the dissolution of the tablets. At this wavelength the standard curves of concentration vs. absorbance for each of the plant materials were linear

(Dry leaf powder r^2 = 0.9978, Dry Extract1 r^2 = 0.9997 and Dry extract 2 r^2 = 0.9998) (see figure11).

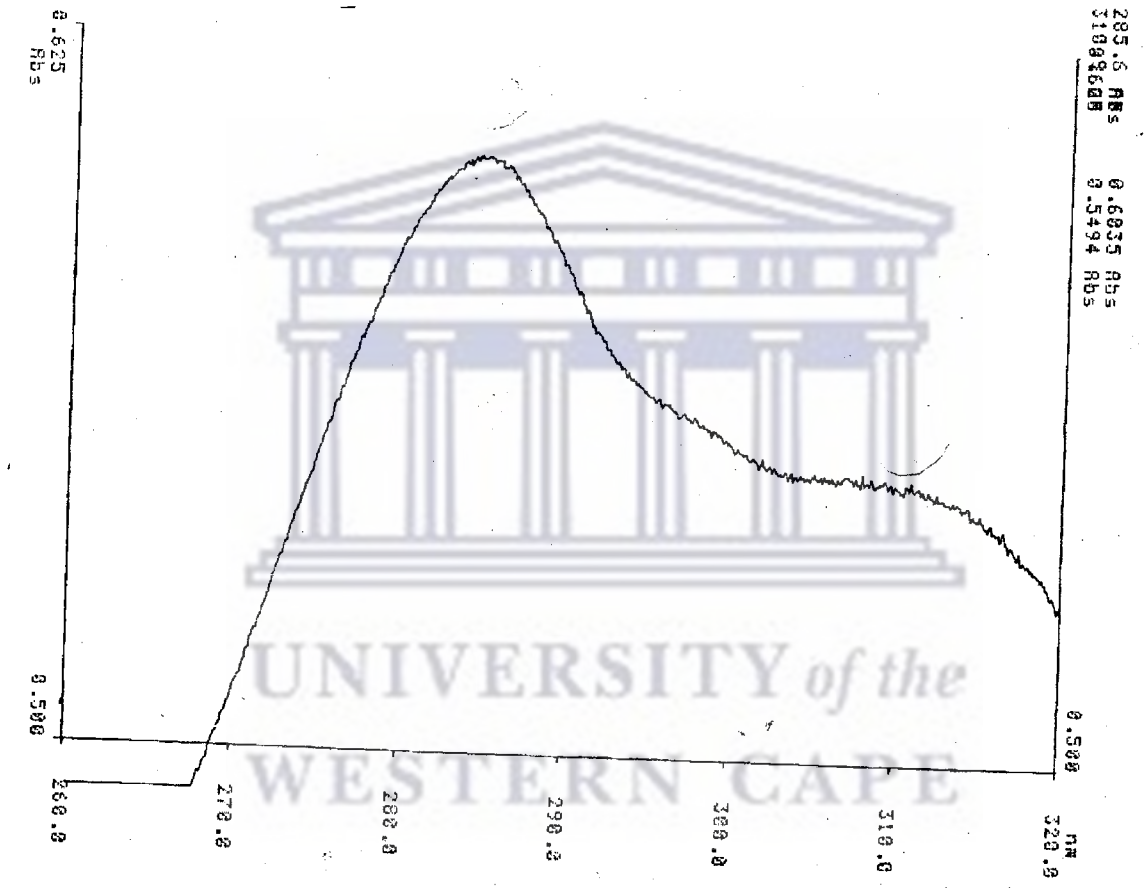


Figure 10: UV-Visible spectrophotometric scan/graph for the aqueous solutions of the *D. angustifolia* plant material

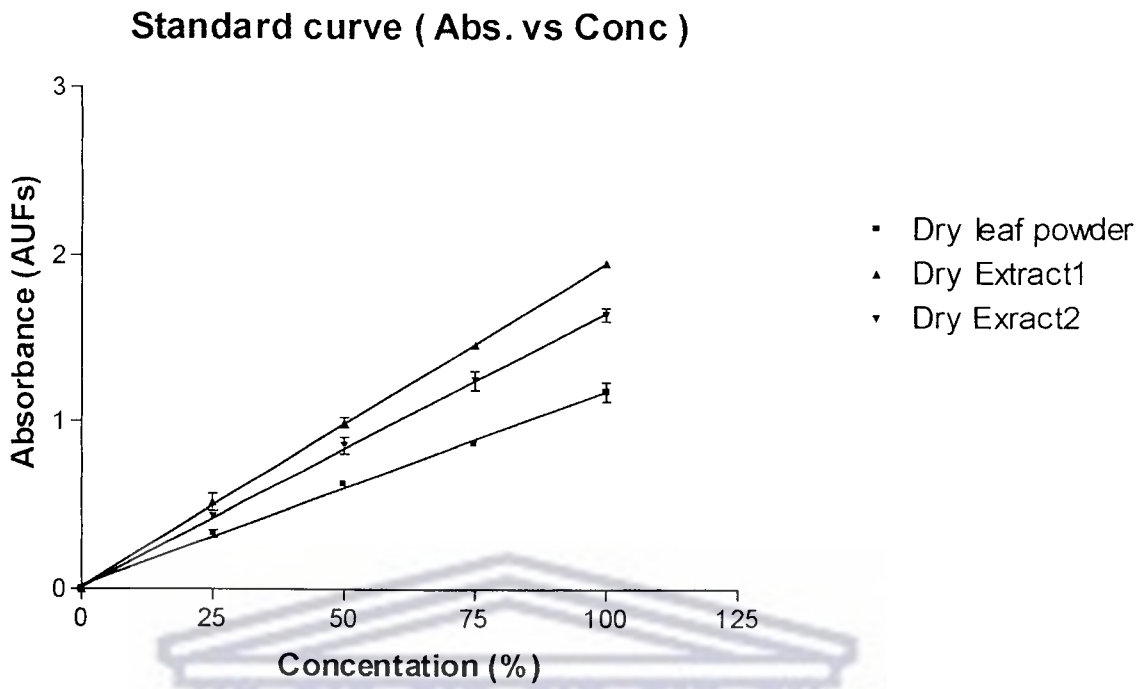


Figure 11: Standard curve of concentrations of plant material powders vs. UV absorption at 285.6 nm.

The results of the dissolution test of the trial-tablets are given in the Appendix 4, and are summarized in figure 12

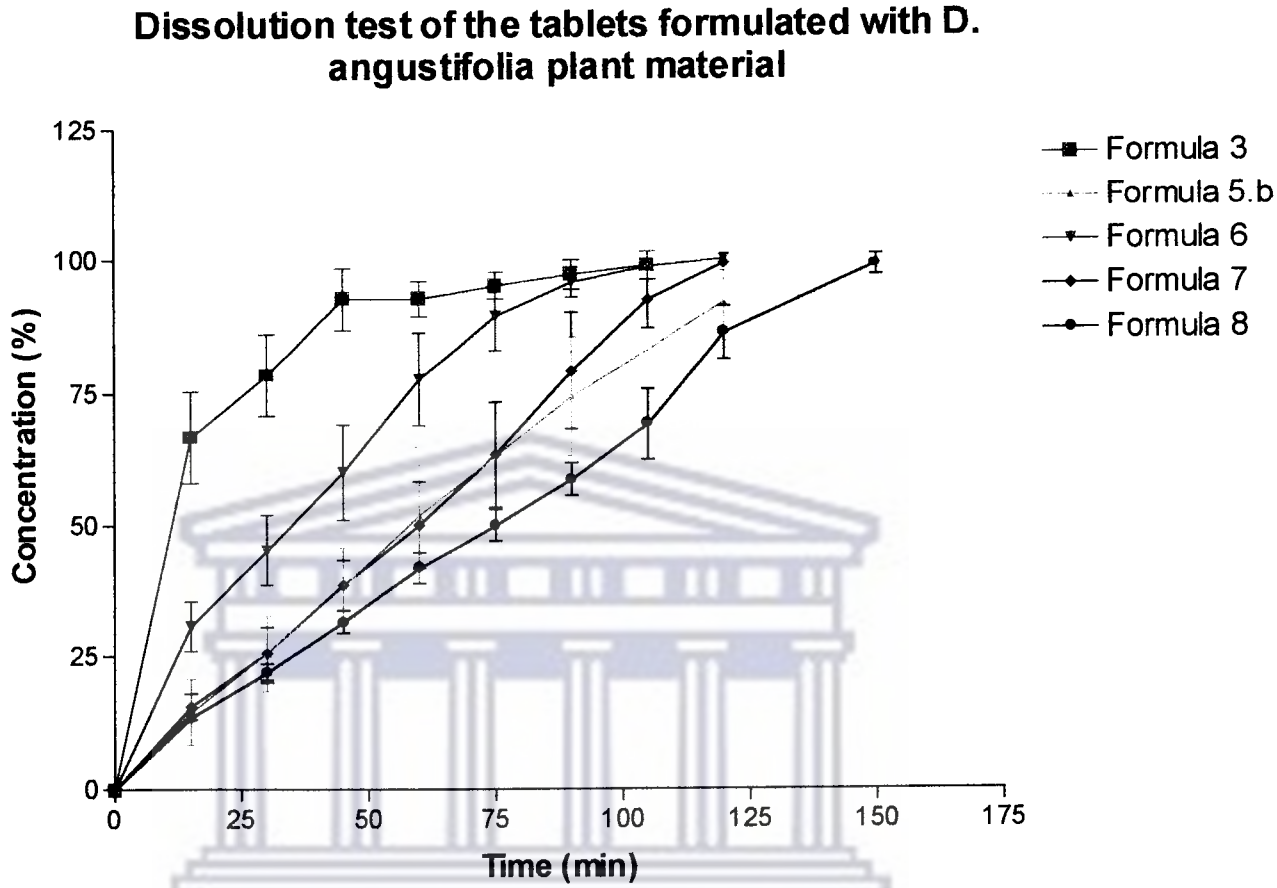


Figure 12. Dissolution profiles of batches of trial- tablets containing dry leaf, Dry Extract 1 and Dry Extract 2 powder

The general dissolution specification proposed in the Pharmacopeial Forum 1981 states that 75% of the labeled amount of active material must dissolve within 45 min (Hanson, A. W., 1982). The British Pharmacopoeia general specification requires that not less 70% of the labeled amount appear in solution in 45 min (British Pharmacopoeia 1993 Addendum, 1996)

There was a difference in dissolution rates obtained for the tablets from the three forms of plant material prepared in this study; dry leaf powder (formula 3), Dry Extract 1 (formula 5.b and formula 6) and Dry Extract2 (formula 7and 8). For

example, after 45 min 92.7% of the dry leaf powder, 60.2% of dry extract 1 and 38.6% of Dry Extract 2 had dissolved. These significant differences (t–test, $p<0.0001$) were most likely due to the differences in physical properties, such as particle size and size distribution, solubility and compressibility, which was shown (chapter 4) to exist between the plant raw materials.

It was further noted that the parameters affecting tablet disintegration, also affected the dissolution of the tablets i.e. an improvement in the disintegration resulted in an improvement of the dissolution rate of the tablets. For example the dissolution rate of the tablets of formula 5.b was improved in formula 6, due to the addition a new disintegrating agent Explotab® in the formulation. Also, the dissolution rate of the tablets was increased when the proportion of disintegrating agent was increased (e.g. formula 8 vs. formula 7).

Based on the British Pharmacopoeia limits and the dissolution rates of the tablets made from the final formulas, viz. formula 3, 6 and 7, it was concluded that the tablets made from the final formulas of the three forms of *D. angustifolia* plant material were acceptable. However, the differences between these tablets were quite distinctive. The tablets containing dry leaf powder had a rapid dissolution rate, the dissolution rate of the tablets containing Dry Extract 1 was slightly below the acceptable limits, while the dissolution rate of the tablets containing Dry Extract 2 was very low.

5.4.3 Conclusion

The above-described evaluation of the trial-tablets aimed to assess if the tablets could contain the maximum amount of *D. angustifolia* plant material and still comply with the usual physical properties required of the tablets.

From the results of the tests performed on the tablets manufactured from the final formulas, the mass uniformity of the tablets was found acceptable. The hardness

of the tablets made from all three forms of *D. angustifolia* plant material was also acceptable, but the hardness of the tablets containing the dry extracts was slightly high. The friability as well as the disintegration time of the tablets of all of the three plant forms were also acceptable. The tablets made from all the three forms of *D. angustifolia* plant material disintegrated within 30 minutes, but differed in their overall disintegration behaviour; the tablets made from dry leaf powder disintegrated faster than the tablets from the dry extracts which disintegrated slowly and without breaking up. The latter characteristics were eventually reflected in the dissolution profile of the manufactured tablets. The dissolution of the tablets containing the dry extracts were slow and occurred without breaking up of the tablet in the dissolution medium, and the dissolution of the tablets containing the dry leaf powder was rapid accompanied with breaking up of the tablets. Despite the low dissolution rate of the tablets containing Dry Extract 1 and Dry Extract 2, the manufactured tablets from the final formula still had a satisfactory dissolution rate.

In summary, one can conclude that the tablets made from *D. angustifolia* leaf material had good physical properties, with the tablets containing the dry leaf powder having the best physical characteristics of all.

5.5 OVERALL CONCLUSION OF CHAPTER

The aim of the work detailed in the present chapter was to formulate, manufacture and evaluate tablets having the equivalent amount of *D. angustifolia* plant material as found in the amount of leaves used in preparation of the current dosage form (viz. decoction) of this traditional medicine. Consequently tablets containing 450 mg of dry leaf powder, 200 mg powder of Dry Extract 1 and 250 mg powder of Dry Extract 2 of *D. angustifolia*, separately, per tablet were formulated, manufactured and tested. Based on the results obtained the following conclusions could be made.

The formulations show that there were differences in the proportion of raw dry and extracted plant material incorporated in the tablet formulations of *D. angustifolia* leaves. That meant that substantially more dry leaf powder than powder of dry leaf extracts can be incorporated into the tablet, mainly due to the differences in the physical properties of the plant materials that lead to the need for different proportions of excipients.

All the three forms of *D. angustifolia* plant material permitted the production of the tablets by the direct compression method. However, the manufacture of the tablets containing the dry leaf powder was easier than the tablets containing the dry extracts. The latter required special conditions of humidity, and much more binder was needed to obtain satisfactory tablets.

The data of the evaluation of the manufactured tablets demonstrate that the tablets obtained from *D. angustifolia* plant material physically complied with criteria set for the acceptability of all the physical properties of the tablets. Differences existed among the tablets and these depended basically on the form of the raw plant material (i.e. whether dry leaf powder or dried extract) and the excipients used in the formulation of each batch of the tablets.

In summary, from the results of the experiments on the formulation, manufacture and evaluation of the trial tablets, we can conclude that tablets having satisfactory physical characteristics can be obtained from the three raw plant materials prepared from the leaves of *D. angustifolia*. However the proportion of dry extract powders incorporated into the tablets were reduced by the increasing proportion of excipients necessary to obtain tablets having the required physical characteristics, especially good disintegration and good dissolution.

CHAPTER 6

CONCLUSION

The primary goal of this study was to present *D. angustifolia* plant material in a solid dosage form which could offer the best convenience for the patient and a greater stability of the active ingredient compared to the currently used dosage form (decoction). After reviewing the advantages offered by the solid dosage forms especially the tablets, it was proposed that the tablet dosage form could be a realistic solution to this problem.

Consequently, the first objective of this study was to formulate and manufacture the tablets using the plant material found in the single dose decoction prepared from *D. angustifolia* plant material.

The second objective was to assess the suitability of the use of the dried leaf powder vs. dry aqueous extract from the leaves of *D. angustifolia,* in formulation and manufacture of the tablets.

It was hypothesized that tablets containing a large amount of *D. angustifolia* plant material (80% of plant material per tablet), and still complying with all the criteria set for a tablet dosage form (i.e. suitable hardness, friability, disintegration and dissolution) could be formulated and manufactured by the direct compression method.

It was also hypothesized that the raw plant material obtained by direct powdering of dried leaves or by extraction of the leaves might have different properties which would require different formulation strategies.

The three forms of *D. angustifolia viz.* dry leaf powder, Dry Extract1 and Dry Extract2 from the leaves of *Dodonaea Angustifolia* were consequently prepared and their physicochemical properties evaluated to assess their suitability for a tablet formulation. Different formulations of the tablets were elaborated using the three different forms of *D. angustifolia* plant material and subjected to the direct compression method of tablet manufacture. Finally, the trial tablets were tested for their physical properties.

From the results of the present study the hypothesis of this study is justified and the following main conclusions can be drawn:

Firstly, directly dried powder or dry extracts raw material derived from *D. angustifolia* leaves possess different physical characteristics (i.e. differences in density, flowability, size and shape of particles and moisture content). These characteristics have a great influence on the formulation of the tablets, on the tabletting process and on the physical properties of the final tablets. Such differences in physical characteristics probably also exist between material prepared from other parts of this and other plants viz. roots, flowers, fruits etc. which are usually used in traditional medicines. Clearly the characteristics of these plant materials must first be established in order to obtain the best chance of successful formulation and manufacture of tablets of plant material.

2. Tablets from *D. angustifolia* leaf material can, despite the presence of poor tabletting properties or even if having poor tabletting properties, be manufactured by the direct compression method, through the appropriate selection and use of excipients, good formulation and appropriate tabletting process conditions.

3. The proportion of plant material derived from the leaves of *D. angustifolia* which can be incorporated into directly compressed tablets is very much dependent upon the form of the raw material. If directly dried leaf powder is used it can form up to 85% of the tablet material mass, whereas only lower proportional

amounts of extracts could be incorporated into satisfactory tablets. Whether this phenomenon or rule will apply to materials obtained from other parts of this plant or with leaves from other plants is not clear and warrants further investigation.

4. Unlike in the case for directly dried leaf powder, the preparation of tablets containing material obtained by aqueous extraction from *D. Angustifolia* leaves is very sensitive to the humidity of the environment. One can assume that the humidity could also affect the manufactured tablets and hence the stability and shelf-life of the product. This too needs further investigation.

5. Finally, the tablets formulated and manufactured from directly dried powder and extracts of *D.Angustifolia* showed distinctly different disintegration and dissolution profiles. The results suggest that the differences were due to both the physical properties of the raw materials as well as the excipients used. The impact that such differences in disintegration and dissolution might have on the bioavailability of such dosage forms derived from plant materials also warrants further investigation.

In summary, *D. angustifolia* plant material presented into the tablet dosage form can offer many advantages in terms of stability, distribution and improved controllability of the dose of plant material in tablet dosage form compared to that in the liquid dosage form viz. decoction. This study confirmed that the formulation and manufacture of tablets meeting acceptable criteria can be made of this plant and presumably other plants as well. Issue like hygroscopicity, compressibility may require further investigation.

In general, the present study shows that medicinal plant can be presented in pharmaceutical dosage forms which are most used in modern healthcare viz. tablets. Although the investigations are not yet done, we can assume that the tablets containing plant materials could provide the same advantages as conventional tablets viz. good physical and microbiological stability, easy

administration and greater control of dosage. These advantages are beneficial for the all users of medicinal plant viz. patients and traditional healers. In addition, considering the number of users of medicinal plant, the economic benefits of use of tablets of traditional plants medicines should be also substantial. The support of both government and private sector is needed to further assist in research on the improvement of the use of medicinal plants.

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ANNEXURES

Annexure1:

Table 28: Index of compressibility vs. flowability of powder

compressibility index (Carr's index)	Flow quality
5-10	Excellent
12-16	Good
18-21	Fair to passable
23-35	Poor
33-38	Very poor
>40	Very very poor

(Wells, J. I., 1988, p.210, table 7.1)

Annexure 2

Table 29:Interpretation of Carr's index for powder flow.

Angle of repose θ	Flow quality
< 25	Excellent
25-30	Good
30-40	Passable
>40	Poor

(Wells, J. I., 1988, p.211)

Annexure 3:

Table 30: Relationship between compressibility and flow quality of powder and suitable method of tablet manufacture

Compressibility	Flow quality	Suitable method in tablet manufacture
Good	Good	Direct compression
Good	Poor	Slug or roller compact
Poor	Good	Wet granulation
Poor	Poor	Wet granulation

(Carstensen, J.T.; 1993, p.77)

APPENDICES

Appendix 1: Particle size of powder prepared from *D.angustifolia* plant material observed by microscope

Appendix 1.1: Elongation and Heywood's ratio(N=L/B) of the particles of dry powder

	L µm	B µm	N		L µm	B µm	N			L µm	B µm	N
1	5	5	1	35	5	5	1		69	20	5	4
2	10	5	2	36	65	50	1.3		70	15	15	1
3	20	15	1.3	37	15	5	3		71	90	60	1.5
4	15	5	3	38	85	50	1.7		72	20	15	1.3
5	25	15	1.6	39	5	5	1		73	40	40	1
6	10	5	2	40	10	5	2		74	10	10	1
7	10	5	2	41	20	15	1.3		75	25	25	1
8	60	40	1.5	42	50	45	1.1		76	55	35	1.5
9	65	35	1.8	43	25	25	1		77	55	30	1.8
10	15	10	1.5	44	15	15	1		78	100	75	1.3
11	5	5	1	45	15	10	1.5		79	15	10	1.5
12	20	10	2	46	50	35	1.4		80	5	5	1
13	5	5	1	47	10	5	2		81	15	10	1.5
14	100	75	1.3	48	30	20	1.5		82	40	35	1.1
15	20	10	2	49	95	45	2.1		83	45	35	1.1
16	15	5	3	50	40	40	1		84	65	50	1.3
17	5	5	1	51	10	5	2		85	15	15	1
18	40	30	1.3	52	25	10	2.5		86	35	25	1.4
19	60	55	1.1	53	50	50	1		87	10	10	1
20	20	5	4	54	30	15	2		88	50	25	2
21	20	15	1.3	55	10	10	1		89	70	40	1.7
22	75	25	3	56	15	10	1.5		90	50	45	1.1
23	10	5	2	57	40	25	1.6		91	70	45	1.5
24	100	30	3.3	58	20	10	2		92	75	50	1.5
25	10	10	1	59	20	20	1		93	20	20	1
26	25	15	1.6	60	20	20	1		94	55	40	1.3
27	40	15	2.6	61	15	10	1.5		95	80	25	3.2
28	20	20	1	62	20	20	1		96	10	5	2
29	10	10	1	63	75	50	1.5		97	25	20	1.2
30	15	5	3	64	5	5	1		98	15	10	1.5
31	10	10	1	65	20	20	1		99	5	5	1
32	15	5	3	66	10	10	1		100	10	10	1
33	20	15	1.3	67	75	35	2.1					
34	5	5	1	68	15	5	3		**M***	**20**	**15**	**1.4**

L= length B= Breadth **M***= Median

Appendix 1.2: Elongation and Heywood's ratio (N=L/B) of the particles of Dry Extract1

	L µm	B µm	N		L µm	B µm	N			L µm	B µm	N
1	400	300	1.3	35	75	50	1.5		69	150	150	1
2	275	175	1.5	36	450	300	1.5		70	400	400	1
3	75	75	1	37	200	200	1		71	350	350	1
4	125	125	1	38	200	175	1.1		72	75	75	1
5	250	200	1.2	39	250	75	3.3		73	75	75	1
6	150	100	1.5	40	25	25	1		74	175	175	1
7	100	75	1.3	41	100	75	1.3		75	100	100	1
8	250	75	3.3	42	100	75	1.3		76	225	175	1.3
9	125	100	1.2	43	175	150	1.1		77	200	100	2
10	75	50	1.5	44	275	200	1.3		78	225	225	1
11	150	25	6	45	200	150	1.3		79	275	200	1.3
12	175	175	1	46	275	175	1.5		80	525	50	10
13	150	50	3	47	500	375	1.3		81	75	75	1
14	500	200	2.5	48	300	275	1.1		82	125	50	2.5
15	150	150	1	49	525	225	2.3		83	425	150	2.8
16	125	75	1.6	50	250	125	2		84	200	200	1
17	250	150	1.6	51	100	100	1		85	200	150	1.3
18	50	50	1	52	550	225	2		86	250	100	2.5
19	75	50	1.5	53	125	100	1.2		87	100	100	1
20	375	300	1.3	54	175	125	1.4		88	150	125	1.2
21	175	75	2.3	55	275	275	1		89	125	75	1.6
22	175	125	1.4	56	325	325	1		90	325	225	1.4
23	100	100	1	57	300	300	1		91	175	150	1.1
24	200	100	2	58	625	625	1		92	150	125	1.2
25	100	75	1.3	59	375	375	1		93	150	75	2
26	200	150	1.3	60	625	625	1		94	500	100	5
27	75	75	1	61	200	200	1		95	125	50	2.5
28	175	100	1.7	62	75	75	1		96	100	75	1.3
29	75	50	1.5	63	200	200	1		97	125	125	1
30	200	125	1.3	64	300	300	1		98	50	25	2
31	300	150	2	65	375	375	1		99	375	275	1.3
32	250	50	5	66	200	200	1		100	250	125	2
33	125	100	1.2	67	200	200	1					
34	125	25	5	68	275	275	1		**M***	**200**	**125**	**1.3**

L= length B= Breadth **M*= Median**

Appendix 1.3: Elongation and Heywood's ratio (N=L/B) of the particles of Dry Extract 2

	L µm	B µm	N		L µm	B µm	N			L µm	B µm	N
1	561	382	1.4	35	230	204	1.1		69	357	306	1.1
2	331	255	1.3	36	306	204	1.5		70	357	306	1.1
3	382	280	1.3	37	230	153	1.5		71	575	433	1.3
4	459	382	1.2	38	357	230	1.5		72	561	408	1.3
5	306	230	1.3	39	408	230	1.7		73	408	331	1.2
6	153	127	1.2	40	331	255	1.3		74	484	382	1.2
7	459	382	1.2	41	357	331	1.07		75	433	380	1.5
8	575	255	2.3	42	204	178	1.1		76	408	357	1.1
9	280	204	1.3	43	230	204	1.1		77	535	178	3
10	382	382	1	44	561	484	1.1		78	357	280	1.2
11	255	204	1.2	45	153	127	1.2		79	510	331	1.5
12	484	306	1.5	46	484	280	1.7		80	459	459	1
13	306	230	1.3	47	153	153	1		81	408	280	1.4
14	433	382	1.1	48	280	280	1		82	433	306	1.4
15	535	408	1.3	49	382	306	1.2		83	459	331	1.3
16	280	153	1.8	50	510	280	1.8		84	76	51	1.5
17	382	382	1	51	280	255	1.1		85	331	255	1.3
18	230	153	1.5	52	408	255	1.6		86	357	178	2
19	204	153	1.3	53	433	255	1.7		87	178	178	1
20	408	408	1	54	306	255	1.2		88	255	153	1.6
21	459	204	2	55	331	230	1.4		89	306	230	1.3
22	76	76	1	56	382	204	1.8		90	255	204	1.2
23	178	178	1	57	459	357	1.2		91	204	204	1
24	204	204	1	58	153	102	1.5		92	76	51	1.5
25	382	382	1	59	357	204	1.7		93	331	306	1.08
26	127	102	1.2	60	230	230	1		94	127	102	1.2
27	382	331	1.1	61	484	408	1.2		95	280	178	1.5
28	230	204	1.1	62	382	178	2.1		96	127	102	1.2
29	178	153	1.1	63	127	76	1.6		97	204	178	1.1
30	357	255	1.4	64	280	102	2.7		98	178	127	1.4
31	510	306	1.6	65	331	255	1.3		99	382	280	1.3
32	230	230	1	66	459	204	2.2		100	382	331	1.1
33	382	255	1.5	67	255	255	1					
34	280	204	1.3	68	178	76	2.3		**M***	**344**	**242**	**1.3**

L= length B= Breadth M*= Median

Appendix 3: Absorbance for standard curve

Appendix 3.1: Solution prepared using dry leaf powder

Absorbance	Concentration of the solution			
	100%	75%	50%	25%
Sample 1(AUFs)	1.137	0.870	0.615	0.311
Sample 2(AUFs)	1.136	0.875	0.610	0.320
Sample 3(AUFs)	1.250	0.945	0.644	0.356
Average(AUFs)	1.174	0.863	0.623	0.329
SD(AUFs)	0.06	0.016	0.018	0.024

Appendix 3.2: Solution prepared using dry extract1

Absorbance	Concentration of the solution			
	100%	75%	50%	25%
Sample 1(AUFs)	1.950	1.463	0.9742	0.512
Sample 2(AUFs)	1.949	1.462	0.973	0.513
Sample 3(AUFs)	2.110	1.505	1.02	0.520
Average(AUFs)	1.950	1.463	0.988	0.515
Std. Dev.(AUFs)	0.002	0.001	0.003	0.05

Appendix 3.3: Solution prepared using dry extract2

Absorbance	Concentration of the solution			
	100%	75%	50%	25%
Sample 1 (AUFs)	1.672	1.215	0.819	0.429
Sample 2 (AUFs)	1.619	1.215	0.828	0.429
Sample 3 (AUFs)	1.746	1.300	0.906	0.477
Average (AUFs)	1.645	1.246	0.851	0.429
Std. Dev .(AUFs)	0.04	0.06	0.05	0.001

Appendix 4: Results of dissolution test

Appendix 4.1: Concentration (%) of drug substance in dissolution medium vs. time of dissolution (Formula 3)

Time (min)	Tablet1 (%)	Tablet2 (%)	Tablet3 (%)	Tablet4 (%)	Tablet5 (%)	Tablet6 (%)	Average (%)	Std. dev.
15	63.14	64.74	77.26	66.92	75.19	53.46	66.79	8.66
30	82.11	69.21	82.30	81.53	87.37	68.81	78.55	7.68
45	92.73	83.46	92.93	90.21	91.98	79.11	92.71	5.76
60	95.21	86.31	94.33	94.34	92.73	93.36	92.71	3.25
75	97.03	91.15	96.87	97.44	93.33	95.32	95.19	2.49
90	99.524	93.671	99.67	99.43	93.95	97.17	97.23	2.81
105	100.37	95.22	102.12	100.56	96.06	99.14	98.91	2.71

Appendix 4.2: Concentration (%) of drug substance in dissolution medium vs. time of dissolution (formula5.b)

Time (min)	tablet 1 (%)	tablet 2 (%)	tablet 3 (%)	tablet 4 (%)	tablet 5 (%)	tablet 6 (%)	Average (%)	Std. dev.
15	13.36	16.20	14.42	14.61	13.68	15.69	14.45	1.10
30	24.74	27.18	24.91	25.70	24.33	26.80	25.61	1.16
45	39.60	39.56	35.94	39.45	38.92	40.81	39.07	1.64
60	52.77	51.34	47.84	58.42	50.10	51.16	51.94	3.57
90	83.81	70.86	67.06	83.84	71.81	68.90	74.38	7.50
120	98.40	87.09	97.93	93.14	83.77	91.53	91.97	5.81

Appendix 4.3: Concentration (%) of drug substance in dissolution medium vs. time of dissolution (Formula 6)

Time (Min)	Tablet1 (%)	Tablet2 (%)	Tablet3 (%)	Tablet4 (%)	Tablet5 (%)	Tablet6 (%)	Average (%)	St.Dev.
15	22.34	30.04	30.2	32.93	32.89	36.32	30.79	4.730
30	36.02	43.12	39.84	53.46	49.62	49.91	45.33	6.740
45	53.14	57.62	56.35	77.33	54.07	62.7	60.20	9.039
60	69.43	74.22	75.44	93.88	73.14	80.42	77.76	8.666
75	80.92	85.58	86.39	97.08	95.66	90.77	89.40	6.254
90	90.95	93.73	96.97	98.36	97.47	97.35	95.81	2.860
105	97.47	98.82	99.39	99.19	99.56	97.53	98.66	0.931
120	99.98	99.74	100.41	99.74	100.52	100.14	100.088	0.330

Appendix 4.4: Concentration (%) of drug substance in dissolution medium vs. time of dissolution (Formula 7)

Time (Min)	Tablet1 (%)	Tablet2 (%)	Tablet3 (%)	Tablet4 (%)	Tablet5 (%)	Tablet6 (%)	Average (%)	St.Dev.
15	15.154	14.85	15.83	11.80	11.80	18.79	15.718	15.718
30	24.68	24.70	24.67	17.84	17.84	31.56	25.669	25.669
45	35.48	34.84	36.79	34.86	34.86	45.42	38.600	38.600
60	43.14	41.47	47.95	47.80	47.80	61.38	50.156	50.156
75	54.13	53.85	64.40	57.94	57.94	77.45	63.492	63.492
90	70.22	69.21	85.71	69.21	69.21	93.21	79.243	79.243
105	95.92	91.75	94.67	82.04	82.04	95.78	92.474	92.474
120	99.15	99.02	99.71	98.89	98.89	98.98	99.302	99.302

Appendix 4.5: Concentration (%) of drug substance in dissolution medium vs. time of dissolution (Formula 8)

Time (Min)	Tablet1 (%)	Tablet2 (%)	Tablet3 (%)	Tablet4 (%)	Tablet5 (%)	Tablet6 (%)	Average (%)	St.Dev.
15	13.67	13.24	13.91	14.04	13.43	12.75	13.512	0.47
30	21.41	19.89	20.18	23.72	24.01	21.82	21.842	1.73
45	32.42	29.12	28.84	32.94	31.69	34.11	31.5259	2.12
60	42.09	38.68	38.02	42.96	46.94	42.21	41.8185	2.95
75	50.94	46.57	46.22	53.80	51.36	50.74	49.945	2.95
90	59.76	54.11	57.03	57.66	62.78	60.80	58.694	3.07
105	61.05	63.01	66.31	74.54	77.81	71.97	69.119	6.68
120	84.29	77.89	84.68	89.51	90.44	90.44	86.211	4.93
150	98.90	97.41	97.14	102.88	98.68	98.91	98.993	2.05