Addis Ababa University

School of Pharmacy

College of Health Sciences

Department of Pharmaceutics and Social Pharmacy

Evaluation of Cactus (*Opuntia stricta*) Mucilage as Sustained Release Excipient in Diclofenac Sodium Matrix Tablet Formulation

By

Elias Zenebe (B.Pharm)

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A Thesis Submitted to the Department of Pharmaceutics and Social Pharmacy, School of Pharmacy, College of Health Sciences, Addis Ababa University, in Partial Fulfillment of the Requirements for the Degree of Master of Science in Pharmaceutics under the Supervision of Dr. Anteneh Belete, Department of Pharmaceutics and Social Pharmacy, School of Pharmacy, Addis Ababa University

December, 2018
Addis Ababa, Ethiopia

Declaration

I declare that the thesis for the MSc. Degree at Addis Ababa University, hereby submitted by me, is my original work and has not been submitted for a degree at this university or any other university, and that all reference materials contained therein have been duly acknowledged.

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Abstract

Nowadays, plant derived polymers have received increasing attention due to their diverse pharmaceutical applications in controlled drug delivery. Among these natural polymers, mucilages and gums are versatile excipients for pharmaceutical formulations. The main objective of the present study was to evaluate cactus (*Opuntia stricta*) mucilage as a matrix forming polymer for sustained release tablet formulations of diclofenac sodium. In this study, mucilage from cactus cladode was extracted by using distilled water as extracting solvent and ethanol as mucilage precipitant. The mucilage powder was characterized for physical properties. A 1% w/v solution of the mucilage in water gave a pH of 6.40, which shows low irritability potential in uncoated tablets. The powder was fairly flowing on the funnel, showing the need of other compressible excipient and granulation to make it better flowable. The Kawakita constants of compressibility and cohesiveness showed that the powder is compressible and cohesive. The solubility and swelling power of the *Opuntia stricta* were generally low at low temperature (20 °C), but increase significantly at higher temperature (85 °C) ($p < 0.05$). Percent moisture sorption ranged from 7.61% at 15% and 79.9% at 100% RH. On viscosity test, the mucilage showed pseudo-plastic property.

The granules prepared with water as granulating solvent showed excellent flow property. The formulated matrix tablets were found to have good uniformity of weight. The tablets of different batches of directly compressed formulations were found to possess acceptable hardness within the range of 76.23 ± 0.24 to 80.51 ± 0.81. Crushing strength of wet granulated formulations was higher than the directly compressed formulations. The *in vitro* dissolution study demonstrated that both directly compressed and wet granulated formulations using *Opuntia stricta* mucilage effectively sustained diclofenac release for more than 12 h, even at low concentration, 10 %. However, granulation showed a better matrix for sustained release of drug from the tablets. All the formulations showed good linearity with respect to Korsmeyer-Peppas equation with $0.45 \leq n \leq 0.89$ indicating that, non Fickian diffusion was the predominant mechanism of drug release from these formulations. So, *Opuntia stricta* mucilage can be used as alternative pharmaceutical excipient in the formulation and manufacture of sustained release matrix tablets.

Key words: *Opuntia stricta* mucilage, direct compression, wet granulation, matrix tablets, *in vitro* drug release

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Acronyms

APIs: Active Pharmaceutical Ingredients

CI: Carr's Index

DW: Dry Weight

DS: Diclofenac Sodium

EC: Ethylcellulose

GIT: Gastro Intestinal Tract

HEC: Hydroxy-Ethyl Cellulose

HPC: Hydroxy-Propyl Cellulose

HPMC: Hydroxy-Propyl-Methyl Cellulose

HR: Hausner's Ratio

NDDS: Novel Drug Delivery System

NSAIDs: Non - Steroidal Anti-Inflammatory Drugs

OFI: *Opuntia Ficus Indica*

OS: *Opuntia Stricta*

PLA: Polylactic Acid

PLGA: Polylactic-Co-Glycolic Acid

PMMA: Poly-(Methyl Methacrylate)

RH: Relative Humidity

SP: Swelling Power

SR: Sustained Release

USP/NF: United States Pharmacopeia / National Formulary

UV: Ultra Violet

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1. Introduction

New drug development is expensive and time consuming process. Increasing safety-efficacy ratio of "existing" drugs has been attempted by different methods such as individualizing drug therapy, dose titration, and therapeutic drug monitoring. Drug delivery at controlled rate, slow delivery, and targeted delivery are other very attractive methods and has been pursued vigorously. Many different types of dosage forms are developed for these purposes (Preekorn *et al*., 1988).

The goal of any drug delivery system is to provide a therapeutic amount of drug to the proper site in the body to achieve promptly and then maintain the desired drug concentration, i.e. the drug delivery system should deliver drug at rate dictated by the needs of the body over a specified period of treatment. The two most important aspects of drug delivery system are spatial placement and temporal delivery of a drug. Spatial placement is targeting a drug to a specific organ or tissue, while temporal delivery stands to control the rate of drug delivery to the target organ or tissue (Wise, 2000).

Matrix tablet is an ideal dosage form for sustained drug delivery and has been pursued vigorously. The pharmaceutical world is in search of polymers for a better success. Nowadays, plant derived polymers have received increasing attention due to their diverse pharmaceutical applications including, among others, as diluents, binders, disintegrants in tablets, thickeners in oral liquids, protective colloids in suspensions, gelling agents in gels and bases in suppositories. Among these natural polymers mucilages and gums are versatile sustained release excipients for pharmaceutical formulations (Bhosale *et al*., 2014).

Oral route is the oldest and most convenient route for administration of therapeutic agents because of ease of administration, patient acceptance, accurate dosing, cost effective manufacturing method and gastrointestinal physiology flexibility in dosage form design than other routes and improved shelf-life of the product (Avachat and Dhamane, 2002).
Conventional immediate-release tablet dosage forms are known by drug plasma level fluctuation. Modifying drug release by using rate controlling dosage forms, like matrix system, is nowadays

common in adjusting the drug plasma level fluctuation. Reducing the blood levels (C_{max}) and increasing the minimum plasma concentration (C_{min}), thus potentially reduces dose related adverse effects and increases efficacy (Sarwar and Hossain, 2012).

1.1. Matrix Tablet

Matrix is defined as a well-mixed composite of one or more drugs with hydrophilic or insoluble hydrophobic matrices or plastics, or can be as the type of controlled drug delivery system, which releases the drug in continuous manner through dissolution controlled and diffusion controlled mechanisms. By the sustained release method, therapeutically effective concentration can be achieved in the systemic circulation over an extended period of time, thus achieving better compliance of patients. Matrix tablet as sustained release (SR) has given a new breakthrough for novel drug delivery system (NDDS). It excludes complex production procedures such as coating and pelletization during manufacturing and drug release rate from the dosage form is controlled mainly by the type and proportion of polymer used in the preparations. Matrix systems are widely used for the purpose of sustained release (Heda and Shivhare, 2004).

Matrix tablets are considered to be the commercially feasible dosage forms that involve the least processing variables utilizing conventional facilities and simple technologies (Khadka *et al.*, 2014) and can accommodate large doses of drug, are highly reproducible and have normally the advantage of stable raw materials and dosage form (Hakulinen *et al.*, 2008). Direct compression of blend of drug, retardant material and additives to formulate a tablet in which the drug is embedded in a matrix of the retardant is one of the least complicated approaches to the manufacture of sustained release dosage forms. Alternatively drug and retardant blend may be granulated prior to compression. There remains an interest in developing novel formulations that allow for sustained drug release using readily available, inexpensive excipients by matrix based formulations. To control the release of the drugs having different solubility properties, the drug is dispersed in swellable hydrophilic substances, an insoluble matrix of rigid non-swellable hydrophobic materials or plastic materials (Banker and Rhodes, 2002).

Matrix tablets maintain therapeutic concentrations over prolonged periods, avoids high blood concentration, reduce toxicity; minimize side effects, improves therapeutic efficacy, enhances drug utilization, minimizes drug accumulation with chronic dosing, can be made to release high molecular weight drugs, increases stability by protecting the drug from hydrolysis or other

degradative changes in GIT, reduces health care cost, and uses less drug and improves patient compliance (Venkatraman *et al*, 2000).

The materials widely used in preparing matrix systems include both hydrophilic and hydrophobic polymers. From the two groups, hydrophilic polymers are the most widely used ones. The hydrophilic materials are potentially swellable and control the release of drug through diffusion. Commonly available hydrophilic polymers includes; Hydroxypropyl methylcellulose (HPMC), Hydroxypropyl cellulose (HPC), Hydroxyethyl cellulose (HEC), Xanthan gum, Sodium alginate, Poly ethylene oxide and cross-linked homopolymers and copolymers of Acrylic acid (Gandhi *et al.*, 2012). The hydrophobic materials, on the other hand, are potentially erodable and control the release of drug through pore diffusion and erosion. Some of most commonly used hydrophobic polymers for their better loading capacity of hydrophobic drugs include: (polyesters); polylactic acid (PLA) and polylactic-co-glycolic acid (PLGA), Carnauba wax, (ammoniomethacrylate copolymers) Eudragit, and Ethylcellulose (EC) (Reja *et al*, 2003).

1.1.1. Controlled-Release Mechanisms in Matrix Tablets

Erosion is one of controlled release mechanisms which involve hydrolysis of hydro-gels and this is useful in the controlled release of macromolecules entangled within their network structure. Solubilization of water-insoluble polymers by reactions is also an erosion mechanism involving pendant groups from the polymer backbone. Of particular interest are polymers that solubilize by ionization of carboxylic acid groups. Cleavage of hydrolytically labile bonds within the polymer backbone is also within this category (Colombo *et al.*, 1996).

Diffusion as another controlled-release mechanism occurs when a drug or other active agent passes through the polymer that forms the controlled-release device. The polymer here is insoluble and rigid, and the polymer mesh size is constant (Xiaoling and Bhaskara, 2006).
Swelling increases the aqueous solvent content within the formulation as well as the polymer mesh size, enabling the drug to diffuse through the swollen network into the external environment which is the other alternative as controlled-release mechanism (Pradum *et al*., 2013)

Using biodegradable polymers that degrade within the body as a result of natural biological processes eliminating the need to remove a drug delivery system after release of the active agent has been completed is also the other latest option (Xiaoling and Bhaskara, 2006).

1.2. The Need for Natural Alternative Polymers

Most of the polymers currently used for matrix tablet formulation are synthetic. However, most synthetic polymers are expensive, need long development time for synthesis and some are toxic and have environment related issues (Narendra *et al*. 2016). Adverse effects like (skin and eye irritation) have been observed in workers handling the related substances methyl methacrylate and poly-(methyl methacrylate) (PMMA) (Sahu and Mishra, 2016). Reports of adverse reactions to povidone $(C_6H_9NO)_n$ primarily concern the formation of subcutaneous granulomas at the injection site. There is also evidence that povidone may accumulate in organs following intramuscular injections (Hizawa *et al*., 1984). Acute oral toxicity studies in animals have indicated that Carbomer-934P $(C_3H_4O_2)_n$ has a low oral toxicity at a dose of up to 8 g/kg. Carbomer dust is irritating to the eyes, mucous membranes and respiratory tract. So, gloves, eye protection and dust respirator are recommended during handling (Manchanda *et al.*, 2014). Studies in rats have also shown that 5% polyvinyl alcohol aqueous solution injected subcutaneously can cause anemia and can infiltrate various organs and tissues (Rathi PC, 2013). It has been shown that poly glycolides, polylactides and their co-polymers have an acceptable biocompatibility, but exhibit systemic or local reactions due to acidic degradation products. An initial mild inflammatory response has been reported when using poly-(propylene fumarate) in rat implant studies, some drugs show incompatibilities with many of the current range of synthetic excipients (Bashir *et al.*, 2016).

1.3. Natural Polymers and Their Growing Concern in Safety, Availability and Affordability

There is growing concern about the development of pharmaceutical excipients derived from natural sources. Cactus has been used as a major food source realizing that its safety as a source of pharmaceutical excipients. The pharmaceutical industries in developing countries should develop excipients and active ingredients from local sources as an alternative for the production

of pharmaceuticals, and they must develop systems that assure the safety and feasibility of excipients and active ingredients from local sources (Tesfay B., 2011).

The use of natural polymers for pharmaceutical applications is attractive, because; they are nontoxic, less expensive, amenable to chemical modifications, potentially biodegradable, and with few exceptions, are also biocompatible (Beneke *et al.,* 2009).

Naturally available biodegradable polymers are produced by all living organisms. They represent truly renewable source and have no adverse impact on humans or environmental health (*e.g.*, skin and eye irritation) (Leung *et al.,* 1996).

Chemically, nearly all of these plant materials are carbohydrates composed of repeating sugar (monosaccharides) units. Hence, they are non-toxic. It is also always cheaper to use natural sources. The production cost is also much lower compared with that for synthetic material. Ethiopia and many developing countries are dependent on agriculture (Narendra *et al*, 2016).

Natural polymers are also environmental-friendly in processing; mucilages (for example) from different sources are easily collected in different seasons in large quantities due to the simple production processes involved (Leung *et al.,* 1996).

In developing countries, governments promote the production of plant like cactus, because of the wide applications in a variety of industries (Beneke *et al.,* 2009).

1.4. Mucilages and Gums

Mucilages are normal products of metabolism, formed within the cell (intracellular formation) and are produced without injury to the plant and form slimy masses in water; while gums are considered to be pathological products formed following injury to the plant or owing to unfavorable conditions, such as drought, by a breakdown of cell walls (extra cellular formation;

gummosis) and readily dissolve in water. Both mucilages and gums are plant hydrocolloids yielding mixture of sugars and uronic acids on hydrolysis (Qadry, 2008).

Mucilages and gums can be classified based on sources; marine origin/algal (seaweed) gums: agar, carrageenans, alginic acid, and laminarin; plant origin: shrubs/tree exudates: gum arabic, gum ghatti, gum karaya, gum tragacanth, and khaya and albizia gums; seed gums: guar gum, locust bean gum; extracts: pectin, larch gum; animal origin: chitin and chitosan, chondroitin sulfate, and hyaluronic acid; microbial origin (bacterial and fungal): xanthan, dextran, curdian, pullulan, zanflo, emulsan, Baker's yeast glycan, schizophyllan, lentinan, krestin, and scleroglucan (Kokate *et al*., 2008).

Originally, the term "gum" was probably applied to natural plant exudates that had oozed from tree barks and hardened upon exposure to air. Gums can be grouped into three major categories, namely, natural gums, modified gums and synthetic gums. Natural gums are found in a natural state such as the tree exudates or seaweed hydrocolloids. Examples include; gum arabic, guar gum and gum tragacanth (Kokate *et al*., 2008).

Natural gums are produced in response to wounding (exudate gums) and extracted from seeds of some legumes (extractive gums). Examples of exudate gums are gum arabic from *Acacia spp*., gum tragacanth from *Asiatic astraglus spp*., gum karaya from *Sterculia spp.* and gum ghatti from *Anogeissus latifolia*. Examples of extractive gums include; locust gum from *Certonia siliqua* and guar gum from *Cyamopsis tetragonolobus*. Modified gums are chemically modified natural gums or derivatives of naturally occurring materials such as cellulose or starch. Synthetic gums are completely synthesized chemical products such as polyvinylpyrolidone (PVP) and ethylene oxide polymers. Tens of thousands of people worldwide, living in regions ranging from semiarid deserts to rainforests depend on the collection of gums as a source of their income. Equally, many millions of people around the world make use of these products in their everyday life (Robbins S. 1988)

1.4.1. Some Natural Mucilages Used as Pharmaceutical Excipients

Fenugreek Mucilage, obtained from seeds of *Trigonella foenum-graceum* (family: *Leguminosae*), dissolve in water, but form viscous tacky mass and swell up when exposed to fluids and contains mannose, galactose, and xylose. The mucilage obtained from fenugreek was found to be better release retardant compared to hypromellose at equivalent content (Ali *et al*, 2008). *Hibiscus Mucilage,* obtained from fresh leaves of *Hibiscus rosa-sinensis* (family: *Malvaceae*) contains L-rhamnose, D-galactose, D-galacturonic acid, and D-glucuronic acid. The use of its mucilage for the development of sustained release tablet has been reported (Jani G. and Shah D. 2008).

Aloe mucilage, obtained from the leaves of *Aloe barbadensis* (family: *Liliaceae*), contains arabinan, arabinorhamnogalactan, galactan, galactogalacturan, glucogalactomannan, galactoglucoarabinomannan, and glucuronic acid containing polysaccharide. A controlled delivery system of glibenclamide using aloe mucilage was studied. Various formulations of glibenclamide with *Aloe barbadensis* miller leaves mucilage were prepared by direct compression technique. The formulated matrix tablets were found to have better uniformity of weight and drug content with low statistical deviation. The swelling behavior and *in vitro* release rate characteristics were studied. The dissolution study proved that the dried *Aloe barbadensis* Miller leaves mucilage can be used as a matrix forming material for making controlled release glibenclamide matrix tablets (Kumar *et al*, 2010).

Cocculus mucilage, obtained from leaves of *Cocculus hirsute* (family: *Menispermaceae*), contains polysaccharides and a gelatinous type of material and is nontoxic to human skin. Gelling property of this mucilage was studied. Dendrophthoe mucilage, obtained from dried as well as fresh stem parasite of *Dendrophthoe falcate* (family: *Loranthaceae*) on *Magnifera indica* (family: *Anacardiaceae*). Mucilage of *Dendrophthoe falcata* was evaluated as a binder for pharmaceutical dosage forms wet granulation was employed to make tablets with *Dendrophthoe falcate* mucilage (Leung and Foster, 1996)

Cassia tora mucilage derived from the seeds of *Cassia tora* (family: *Caesalpiniaceae*), contains cinnamaldehyde, gum, tannins, mannitol, coumarins, and essential oils (aldehydes, eugenol, and

pinene); it also contains sugars, resins, and mucilage among other constituents. Studies were performed on *Cassia tora* mucilage for its binding property. It was observed that increasing the concentration of mucilage increases hardness and decreases the disintegration time of the tablets which were formulated with different concentrations of *cassia tora* gum. This mucilagewas also evaluated for its suspending agent. The suspending ability of *Cassia tora* mucilage was compared with that of tragacanth, acacia, and gelatin. The suspending ability of all the materials was found to be in the order: *Cassia tora* > tragacanth gum > acacia gum. Results suggest that suspending action of the mucilage is due to high viscosity of the gum (Mann *et al*, 2007).

1.4.2. Some natural gums used as Matrix Morming Mgent

Tamarind seed Polysaccharide gum, obtained from the endosperm of the seed of the tamarind tree, *Tamarindus indica* (family *Fabaceae*) is composed of glucosyl: xylosyl: galactosyl in the ratio of 3:2:1. The polysaccharide obtained from tamarind seeds was made use of in formulating matrix tablets by wet granulation technique and was evaluated for its drug release characteristics (Mishra and Khandare, 2011).

Honey Locust Gum, obtained from the seeds of the plant *Gleditsia triacanthos* (family: *Leguminosae*). Honey locust gum has been used to produce matrix tablets at different concentrations (5% and 10%) by wet granulation method (Uner M. and Altinkurt T. 2004)

Neem Gum, obtained from the trees of *Azadirachta indica* (family: *Meliaceae*), contains mannose, glucosamine, arabinose, galactose, fucose, xylose, and glucose. Studies were performed on neem gum for its binding property matrix forming property (Gangurde A. *et al* 2008).

Gum Copal gum from plant *Bursera bipinnata* (family: *Burseraceae*), contains agathic acid along with ciscommunic acid, transcommunic acid, polycommunic acid, sandaracopimaric acid, agathalic acid, monomethyl ester of agathalic acid, agatholic acid, and acetoxy agatholic acid. Copal gum has been evaluated as matrix-forming material for sustaining the drug delivery (Osete L. and Domenech M. 2005).

Mimosa scabrella gum obtained from seeds of *Mimosa scabrella* (family: *Mimosaceae*), is highly hydrophilic galactomannan that provides 20–30% of galactomannan (G) with a mannose: galactose ratio of 1.1: 1. Studies were performed on *Mimosa scabrella* gum for its controlled release matrix forming property (Vendruscolo *et al*, 2005).

1.5. Advantages of natural mucilages and gums

Mucilages and gums are naturally available biodegradable polymers produced almost by all living organisms. They represent truly renewable source and they have no adverse impact on humans or environmental health (no skin and eye irritation) and non-toxic chemically, nearly all of these plant materials are carbohydrates composed of repeating sugar (mono-saccharides) units. Hence, they are non- toxic (Narendra *et al*. 2016).

Mucilages and gums are always cheaper, because can be easily collected from different sources and in different seasons in large quantities. The production cost is also much lower as compared with that for synthetic material due to the simple production processes involved. Processing of gums and mucilages is also environmental-friendly. Governments promote the cultivation of plants for production of gums and mucilages because of local availability and the wide applications in a variety of industries. Mucilages and gums have better patient tolerance as well as public acceptance. There is less chance of side and adverse effects with natural materials compared with synthetic one; since most gums and mucilages are obtained from edible sources (Kulkarni *et al*, 2009).

1.6. Applications of Gums and Mucilages

Mucilages of different sources and their derivatives represent a group of polymers widely used in pharmaceutical dosage forms. Various kinds of gums and mucilages are used in the food industry and are regarded as safe for human consumption. Plant gums and mucilages are now screened for their use as pharmaceutical adjuvants. Mucilages of different origins are also used in

conventional dosage forms of various drugs for their binding, thickening, stabilizing and humidifying properties in medicine (Raymond *et al*, 2006).

Newer uses of different gums and mucilages in cosmetics and textiles have increased the demand and screening of gums and mucilages. Gums can also used in cosmetics (acacia, tragacanth and karayagum), textiles (tamarind gum), adhesives (acacia gum, and tragacanth), lithography (gum arabic, tragacanth, and locust bean gum) and paper manufacturer (tamarind).

1.6.1. Applications in food industry

Gums and mucilages have a variety of applications in the food industry**.** The use of gums and mucilages in food is due to their ability to modify the rheology of food system. In concentrated system, these molecules begin to come into contact with one another; thus, the movement of molecules becomes restricted. The transition from free moving molecules to an entangled network is the process of thickening. Different gums have different uses like water retention and stabilization (guar and locust bean gum), stabilizers for ice-cream, meat products and instant pudding (carrageenanas), dairy, confectionary and meat products (agar), beverages, backed product, and sauces (gum arabic, tragacanth, pectins, alginates and xanthan gum) (Verbeken *et al*, 2003).

1.6.2. Pharmaceutical applications

Gums and mucilages have a variety of applications in pharmacy. They are ingredients of dental and other adhesives and can be used as bulk laxatives. These hydrophilic polymers are useful as tablet binders (Kulkarni *et al*., 2002), disintegrants, emulsifiers, suspending agents (Gebresamuel and Gebremariam, 2012), gelling agents, stabilizing agents, thickening agents, film forming agents in transdermal and periodontal films, buccal tablets as well as sustaining agents in matrix tablets and coating agents in microcapsules including those used for protein delivery (Koocheki *et al*.,2009).

1.7. Cactus

Cactus is a member of the plant family **Cactaceae**, a family comprising 127 genera with some 1750 known species of the order Caryophyllales (Gómez-hinostrosa and Hernández, 2000). Cactus is treelike, shrubby or caespitose plant; stem-segments cylindrical, club-shaped, sub-spherical, or more or less flattened, sometimes tuberculate, very rarely ribbed. Cactus (*Opuntia* spp.), *Cactaceae* family, is well adapted to arid and hot dry lands, where the plants have a marked capacity to withstand prolonged drought (Figure 1.1). The ability of *Cactaceae* to retain water under an unfavorable climatic condition is due, in part, to the water-binding capacity of mucilage.

Opuntia spp. is widely distributed in the globe. Interest in *Opuntia* (also known as cactus pear) dates back many thousands of years. Its origin and history are closely related to the ancient Mesoamerican civilizations and particularly to the Aztec culture. In his *General History of New Spain*, Fray Bernardino de Sagahún skillfully described the many ways of using cactus pear. He said: *"*There are some treelike, shrubby or caespitose plant in this land that are called nopalli, which means cactus pear or a plant that produces cactus pears. It is a huge plant whose trunk is made up of the leaves and offshoots from them; the leaves are wide and thick, with abundant juice, and are sticky; the leaves have spines. The fruit from these plants, called cactus pear, is good to eat; it is a valuable fruit. The leaves from the tree are eaten both raw and cooked. Some trees produce cactus pear fruit that are yellow inside, while others are red or pink inside, which are good to eat; others have green leaves with red markings, bearing fruit that are purple in color both inside and out'' (Viale, 2001).

Almost 300 species of the *Opuntia* species are known but, so far, only 10 to 12 species have been utilized for their fruit, tender leaves (cladodes), forage or cochineal for colorant production. The most widely cultivated species throughout the world is *Opuntiaficus-indica* (Gómez-hinostrosa and Hernández, 2000).

1.7.1. Global Distribution

The main countries where cactus naturally grows are Argentina, Bolivia, Brazil, Eritrea, Ethiopia, Israel, Italy, Mexico, Morocco, Peru, South Africa, Spain, Tunisia and the United States (Texas) (Gómez-hinostrosa and Hernández, 2000).

Figure 1.1 World distribution of *Opuntia spp*.

1.7.2. Distribution in Ethiopia

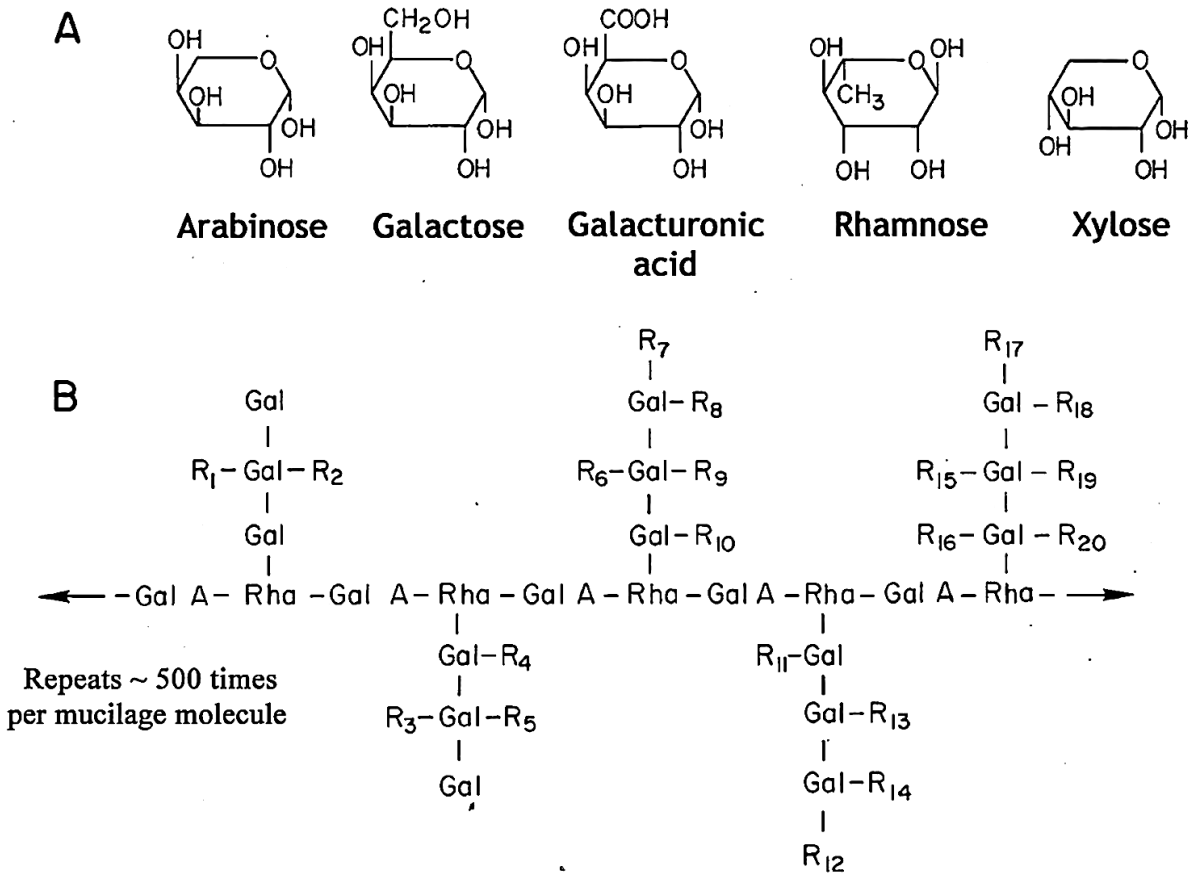
In Ethiopia (especially in the northern part) this cactus species (*Opuntia spp.*) is considered the 'Bridge of life'; because, the stems and fruit store large quantities of water and provide both feed for cattle in times of drought and food for livestock herders, so contributing to the survival of both farmers and their animals. If people in countries such as Ethiopia (and elsewhere) were to be informed of the widespread uses of cactus pear, for example, it may be possible to reduce malnutrition and to improve their quality of life. In Ethiopia the two opuntia species, *Opuntia stricta* and *Opuntia ficus-indica* are found in 2/3 and 1/3 ratio respectively (Tesfay B., 2011). In Tigray (northern Ethiopia) Cactus fruits (*Opuntia ficus indica* and *Opuntia stricta*) are the major

fruits that consumed directly by the people of the region. In this region it is estimated that, there is about 360, 000 hectare of cactus plant, of which about two thirds consists of spiny plants, about half of the existing area of *Opuntias* was planted and the remainder has been invaded by the naturalized cactus (Tesfay B., 2011, Shushay 2014).

Figure1.2: *Opuntia stricta* plant (photograph taken by E. Zenebe)

1.8. Cactus Mucilage

Cactus mucilage is a complex carbohydrate with a highly branched structure (Fig. 1.3), which contains varying proportions of L-arabinose, D-galactose, L-rhamnose and D-xylose, as well as galacturonic acid in different proportions. In decreasing order, sugars found in the mucilages were: L-arabinose (26.83–35.36%), D-galactose (21.59–45.48%), D-xylose (12.23–17.05%), uronic acids (5.59–13.91%) and L-rhamnose (1.41–5.40%),. The ability of *Cactaceae* to retain water under an unfavorable climatic condition is due to the water-binding capacity of the mucilage (Zhao *et al.*, 2007).



R = Arabinose or Xylose

Figure 1.3: Units and structure of cactus mucilage (Lothar *et. al.* 1975)

1.8.1. Cactus Mucilage Yield

The mucilage content varies depending on climatic conditions, species and age of the plant. According to Adriana Ca´rdenas *et al* (2007), mucilage content of OFI is 17.9% of total dry weight of the cladodes. They pointed out that the mucilage pads content could vary depending on climatic conditions, such as cold and rain due to the ability of these polysaccharides to absorb water as a plant defense against stress conditions. Another study by Zhao *et al.* (2007) showed that the average mucilage yield after drying was 1.48% based on fresh weight (f.w.) and 19.4% based on dry weight (d.w.) (for *Opuntia monacantha*).

In Tigray (northern Ethiopia) Cactus fruits (*Opuntia ficus indica* and *Opuntia stricta*) are the major fruits that are consumed directly by the people of the region. In this region, it is estimated that, there is about 360 000 hectares of cactus plant, of which about two thirds consists of spiny plants, about half of the existing area of *Opuntias* was planted and the remainder has been invaded by the naturalized cactus (Tesfay, 2011).

1.8.2. *Opuntia stricta* mucilage and Diclofenac Sodium

Mucilage from OS has superior quality to mucilage of OFI for use as pharmaceutical and food excipients/additives (Gebre-Samuel and Gebre-Mariam, 2012). According to this study, the mucilage yield of the two species found in Ethiopia is 1.17/17.5% and 1.7/19% for OFI and OS respectively, in fresh/dried form, showing somewhat better yield for OS. Based on Hausner ratio and the value of Carr's index, the OS mucilage exhibits better flow property. The fat (0.42% for OFI, 0.38% for OS) and protein (6.82% for OFI, 5.18% for OS) content is slightly lower for OS mucilage. The swelling power of the mucilage of OS was higher and has low hygroscopic nature. The conductivity result also showed the low electrolyte content of OS mucilage it was devoid of alkaloids and flavonoids and had low content of steroidal compounds, saponins and tannins indicating its neutrality as excipient. According to microbial load result OS had very low colony forming units than OFI (Gebre-Samuel and Gebre-Mariam, 2012).

Diclofenac sodium (DS) is nonsteroidal anti-inflammatory drug. This drug works by reducing substances in the body that cause pain and inflammation. DS is used to treat mild to moderate pain, or signs and symptoms of osteoarthritis or reumatoid arthritis, and these chronic diseases requires thrice a day dosing of DS due to its short half life (1-3 h). Even though DS is sparingly soluble, the high water binding property of OS mucilage suits with criterion for sustained release (Willis *et al*., 1979).

1.9. Significance of The Study

The specific purpose of the present study was to evaluatie cactus (*Opuntia stricta*) mucilage as sustained release excipient in matrix tablet formulation. Since, many of pharmaceutical companies in developing countries are dependent on import. The cactecae family especially, the *Opuntia spp* are well adapted to arid and hot dry lands to be easily cultivated. This study can fill this gap by evaluating the OS mucilage as sustaining agent as an alternating locally produced excipient.

The study includes extraction of the mucilage from locally available cactus plant, tablet formulation and granule preparation, tablet compression, characterization of tablets and finally evaluation of release characteristics of tablets containing different concentration of the mucilage.

The pharmaceutical industries in developing countries import excipients and active ingredients despite the availability of local sources. But, producing and manufacturing excipients may not be as difficult as active ingredients which should be practiced locally, and in addition most of these imported excipients are almost synthetic polymers (Arnum, 2011).
The need for pharmaceuticals is growing with the increasing of human population and health problems which in turn increases the demand of pharmaceutical excipients. So, searching for alternative excipients to fulfill the demand is another erea of solving the problem.

The synthetic polymers have certain disadvantages such as high cost, toxicity, environmental pollution during synthesis, non-renewable sources, side effects, and poor patient compliance. Acute and chronic adverse effects (skin and eye irritation) have been observed in workers handling the related substances methyl methacrylate and poly-(methyl methacrylate) (PMMA) Reports of adverse reactions to povidone primarily concern the formation of subcutaneous granulomas at the injection site produced by povidone. There is also evidence that povidone may accumulate in organs following intramuscular injections. Acute oral toxicity studies in animals have indicated that carbomer-934P has a low oral toxicity at a dose of up to 8 g/kg. Carbomer dust is irritating to the eyes, mucous membranes and respiratory tract (Hizawa, *et al*. 1984).

2. Objectives

2.1. General Objective

To evaluate Cactus (*Opuntia stricta*) mucilage as a matrix forming polymer for sustained release tablet formulations using diclofenac sodium as a model drug.

2.2. Specific Objectives

- To extract and characterize the mucilage from Cactus (*Opuntia stricta*)
- To formulate tablets
- To prepare powder blends and granules for tablet compression and characterize them
- To evaluate release characteristics of my tablets and The innovator SR tablets (Diclo-denk)
- To compare direct compression and wet granulated formulations
- To compare my tablets with the innovator SR tablets

3. Materials and methods

3.1. Materials

Fresh cladode of *Opuntia stricta* (OS) obtained from north of Addis Abeba 3 kms north of Kenya Embassy, Ethyl alcohol (NALF, Ethiopia), Magnesium stearate (BDH Laboratory supplies, England), lactose and NaOH (LOBA CHEMIE PVT.LTD, India), anhydrous diclofenac sodium working standard (Aarti Drugs Ltd, India) and HCL, Potassium phosphate monobasic (FARMITALIA CAROERBA, Italy).

3.2. Methods

3.2.1. Sample Identification

A sample of the material was identified as *Cactaceae family, Opuntia stricta (Haworth)* by Mr. Melaku Wendafrash, an expert at the Natural Herbarium Department of Biology AAU on September 2017.

3.2.2. Extraction of mucilage

Fresh cactus cladodes were collected and washed with purified water to remove dirt and debris. The cladodes were then cut into pieces using knife and homogenized using blender and soaked in water, in a proportion of 1:1 (g:ml), and kept for 3 h. Then, it was heated to 60 ^{o}C and then filtered through a fine cloth. Ethanol was added to the water extract at a proportion of 1:3 extract to ethanol ratio to precipitate the mucilage out and dried in an oven at 40 °C for 12 hrs (Sepu´lveda . *et al.*, 2007). Dried mucilage was then grounded and passed through 224 µm sieve size and kept in airtight plastic container (Femenia *et al.*, 2003)

3.2.3. Yield Determination

Fresh 100 g cladode was homogenized and extracted as per the procedure described earlier in section 3.2.2 for fresh weight yield determination. Oven dried (at 40 ^{o}C) 20 g homogenized cladode was dissolved in distilled water and extracted as per the same procedure for dry weight yield determination. Yields were recorded as averages of three determinations (Belete and Gebre-Mariam, 2003)

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3.2.4. Density and Related Properties

3.2.4.1. Bulk Density

Bulk density was determined by carefully pouring 30 g of powdered mucilage into a graduated glass measuring cylinder. The cylinder was then lightly tapped twice to collect all the powder sticking on the wall of the cylinder. The volume was then read directly from cylinder and used to calculate the bulk density (g/ml). The experment was done in triplicate and mean values were taken.

Bulk Density (ρ_b) $=M/V_b$ Eq. 3.1

Where M is the weight of the powder in grams and V_b is bulk volume in milliliter (Belete and Gebre-Mariam, 2003)

3.2.4.2. Tapped Density

30 g of sample powder was tapped in graduated measuring cylinder 500 times using tapped densitometer (ERWEKA, Germany). The volume was read and used to calculate the tapped; the experiment was done in triplicate and mean values taken.

Tapped Density (ρt) $= M/V_t$ Eq.3.2

Where M is the weight of the powder in grams and V_t is the tapped volume in milliliter

3.2.4.3. Hausner ratio (HR) and Carr's index (CI)

Hausner ratio (HR) and Carr's index (CI) were calculated from the bulk and tapped densities of the powder.

$HR = \rho t/ \rho b$ Eq. 3.3

$$CI = \left((\rho t - \rho b)/\rho t\right) \times 100 \qquad \text{Eq. 3.4}$$

3.2.5. Angle of Repose and Flow Rate

Angle of repose was evaluated using the standard funnel method. It was determined from the dimensions of the powder pile, which was formed when 30 g of powder mass was placed in a stem-less funnel and allowed to flow. The 15 mm orifice of the funnel was fixed at 10 cm above the base. Flow rate was measured from the time taken for the samples to flow. The values of angle of repose are flow rate averages of three measurements.

$$\Theta = \tan^{-1} h/r \qquad \text{Eq. 3.5}$$

Where r is radius of base of powder cone, h is the height of the powder cone and Θ is the angle of repose.

3.2.6. Kawakita analysis

Kawakita analysis was done following the method specified by Prakash *et al.*, (2011). Kawakita equation was applied to study the powder compression using the degree of volume reduction (C). Graduated measuring cylinder containing 30 g of powder was tapped with the help of tappied densitometer, 5, 10, 20, 30, 40, 50, 75, 100, 300, 400, 500 and 1000 times and the reduction in volumes were measured.

Measure of compressibility and cohesibity;

$$N/C = N/a + 1/ab \qquad \text{Eq.3.6}$$

Where, a = compressibility, 1/b = cohesibity

$$C = (V_O - V_N)/V_O \qquad \text{Eq3.7}$$

Where ‘N’ is Number of taps, ‘C’ is degree of volume reduction, ‘V_o’ loose volume, ‘V_N’ average tapped values of trials after tapping, ‘a’ and ‘b’ are constants for ‘N/C’ vs. ‘C’ calculated from the slope and intercept (Kawakita, 1969)

3.2.7. Solubility and Swelling Power

These properties were determined based on the method of Takizawa *et al.* (2004). 0.125 g sample was dispersed in 10 ml of distilled water in a centrifuge test tube. The dispersion was heated, under mild agitation, in a thermostat at 20, 40, 65, 75 and 85 °C for 10 min. The tube was then removed from the water bath and immediately immersed in cold water for 5 min and centrifuged for 15 min at 3000 rpm. The supernatant was dried to constant weight in an oven at 105 °C. The precipitated paste and the dried supernatant were then weighed. The swelling power (SP) and solubility were calculated using Equations (3.8) and (3.9), respectively. The results ware averages of three determinations.

Swelling Power (g/g of mucilage) = $M_{sw}/(M_o-M_s)$ Eq.3.8

Solubility (g/100g mucilage) = $(M_s/M_o) \times 100$ % Eq.3.9

Where, 'M_{sw}' is weight of swollen mucilage, 'M_o' is sample weight and 'M_s' is weight of dried supernatant

3.2.8. Determination of Moisture Sorption Pattern

Moisture sorption pattern was studied using the method described by Odeku and Picker-Freyer (2007). Pyrex desiccators containing distilled water, saturated solution of NaCl, and appropriate concentration of sodium hydroxide solution were prepared to obtain different relative humidity (RH) chambers (15, 40, 60, and 100) and stored at room temperature. Mucilage powder samples were pre-dried in an oven for 4 h at 120 ^{o}C. Two grams of mucilage was spread evenly on each Petridish (dried and weighed) and transferred to a particular RH chamber. Samples were equilibrated for four weeks at room temperature. The weights were recorded and moisture uptake of each sample was calculated as the weight difference of the mucilage before and after equilibrium in a given RH chamber. Water sorption capacity of the mucilage was expressed as percent moisture uptake. Results are expressed as mean of three parallel determinations.

3.2.9. Viscosity

a) Effect of Shear Rate on Apparent Viscosity

Mucilage powder (6 g) was dispersed in portion of distilled water for different shear rates. The dispersion was adjusted to volume (50 ml) using distilled water with continuous stirring. The preparation was then kept overnight at room temperature. The measurements of the viscosities of the dispersion were made using spindle number 4 of the rotational viscometer at various shear rates (20 - 200 rpm) (adapted from the United States Pharmacopeia, ed. 2010, Test Procedure 430-1). Results of the property recorded are averages of three determinations.

b) Effect of Mucilage Concentration on Apparent Viscosity

Mucilage of 3 g, 5 g, 7.5 g, 10 g and 12 g of powder were dispersed in a portion of distilled water and they were adjusted to get 100 ml with continuous mixing. The dispersions were kept overnight at room temperature and viscosity measurements of each dispersion was made at 20 ± 0.5 ^{o}C using spindle number 4 of rotational viscometer at a shear rate of 20 rotation per minute (rpm). Results of the property recorded were averages of three determinations.

3.2.10. Drug Polymer Compatibility Studies

The compatibility studies of drug and mucilage were carried out using Fourier Transform Infrared Spectrophotometer (FTIR8400-S SHIMADZU, Japan). The pure drug, the mucilage and the physical mixture (1:1) of drug polymer were first ground in a mortar to reduce the average particle size. 5 mg of finely ground powder of each sample was mixed with an oily mulling agent (Nujol) in a mortar and pestle. The sample mixture was then placed onto the face of a potassium bromide (KBr) disk, and the second window was placed on top of the first salt plates to form a thin film of the mull by compression between two plates. The sandwiched plates were placed in the infrared spectrometer and the spectra were obtained by scanning the sample in the resolution range of 4000-400 cm^{-1} once at a time to be interpreted in PerikinElmer spectrum^{TM} 10 software.

3.2.11. Construction of Calibration Curve

Stock solution containing, 100 µg/ml, Diclofenac Sodium reference standard (99.4%) in phosphate buffer of pH 6.8, was prepared. Then, from this stock solution 6 µg/ml, 9 µg/ml, 12 µg/ml, 15 µg/ml, 18 µg/ml and 21 µg/ml were prepared for calibration curve in phosphate buffer. For 0.1N HCl, stock solution of Diclofenac sodium reference standard was prepared by transferring 68 mg of Diclofenac Sodium into 100 ml volumetric flask containing 10 ml of 0.1N NaOH and diluted in water to the volume. Then from this stock solution, 1, 1.5, 2, 2.5, 3 and 3.5 ml were transferred to 100 ml volumetric flasks and diluted with a mixture of 0.1N HCl and 5N NaOH (90:20) to volume using the blank (USP, 2007). Then, the absorbance of each of these concentrations was measured at λ_{max} (276 nm) in UV-Visible Spectrophoto-meter (CECIL, CE, 1021, Cambridge, England) using the respective buffer solutions as a blank.

3.2.12. Preparation of Granules

The compositions of the tablet formulations are shown in (Table 3.1). The amount of the mucilage was chosen based on researches of related plant mucilages and the drug and lubricant was constant and the filer was varied as per the mucilage amount (Zhao et al., 2007). The drug, polymer and diluent were dry mixed manually with mortar and pestle for 5 min. The lubricant was then, added and the mixture was blended for additional 5 min in case of direct compression formulations. Wet granulated formulations were prepared by the method described by Shanmugam (2015). Water was used as a granulating fluid. The wet mass was then passed manually through 1600 µm sieve. The formed granules were dried at 40 ºC overnight in tray dryer (Kottermann® 2711, Germany). The dried granules were passed through a sieve size of 1000 µm. After drying, granules having a size greater than 224 µm were selected and characterized for flow and compressibility. For compression of granules, the lubricant was added lastly (Mayuri *et al.*, 2010).

Table 3.1: Composition of diclofenac sodium tablet formulations using *Opuntia stricta* mucilage

S.NO	Ingredients	F1/F5	F2/F6	F3/F7	F4/F8
1	Diclofenac sodium(mg)	100	100	100	100
2	*Opuntia stricta* mucilage (mg	35	65	95	125
3	Lactose (mg)	211.5	181.5	151.5	121.5
4	Magnesium stearate (mg)	3.5	3.5	3.5	3.5
	Total (mg)	**350**	**350**	**350**	**350**

F1-F4 is directly compressed formulations; F5-F8 is wet granulated formulations

3.2.13. Characterization of Granules

3.2.13.1. Size Distribution of Granules

The size distribution of granules was determined by the method described by Iveson *et al.* (2001). Thirty grams of granules, ranging from 224 – 1000 μm in size, from each batch were put in a set of sieves fixed on the universal drive unit (ERWEKA, Type AR 401, and Germany) arranged in mesh size from top to bottom with the coarsest sieve on the top. Then, the sieves were shaken for 4 min. The granules remaining on each sieve were weighed and percent granules retained on each sieve was recorded. Then, mean granule size was calculated for each batch.

The average granule size on any sieve was determined in microns by averaging the size of the openings of the sieve through which the granules passed and the size of the openings of the sieve upon which the granules were retained. The weight retained on each sieve was converted to percentage retention and multiplied by the average of two successive sieves. The sum of these products divided by 100 yielded the average granule size.

3.2.13.2. Determination of Density and Density Related Properties

Thirty grams of each batch of dry powder mix and granules, ranging from 224-1000 μm in size, were placed in 250 ml measuring cylinder. The bulk density, tapped density, Carr's index and Hausner ratio of the granules were calculated in the same ways described for *Opuntia stricta* mucilage powders above (Section 3.2.4).

3.2.13.3. Determination of Flow Rate and Angle of Repose

Flow rate and angle of repose of dry mix and wet granulated formulations were determined by using the funnel method described for *OS* mucilage powders above (Section 3.2.5).

3.2.14. Compression of Tablets

For evaluation of *O.stricta* mucilage as matrix forming agent, both direct compression and wet granulated formulations were blended with 1% Mg stearate for 4 min in a Turbula mixer (Willy A. Bachofen AG, Turbula 2TF, Basel, Switzerland) and compressed at a certain fixed compression force (adjusted to give tablets with a crushing strength between 70-80 N) on eccentric tablet machine (EKO Korsch, 8410-68, Berlin, Germany) which was fitted with 10 mm diameter flat-faced punches. Target tablet weight was 350 mg.

3.2.15. Evaluation of Tablets

3.2.15.1. Weight and Thickness

From each formulation, 20 tablets were randomly selected and weighed individually on an analytical balance (Mettler Toledo PR 203, Switzerland). Ten tablets were randomly selected and the thickness of each was measured. Then, mean and standard deviation for both measurements were calculated.

3.2.15.2. Crushing Strength

Ten tablets were taken from each batch and the crushing strength was determined using hardness tester (Schleuniger, 2E/205, Switzerland). Each tablet was placed between two anvils and force was applied to the anvils, and the crushing strength in Newton (N) that just caused the tablet to break was recorded. Then, mean and standard deviation for both measurements were calculated.

3.2.15.3. Friability

Ten tablets of known weight from each batch were subjected to combined effects of abrasion and shock by placing them in the plastic chamber of friability tester (ERWEKA TAR 20, Germany) that revolves at 25 rpm for 4 min. The tablets were then sieved and weighed, and the percent loss in weight was calculated as friability.

3.2.15.4. Disintegration Time

Disintegration time test was carried out according to USP/NF specification (USP30/NF25, 2007). Six tablets were placed in a disintegration tester (CALEVA, G.B. Caleva Ltd., UK) filled with distilled water at 37± 2 °C. The tablets were considered completely disintegrated when all the particles passed through the wire mesh.

3.2.15.5. Water Uptake Studies

Water uptake of formulations having 27.14 % w/w (F_3 and F_7) and 35.71 % w/w (F_4 and F_8) of the polymer (in triplicate for each batch) that maintain their structural integrity for 6 h was computed according to Eq. 3.10 by the method described by Reddy *et al.* (2012). Three metallic baskets were weighed with a matrix tablet of each formulation, and placed into Petri-dish containing 0.1 N HCl and phosphate buffer of pH 6.8 separately and placed in water bath at 37 ± 0.5 °C. At hourly intervals, the previously weighed baskets containing the tablet were removed, gently wiped with a tissue paper to remove surface water, reweighed, and then placed back into the vessel as quickly as possible. The swollen weight of tablets was determined (Ts).

$$\text{Water Uptake}(\%) = \frac{(Ts - T)}{T} \times 100 \qquad \text{Eq.3.10}$$

Where, Ts is the weight of the swollen tablet and T is the initial weight of the tablet prior to the test in gram

3.2.15.6. Dissolution Test

The dissolution test was done in six replicates according to the USP/NF specification (USP30/NF25, 2007) using dissolution apparatus Type I (ERWEKA, DT600, Germany) with rotating basket that was adjusted to rotate at 50 rpm. The release studies were performed in 900 ml of 0.1 N HCl at 37 ± 0.5 ^{o}C for the first 2 h; samples of dissolution medium (10 ml each) were withdrawn at predetermined time intervals (15, 30, 60 and 120 min) and immediately

replaced with equal volumes of fresh medium at the same temperature. At 2h, the tablets were transferred to 900 ml phosphate buffer medium of pH 6.8 at 37 ± 0.5 ^{o}C for further studies. Aliquots were withdrawn at predefined intervals (1, 2, 4, 6, 8, 10 h), and the volume of the dissolution medium was maintained by replacing the same volume of fresh pre-warmed dissolution medium. The absorbance of the withdrawn samples was measured spectrophotometrically at 276 nm in triplicate and the drug release was calculated.

Dissolution study of a marketed product (Diclo-Denk 100 mg SR) was performed in the same apparatus and test condition for comparison. Before dissolution, the assay of the marketed product was done. Twenty tablets were weighed and crushed using mortar and pestle. Quantity of powder equivalent to 100 mg of Diclofenac sodium was weighed accurately and transferred to 100 ml volumetric flask. Approximately 70 ml of methanol AR grade was added and shacked for 15 min. The volume was made up to 100 ml with methanol and filtered. From the clear filtrate and aliquot equivalent to 100 ppm was pipette out and transferred to 10 ml volumetric flask. The volume was made up to 10 ml with Methanol (10 µg/ml solution) (USP, 2011). The absorbance of this solution after filtered by Whatman filter paper was measured on UV spectrophotometer at 276 nm. The drug content was calculated by simultaneously measuring the absorbance of a standard 10 µg/ml solution of Diclofenac sodium by the UV machine.

To interpret the drug release rate from the matrix tablets, the data obtained from *in vitro* drug release studies were plotted in various kinetics models.

i. Zero-order Release Model

Zero order kinetics defines the process of constant drug release from a drug delivery system and drug level in the blood remains constant throughout the delivery. Drug release kinetics data obtained from *in-vitro* dissolution study is plotted against time i.e., cumulative drug release *vs.* time.

$$W=Kt \qquad \text{Eq.3.11}$$

Where ‘W’ is the cumulative percent of drug released at time ‘t’, ‘k’ is the zero-order rate constant expressed in the units of concentration/time and “ t ” is the time in hours.

ii. First order Release Model

First order process is the one whose rate is directly proportional to the concentration of drug undergoing reaction i.e., greater the concentration faster the reaction.

The release of drug which follows first order kinetics can be represented by the equation;

$$\text{Ln}\ (W_0\text{-}W) = \ln W_0\text{-}Kt \qquad \text{Eq.3.12}$$

'W' is the cumulative percent of drug released at time 't', 'W_0' is amount of drug remaining at Atime 0, 'k' is the zero-order rate constant expressed in the units of concentration/time and " t " is the time in hours.

Hence, to study the drug release kinetics data obtained from *in-vitro* dissolution study is plotted against time i.e., ln % of drug remaining *vs.* time and the slope of the plot gives the first order rate constant.

iii. Higuchi Square root Model

The classical basic Higuchi equation is represented by;

$$W = A\sqrt{((D\ (2Co - Cs)\ Cst)}$$

Where W is the cumulative amount of drug released in time t per unit area, C_o is the initial drug concentration, C_S is the drug solubility in the matrix and D is the diffusion coefficient of the drug molecule in the matrix.

This relation is valid until total depletion of the drug in the dosage form is achieved. To study the dissolution from a planar heterogeneous matrix system, where the drug concentration in the matrix is lower than its solubility and the release occurs through porous system, the expression can be given by equation.

$$W = \sqrt{(D\delta/\ \tau)\ (2C - \delta Cs)\ Cst}$$

Where D is the diffusion coefficient of the drug molecule in the solvent; δ is the porosity of the matrix; τ is the tortuisity of the matrix and W, A, Cs and t have the meaning described above. Tortuisity is defined as the dimensions of radius and branching of the pores and canals in the matrix. After simplifying the above equation, Higuchi equation can be represented in the simplified form;

$$W = Kt^{1/2} \qquad \text{Eq.3.13}$$

Where ‘W’ is cumulative amount of drug released in time ‘t’, ‘K’ is Higuchi dissolution rate constant of the system and while t is the time in hours.

iv. Hixson-Crowell Cube root Model

The Hixson-Crowell cube root law describes the release from systems where there is a change in surface area and diameter of particles or tablets. Hence, particles of regular area are proportional to the cube root of its volume. From the above concept Hixson-Crowell established a relationship between drug release and time which can be represented by equation as;

$$(W_0-W)^{1/3}=W_0^{1/3}-Kt \qquad \text{Eq.3.14}$$

Where ‘K’ is the rate constant for Hixson Crowell’s equation, ‘(W_0-W)’ is the amount of drug remaining at time t, ‘W’ is amount of drug released at time t, ‘W_0’ is amount of drug remaining at time 0.

v. Korsemeyer-Peppas Release Model

To understand the dissolution mechanisms from the matrix, the release data were fitted using the well-known empirical equation proposed by Korsmeyer and Peppas. Korsmeyer and Peppas put forth a simple relationship which described the drug release from a polymeric system follow which type of dissolution.

$$Mt/M_\infty = K_{kp}t^n \qquad \text{Eq.3.15}$$

Where $M_t/M\infty$ is the fractional solute release, M_t is the amount of drug released in time t, $M\infty$ is the amount of drug released after time ∞, n is the diffusional exponent or drug release exponent, K_{kp} is the Korsmeyer release rate constant.

To study release kinetics a graph is plotted between log cumulative % drug release log ($Mt/M\infty$) *vs.* log time (log t). Hence, n value is used to characterize different release mechanisms for cylindrical shaped matrices.

3.2.15.7. Model Independent Tests

Dissimilarity and Similarity factors (f1 and f2, respectively) for comparison of formulations with marketed product were performed.

$$f_1 = \{[\sum_{t=1}^{n} |R_t - T_t|] / [\sum_{t=1}^{n} R_t]\} \times 100 \quad \text{.....Eq. 3.16}$$

$$f_2 = 50 \times \log \{[1 + (1/n) \sum_{t=1}^{n} (R_t - T_t)^2]^{1/2} \times 100\} \quad \text{.....Eq. 3.17}$$

Where, R_t is % API dissolved of reference product at time t, T_t is % API dissolved of test product at time t and n is number of time points.

3.2.15.8. Statistical Analysis

The data were subjected to further statistical analysis to compare the properties of direct compression formulations with those of wet granulated formulations and better formulations with Diclo-Denk 100 mg SR using Analysis of Variance (ANOVA) on Origin 7.0 statistical software. A confidence limit of $P < 0.05$ was fixed for interpretation of the result.

4. Result and Discussion

4.1. Physical Properties of the Mucilage

4.1.1. Physical Properties

Table 4.1 shows some of the physical properties of the *Opuntia stricta* mucilage. The yield was low compared to other pharmaceutical excipients like starch, but it was comparable with findings of 17.9% of total dry weight of the cladodes (Cardenas *et al*., 2007) and the species of OFI and OS found in Ethiopia 1.17/17.5% and 1.7/19%, respectively in fresh/dried forms (Gebre-Samuel and Gebre-Mariam, 2012). But, due to easy cultivation of the plant and simple extraction (a ethanol alcohol which can be recovered after extraction) it is considered promising. The appearance of the powder is somewhat greenish- yellow. The extraction and purification with ethanol dissolves part of the chlorophyll, similar to other commercial gums used in the food industry. Further chlorophyll separating procedure may completely whiten the powder. The mucilage was soluble in water producing viscous solution. The moisture content (10%) of the mucilage was slightly higher than the USP monograph specification limit (not more than 7%), but the findings by Gebre-Samuel and Gebre-Maryam (2012) was 7.7% which was somewhat higher than the specified upper limit, suggesting that the need for tight container. Optimization of production processes such as drying, packaging and storage is of economic importance for an excipient with industrial application (Martins *et al.*, 2009). So, the need for drying, packaging and storage of the mucilage is obvious.

The pH of an excipient is an important parameter in determining its suitability in formulations; since, the stability and physiological activity of most preparations depends on pH (Martins *et al.*, 2009). A 1% w/v solution of the mucilage in water gave a near neutral pH of 6.43, implying its less irritability in uncoated tablets which was comparable with findings (Gebresamuel and Gebre-Mariam, 2012). It suggests its potential useful applications in formulation of acidic, basic and neutral drugs.

Table 4.1: Physical properties of the mucilage

Physical Properties	Observation
Appearance	Greenish-Yellow
Percent yield (Dry weight basis) (%)	19.1% ± 0.21
Weight loss on drying (%)	10.53 ± 1.78
p^H (1%)	6.43 ± 0.01

4.1.2. Powder Properties of *Opuntia stricta* Mucilage

Flow and compressibility of the dried mucilage, including bulk and tapped density, Carr's index, Hausner ratio, and the angle of repose are shown in Table 4.2. Bulk and tapped densities give an insight on the packing arrangement of the particles and the compaction profile of a material Prakash *et al*. (2011). The powder was free flowing on the funnel suggesting that its amenability to direct compression. And the results from the Carr's index, Hausner's ratio and angle of repose showed fair flow and compressibility after some agitation.

Table 4.2: Flow properties of the powdered cactus (*Opuntia stricta*) mucilage

S/N	Parameters	Value Mean ± SD
1	Bulk density (g/ml)	0.61 ± 0.04
2	Tapped density (g/ml)	0.71 ± 0.03
3	Carr's index (%)	14.1 ± 0.07
4	Hausner's ratio	1.16 ± 0.05
5	Angle of repose (degree)	30 ± 1.13
6	Flow rate (g/sec.)	2.17 ± 0.21

Compressibility and cohesiveness can be further confirmed by Kawakita constants that indicate the behavior of the powder from the bulk density state to the tapped density state. The constants

of the Kawakita equation were computed from the slope and intercept of the line from the graphs N/C versus N (Fig. 4.1). Constants 'a' (compressibility, or the amount of densification due to tapping) and '1/b' (cohesiveness, or how fast or easily the final packing state was achieved) indicate good flow ability and small cohesiveness (Klevan *et al.*, 2010). The values show that the powder is compressible and cohesive.

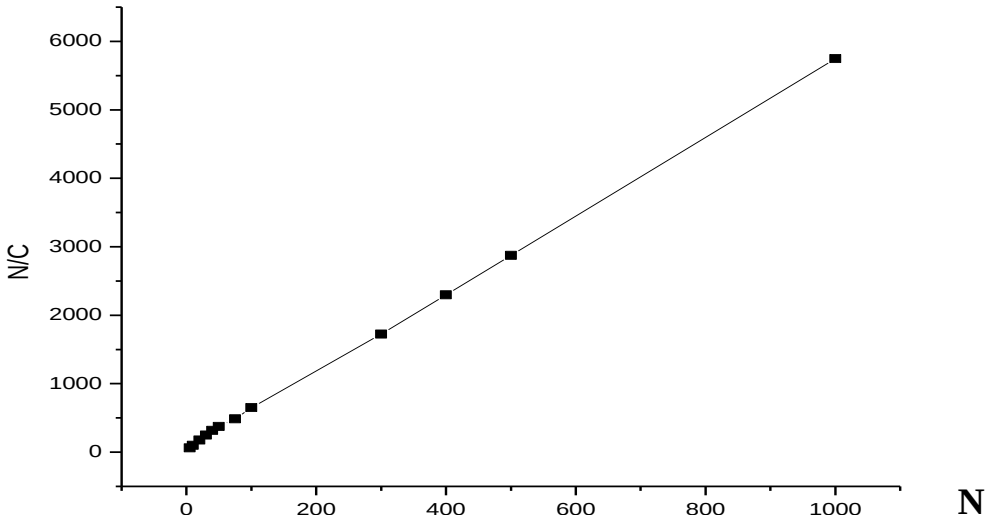


Figure 4.1: The plot of N/C versus N of cactus (*Opuntia stricta*) mucilage powder with equation of Y = 5.660X + 61.46(R^2 = 0.999); where Y is N/C and X is N, where a = 0.176 and b = 0.09

4.1.3. Solubility and Swelling Power of *Opuntia stricta* Mucilage

The solubility and swelling power of the OS is shown in Figure 4.2 and 4.3 respectively. The solubility and swelling power of the OS were generally low at low temperature (20 °C) but increase significantly at higher temperature (85 °C) ($p < 0.05$). These could be due to the degree of macromolecular disorganization and also to variations in the degradation of OS powder during thermal treatment. There is also an increase in kinetic energy which favors solvent accessibility (Takizawa *et al.*, 2004).

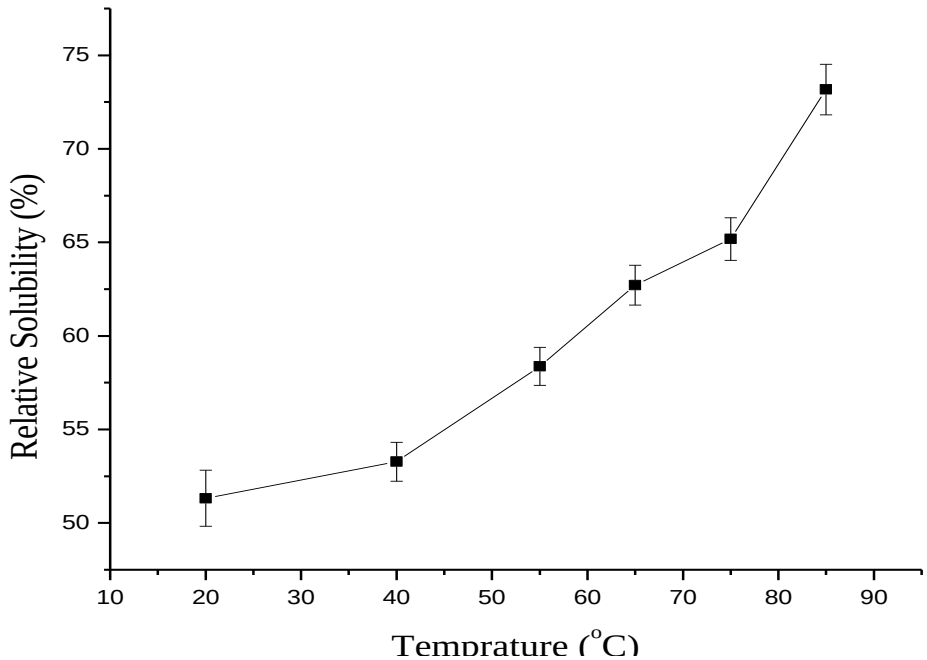


Figure 4.2: Solubility of cactus (*Opuntia stricta*) mucilage powder at different temperature

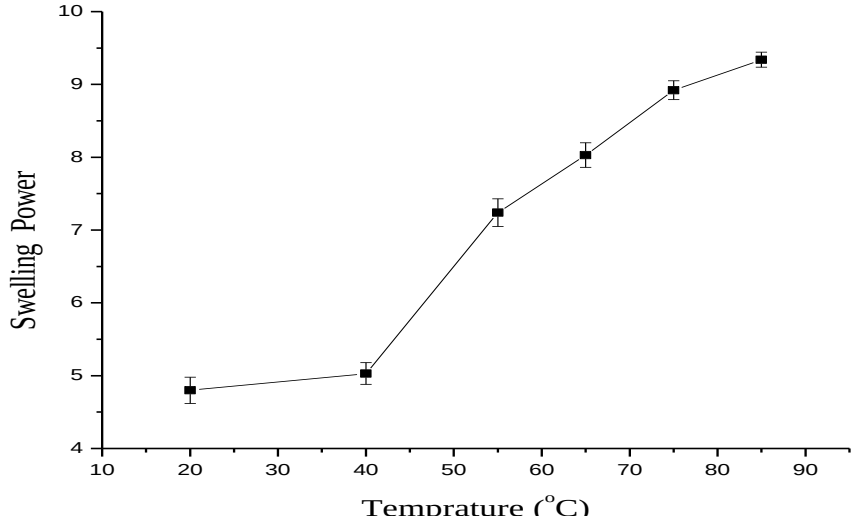


Figure 4.3: Swelling power of cactus (*Opuntia stricta*) mucilage at different temperatures

4.1.4. Moisture Sorption Property of *Opuntia stricta* Mucilage

Moisture sorption profile of OS mucilage is depicted in Figure 4.4. Percent moisture sorbed ranged between 7.61% at 15% RH and 79.9% at 100% RH. The hydrophilic nature of the OS molecule is probably responsible for the observed high moisture sorption by the powder at high RH and reinforces the necessity for moisture preclusion during storage. Higher levels of water can lead to microbial spoilage and subsequent deterioration in OS mucilage quality. Furthermore, water is also known to affect the flow properties of powder. Therefore, during tablet production and storage, the RH should be carefully controlled to obtain the powder with optimum flow and compaction properties and also to prevent the deterioration of the tablets (Sáenz 2000).

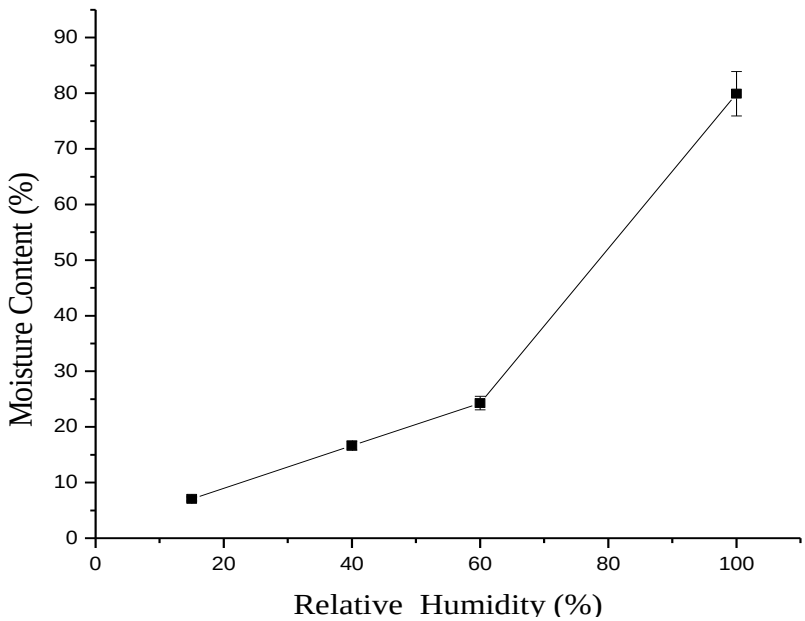


Figure 4.4: Moisture sorption patterns of cactus (*Opuntia stricta*) mucilage powder

4.1.5. Viscosity of *Opuntia stricta* Mucilage

4.1.5.1. Viscosity at Different Shear Rates

Shear rate showed indirect effect on apparent viscosities for OS mucilage. The effect of shear rate on apparent viscosities of the dispersions from the mucilage samples is depicted in Figure 4.5. We can see from the graph that the mucilage has pseudo-plastic property. The pseudo-plasticity property shows the uniform distribution of the mucilage which may help to achieve uniform drug distribution. For example, in case of wet massing for granulation, when we

increase mixing force viscosity will decrease due to pseudo-plastic property of mucilage. Hence, the drug uniformity will be good, which in turn helps uniform release (Kato *et al*., 2004).

4.1.5.2. Viscosity at Different Concentrations

The viscosity increased upon increasing the mucilage concentration as shown in Figure 4.6. This shows as concentration increases in matrix tablets the more viscous gel layer will be formed with the entry of water into the matrix, and greater resistance to polymer erosion and slower release rate of the drug will be expected. This suggests that viscosity is one of the potential parameters that controls drug release and determines the mechanism of release (Goldstein *et al.*, 1991).

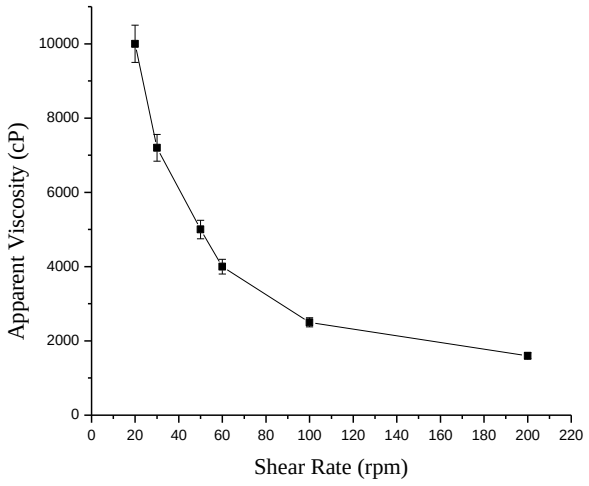


Figure 4.5: Apparent viscosities of cactus (*Opuntia stricta*) mucilage dispersions (12% w/v) at different shear rates

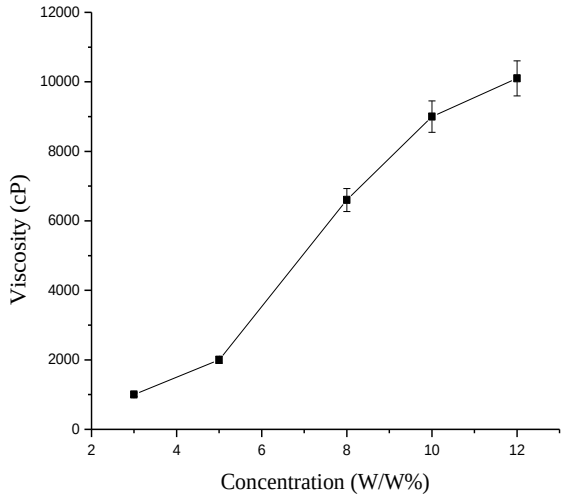


Figure 4.6: Apparent viscosities of cactus (*Opuntia stricta*) mucilage dispersions at different concentration (3%, 5%, 7.5 %, 10 % and 12 % w/v)

4.2. Drug-Excipient Compatibility Studies

FTIR test result of diclofenac sodium is depicted in Figure 4.7. The characteristic peaks at 3384.84 cm^{-1} indicating N-H stretching, 1340.43 indicating C-N stretching, 1043.42 indicating C-O stretching, 1303.79 cm^{-1} indicating C-CO-C stretching and 667.32 cm^{-1} indicating C-Cl stretching are the major peaks of diclofenac sodium.

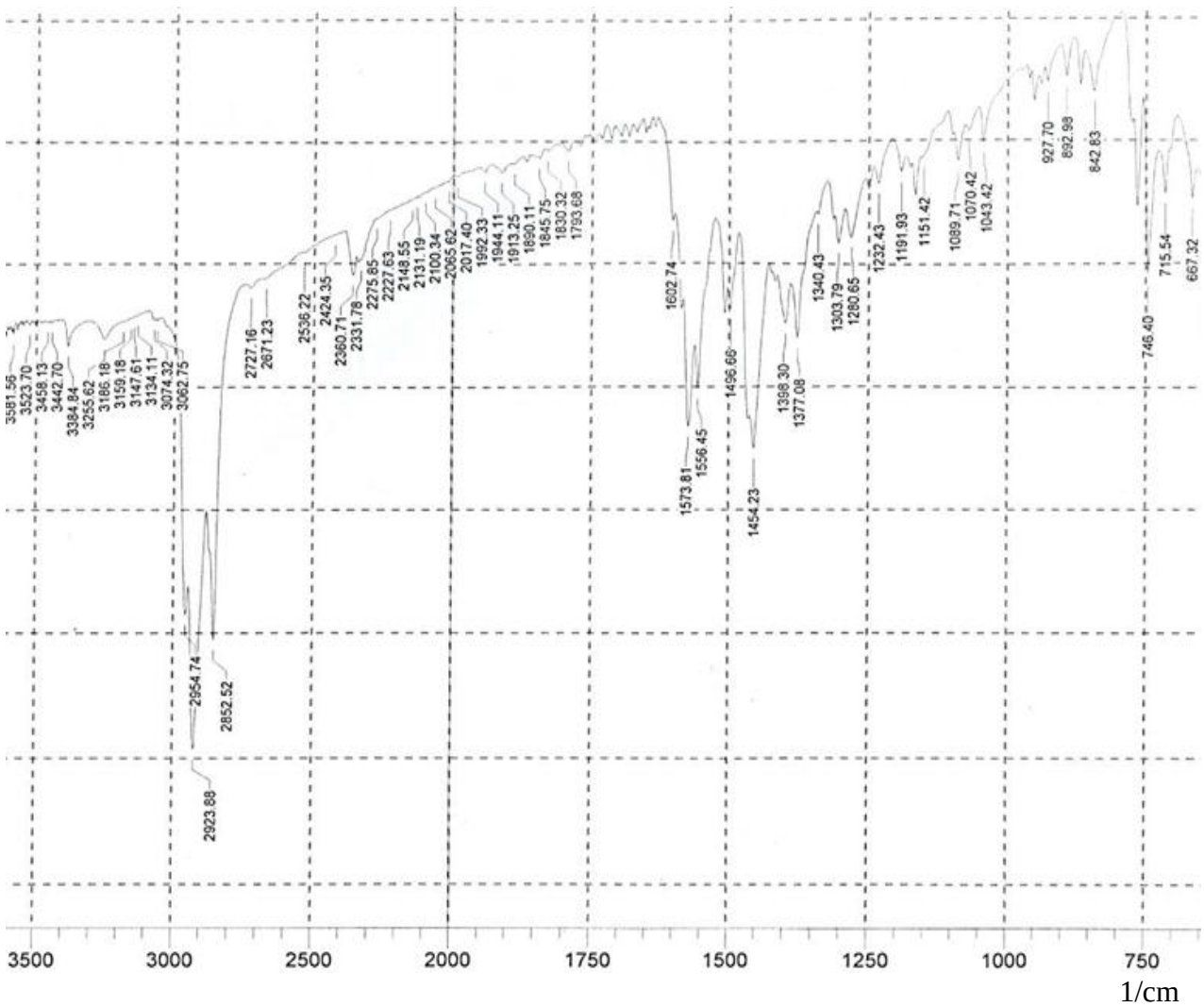


Figure 4.7: IR spectrum of diclofenac sodium [%T (0-70) vs 1/cm]

The IR spectrum of OS mucilage powder (Figure 4.8) shows peaks at 3292.26 cm^{-1} indicating carbohydrate O-H stretching, at 2923.88 cm^{-1} indicating carbohydrate C-H stretching, 1772.46 cm^{-1} indicating C-H absorption that indicate the presence of methyl group which is comparable to results of Han *et al*., (2016). The peaks 1695.31 cm^{-1} , 1589.23 cm^{-1}, and 1458.08 cm^{-1} are to deprotonated carboxylic acid groups ($–COO^{–}$) in uronic acid which is comparable to results of (Zhao *et al*., 2007) in *O. monacantha*. The bands found at ~1431–1264 cm^{-1} can be assigned to C–O stretching and O–H deformation vibrations, according to Han *et al*., 2016, and the bands at 1431–1393 cm^{-1}indicate C–N stretching modes. The peak at 721.33 is attributed to N–H out-of-plane vibrations and the bands at 1431–1393 cm^{-1}indicate C–N stretching modes (1393) from impurities like chlorophyll.

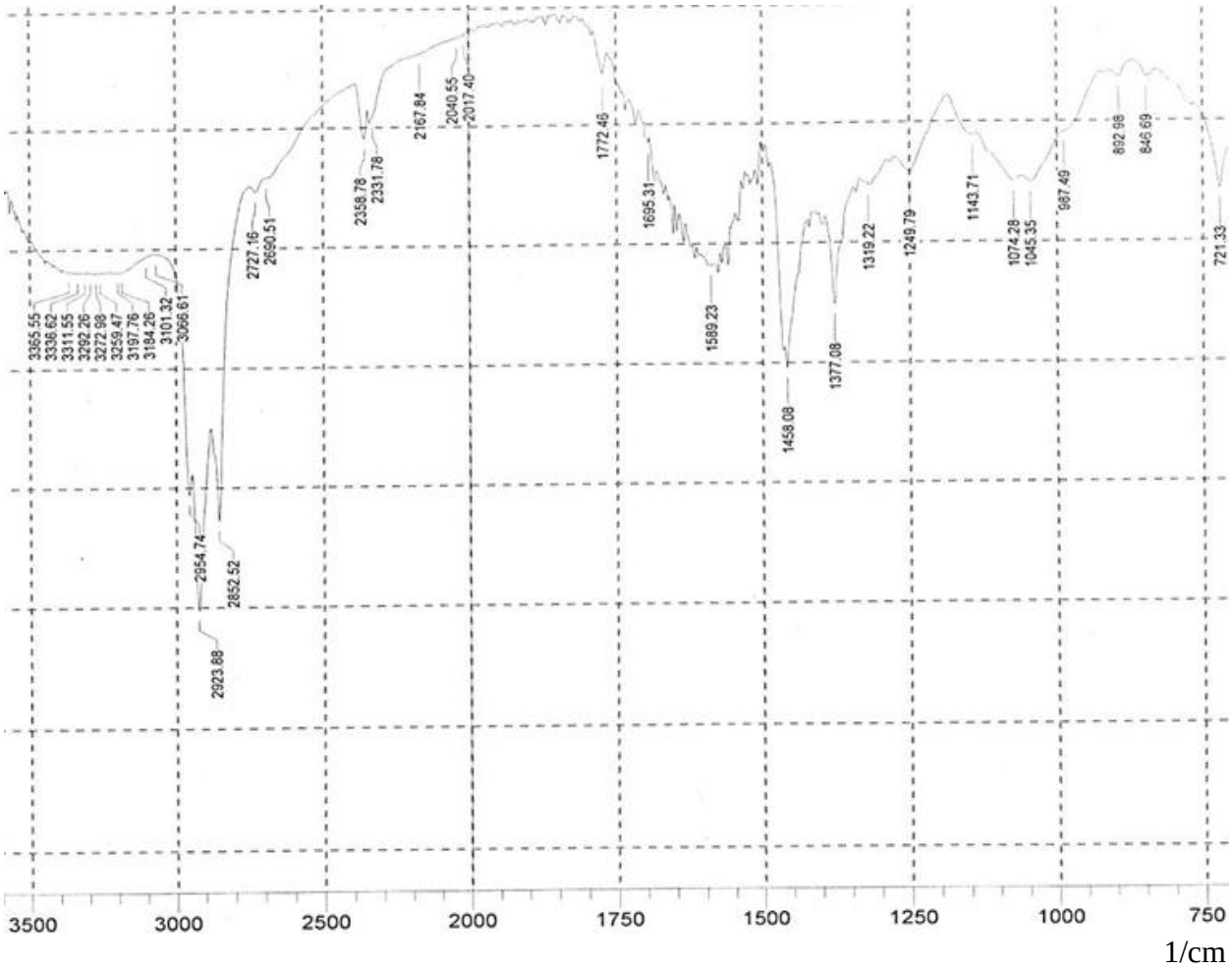


Figure 4.8: IR spectrum of *OS* mucilage leaf mucilage powder [%T (0-70) vs 1/cm]

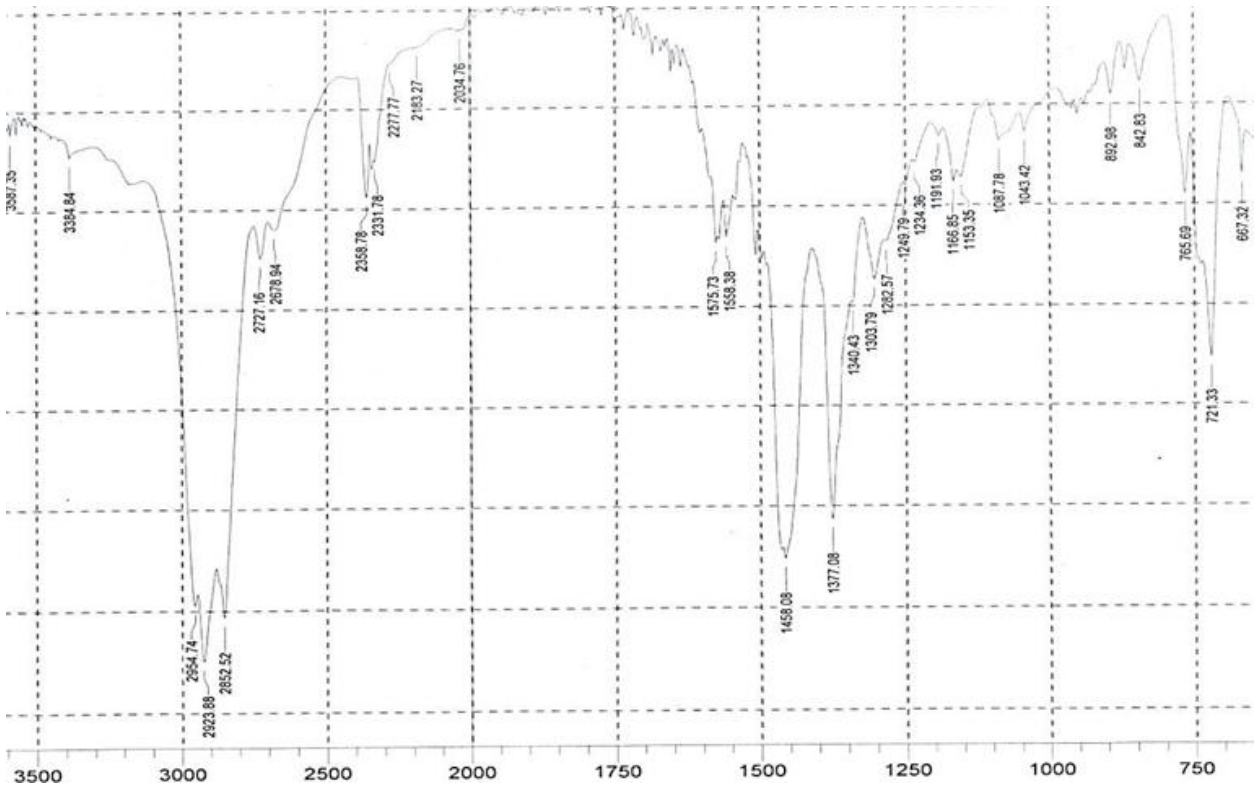


Figure 4.9: IR spectra of physical mixture diclofenac sodium with *OS* mucilage at 1:1 ratio [%T (0-70) vs 1/cm].

IR spectrum (Figure 4.9) of drug: polymer mixture also showed the characteristic peaks of the pure drug and the polymer. This suggests that there is no significant interaction.

4.3. Granule Properties

4.3.1. Particle Size Distributions

Granulation is necessary to overcome the significant compression difficulties and erratic flow properties of many APIs, characteristics that often limit the successful production of acceptable dosage forms (Andrews, 2011). Table 4.3 shows the particle size distributions of diclofenac sodium granules prepared with OS mucilage at different concentrations.

Table 4.3: Mean granule size and granule size distribution of formulations prepared with OS mucilage at different polymer concentrations.

Formulation	PC (%w/w)	MGS (µm) ± SD	% of granule retained 1000/710 ± SD	710/315 ± SD	315/224 ± SD
F5	10	683.64 ± 0.19	55.09 ± 0.12	37.96 ± 0.51	7.22 ± 0.08
F6	18.57	691.56 ± 0.08	56.87 ± 0.21	36.66 ± 0.40	6.47 ± 0.09
F7	27.14	685.94 ± 0.23	55.6 ± 0.02	37.41 ± 0.15	6.99 ± 0.32
F8	35.71	714.84 ± 0.74	62.79 ± 0.05	31.9 ± 0.07	5.38 ± 0.07

PC: polymer concentration, MGS: Mean granule size, F (5-8): wet granulated formulation

From the table, we can see that the mean granule size for all formulations lay in the oral acceptable granule size range (100 µm -1000 µm) (Burgess *et al*., 2004), suggesting that, the granulation binding capacity of the mucilage even at low OS mucilage concentration.

4.3.2. Flow Rate and Angle of Repose

Flow rate and angle of repose are depicted in Table 4.4 below. Flow rate and angle of repose are direct method of determining powder and granule flow property. The results of angle of repose ($<30^{o}$) indicate good flow properties of the formulation (Persson, 2013). Angle of repose in direct compression formulations ranged from 27.97 to 29.97 indicating good flow properties of the powder mix, which was further supported by higher Carr's index and Hausner's ratio values.

Generally, Carr's index and Hausner ratio values up to 15% and <1.25, respectively, show good to excellent flow properties (Persson, 2013).

Flow properties of the formulations increase with the concentration in both direct compression and wet granulated formulations. Wet granulated formulations were found to be higher in flow and compression characteristics ($p < 0.05$).

Table 4.4: Flow properties of *Opuntia stricta* mucilage powder mixes and granules

Formulations	Angle of Repose(^{0}) ± SD	FlowRate (g/sec) ± SD	Bulk Density (g/ml) ± SD	Tapped Density± SD	Carr's Index (%)± SD	Hausner's Ratio
F1	29.97 ± 0.71	2.91 ± 0.17	0.46 ± 0.17	0.52 ± 0.03	16.72 ± 1.10	1.73 ± 0.03
F2	28.48 ± 1.12	2.95 ± 0.15	0.47 ± 0.21	0.50 ± 0.02	17.34 ± 1.51	1.63 ± 0.10
F3	28.66 ± 0.53	3.12 ± 0.09	0.47 ± 0.18	0.50 ± 0.01	15.94 ± 1.30	1.42 ± 0.01
F4	27.97 ± 0.65	3.05 ± 0.19	0.46 ± 0.10	0.52 ± 0.03	15.07 ± 1.29	1.67 ± 0.02
F5	26.19 ± 0.48	3.25 ± 0.21	0.24 ± 0.25	0.26 ± 0.02	8.67 ± 1.90	1.05 ± 0.04
F6	26.75 ± 0.42	3.41 ± 0.22	0.26 ± 0.14	0.28 ± 0.02	7.28 ± 0.98	1.14 ± 0.03
F7	25.74 ± 0.41	3.39 ± 0.18	0.29 ± 0.03	0.31 ± 0.01	7.09 ± 0.94	1.08 ± 0.02
F8	25.88 ± 0.39	3.67 ± 0.14	0.21 ± 0.19	0.22 ± 0.02	7.15 ± 1.23	1.13 ± 0.05

All values are expressed as mean ± SD, n=3; F1-F4 are direct compression formulations and F5-F8 are wet granulated formulations.

4.4. Tablet Properties

The results of the evaluation of tablet properties are shown in Table 4.5. Weight variations of the tablets were within acceptable range of ± 5% which is the limit of the percentage deviation allowed by the British Pharmacopoeia (BP) (2009) for tablets weighing 250 mg or more. The weight and thickness of the direct compression and wet granulated formulations were found to be similar. All these results indicate that the physical mixture of powder and granules showed uniformity of process and formulation variables.

The tablets of different batches of direct compression formulations were found to possess acceptable hardness within the range of 80N to 110N. Crushing strength of wet granulation was

higher than direct compression formulations. Both direct compression and wet granulated formulations were observed to have increased crushing strength with polymer concentration. Friability which was another measure of strength was below 0.2% for all formulations that lies within an acceptable range of Pharmacopoeias. The thickness of all formulations was the same (3.3mm) as per sensitivity of the apparatus.

Table 4.5: Post compression parameters of diclofenac sodium tablets prepared by direct compression and wet granulation methods using OS mucilage as matrix forming polymer

Formulations	**Weight Variation n=20 (g)**	**Crushing strength (N) n=10 ± SD**	**Friability % n=20 ± SD**
F1	0.350 ±0.003	76.23 ± 0.24	0.17 ± 0.002
F2	0.348 ± 0.002	77.75 ± 0.09	0.15± 0.010
F3	0.347 ± 0.003	78.48 ± 1.20	0.11± 0.041
F4	0.353 ± 0.002	80.51 ± 0.81	0.10± 0.005
F5	0.350 ± 0.003	79.61± 0.32	0.17± 0.017
F6	0.351 ± 0.002	85.35 ± 0.30	0.13± 0.011
F7	0.352 ± 0.001	91.75 ± 0.08	0.11± 0.008
F8	0.353 ± 0.001	93.21 ± 0.42	0.10± 0.016

Tensile strength of the tablet which is the force needed to fracture the tablet per unit fracture area is fundamental measure of the mechanical strength of the tablets. All tablets possessed good mechanical strength that can withstand shock during transportation and handling. Tablets having high polymer concentration showed higher crushing strength and the wet granulation showed higher than direct compression formulations of the same polymer concentration.

4.5. Water Uptake Studies

A swelling/hydration rate of different matrices is an indication of drug release with the rates of polymer hydration and to evaluate the extent of water penetration into the tablets (Sankalia, *et al*., 2008). Figures 4.10 and 4.11 showed the water uptake profiles for the formulation F_3 and F_4 in direct compression and F_7 and F_8 in wet granulated formulations in 0.1 N HCl and phosphate

buffer of pH 6.8, respectively. In both cases water uptake was continuously rising throughout the study time. After 6 h study, water uptake for F_3 and F_4 were 186.24 % ± 0.24 and 223.35%± 0.15 in 0.1 N HCl and that of F_7 and F_8 167.14% ± 0.09 and 209.37%± 0.25 , respectively. The water uptake profile of F_3 and F_4 in phosphate buffer of pH 6.8 was 174.71% ± 0.24 and 219.58%± 0.26, and that of F_7 and F_8 168.53% ± 0.31 and 198.74% ± 0.27, respectively.

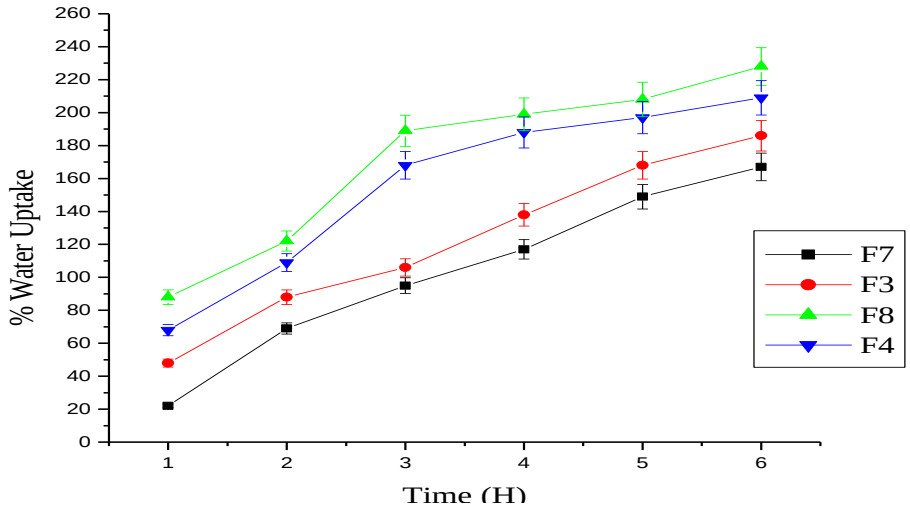


Figure 4.10: Water uptake study of tablets of direct compression (F_3 and F_4) and wet granulated (F_7 and F_8) formulations of 100mg diclofenac sodium in *Opuntia stricta* mucilage matrix at 27.14 % and 35.71 % in 0.1 N HCL

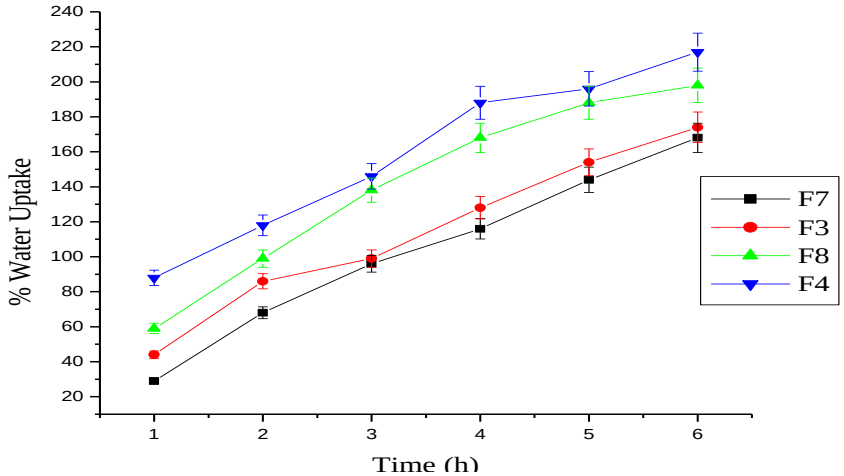


Figure 4.11: Water uptake study of tablets of direct compression (F_3 and F_4) and wet granulated (F_7 and F_8) formulations of 100mg diclofenac sodium in *Opuntia stricta* mucilage matrix at 27.14 % and 35.71 %, respectively in phosphate buffer of pH6.8

Water uptake in formulations containing higher proportions of the polymer in both formulations was higher and this could be due to the presence of increased hydroxyl groups as it is a complex carbohydrate that can hold water better with increased polymer concentration by capillary forces, suggesting that water uptake for formulations containing 10% will be much lower. As we can see from the graph there even though not significant, there is variation between direct compression and wet granulated formulations, which may be due to the increase in compaction of the tablets which limits the penetration power of water.

Water uptake was influenced by the pH of the media which indicates that as the pH of the media increased, the percentage of water uptake decreased which verifies increasing of the rate of drug release.

4.6. Construction of Calibration Curve

The absorbance readings were plotted against concentration (Fig. 4.12 and Fig. 4.13). The linear regression equations obtained were Y=0.039X + 0.018 (R^2=0.999) and Y = 0.0305X - 0.00225 (R^2=0.999) in phosphate buffer pH 6.8 and 0.1 N HCl, respectively, where Y is absorbance and X is concentration in µg/ml.

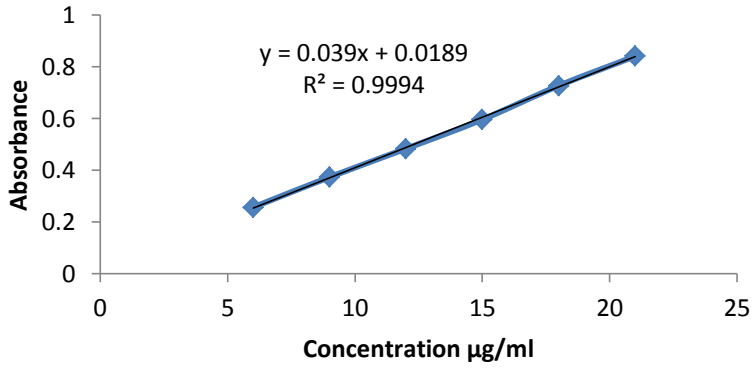


Figure 4.12: Standard calibration curve of diclofenac sodium in phosphate buffer pH 6.8 with upper and lower 95% confidence limits

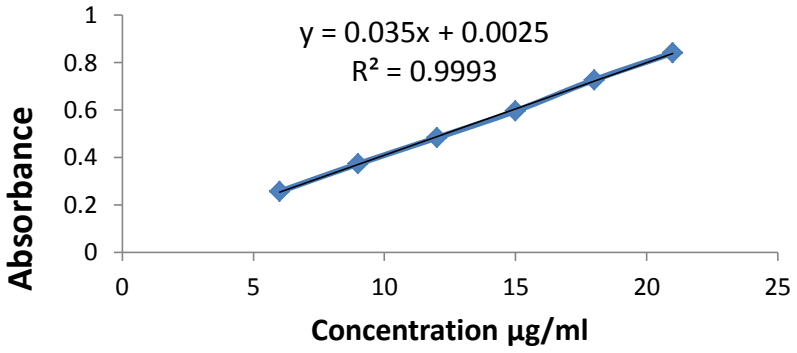


Figure 4.13: Standard calibration curve of diclofenac sodium in 0.1 N HCl with upper and lower 95% confidence limits

4.7. *In vitro* Drug Release Studies

The *in vitro* drug release characteristics were studied in simulated gastric and intestinal fluids for a period of 12 h using USP dissolution apparatus I. The plot of cumulative percentage released versus time for matrix embedded sustained release tablets prepared using different proportions of polymer is shown in Fig. 4.14 and Table 4.6. For all formulations in initial hours (0.25 and 0.5 h), the release profile was similar which could be due to surface drug release and slow water penetration even for low polymer concentration formulations. Even though there was no significant difference (at $p<0.05$), the release for low polymer concentration formulations showed rapid swelling of matrices with less tight hydro-gel structure resulting in higher initial drug release showing inverse relation between release and polymer concentration for the two hours study (in acidic medium). As the amount of mucilage in the matrix increased, there would be greater degree of hydration with simultaneous swelling which results in higher tortuosity and reduced drug release rate. The release became significant for polymer concentrations for study hours 3, 4, 6, 8, 10 and 12 (basic medium) even though there was no significant difference between direct compressed and wet granulated formulations of the same polymer concentration.

All formulations exhibited extended drug release of more than 12 h in both direct and wet granulation formulations. Formulations with low polymer concentration (10 % w/w) from both

direct and wet granulation showed almost 90% release in 12 h. The findings showed the sustaining efficiency of OS mucilage.

Table 4.6: % Cumulative drug releases of diclofenac sodium in direct compression (F_1-F_4) and wet granulated (F_5-F_8) formulations at different polymer concentrations

Study hrs	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**
0.25	0.791	0.764	0.675	1.201	1.215	0.855	0.675	1.22
0.5	6.414	5.852	1.47	1.61	4.982	2.106	1.608	2.121
1	11.241	10.945	3.375	6.06	9.609	6.618	5.019	7.17
2	20.312	18.13	14.74	12.17	19.52	14.16	12.46	11.53
3	35.076	25.768	17.73	14.652	29.676	20.772	16.308	13.542
4	42.37	34.24	23.69	19.05	40.46	26.69	20.46	17.78
6	59.09	51.74	40.23	27.44	55.06	45.231	34.59	25.02
8	68.95	61.55	48.04	33.74	69.7	55.38	42.84	32.28
10	83.71	69.63	60.3	42.77	79.16	66.46	56.67	39.58
12	90.01	78.12	66.78	54.219	88.05	73.14	62.16	47.83

When compared, formulations F1 and F5 having 10 % OS mucilage concentration (from direct compression and wet granulated formulations respectively), there was no significant difference in drug release ($R = 0.98\ 64$, $SD = 5.66187$, $P < 0.0001$) at ($\alpha = 0.05$) over the entire study period, which could be due to the formation of liquid bridges in the two formulations that impart similar strength in both the direct compression and wet granulated formulations. The release was not significantly different at ($\alpha = 0.05$) for same polymer concentration for direct and wet granulation formulations. But due to the low flow property of direct compression mix than wet granulation as discussed earlier wet granulation is preferred for this formulation.

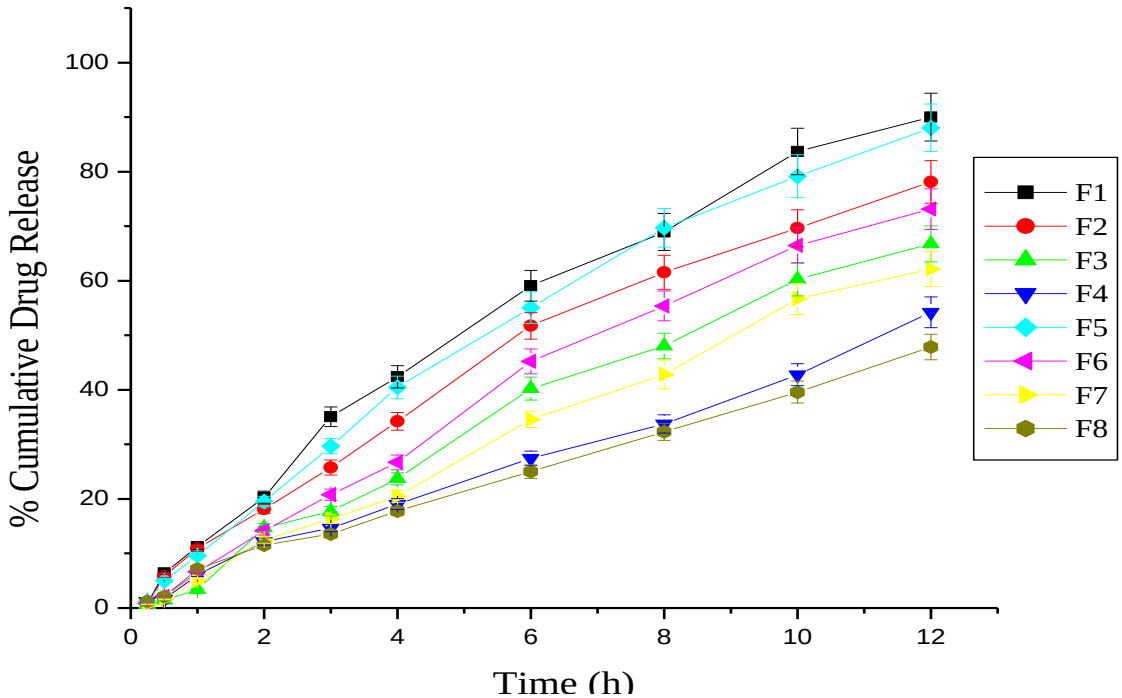


Figure 4.14: % Cumulative drug releases of diclofenac sodium in direct compression (F_1-F_4) and wet granulated (F_5-F_8) formulations at different polymer concentrations

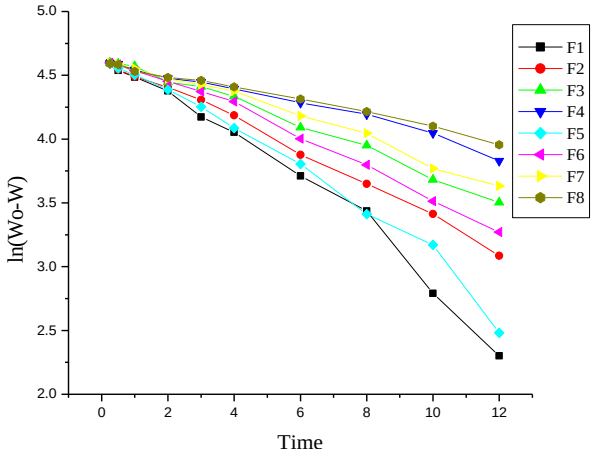
Diclofenac sodium is poorly soluble in acidic pH (1.3), with respect to the polymer in a matrix system based on hydrophilic polymer; the system becomes less porous in formulations containing higher polymer concentration and generally for all formulations in acidic medium, leading to a slower release rate compared to the alkaline medium (5-8). Water soluble drug would act to form micro-cavities in the gel layer, through which it is able to access the dissolution medium (Maderuelo *et al*., 2011). All these findings showed good sustaining efficiency of OS mucilage.

High polymer concentration retards the drug release process from the matrix, by making it less porous. These are generally true for all polymers; in case of OS mucilage, low polymer concentration of 10 % was also to sustain drug release for longer time. An increase in the percentage of polymer elicits an increase in its viscosity, which in turn decreases the leaching of drug from the surface and increases the concentration of the gel and its tortuosity (Karen Mitchell *et al*., 1990). Therefore, the greater the degree of viscosity of OS mucilage due to

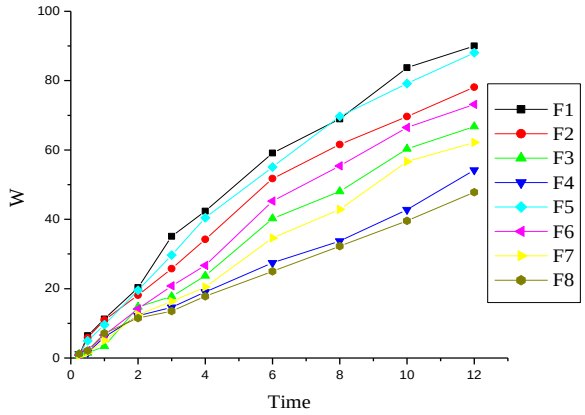
increased concentration, the greater the resistance to polymer erosion, which decreases the drug release rate. Percentage of swelling and erosion are completely dependent upon the viscosity of the polymer (Ravi *et al.*, 2008).

As seen from the rheological study, OS was highly viscous and the ability of viscous polymers to capture water is greater, reflected in a rapid swelling of the polymers, and formation of strong and homogeneous structures. So, it is possible to achieve release kinetics controlled by diffusion by using the high viscosity OS mucilage.

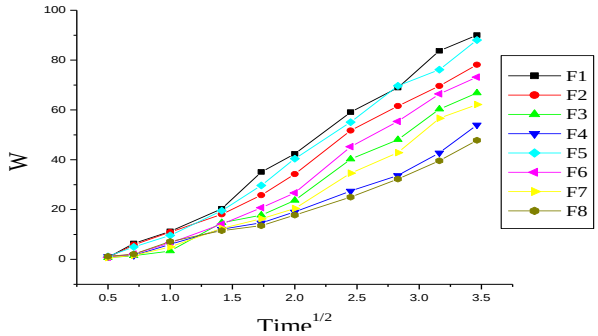
Comparing this study with the study by Asmare (2013) on aloe mucilage as matrix forming agent theophiline as a model drug having similar solubility with diclofenac sodium and comparable polymer concentration, OS mucilage showed comparable sustaining effect.



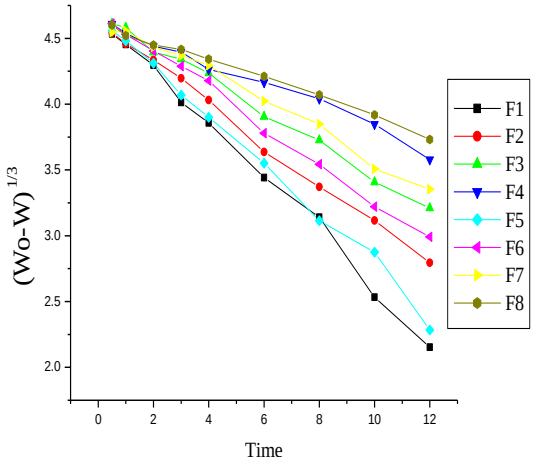
I: First order release model



II: Zero order release model



III: Higuchi release model



IV: Hixon-Crowell m

Figure 4.15 Drug release kinetic mode

4.7.1. Korsmeyer-Pappas release model

Korsmeyer-Pappas release model is a decision parameter to identify drug transport mechanism. The value of *n* is used to differentiate between the various drug releases mechanisms. The use of the *n* value as a criterion to discriminate dissolution mechanisms is influenced by the nature and geometries of the drug delivery system. Generally, an early portion of a release profile ($F < 60\%$) is used in the model. The model is depicted in Figure 4.16. When n = 0.45, the release is Fickian and non-Fickian when $0.45 \leq n \leq 0.89$, while 0.98value of "n" exponent indicates typical zero-order release (Akhlaq *et al.*, 2010). The n value for all formulations laid in $0.45 \leq n \leq 0.89$ range (table 4.8), indicating that non-Fickian diffusion was the predominant mechanism of drug releas

from these formulations and that the release mechanism was non-Fickian or anomalous release. It can be inferred that the release was dependent on both drug diffusion and polymer relaxation.

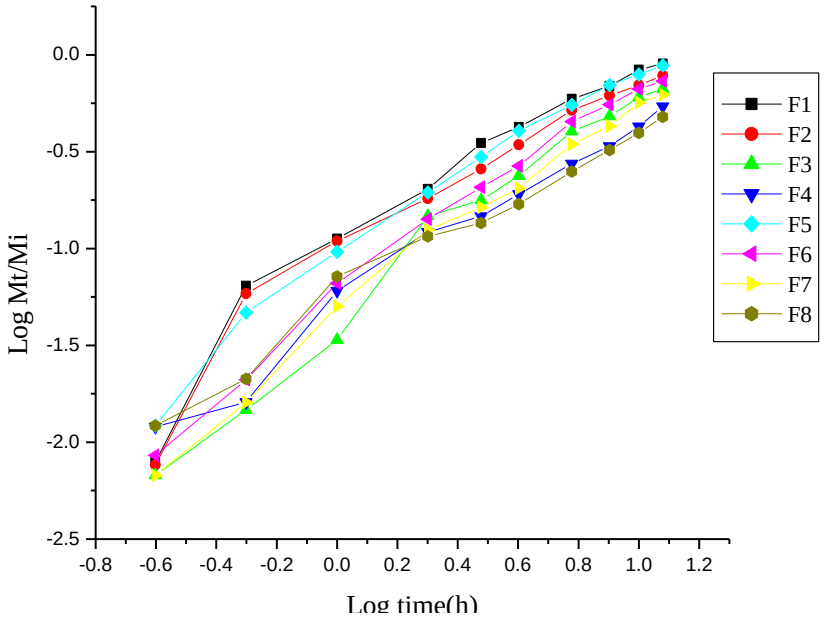


Figure 4.16: Krosmeyer-Pappas release kinetics

Table 4.7: Drug release parameters and statistical estimates of the Zero order, first order, Higuchi, Korsmeyer-Peppas and Hixson-Crowell models fitted to dissolution data

Model	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	
First Order	0.979	0.996	0.992	0.981	0.978	0.992	0.987	0.992	R^2
Zero-Order	0.973	0.978	0.989	0.993	0.979	0.988	0.994	0.994	R^2
Higuchi Model	0.992	0.989	0.974	0.964	0.990	0.977	0.966	0.971	R^2
Hixson- Crowell	0.996	0.997	0.995	0.986	0.995	0.996	0.99	0.994	R^2
Korsmey er-Pappas	0.933	0.934	0.984	0.981	0.977	0.988	0.988	0.981	R^2
	0.5	0.5	0.746	0.656	0.507	0.639	0.682	0.31	n

As we can see from the above table Hixson-Crowell release kinetics has the best fit for all

formulations, showing that there was a change in surface area and diameter of the drug matrix with time. This is an indication of swelling capacity of the polymer even at lower concentration.

4.7.2. Comparison of Formulations with Marketed Product (Diclo-Denk 100 mg SR)

The assay study for marketed product (Diclo-Denk) showed 98.72 ± 0.012 % drug content, which complied with the USP 90-110 % range. The release profile the marketed product is shown below in Figure 4.17 in comparison with F1 and F5 that fit with acceptance criteria. F1 (11.24%, 59.09%, 90.015) and F5 (9.615, 55.06%, 88.05%) complied with the USP stated label claim for sustained release (1h time-point, (6h), a middle time-point and the last time-point should be at least 10 %, 50-70 % and 80 %, respectively) providing assurance of full release. The f_1 and f_2, dissimilarity and similarity factors were calculated for formulations. The result showed the FDA requirement < 15 for f_1 and 50-100 for f_2. The results were f_1= 3.31, f_2= 97.35 for F5 and f_1= 3.35, f_2= 95.73 for F1 respectively. Two formulations F1 and F5 are in line with the above acceptance criteria.

Table: 4.8 Factors for comparison of formulations with Marketed Product

Comparison	**f_1**	**f_2**
F1 with MP	3.35	95.73
F2 with MP	17.27	39.76
F3 with MP	31.12	29.04
F4 with MP	44.07	19.62
F5 with MP	3.31	97.35
F6 with MP	23.43	34.52
F7 with MP	35.28	28.73
F8 with MP	50.25	17.02

MP- Marketed Product

The release profile of Diclo-Denk 100 mg SR was compared with F1 and F5 using Analysis of Variance (ANOVA) on Origin 7.0 with Statistical software at confidence limit of $\alpha < 0.05$. And the p=0.001 result showed similarity of F1 and F5 with Diclo-Denk marketed product.

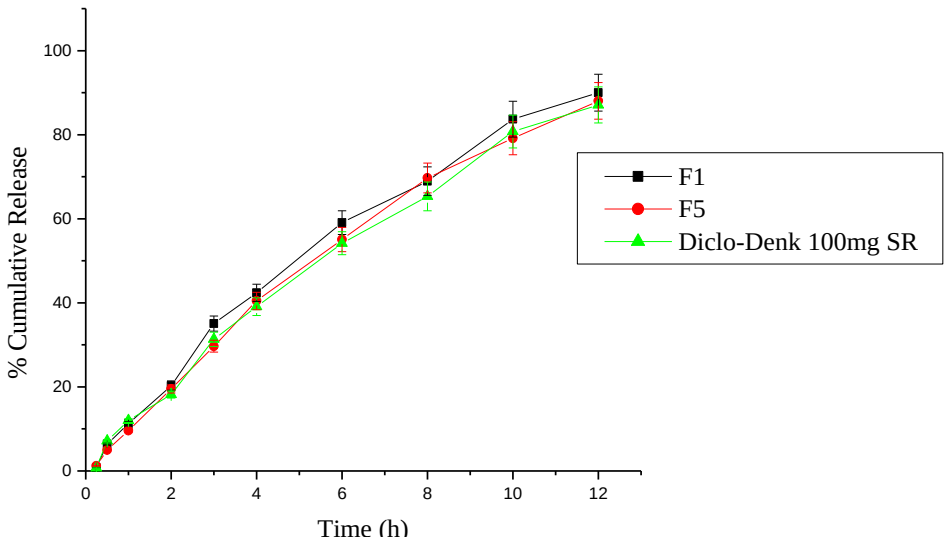


Figure 4.17: Comparative elucidation of the two better formulations with respect to Diclo-Denk 100 mg SR

According to Diclo-Denk 100 mg SR release profile study, the two formulations were significantly comparable with the brand product, but F1 (direct compression) is not the best formulation with regard to powder properties. So, the final best formulation is F5.

5. Conclusion

This study revealed good flow and good compressible properties of OS mucilage. And, granulation had further improved the flow as well as compressibility of the formulations. The findings of this study showed that direct compression of drug and OS mucilage and wet granulation formulations effectively sustained diclofenac sodium release for more than 12 h. Wet granulation showed a better matrix for sustained release tablets by improving flow in processing. Therefore, the mucilage of *Opuntia Stricta* leaves can be used as an alternative pharmaceutical excipient in the formulation and manufacture of sustained release matrix tablets.

6. Suggestions for Further Work

In this study matrix forming ability of OS mucilage was evaluated and was found to be promising. Therefore the complete characterization of the mucilage such as composition, morphology and structure is recommended.

It is also recommended to develop a method that give better yield and reduce precipitant consumption.

Stability study to know the stability profile of the formulation during storage and chronic toxicity profile of the mucilage should be studied.

In addition, it is recommended to evaluate the binding, film forming, thickening, stabilizing and humidifying properties of OS mucilage. It is also recommended work on polymer modification for further pharmaceutical application.

It is also recommended to do *in vivo* evaluation.

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