EVALUATION OF *Cicer arietinum* AND *Pisum sativum* STARCH AS THE ALTERNATIVE TABLET BINDER TO MAIZE STARCH: ASSESSMENT BY PREFORMULATION AND FORMULATION STUDIES

Dissertation submitted to
The Tamilnadu Dr. M.G.R Medical University, Chennai
In partial fulfillment for the award of the Degree of

MASTER OF PHARMACY

(Pharmaceutics)

APRIL-2014

DEPARTMENT OF PHARMACEUTICS
KMCH COLLEGE OF PHARMACY
KOVAI ESTATE, KALAPPATTI ROAD,
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Submitted by

Reg.No:261210905

Under the Guidance of

J. PADMA PREETHA, M. Pharm.,
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CERTIFICATE

This is to certify that the dissertation work entitled **"EVALUATION OF *Cicer arietinum* AND *Pisum sativum* STARCH AS THE ALTERNATIVE TABLET BINDER TO MAIZE STARCH: ASSESSMENT BY PREFORMULATION AND FORMULATION STUDIES"** submitted by **Reg. No: 261210905** is a bonafide work carried out by the candidate under the guidance of **Mrs. J. Padma preetha, M.Pharm.,** to the Tamil Nadu Dr. M.G.R. Medical University**,** Chennai, in partial fulfillment for the Degree of **Master of Pharmacy** in **Pharmaceutics** at KMCH College of Pharmacy, Coimbatore, Tamil Nadu during the academic year 2013-2014.

Date:
Place: Coimbatore

Dr. A. Rajasekaran, M.Pharm., Ph.D.,
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Assistant Professor,
Department of Pharmaceutics,
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Date:
Place: Coimbatore

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Department of Pharmaceutics.

DECLARATION

I hereby declare that this dissertation entitled **"EVALUATION OF *Cicer arietinum* AND *Pisum sativum* STARCH AS THE ALTERNATIVE TABLET BINDER TO MAIZE STARCH: ASSESSMENT BY PREFORMULATION AND FORMULATION STUDIES"** submitted to the Tamil Nadu Dr. M.G.R. Medical University, Chennai, in partial fulfillment for the award of Degree of **Master of Pharmacy in Pharmaceutics** was done by me under the institutional guidance of **Mrs. J. Padma preetha, M. Pharm.,** Assistant Professor, Department of Pharmaceutics, KMCH College of Pharmacy, Coimbatore, during the academic year 2013-2014.

Date:
Place: Coimbatore **Reg. No: 261210905**

EVALUATION CERTIFICATE

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Examination Centre: KMCH College of Pharmacy, Coimbatore-48.

Date:

Internal Examiner **External Examiner**

Convener of Examination

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Above all I dedicate myself before the unfailing presence of **God** and constant love and encouragement given to me by my beloved **Father Kannan, Mother Sagunthala, Brother Rajasekar** and my remaining family members who deserve the credit of success in whatever work I did.

Reg. No: 261210905

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ABBREVIATIONS USED

e.g.	Example
i.e.	That is
%	Percentage
Kg.	Kilogram
gm.	gram
mg.	Milligram
µg.	Micro gram
ml.	Milliliter
cm.	Centimeter
mm.	Millimeter
nm.	Nanometer
W/w.	Weight by weight
W/v	weight by volume
avg.	Average
hrs.	Hours
pH.	Hydrogen ion concentration
^{o}C	Degree centigrade
RH.	Relative Humidity
HCL.	Hydrochloric acid
RPM.	Revolution per minute
Abs.	Absorbance
Conc.	Concentration
Fig.	Figure
UV-VIS	Ultra violet and visible spectroscopy
FTIR	Fourier Transform Infrared spectroscopy
C.I	Compressibility Index
CR	Cumulative Release
IR	Immediate Release
SR	Sustained Release
USP	United State Pharmacopoeia
BP	British Pharmacopoeia
R^2	Regression coefficient

1. INTRODUCTION

As legume grains are the major group of agricultural commodities, which are widely grown and consumed globally. With increasing evidence of natural benefits, they are also potentially sources of novel ingredients including starches. Present day consumer's looks for natural ingredients in foods, drugs and cosmetics as they trust that anything natural will be more safe and free from side effects. Most of the natural ingredients used in the food industries and pharmaceutical industries are regarded as safe for human consumption [1, 2].

Solid dosage forms like tablets and capsules are the most popular and preferred drug delivery systems because they have high patient compliance, relatively easy to produce, easy to market, accurate dosing and good physical and chemical stability. Tablet dosage form is mainly composed of the drug and the excipients. The excipients have a direct influence on the quality and effectiveness of the final product [3, 4 and 5].

Natural excipients are inert, safe, non-toxic, biocompatible, biodegradable, low cost, eco-friendly and abundantly available in nature. Although excipients are termed as inert, they have a large influence on stability, bioavailability and the process by which the dosage forms are prepared. Starch is most widely used one of the excipients in food as well as pharmaceutical industries, where they are used as binders, fillers, thickeners, glidants, disintegrants as well as gelling, bulking and water retention agent. Marketable starches are obtained from cereals such as corn, wheat and from roots and tubers particularly potato, cassava and they lead the world markets for starches in the food and pharmaceutical industries [6, 7 and 8].

Recently more attention has been focused on the development of some of the starches from different botanical sources as excipients in pharmaceutical formulation. With the versatility of starch in various dosage forms, there is a need to continue to develop a prudent choice of starch excipients with suitable properties to meet the special needs of drug formulators. Lot of studies showed the nutritional value of the edible varieties of pulses, and more studies even showed disease curing or therapeutic properties of legumes, As legumes are fiber rich starchy vegetables that improve blood sugar control and reduce cardiovascular risk in diabetics, that there is a need still exists to examine the various pharmaceutical properties of the starch isolated from the seeds of Pisum sativum and Cicer arietinum to assess its functionality as pharmaceutical excipients [9, 10 and 11].

1.1 Diabetes:

Diabetes is a chronic disease that occurs when adequate insulin was not produced by the pancreas, or when the body cannot efficiently use the insulin it produces. Hyperglycemia is a common effect of uncontrolled diabetes and at last leads to serious damage to most of the body's systems, mainly the nerves and blood vessels.

The most common forms of diabetes are as follows;

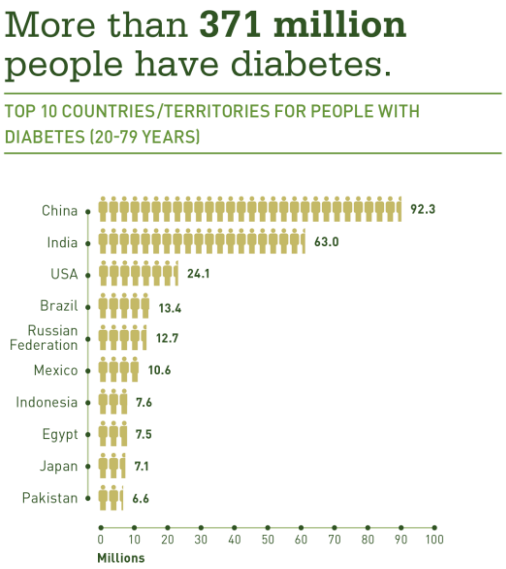
- Type 1 diabetes,
- Type 2 diabetes, and
- Gestational diabetes.

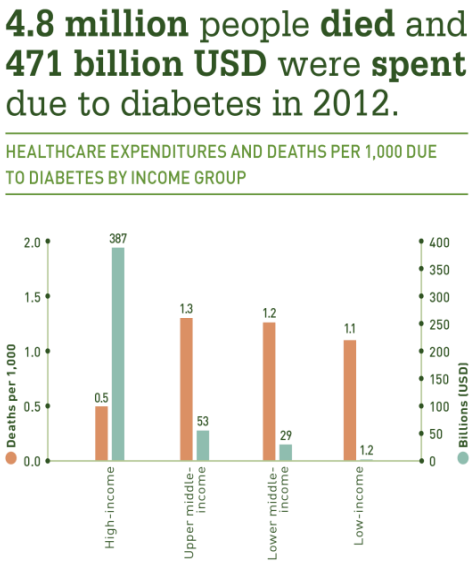
1.1.1 Diabetes in world [12, 13]:

Diabetes can be found in every country in the world and the burden will continue to increase globally due to lack of effective prevention and management programmes. Type 2 diabetes (85 to 95%) is now a common as well as serious global health problem for most of the countries.

As per the latest estimate of International Diabetes Federation (IDF) 2012;

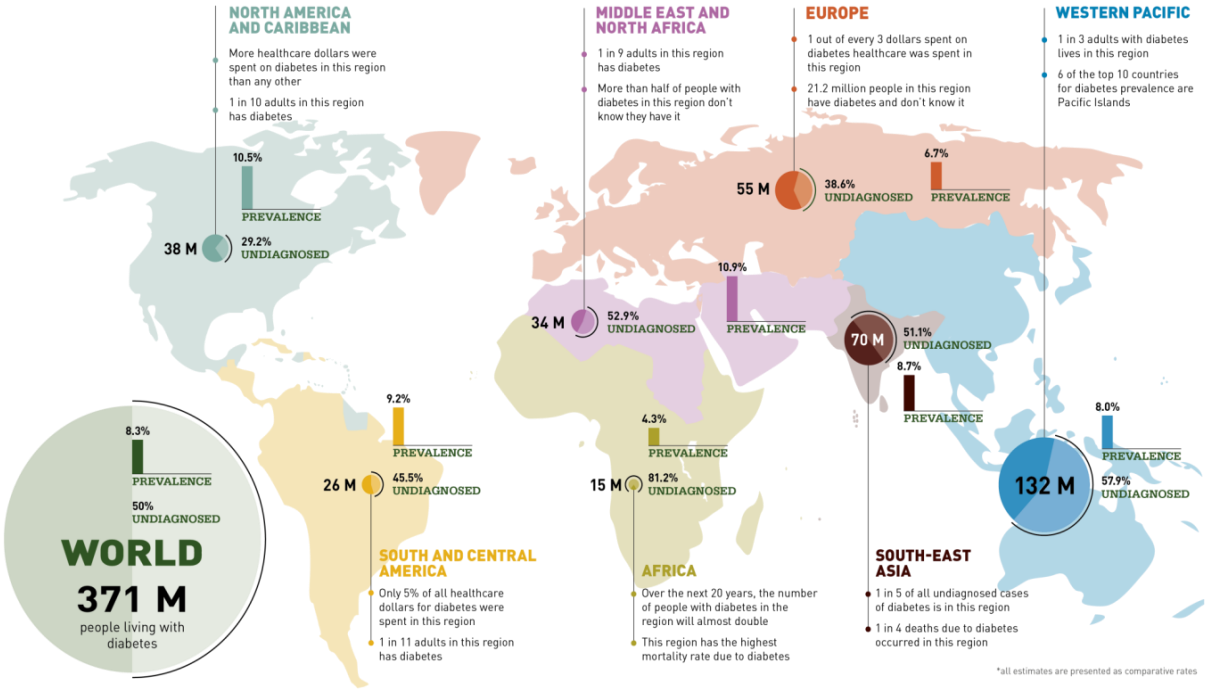
- More than 371 million people worldwide have diabetes.
- Half of people with diabetes are undiagnosed.
- 4.8 million Peoples died due to diabetes.





Source: IDF DIABETES ATLAS (Update 2012) [12]

IDF DIABETES ATLAS 2012 UPDATE[12]



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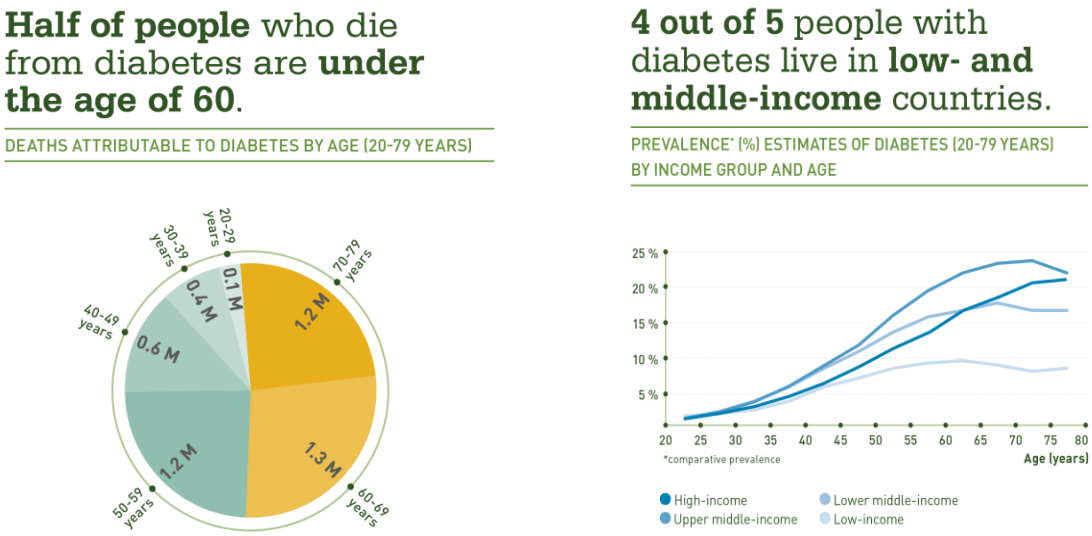


Figure 1.01: International Diabetes Federation Atlas Update 2012

1.1.2 Diabetes in India[14]:

According to the International Diabetes Federation (IDF), India has 70 million diabetics between 20-79 years. Major numbers of diabetics were found in middle and low income countries. In fact by 2030, according to the estimates, 8.4 percent of India's adult population will have diabetes, but the bigger worry is the numbers that go undiagnosed.

The risk factors for diabetes in Indians are;

- Age
- Family History
- Central Obesity
- Physical Inactivity and Sedentary Living
- Insulin Resistance
- Urbanization
- Stress

1.2 Cereals and pulses [15, 16]:

Cereals and pulses are the two main grain group crops that are grown in different parts of the world. These two crop groups are regularly consumed by most of the world population. Some part of the world might favour one over the other, but often they are consumed in combination.

Table 1.01: A comparison of world production of cereals, pulses and roots & tubers in year 2012

Grouping of Commodities		Production quantity (tonnes) in year 2012	
		World	India
01.	Cereals, Total	2,546,631,494	286,500,000
02.	Pulses, Total	70,418,680	16,280,000
03.	Roots and Tubers, Total	805,824,378	54,176,000
Source: Food and Agriculture Organization of the United Nations (FAOSTAT)[17]			

1.2.1 Legumes[18]:

The term "legume" refers to the plants whose fruit is enclosed in a pod. Legumes represent a huge family of plants together with more than 600 genera and more than 13,000 species. While growing, legumes fix nitrogen into the soil, which reduces the need for chemical fertilizers. Well-known legumes include alfalfa, clover, fresh peas, lupins, mesquite, soy and peanuts.

1.2.2 Pulses [15, 16 and 18]:

Pulses are part of the legume family, but the term "pulse" refers only to the dried seed. Dried peas, edible beans, lentils and chickpeas are the most common varieties of pulses. They have important nutritional and health advantages for consumers. Pulses are consumed for proteins and slow release carbohydrates especially starch. Most of the pulses are rich in complex carbohydrates and have a total carbohydrate content ranging from 24 to 68% on dry weight basis. Pulses elicit the lowest blood glucose response. Several reports claim that inclusion of pulses in the daily diet has several beneficial physiological effects in controlling and preventing various metabolic diseases such as diabetes mellitus, coronary heart disease and colon cancer. The role of pulses gains more importance among the people suffering from metabolic disorder.

Table 1.02: World Pulses Production 2012

World Pulses Production 2012		
Production (tonnes)		
Country	**Item**	**2012**
World + (Total)	Bambara beans	150,500
	Beans, dry	23,140,276
	Broad beans, horse beans, dry	4,057,922
	Chick peas	11,308,684
	Cow peas, dry	5,737,836
	Lentils	4,550,358
	Lupins	1,290,656
	Peas, dry	9,861,758
	Pigeon peas	4,329,078
	Pulses, nes	5,049,539
	Vetches	942,074
	Pulses, Total + (Total)	**70,418,680**
Source: Food and Agriculture Organization of the United Nations (FAOSTAT)[17]		

Table 1.03: India Pulses Production 2012

India Pulses Production 2012		
Production (tonnes)		
Country	**Item**	**2012**
India + (Total)	Beans, dry	3,630,000
	Chick peas	7,700,000
	Lentils	950,000
	Peas, dry	625,000
	Pigeon peas	2,650,000
	Pulses, nes	725,000
	Pulses, Total + (Total)	**16,280,000**
Source: Food and Agriculture Organization of the United Nations (FAOSTAT)[17]		

1.2.3 Chickpea [19, 20]:

Chickpea (*Cicer arietinum* L.), also called as Bengal gram or garbanzo bean, is an old world pulse and one of the seven Neolithic founder crops in the fertile crescent of near east[19]. Currently, chickpea is grown in over 50 countries around the world. Globally, chickpea is the third most important pulse crop in production, next to dry beans and field pea[20]. India is the largest producer and consumer of chickpeas in the world, while in 2012-13 (second advance estimates) record production of chickpea is 8567.8 thousand tonnes[21].

Figure 1.02: Flowering and fruiting chickpea plant and chickpea pods.

Table 1.04: Scientific Classification of Chickpea:

Scientific Classification	
	Chick pea **Cicer arietinum L.**
Rank	**Scientific Name & Common Name**
Kingdom	Plantae – Plants
Subkingdom	Tracheobionta – Vascular plants
Super division	Spermatophyta – Seed plants
Division	Magnoliophyta – Flowering plants
Class	Magnoliopsida – Dicotyledons
Subclass	Rosidae
Order	Fabales
Family	Fabaceae – Pea family
Genus	Cicer L. - cicer
Species	Cicer arietinum L. – chick pea
Source : United States Department of Agriculture (USDA)	

Table 1.05: World Chickpea Production:

World Chickpea Production				
Top 10 Destinations by Crop Year				
	2011	Tonnes	**2012**	tonnes
	World + (Total)	**11,609,723**	**World + (Total)**	**11,308,684**
01.	India	8,220,000	India	7,700,000
02.	Australia	513,338	Australia	673,371
03.	Pakistan	496,000	Turkey	535,000
04.	Turkey	487,477	Myanmar	473,102
05.	Myanmar	473,102	Ethiopia	400,207
06.	Ethiopia	322,829	Iran	315,000
07.	Iran	290,243	Pakistan	291,000
08.	United states of America	99,881	Canada	157,280
09.	Canada	90,800	United states of America	150,638
10.	Mexico	72,143	United republic of Tanzania	74,000
Source: Food and Agriculture Organization of the United Nations (FAOSTAT)[17]				

Globally, chickpea is mostly consumed as a seed food in several different forms and preparations. These different forms of consumption provide consumers with valuable nutrition and potential health benefits. There are two different types of cultivated chickpea, Desi and Kabuli. The Desi types report for about 80-85% of the total chickpea area and are typically grown in Asia and Africa. The Kabuli types are mainly grown in West Asia, North Africa, North America and Europe. There is a growing demand for chickpea due to its nutritional value[20].

Chickpeas have been and are being consumed by humans since ancient times. Despite chickpea being a member of the "founder crop package" with potential nutritional/medicinal qualities, it has not received as much as necessary attention for research like other founder crops (e.g. wheat). Although publications have described the physicochemical and nutritional characteristics of chickpea, there is limited information relating to the starch and its pharmaceutical uses. So there is a need to isolate starch from chickpea and examine their various pharmaceutical properties to assess its functionality as pharmaceutical binder.

1.2.4 Dry Pea [9, 11]:

Dry pea (*Pisum sativum* L.), also called as Garden pea, green pea or field pea, is now grown all over the world and are widely consumed in both dried and fresh form. The green pea is widely accepted as one of the first food crops to be cultivated by humans. Canada is currently the largest world producer and exporter of peas. Russia, china, India

and France are also large scale producer of this legume. Even though being a large-scale producer of peas, India is also the world's largest importer of this food due to its vast popularity in that country[11].

Peas are starchy vegetables that are rich in fiber, which helps to lower cholesterol, reduces your risk of type-2 diabetes and keeps you feeling full, by this means helping with weight loss. As a good source of Folate and Vitamin-B, they may help to reduce the risk of cardiovascular disease. Peas also supply vitamin C, which helps to keep skin, hair and eyes healthy and Vitamin-K, which some research suggests may help to preserve bone health[9].

Figure 1.03: Flowering and fruiting Green pea plant and Green pea pods.

Table 1.06: Scientific Classification of Dry Pea:

Scientific Classification	
	Dried pea **Pisum sativum L.**
Rank	**Scientific Name & Common Name**
Kingdom	Plantae – Plants
Subkingdom	Tracheobionta – Vascular plants
Super division	Spermatophyta – Seed plants
Division	Magnoliophyta – Flowering plants
Class	Magnoliopsida – Dicotyledons
Subclass	Rosidae
Order	Fabales
Family	Fabaceae – Pea family
Genus	Pisum L. – pea
Species	Pisum sativum L. – green pea
Source : United States Department of Agriculture (USDA)	

Table 1.07: World Dry Pea Production:

World Dry Pea Production				
Top 10 Destinations by Crop Year				
	2011		2012	
		tonnes		Tonnes
	World + (Total)	**9,729,673**	**World + (Total)**	**9,861,758**
01.	Canada	2,115,600	Canada	2,803,000
02.	Russian federation	2,021,000	Russian federation	1,660,016
03.	China	1,190,000	China	1,114,000
04.	France	670,079	India	625,000
05.	India	593,200	France	565,322
06.	Australia	394,675	United states of America	493,150
07.	Ukraine	364,300	Ukraine	351,400
08.	Ethiopia	257,031	Australia	342,500
09.	United states of America	255,150	Ethiopia	263,266
10.	Spain	253,427	Germany	139,000
Source: Food and Agriculture Organization of the United Nations (FAOSTAT)[17]				

Pea starch is widely used in the food industry because of its excellent thickening and binding properties and also its ability to optimize the gelling process. Several manufacturers use starch made from peas especially when producing meat and dairy products. Though, pea starch is popular in food industry due to their nutritional properties, there is a need still exists to examine various pharmaceutical properties of the starch to assess its functionality as pharmaceutical binder.

1.2.5 Comparison of Chickpea and Dried peas:

Chickpeas and Dried peas are the rich source of 'lente' carbohydrates, which provides several beneficial physiological effects. In recent years, glycemic index (GI) has became a useful tool for planning diets for the patients of diabetes, dyslipidemia, cardiovascular disease, and even certain cancers in the general population.

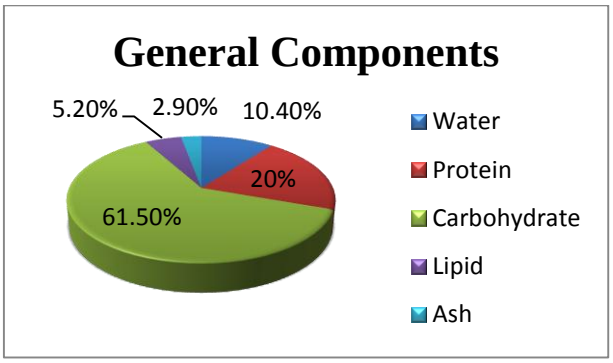


Figure 1.04: Chickpea (whole, dried, raw) [22]

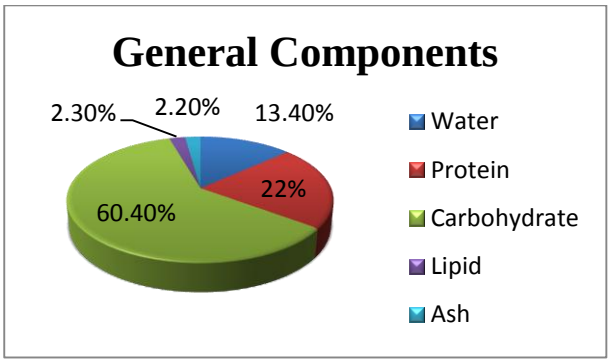


Figure 1.05: Pea (whole, dried, raw) [23]

Table 1.08: A Comparison of Nutritional value of Chickpea and Dried Peas

		Chickpea, raw	Dried pea, raw
Nutrients	Unit	Value per 100g	Value per 100g
Proximates			
Carbohydrates, by difference	g	60.65	60.37
Fiber, Total dietary	g	17.4	25.5
Protein	g	19.30	24.55
Total Lipid (fat)	g	6.04	1.16
Water	g	11.53	11.27
Energy	Kcal	364	341
Sugars, total	g	10.70	8.00
Minerals			
Calcium, Ca	mg	55	105
Iron, Fe	mg	4.43	6.24
Magnesium, Mg	mg	115	115
Phosphorus, P	mg	366	366
Potassium, K	mg	981	875
Sodium, Na	mg	15	24
Zinc, Zn	mg	3.01	3.43
Vitamins			
Vitamin-C	mg	1.8	4.0
Thiamin	mg	0.726	0.477
Riboflavin	mg	0.215	0.212
Niacin	mg	2.889	1.541
Vitamin-B6	mg	0.174	0.535
Folate, DFE	µg	274	557
Vitamin-B12	µg	0	0
Vitamin A, RAE	µg	7	3
Vitamin A, IU	IU	149	67
Vitamin E	mg	0.09	0.82
Vitamin D (D_2+D_3)	µg	0	0
Vitamin D	IU	0	0
Vitamin K	µg	14.5	9.0
Lipids			
Fatty acids, total saturated	g	0.161	0.626
Fatty acids, total mono unsaturated	g	0.242	1.358
Fatty acids, total poly unsaturated	g	0.495	2.694
Cholesterol	mg	0	0
Source : Agriculture Research Service, United States Department of Agriculture (USDA)			

1.3 Diabetes and diet [24]:

Eating right is vital if a person is trying to prevent or control diabetes. Even though exercise is also important, what the person takes have the biggest impact when it comes to weight loss.

Now-days we hear about carbohydrates all the time. The term "total carbohydrate" includes three types of carbohydrates, namely starches, sugars and fibers. Starches are also known as complex carbohydrates. Starch rich diet includes peas, split peas, black eyed peas, corn, lima beans, pinto beans, kidney beans, dried beans, lentils, potatoes and grains like oats, barley and rice. Sugars are referred as simple or fast-acting carbohydrates, which includes naturally occurring sugars and added sugars. Fibers are the indigestible part of plant foods, including fruits, vegetables, whole grains, nuts and legumes. For good health, adults need to try to eat 25 to 30 grams of fiber each day. It is important to increase the fiber intake gradually, in order to prevent stomach irritation.

Carbohydrates have a big impact on your blood sugar levels, so it is very important to choose high-fiber, slow release carbohydrate diet. Slow release carbohydrates helps to keep your blood sugar levels constant because they are digested more slowly, thus preventing your body from producing too much insulin. They also provide lasting energy and help you stay full longer.

Table 1.09: Diabetes and diet:

Choosing carbohydrates that are packed with fibers (and don't spike your blood sugar)	
Instead of	**Try these high fiber option**
White rice	Brown rice or Wild rice
White potatoes	Sweet potatoes, yams, winter squash, cauliflower mash
Regular pasta	Whole-wheat pasta
White bread	Whole-wheat or whole-grain bread
Sugary breakfast cereal	High-fiber breakfast cereal (Raisin Bran, etc.)
Instant oatmeal	Steel-cut oats or rolled oats
Cornflakes	Bran flakes
Corn	Peas or leafy green

The glycemic index (GI) provides a measure that how quickly a food turns into sugar in your body. Glycemic load is a newer term which includes both the glycemic index and the carbohydrate amount that present in a food, which gives an accurate idea of how a food may affect our blood sugar level. High GI foods spike our blood sugar rapidly, while low GI foods have the least effect.

1.4 Resistant starch [25]:

Resistant starch is the total amount of starch and starch degradation product that resists digestion in the small intestine of healthy people. Resistant starch is considered as the third type of dietary fiber, as it can deliver some of the benefits of insoluble fiber and some of the benefits of soluble fiber. Usually carbohydrates are rapidly digested and absorbed as glucose into body through small intestine and subsequently used for short-term energy needs or stored. Resistant starch resists digestion and passes to large intestine where they act as dietary fibers.

Table 1.10: Resistant starch in Foods:

Resistant Starch in Foods	
Food	**Resistant Starch (g/100g)**
Chickpeas	**10.0**
Beans	**5.2**
Corn kernels	**3.9**
Red kidney beans	**2.6**
Boiled potato (cooled)	**2.4**
Oats	**1.8**
White bread	**0.8**
Whole meal bread	**0.8**
Source: CSIRO Division of Human Nutrition, Australia.	

Types:

Resistant starch (RS) has been categorized into 4 types:

1. RS1: Includes physically inaccessible or digestible resistant starch (found in seeds/legumes and unprocessed whole grains).
2. RS2: Includes starch of natural granular form (uncooked potatoes, green banana flour, high amylose corn).
3. RS3: starch formed when starch containing foods are cooked and cooled such as legumes, bread, cornflakes and cooked and chilled potatoes. The process of cooking out the starch and cooling is called retrogradation.
4. RS4: Includes chemically modified starch that resist digestion (have wide variety of structure and are not found in nature).

When the resistant starch enters the large intestine, it gets fermented by bacteria and forms short-chain fatty acids, which plays a major role in health as mentioned below;

Advantages of resistant starch:

1) Lowers blood glucose level
2) Lowers blood cholesterol level
3) Promotes colon health
4) Prevents colon cancer
5) Boosts the immune system
6) Reduces appetite
7) Increases the amount of fat used for fuel
8) Helps with weight loss.

In fact, one study exposed that when subjects replaced carbohydrates with resistant starch, they had 20% to 30% higher fat oxidation. In particular butyrate (short-chain fatty acid) appears to block the body's ability to use carbohydrate as a fuel; which responds body to burn more fat instead. Resistant starch may help the people who are at risk of diabetes/pre-diabetes by improving insulin sensitivity. Legumes (beans, dried peas, lentils) contain the highest amount of the resistant starch.

1.5 Dosage Forms:

Drugs are substances that are used in the diagnosis, cure, mitigation, prevention/treatment of disease in human beings/animals. Drugs are obtained from different sources and are not administered in their pure form. They are converted into suitable preparations and then administered to patients; such preparations are known as Dosage Forms. Dosage form includes Solid, Semi-solid and Liquid dosage forms. Drug substances were frequently administered orally in the type of solid dosage forms as tablets and capsules.

1.5.1 Tablets [26]:

Tablets are defined as the compressed solid dosage form having medicaments with or without excipients. According to the Indian Pharmacopoeia Tablets are solid, flat / biconvex dishes, unit dosage form, prepared by compressing the drugs or the mixture of drugs, with or without diluents. They differ in shape and vary greatly in size and weight, depending on amount of medicinal substances and the intended mode of administration. It is the most accepted dosage form and 70% of the total medicines are dispensed in the form of tablet. All medicaments are obtainable in the tablet form except where it is hard to formulate or administer.

Different types of tablets [26]:

A. Tablets ingested orally:
    1. Compressed tablet
    2. Multiple compressed tablet
    3. Repeat action tablet
    4. Delayed release tablet
    5. Sugar coated tablet
    6. Film coated tablet
    7. Chewable tablet

B. Tablets used in oral cavity:
    1. Buccal tablet
    2. Sublingual tablet
    3. Torches or lozenges
    4. Dental cone

C. Tablets administered by other route:
    1. Implantable tablet
    2. Vaginal tablet

D. Tablets used to prepare solution:
    1. Effervescent tablet
    2. Dispersing tablet
    3. Hypodermic tablet
    4. Tablet triturates

General properties of tablet dosage forms:

1) Must have elegant product identity, free from defects like chips, cracks, discoloration, and contamination.
2) Must have sufficient strength to withstand mechanical shock during its production packaging, shipping and dispensing.
3) Must have chemical and physical stability to maintain its physical attributes over time.
4) Must be able to release the medicinal agents in a predictable and reproducible manner.
5) Must have chemical stability ultimately so as not to follow modification of the medicinal agents.

Advantages of tablet dosage form[27]:

1) Unit dosage form, offer greatest capabilities of all oral dosage form for the greatest dose precision and least content variability.
2) Reduced cost of all oral dosage form.
3) Lighter and compact.
4) Easy and cheap to pack and strip.
5) Easy to swallow with least tendency for hang-up.
6) Sustained release product is achievable by enteric coating.
7) Bitter taste and objectionable odor can be masked by coating method.
8) Appropriate for large scale production.
9) Great chemical, mechanical and microbial stability.
10) Product identification is easy.

Disadvantages of tablet dosage form[27]:

1) Difficulty in swallowing incase of children's and unconscious patients.
2) Some of the drugs resist compression into dense compacts, owing to amorphous nature, low density character.
3) Drugs with poor wetting, slow dissolution properties, optimum absorption high in the gastrointestinal tract may be difficult to formulate as tablet.
4) Drugs with bitter taste and objectionable odor may require encapsulation or coating. In such cases, capsule may offer the best and lowest cost.

Tablet Ingredients[26]:

In addition to active ingredients, tablet contains a number of inert materials known as additives or excipients.

Commonly used excipients are:

1) Diluents
2) Binders and adhesives
3) Disintegrants
4) Lubricants and glidants
5) Coloring agents
6) Flavoring agents
7) Sweetening agents

1) **Diluents:**

Diluents are fillers used to make required bulk of the tablet when the drug dosage itself is inadequate to produce the bulk. Lactose, dicalcium phosphate, calcium sulphate are used as diluents.

2) **Binders and adhesives:**

Binders or granulators give cohesiveness to the powdered materials so that the powder can be converted in to granules. This ensures that the tablet remains intact after compression. Binders are used in the form of solution or in powder form. Acacia, starch, starch mucilage, methyl cellulose are commonly used as binders.

3) **Disintegrants:**

Disintegrants are substances included in tablet formulation to facilitate the disintegration of the tablet after administration. The active ingredients must be released from the tablet as efficiently as possible to allow for its dissolution. Starches are commonly used as disintegrants.

4) **Lubricants and glidants:**

Lubricants are substances which improve the rate of flow of granules, prevent adhesion of granules to the surface of the dies and punches and facilitate the ejection of tablets from the die cavity. Talc, magnesium stearate, calcium stearate are commonly used as lubricants.

Glidants improves the flow properties of granules from the hopper. Magnesium stearate, calcium stearate are used as glidants.

5) **Coloring agents:**

It gives elegant appearance to the tablets. Amaranth, tartrazine, sunset yellow are used as coloring agent.

6) **Flavoring agents:**

It gives good flavor to the tablets. Flavoring agents are mixed with dry granules by spraying the flavors on the granules before compression. Volatile oils are used as flavoring agents.

7) **Sweetening agents:**

It masks the bitter taste of the drug. Dextrose, lactose, mannitol, cyclamates, saccharin are used as sweetening agents.

1.5.2 Various methods for preparation of tablets [26]:

Tablets are prepared by three methods namely;

1. Dry granulation,
2. Wet granulation, and
3. Direct compression.

1. Dry granulation:

Processing steps are:

Raw material → Weighing → Screen → Mixing → Slugging → Milling → Screening → Mixing → Compression.

When tablet ingredients are sensitive to moisture or unable to withstand elevated temperature during drying and when the tablet ingredients doesn't have enough cohesive properties, slugging may be used to form granules. This method is referred as dry granulation.

2. Wet granulation:

Processing steps are:

Raw materials → Weighing → Screening → Wet massing → Sieving/Milling → Drying → Screening → Mixing → Compression.

The most general and widely used method of tablet preparation is the wet granulation method. The active ingredients, diluent and disintegrant are mixed thoroughly and the powder mass is wetted with the binding solution until the mass has the consistency of damp snow. The wet mass is forced through mesh to obtain granules, which is then dried. After drying granulation, the lubricant/glidants are added to promote flow of granules. These granules are then compressed to get tablet.

3. Direct compression:

Processing steps are:

Raw material → Weighing → Screening → Mixing → Compression.

Direct compression consists of compressing tablets directly from powdered materials without modifying physical nature of materials. This method is appropriate for crystalline chemicals having good compressible characteristic and flow properties.

2. LITERATURE REVIEW

S.No	Author's detail	Journal name	Objective	Conclusion
01.	**Luis Fernando Polesi et al.,**	Brazilian Journal of Food Technology, 2011; vol. 14(1): pp no. 74-81.	Evaluated the physicochemical, structural and functional characteristics of starches from two legumes: green pea and chick pea.	Pea starch showed simple and composite granules, B-type crystallinity pattern, and gelatinization peak temperature of 74.8˚C, reduced granule swelling with increased temperature and did not generate high viscosity in Rapid Visco Analyzer (RVA). Chickpea starch showed large oval shaped and small spherical shaped granules, C-type crystallinity pattern, and gelatinization peak temperature of 64.6˚C, good granule swelling and high viscosity in the RVA.
02.	**Emeje Martins Ochubiojo et al.,**	Scientific, Health and Social Aspects of the Food Industry, 2012; pp no. 355-379.	Starch has moved from its traditional role as food to being an indispensable medicine	Starch has proven to be the formulator's "friend" in that, it can be utilized in the preparation of various drug delivery systems with the potential to achieve the formulator's desire for target or protected delivery of bioactive agents. It is possible to conclude that, although starch is food, it is also medicine.
03.	**Olaf Hausler et al.,**	www.roquette-pharma.com	Compared native starches such as pea starch, maize starch and potato starch as tablet disintegrants.	Pea starch is an interesting alternative to the widely used maize and potato starch.

04.	**Kawaljit Singh Sandhu, Seung-Taik Lim**	Carbohydrate Polymers 71, 2008; pp no. 245-252.	Evaluated the digestibility of legume starches as influenced by their physical and structural properties.	Legume starches have been reported to have lower digestibility as compared to cereal starches, which makes it more suitable for the diabetic patients.
05.	**Daniela Mikulikova, Jan Kraic**	Journal of Food and Nutrition Research, 2006; vol. 45(2): pp no. 69-76.	Evaluated Natural sources of health-promoting starch.	There is more resistant and less total starch in legumes in comparison to cereals and pseudo cereals. Pea contains the most RS3 of all 18 plant-crops evaluated.
06.	**Kawaljit Singh Sandhu, Seung-Taik Lim**	Food Chemistry 107, 2008; pp no. 92–97.	Evaluated structural characteristics and in vitro digestibility of Mango kernel starches	Mango kernels wasted after industrial processing of mango could become a useful source of starch, especially in terms of its beneficial digestibility behavior and high RS content.
07.	**Panuwat Dangsungnoen et al.,**	International Proceedings of Chemical, Biological and Environmental Engineering, 2012; vol. 45.	Compared Resistant Starch Content and Survival of *Lactobacillus spp.* on Four Different Sources of Resistant Starch.	Different sources of resistant starch had different the resistant starch contents ($p \leq 0.05$). Cowpea flour had lowest level of resistant starch (6.31%), whereas the highest values were 38.41% found in green banana flour.
08.	**Nednapis Vatanasuchart et al.,**	Maejo International Journal of Science and Te chnology, 2012; vol. 6(2): pp no. 259-271.	Evaluated Resistant starch content, in vitro starch digestibility and physico - chemical properties of flour and starch from Thai bananas.	The high content of RS found in both starch and flour samples of all six cultivars of Thai bananas indicates that they are a healthy choice for consumption

09.	**Shiihii su et al.,**	Asian Journal of Pharmaceutical and Clinical Research, 2011; vol. 4(1): pp no. 22-25.	Evaluated finger millet (*Eleusine coracana*) starch as a binder in high dose tablets.	The native *Eleusine corocana* starch when used as a binder in comparison with maize starch, competes favorably with maize starch.
10.	**Anuchita Moongngarm**	American Journal of Agricultural and Biological Sciences, 2013; vol. 8(2): 107-113.	Evaluated chemical compositions and resistant starch content in starchy foods.	The legume seeds and lesser yam had a high concentration of protein and moderate amount of RS, whereas green bananas had highest amount of RS.
11.	**Grelda A. Yaiiez-Farias et al.,**	Starch/starke, 1997; vol. 49(9): 341-345.	Isolated and partially characterized starches from dry beans (*Phaseolus vulgaris*) and chick peas (*Cicer arietinum*).	The isolated starches showed oval shaped granules and average sizes in the range of 20-25p. The DSC results showed that pinto bean starch had a higher range of gelatinization temperature and higher fusion enthalpy than chickpea starch.
12.	**Anoop Kumar Singh et al.,**	International Journal of Pharmaceutical and Biomedical Research, 2010, vol. 1(2): pp no. 35-41.	Isolation, characterisation and formulation properties of a new plant gum obtained from *Mangifera indic*a.	The gum performed as a better binding agent than Gum Acacia at 5% w/w. It was also found that *Mangifera indic*a gum is pH sensitive and therefore it has a scope in the development and formulation of intestinal drug delivery systems.
13.	**Gangwar Satyam et al.,**	International Journal of PharmTech Research, 2010; vol. 2(2): pp no. 1508-1512.	Isolated and Evaluated the Binding Property of Pappaya Starch in Diclofenac Sodium Tablet.	Tablets prepared using the pappaya starch as binder showed significant hardness and friability. So it can be used as tablet binder in pharmaceutical formulations.

14.	**B. Narkhede Sachin et al.,**	Journal of Chemical and Pharmaceutical Research, 2010; vol. 2(6): pp no. 161-166.	Isolation and evaluation of mucilage of *Artocarpus heterophyllus* as a tablet binder.	The tablet prepared with 6.0 %w/v *A. heterophyllus* showed the hardness nearly equal to the tablet prepared by using 6.0 % w/v of starch gum
15.	**P. Rajeev Kumar et al.,**	Journal of Chemical and Pharmaceutical Research, 2012; vol. 4(6): pp no. 3134-3138.	Studies on *Carica papaya* starch as a pharmaceutical excipients.	*Carica papaya* starch could be used as a promising pharmaceutical excipient in tablet technology as, it showed adequate binding and disintegrating properties.
16.	**Bodempudi Sravani et al.,**	Journal of Chemical and Pharmaceutical Research, 2011; vol. 3(2): pp no. 118-125.	Studies on *Vigna mungo* Mucilage as a pharmaceutical excipients.	*Vigna mungo* (Black gram seeds) and can be used as an effective suspending agent and tablet binder in oral pharmaceutical formulations.
17.	**M. Marimuthu, Krishnamoorthi**	Journal of Chemical and Pharmaceutical Research, 2013; vol. 5(5): pp no. 390-394.	Evaluated Nutrients and functional properties of *Macrotyloma uniflorum* an underutilized south Indian food legume.	*Macrotyloma uniflorum* can be used as alternative binders owing to its appreciably values of swelling power and solubility.
18.	**A.R. Oyi et al.,**	Research Journal of Applied Sciences, Engineering and Technology, 2009; vol. 1(2): pp no. 77-80.	Compared Binding Effects of Wheat, Rice and Maize Starches in Chloroquine Phosphate tablet formulations.	Wheat starch formulations give stronger tablets in comparison to rice and standard maize starches and this is advantageous especially when high bond strength is desired and quick disintegration is not desirable.

19.	**Singh Akilesh Vikram and Nath LK**	International Journal of PharmTech Research, 2009; vol. 1(2): pp no. 365-368.	Evaluated binder property of Moth bean starch in compressed solid dosage form.	Starch obtained from Moth bean starch possesses better binding properties at low concentration when compared with potato starch as standard binder.
20.	**Jose Antonio Garzon Tiznado et al.,**	Food and Nutrition Sciences, 2012; vol. 3, pp no. 1281-1289	Evaluated Acceptability Properties and Antioxidant Potential of Desi Chickpea (*Cicer arietinum* L.) Cultivars.	Desi chickpea could contribute significantly to the management and/or prevention of degenerative diseases associated with free radical damage.
21.	**P. Rajeevkumar et al.,**	Journal of Chemical and Pharmaceutical Research, 2010; vol. 2(4): pp no. 284-290.	Investigated studies on *musa paradisiaca* starch as a pharmaceutical excipients.	Musa paradisiaca starch could be used as a promising pharmaceutical excipient in tablet technology as, it showed adequate binding and disintegrating properties.
22.	**S. Sasanam et al.,**	World Academy of Science, Engineering and Technology, 2011; vol. 57.	Compared resistant starch content, and pasting properties of Cowpeas (*Vigna unguiculata*).	Cowpeas had a resistant starch content of 4.59-10.63%, a solubilized starch content of 29.52-48.18 and a total starch content of 40.15-56.37%.
23.	**Patel Shailendra et al.,**	International Journal of Pharmaceutical & Biological Archives, 2012; vol. 3(3): pp no. 466-473.	Evaluated Natural Binding agents in tablet formulation.	Natural polymers shown good binding property in wet granulation, granules are stable and less friable in comparison with other binders. They can also be used to modify the release of drug, thereby, influencing the absorption and bioavailability of the incorporated drug.

3. AIM AND OBJECTIVE

Aim of study:

- The aim of this study is to evaluate *Cicer arietinum* and *Pisum sativum* starch as an alternative tablet binder to maize starch by the assessment of preformulation and formulation studies.

Objective of study:

- To formulate and develop paracetamol tablets by wet granulation technique using various concentrations of *Cicer arietinum* and *Pisum sativum* starch as binder.
- To find out the effect of starches on mechanical properties of paracetamol tablet formulation.
- To evaluate the *in vitro* release profile of paracetamol and evaluate the release mechanism on the basis of various kinetic models.
- To compare the binding capacity, friability, disintegration time and *in-vitro* drug release of the formulation containing isolated starches with that of the formulation containing commercially available maize starch.
- To perform the stability studies of optimized paracetamol formulation.

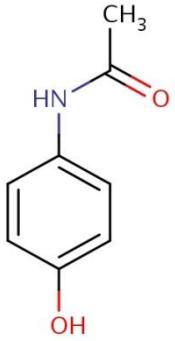
4. PLAN OF WORK

The present work is planned according to the following steps:

1. Literature survey
2. Isolation of starch
3. Preformulation studies of starch
    - Solubility
    - Loss on drying
    - pH determination
    - Angle of repose
    - Bulk density & Tap density
    - Hausner's index
    - Compressibility index
    - DSC analysis
    - FTIR
    - X-ray powder diffraction
    - Micro structure studies by SEM
    - Phytochemical screening
    - Microbial load
4. Preformulation studies of Paracetamol
    - Determination of Melting point
    - Solubility
    - Determination of λ_{max}
    - Compatibility studies
5. Pre-compression evaluation
    - Moisture content
    - Angle of repose
    - Bulk density & tap density
    - Compressibility index
    - Hausner's ratio
6. Formulation of Paracetamol tablets

7. Post-compression evaluation
    - Thickness
    - Weight variation test
    - Hardness
    - Friability
    - Drug content
    - Disintegration test
8. *In vitro* dissolution studies
9. Release kinetic studies
10. Stability studies.

5. DRUG PROFILE [28, 29]

Generic Name (IP)	Paracetamol
Generic Name (USP)	Acetaminophen
Chemical IUPAC Name	N-(4-hydroxyphenyl) acetamide
Physical properties:	
Structural formula	
Molecular formula	$C_8H_9SO_2$
Molecular weight	151.16
State	Solid
Melting point	170˚C
Macroscopic appearance	White, crystalline powder.
Solubility	Water 1:70, Boiling water 1:20, Alcohol 1:10, Chloroform 1:50, Glycerin 1:40, and Slightly soluble in ether.
Chemical properties: Acetaminophen is a synthetic, nonopiate, centrally acting analgesic derived from *p*-aminophenol. The full chemical name is N-acetyl-*p*-aminophenol.	
PKa	9.51 at 25˚C
Stability	Stable to temperature, light, and moisture.
pH range over which drug is stable in solution.	Acetaminophen is stable at pH between 4 and 7 at 25˚C.
pH of commercially available liquid products.	Acetaminophen oral solution has a pH of 3.8 to 6.1 and the oral suspension has the pH of 5.4 to 6.9.

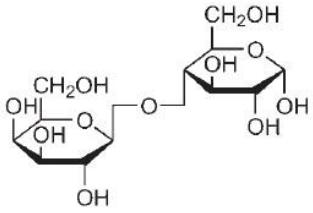
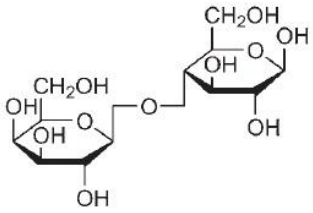
Clinical pharmacology	
General	Generally used for its analgesic and antipyretic effects. Its therapeutic effects are similar to salicylates, but it lacks anti-inflammatory, antiplatelet and gastric ulcerative effects.
Indication	For temporary relief of fever, minor aches, and pains.
Pharmacodynamics	Acetaminophen is widely used as analgesic and antipyretic drug which is used for the relief of fever, headaches, and other minor aches and pains. At therapeutic doses acetaminophen does not irritate the lining of the stomach nor affect blood coagulation, kidney function, or the fetal ductus arteriosus (as NSAIDs can). Like NSAIDs and unlike opioid analgesics, acetaminophen does not cause euphoria or alter mood in any way.
Mechanism of action	Acetaminophen is thought to act primarily in the CNS, increasing the pain threshold by inhibiting both isoforms of cyclooxygenase, COX-1, COX-2, and COX-3 enzymes involved in prostaglandin (PG) synthesis.
Absorption	Rapid and almost complete.
Protein binding	25%
Half life	1 to 4 hours
Elimination	Approximately 80% of acetaminophen is excreted in the urine after conjugation and about 3% is excreted unchanged.
Category	Antipyretics Analgesic, Non-Narcotic.
Food interactions	Avoid alcohol (may increase risk of hepatotoxicity) and take without regard to meals.
Affected organisms	Humans and other mammals.

Dosage range	For adults and children 12 years of age and older, the recommended dose of acetaminophen is 650 to 1000 mg every 4 to 6 hours as needed, not to exceed 4000 mg in 24 hours. For children under 12 years of age, the recommended dose of acetaminophen is 10 to 15 mg/kg every 4 to 6 hours, not to exceed five doses (50-75 mg/kg) in 24 hours

6. EXCIPIENT'S PROFILE [30]

6.1 Lactose:

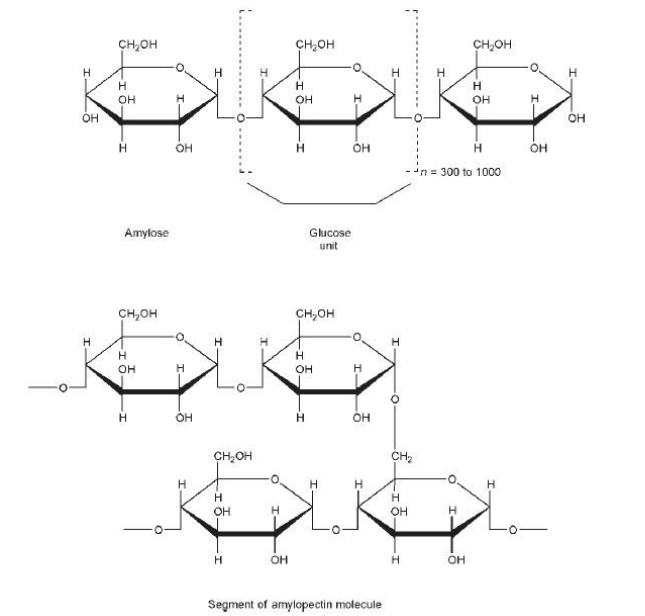
Table 6.01: Physico-chemical characteristics of Lactose

Synonyms	Lactosum anhydricum; lattosio; Lactopress anhydrous; milk sugar; saccharum lactis.
Empirical Formula	$C_{12}H_{22}O_{11}$
Molecular weight	342.30
Structural Formula	 Anhydrous α-lactose  Anhydrous β-lactose
Description	White to off-white crystalline particles or powder, it is odorless and slightly sweet taste.
Functional Category	Directly compressible tablet excipients; dry powder inhaler carrier; lyophilization aid; tablet and capsule diluent; tablet and capsule filler.
Solubility	Soluble in water; sparingly soluble in ethanol (95%) and ether.
Moisture Content	Anhydrous lactose contain 1%w/w of water, Lactose monohydrate contains 5%w/w of water.
Melting Point	223.0˚C for anhydrous α-lactose; 252.2˚C for anhydrous β-lactose; 232.0˚C for commercial anhydrous lactose.

True density	1.589g/cm^3 for anhydrous β-lactose
Bulk density	0.71g/cm^3
Tapped density	0.88g/cm^3
Stability and Storage conditions	Stored in a well-closed container in a cool, dry place.
Incompatibilities	Incompatible with strong oxidizers, Incompatible with amino acids, aminophylline, amphetamine and lisinopril.
Safety	Adverse reactions to lactose are largely due to lactose intolerance, which occurs in individuals with a deficiency of the intestinal enzyme lactase.
Application	Anhydrous lactose is widely used in direct compression tableting applications, and as a tablet and capsule filler and binder. Anhydrous lactose can be used with moisture-sensitive drugs due to its low moisture content. It may also be used in intravenous injections.

6.2 Starch:

Table 6.02: Physico-chemical characteristics of Starch

Synonyms	Amido; amidon; amilo; amylum; Eurylon; fecule; maydis amylum; solani amylum.
Empirical Formula	$(C_6H_{10}O_5)_n$ where n=300-1000.
Structural Formula	
Description	Odorless and tasteless, fine, white to off-white powder. It consists of very small spherical or ovoid granules.
Functional Category	Tablet and capsule diluent; tablet and capsule disintegrant; tablet binder; thickening agent.
Solubility	Practically insoluble in cold ethanol (96%) and in cold water, Soluble in hot water above the gelatinization temperature.
Acidity/alkalinity	pH 4.0-8.0
Amylose content	24-28% for corn starch
True density	1.478g/cm^3 for corn starch
Bulk density	0.45-0.58g/cm^3 for corn starch
Tapped density	0.69-0.77g/cm^3 for corn starch
Gelatinization temperature	71˚C for corn starch
Swelling temperature	64˚C for corn starch

Moisture Content	12% for corn starch
Particle size distribution	Corn starch: 2-32µm; average particle diameter 13µm.
Stability and Storage conditions	Stored in an airtight container in a cool, dry place.
Incompatibilities	Starch is incompatible with strongly oxidizing substances. Colored inclusion compounds are formed with iodine.
Safety	Allergic reactions to starch are extremely rare and individuals apparently allergic to one particular starch may not experience adverse effects with a starch from a different botanical source. The wheat proteins (gluten) are problematic for conditions such as celiac disease. Contamination of surgical wounds with the starch glove powder used by surgeons has resulted in the development of granulomatous lesions.
Application	Starch is a versatile excipients used primarily in oral solid-dosage formulations where it is utilized as a binder, diluent, and disintegrant.

6.3 Talc:

Table 6.03: Physico-chemical characteristics of Talc

Synonyms	Hydrous magnesium silicate; powdered talc; Purified French chalk; soapstone; steatite; talcum.
Empirical Formula	$Mg_6(Si_2O_5)_4(OH)_4$
Description	Very fine, white to grayish-white, odorless, impalpable, unctuous, crystalline powder. Readily adheres to the skin and is soft to touch and free from grittiness.
Functional Category	Anticaking agent; glidant; tablet and capsule diluent; tablet and capsule lubricant.
Solubility	Practically insoluble in dilute acids and alkalis, organic solvents, and water.
Acidity/alkalinity	pH 7-10 for a 20% w/v aqueous dispersion.
pH	7.0-9.0
Stability and Storage conditions	Talc is a stable material and may be sterilized by heating at 160˚C for not less than 1 hour. Talc should be stored in a well-closed container in a cool, dry place.
Incompatibilities	Incompatible with quaternary ammonium compounds.
Application	Talc was once widely used in oral solid dosage formulations as a lubricant and diluent, today it is less commonly used. However, it used as a dissolution retardant in the controlled-release products. Talc is also used as a lubricant in tablet formulation; in a novel coating for extended-release pellets; and as an adsorbent. In topical preparations, talc is used as a dusting powder.

6.4 Magnesium stearate:

Table 6.04: Physico-chemical characteristics of Magnesium stearate.

Synonyms	Dibasic magnesium stearate; magnesium salt; magnesium distearate; octadecanoaic acid; octadecanoate; synpro 90.
Empirical Formula	$C_{36}H_{70}MgO_4$
Molecular weight	591.24
Structural Formula	$[CH_3(CH_2)_{16}COO]_2Mg$
Description	Very fine, light white, precipitated or milled, impalpable powder of low bulk density, having a faint odor, the powder is greasy to touch and readily adheres to the skin.
Functional Category	Tablet and capsule lubricant.
Solubility	Practically insoluble in ethanol, ether and water; Slightly soluble in warm benzene and warm ethanol.
Flowability	Poorly flowing, cohesive powder.
Melting Point	117-150˚C
True density	$1.092 g/cm^3$
Bulk density	$0.159 g/cm^3$
Tapped density	$0.286 g/cm^3$
Stability and Storage conditions	Stable and should be stored in a well-closed container in a cool, dry place.
Incompatibilities	Incompatible with strong acids, alkalis, and iron salts.
Safety	Oral consumption of large quantities may produce a laxative effect or mucosal irritation.
Application	Used in cosmetics, food & pharmaceutical formulations and as a lubricant in capsule & tablet at concentration between 0.25-5.0%.

7. MATERIALS AND METHODS

7.1 MATERIALS

Table 7.01 List of Materials used:

S.No	MATERIALS	SOURCES
01.	PARACETAMOL	GRANULES INDIA LIMITED
02.	MAIZE STARCH	CAPLIN POINT LABORATORIES
03.	LACTOSE	CAPLIN POINT LABORATORIES
04.	MAGNESIUM STEARATE	CAPLIN POINT LABORATORIES
05.	TALC	CAPLIN POINT LABORATORIES
06.	METHYL PARABEN	KMCH LABORATORY
07.	PROPYL PARABEN	KMCH LABORATORY

Table 7.02 List of Instruments used:

S.No	INSTRUMENTS	MANUFACTURERS
01.	FT/IR SPECTROSCOPY/4100	JASCO
02.	HYDRAULIC/PELLET PRESS	KIMAYA ENGINEERS
03.	UV SPECTROPHOTOMETER	SYSTRONICS
04.	BULK & TAPPED DENSITY APPARATUS C-TDA2	CAMPBELL ELECTRONICS
05.	ROCHE FRIABILATOR	CAMPBELL ELECTRONICS
06.	TABLET COMPRESSION MACHINE	REMIK MINIPRESS/II MT AHMEDABAD.
07.	WEIGHING BALANCE BL 220H	SCHIMADZU
08.	HOT AIR OVEN	TECHINO
09.	HARDNESS TESTER	TAB MACHINE
10.	TABLET DISINTEGRATION APPARATUS	TAB MACHINE
11.	DISSOLUTION APPARATUS	TAB MACHINES, MUMBAI
12.	pH METER	EUTECH
13.	B.O.D INCUBATOR	TECHINO, CHENNAI
14.	COLONY COUNTER	DEEP VISION
15.	STABILITY CHAMBER	TECHINO, MUMBAI.
16.	VERNIER CALIPER	ABSOLUTE DIGIMATIC, MITUTOYO
17.	SEM JSM 9390	JEOL, JAPAN
18.	DSC	DSC Q20 V24.2 Build 107

7.2 METHODS

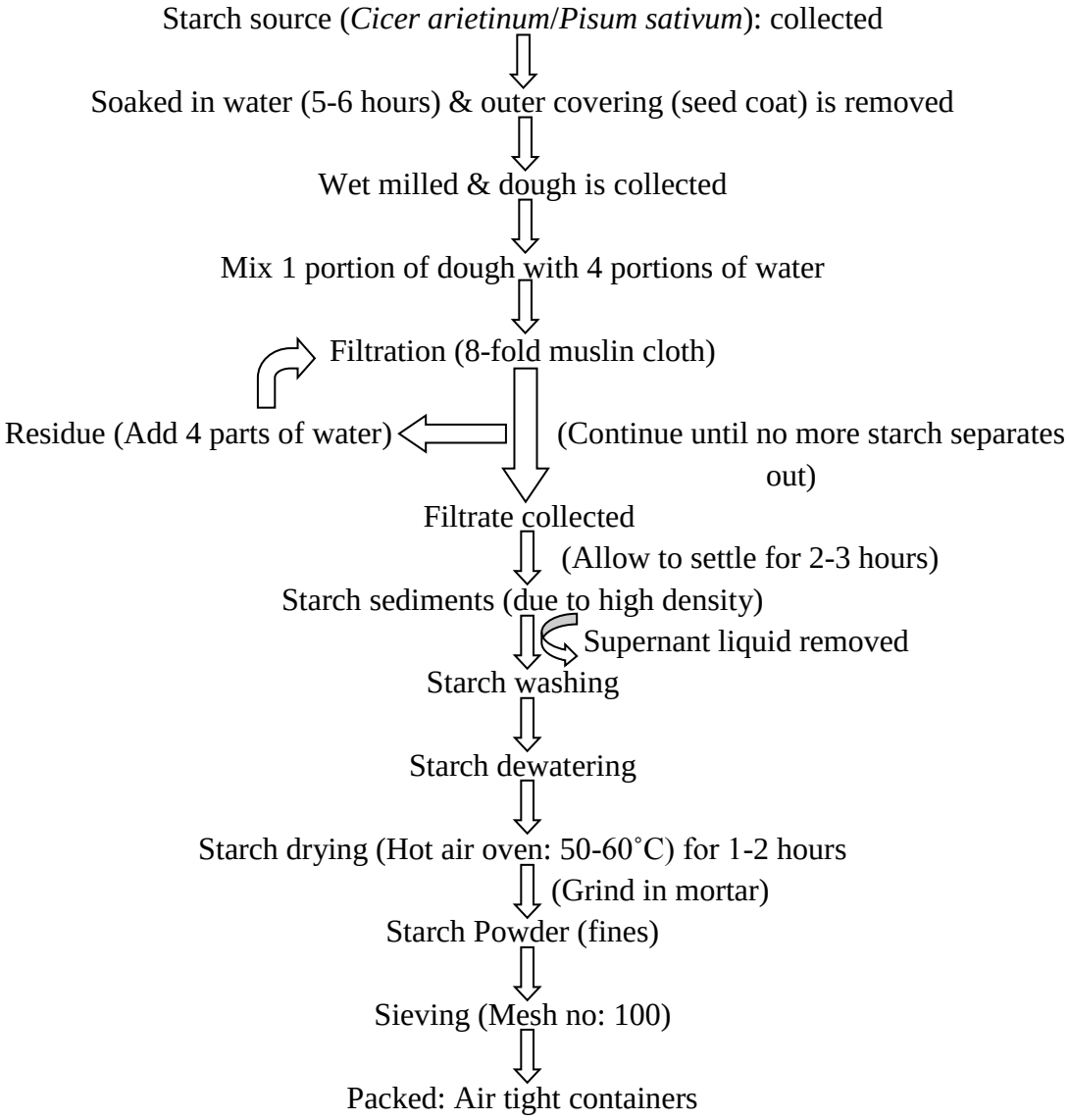
7.2.1 Preformulation studies of *Cicer arietinum* and *Pisum sativum* starch:

Preformulation studies were performed on the *Cicer arietinum* and *Pisum sativum* starch, which includes isolation, purification and physicochemical characterization of starches.

7.2.2 Isolation and Purification of *Cicer arietinum* and *Pisum sativum* starch:

- **Isolation of *Cicer arietinum* and *Pisum sativum* starch[31]:**

Process Flow chart:



- **Appearance of *Cicer arietinum* & *Pisum sativum* used in this study:**

Figure 7.01: *Cicer arietinum*

Figure 7.02: *Pisum sativum*

- **Separation of starch from *Cicer arietinum* & *Pisum sativum* in this study:**

Figure 7.03: Separation of starch from *Cicer arietinum* slurry

Figure 7.04: Separation of starch from *Pisum sativum* slurry

- **Purification of *Cicer arietinum* & *Pisum sativum* starch[31]:**

To Starch powder add 0.08 M NaOH slowly

⇓ To promote flocculation of proteins

pH adjusted to 7.6 using pH paper

⇓ Supernant was discarded

Decanted Starch re-suspended in distilled water

⇓ Repeat starch washing & dewatering

Starch is dried, powdered, sieved and packed.

7.2.3 Physicochemical characterization of *Cicer arietinum* and *Pisum sativum* starch:

1. Solubility test

The separated starches were evaluated for solubility in water, ethanol and hot water in accordance with the pharmacopoeial monograph specification.

2. Loss on drying

0.2g of powder sample was dried in an oven at 105˚C until a constant weight was obtained. The moisture content was then determined as the ratio of weight of moisture loss to weight of sample expressed as a percentage.

3. pH determination

This was done by 1% w/v dispersion of the sample in water and the pH was determined using a digital pH meter.

4. Angle of repose

The angle of repose, θ, was measured according to the fixed funnel and standing cone method. A funnel was clamped with its tip 2 cm above a graph paper placed on a flat horizontal surface. The sample was carefully poured through the funnel until the apex of the cone touches the tip of the funnel. The diameter of the sample base was noted and the tangent of the angle of repose was calculated using the equation.

$$tan\theta = \frac{2h}{D}$$

5. Bulk and tap densities

10g of powder sample was placed in a 50ml measuring cylinder and the volume, V_0, occupied by each sample without tapping was noted. After 1000 taps, the occupied volume V_{1000} was noted. The bulk and tap densities were calculated as the ratio of weight to volume.

$$Bulk\ density = \frac{weight\ of\ the\ sample}{Bulk\ volume}$$

$$Tap\ density = \frac{weight\ of\ the\ sample}{Tap\ volume}$$

6. Hausner's index

Hausner's index of the sample was calculated by the ratio of tapped density to bulk density.

$$Hausner's\ ratio = \frac{Tap\ density}{Bulk\ density}$$

7. Compressibility index

Compressibility index indicates powder flow properties, and was calculated using the equation.

$$Carr's\ index = \frac{Tap\ density - Bulk\ density}{Tap\ density} \times 100$$

8. Differential scanning calorimetric (DSC) analysis

Thermal properties of the sample were characterized using DSC. Nitrogen at the rate of 20ml/min was used as purge gas; 1.0000 mg of powdered material were sealed in an aluminium pan and heated from 20˚C up to 200˚C at the rate of 10˚C/min. A graph was generated for each sample; peak, onset, offset and enthalpy were calculated.

9. Fourier transform infra red (FT-IR)

The FT-IR spectrum of the sample was recorded in Jasco FT/IR 4100 spectrometer, using potassium bromide (KBr) discs prepared from powdered samples mixed with dry KBr. Measurements were made from scanning range of 4000 to 400 cm^{-1} and the spectrum with the clearest identifiable peaks was chosen. The IR spectra of the isolated starches were compared to that of the standard maize starch and the interactions were analyzed.

10. X-ray powder diffraction (XRD)[31]

X-ray diffraction of the starches were analyzed using a X-ray diffractometer. Powder samples were packed in rectangular aluminium cells and illuminated using CuKα radiation (λ=1.00000 A˚) at 40 kV and 30 mA. Samples were scanned between different angles of 4˚ to 90˚C 2θ. Scan speed of 5.0000 (deg/min) was used and the preset time was 1.20 (sec). A nickel filter was used to reduce the Kβ contribution to the X-ray signal. The 'd' spacing's were computed according to Bragg's law of diffraction and measurements were made at ambient temperature.

11. Microstructure studies by SEM[31]

Morphological features of the starches were studied with a JSM 9390 scanning electron microscope of JEOL, Japan. The dried sample was mounted on a

metal stub and sputtered with gold in order to make the sample conductive, and the images were taken at an accelerating voltage of 5 kV with different magnifications.

12. Phytochemical screening of starch samples

Preliminary tests were performed to verify the nature of starch obtained. The chemical tests such as Molisch's test, Ferric chloride test, Keller-killaini test, Wagner's test, Salkowski test, Foam test, shinoda test, Biuret test and Iodine test were performed and reported.

13. Microbial load for starch samples[32, 33 and 34]

Spread plate method was used to cultivate 1ml of starch samples solution on Muller Hilton Agar Medium for enumeration of bacteria and Sabouraud Dextrose Agar Medium for fungi.

Muller Hilton Agar Medium:

1.52 gm of Muller Hilton agar medium with 1gm of agar was dissolved in 40ml of distilled water. Then it is sterilized by autoclaving at 121˚C for 15min. 20ml of the medium was poured in each plate. By serial dilution method, 1gm of starch sample dissolved in 10ml hot water, five serial dilutions were made with distilled water. 1ml of starch solution was spread on the plate and incubated at 37˚C for 72 hours. At the end of incubation period, the bacterial colonies formed were counted by colony counter.

Sabouraud Dextrose Agar Medium:

2.60 gm of Sabouraud Dextrose agar medium with 1gm of agar was dissolved in 40ml of distilled water. Then it is sterilized at 121˚C for 15min. 20ml of the medium was poured in each plate. By serial dilution method, 1gm of starch sample dissolved in 10ml hot water, five serial dilutions were made with distilled water. 1ml of starch solution was spread on the plate and incubated at 27˚C for 72 hours. At the end of incubation period, the fungal colonies formed were counted by colony counter.

7.2.4 Preformulation studies of paracetamol

Preformulation studies were performed on the drug, which includes melting point determination, solubility and compatibility studies.

1. Determination of melting point

By Capillary method, melting point of paracetamol was determined. Previously sealed capillary tube on one end was taken and filled with fine powder of paracetamol which is then placed in melting point apparatus. The temperature at which the paracetamol powder melts was noticed.

2. Solubility

Solubility of drug was determined in ethanol, and acetone. Solubility studies were done by taking excess amount of drug in different beakers containing the solvents. The mixtures were shaken at regular intervals for 24 hrs and filtered using whattmann's filter paper. The filtered solutions were analyzed spectrophotometrically at 243nm.

3. Determination of λ_{max}

Paracetamol solution containing the concentration of 0.1µg/ml was prepared with 0.1 N HCl and UV spectrum was taken using UV spectrophotometer. The solution was scanned in the range of 200-400nm.

a) Preparation of standard calibration curve of paracetamol

100mg of Paracetamol was weighed accurately and transferred into 100ml volumetric flask. 0.1N HCl was added to dissolve and made up to the volume to give the stock solution containing 1000µg/ml. From the standard stock solution, 10ml solution was diluted with 100ml 0.1N HCl (100µg/ml). Appropriate aliquots were taken into different volumetric flask and made up to 100ml with 0.1N HCl so as to get five different concentrations (0.2, 0.4, 0.6, 0.8, 1.0µg/ml). The UV absorbance were measured by UV spectrophotometer at 243nm using 0.1N HCl as a blank. Beer-Lambert curve was drawn and correlation coefficient was calculated.

4. Compatibility studies

The FT-IR spectrum of the sample was recorded in Jasco FT/IR 4100 spectrometer, using potassium bromide (KBr) discs prepared from powdered samples mixed with dry KBr. Measurements were made from scanning range of 4000 to 400 cm^{-1} and the spectrum with the clearest identifiable peaks was chosen. The IR spectra of the pure drug and pure excipients were compared to that of the mixture of drug & excipients and the interactions were analyzed.

7.2.5 Formulation of paracetamol tablets

Table 7.03 Paracetamol formulations containing different starch as binder. (For 1 tablet)

Ingredients (mg)	Formulations			
	2.5% Binder	5% Binder	7.5% Binder	10% Binder
Paracetamol	500	500	500	500
Binder	16.25	32.5	48.75	65
Starch	32.5	32.5	32.5	32.5
Lactose	87.275	71.025	54.775	38.525
Magnesium stearate	6.5	6.5	6.5	6.5
Talc	6.5	6.5	6.5	6.5
Methyl paraben	0.65	0.65	0.65	0.65
Propyl paraben	0.325	0.325	0.325	0.325
Total	650	650	650	650

Table 7.04 Paracetamol formulations containing *Cicer arietinum* starch as binder. (For 100 tablets)

Ingredients (mg)	F1	F2	F3	F4
	2.5% Binder	5% Binder	7.5% Binder	10% Binder
Paracetamol	50,000	50,000	50,000	50,000
Cicer arietinum starch	1625	3250	4875	6500
Starch	3250	3250	3250	3250
Lactose	8727.5	7102.5	5477.5	3852.5
Magnesium stearate	650	650	650	650
Talc	650	650	650	650
Methyl paraben	65	65	65	65
Propyl paraben	32.5	32.5	32.5	32.5

Table 7.05 Paracetamol formulations containing *Pisum sativum* starch as binder. (For 100 tablets)

Ingredients (mg)	F5	F6	F7	F8
	2.5% Binder	5% Binder	7.5% Binder	10% Binder
Paracetamol	50,000	50,000	50,000	50,000
Pisum sativum starch	1625	3250	4875	6500
Starch	3250	3250	3250	3250
Lactose	8727.5	7102.5	5477.5	3852.5
Magnesium stearate	650	650	650	650
Talc	650	650	650	650
Methyl paraben	65	65	65	65
Propyl paraben	32.5	32.5	32.5	32.5

Table 7.06 Paracetamol formulations containing *Zea mays* starch as binder. (For 100 tablets)

Ingredients (mg)	F9	F10	F11	F12
	2.5% Binder	5% Binder	7.5% Binder	10% Binder
Paracetamol	50,000	50,000	50,000	50,000
Zea mays starch	1625	3250	4875	6500
Starch	3250	3250	3250	3250
Lactose	8727.5	7102.5	5477.5	3852.5
Magnesium stearate	650	650	650	650
Talc	650	650	650	650
Methyl paraben	65	65	65	65
Propyl paraben	32.5	32.5	32.5	32.5

Wet granulation Method:

By wet granulation technique the granules of different formulation was prepared by using paracetamol IP as model drug. The binder concentrations used were 2.5, 5.0, 7.5 & 10% w/w. By reducing the level of lactose in the formula the binder level was adjusted. All the ingredients are dry mixed in the mortar and water is used as the granulating fluid. Wet mass was granulated manually in 12 mesh sieve and granules were dried at 60˚C for 1hr in hot air oven. The dried granules were passed through sieve no. 22, after adding lubricants they were compressed by using Remik minipress/II MT with flat faced punches. Tablet formulation was developed for 650 mg tablet weight.

7.2.6 Pre-compression evaluation

1. Moisture content

Moisture content of the granules was determined by taking 5gm of granules from each batch and heating it in an oven at 120˚C for 1 hour. The granules were weighed immediately; from the loss in weight the moisture content was calculated.

2. Determination of angle of repose

The angle of repose of the granules was determined by the funnel method. The weighed granules were taken in the funnel. The height of the funnel was adjusted in such a way that the tip of the funnel just touches the apex of the granules. The granules were allowed to flow freely and the diameter of the granules cone was measured and angle of repose was calculated using the following equation.

$$\tan\theta = \frac{h}{r}$$

$$\theta = \tan^{-1}\left(\frac{h}{r}\right)$$

Where; θ = angle of repose

h = height of the cone

r = radius of the cone

Table 7.07 Flow property and corresponding angle of repose

Flow property	Angle of repose
Excellent	25-30
Good	31-35
Fair	36-40
Passable	41-45
Poor	46-55

3. Determination of bulk and tapped density

Initially Loose bulk density (LBD) and Tapped bulk density (TBD) was determined. 20gm of granules from each formula was weighed accurately and introduced in to 50ml measuring cylinder. After that the initial volume was noted, tapping was continued to obtain tapped volume (continued until no further change in volume is noted).

$$LBD = \frac{weight\ of\ the\ powder}{volume\ of\ the\ granule\ packing\ before\ tapping}$$

$$TBD = \frac{weight\ of\ the\ powder}{Tapped\ volume\ of\ the\ granule\ packing}$$

4. Compressibility index

The compressibility index of the granules was calculated from the difference between the tap and bulk densities divided by tap density and the ratio expressed as a percentage.

$$Carr's\ index = \frac{Tap\ density - Bulk\ density}{Tap\ density} \times 100$$

5. Hausner's ratio

Hausner's ratio was calculated by dividing the tap density by bulk density of the granule.

$$Hausner's\ ratio = \frac{Tap\ density}{Bulk\ density}$$

Table 7.08 Scale of flowability

Compressibility index (%)	Flow character	Hausner's ratio
≤ 10	Excellent	1.00-1.11
11-15	Good	1.12-1.18
16-20	Fair	1.19-1.25
21-25	Passable	1.26-1.34
26-31	Poor	1.35-1.45
32-37	Very poor	1.46-1.59

7.2.7 Post-compression evaluation of paracetamol tablets

1. Thickness

Thickness of the tablets was determined by vernier calipers. 5 tablets were used and the average was taken.

2. Weight variation test

20 tablets of each formulation were weighed using a balance and test was performed according to the official method. 20 tablets selected randomly and weighed individually to check weight variation.

Table 7.09 Table Specification for tablets weight variation (as per USP)

Average weight of tablets (mg)	Percent deviation
130 or less	10
130-324	7.5
More than 324	5

3. Hardness test

Three tablets were randomly picked and the hardness was determined by Pfizer tablet hardness tester. It is expressed in kg/cm^2.

4. Friability test

Friability of the tablet was determined by using Roche Friabilator. It is expressed in percentage (%). 10 tablets were initially weighed and transferred in to friabilator, which was operated at 25rpm for 4 minutes. The tablets are weighed again and the % friability was calculated. The % friability of tablets less than 1% are considered acceptable.

$$Percentage\ friability = \frac{(initial\ weight - final\ weight)}{initial\ weight} \times 100$$

6. Drug content

5 tablets were individually weighed and powdered, powder equivalent to average weight was weighed and drug was extracted in acetone and the drug content was determined by measuring the absorbance at 243nm after suitable dilution using UV-pharmspec-1700, Shimadzu.

7. Disintegration test[35]

6 tablets were placed in a disintegration tester (camp-bell electronics, Mumbai), filled with distilled water at 37˚C±0.20C. When all the particles of the tablet passes through the wire mesh the disintegration time was recorded by the mean of two determinations.

7.2.8 *In vitro* dissolution studies[35]

The release rate of paracetamol from tablets was performed with USP specifications using (Tab machine) six stage dissolution rate apparatus (BP/IP/USP) paddle type. The dissolution test was performed using 900ml of 0.1 N HCl at 37˚C and 50 rpm. Sample of the solution was withdrawn from the dissolution apparatus, and replaced with fresh dissolution medium. Sample was diluted with 0.1N HCl to get a suitable concentration. Solutions absorption was measured at 243 nm using UV spectrophotometer. Cumulative percentage of drug release was calculated by means of the equation obtained from the standard curve.

7.2.9 Release kinetics[38]

When a novel solid dosage form is developed, there is the need to make sure that drug dissolution occurs in an appropriate manner. In such case, drug's dissolution of solid dosage form has been described by various kinetic models (zero order, first order and higuchi kinetics). In order to study the release kinetics, data's obtained from *in-vitro* drug release studies were plotted in various kinetic models;

1. Zero order: % cumulative drug release Vs time

$$C = K_0 t$$

2. First order: log % cumulative drug remains Vs time

$$\text{Log } C = \text{Log } C_0 - Kt / 2.303$$

3. Higuchi's model: $Mt/M\infty$ Vs Square root time

The drug release data for the various tablets that formulated was graphically evaluated for their regression coefficient values. From the regression coefficient data's, the values that found to be nearest 1 follow the appropriate order of kinetics.

7.3.0 Stability studies

Stability study provides proof that how a drug substance/drug product's quality varies with the influence of wide range of environmental factors. Accelerated stability study was carried out in stability chamber, in accordance with ICH guidelines; Best fit formulation was selected and evaluated for the following stability study.

Parameters:

Type: Accelerated Condition

Testing conditions: 40˚C ± 2˚C/ 75%RH ± 5%RH

Sampling: Initial, 3rd month and 6th month

Evaluated parameters:

1. Physical appearance,
2. Hardness (kg/cm^2),
3. Friability (%),
4. Drug content (%),
5. Disintegration time (minutes), and
6. Dissolution (%CR in 120 min).

8. RESULTS AND DISCUSSION

8.1 PREFORMULATION STUDIES OF STARCH:

8.1.1 Isolation and purification of *Cicer arietinum* and *Pisum sativum* starch:

Figure 8.01: ***Cicer arietinum***

Figure 8.02: ***Pisum sativum***

Figure 8.03: ***Cicer arietinum*** **starch**

Figure 8.04: ***Pisum sativum*** **starch**

Yield Obtained:

Table 8.01 Yield obtained from starch rich sources

S.No	Source	Amount used	Yield Obtained
01.	*Cicer arietinum* L.	1 Kg	36.21%
02.	*Pisum sativum* L.	1 Kg	34.59%

8.1.2 Physiochemical properties of *Cicer arietinum* and *Pisum sativum* starch:

Table 8.02 Physiochemical properties of *Cicer arietinum* and *Pisum sativum* starch

S.No	Parameters	*Cicer arietinum* starch	*Pisum sativum* starch
01.	Description	Fine, white powder	Fine, white powder
02.	Odour	Odourless	Odourless
03.	Taste	Tasteless	Tasteless
04.	Solubility	Insoluble in water and 95% ethanol	Insoluble in water and 95% ethanol
05.	Loss on drying	6.24%	5.98%
06.	Bulk density (g/cc)	0.52	0.52
07.	Tapped density (g/cc)	0.71	0.71
08.	Compressibility index	26.30%	26.30%
09.	Hausner's ratio	1.35	1.35
10.	Angle of repose	52.22˚	54.05˚
11.	pH	7.55	7.61

DSC

Parameters

Instrument used: DSC Q20 v24.2 Build 107

Temperature range: 20˚C to 200˚C

Rate: 10˚C/min

***Cicer arietinum* starch** ***Pisum sativum* starch**

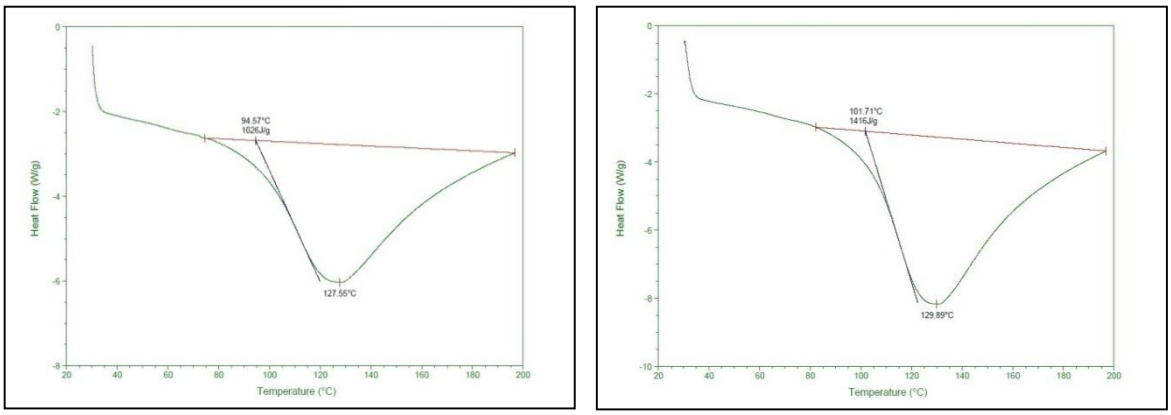


Figure 8.05: DSC results of *Cicer arietinum* starch and *Pisum sativum* starch

Table 8.03 DSC characteristics of *Cicer arietinum* and *Pisum sativum* starch

S.No.	Starch	T_p (˚C)	ΔH (Jg^{-1} starch)
01.	*Cicer arietinum* starch	127.55˚C	1026 J/g
02.	*Pisum sativum* starch	129.89˚C	1416 J/g

FT-IR of isolated starches:

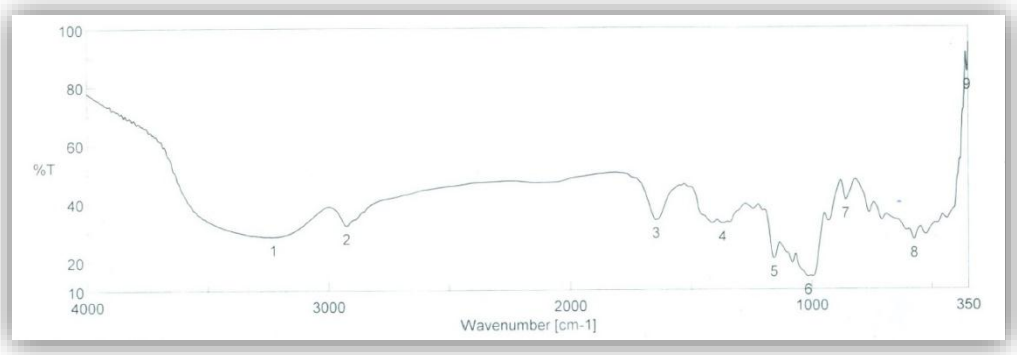


Figure 8.06: IR spectrum of *Cicer arietinum* starch

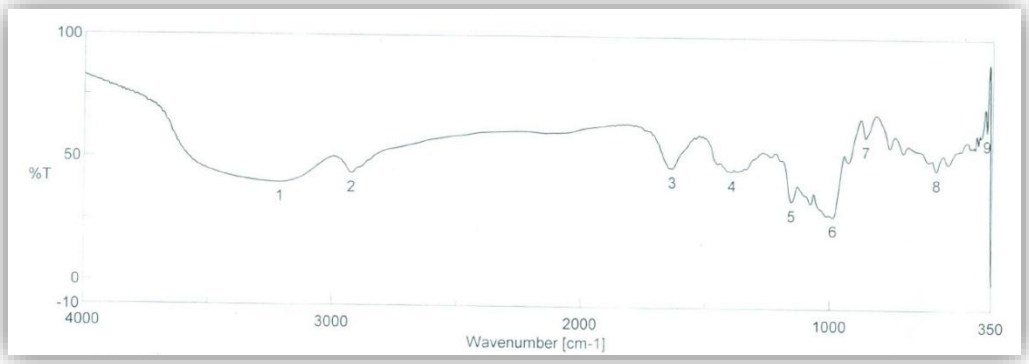


Figure 8.07: IR spectrum of *Pisum sativum* starch

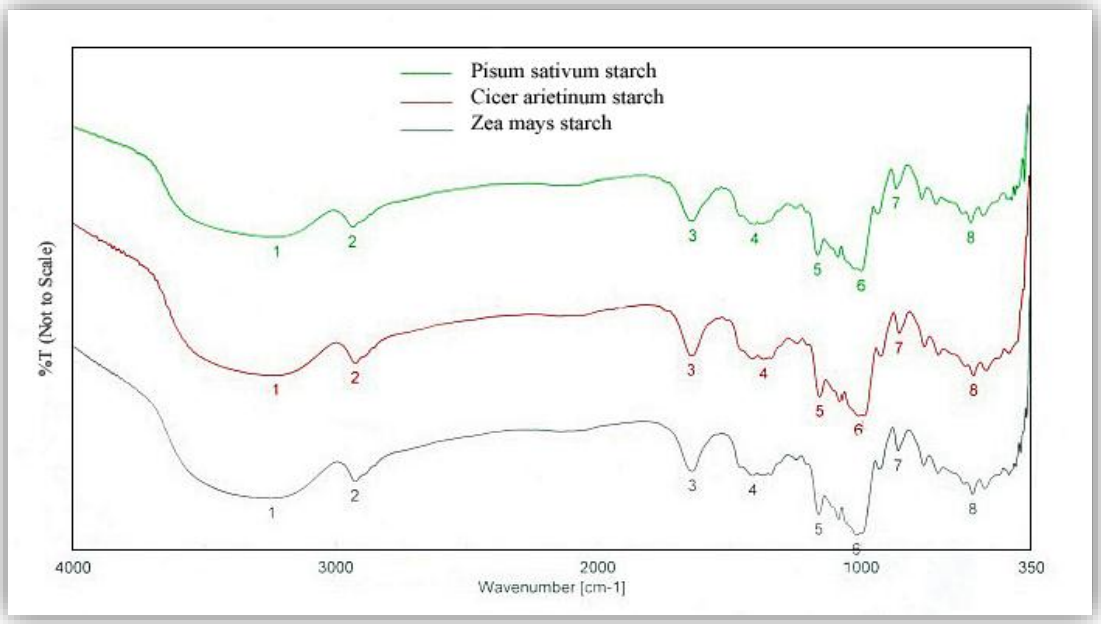


Figure 8.08: IR spectrum comparison of *Cicer arietinum*, *Pisum sativum* & *Zea mays* starch.

XRD

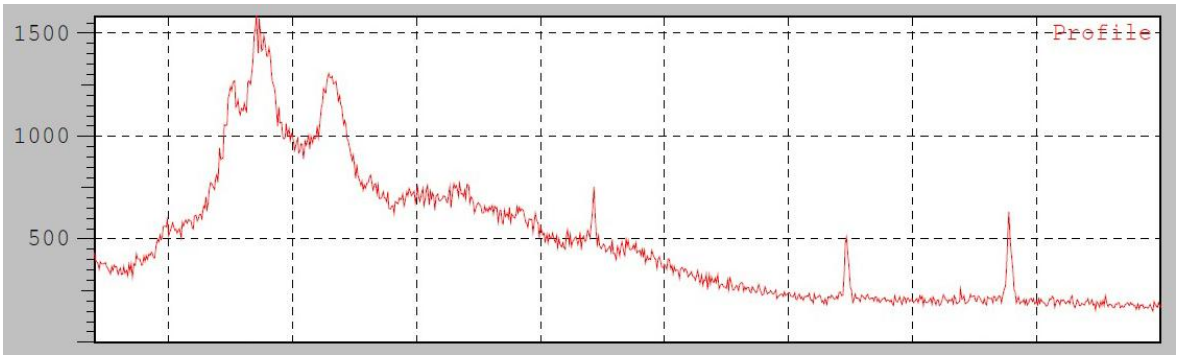


Figure 8.09: X-ray diffraction pattern of *Cicer arietinum* starch

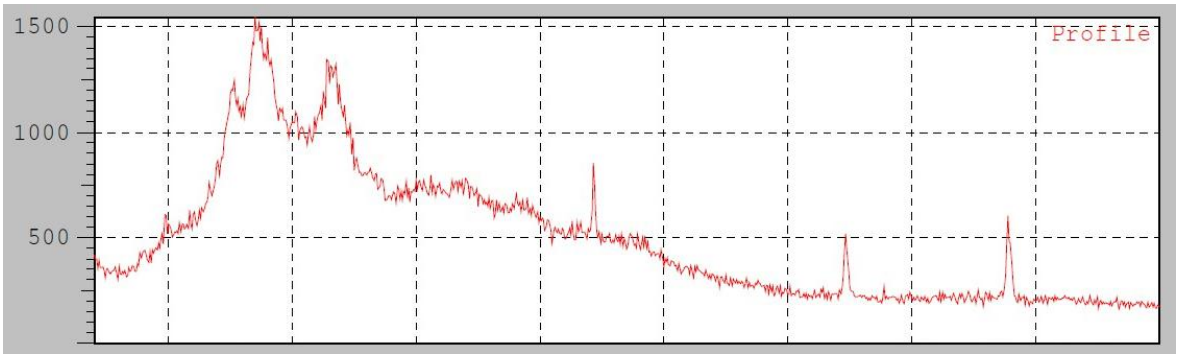


Figure 8.10: X-ray diffraction pattern of *Pisum sativum* starch

Table 8.04 X-ray diffraction characteristics of *Cicer arietinum* and *Pisum sativum* starch

S.No	Starch	Peak 1		Peak 2		Peak 3	
		Intensity (counts)	Bragg angle (˚2θ)	Intensity (counts)	Bragg angle (˚2θ)	Intensity (counts)	Bragg angle (˚2θ)
01.	*Cicer arietinum* starch	663	16.8000	548	23.0000	251	33.1000
02.	*Pisum sativum* starch	656	17.2000	552	23.0000	264	33.1000

The X-ray pattern of the laboratory isolated *Cicer arietinum* starch and *Pisum sativum* starch revealed C-type starch X-ray pattern. This was characterized by strong intensity peaks corresponding approximately to 17˚, 23˚ and 33˚. The exact values of peak position of legume starches are shown in the table above.

SEM

***Cicer arietinum* starch:**

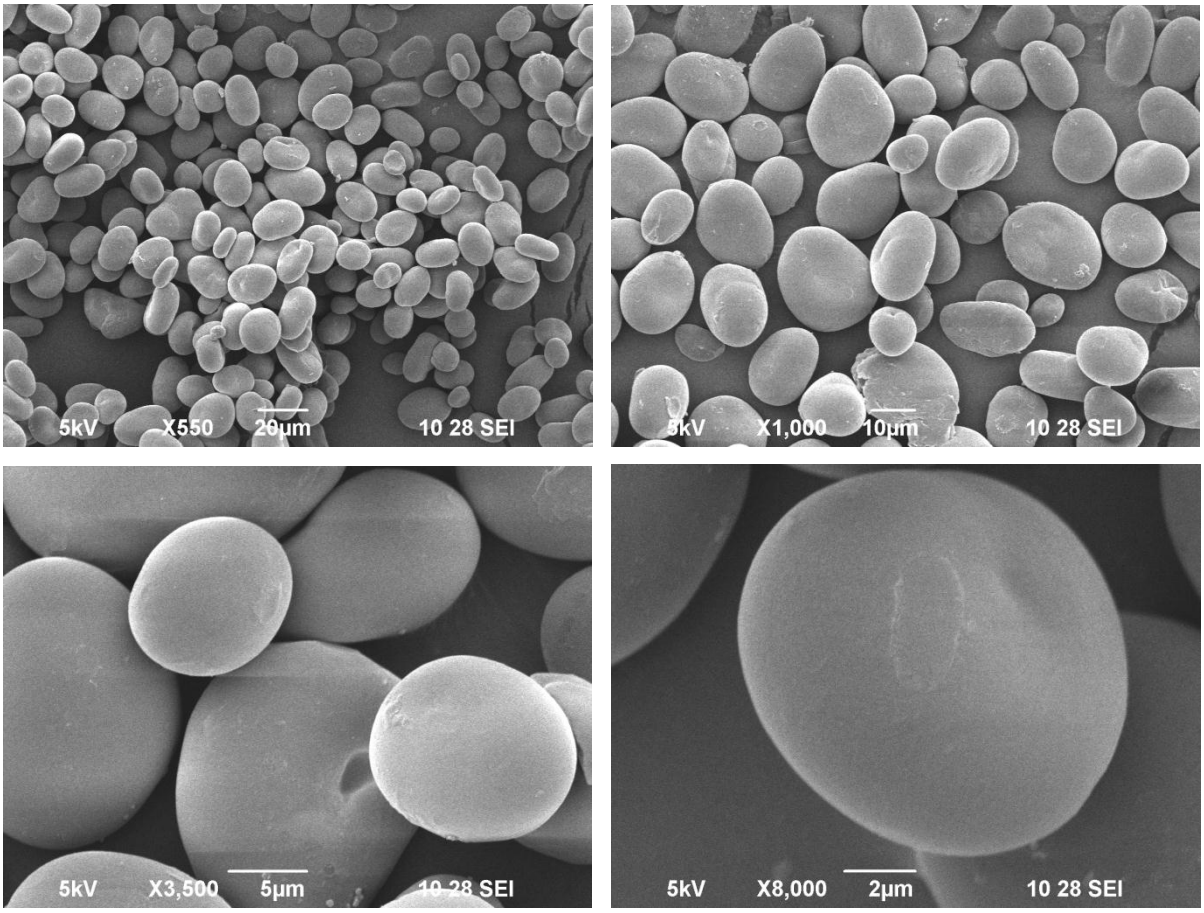
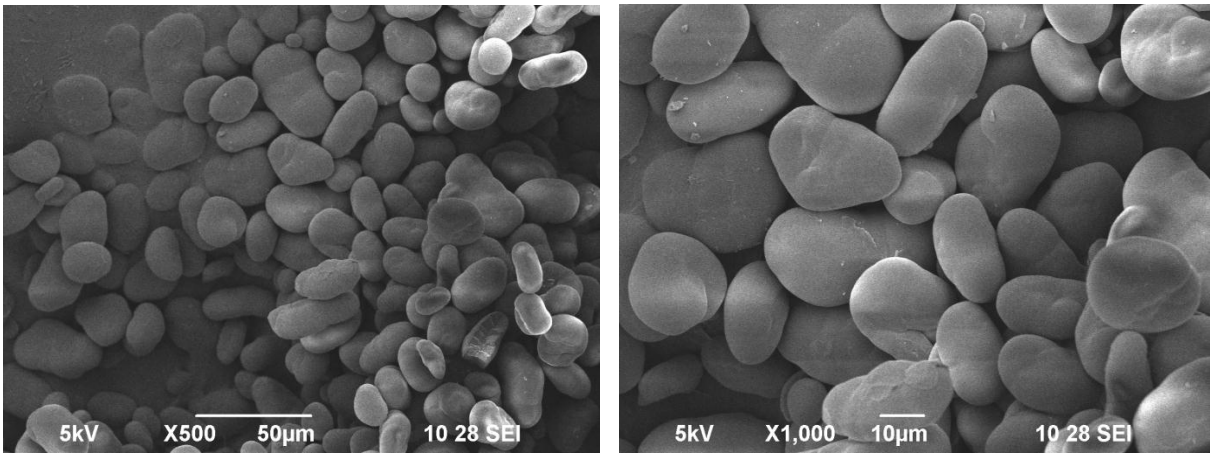


Figure 8.11: *Cicer arietinum* starch viewed by SEM under various magnifications

***Pisum sativum* starch:**



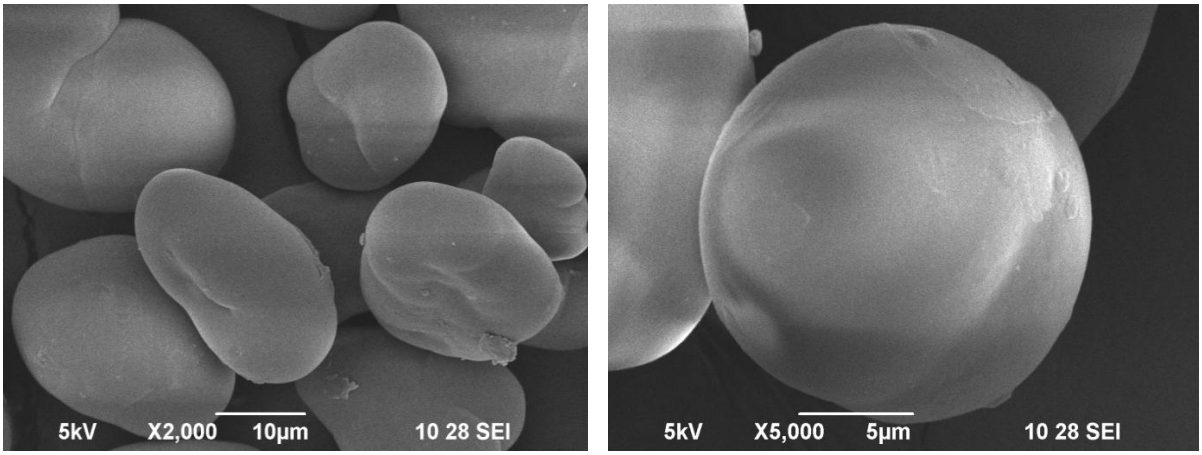


Figure 8.12: *Pisum sativum* starch viewed by SEM under various magnifications.

Table 8.05 SEM observation of *Cicer arietinum* starch and *Pisum sativum* starch

S.No	Starch (SEM)	Current observations	Granule size(µm)
01.	*Cicer arietinum* starch	Ellipsoidal, spherical (small granules)	9-20µm
02.	*Pisum sativum* starch	Rounded but irregular shapes, some of the smaller granules appeared to be ellipsoidal and spherical (simple and composite granules).	12-30µm

8.1.3 Phytochemical screening of *Cicer arietinum* and *Pisum sativum* starch:

Table 8.06 Phytochemical test of *Cicer arietinum* and *Pisum sativum* starch

S.No	Chemical test	*Cicer arietinum* starch	*Pisum sativum* starch
01.	Test for Carbohydrates	+	+
02.	Test for Alkaloids	-	-
03.	Test for Steroids & sterols	-	-
04.	Test for Glycosides	-	-
05.	Test for Saponins	-	-
06.	Test for Flavonoids	-	-
07.	Test for Tannins & phenolic compounds	-	-
08.	Test for Proteins & amino acids	+	+
09.	Test for Starch	+	+
(+) = Present and (-) = Absent			

8.1.4 Microbial load of *Cicer arietinum* and *Pisum sativum* starch:

Spread plate method was used to cultivate the isolated starch samples solution on Muller Hilton agar medium for enumeration of bacteria and Sabouraud Dextrose agar medium for fungi. After the incubation period, the bacterial & fungal colonies formed were counted.

Bacterial growth

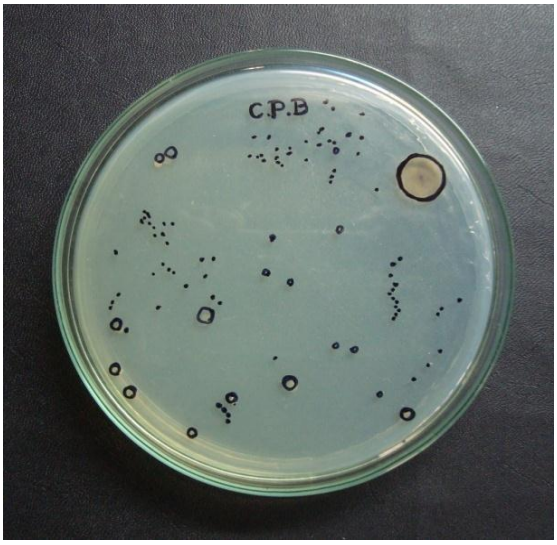


Figure 8.13: *Cicer arietinum* starch

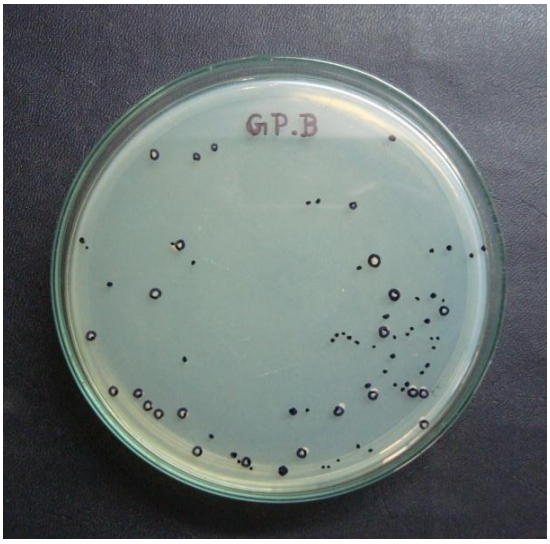


Figure 8.14: *Pisum sativum* starch

Fungal growth

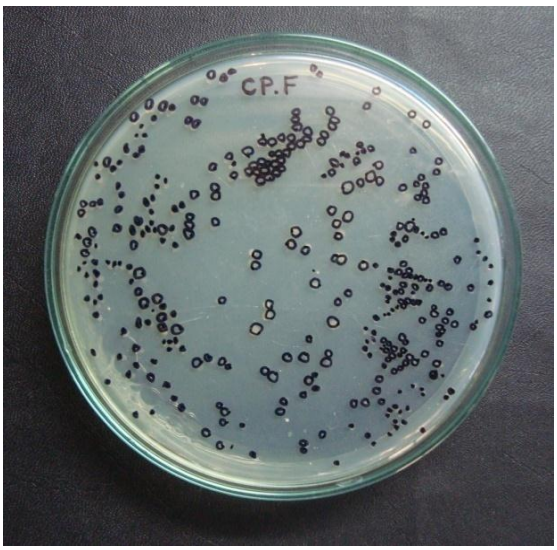


Figure 8.15: *Cicer arietinum* starch

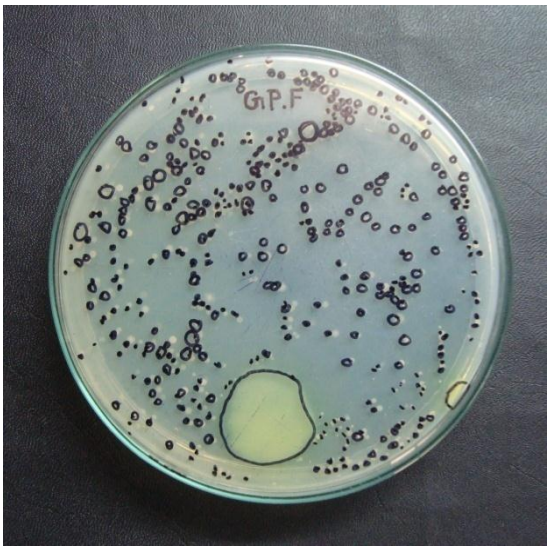


Figure 8.16: *Pisum sativum* starch

Table 8.07 Microbial load of *Cicer arietinum* starch and *Pisum sativum* starch

S.No	Starch sample	Bacterial growth (No. of colonies)	Fungal growth (No. of colonies)
01.	***Cicer arietinum* starch**	**96 CFU**	**222 CFU**
02.	***Pisum sativum* starch**	**75 CFU**	**273 CFU**

The *Cicer arietinum* and *Pisum sativum* starches were from the natural source and hence microbial load test was done. The results show that the bacterial and fungal growth obtained was under the limit specified by united state pharmacopoeia.

8.2 PREFORMULATION STUDIES OF PARACETAMOL:

8.2.1 Solubility:

Solubility of pure drug in solvents were carried out and found to be soluble in acetone, ethanol and insoluble in water.

8.2.2 Melting point:

Melting point of pure drug was found to be 169˚C.

8.2.3 Determination of λ_{max} for paracetamol:

The λ_{max} of paracetamol was found to be 243 or 244 nm.

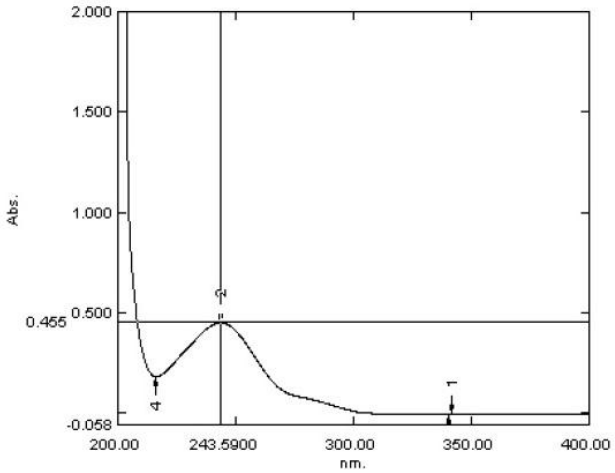


Figure 8.17: UV absorption spectrum of paracetamol

8.2.4 Calibration curve of paracetamol:

The absorbance data's for calibration curve of paracetamol at 243 nm.

Table 8.08 Absorbance data for calibration curve of paracetamol

S.No	Concentration (µg/ml)	Absorbance in 0.1M HCl
01.	**0.2**	**0.155**
02.	**0.4**	**0.291**
03.	**0.6**	**0.436**
04.	**0.8**	**0.575**
05.	**1.0**	**0.740**

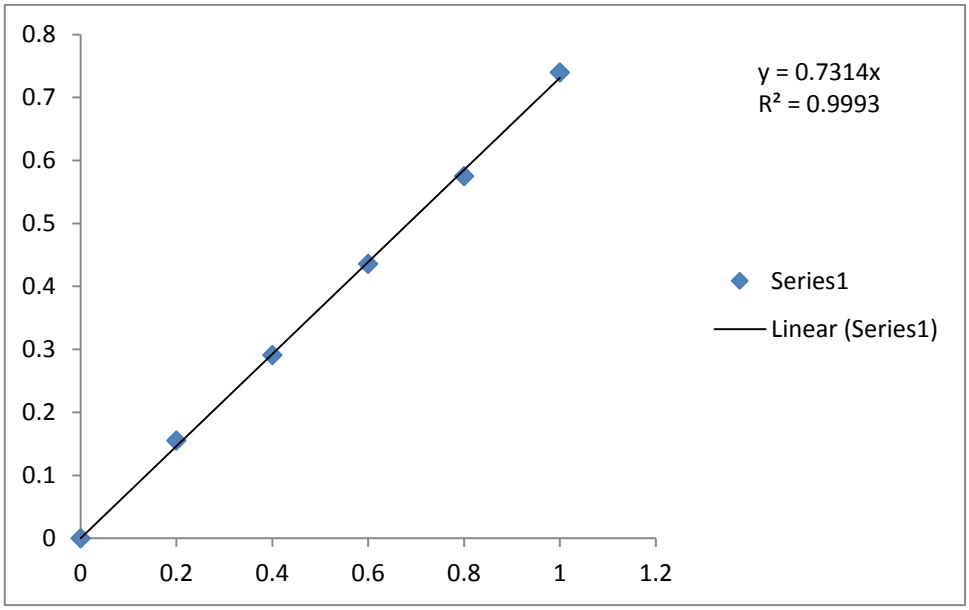


Figure 8.18: Standard calibration curve of paracetamol in 0.1N HCl

A Calibration curve for paracetamol was done in 0.1N HCl by scanning the proper diluted drug solution at 243nm using UV spectrophotometer. The linearity of the calibration curve was found to be in the range of 0.2-1.0µg/ml. A regression coefficient value of 0.999 was noticed for paracetamol.

8.2.5 Compatibility studies:

The drug excipients compatibility study was done by using Jasco FT/IR spectrometer. The IR spectra for pure drug, excipients and drug-excipients mixture were shown in the following figures.

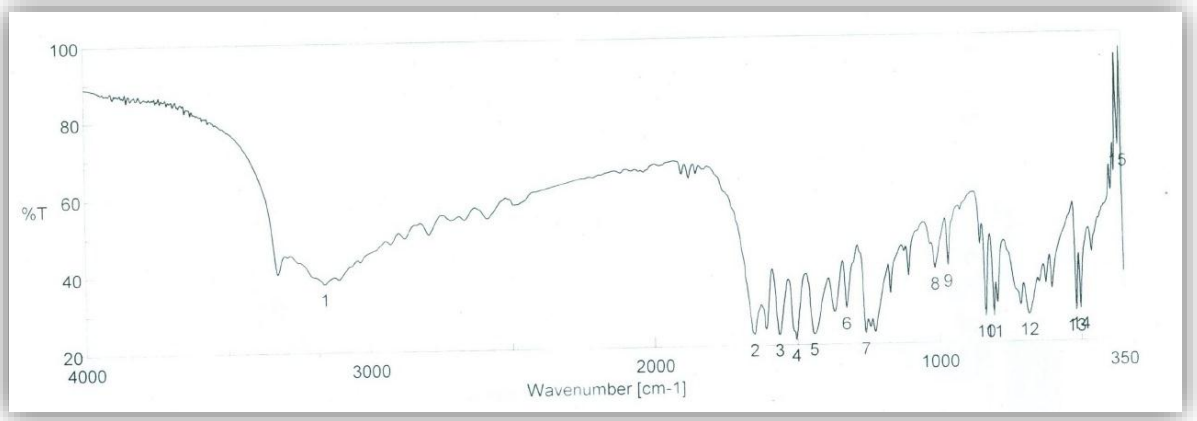


Figure 8.19: IR spectrum of paracetamol

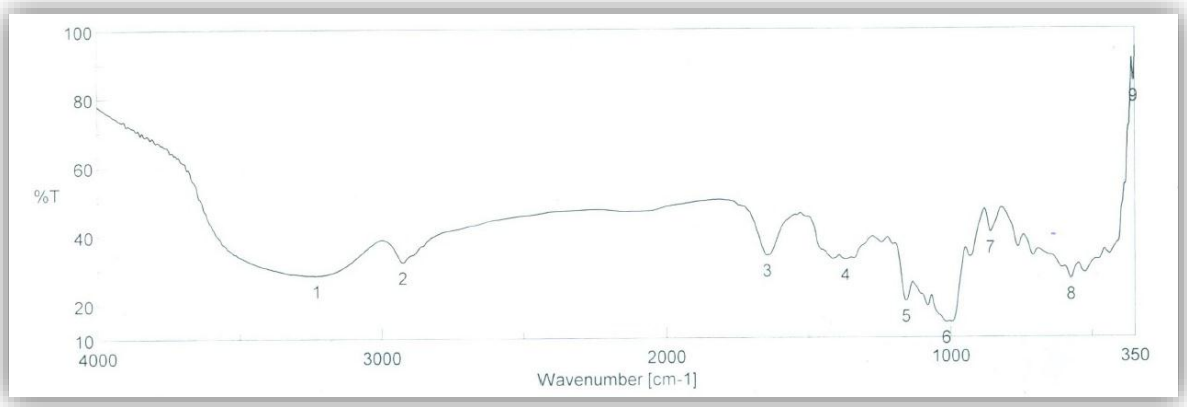


Figure 8.20: IR spectrum of *Cicer arietinum* starch

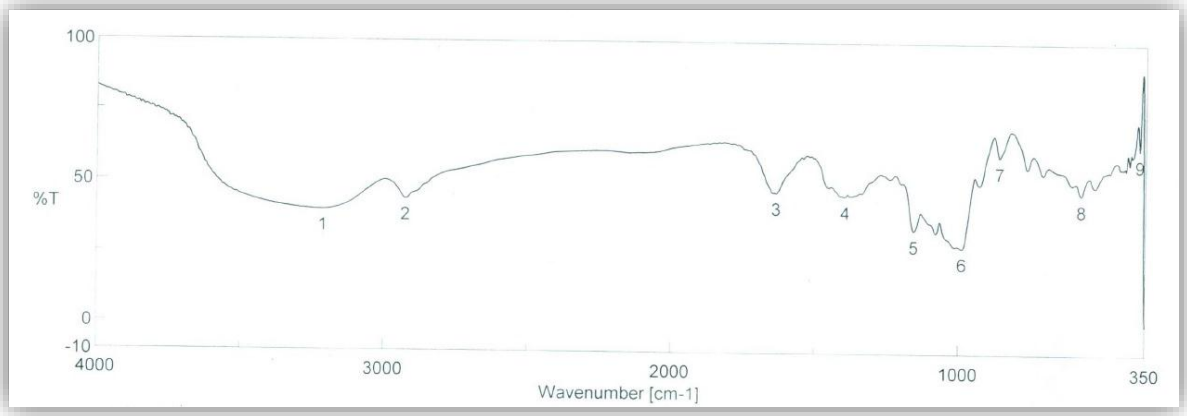


Figure 8.21: IR spectrum of *Pisum sativum* starch

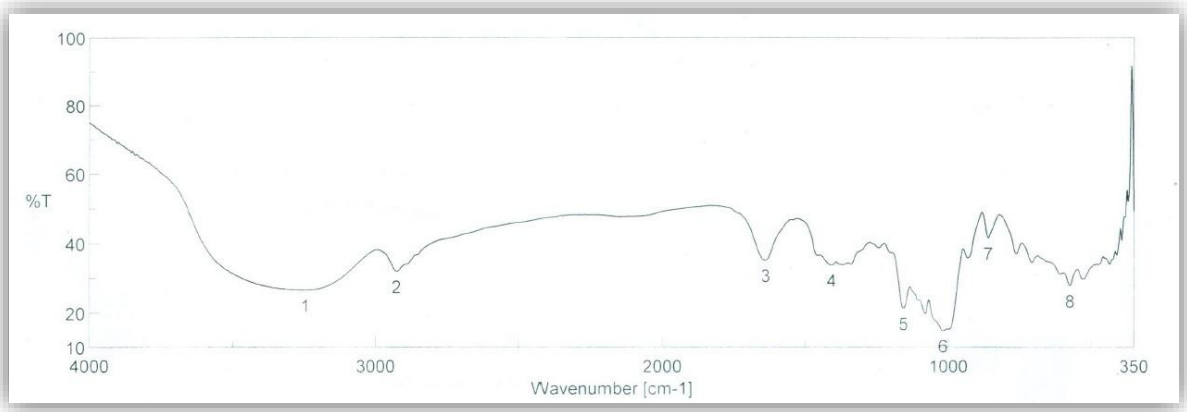


Figure 8.22: IR spectrum of *Zea mays* starch

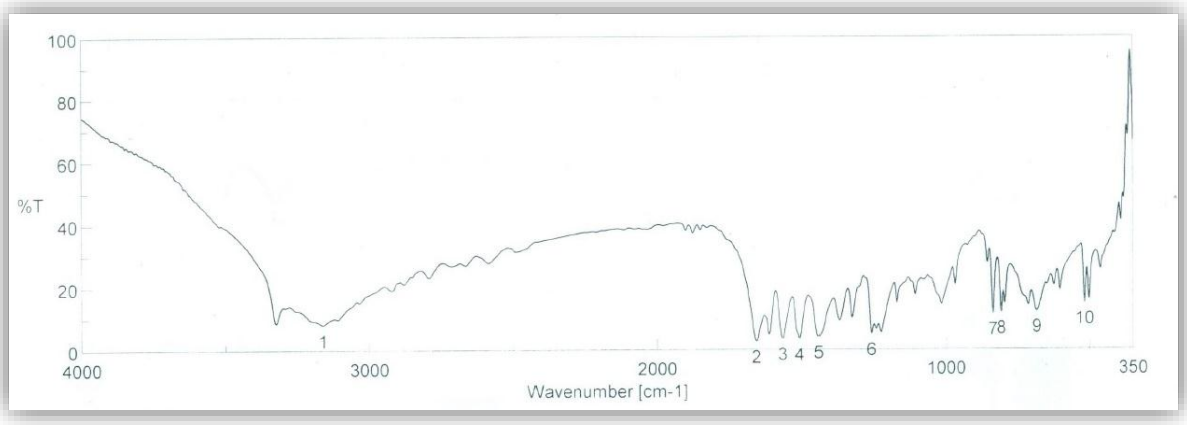


Figure 8.23: IR spectrum of Combination (Paracetamol + *Cicer arietinum* starch)

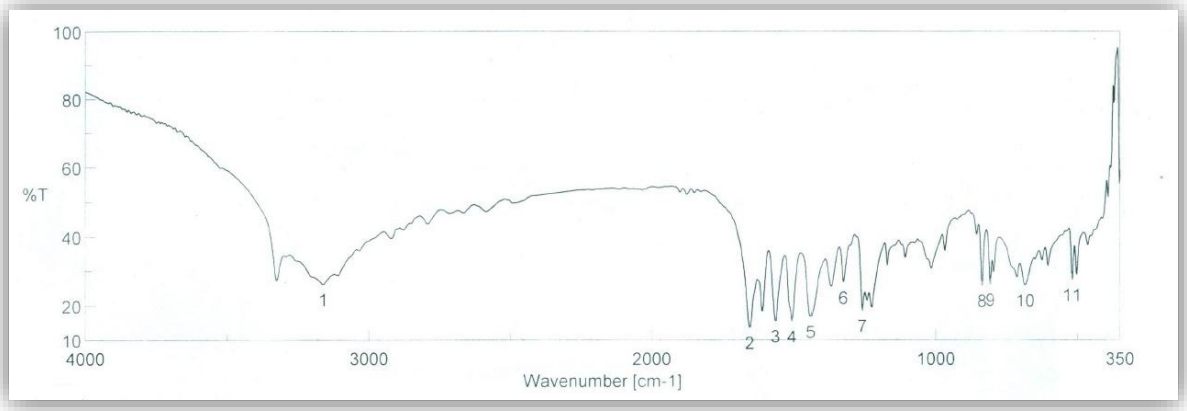


Figure 8.24: IR spectrum of Combination (Paracetamol + *Pisum sativum* starch)

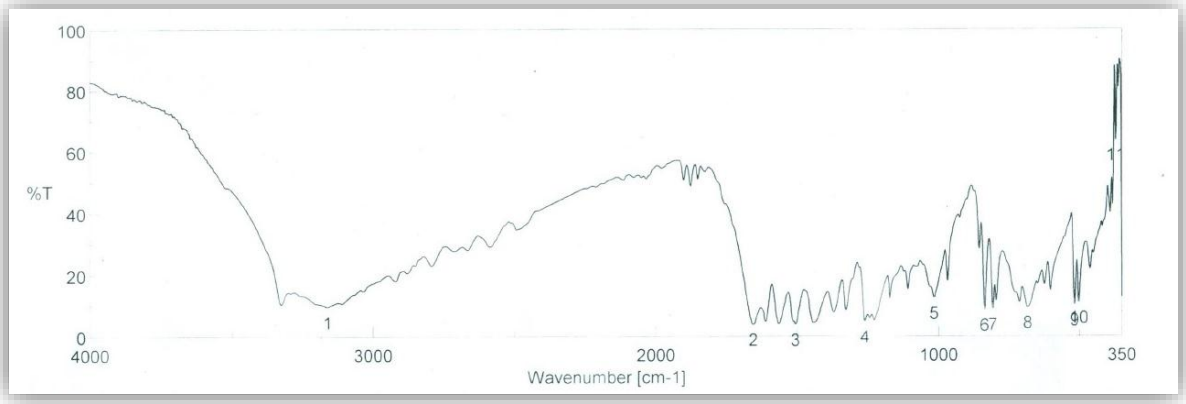


Figure 8.25: IR spectrum of Combination (Paracetamol + *Zea mays* starch)

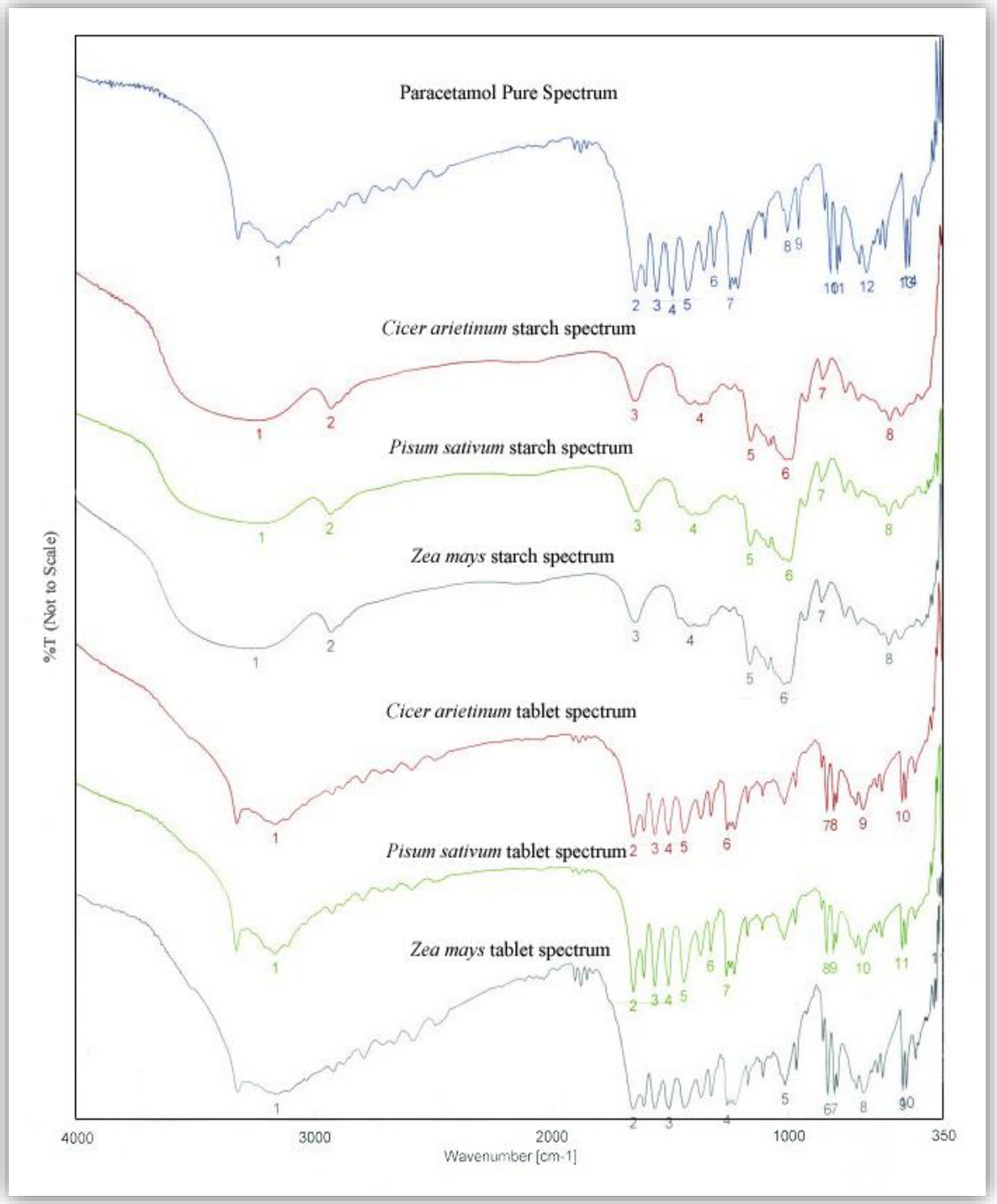


Figure 8.26: IR spectrum of pure drug, excipients and combination

The spectrum of the drug-excipients mixture was found to be a mere summation of the individual spectrum of the drug and excipients which suggest that there were no interaction and were compatible with each other.

Interpretation of FT-IR spectrums

Table 8.09 Interpretation of FT-IR spectrum of pure drug, excipients and combination

S.No	Samples	Reported peaks (cm^{-1})	Observed peak (cm^{-1})	Inference
01.	Paracetamol	3400-3200	3326.35	O-H stretching
		3500-3100	3160.76	N-H stretching
		1655-1620	1652.7	C=O (amide) stretching
		1570-1515	1564.95	Amide II band
		1250	1259.29	C-N-H group
		850-750	836.95	Para-disubstituted aromatic ring
02.	*Cicer arietinum* Starch	3400-3200	3230.18	O-H Stretching
		2950-2850	2925.48	C-H Stretching
		1645	1645.95	H-O-H Bending
03.	*Pisum sativum* Starch	3400-3200	3213.79	O-H Stretching
		2950-2850	2926.45	C-H Stretching
		1645	1635.34	H-O-H Bending
04.	*Zea mays* Starch	3400-3200	3245.61	O-H Stretching
		2950-2850	2926.45	C-H Stretching
		1645	1638.23	H-O-H Bending
05.	Combination	3500-3100	3161.72	N-H stretching
		1655-1620	1654.62	C=O (amide) stretching
		1250	1259.29	C-N-H group
		850-750	836.95	Para-disubstituted aromatic ring

8.3 PRE-COMPRESSION EVALUATION OF PARACETAMOL TABLETS:

8.3.1 Moisture content:

Moisture content of the prepared granules of paracetamol was found to be 3%.

8.3.2 Determination of densities and related properties:

Table 8.10 Densities and related properties of paracetamol granules

Formulations	Bulk density (g/ml)	Tapped density (g/ml)	Hausner's ratio	Carr's index (%)	Angle of repose (degrees)
F1	0.4347	0.4819	1.1085	09.79	34.59
F2	0.4310	0.4796	1.1127	10.13	35.06
F3	0.4301	0.4796	1.1150	10.32	35.22
F4	0.4296	0.4807	1.1189	10.63	35.21
F5	0.4329	0.4761	1.0997	09.07	33.98
F6	0.4310	0.4784	1.1099	09.90	34.28
F7	0.4301	0.4784	1.1122	10.09	34.43
F8	0.4301	0.4796	1.1150	10.32	34.28
F9	0.4329	0.4761	1.0997	09.07	33.68
F10	0.4310	0.4784	1.1099	09.90	34.74
F11	0.4310	0.4807	1.1153	10.33	35.05
F12	0.4301	0.4807	1.1176	10.52	34.89

8.4 POST-COMPRESSION EVALUATION OF PARACETAMOL TABLETS:

Table 8.11 Post-compression evaluation of paracetamol tablets

Formulations	Compression force (KN)	Tablet thickness	Weight variation	Hardness (kg/cm^2)	Friability (%)	Drug content (%)
F1	30	4.28mm	651±2 mg	02.76	0.41	100.12
F2	30	4.29mm	652±2 mg	03.08	0.33	99.97
F3	30	4.31mm	652±2 mg	03.22	0.36	100.10
F4	30	4.35mm	654±2 mg	03.46	0.29	99.65
F5	30	4.31mm	653±3 mg	02.60	0.44	99.92
F6	30	4.32mm	651±4 mg	02.78	0.38	99.47
F7	30	4.35mm	651±3 mg	02.86	0.35	100.23
F8	30	4.41mm	653±2 mg	03.00	0.27	99.95
F9	30	4.29mm	652±2 mg	02.80	0.47	100.03
F10	30	4.30mm	653±3 mg	03.06	0.39	99.63
F11	30	4.35mm	652±3 mg	03.14	0.34	99.87
F12	30	4.42mm	652±4 mg	03.36	0.30	99.89

Table 8.12 Disintegration time of paracetamol tablets containing different binder concentrations

Binder Concentrations	Disintegration time		
	***Cicer arietinum* starch**	***Pisum sativum* starch**	***Zea mays* starch**
2.5%	**(F1)** 02 min.19 sec	**(F5)** 01 min.59 sec	**(F9)** 02 min.20 sec
5%	**(F2)** 07 min.13 sec	**(F6)** 03 min.53 sec	**(F10)** 05 min.43 sec
7.5%	**(F3)** 10 min.37 sec	**(F7)** 05 min.40 sec	**(F11)** 08 min.29 sec
10%	**(F4)** 12 min.54 sec	**(F8)** 08 min.03 sec	**(F12)** 11 min.22 sec

8.5 DRUG RELEASE PROFILE STUDIES:

8.5.1 In-vitro drug release data of paracetamol tablets:

Parameters:

Dissolution medium	0.1N HCl (900ml) [USP]
Method	Paddle method
Temperature	37 ± 0.5˚C
Speed	50 rpm
Time	120 minutes
Absorbance	243 nm

Table 8.13 Cumulative drug release of paracetamol tablets containing different binder concentrations

TIME (Min)	% Cumulative drug release of different concentrations of paracetamol formulations											
	***Cicer arietinum* starch**				***Pisum sativum* starch**				***Zea mays* starch**			
	F1 (%)	**F2 (%)**	**F3 (%)**	**F4 (%)**	**F5 (%)**	**F6 (%)**	**F7 (%)**	**F8 (%)**	**F9 (%)**	**F10 (%)**	**F11 (%)**	**F12 (%)**
10	**38.07**	**23.16**	**26.02**	**23.16**	**32.59**	**31.69**	**31.06**	**36.76**	**24.49**	**27.48**	**27.89**	**29.49**
20	**46.52**	**45.36**	**40.19**	**35.94**	**57.62**	**58.39**	**57.27**	**41.22**	**54.21**	**52.41**	**53.68**	**39.78**
30	**65.36**	**57.63**	**55.46**	**44.78**	**66.73**	**67.98**	**66.83**	**49.62**	**63.32**	**61.11**	**62.37**	**54.34**
40	**73.72**	**65.34**	**63.32**	**57.03**	**75.90**	**76.96**	**75.72**	**60.19**	**70.67**	**71.9**	**69.74**	**61.48**
50	**81.66**	**72.73**	**72.77**	**63.11**	**83.71**	**82.61**	**82.67**	**67.73**	**77.85**	**78.99**	**79.06**	**65.09**
60	**89.43**	**80.53**	**80.14**	**72.34**	**91.01**	**85.01**	**90.93**	**75.94**	**87.55**	**88.29**	**87.55**	**74.57**
90	**94.61**	**89.28**	**88.71**	**81.28**	**96.69**	**95.67**	**93.74**	**86.81**	**95.61**	**93.73**	**94.53**	**83.31**
120	**-**	**95.12**	**92.37**	**88.16**	**-**	**98.68**	**96.49**	**93.73**	**-**	**97.47**	**95.08**	**92.87**

Table 8.14 Cumulative drug release of paracetamol tablets containing 2.5% binder concentration

TIME (Min)	% Cumulative drug release of 2.5% starch as Binder		
	***Cicer arietinum* starch (F1)**	***Pisum sativum* starch (F5)**	***Zea mays* starch (F9)**
10	38.07	32.59	24.49
20	46.52	57.62	54.21
30	65.36	66.73	63.32
40	73.72	75.90	70.67
50	81.66	83.71	77.85
60	89.43	91.01	87.55
90	94.61	96.69	95.61
120	38.07	32.59	24.49

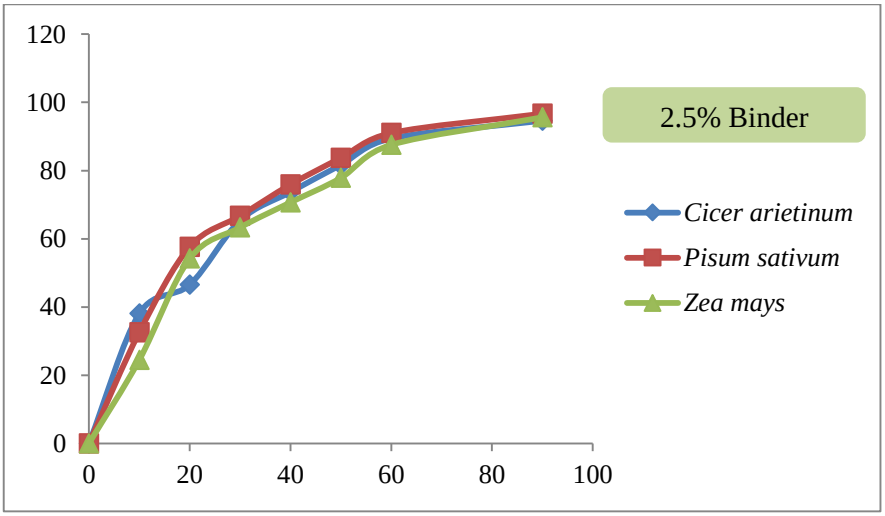


Figure 8.27: Dissolution profile of prepared paracetamol formulations using 2.5% binder

Table 8.15 Cumulative drug release of paracetamol tablets containing 5% binder concentration

TIME (Min)	% Cumulative drug release of 5% starch as Binder		
	***Cicer arietinum* starch (F2)**	***Pisum sativum* starch (F6)**	***Zea mays* starch (F10)**
10	23.16	31.69	27.48
20	45.36	58.39	52.41
30	57.63	67.98	61.11
40	65.34	76.96	71.90
50	72.73	82.61	78.99
60	80.53	85.01	88.29
90	89.28	95.67	93.73
120	95.12	98.68	97.47

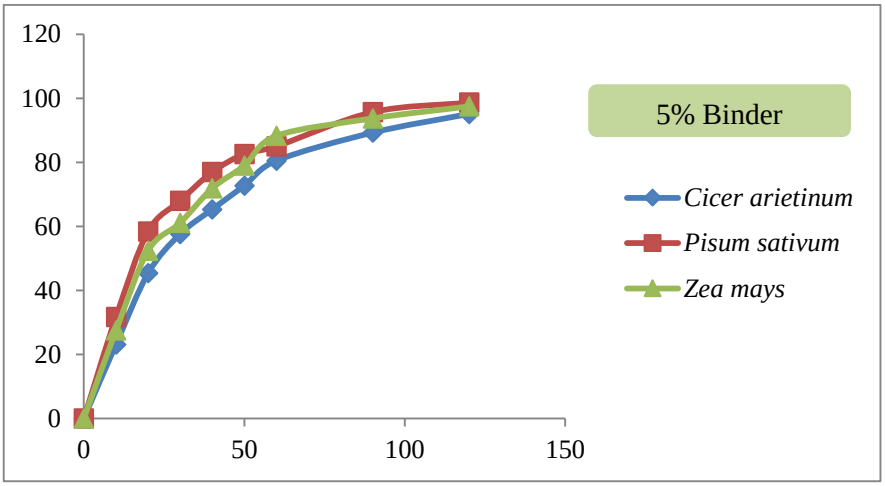


Figure 8.28: Dissolution profile of prepared paracetamol formulations using 5% binder

Table 8.16 Cumulative drug release of paracetamol tablets containing 7.5% binder concentration

TIME (Min)	% Cumulative drug release of 7.5% starch as Binder		
	***Cicer arietinum* starch (F3)**	***Pisum sativum* starch (F7)**	***Zea mays* starch (F11)**
10	26.02	31.06	27.89
20	40.19	57.27	53.68
30	55.46	66.83	62.37
40	63.32	75.72	69.74
50	72.77	82.67	79.06
60	80.14	90.93	87.55
90	88.71	93.74	94.53
120	92.37	96.49	95.08

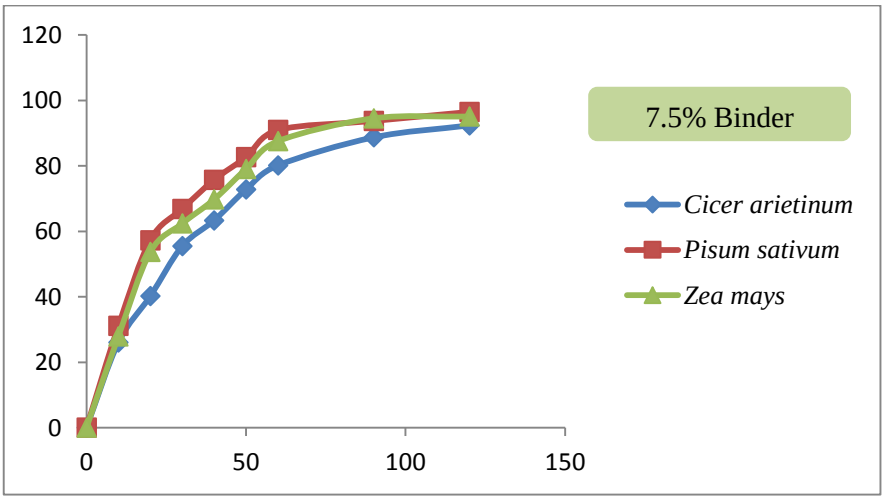


Figure 8.29: Dissolution profile of prepared paracetamol formulations using 7.5% binder

Table 8.17 Cumulative drug release of paracetamol tablets containing 10% binder concentration

TIME (Min)	% Cumulative drug release of 10% starch as Binder		
	***Cicer arietinum* starch (F4)**	***Pisum sativum* starch (F8)**	***Zea mays* starch (F12)**
10	23.16	36.76	29.49
20	35.94	41.22	39.78
30	44.78	49.62	54.34
40	57.03	60.19	61.48
50	63.11	67.73	65.09
60	72.34	75.94	74.57
90	81.28	86.81	83.31
120	88.16	93.73	92.87

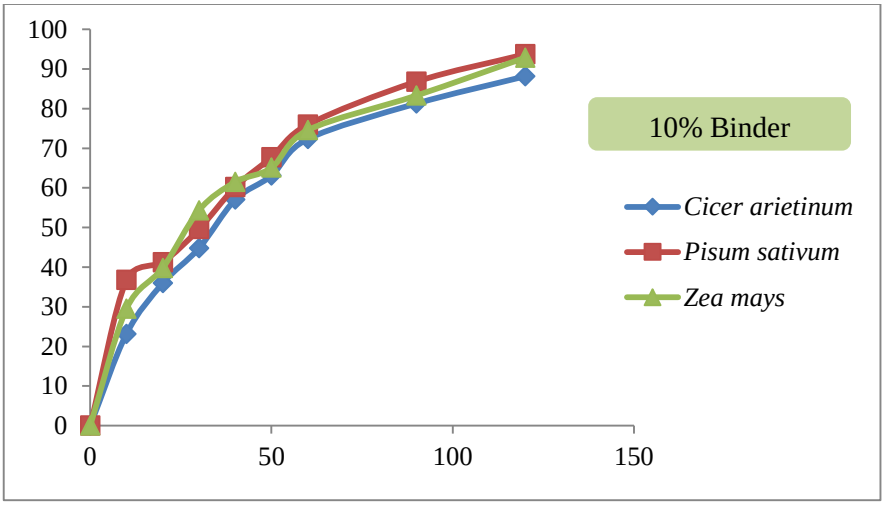


Figure 8.30: Dissolution profile of prepared paracetamol formulations using 10% binder

8.5.2 Dissolution characteristics of paracetamol tablets:

Table 8.18 Dissolution characteristics of paracetamol tablets

Binder	Formulation	Binder conc. (%w/w)	Time (min)	% cumulative release	T_{50} (min)	T_{80} (min)	Regression coefficient r^2
***Cicer arietinum* starch**	**F1**	**2.5%**	90	94.61	22.94	48.98	0.871
	F2	**5%**	90	89.28	26.02	59.60	0.873
	F3	**7.5%**	90	88.71	27.04	59.89	0.901
	F4	**10%**	90	81.28	35.07	88.58	0.931
***Pisum sativum* starch**	**F5**	**2.5%**	90	96.69	17.35	47.78	0.837
	F6	**5%**	90	95.67	17.12	48.42	0.816
	F7	**7.5%**	90	93.74	17.46	48.38	0.801
	F8	**10%**	90	86.81	33.23	82.93	0.964
***Zea mays* starch**	**F9**	**2.5%**	90	95.61	18.44	54.82	0.843
	F10	**5%**	90	93.73	19.08	54.36	0.849
	F11	**7.5%**	90	94.53	18.62	54.82	0.859
	F12	**10%**	90	83.31	27.60	86.42	0.918

8.5.3 Release kinetics of paracetamol tablets:

Table 8.19 Release kinetics of paracetamol tablets

Binder	Formulation	Binder conc. (%w/w)	Zero order (r^2)	First order (r^2)	Higuchi kinetics (r^2)
***Cicer arietinum* starch**	**F1**	**2.5%**	0.816	**0.978**	0.975
	F2	**5%**	0.858	**0.993**	0.980
	F3	**7.5%**	0.876	**0.993**	0.986
	F4	**10%**	0.902	**0.988**	0.988
***Pisum sativum* starch**	**F5**	**2.5%**	0.799	**0.992**	0.970
	F6	**5%**	0.782	**0.987**	0.963
	F7	**7.5%**	0.782	**0.957**	0.960
	F8	**10%**	0.867	**0.986**	0.969
***Zea mays* starch**	**F9**	**2.5%**	0.833	**0.987**	0.970
	F10	**5%**	0.830	**0.983**	0.974
	F11	**7.5%**	0.831	**0.990**	0.976
	F12	**10%**	0.857	**0.988**	0.990

The regression coefficient value for First order equation was found to be near to 1 revealing that the dissolution profile of the formulations may follow "First order kinetics".

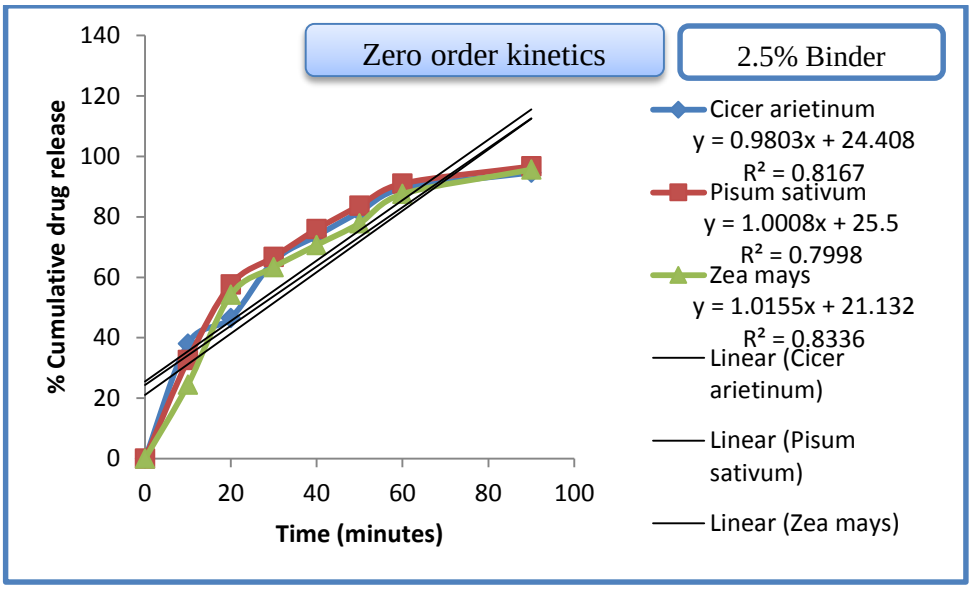


Figure 8.31: Zero order kinetics profile of prepared paracetamol formulations containing 2.5% binder

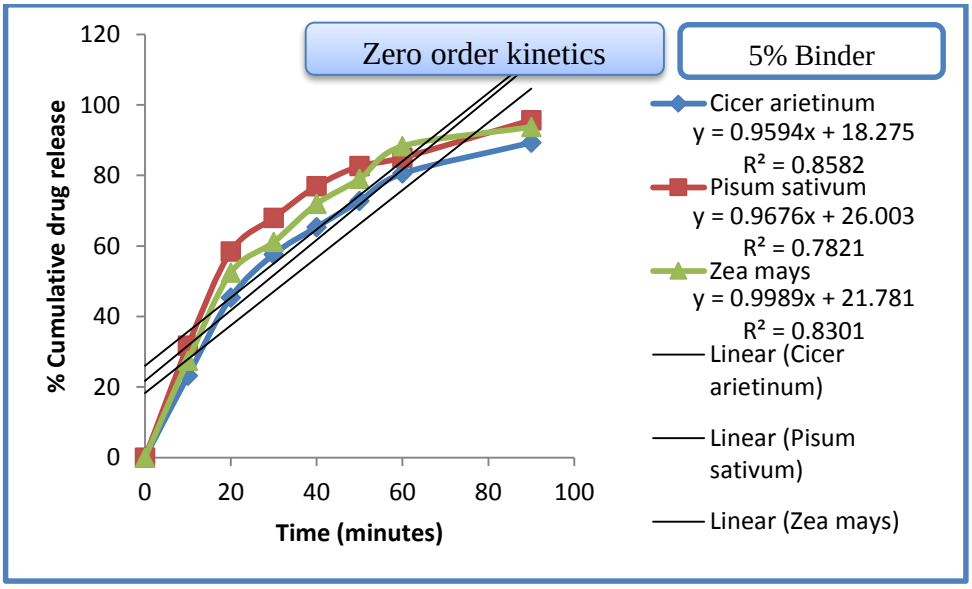


Figure 8.32: Zero order kinetics profile of prepared paracetamol formulations containing 5% binder

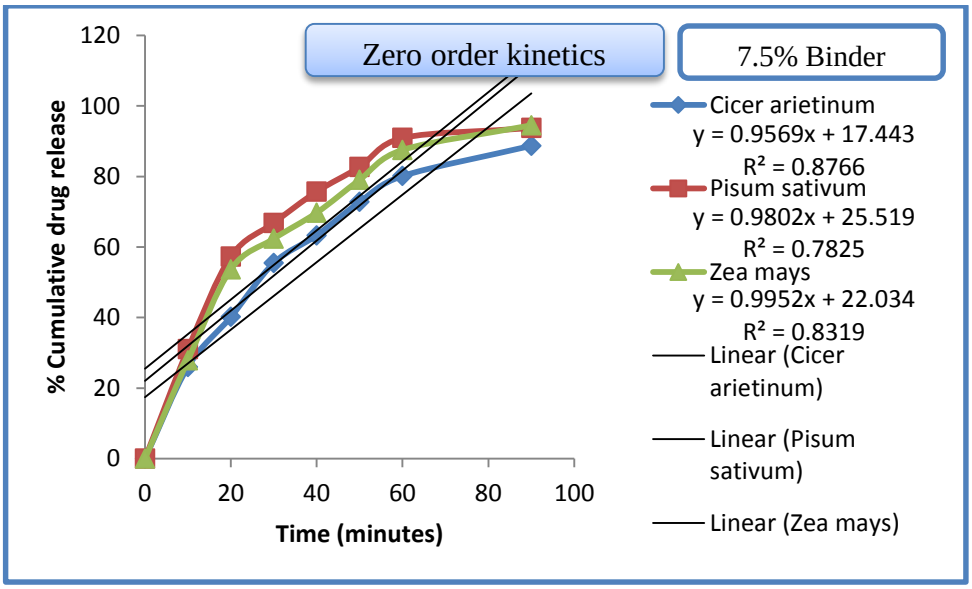


Figure 8.33: Zero order kinetics profile of prepared paracetamol formulations containing 7.5% binder

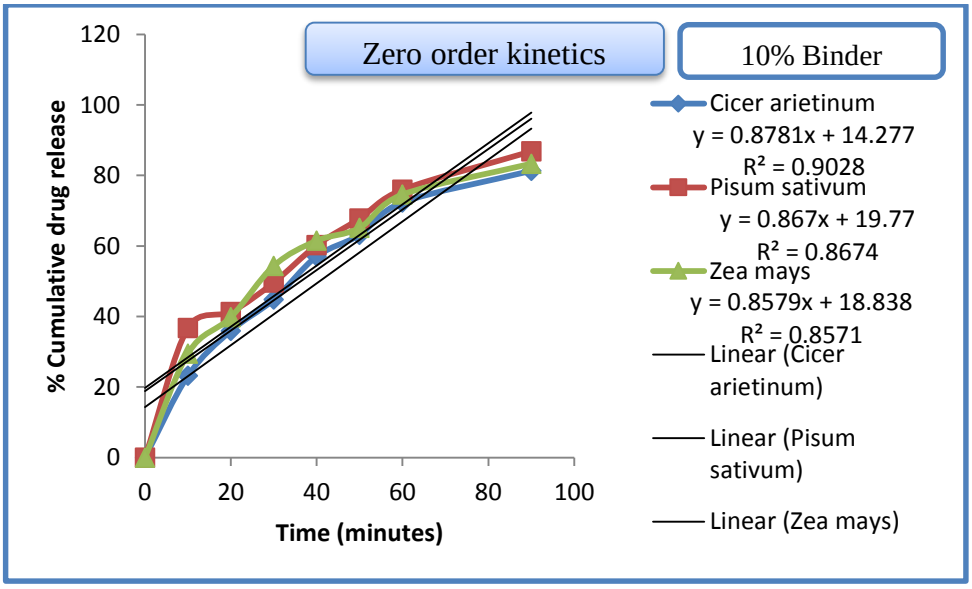


Figure 8.34: Zero order kinetics profile of prepared paracetamol formulations containing 10% binder

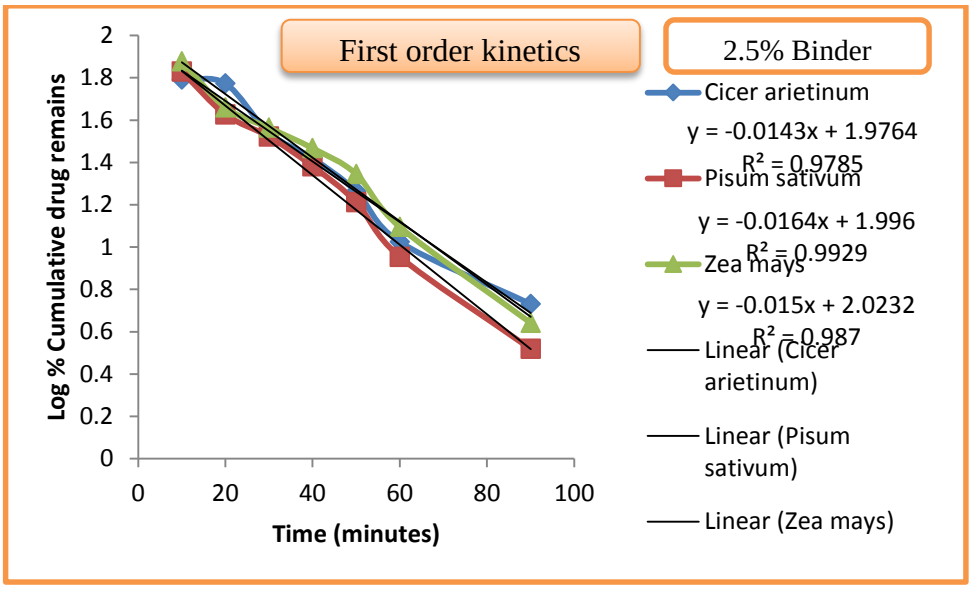


Figure 8.35: First order kinetics profile of prepared paracetamol formulations containing 2.5% binder

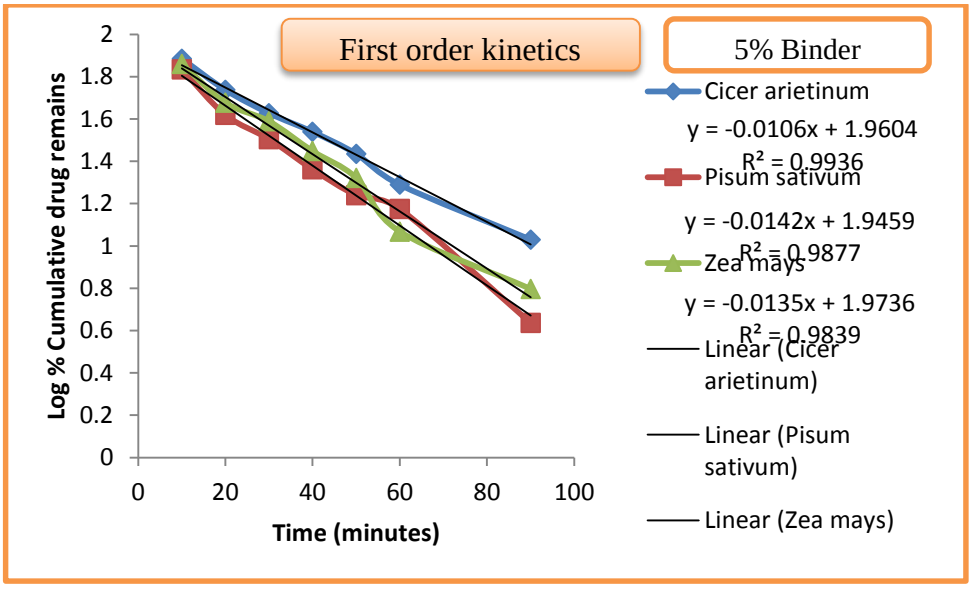


Figure 8.36: First order kinetics profile of prepared paracetamol formulations containing 5% binder

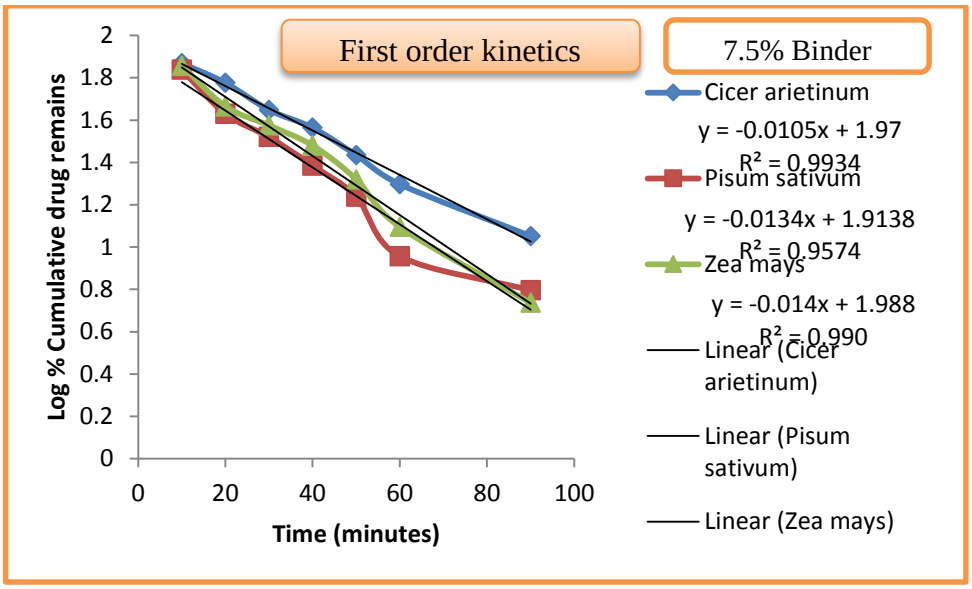


Figure 8.37: First order kinetics profile of prepared paracetamol formulations containing 7.5% binder

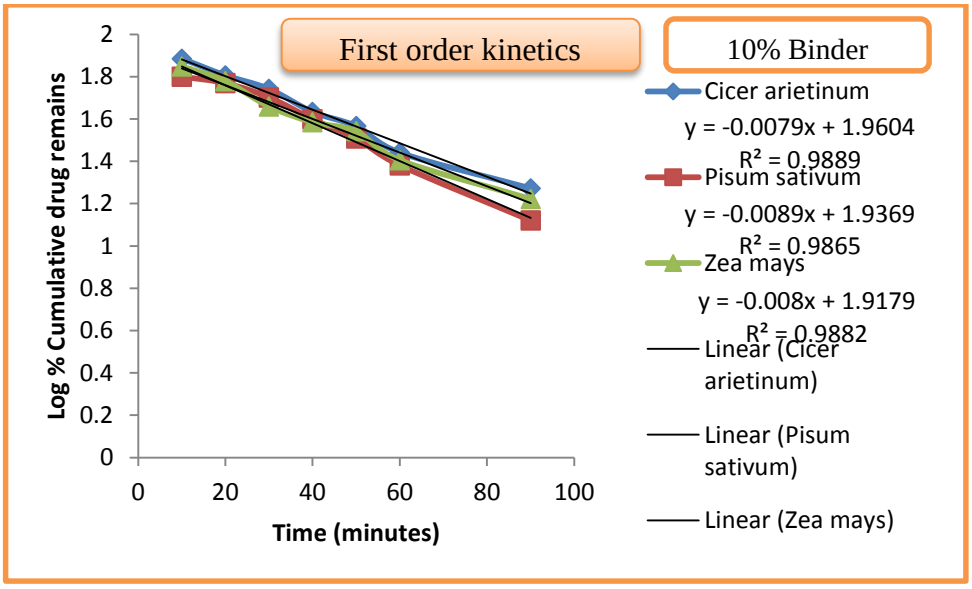


Figure 8.38: First order kinetics profile of prepared paracetamol formulations containing 10% binder

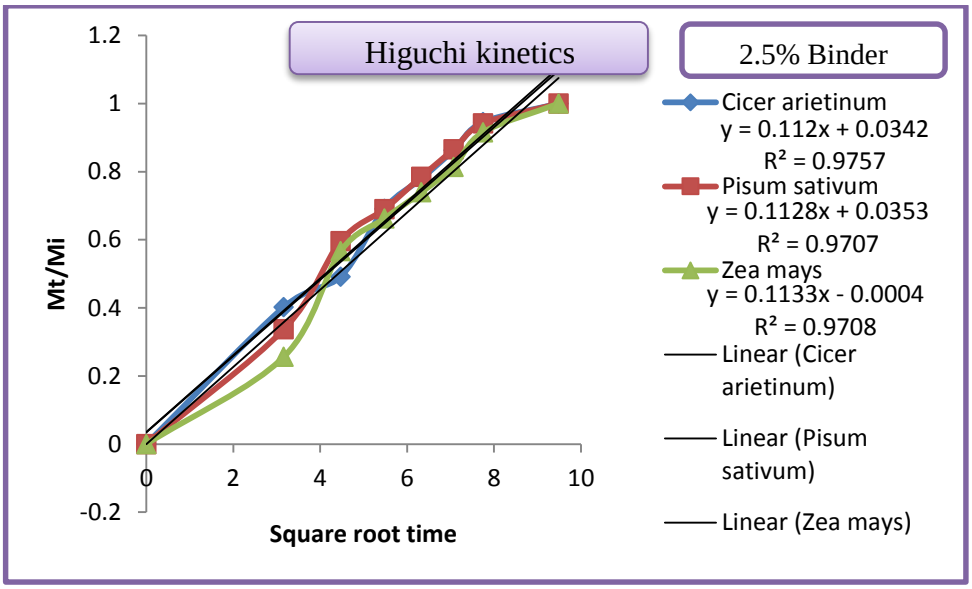


Figure 8.39: Higuchi kinetics profile of prepared paracetamol formulations containing 2.5% binder

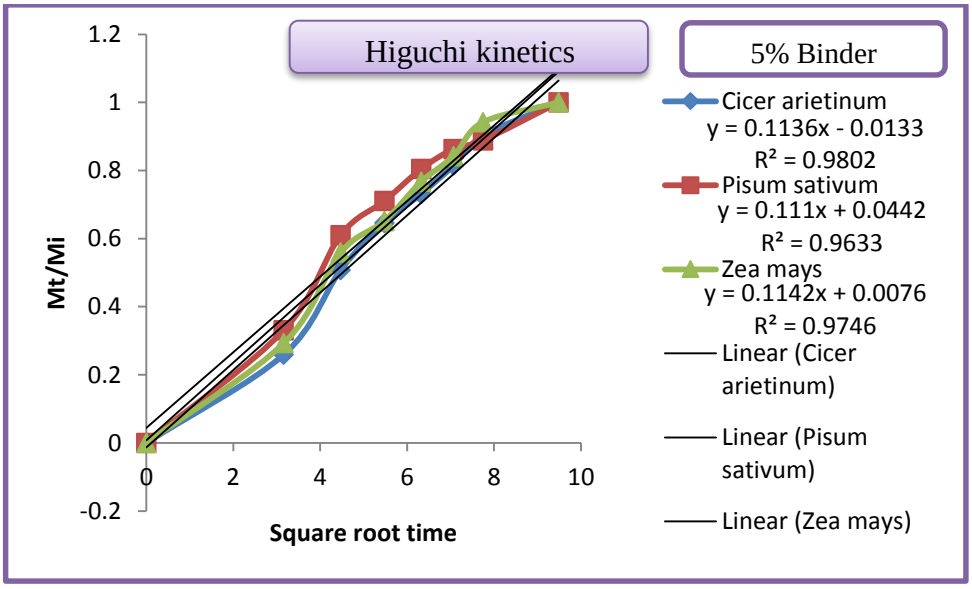


Figure 8.40: Higuchi kinetics profile of prepared paracetamol formulations containing 5% binder

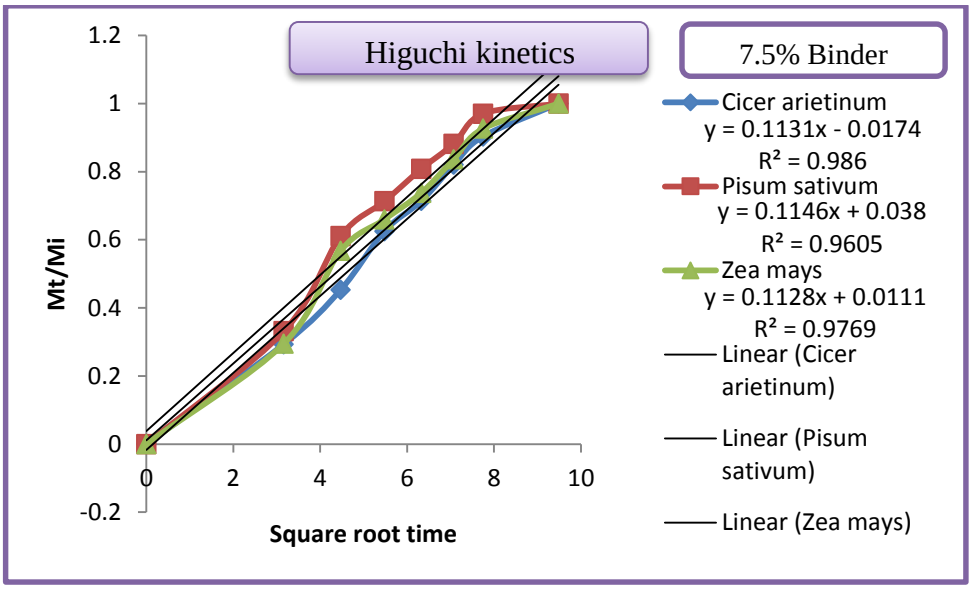


Figure 8.41: Higuchi kinetics profile of prepared paracetamol formulations containing 7.5% binder

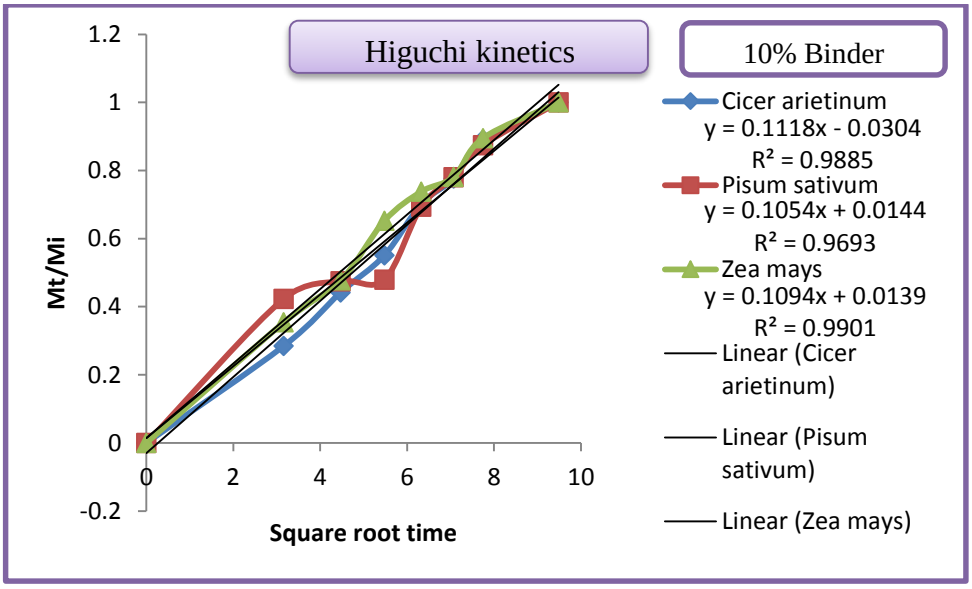


Figure 8.42: Higuchi kinetics profile of prepared paracetamol formulations containing 10% binder

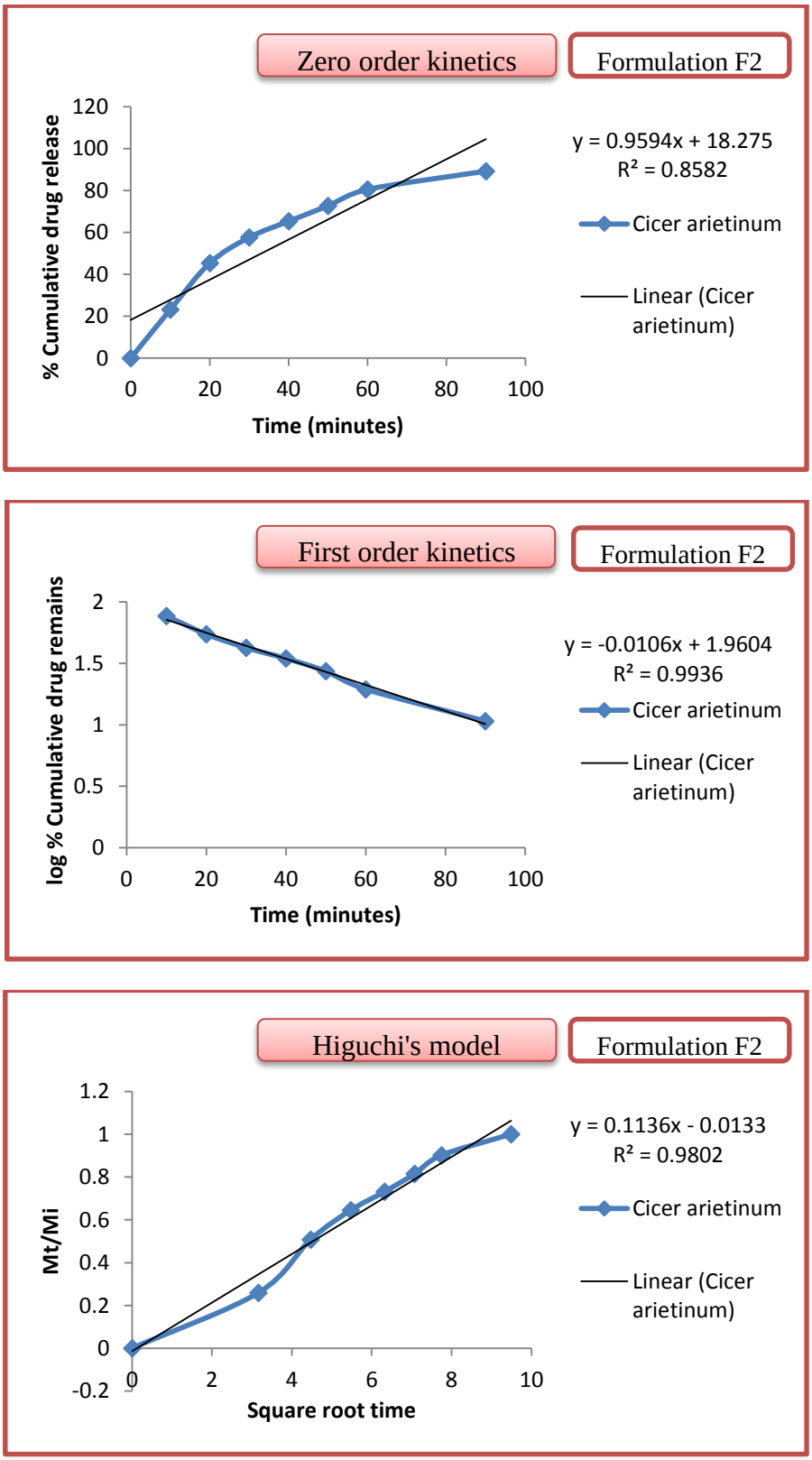


Figure 8.43: Best fit kinetic release profile of formulation (F2).

8.6 Stability studies of paracetamol tablets:

Table 8.20 Stability studies of paracetamol tablets

Stability study of formulation F2 (5% *Cicer arietinum* starch)				
Condition : 40˚C ± 2˚C/ 75%RH ± 5%RH (Accelerated)				
S.No	**Parameters**	**Initial**	**3rd month**	**6th month**
01.	Physical appearance	White	White	White
02.	Hardness	03.08 kg/cm^2	03.12 kg/cm^2	03.10 kg/cm^2
03.	Friability	0.33%	0.27%	0.31%
04.	Drug content	99.97%	99.99%	100.04%
05.	Disintegration time	07 min & 13 sec	08 min & 37 sec	07 min & 54 sec
06.	Dissolution (%CR in 120 min)	95.12%	94.33%	94.81%

Stability studies were done as per ICH guidelines. The formulation was kept at accelerated condition for the period of six months and evaluated during third and sixth month for their physical appearance, hardness, friability, drug content, disintegration and dissolution. The studies were done and the results show that the tablets were stable at room temperature.

9. SUMMARY AND CONCLUSION

SUMMARY

The Preformulation studies were performed on the *Cicer arietinum* and *Pisum sativum* starch, which includes isolation, purification and physicochemical characterization of starches (including XRD, SEM, and DSC). Physicochemical characterization of starches shows that it has poor flow property, where XRD results show that the laboratory isolated *Cicer arietinum* starch and *Pisum sativum* starch revealed C-type starch X-ray pattern. SEM observation of *Cicer arietinum* starch shows ellipsoidal, spherical granules of size range 9-20µm and *Pisum sativum* starch shows rounded, irregular granules of size range 12-30µm. As *Cicer arietinum* and *Pisum sativum* starches were from the natural source, microbial load test was done using pour plate method. The result shows that the bacterial and fungal growth obtained were under the limit specified by USP.

Compatibility studies were done by using FTIR, the examined spectra of pure drug, polymers and combination reveals that there is no significant interaction between drug and polymers.

Four formulations were made for each binder using different concentrations (2.5%, 5%, 7.5%, and 10%), three different binders were used to formulate twelve formulations and evaluated. The efficiency of various binders was studied by wet granulation technique. The prepared granules were evaluated for the pre-compression studies like moisture content, angle of repose, bulk density, tapped density, compressibility index and Hausner's ratio. The results show that it has good flow property and compression characteristics suitable for compression.

The paracetamol tablets prepared were evaluated for the post-compression studies like thickness, weight variation, hardness, friability, drug content, disintegration and *in-vitro* dissolution studies. The obtained results show that all the twelve formulations were under the specified limits as stated in the Pharmacopoeial monograph.

Among twelve formulations, formulation F2 (5% *Cicer arietinum* starch) shows good binding capacity (hardness), decrease in friability and slow disintegration with slow drug release in comparison with commercially available binder like *Zea mays* starch.

Release kinetics of paracetamol tablets were done and the regression coefficient value for first order equation was found to be near to 1 revealing that the dissolution profile of the formulations may follow "First order kinetics".

Stability studies were done as per ICH guidelines. The formulation was kept at accelerated condition for the period of six months and evaluated during third and sixth month for their physical appearance, hardness, friability, drug content, disintegration and dissolution. The studies were done and the results show that the tablets were stable at room temperature.

CONCLUSION

Resistant starch is the total amount of starch and starch degradation product that resists digestion in the small intestine of healthy people, passes to large intestine where they act as dietary fibers. Resistant starches studies exposed that when carbohydrates are replaced by resistant starch they had 20 to 30% higher fat oxidation. In particular resistant starch appears to block the body's ability to use carbohydrate as a fuel. Therefore resistant starch may help the people who are at the risk of diabetes/pre-diabetes by improving insulin sensitivity.

These suggested that *Cicer arietinum* starch could be an useful binding agent especially where high mechanical strength and slower release concern.

Our studies concluded that *Cicer arietinum* starch (resistant starch) can be used as an appropriate binder in any anti-diabetic drug formulations.

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ABSTRACT

In the present study, we evaluated pharmaceutical properties of the novel starch isolated from the seeds of *Cicer arietinum* and *Pisum sativum* to assess its functionality as pharmaceutical binder in tablet formulations.

The isolated starches were subjected for pre-formulation studies (including DSC, SEM and XRD), where the physicochemical characterization of starches showed poor flow property. Compatibility studies confirmed that there was no significant interaction between drug and polymers. Microbial load test showed that the bacterial and fungal growth was under the limit specified.

Efficiency of various binders were studied by wet granulation technique. Four formulations were made for each binder using different concentrations (2.5%, 5%, 7.5%, and 10%), three different binders used to formulate twelve formulations. Pre-compression studies of granules exhibited good flow property and compression characteristics suitable for compression. The formulated tablets were evaluated for post-compression parameters. It was found that tablets with *Cicer arietinum* starch showed good binding capacity (hardness), friable within limit and slow disintegration with slow drug release in comparison with commercially available binder like *Zea mays* starch. Release kinetics reveals that the drug release might follow "First order kinetics". Stability studies were done as per ICH guidelines and the tablets were found to be stable.

These findings suggested that *Cicer arietinum* starch could be an useful binding agent especially where high mechanical strength and slower release concern.

Our studies concluded that *Cicer arietinum* starch (resistant starch) can be used as an appropriate binder in any anti-diabetic drug formulations.

Key words: Resistant starch, *Cicer arietinum, Pisum sativum,* Natural binder, Starch, Natural excipients, Paracetamol, Tablets and Anti-diabetic formulations.

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