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FORMULATION AND EVALUATION OF ORODISPERSIBLE TABLETS OF PALIPERIDONE

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ABSTRACT

Optimized orally disintegrating tablets (ODTs) containing Paliperidone were prepared by direct compression method. Two factors, three levels (3^2) full factorial design was used to optimize the effect of superdisintegrant (crospovidone; X1) and; Binder (PVP K30S; X2) on tablet properties. The prepared ODTs were characterized for their drug content, hardness, friability and wetting time. The optimized ODT formulation (P4) was evaluated in term of in vitro disintegration and dissolution. The manufactured ODTs were complying with the pharmacopeia guidelines regarding hardness, friability, weight variation and content. PVP K30 had a very slightly enhancing effect on tablets disintegration. However, the effects of both Crospovidone (X1) and PVP K30 (X2) on ODTs drug release (Y1) were significant ($p < 0.05$). Moreover, X1 exhibited significant effect on the disintegration time. Furthermore, the optimized ODTs formula showed 1 month stability, and in vitro disintegration time of this formula was about 33 s.

Key Words: Paliperidone, orally disintegrating tablets

1. INTRODUCTION

1.1 Introduction of Drug Delivery System

1.1.1 Tablets as oral route of administration:[1-2]

The oral course of medication organization is most favored and generally acknowledged course of organization for assortment of medications and nutraceuticals. It offers various preferences, for example, simplicity of organization, more prominent adaptability in measurement frame and configuration space alongside quick large scale manufacturing with high level of computerization and low assembling expense. The parenteral course of organization is critical in the event of medicinal crises, while topical course is chiefly utilized to convey medications to fundamental dissemination through epidermis. Relatively 90% of the recommended medications are controlled by oral course for their undeniable points of interest over other course of organization and subsequently have turned into the most famous course of organization.

The measurements frame accessible for oral organizations are arrangements, suspensions, powders, tablets and cases. The medications controlled by oral course are adaptable, adaptable in dose quality, generally steady, present lesser issue in detailing and bundling and are advantageous to maker, store, handle and utilize. Strong measurements shapes give best assurance to drugs against temperature, light, oxygen and worry amid transportation. Most generally utilized strong oral measurements frames are tablet and case. Tablet has number of focal points over other dose frames.

1.1.2 Advantages of Tablets:[3]

- ✓ They are unit measurement frame, and they offer the capacities of all oral dose shapes for the portion accuracy and the slightest substance changeability amid dosing.
- ✓ Their cost is most minimal of all oral dose shapes.
- ✓ They are the most minimal of all oral measurements frames.

✓ They are when all is said in done the simpler and less expensive to bundle and ship as contrast with other oral dose shapes.
✓ Product distinguishing proof is straightforward and shoddy, requiring no extra Processing ventures with an emblazoned or monogrammed punch confront.
✓ They are anything but difficult to manage, does not require an authority.
✓ They are more qualified to vast scale creation than other unit oral structures.
✓ They have the better compound, mechanical and microbiological properties.

1.1.3 Disadvantages of Tablets: [4]

✓ Some drugs oppose pressure into thick compacts attributable to their indistinct or hairy nature, low-thickness character and so forth.

✓ Drugs with poor wetting ease back disintegration properties middle to substantial doses ideal ingestion high in the gastrointestinal tract, or any mix of these highlights might be hard to figure as a tablet that will even now give sufficient or full medication bioavailability.

✓ Bitter drugs, drugs with a questionable smell, or medications that are delicate to oxygen or climatic dampness may require epitome or entanglement before pressure or the tablets may require covering.

1.1.4 Classification of Tablets: [5]

A. Oral tablets for ingestion:

✓ Compressed tablets or standard compressed tablets
✓ Multiple compressed tablets
✓ Layered tablets
✓ Compression –coating tablets
✓ Repeat action tablets
✓ Delayed action tablets
✓ Chewable tablets
✓ Orally disintegrating or Fast dissolving tablets or melt -in- mouth tablets

B. Tablets used in oral cavity:

✓ Buccal tablets
✓ Sublingual tablets
✓ Troches and lozenges
✓ Dental cones

C. Tablets administered by other routes:

✓ Implants
✓ Rectal
✓ Vaginal

D. Tablets used to prepare solutions:

✓ Effervescent tablets
✓ Hypodermic tablets
✓ Tablet triturates
✓ Dispersible tablets

1.1.5 Ideal properties of tablets: [6]

The targets of the plan and produce of the compacted tablet is to convey orally the right measure of medication in the best possible frame, at or over the best possible time and in the coveted area.

Adjacent to the physical and concoction properties of therapeutic operators defined as a tablet, it should gangs following qualities

- ✓ Should be an exquisite item having its own character, while being free from all assembling deformities, for example, chips, splits, staining, tainting and such.
- ✓ Should have the solidarity to withstand rigors of mechanical stuns experienced in its generation, bundling, dispatching and administering.
- ✓ Should have the concoction and physical security to keep up its physical/synthetic characteristics after some time.
- ✓ It must have the capacity to discharge the restorative operators in the body in an anticipated and reproducible way.
- ✓ Must have reasonable physical steadiness over a period.

1.1.6 Orally Disintegrating Tablet (ODT): [7]

Numerous pharmaceutical measurements are directed as pills, granules, powders, and fluids. By and large, a pill configuration is for gulping unblemished or biting to convey an exact portion of prescription to patients. Be that as it may, a few patients, especially pediatric, geriatric, out of commission, psychiatry and voyaging patients experience issues for gulping or biting strong measurements frames. These patients create reluctant inclination to take these strong arrangements because of dread of gagging and inaccessibility of water amid voyaging.

One examination demonstrates that an expected half of the populace experiences dysphagia issue. It indicate requirement for another measurement shape that can enhance tolerant consistence.

With the end goal to help these patients, orally breaking down tablets have been created. An orodispersible tablet or orally breaking down tablet, by and large, is a tablet that breaks up or deteriorates in the oral pit without the need of water or biting. Maybe the most straightforward meaning of an ODT is: a solitary unit portion that breaks down in the oral depression without water.

The Center for Drug Evaluation and Research expresses an ODT to be: "A strong measurement shape containing therapeutic substances, which deteriorates quickly, generally inside merely seconds, when put upon the tongue." This framework is perceived with different equivalent words like quick dissolving tablets; soften in mouth tablets, permeable tablets, quickly breaking down tablets, snappy dissolving, and rapimelt tablets. In spite of different terminologies the capacity and idea of all these Drug Delivery System (DDS) is same.

Against maniacal prescription go under unending treatment where persistent needs to take medicine for draw out span or some of the time long lasting and rate of non participation and rebelliousness is as high as 90% and subsequently in such cases enjoyably enhanced doses frame are favored.

ODT crumble as well as break down quickly in the spit without the requirement for water. A few medications are retained from mouth, pharynx and throat as the salivation goes down into stomach. In such cases bioavailability of medication is essentially more noteworthy than those saw from ordinary tablet measurements frame.

ODT conveys enhanced bioavailability because of decreased dose, and enhanced clinical execution through a decrease of undesirable impacts.

1.1.7 Salient features of Orally Disintegrating Tablet (ODT) formulation: [8]

- ✓ Improved persistent consistence is the essential advantage of this innovation.
- ✓ Administration to patients who can't swallow and patients who decline to swallow, for example, pediatric, geriatric and mental patients.

✓ No need of water for gulping the measurement frames. This is very helpful component for the patients who are voyaging or don't have quick access to water.
✓ Superior taste of the tablet changes the fundamental perspective of meds as the "unpleasant pill" especially for pediatric patients. Included advantages of comfort and precise dosing when contrasted with fluids.
✓ Rapid sedate treatment intercession is conceivable.
✓ More quick medication ingestion through pre-gastric assimilation from the mouth, pharynx and throat.
✓ Easily compact and appropriate for transportation by patients.
✓ Can be created at mechanical scale all the more basically and all the more effectively.
✓ The quick dissolving measurement shapes joins the advantage of fluid plan with those of strong oral dose frames.
✓ A extensive variety of medications can be considered as perfect possibility for this dose shapes, (e.g. against pyretic, analgesics, calming specialists, coronary vasodilators, anti-microbials, hostile to asthmatic operators, diuretics, against arrhythmic, enemies of epileptics, antihistamines, hostile to emetic and hostile to hypertensive).

1.1.8 Characteristics of an Orally Disintegrating Tablet (ODT): [9]

Taste of the medicament:

As most of drugs are unpalatable, Orodispersible drug delivery system usually contain the medicament in a taste masked form. Delivery systems dissolve or disintegrate in the patient's mouth, thus releasing the active ingredients which come in contact with the taste buds and hence, taste masking of drug becomes critical for patient compliance.

Hygroscopicity:

Several Orodispersible dosage forms are hygroscopic and cannot maintain physical integrity under normal conditions of temperature and humidity. Hence, they need protection from humidity which calls for specialized product packaging.

Friability:

In order to allow Orodispersible tablets to dissolve or disintegrate in oral cavity, they should posse's high porosity or are compressed into tablets with very low compression force, which makes the tablets friable and hence are difficult to handle, often requiring specialized peel-off blister packing.

Mouth Feel

Mouth feel is critical and patient should receive a product that is pleasant and make him happy. Any large particles from the suspension of the tablet in water are insoluble or slowly soluble in water would lead to an unpleasant gritty feeling. This can be overcome by keeping the majority of particles below the detectable size limit. In certain cases, certain flavors can imbibe an improved mouth feel perception, resulting in a product that is perceived as being gritty, even if the only change is the flavor.

1.1.9 Desired Criteria for Orally Disintegrating Tablet (ODT): [9]

Orodispersible Tablets should;

✓ Not expect water to swallow, yet it should break up or crumble in the mouth in 60 seconds.
✓ Be convenient without delicacy concern.
✓ Have a satisfying mouth feel.
✓ Leave negligible buildup in the mouth after oral organization.
✓ Exhibit low affectability to ecological conditions as moistness and temperature.
✓ Allow the fabricate of tablet utilizing traditional preparing and bundling gear requiring little to no effort.

1.1.10 Methods used in the preparation of Orally Disintegrating Tablets: [10]

a. Tablet molding:

In this strategy, the tablet is readied utilizing water-solvent added substances. These water-solvent added substances break down quickly and totally in mouth. All ingredients of the plan are gone through fine work. At that point this dry mix is wetted with a hydro-alcoholic dissolvable and afterward formed into tablets utilizing low pressure powers. The dissolvable present inside the tablets is evacuated via air drying. Along these lines shaped formed tablets contain a permeable structure, which upgrades the disintegration. The shaped tablets arranged by this strategy have low mechanical quality. To enhance mechanical quality, restricting operator like sucrose, polyvinyl pyrrolidone, cellulosic polymers like hydroxylpropyl methylcellulose might be added to the dissolvable framework.

The extent of taste covering in formed tablets is extremely restricted. To veil the unpalatable taste of the medicament, the medication to be fused must be pretreated with various procedures accessible like shower solidifying or flavor expansion, smaller scale particulate arrangement of the medication and so forth.

b. Spray Drying:

As the preparing dissolvable is dissipated quickly amid shower drying, it gives exceptionally permeable and fine powders. Shower dryers are constantly utilized in the pharmaceutical business to deliver profoundly permeable powders. Allen and Wang have utilized splash drying system to plan quick dissolving tablets. They created detailing by utilizing mannitol as building specialist, hydrolyzed and non hydrolyzed gelatin as help framework, sodium starch glycolate as disintegrant and acidic material (citrus extract) and/or soluble base material (ex. NaHCO3) to upgrade breaking down and disintegration. Tablets produced from this powder deteriorated in under 20 sec in a fluid medium.

c. Lyophillization:

Lyophilization procedure is for the most part utilized for warmth delicate medications and biologicals. A procedure, which includes sublimation of water from the item in the wake of solidifying. It is likewise called stop drying. Stop dried structures offer more fast disintegration than other accessible strong items as process gives gleaming undefined structure to the building specialist and some of the time to the medications. Lyophilization results in arrangements, which are exceptionally permeable, with a high surface territory, which break up quickly and demonstrate enhanced retention and bioavailability. Tablets arranged by lyophilization, are delicate, have low mechanical quality, which makes them hard to deal with and they likewise display poor physical dependability. Other real drawback of frame incorporates absence of opposition in standard rankle packs.

d. Sublimation:

Compacted tablets made out of profoundly water-insoluble excipients don't break down quickly in the water in light of its low porosity, so permeable tablets that display great mechanical quality and disintegrate rapidly is the best solution for above issue.

The essential guideline associated with planning Orodispersible tablets by sublimation method is expansion of a radiant salt (e.g. ammonium carbonate, ammonium bicarbonate and ammonium acetic acid derivation) to the tabletting parts. Blending the segments to get a generously homogenous blend and volatilizing the radiant salt. The expulsion of magnificent salt makes pores in the tablet, which help in accomplishing quick deterioration when tablet interact with salivation.

1.2 Introduction of Disease

- **Schizophrenia** [(11)]

Schizophrenia is a psychological issue that typically shows up in late puberty or early adulthood. Described by dreams, visualizations, and other subjective challenges, schizophrenia can regularly be a deep rooted battle.

Schizophrenia most regularly strikes between the ages of 16 and 30, and guys will in general show side effects at a somewhat more youthful age than females. By and large, the confusion grows so gradually that the individual does not realize that they have had it for a long time. In any case, in different cases, it can strike all of a sudden and grow rapidly.

→ **Symptoms of schizophrenia:-**

Symptoms and signs of schizophrenia will vary, depending on the individual.

The symptoms are classified into four categories:

- **Positive symptoms** - also known as psychotic symptoms. For example, delusions and hallucinations.
- **Negative symptoms** - these refer to elements that are taken away from the individual. For example, absence of facial expressions or lack of motivation.
- **Cognitive symptoms** - these affect the person's thought processes. They may be positive or negative symptoms, for example, poor concentration is a negative symptom.
- **Emotional symptoms** - these are usually negative symptoms, such as blunted emotions.

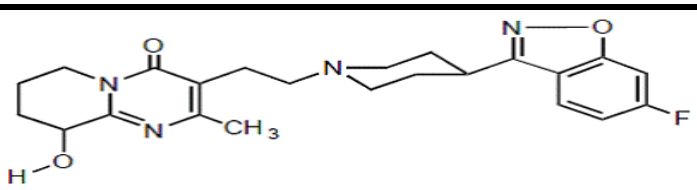
Below is a list of the major symptoms:

- **Delusions** - the patient displays false beliefs, which can take many forms, such as delusions of persecution, or delusions of grandeur. They may feel others are attempting to control them remotely. Or, they may think they have extraordinary powers and abilities.
- **Hallucinations** - hearing voices is much more common than seeing, feeling, tasting, or smelling things which are not there; however, people with schizophrenia may experience a wide range of hallucinations.
- **Thought disorder** - the person may jump from one subject to another for no logical reason. The speaker may be hard to follow or erratic.

1.3 Introduction of Drug

- **Paliperidone:-**[12-16]

Table 1 Drug Information

General Properties:-	
Name	Paliperidone
Description	Paliperidone is the primary active metabolite of the older antipsychotic risperidone. While its specific mechanism of action is unknown, it is believed that paliperidone and risperidone act via similar if not the same pathways
Appearance	Paliperidone is white crystalline powder
Structure	
CAS number	144598-75-4
Category	Psychotropic agent
Molecular Weight	426.48 g/mol
Chemical Formula	$C_{23}H_{27}FN_4O_3$

IUPAC Name	3-{2-[4-(6-fluoro-1,2-benzoxazol-3-yl)piperidin-1-yl]ethyl}-9-hydroxy-2-methyl-4H,6H,7H,8H,9H-pyrido[1,2-a]pyrimidin-4-one
Solubility	Paliperidone is sparingly soluble in 0.1N HCl and methylene chloride; 0.1N NaOH, and hexane; and slightly soluble in N,N-dimethylformamide.
Water Solubility	0.03 mg/ml
Log P	1.8
pKa	13.74
Melting point (°C)	179.8°C
Identification	FTIR, UV, HPLC
BCS Class	II
Dose	1.5/3/6/12 mg
Pharmacokinetic Properties:-	
Absorption	The absolute oral bioavailability of paliperidone following Paliperidone administration is 28%.
Bioavailability	28%
Protein binding	74%
Metabolism	Although in vitro studies suggested a role for CYP2D6 and CYP3A4 in the metabolism of Paliperidone, in vivo results indicate that these isozymes play a limited role in the overall elimination of Paliperidone.
Half life	23 hours
Excretion	One week following administration of a single oral dose of 1 mg immediate-release 14C-paliperidone to 5 healthy volunteers, 59% (range 51% – 67%) of the dose was excreted unchanged into urine, 32% (26% – 41%) of the dose was recovered as metabolites, and 6% – 12% of the dose was not recovered.
Pharmacological Properties:-	
Indication	For the treatment of schizophrenia.
Mechanism of action	Paliperidone is the major active metabolite of risperidone. The mechanism of action of Paliperidone, as with other drugs having efficacy in schizophrenia, is unknown, but it has been proposed that the drug's therapeutic activity in schizophrenia is mediated through a combination of central dopamine Type 2 (D2) and serotonin Type 2 (5HT2A) receptor antagonism.
Marketed Preparations:-	

Brand/Generic Name	Availability	Company Name
INVEGA	Extended release Tablet:- 1.5/3/6/12 mg	Janssen-Cilag
Paliperidone	Extended release Tablet:- 1.5/3/6/12 mg	Mylan

1.4 Introduction of Excipients

1.4.1 Crospovidone:-

Non proprietary Names

BP: Crospovidone

PhEur: Crospovidonum USPNF: Crospovidone

Synonyms

Cross linked povidone; E1202; Kollidon CL; Kollidon CL-M; Poly plasdone XL; Poly plasdone XL-10, polyvinyl poly pyrrolidone; PVPP, 1- vinyl-2-pyrrolidinonehomopolymer.

Chemical Name and CAS Registry Number

1-Ethenyl-2-pyrrolidinone homo polymer [9003-39-8]

Empirical Formula and Molecular Weight

(C_6H_9NO) n >1000000

The USPNF 23 describes crospovidone as a water-insoluble synthetic cross linked homo polymer of N-vinyl-2-pyrrolidinone. An exact determination of the molecular weight has not been established because of the insolubility of the material.

Functional Category

Tablet disintegrant

Applications in Pharmaceutical Formulation or Technology

Crospovidone is a water-insoluble tablet disintegrant and dissolution agent used at about 2–5% concentration in tablets prepared by direct-compression or wet and dry granulation methods. It rapidly exhibits high capillary activity and pronounced hydration capacity, with little tendency to form gels. Studies suggest that the particle size of the crospovidone strongly ikonfluences disintegration of analgesic tablets. Larger particles provide a faster disintegration than smaller particles. Crospovidone can also be used as a solubility enhancer. With the technique of co evaporation, crospovidone can be used to enhance the solubility of poorly soluble drugs.

Description

Crospovidone is a white to creamy-white, finely divided, free flowing, practically tasteless, odorless or nearly odorless, hygroscopic powder.

1.4.2 Sodium Starch Glycolate

Non proprietary Names

BP: Sodium Starch Glycolate

PhEur: Sodium Starch Glycolate

USP-NF: Sodium StarchGlycolate

Synonyms

Carboxymethyl starch, sodium salt; carboxymethylamylumnatricum; Explosol; Explotab; Glycolys; Primojel; starchcarboxymethyl ether, sodium salt; Tablo; VivastarP.

Chemical Name and CAS Registry Number

Sodium carboxymethyl starch [9063-38-1]

Empirical Formula and Molecular Weight

The USP32–NF27 describes two types of sodium starch glycolate, Type A and Type B, and states that sodium starch glycolate is the sodium salt of a carboxymethyl ether of starch or of a crosslinked carboxymethyl ether of starch. The PhEur 6.0 describes three types of material: Type A and Type B are described as the sodium salt of a crosslinked partly Ocarboxymethylated potato starch. Type C is described as the sodium salt of a partly O- carboxymethylated starch, crosslinked by physical dehydration. Types A, B, and C are differentiated by their pH, sodium, and sodium chloride content. The PhEur and USP–NF monographs have been harmonized for Type A and Type B variants.

Functional Category

Tablet and capsule disintegrant.

Applications in Pharmaceutical Formulation or Technology

Sodium starch glycolate is widely used in oral pharmaceuticals as a disintegrant in capsule and tablet formulations. It is commonly used in tablets prepared by either direct-compression or wet-granulation processes. The usual concentration employed in a formulation is between 2% and 8%, with the optimum concentration about 4%, although in many cases 2% is sufficient. Disintegration occurs by rapid uptake of water followed by rapid and enormous swelling.

1.4.3 Lactose

Synonyms

Lactochem, milk sugar

Molecular Weight

342.30 (anhydrous), 360.31(monohydrate)

Functional Category

Tablet and capsule diluent

Description

white to off-white crystalline particles or powder.

Pharmaceutical Uses

Lactose is widely used as a filler or diluent in tablets, capsules and to a more limited extent in lyophilized products and infant feed formulas. Other applications of lactose include as a carrier/diluents for inhalation products and in lyophilized products, where lactose is added to freeze- dried solutions to increase plug size and aid caking. Lactose is also used in combination with sucrose (approximately 1:3) to prepare sugar coating solutions.

Solubility

It is freely but slowly soluble in water and insoluble in ethanol.

1.4.4 Magnesium Stearate

Synonyms

Stearic acid magnesium salt, magnesium octadecanoate.

Molecular Weight

125 g/mol

Description:

Magnesium stearate is a fine, white, precipitated, milled, impalpable powder of low bulk density, having a faint, characteristic odour and taste. The powder is greasy to touch and readily adheres to skin.

Pharmaceutical Uses:

Magnesium stearate is widely used in cosmetics, foods and pharmaceutical formulations. It is primarily used as lubricant in capsule and tablet manufacturing at concentration between 0.25-5.0% w/w.

Solubility:

It is practically insoluble in ethanol, ethanol (95%), ether and water, slightly soluble in warm benzene and warm ethanol (95%).

1.4.5 Talc:

Synonyms

Altalc, Magsil Star; Purtalc.

Description

Talc is a very fine, white to greyish-white, odourless, impalpable, unctuous, crystalline powder.

Functional Category

Anticaking agent; glidant; tablet & capsule diluent; tablet & capsule lubricant.

Solubility

Practically soluble in dilute acids and alkalis; organic solvents, water.

Stability & Storage

Talc is stable and should be stored in well closed container in a cool and dry place.

1.4.6 PEG 6000

1.4.7 Croscarmellose Sodium

Non proprietary Names

BP: Croscarmellose Sodium

JP: Croscarmellose Sodium

PhEur: Croscarmellose Sodium

USP-NF: Croscarmellose Sodium

Synonyms

Ac-Di-Sol; carmellosum natricum conexum; crosslinked carboxymethylcellulose sodium; Explocel; modified cellulose gum; Nymcel ZSX; Pharmacel XL; Primellose; Solutab;Vivasol.

Chemical Name and CAS Registry Number

Cellulose, carboxymethyl ether, sodium salt, cross linked [74811-65-7]

Empirical Formula and Molecular Weight

Croscarmellose sodium is a cross linked polymer of carboxymethylcellulose sodium.

Functional Category: Tablet and capsule disintegrant.

Applications in Pharmaceutical Formulation or Technology

Crospovidone is a water-insoluble tablet disintegrant and dissolution agent used at about 2–5% concentration in tablets prepared by direct-compression or wet and dry granulation methods.

2. LITERATURE REVIEW

2.1 Review of Literature on Drug Delivery System

Harshal P et al [17] prepared Valsartan ODT tablets using different concentrations (1%, 2.5%, 5%, and 7.5% w/w) of isolated C. tora seed polysaccharide (natural) and sodium starch glycolate (synthetic) as superdisintegrant by the direct compression method. Evaluation of tablets was done for various pre- and post compression parameters. The stability studies were performed on optimized formulation F4. The disintegration time and in vitro drug release of the formulation F4 were compared with marketed formulations (conventional tablets).

Witold B et al [18] compared different methods and correlates them with in vivo results. Six series of ODTs were prepared by direct compression. Their mechanical properties and disintegration times were measured with pharmacopoeial and alternative methods and compared with the in vivo results.

Mohamed A et al [19] Optimized orally disintegrating tablets (ODTs) containing furosemide (FUR) was prepared by direct compression method. Two factors, three levels (3^2) full factorial design was used to optimize the effect of taste masking agent (Eudragit E100; X1) and superdisintegrant; croscarmellose sodium (CCS; X2) on tablet properties. A composite was prepared by mixing ethanolic solution of FUR and Eudragit E100 with mannitol prior to mixing with other tablet ingredients. The prepared ODTs were characterized for their FUR content, hardness, friability and wetting time. The optimized ODT formulation (F1) was evaluated in term of palatability parameters and the in vivo disintegration.

Kadria A et al [20] formulated orodispersible tablets of flutamide (FTM) to increase its bioavailability. Orodispersible tablets were prepared by direct compression technique using three different approaches namely; super-disintegration, effervescence and sublimation. Different combined approaches were proposed and evaluated to optimize tablet characteristics. Sodium starch glycolate (SSG) was used as the superdisintegrant.

Rabab A et al [21] formulated FDT's of Valsartan for the treatment of hypertension in children who could find difficulties in swallowing conventional solid dosage forms. The tablets were prepared by wet granulation technique. Superdisintegrants such as

sodium starch glycolate (SSG) and crospovidone were optimized as 5% on the basis of least disintegration time. Different binders such as gelatin and HPMC k15m, at varying concentrations, were used along with the optimized superdisintegrant concentration. All the formulations were evaluated for content uniformity, disintegration time, friability, hardness and in vitro dissolution.

Omer T et al [22] aimed to take the advantage of convenient direct compression method for preparation of Orally Disintegrating Tablets (ODTs) containing 30 mg FFH per tablet. Six ready-to-use commercial tablet excipients (F-Melt® , Pearlitol® Flash, Pharmaburst® 500, Prosolv® Easytab SP, Ludiflash® , Parteck® ODT®) were used for direct compression and suitability of these excipients were evaluated.

Uday K et al [23] formulate diclofenac sodium as fast dissolving tablets (FDTs) using fenugreek gum as a natural superdisintegrant which also possess anti-inflammatory activity. FDTs of diclofenac sodium was formulated by direct compression technique using different concentrations (1%-6%, w/w) of fenugreek gum as a natural superdisintegrant and compared with renowned synthetic superdisintegrants like sodium starch glycolate and croscarmellose sodium.

Xuelian H et al [24] prepare and evaluate a taste-masked berberine hydrochloride orally disintegrating tablet for enhanced patient compliance. Taste masking was performed by coating berberine hydrochloride with Eudragit E100 using a fluidized bed. It was found that microcapsules with a drug–polymer ratio of 1:0.8

masked the bitter taste obviously. The microcapsules were formulated to orally disintegrating tablets and the optimized tablets containing 6% (w/w) crospovidone XL and 15% (w/ w) microcrystalline cellulose showed the fastest disintegration, within 25.5 s, and had a pleasant taste. The dissolution profiles revealed that the taste-masked orally disintegrating tablets released the drug faster than commercial tablets in the first 10 min.

Zahra H et al [25] focused on taste masking and formulation of ranitidine ODT which disintegrates rapidly in the mouth within 60 sec using super-disintegrants, special polymers, water soluble and even insoluble excipients, sweeteners and essence. Various formulations were designed and made in four series. The amount of ranitidine in each formulation was 150 mg, and the final weight of tablets was around 500 mg. Prepared formulations were evaluated in terms of several physicochemical tests including powder/granule flowability, appearance, thickness, uniformity of weight, hardness, friability and disintegration time.

Tong W et al [26] prepared a mosapride citrate-resin (Amberlite® IRP 88) complex and orally fast-disintegrating tablets of the resin complex. The resinate complex of mosapride-Amberlite® IRP 88, mass ratio 2:1, was prepared in an ethanol-water solution. The effects of alcohol concentration, temperature, and pH of the solution on complex formation were evaluated. The complex physicochemical properties were characterized by differential scanning calorimetry, X-ray diffraction and scanning electron microscopy. Orally disintegrating tablets were prepared by direct compression and were optimized using the response surface method. Optimized orally fast-disintegrating tablets disintegrated within 18 s.

2.2 Review of Literature on Drug

Smita R et al [27] worked on Paliperidone formulation in which ethyl cellulose was used as polymer for formulation of microspheres of antipsychotic agent paliperidone. Emulsion solvent diffusion technique was employed for preparing microspheres by using liquid paraffin as a continuous phase. The prepared microspheres were evaluated for production yield, particle size, drug content, encapsulation efficiency, surface morphology and in vitro drug release. Dissolution study revealed drug release from the microspheres was affected by drug polymer ratio.

Abdul H et al [28] developed nanocrystals of Paliperidone in order to enhance solubility and dissolution rate by decreasing particle size of drug and also sustained the drug release profile by using Eudragit L100 as polymer. The Paliperidone nanocrystals with small and uniform particle size were successfully prepared by nano precipitation method using Eudragit L100 as polymer at different ratios in the presence of stabilizers (PVP K30, Poloxamer 188, Poloxamer 407, combination of PVP K30 and Poloxamer 407 and combination of PVP K30 and Poloxamer 188).

Aastha H et al [29] formulated Paliperidone as matrix type sustained release tablets using natural and synthetic polymers separately or in combination. The aim of sustained release formulation is to reduce the frequency of dosing. Tablets were prepared by direct compression method. The optimized formulations contain Paliperidone as active ingredient and hydroxy propyl methyl cellulose, ethyl cellulose, kollidone SR, polyethylene oxide, sodium alginate are used as polymers.

Swetha K et al [30] aimed to improve the oral delivery of paliperidone by loading into self emulsifying drug delivery systems (SEDDS). Oleic acid, Tween 80, and capmul MCM L8 were selected as oil, surfactant, and co-surfactant, respectively and phase diagram was constructed and the region was identified for the formation of SEDDS. The stable formulations were analyzed for globule size, robustness to dilution and in vitro drug release. The globule size of all the formulations was found to be in the range of 205 to 310 nm with good size uniformity and seems to be dependent on the proportion of oil in SEEDS formulation. The optimized formulation (F3) has been adsorbed onto neusilin and characterized.

Injavarapu Det al [31] developed simple, economic, sensitive, reproducible and rapid UV-Spectrophotometric method have been developed and validated for the determination of Paliperidone (PP) in pharmaceutical dosage forms and in bulk drug. The absorption maxima was found to be at 235 nm in methanol and shows linearity over the concentration range of 1-30µg ml-1with regression equation 0.032x + 0.011(r2 = 0.999) and 0.0312x+0.007(r2=0.999) at 278nm. The proposed method can be successfully

applied for the determination of Paliperidone in dosage forms. The methods were validated as per the ICH guidelines.

2.3 Summary of PSAR Report

Sr. No.	Patent Application number	Title of Patent
	9,439,906	Dosing regimen associated with long acting injectable Paliperidone esters
	US2011052687 A1	Extended release pharmaceutical composition of Paliperidone
	EP2331083 (A1)	Prolonged Release Multiparticulate Pharmaceutical Composition Comprising Paliperidone
	35/2015	Paliperidone Implant Formulation
	10/2014	Extended Osmotic Release Compositions of Paliperidone

- **Looking at above 05 patents, your Dissertation project is novel up to what extent?**

Novelty grade: 50 to 90%

- **RATIONAL OF PATENT**

Above five patents describes Formulation of Paliperidone in different dosage form. No any patented work done on ODT tablets of Paliperidone. Hence, the selected title is novel.

3. AIM & OBJECTIVES

3.1 Aim of Work

"Formulation and Evaluation of Orodispersible Tablets of Paliperidone"

3.2 Rationale

✓ Paliperidone is an atypical antipsychotic belonging to the chemical class of benzisoxazole derivatives.

✓ Paliperidone is indicated for the treatment of schizophrenia.

✓ Its oral dose is ***1.5/3/6/12 mg*** once in a day.

✓ Half life is 23 hours.

✓ The oral bioavailability of Paliperidone is ***28%.***

✓ It's undergoes extensive hepatic first pass metabolism.

✓ Its Log P value is ***1.8.***

✓ Its pKa value is ***13.74***.

✓ Based on Log P and pKa values, Paliperidone is good candidate for buccal absorption.

✓ Hence, an attempt is made to prepare Orodispersible tablets of Paliperidone which rapidly disintegrate in mouth and give quick onset of action, minimize the first pass effect and improve oral bioavailability.

3.3 Objectives of Work

✓ To carry out pre-formulation studies for possible drug and excipient interactions. (Drug: Excipient Compatibility study)

- ✓ To develop and formulate Paliperidone ODT tablets.
- ✓ To optimize the disintegrant concentration.
- ✓ To achieve drug release more than 90% of drug within 10 min.
- ✓ To achieve disintegration time within 60 sec.
- ✓ To evaluate the optimized formulated dosage form for various physico-chemical parameters like weight variation, Hardness, thickness, drug content, disintegration time and Dissolution.

To carry out accelerated stability studies on the most satisfactory formulation as per ICH guideline.

4. MATERIALS AND EQUIPMENTS

4.1 List of Materials

Table 2 List of materials

Sr. No.	Material	Function	Sources of Material
1.	Paliperidone	API	Zydus Research Centre, Ahmedabad.
2.	Crospovidone, Sodium Starch Glycolate, Croscarmellose Sodium	Super disintegrating agent	Balaji Chemicals, Ahmedabad.
3.	Sodium Saccharine	Sweetener	Balaji Chemicals, Ahmedabad.
4	Magnesium Stearate	Lubricant	Balaji Chemicals, Ahmedabad.
5	Talc	Glidant	Balaji Chemicals, Ahmedabad.
6	MCC, Lactose	Diluent	ACS Chemicals, Ahmedabad.
7	PVP K30	Binder	ACS Chemicals, Ahmedabad.
8	PEG 6000	Solubilizer	Balaji Chemicals, Ahmedabad.

4.2 List of Equipments

Table 3 List of equipments

Sr. No.	Equipments	Manufacturers
1.	Digital weighing balance	Reptech weighing balance ltd., Ahmedabad.

2.	Tablet compression machine	Cadmach, Ahmedabad.
3.	Dissolution apparatus	Electro lab ltd, Mumbai.
4.	U.V. Visible Spectrophotometer	Shimadzu-1601, Kroyoto, Japan.
5.	pH meter	Electrolab, Mumbai, India.
6.	Roche Friabilator	Electrolab, Mumbai, India.
7.	Hardness Tester	Monsanto hardness tester, Shivani Scientific Industries Pvt. Ltd., Mumbai.
8.	FTIR	FTIR 8400S, Shimadzu, Kroyoto, Japan.
9.	DSC	Mettler, DSC 823, Germany

5. EXPERIMENTAL WORK

5.1 Preliminary studies on Paliperidone API

First, physicochemical properties of Paliperidone powder were investigated such as powder purity, organoleptic properties (color, texture, taste and smell) and flowability (by measuring the Carr's index and Hausner's ratio).

- ***Angle of Repose:***

The precisely weight powder mix were taken in the channel. The tallness of the pipe was balanced in such a way the tip of the pipe simply touched the zenith of the powder mix. The powder mix was permitted to move through the pipe uninhibitedly on to the surface. The distance across of the powder cone was estimated and point of rest was ascertained utilizing the accompanying condition.

$\tan \theta = h/r$

Where, h and r are the height and radius of the powder cone.

- ***Bulk Density:***

Both loose bulk density (LBD) and tapped bulk density (TBD) was determined. A quantity of 2 gm of powder blend from each formula, previously shaken to break any agglomerates formed, was introduced in to 10 ml measuring cylinder. After that the initial volume was noted and the cylinder was allowed to fall under its own weight on to a hard surface from the height of 2.5 cm at second intervals. Tapping was continued until no further change in volume was noted. LBD and TDB were calculated using the following equations.

LBD= Weight of the powder blend/Untapped Volume of the packing

TBD=Weight of the powder blend/Tapped Volume of the packing

- ***Compressibility Index***:

The Compressibility Index of the powder blend was determined by Carr's compressibility index. It is a simple test to evaluate the LBD and TBD of a powder and the rate at which it packed down. The formula for Carr's Index is as below:

Carr's Index (%) = [(TBD-LBD) x100]/TBD

- ***Hausner's Ratio:***

It is calculated from bulk density and tap density.

Hausner's ratio = Tapped density / Bulk density.

Values less than 1.25 indicate good flow (20% Carr index.) and the value greater than 1.25 indicates poor flow (33% Carr index.). If it is between 1.25-1.5 added glidant normally to improve flows.

5.2 Drug Excipient Compatibility Study

- **FTIR Study:**

Pure drug and Drug with excipients mixture spectrum analysis performed in mixture at range of 400 to 4000 $cm^{-1}$and the degree was 1.5 cm^{-1}using FTIR spectrophotometer.

- **DSC Study:**

Differential examining Calorimetry (DSC) was performed utilizing diffractometer. The physical blends/API powder with various Excipients for similarity examines were set up by triturating medication and added substances in a dried mortar for 5 min.

5.3 Calibration curves of Paliperidone

- **Preparation of Standard Stock Solution:**

The standard solution of Paliperidone was prepared by dissolving accurately about 10 mg of the Paliperidone with 6.8 phosphate buffer in a 100 ml volumetric flask and sonicated for 20 mins. This stock solution was further diluted with 6.8 phosphate buffer as per the requirement.

- **Preparation of Sample Solution:**

The powder of 10 mg Paliperidone was weighed accurately and transferred into a 100 ml standard volumetric flask. The contents were dissolved in 6.8 phosphate buffer and sonicated for 30 minutes. This entire solution was filtered through 0.45 micron Whatmann filter paper (No. 41) and the final solution was made with 6.8 phosphate buffer to get the solution of 1000 µg/ml. This solution was further diluted with methanol as per the requirement.

Procedure:

The drug solution was scanned (200-400 nm) against reagent blank i.e. 6.8 phosphate buffer and the absorption spectrum was recorded. The absorption maximum (λmax) was observed at 237 and the absorbance of a series of solutions (1-30µg ml) was recorded at that λmax. A graph was plotted by taking the concentration of the drug solutions on the x-axis and the corresponding absorbance values on the y-axis.

5.3 Solubility enhancement of Paliperidone by Solid Dispersion

As we know that Paliperidone belongs from BCS class II which have low solubility. Therefore, Enhancement of solubility of Paliperidone was performing by solid dispersion method.

5.3.1 Preparation of Solid Dispersion of Paliperidone by Solvent Evaporation Method

Paliperidone and PEG 6000 were taken in ratio of 1:0.25, 1:0.5, 1:0.75, 1:1 and 1:1.25. The polymer was dissolved in an adequate amount of methanol. Then add Valsartan into the solution under continuous stirring. The solvent was then rapidly evaporated then sized into different sieve fractions and stored.

Table 4 Solid dispersion formulation of Paliperidone

Formulation Code	Drug : Carrier ratio
SD1	1:0.25
SD2	1:0.5
SD3	1:0.75
SD4	1:1
SD5	1:25

5.3.2Evaluation of Solid Dispersion of Paliperidone

- **Physical Appearance**

All the ratios of Paliperidone solid dispersions were evaluated for colour and appearance.

- **% Drug Content**

Equivalent to 10 mg of Paliperidone, powder taken and was accurately weighed and transferred to 100ml volumetric flask. Then the volume was completed up with, 6.8 phosphate buffer and shaken for 10 min to ensure complete solubility of the drug. after that the solution was filtered and filtrate was diluted suitably and assayed for drug content at 237 nm by using UV-Visible spectrophotometer.

- ***In vitro* dissolution study**

Solid dispersions were subjected to *in vitro* dissolution. Dissolution test was carried out using USP Paddle method [apparatus 2]. The stirring rate was 50 rpm, 6.8 phosphate buffer was used as dissolution medium and dissolution medium was37$\pm$1^{o}C maintained. Samples of 5 ml was reserved at usual intervals of time, filtered and replaced with 5 ml of fresh dissolution medium, dilutions were made and analysed for Valsartan at 237 nm by using UV-visible spectrophotometer.

5.4 Formulation of Paliperidone ODT:-

Paliperidone ODT tablets were prepared by direct compression.

→ Accurate quantities of all ingredients were weighed and passed through sieve no #40.
→ Add Drug and Diluent for mixing.
→ Add Sweetener and Disintegrants and Mix well.
→ Add glidant in above mixture and mix well.
→ Lubricate the above blend by adding magnesium stearate.

Table 5 Formulation of Batch F1-F15

Ingredients (mg)	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
Paliperidone SD (1:1)	3	3	3	3	3	3	3	3	3	3	3	3	3	**3**	3
CCS	2	4	6	8	10	-	-	-	-		-	-	-	**-**	-
SSG	-	-	-	-	-	2	4	6	8	10	-	-	-	**-**	-
Crospovidone	-	-	-	-	-	-	-	-	-	-	2	4	6	**8**	10
Sodium saccharine	6	6	6	6	6	6	6	6	6	6	6	6	6	**6**	6
Lactose DCL 11	32	30	28	26	24	32	30	28	26	24	32	30	28	26	24
PVP K30	4	4	4	4	4	4	4	4	4	4	4	4	4	**4**	4
MCC	50	50	50	50	50	50	50	50	50	50	50	50	50	**50**	50
Talc	2	2	2	2	2	2	2	2	2	2	2	2	2	**2**	2
Magnesium Stearate	1	1	1	1	1	1	1	1	1	1	1	1	1	**1**	1
Total Weight (mg)	**100**	**100**	**100**	**100**	**100**	**100**	**100**	**100**	**100**	**100**	**100**	**100**	**100**	**100**	**100**

- **3^2 Factorial Design for Optimization of Paliperidone ODT Formulation**

Factorial design is suitable for exploring quadratic response surface and constructing second order polynomial models. The design consists of replicated center points and the set of points lying at the midpoint of the multidimensional cube that defines the region of interest. This study investigated ODT's prepared by Direct compression method. Amounts of Crospovidone (X1) and PVP K30 (X2) were selected as the independent variables whereas Disintegration time and Drug release at 5 min were selected as dependent variables. Below table showed the composition and experimental runs as per factorial designs.

Table 6 Factorial batch composition of Paliperidone ODT Formulation

Batch	Coded Factors		Actual factors	
	X1	X2	X1	X2
P1	-1	-1	6	2
P2	-1	0	6	4
P3	-1	1	6	6
P4	0	-1	8	2
P5	0	0	8	4
P6	0	1	8	6
P7	1	-1	10	2
P8	1	0	10	4
P9	1	1	10	6

levels of 3^2 Full Factorial Designs			
Independent Factors	Levels		
	Low (-1)	Medium (0)	High (1)
X1= Amount of Crospovidone (mg)	6	8	10
X2= Amount of PVP K30*(mg)*	2	4	6

Ingredients/Tablet	P1	P2	P3	P4	P5	P6	P7	P8	P9
Paliperidone SD (1:1)	3	3	3	3	3	3	3	3	3
Crospovidone	6	6	6	8	8	8	10	10	10
PVP K30	2	4	6	2	4	6	2	4	6
Sodium saccharine	6	6	6	6	6	6	6	6	6
Lactose DCL 11	30	28	26	28	26	24	26	24	22
MCC	50	50	50	50	50	50	50	50	50
Talc	2	2	2	2	2	2	2	2	2
Magnesium Stearate	1	1	1	1	1	1	1	1	1
Total Weight (mg)	**100**	**100**	**100**	**100**	**100**	**100**	**100**	**100**	**100**

5.5 Post-compression parameters [23, 24, 25]

5.5.1 Weight variation

Twenty tablets were randomly selected and individually weighed. The average weight of tablets was calculated. Then the individual weight was compared with that of average weight and the amount of weight variation was determined.

5.5.2 Thickness

Tablet thickness can be measured using a simple procedure. Five tablets were taken and their thickness was measured using Vernier calipers. The thickness was measured by placing tablet between two arms of the Vanier calipers.

5.5.3 Hardness

The tablets to be tested are held between a fixed and a moving jaw of hardness test apparatus (Monsanto) and reading of the indicator is adjusted to zero. The screw knob was moved forward until the tablet breaks and the force required for breaking the tablet was noted.

5.5.4 Friability

Friability test was performed by using Roche friabilator. Ten tablets were weighed and placed in the friabilator, which was then operated for 25 revolutions per minute. After four minutes (100 revolutions) the tablets were dusted and reweighed. The percentage friability was determined using the formula,

Percentage friability = Initial weight - Final weight × 100/ Initial weight

5.5.5 Wetting time and water absorption ratio

Wetting time is closely related to the inner structure of the tablets and hydrophilicity of the excipients. A piece of tissue paper, folded double, was placed in a Petri plate containing 6 ml of distilled water. A pre weighed tablet was placed on the paper and the time for complete wetting of the tablet was measured. The wetted tablet was then taken out and weighed. Water absorption ratio of this tablet was determined by using the formula,

$R = (W_a - W_b) / W_a \times 100$

Where,

R = Water absorption ratio

W_a= Weight of tablet after wetting. W_b= Weight of tablet before wetting.

5.5.6 Estimation of drug Content

Ten tablets from each formulation were weighed individually and powdered. The Powder equivalent to 1.5 mg of Paliperidone was weighed and dissolved in 20 ml of 6.8 phosphate buffer and the volume was adjusted to 100 ml with 6.8 pH phosphate buffer. From this solution 1 ml was taken and made up to 100 ml using 6.8 pH phosphate buffer and the solution was analyzed at 237 nm by UV–visible spectrophotometer using 6.8 pH phosphate buffer as the blank.

5.5.7*In-vitro* disintegration time

The test was carried out in a disintegration test apparatus using distilled water (at 37 ºC ± 0.5 ºC) as disintegration medium. A tablet was placed in each of six tubes of the apparatus and one disc was added to each tube. The time taken for complete disintegration of the tablet with no mass remaining in the apparatus was measured.

5.5.8*In-vitro* drug release

In-vitro dissolution studies for all the formulated tablets of Paliperidone was carried out using USP II paddle method at 50 rpm in 900 ml of pH 6.8 buffer solution as a dissolution medium. The dissolution medium was maintained at 37±0.5 ºC.10ml of sample was withdrawn at 5 minutes intervals of time. 10 ml of buffer solution (pH 6.8) was replaced to maintain the constant volume throughout the experiment. The samples were suitably diluted and the percentage of drug released from each formulation was measured at 237 nm using UV–visible spectrophotometer.

5.5.9StabilityStudies

The stability test was carried out to evaluate the stability of Paliperidone in formulations. The prepared tablets were kept at 40 ºC ± 2 ºC, 75% RH for 30 days. Every 15 days interval, the tablets were evaluated for drug content, disintegration time and in-vitro drug release studies

6. RESULTS AND DISCUSSION

6.1 CHARACTERIZATION OF PALIPERIDONE API

Table 7 Characterization of Drug (Paliperidone)

Sr. No.	Characteristic Properties		Observation/Result
1	Organoleptic Characteristics	Colour	White to light yellow Powder
		Odour	Odorless
2	Flow Properties	Bulk density (g /ml)	0.278
		Tapped density (g /ml)	0.502
		Carr's index (%)	44.24
		Hausner's ratio	1.805
		Angle of repose (θ°)	48.12º
3	Solubility	Water	0.039 ± 0.012 mg/ml
		Phosphate buffer solution pH 6.8	0.410 ±0.100 mg/ml
4	Melting Point		181.2 °C

Based on above physical characterization of API it concluded that the API has a very poor flow itself so granular grade diluents need to be used for direct compression. Further solubility of drug is sufficient for ODT Formulation point of view. Melting point matches with the reference data which confirms the purity of drug.

Additionally the API having a BCS class II molecule so Water solubility was low hence solubility enhancement is required to improve the solubility.

6.2 DRUG EXCIPIENT COMPATIBILITY STUDY

FTIR Study of Pure drug Paliperidone and Physical mixture of all excipients with drug done and results attached in below figure 1 and 2. From the below results it concluded that no any interaction found between drug and Excipients.

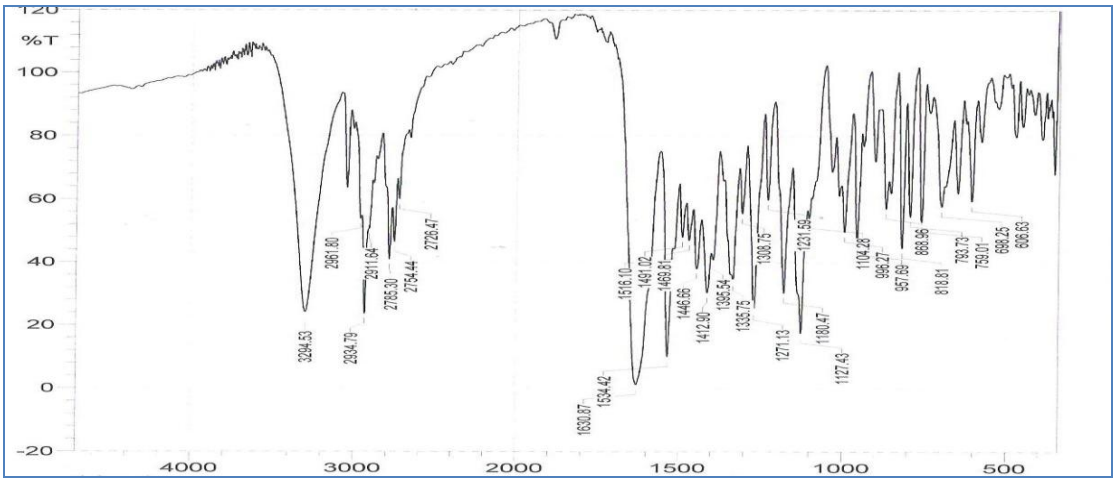


Figure 1 FTIR Spectra of Pure Drug Paliperidone

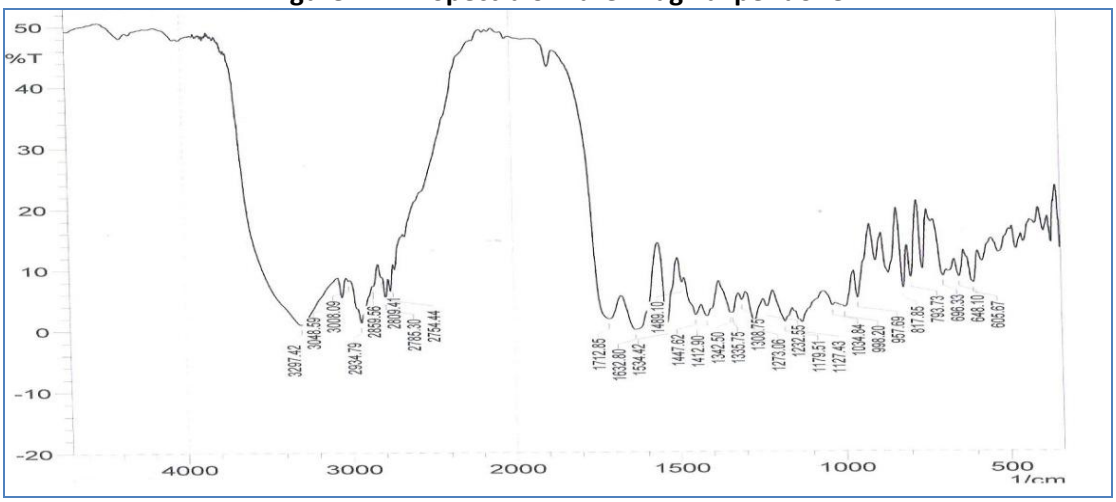


Figure 2 FTIR Spectra of Physical Mixture

Table 8 FTIR Data of Paliperidone and Physical Mixture

Stretching	Pure Drug Peak (cm^{-1})	Physical Mixture Peak (cm^{-1})
O-H stretch	3294.53	3297.42
C-H stretch	2934.79	2934.79
C=C stretch	1632.80	1630.87
C=N stretch	1534.42	1534.42
C-F stretch	1127.43	1127.43

DSC Study of Pure drug Paliperidone and Physical mixture with drug performed and results attached in below figure 3 and 4. From the below results it concluded that no any interaction found between drug and Excipients. Pure API melting point observed at 181.2 °C and Physical Mixture melting point observed at182.64 °C. That means the drug remains its melting property in physical mixture also.

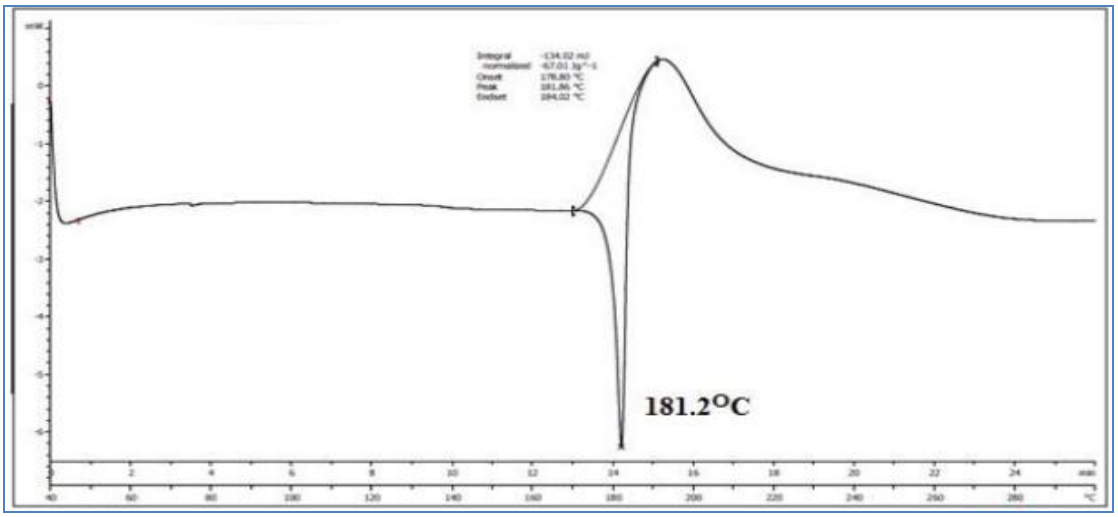


Figure 3 DSC Spectra of Pure Drug Paliperidone

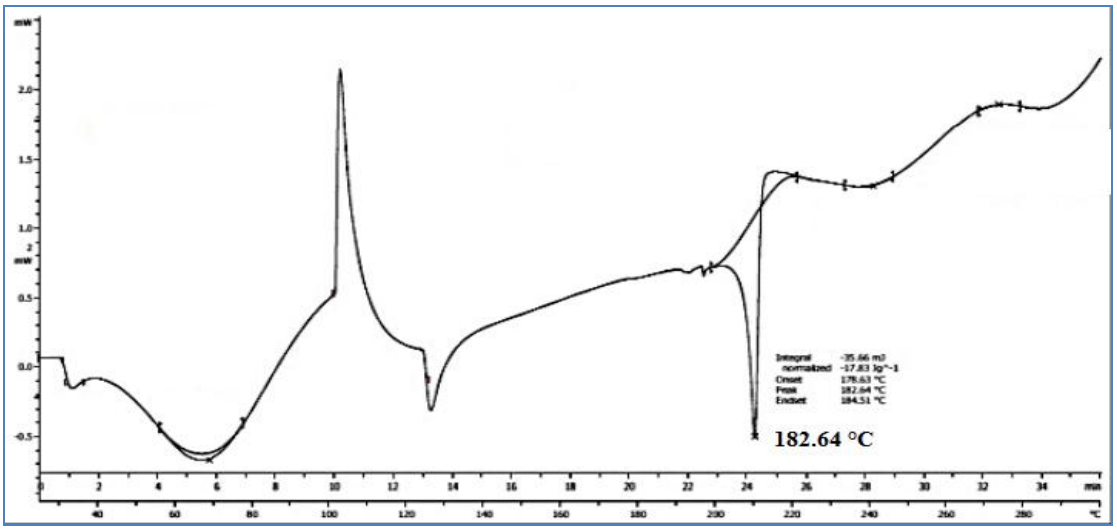


Figure 4 DSC Spectra of Physical Mixture

6.3 CALIBRATION CURVE OF PALIPERIDONE

The Paliperidone showed λmax in buffer (pH 6.8) at 237.04 nm and 276.95 nm (Fig. 5). Among these two wavelengths, 237 nm was used as a wavelength for Calibration Curve preparation.

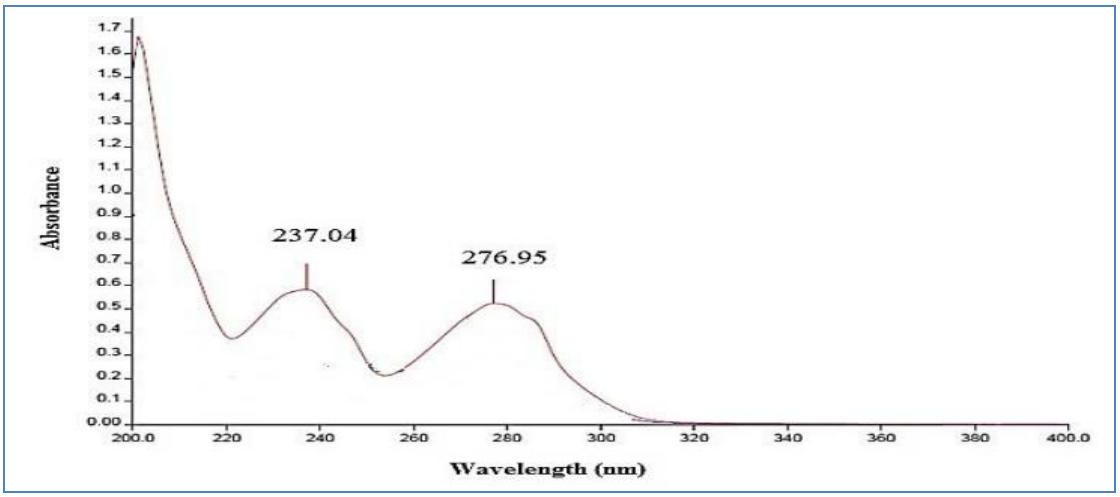


Figure 5 λmax of Paliperidone

The standard curve of Paliperidone in is depicted in Fig. 6. The intercept, slope and regression coefficient (R^2) were found to be 0.0030 and 0.999, respectively.

Table 9 Calibration curve of Paliperidone in 6.8 Phosphate buffer at 237 nm

Sr. No	Concentration (µg/ml)	Absorbance ± SD(n=3)
1	0	0
2	5	0.156 ± 0.002
3	10	0.305 ± 0.008
4	15	0.448 ± 0.002
5	20	0.605 ± 0.003
6	25	0.753 ± 0.001
7	30	0.912 ± 0.004

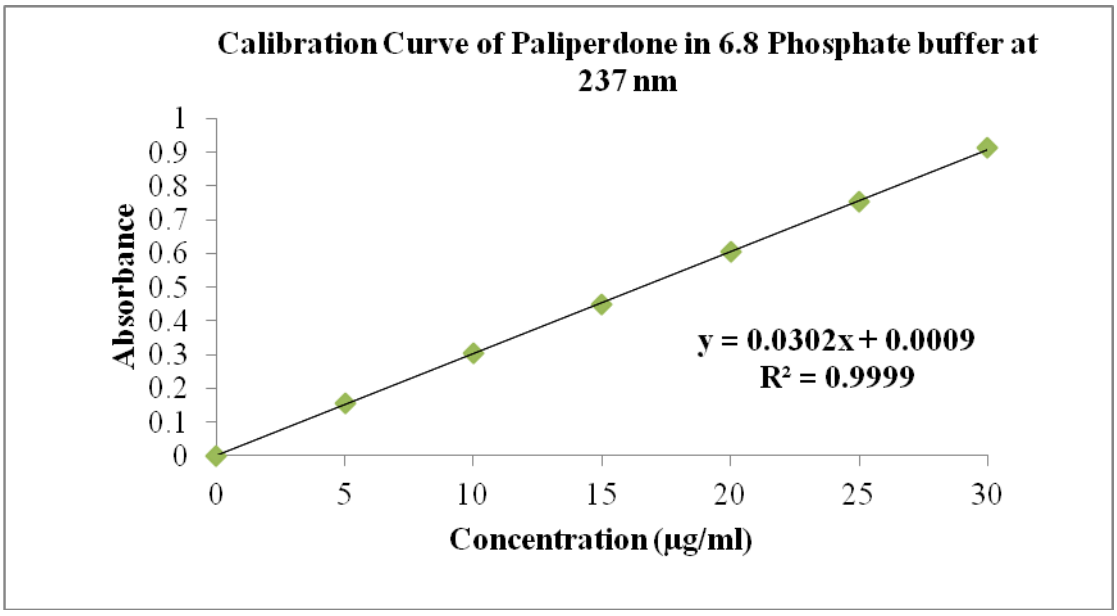


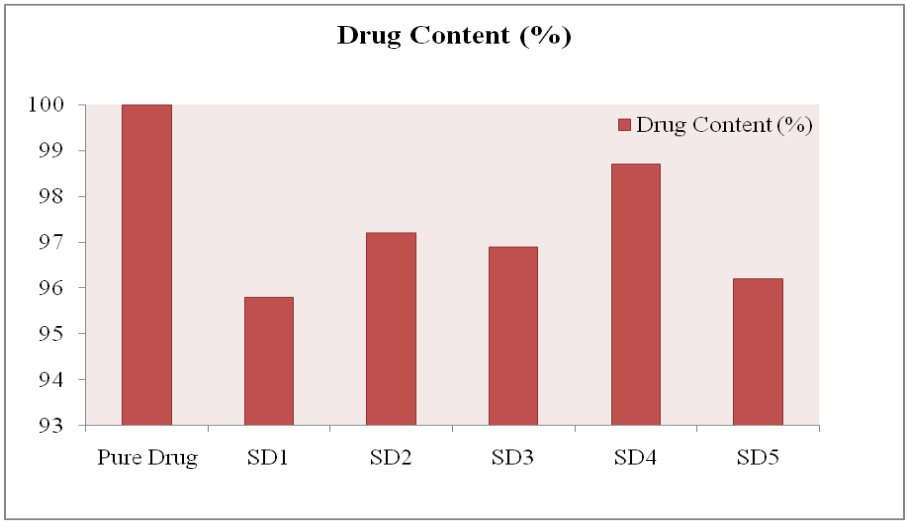
Figure 6 Calibration curve of Paliperidone in 6.8 Phosphate buffer at 237 nm

6.4 EVALUATION OF SOLID DISPERSION OF PALIPERIDONE WITH PEG 6000

Table 10 Evaluation Parameters of Paliperidone Solid Dispersion

Sr. No.	Ratios of solid dispersion	Colour	% Drug content (n=3)	Solubility in water (mg/ml) (n=3)
1.	Pure Drug	White powder	100 %	0.039 ± 0.012
2.	SD1		95.8 ± 0.6	0.052± 0.045

3.	SD2		97.2 ± 0.7	0.084± 0.035
4.	SD3		96.9 ± 0.5	0.235±0.102
5.	**SD4**		**98.7 ± 0.3**	**0.953 ±0.199**
6.	SD5		96.2 ± 0.9	0.901± 0.116



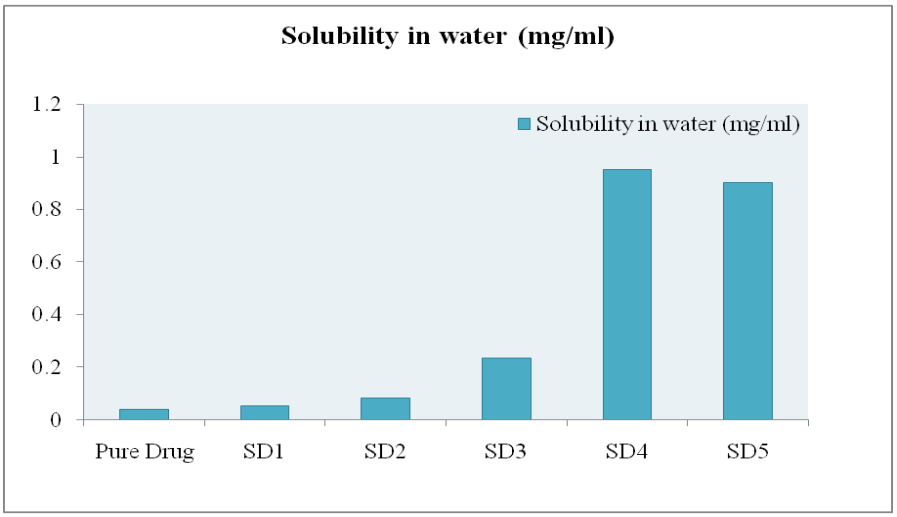


Figure 7 Drug content and solubility comparison of Paliperidone Solid Dispersion

Table 11 Drug release study of Paliperidone Solid Dispersion

Ratios of solid dispersions	**% Drug Release in minutes**			
	5	**10**	**15**	**30**
Pure Drug	4.9 ± 0.6	9.2 ± 0.5	15.8± 0.9	21.4 ± 0.4
SD1	14.8± 0.5	29.7± 0.5	37.6± 0.5	48.2± 0.5
SD2	15.8± 0.5	31.4± 0.3	35.7± 0.3	62.3± 0.7
SD3	19.7± 0.8	37.1± 0.5	48.7± 0.7	74.2± 0.5
SD4	**26.9 ± 0.4**	**50.1± 0.5**	**71.9 ± 0.6**	**86.5 ± 0.9**
SD5	20.7± 0.4	49.5 ± 0.7	69.7± 0.4	84.2 ± 0.9

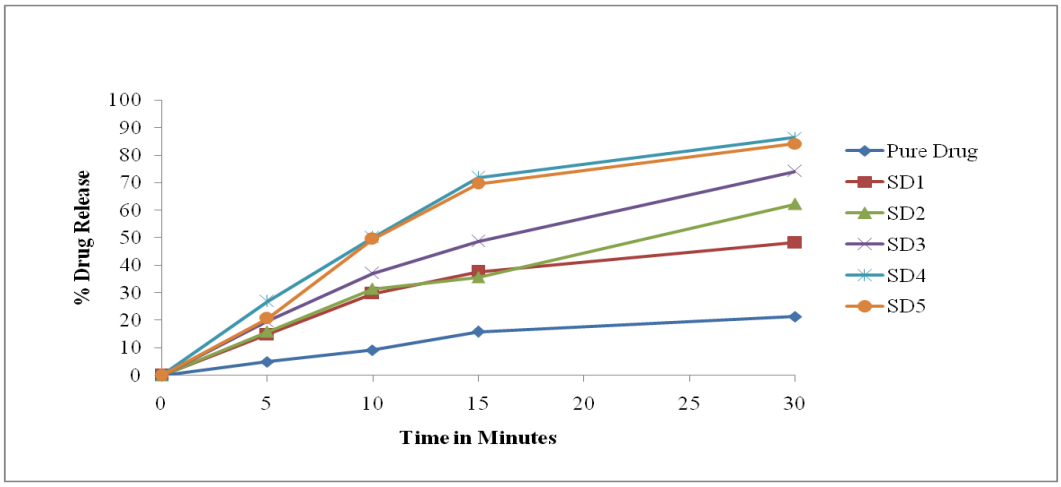


Figure 8 Drug release study of Paliperidone Solid Dispersion

Evaluation parameters of Paliperidone solid dispersion checked and concluded that in all ratio solid dispersion, white colour mixture obtained which have drug content range 95.8%-98.7%.Dissolution rate profile of intact Paliperidone and solid dispersions are shown in figure no. 8. It is obvious from the figure that all solid dispersions of Paliperidone showed superior dissolution rate compared with intact Paliperidone. Solid dispersions of Paliperidone with PEG 6000 in different ratios showed a marked enhancement in the drug dissolution rate, in which about 48%-84% of the incorporated Paliperidone was dissolved within the first 30 minutes from solid dispersions. Also the dissolution data shows that compare to pure drug and others ratios, 1:1 ratio of Paliperidone and PEG 6000 give satisfactory drug release which one is desirable for further formulation development. So it was concluded that 1:1 ratio of solid dispersion was optimized for further development. This study clearly shows that solid dispersion of Paliperidone and PEG 6000prepared successfully improved the dissolution rate compared with intact Paliperidone and PEG 6000.

6.5 EVALUATION OF FORMULATION F1-F15

6.5.1 Pre Compression Parameters:

Results of pre compression parameters evaluated were within limits and indicated good free flowing property which is described in table12.

Table 12 Pre Compression Parameters of F1-F15 formulation

Formulation	Bulk density (g/ml)	Tapped density (g/ml)	Carr's index (%)	Hausner's ratio	Angle of repose (Θ)
F1	0.438±0.02	0.524±0.05	16.41	1.20	23.48±0.16
F2	0.492±0.06	0.593±0.06	17.03	1.21	22.59±0.14
F3	0.468±0.03	0.508±0.04	7.87	1.08	22.98±0.17
F4	0.505±0.04	0.583±0.08	13.55	1.16	23.67±0.14
F5	0.408±0.06	0.496±0.07	17.74	1.22	24.87±0.12
F6	0.396±0.05	0.492±0.04	19.51	1.24	23.68±0.16

F7	0.487±0.02	0.526±0.06	7.38	1.08	24.59±0.18
F8	0.542±0.07	0.598±0.04	9.36	1.10	23.61±0.14
F9	0.473±0.03	0.529±0.06	10.58	1.12	24.05±0.15
F10	0.479±0.04	0.521±0.05	8.06	1.09	23.13±0.17
F11	0.488±0.05	0.563±0.09	15.36	1.15	21.23±0.14
F12	0.439±0.06	0.531±0.02	20.95	1.21	20.19±0.20
F13	0.481±0.06	0.568±0.04	18.08	1.18	24.34±0.15
F14	**0.465±0.07**	**0.549±0.06**	**18.06**	**1.18**	**22.32±0.12**
F15	0.473±0.08	0.523±0.09	10.57	1.11	21.56±0.18

6.5.2 Post Compression Parameters:

- Tablets were evaluated for weight variation test, hardness, friability, wetting time, water absorption test, drug content, disintegration test. Results were illustrated in table 13& 14.

- Hardness of all tables was between 1.0 – 2.9 Kg/cm^2 while friability below 1% showed that all tablets have good mechanical strength. Disintegration time of all tablets was observed within fraction of seconds. Table 14.

- All formulations containing Crospovidone as super disintegrants showed highest water absorption ratio. It was found that formulation containing Crospovidone (8 % w/w); disintegration time was significantly with single use of super disintegrants compared to rest of formulations. Table 14.

Table 13 Results of post compression parameters

Formulation	Weight variation (mg)	Hardness (Kg/cm^2)	ability	Thickness (mm)
F1	102 ± 2	2.9±0.5	0.49±0.04	3.11 ±0.04
F2	103 ± 1	2.5±0.6	0.51±0.05	3.12 ±0.05
F3	101 ± 4	2.0±0.7	0.52±0.06	3.10 ±0.04
F4	102 ± 3	1.3±0.8	0.85±0.04	3.12 ±0.03
F5	101 ± 2	1.0±0.2	0.91±0.08	3.13 ±0.07
F6	99 ± 2	2.8±0.7	0.48±0.04	3.12 ±0.06
F7	98 ± 1	2.5±0.8	0.53±0.05	3.11 ±0.04

F8	101 ± 2	2.2±0.4	0.78±0.06	3.11 ±0.03
F9	99 ± 1	1.8±0.9	0.95±0.03	3.10 ±0.02
F10	100 ± 3	1.7±0.5	0.98±0.06	3.12 ±0.07
F11	102 ± 4	2.2±0.6	0.59±0.04	3.11 ±0.08
F12	98 ± 5	2.1±0.8	0.62±0.05	3.11 ±0.06
F13	102 ± 1	1.2±0.7	0.92±0.06	3.10 ±0.04
F14	**101 ± 3**	**2.3±0.6**	**0.82±0.04**	**3.12 ±0.05**
F15	102 ± 4	2.5±0.5	0.74±0.06	3.11 ±0.03

Table 14 Results of post compression parameters

Formulation	etting time (sec)	Water absorption ratio	Drug content (%)	Disintegration time (sec)
F1	98±0.65	12.4±0.34	98.7±1.5	186±1.0
F2	74±0.43	13.15±0.28	98.5±1.4	168±0.3
F3	61±0.56	16.52±0.36	97.3±1.2	136±0.8
F4	48±0.38	19.45±0.38	99.4±1.6	114±0.9
F5	42±0.72	25.24±0.41	99.7±1.2	98±0.6
F6	54±0.49	15.33±0.45	98.5±1.4	174±0.8
F7	38±0.56	19.21±0.39	99.4±1.1	142±0.6
F8	32±0.82	21.28±0.42	98.2±1.4	126±0.8
F9	22±0.75	26.27±0.37	98.1±1.2	116±0.7
F10	20±0.62	29.16±0.44	99.9±1.4	92±0.6
F11	68±0.58	14.19±0.41	98.2±1.6	126±0.6
F12	44±0.62	22.44±0.40	99.2±1.3	118±0.5
F13	34±0.64	29.71±0.43	98.2±1.6	97±0.8

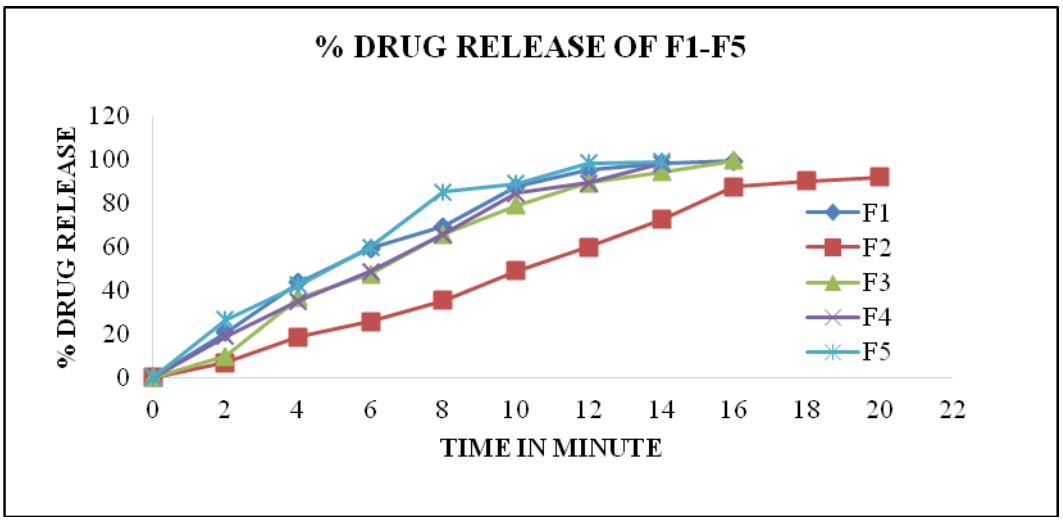
F14	**36±0.74**	**30.42±0.28**	**99.2±1.5**	**45±0.6**
F15	48±0.81	28.54±0.32	99.5±1.8	86±0.5

6.5.3 *In-vitro* drug release study of Paliperidone ODT tablet

The *in-vitro* drug release characteristics of Paliperidone tablets were studied in phosphate buffer PH 6.8 dissolution medium for a period of 20 to 25 minutes using USP type-II paddle type dissolution apparatus. The rate of dissolution increased by increasing the concentration of super disintegrant. Formulation F14 having super disintegrants concentration of 8 % Crospovidone release the drug within 10 minutes. Combination of MCC with disintegrants worked good as diluents so it was used in all the formulations.

Table 15 % Drug Release of formulation F1-F15

Time (min)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13	F14	F15
0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
2	20.6	6.9	9.8	18.9	26.4	10.5	12.5	15.7	20.5	19.4	12.5	15.4	10.6	**18.5**	16.5
4	43.5	18.5	36.5	35.2	42.5	15.8	19.7	29.4	32.5	29.1	20.9	34.5	48.2	**35.6**	23.5
6	59.4	25.6	47.6	48.8	59.8	23.5	26.4	36.4	40.2	35.4	35.8	45.8	56.4	**46.9**	48.5
8	69.4	35.4	65.9	65.9	85.14	29.5	39.7	49.7	51.9	44.1	48.9	79.8	64.2	**70.5**	65.9
10	87.5	48.9	78.9	84.5	89.15	39.7	48.1	61.4	65.4	59.4	65.87	87.8	70.4	**99.2**	80.5
12	95.2	59.8	89.5	89.5	98.4	45.7	65.5	78.9	73.1	63.4	78.5	89.5	75.8	-	91.6
14	98.5	72.5	94.5	98.1	99.2	72.1	72.6	89.4	84.7	69.4	88.12	94.5	82.3	-	98.7
16	99.4	87.6	99.8	-	-	79.8	79.4	96.5	89.4	88.9	95.1	96.2	88.9	-	-
18	-	90.1	-	-	-	82.3	87.2	97.4	94.2	95.2	97.4	-	91.7	-	-
20	-	92.1	-	-	-	89.4	92.5	99.1	99.1	99.7	98.9	-	95.2	-	-



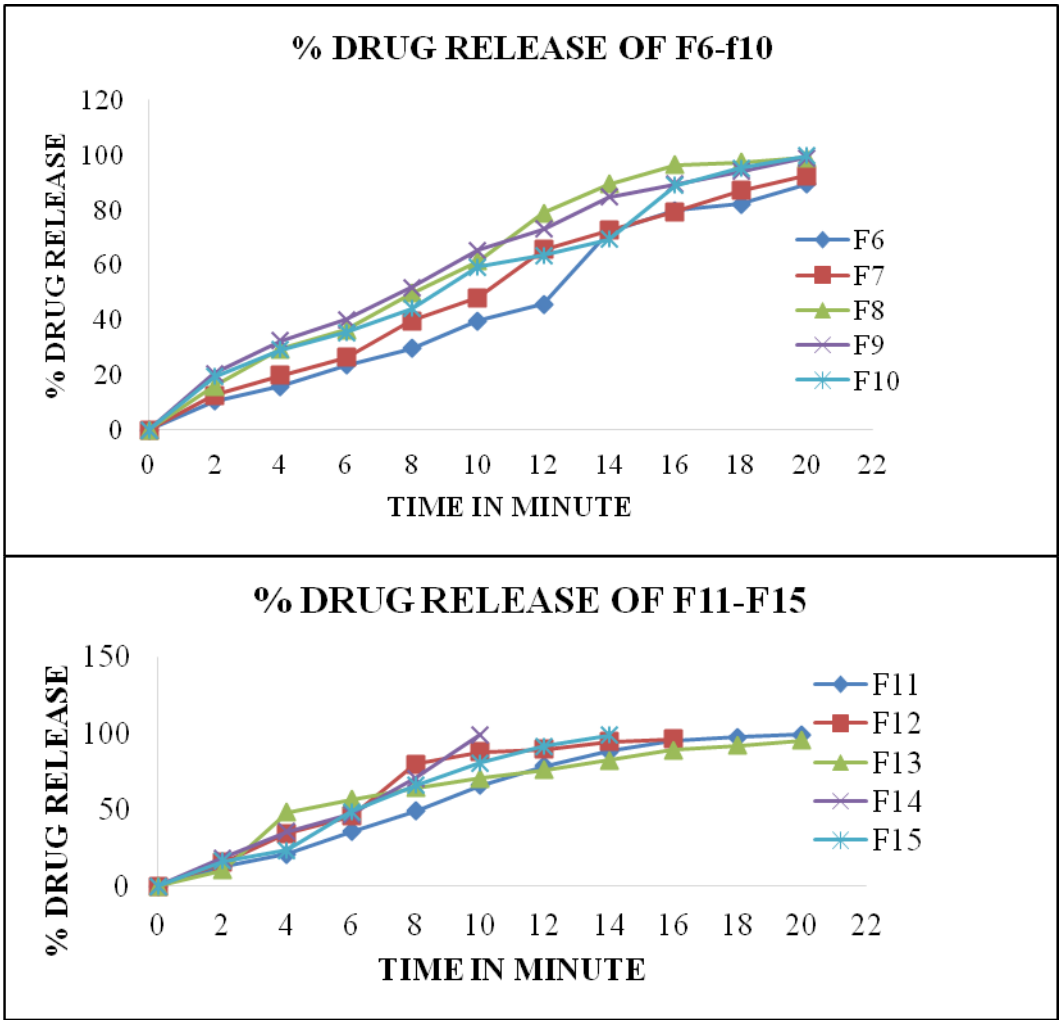


Figure 9 % Drug release study of formulation F1-F15

6.6 EVALUATION OF FACTORIAL BATCHES P1-P9

Based on trial batches results two factors were selected for application of factorial design. There two factors were disintegrants and binder. F14 formulation was found good among all the formulation from trial batches. In F14 formulation disintegrants was Crospovidone and binder was PVP K30. Hence these two factors in different range selected for further screening. The main parameters of ODT formulation, Disintegration time and Drug release study (at 6 min) were further checked. Evaluation of factorial batches was done same as per trial batches evaluation parameters and the results were tabulated in below table.

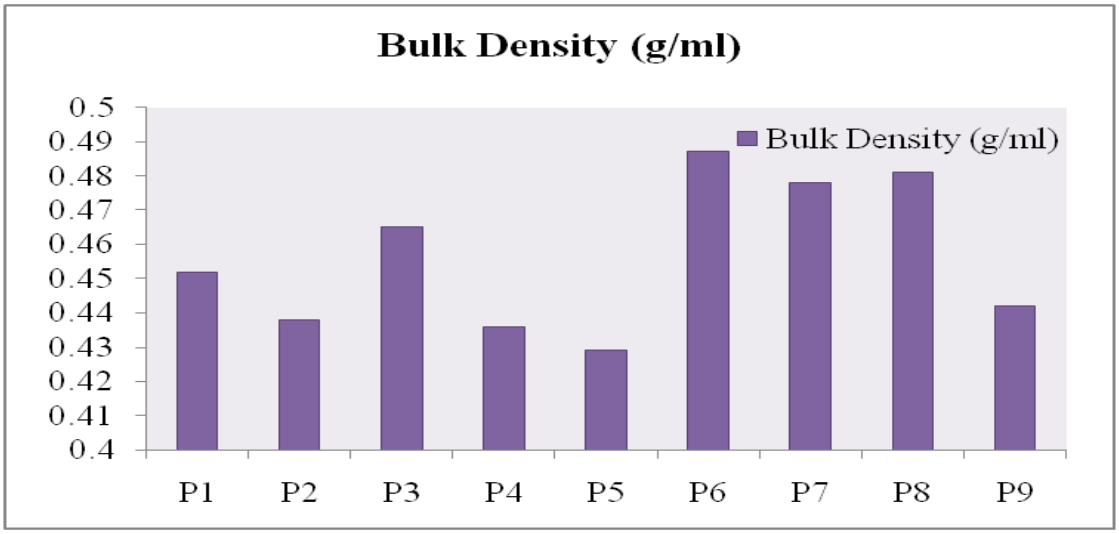
6.6.1 Pre Compression Parameters of factorial batches:

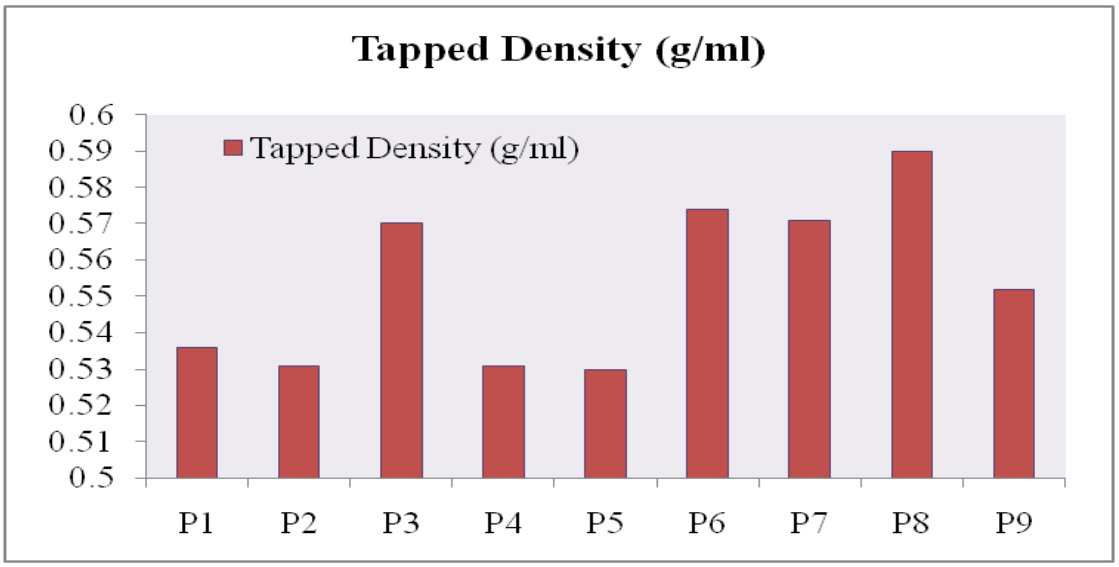
Pre compression parameters of factorial batches were checked to confirm the flow properties and the results were recorded in below table 16. From the Results of pre compression parameters it can concluded that the blend flow was good enough to help the compression.

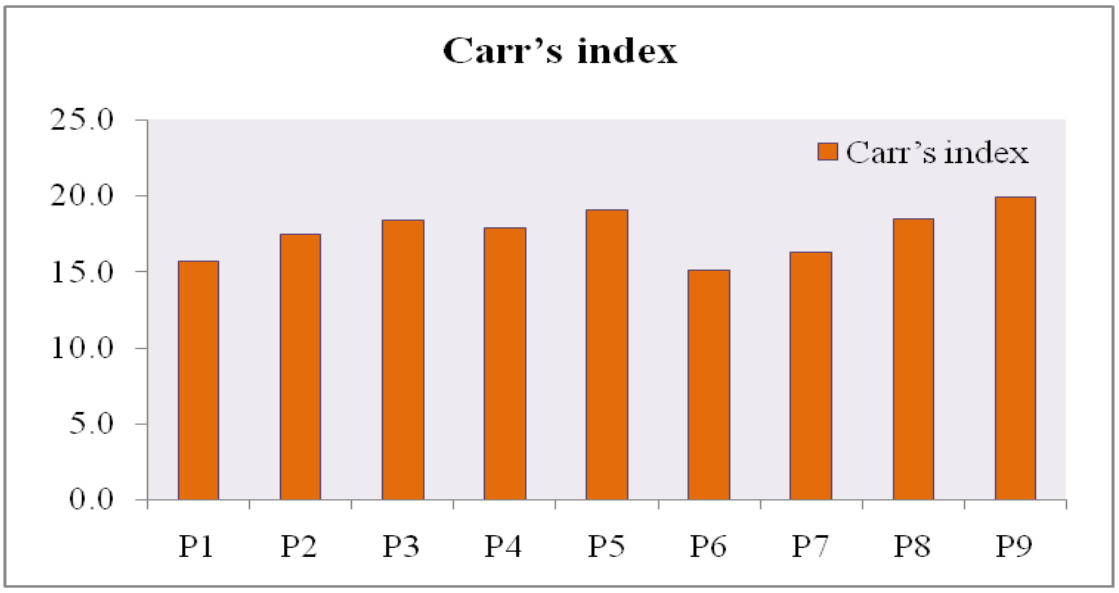
Table 15 Pre Compression Parameters of factorial batches P1-P9

Formulation	Bulk density (g/ml)	Tapped density (g/ml)	Carr's index (%)	Hausner's ratio	Angle of repose (Θ)
P1	0.452±0.05	0.536±0.05	15.67	1.19	24.5±1.2

P2	0.438±0.09	0.531±0.01	17.51	1.21	27.6±2.3
P3	0.465±0.04	0.570±0.06	18.42	1.23	24.9±1.8
P4	0.436±0.07	0.531±0.02	17.89	1.22	23.8±2.1
P5	0.429±0.06	0.530±0.08	19.06	1.24	29.4±2.3
P6	0.487±0.04	0.574±0.08	15.16	1.18	24.6±1.8
P7	0.478±0.05	0.571±0.06	16.29	1.19	23.9±1.7
P8	0.481±0.06	0.590±0.04	18.47	1.23	31.5±3.1
P9	0.442±0.08	0.552±0.03	19.93	1.25	24.3±1.5






Carr's index
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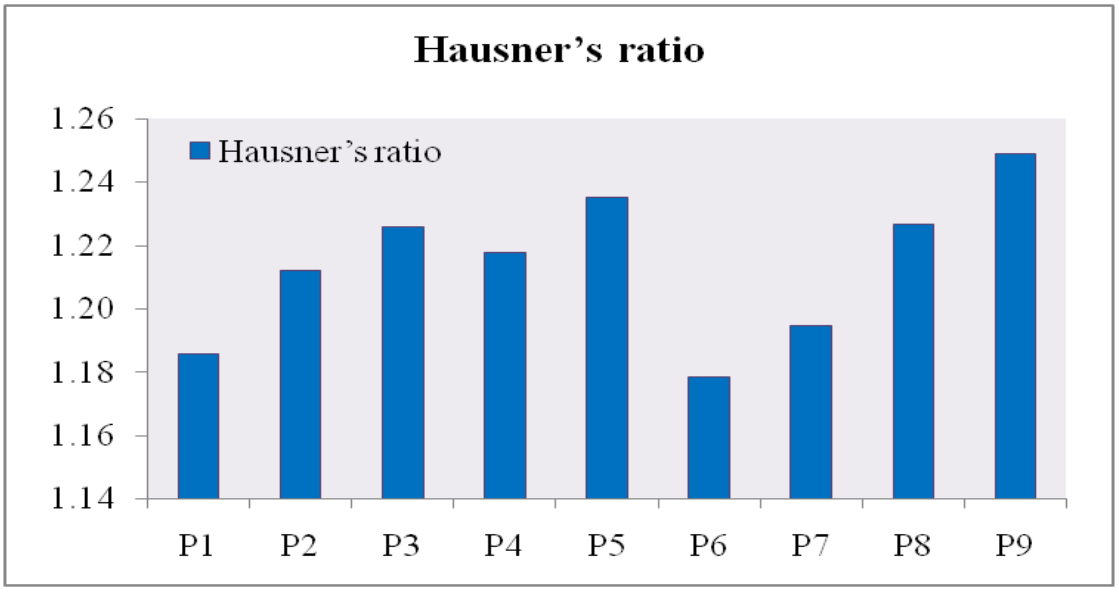
20.0
15.0
10.0
5.0
0.0
Carr's index
P1
P2
P3
P4
P5
P6
P7
P8
P9


Hausner's ratio
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1.24
1.22
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1.14
Hausner's ratio
P1
P2
P3
P4
P5
P6
P7
P8
P9

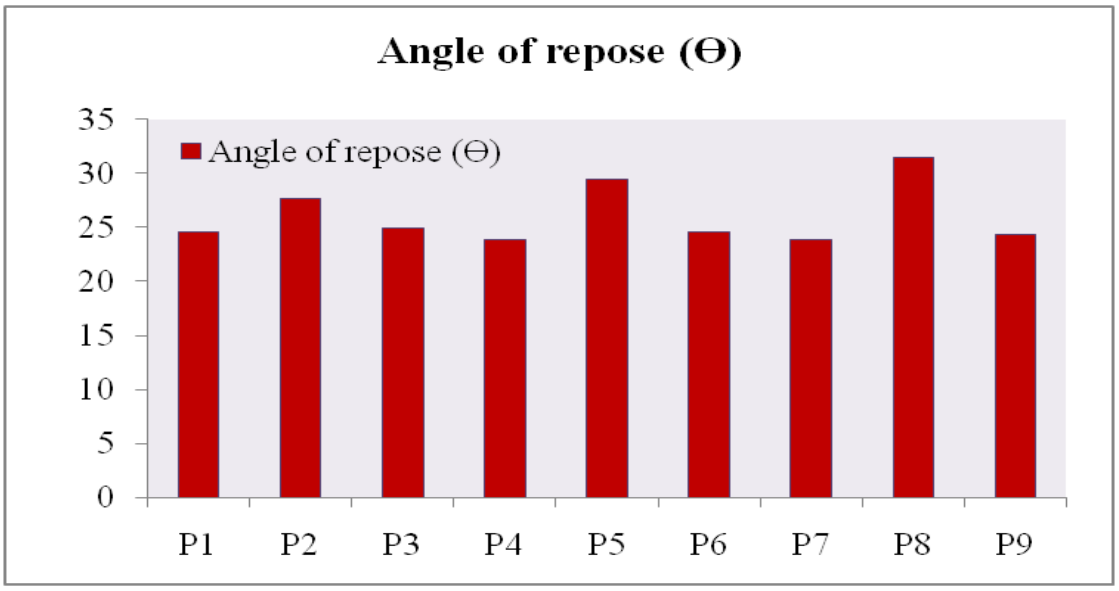


Figure 9 Pre compression evaluation of factorial batches P1-P9

6.6.2 Post Compression Parameters:

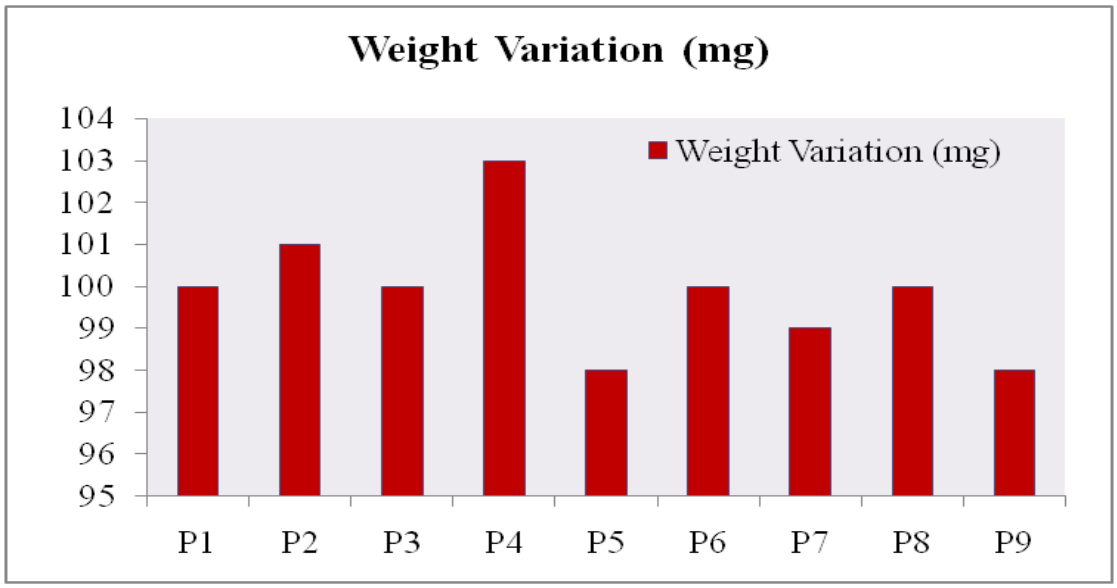
After completion of pre compression parameters evaluation the blend of each batch was compressed using rotary compression machine. Tablets were subjected for post evaluation parameters like weight variation test, thickness, hardness, friability, wetting time, water absorption test, drug content, disintegration test and dissolution. The results were recorded for all the evaluation parameters and tabulated below.

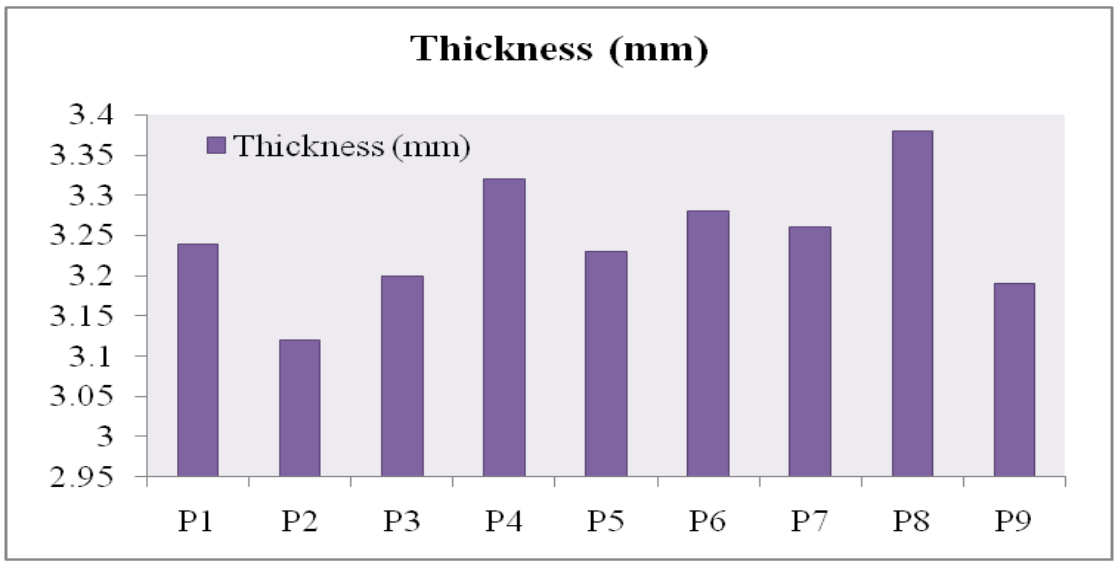
Based on the results, weight variation was found well within weight variation limit as per pharmacopeia. All batches pass the weight variation test. Thickness of formulation P1-P9 found uniform in all batches. Hardness was found good enough and pass the friability test. The friability was below 1 in all formulation batches.

Table 16 Pre Compression Parameters of factorial batches P1-P9

Formulation	Weight variation (mg)	Thickness (mm)	Hardness (Kg/cm^2)	ability
P1	100 ± 1	3.24 ±0.09	2.8±0.8	0.53±0.03
P2	101 ± 2	3.12 ±0.07	2.5±0.5	0.41±0.04
P3	100 ± 2	3.20 ±0.08	2.6±0.6	0.45±0.02
P4	**103 ± 3**	**3.32 ±0.06**	**2.7±0.5**	**0.60±0.04**
P5	98 ± 2	3.23 ±0.07	2.5±0.6	0.84±0.09
P6	100 ± 1	3.28 ±0.05	2.9±0.7	0.40±0.03

P7	99 ± 3	3.26 ±0.03	2.5±0.9	0.45±0.04
P8	100 ± 1	3.38 ±0.08	2.6±0.2	0.30±0.02
P9	98 ± 2	3.19 ±0.09	2.8±0.9	0.40±0.03





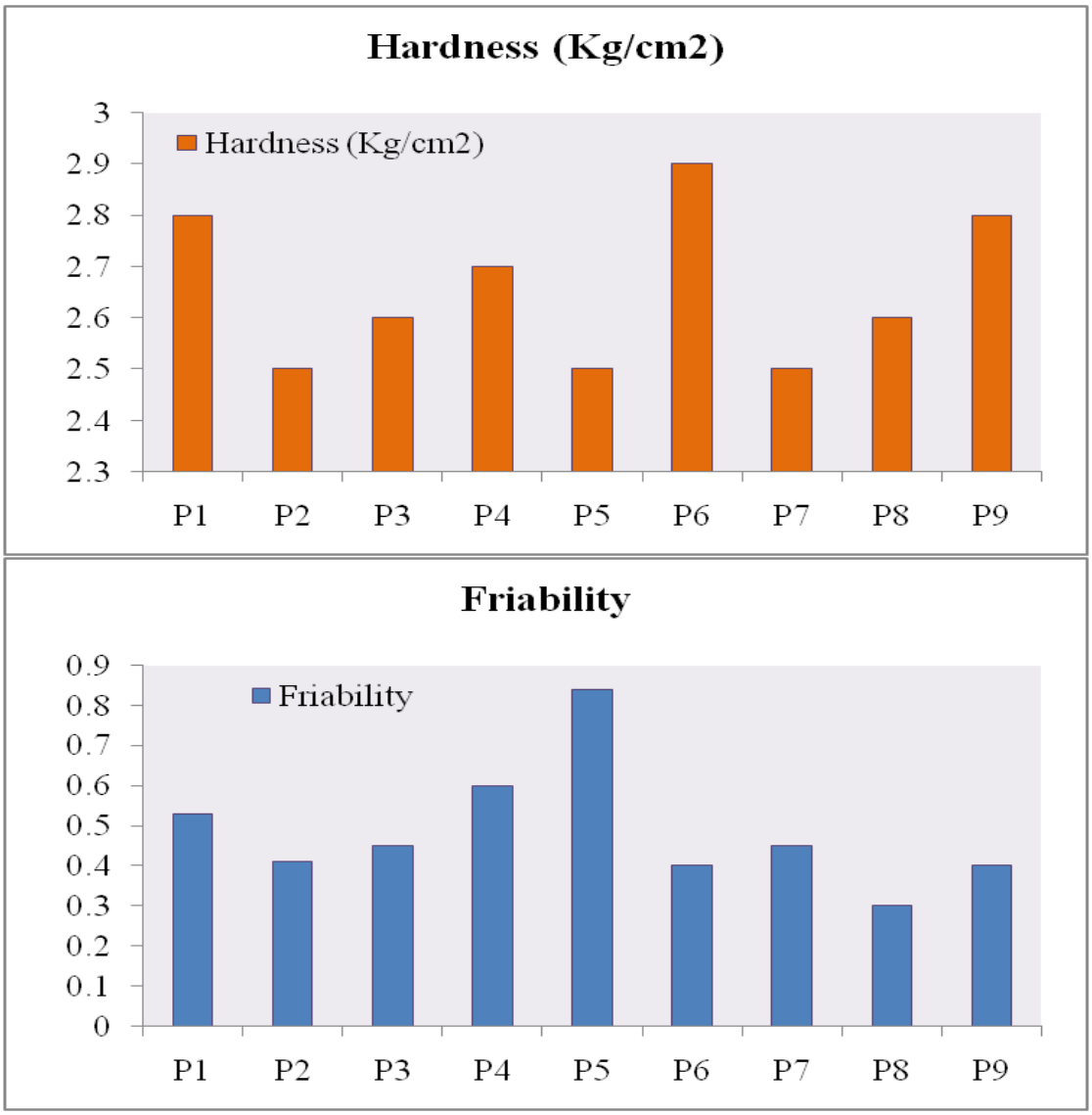


Figure 10 Evaluation Parameters of factorial batches P1-P9

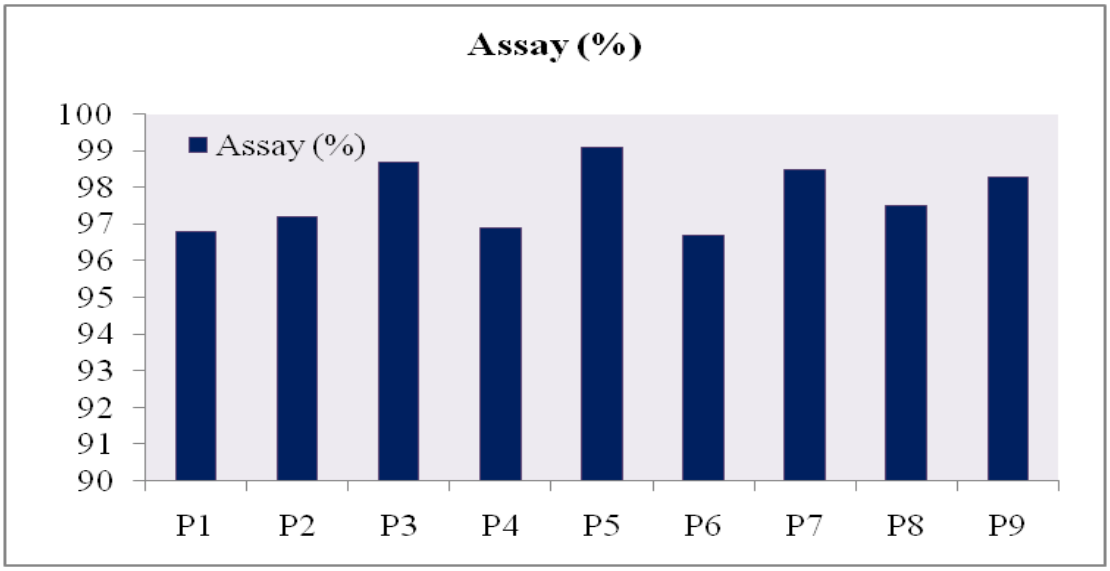
Assay (Drug content %) of factorial batches checked and found well within acceptable limit. Water absorption ratio also calculated and recorded below. As the MCC was in formulation, the ration was good in all batches. Wetting time and Disintegration time both parameters was important for ODT formulation. Both the parameters were evaluated and recorded in below table.

Table 17 Results of post compression parameters

Formulation	Drug content (%)	Water absorption ratio (%)	etting time (sec)	Disintegration time (sec)
P1	96.8 ± 2.6	29.5 ± 3.25	41± 3.5	89± 3.1
P2	97.2 ±1.9	23.8 ± 6.50	49± 2.6	96± 3.6
P3	98.7 ±1.8	21.5 ± 3.56	60± 3.1	109± 1.5

P4	**96.9 ± 2.5**	**22.6 ± 2.20**	**20 ± 1.9**	**33 ± 4.5**
P5	99.1 ± 0.8	19.2 ± 1.96	34± 2.6	49± 3.9
P6	96.7 ± 3.5	17.8 ± 6.16	50± 1.2	65± 1.5
P7	98.5 ±1.8	26.4 ± 2.35	41± 4.6	49± 2.8
P8	97.5 ± 2.5	24.1 ± 5.10	44± 2.7	55± 2.4
P9	98.3 ± 3.9	20.9 ± 4.21	52± 4.1	70± 3.9

The results of Disintegration time reveal that the amount of Crospovidone was significantly effects on DT times. It also shows that the amount of Crospovidone in formulation was optimum impact up to 8 mg. after that the DT time was increased. The P4 batch among all batches, less DT time which contains 8 mg of Crospovidone and 2 mg of binder. Hence it conclude that the lesser the binder DT was fast. Also the lower amount of Crospovidone and higher amount of binder gives longer DT. Wetting time was within 1 min in all formulation. It just because of the formulation has a microcrystalline cellulose and lactose which was good candidate to absorb the water in tablet. Formulation wise comparison in graphical form also given below



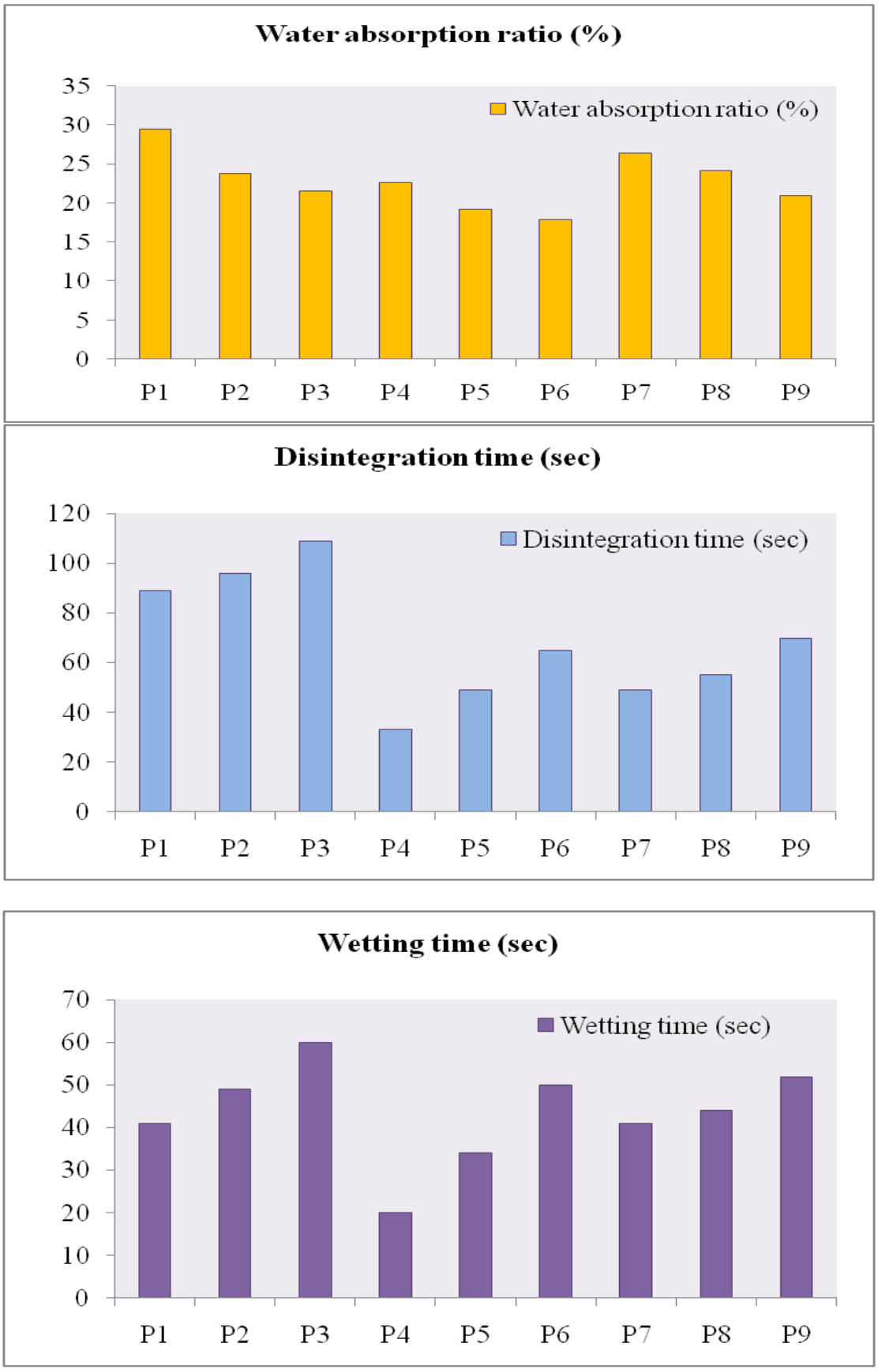


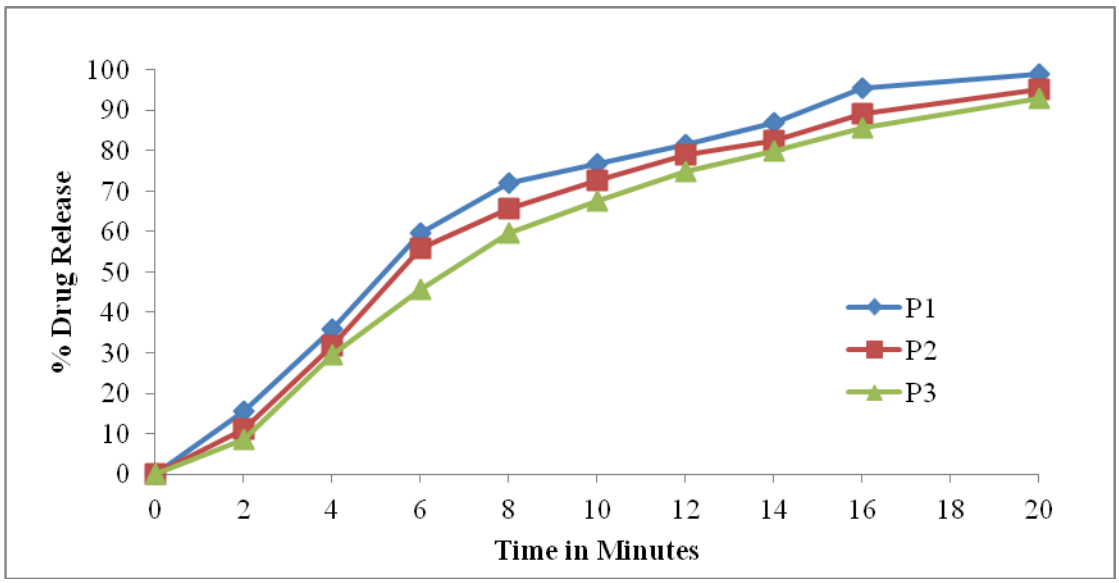
Figure 11 Evaluation Parameters of factorial batches P1-P9

- **Drug release study of factorial batches:-**

Dissolution study of factorial batches performed and the results were recorded in below table. The drug release shows the clear impact of PVP K30 and crospovidone. The batches which contains higher amount (6 mg) of binder gives slow release as compared to the lower amount of binder (2 mg). Additionally the higher the amount of crospovidone the drug release was faster as the DT time is low. Hence the batch P4 which contains 8 mg crospovidone and 2 mg binder was release more than 80% of drug in 8 min. Hence the P4 batch selected from the factorial batches as an optimized batch.

Table 18 Drug release of factorial batch P1-P9

Time (min)	P1	P2	P3	P4	P5	P6	P7	P8	P9
0	0	0	0	0	0	0	0	0	0
2	15.6±1.5	11.3±5.6	8.6±6.1	**25.9**±5.2	19.2±6.9	14.5±7.4	17.9±4.8	15.8±4.1	10.8±9.7
4	35.9±2.5	31.6±4.1	29.4±1.9	**41.5**±3.9	36.8±5.0	29.4±1.9	29.5±3.7	27.6±2.9	23.5±5.8
6	59.6±3.9	55.9±2.8	45.6±2.3	**56.9**±2.4	49.7±4.1	42.8±1.5	52.6±2.4	49.8±2.5	36.8±6.7
8	71.9±1.6	65.7±1.6	59.7±5.4	**84.6**±1.5	72.9±2.3	65.7±1.4	70.9±3.9	67.3±2.4	59.7±4.9
10	76.8±2.5	72.5±2.0	67.5±6.7	**99.9**±1.0	99.1±3.7	85.3±2.3	85.4±1.8	82.9±1.9	74.9±2.5
12	81.5±3.9	78.9±0.9	74.9±1.6		99.8±0.5	98.6±0.9	91.6±1.5	92.6±1.4	81.8±2.1
14	86.9±1.1	82.5±0.5	79.8±1.1			99.5±0.7	99.2±0.9	98.3±0.6	89.7±1.9
16	95.4±0.8	89.1±0.4	85.6±2.1					99.1±0.4	95.6±3.4
20	98.9±0.4	95.1±0.6	92.9±0.8						97.8±1.5



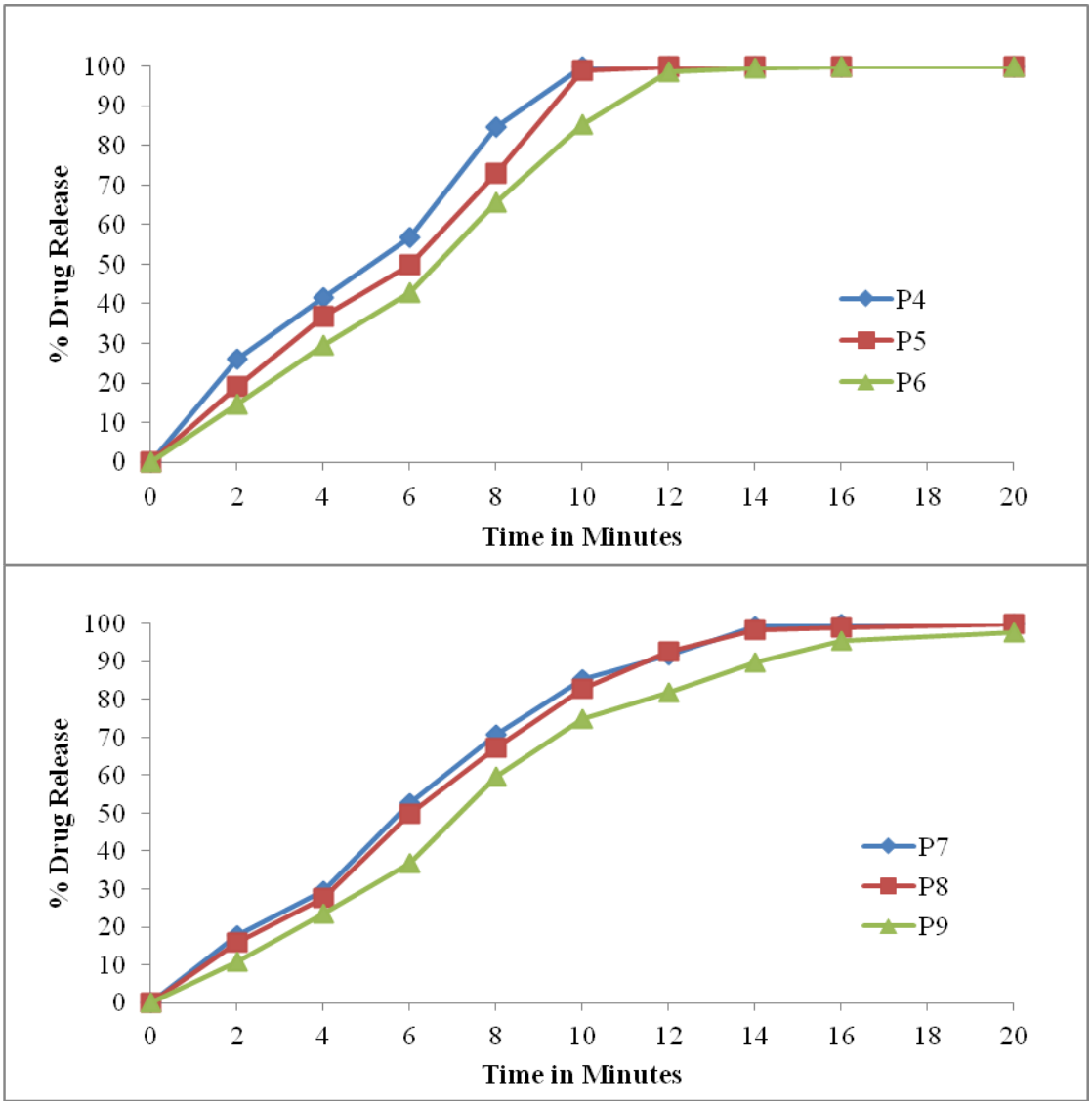


Figure 12 Drug release comparison of factorial batches P1-P9

6.7 ANALYSIS OF FACTORIAL DESIGN

The factorial design was applied for formula optimization using Minitab software for Design of Experiment study. For analysis purpose following data fitted in to software for 3^2 design and the outcome of the regression analysis recorded below.

Table 19 Factorial design table

Batch	Coded Factors		Actual factors		Response	
	X1	X2	X1	X2	Y1	Y2
P1	-1	-1	6	2	89	59.6
P2	-1	0	6	4	96	55.9
P3	-1	1	6	6	109	45.6
P4	0	-1	8	2	33	56.9
P5	0	0	8	4	49	49.7
P6	0	1	8	6	65	42.8

P7	1	-1	10	2	49	52.6
P8	1	0	10	4	55	49.8
P9	1	1	10	6	70	36.8

levels of 3^2 Full Factorial Designs			
Independent Factors	**Levels**		
	Low (-1)	**Medium (0)**	**High (1)**
X1= Amount of Crospovidone (mg)	6	8	10
X2= Amount of PVP K30*(mg)*	2	4	6
Dependent Factors			
Y1=Disintegration Time (sec)			
Y2=% Drug release at 6 min			

Table 20 Analysis of Variance for Disintegration time

Source	DF	Seq SS	Adj SS	F value	P value	Remarks
Main Effects	2	3288.17	3288.17	4.71	0.071	***Significant***
Crospovidone (mg)	1	2400.00	2400.00	6.87	0.047	***Significant***
PVP K30 (mg)	1	888.17	888.17	2.54	0.172	*Non-Significant*
2-Way Interactions	1	0.25	0.25	0.00	0.980	*Non-Significant*
Crospovidone (mg) * PVP K30 (ml)	1	0.25	0.25	0.00	0.980	*Non-Significant*
Residual Error	5	1745.58	1745.58	-	-	-
Total	8	5034.00	-	-	-	-

Analysis of variance for disintegration time checked by using factorial design software minitab 16 and the ANOVA table as well as co-efficient table recorded. Based on the data it concluded that the Disintegrants effects are more significant over Binder PVPK30. Binder effect found non significant and its clearly indicated in pareto chart.

Table 21 Estimated Coefficients for Disintegration time

Term	Co efficient
Constant	126.000
Crospovidone (mg)	-10.2500
PVP K30 (mg)	5.5833
Crospovidone (mg) * PVP K30 (ml)	0.06250

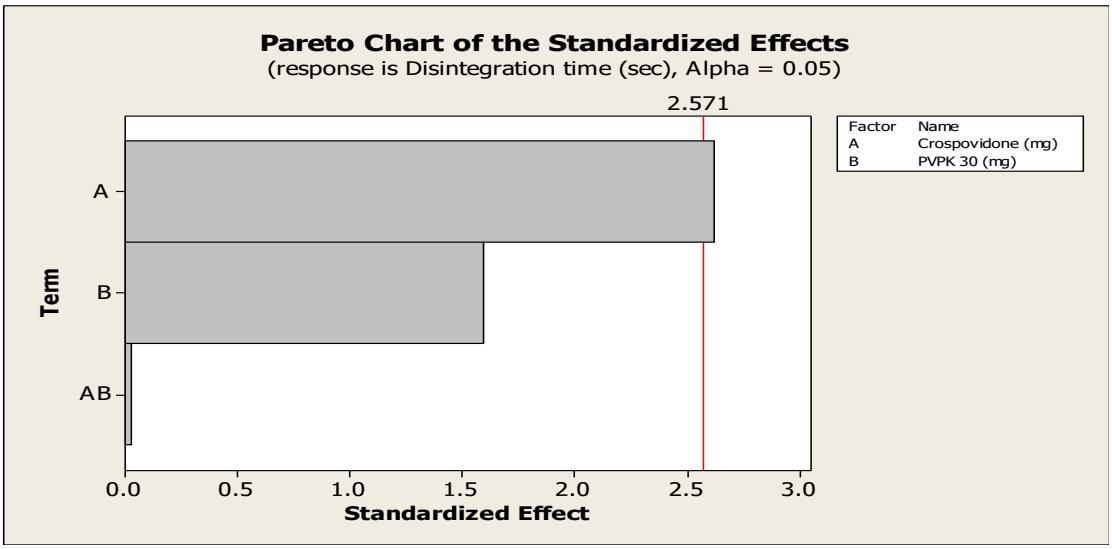


Figure 13 Pareto chart for Disintegration time

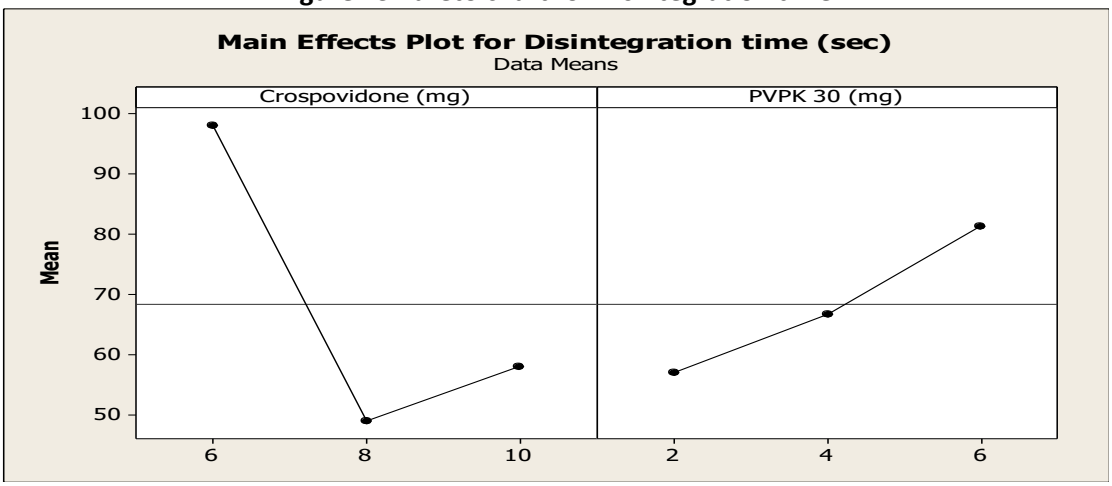


Figure 14 Main effect plot for Disintegration time

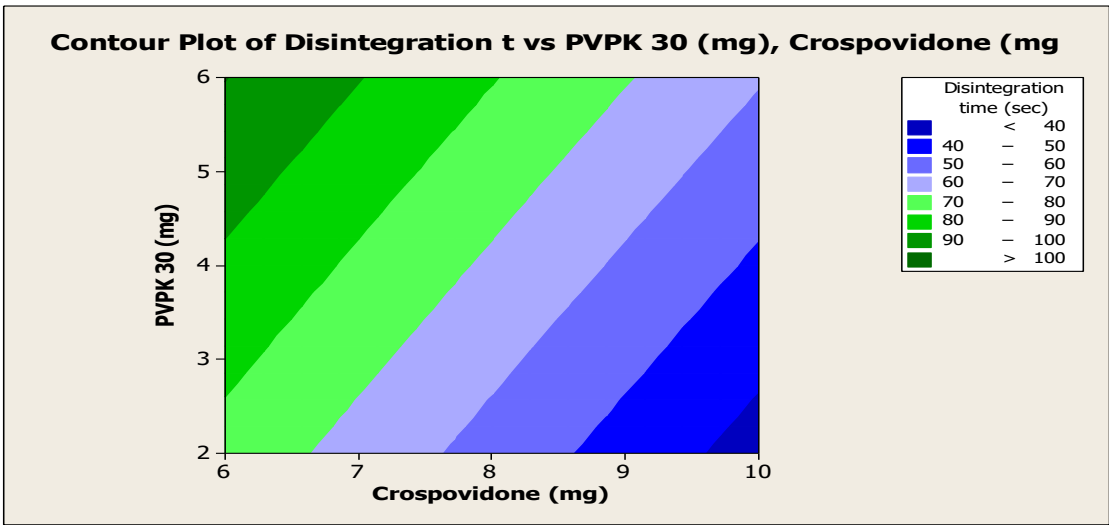


Figure 15 Counter plot for Disintegration time

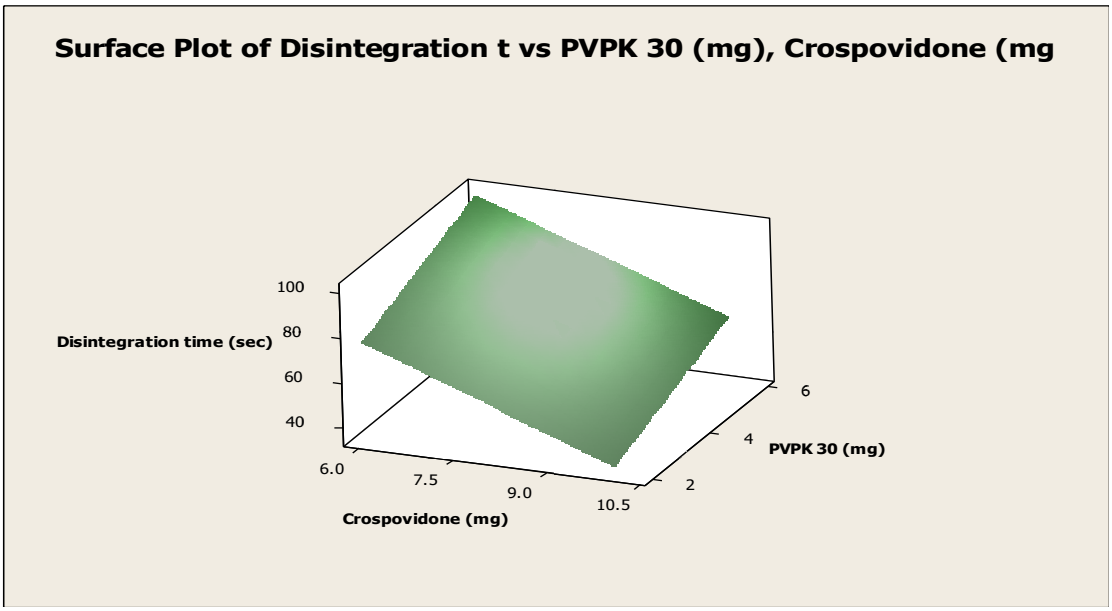


Figure 16 Surface plot for Disintegration time

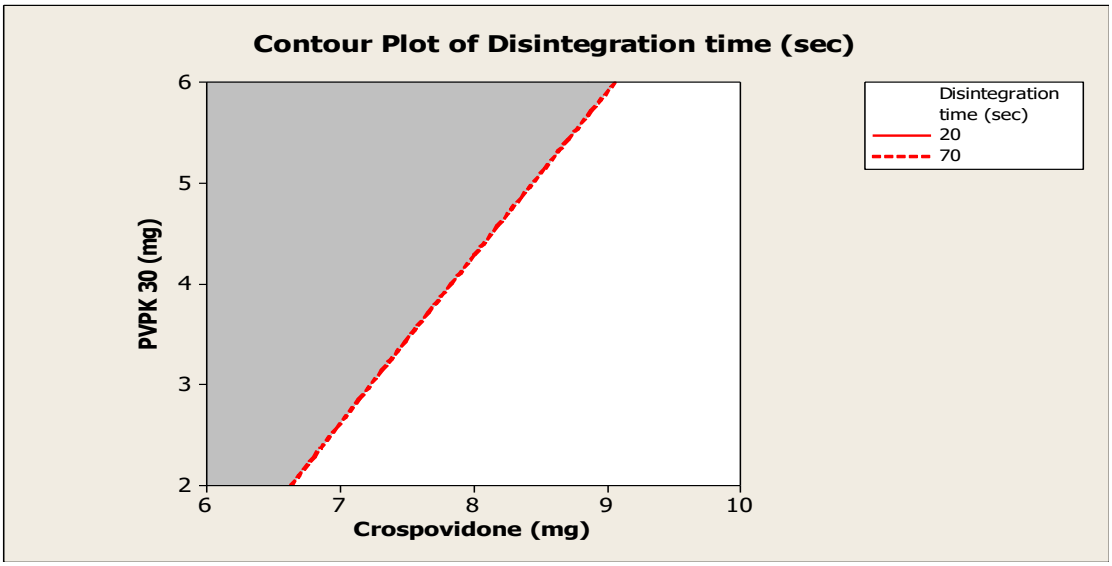


Figure 17 Contour plot for Disintegration time

Table 22 Analysis of Variance for % Drug release at 8 hour

Source	DF	Seq SS	Adj SS	F value	P value	Remarks
Main Effects	2	401.137	401.137	40.19	0.001	***Significant***
Crospovidone (mg)	1	79.935	79.935	16.02	0.010	***Significant***
PVP K30 (mg)	1	321.202	321.202	64.36	0.000	***Significant***
2-Way Interactions	1	0.810	0.810	0.16	0.704	*Non-Significant*
Crospovidone (mg) * PVP K30 (ml)	1	0.810	0.810	0.16	0.704	*Non-Significant*

Residual Error	5	24.953	24.953	-	-	-
Total	8	426.900	-	-	-	-

ANOVA table for % Drug release at 6 min shows both the factors, Crospovidone and PVP K30have a significant impact on drug release. Additionally the interaction found non significant.
The co-efficient table was given below for drug release at 6 min.

Table 23 Estimated Coefficients for % Drug release at 8 hour

Term	Co efficient
Constant	75.6000
Crospovidone (mg)	-1.37500
PVP K30 (mg)	-2.75833
Crospovidone (mg) * PVP K30 (ml)	-0.112500

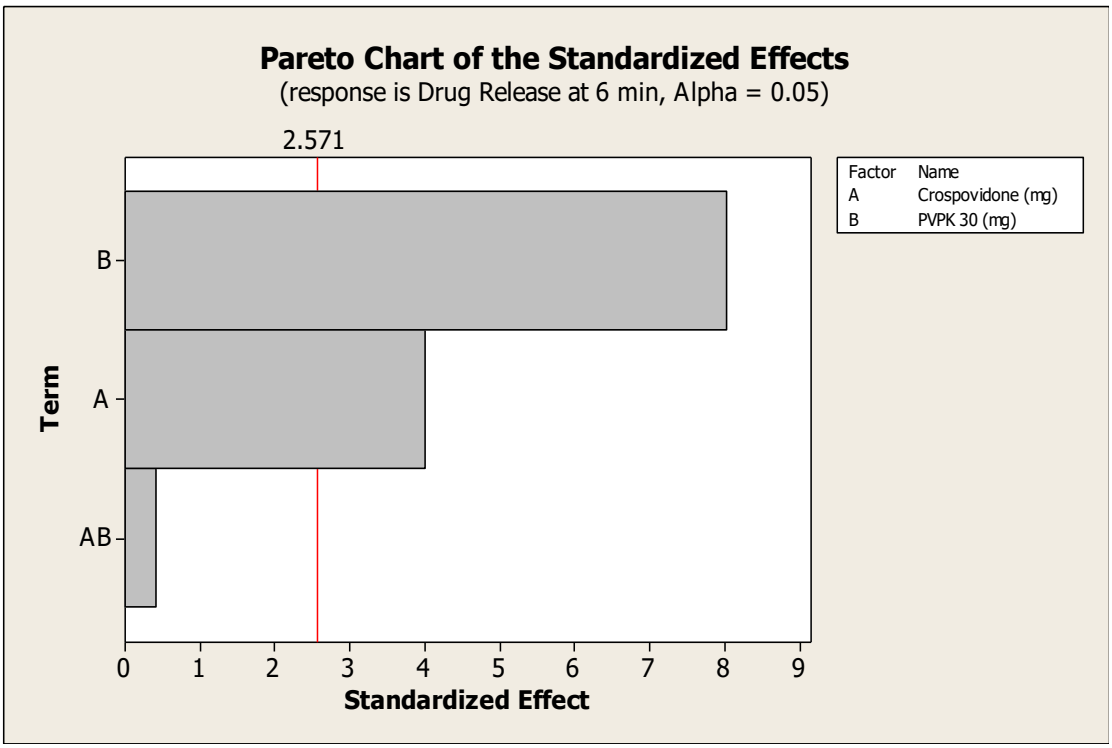


Figure 18 Pareto chart for Drug release at 6min

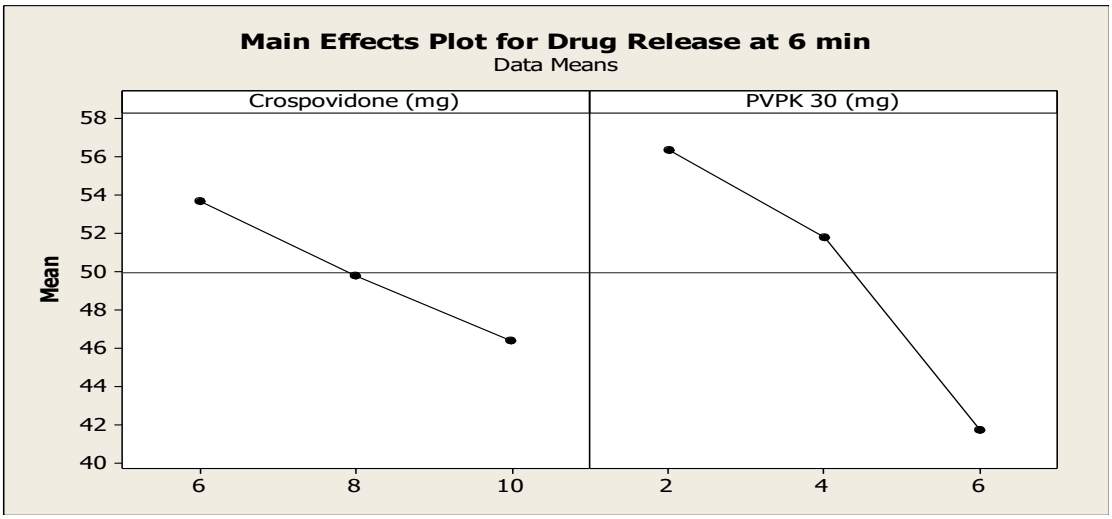


Figure 19 Main effect plot for Drug release at 6 min

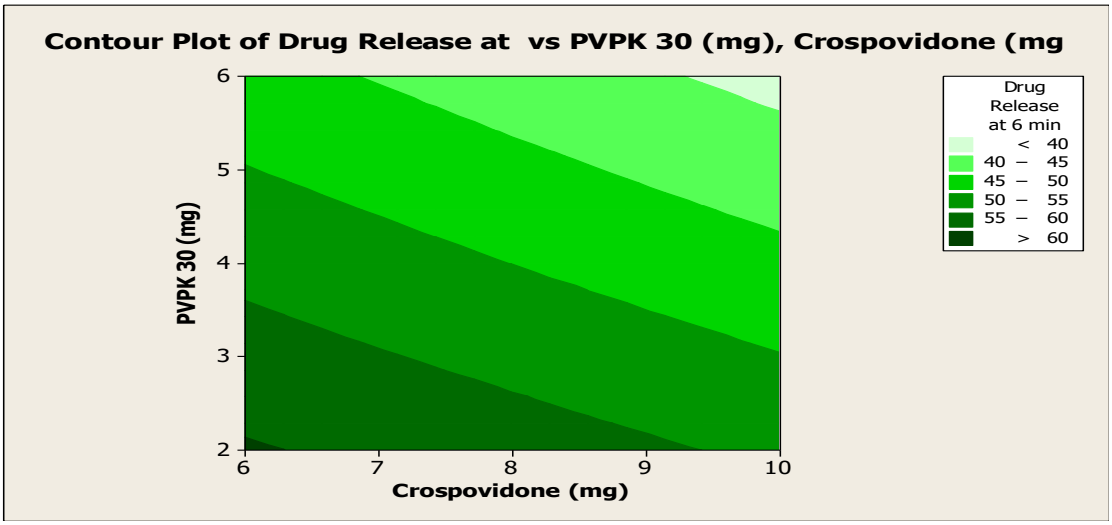


Figure 20 Counter plot for Drug release at 6 min

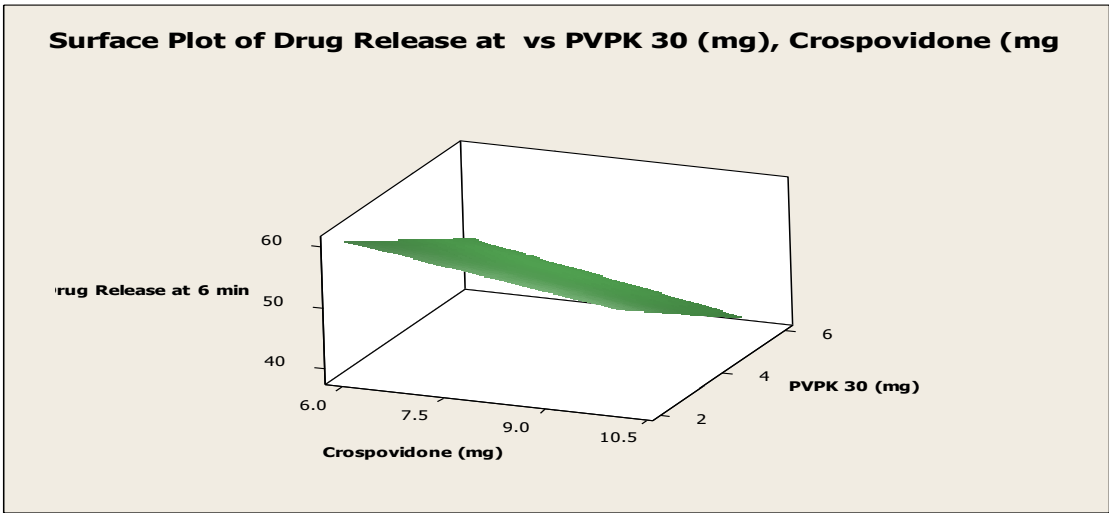


Figure 21 Surface plot for Drug release at 6 min

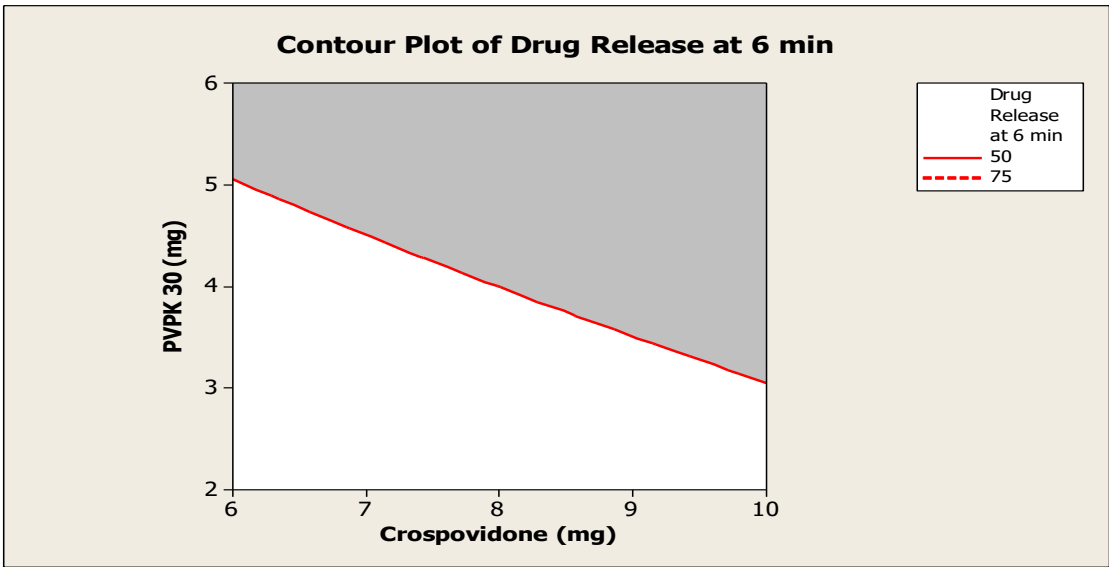


Figure 22 Counter plot for drug release at 6 min

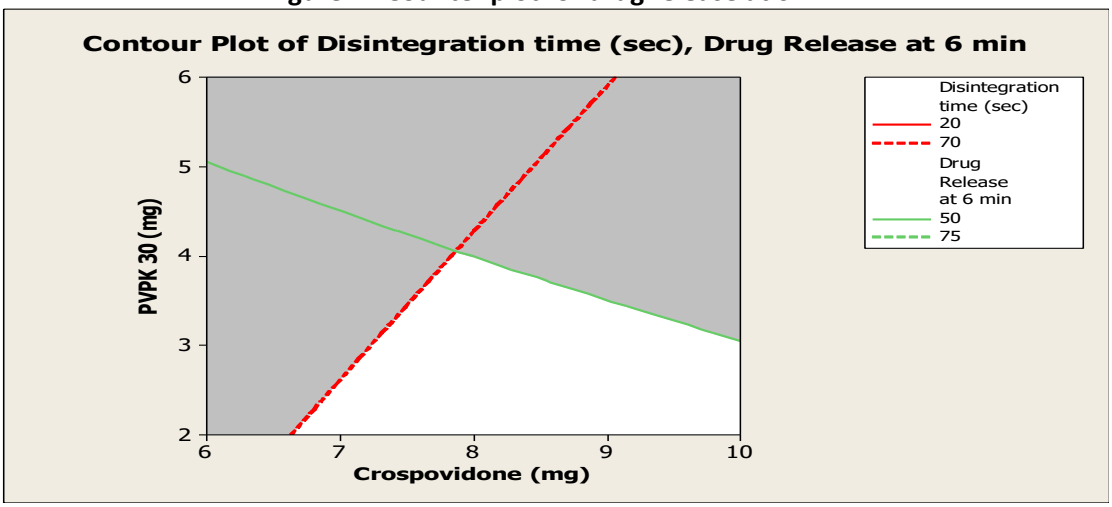


Figure 23 Overlay counter plot

Based on above all data, P4 batch which gives fact release and minimum disintegration time was optimized and further stability study was done on P4 batch.

6.8 STABILITY STUDY

Optimized batch P4 taken for 1 month stability study at 40°C and 75% RH. Initial results and after 1 month results were compared for any loss or change during stability. The batch was found stable and results were found satisfactory. The comparative results of initial and after 1 month were recorded in below table.

Table 24 Stability study of optimized batchP4

Parameter	Initial	After 1 Month
Appearance	White colour round tablet	White colour round tablet
Average Weight (mg)	103 ± 3	103 ± 2
Disintegration time(sec)	33 ± 4.5	35 ± 3.9

% Drug Content	96.9 ± 2.5	97.1 ± 2.7
% Drug release after 10 min	99.9±1.0	99.8 ±1.9

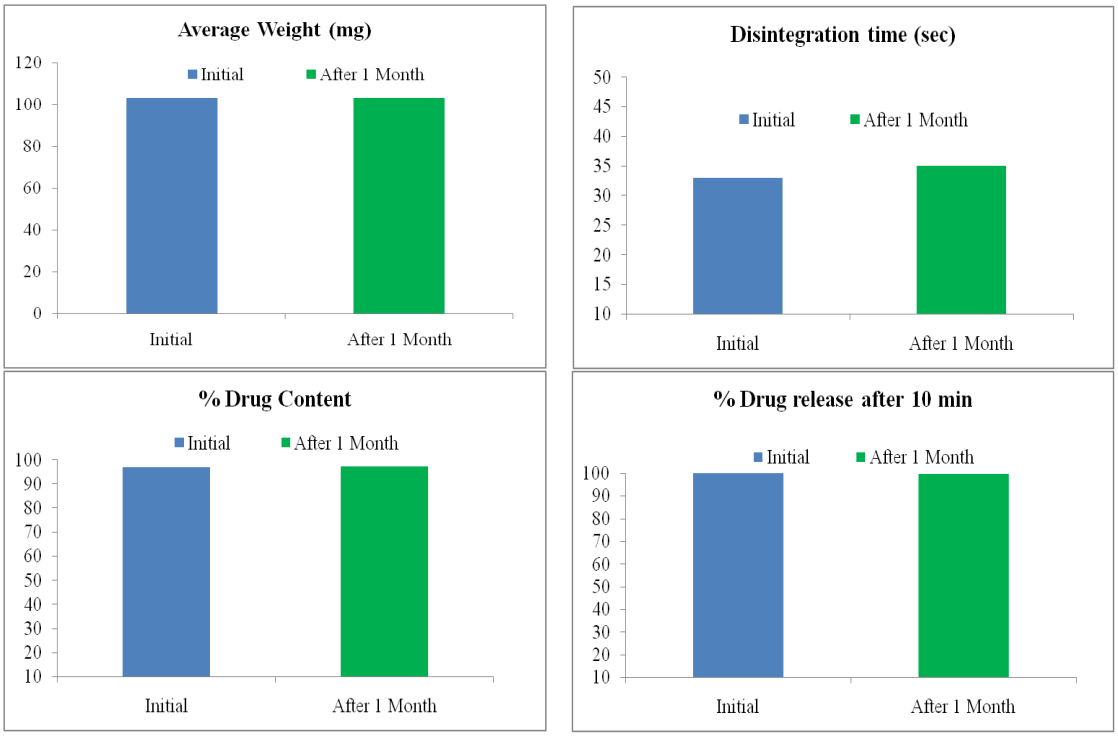


Figure 24 Stability study of batch P4

7. CONCLUSION

Paliperidone ODT tablets were prepared by direct compression technique using different types of disintegrants like, Crospovidone, SSG and CCS. Trial batches F1-F15 was prepared with 2-10 % of disintegrating agents and results were evaluated for pre and post compression parameters. All parameters are found within limit and good mechanical strength. Drug release was found 99 % within 10 min in F14 batch. Based on that the factorial design was applied by taking Crospovidone and PVP K30 as independent factors and the disintegration time and dissolution rate of the ODTs containing Paliperidone optimized by controlling the both the formulation parameters as disintegrant agent (Crospovidone; X1) and binder (PVP K30; X2).Final batch P4 have 33 sec disintegration time and fast drug release within 10 min. also P4 found stable during stability study for 1 month. Hence, P4 was optimized batch.

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