The preparation of orodispersible tablet & study effect of processing condition on Tablet

[1*]Snehal Dhewale, [2]Bhagwan Kale, [3]Vaishanvi Chivte, [4]Rutuja Dhakne [5]Dr. Santosh Shep

[1]Assistant Professor, [2] Principal, [3]Assistant Professor, [4]Assistant Professor, [5] Principal
[1]Pharmaceutics
[1]Shree Gorakasha College of Pharmacy & Research Center, Khamgaon, Aurangabad, India.

ABSTRACT

In the solid dosage formulation processing condition effect on tablet in that type of tablet and different parameter main source effect on the quality for overcome this quality design product maintain all condition and term given standard result. In the research we take different batches or -dispersible tablet formulation API risperidone as super disintegrants combination sodium starch glycollate and cross carmellose sodium ratio 100 + 300 mg is showing best results .on this batch then we test effect of processing condition on tablet in tat moisture content ,humidity, temperature Moisture may have a significant impact on a wide range of chemical ,physical, and microbial properties of the finished pharmaceutical product Moisture in dosage forms comes from many sources including bulk drug, inactive excipients, manufacturing processes, and environmental conditions, and is a result of a variety of causes Water may interact in distinct ways including surface adsorption ,as a crystal hydrate, by deliquescence, and by capillary condensation .Water may have significant effects on product stability, tablet compaction ,wet granulation, powder flow properties, and microbial growth• Compliance personnel must be knowledgeable of areas with potential for moisture problems. Change control of these areas is especially important to maintain compliant manufacturing. Be prepared for potential problems. The effects of moisture should be considered in trouble shooting investigations and root cause analyses we take batches F1 to F 9 different humidity and temperature appropriate result shown by F5 batch then again we test compressibility for all physical properties and nature ingredients and API , elasticity and plasticity effect on compressibility of tablet then different compressibility test fromC1 to C5 best result shown by C3 .

Key words- CP- Co process excipient ,ssg- Sodium starch glyoclate ,ccs- Cross carmellose sodium,RT- Room temperature, IP- Indian pharmacopeia, FTIR -Fourier transform Infrared, DSC- Differential scanning calorimetry uv- Ultraviolet

I. INTRODUCTION

Quality of pharmaceutical product is very important because pharmaceuticals drugs should be safe and therapeutically active formulation performance should be consistent and predictable. Final product quality depends on all ingredients which is used for making the final product tablet It is may affect the physical and chemical properties of final product. Moisture content affects the physical, chemical and microbiological properties of pharmaceutical finished dosage forms. In direct compression process, high and extra low moisture content could be it affects the hardness of tablet. For satisfactory hardness of tablet, room temperature and humidity must be maintained in a specific limit. Tablet hardness is also most import parameter for any solid dosage form for many drug substance ,conventional immediate release formulation provide clinically effective therapy while maintaining required balance of pharmacokinetics and pharmacodynamics profile

MOISTURE EFFECT ON TABLET

• Moisture may have a significant impact on a wide range of chemical, physical, and microbial properties of the finished pharmaceutical product Moisture in dosage forms comes from many sources including bulk drug, inactive excipients, manufacturing processes, and environmental conditions, and is a result of a variety of causes Water may interact in distinct ways including surface adsorption, as a crystal hydrate, by deliquescence, and by capillary condensation.

• Water may have significant effects on product stability, tablet compaction, wet granulation, powder flow properties, and microbial growth.

• Compliance personnel must be knowledgeable of areas with potential for moisture problems. Change control of these areas is especially important to maintain compliant manufacturing. Be prepared for potential problems.

• The effects of moisture should be considered in trouble shooting investigations and root cause analyses.

MOISTURE ROLE

Moisture plays remarkable negative role in pharmaceutical product, particularly for solid dosage forms. Both physical and chemical stability of some drugs are affected by moisture. Moisture is absorbed on the surface of solid drugs and increases the rate of decomposition, causes agglomeration and dissolution of drugs. Presence of moisture possesses a critical challenge on drug stability. Moisture accelerates the hydrolysis of drug as well as facilitates reaction with other excipients, thereby affecting stability and shelf life of the final product. The effect of moisture absorption on the shelf life of coated tablets. The hygroscopic nature of excipients and active ingredients should be considered in designing the formulation. Water sorption or desorption by drugs and excipients is not always reversible and absorbed moisture may not be easily removed during drying which directly affects the drug stability. The moisture content and rate of moisture uptake are the functions of temperature and humidity. Moisture affects the tableting characteristics in granulation process .Hygroscopicity data can aid in the design of tablet manufacturing areas. Moisture sensitive drugs should not be combined with hygroscopic excipients .Packing material should be chosen to. Investigators have described moisture uptake rate of various commercial brands of tablet in and inter–brand variability in the rate and extent of moisture

absorption. The aim of the present study was to investigate the effect of % relative humidity ,excipients (especially diluents, binders, lubricants),various dosage forms and packing materials on moisture absorption of hygroscopic drug .The moisture content of drugs, excipients com -binned with the drugs to manufacture a final dosage form(i.e., compressed tablets), and/or processing manipulations involving moisture may have a significant impact on a wide range of chemical and physical properties of the finished product. Properties such as powder compressibility, flow rate, compatibility, drug degradation, and microbial growth may be affected. Various processing steps require water (or other solvent) to accomplish their intended result.

EFFECTS OF WATER ON TABLET FORMULATION

Water may significantly affect the chemical, physical, and microbial properties of tablets. Examples of these interactions include the following:

• Product stability

Hydrolysis is a well-known mechanism for drug degradation reactions. High moisture levels might also cause drug dissolution to be adversely affected, potentially resulting in reduced drug bioavailability. In this case, the drug would be fully potent ,but would not dissolve as needed for absorption and product therapeutic efficacy.

• Tablet compaction

Tensile strength is generally low at low moisture content (approximately 0.1 to 0.2% w/w).As the moisture level increases, the compact tensile strength also increases to a maximum level; higher moisture contents then lead to decreased compact tensile strength (5). Due to stability requirements ,moisture levels above 1.5% w/w are seldom found in compressed tablets. Possible mechanisms for increasing the tensile strength are adsorbed water may alter surface structure such that there are more solid bridges, or immobile water at a particle surface may enhance interactions between particles. With the presence of relatively more surface moisture, it is possible for permeation into the particle, which may plasticize or soften the material

• **Solids flow properties**-Change in moisture levels of all associated with these areas of concern is critically important. Changes maybe unintended, such as seasonal variation of environmental conditions. Changes may also be planned, such as with a new source of raw material with different moisture content. Change control of planned changes is critically important. Changes in moisture levels, both increased and decreased levels, should be considered as possible causes of manufacturing or stability problems in troubleshooting and root cause analysis.

Manufacturing process

Change in moisture levels of all associated with these areas of concern is critically important. Changes maybe unintended, such as seasonal variation of environmental conditions. Changes may also be planned, such as with a new source of raw material with different moisture content. Change control of planned changes is critically important. Changes in moisture levels, both increased and decreased levels, should be considered as possible causes of manufacturing or stability problems in troubleshooting and root cause analysis.

• Moisture-activated dry granulation
• Wet granulation
• Effervescent tablets
• Microbial growth

DRUG EXCIPIENT PROFILE

DRUG PROFILE (RISPERIDONE)

DESCRIPTION

Schizophrenia and various mood disorders are thought to be caused by an excess of dopaminergic D2 and serotonergic 5-HT2A activity, resulting in over activity of central mesolimbic pathways and mesocortical pathways, respectively [Risperidone inhibits dopaminergic D2 receptors and serotonergic 5-HT2A receptors in the brain. It is also said to block histamine receptors, and other neural receptors which are currently being studied Risperidone binds with a very high affinity to 5-HT2A receptors, approximately 10-20 fold greater than the drug's binding affinity to D2 receptors .solid, White to slightly beige powder.

Chemical structure:

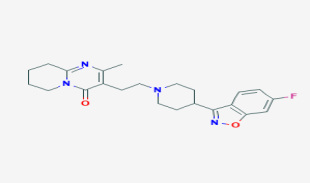


Fig ii structure of risperidone

Chemical properties

IUPAC Name -3-{2-[4-(6-fluoro-1,2-benzoxazol-3-yl)piperidin-1-yl]ethyl}-2-methyl-4H,6H,7H,8H,9H-pyrido[1,2-a]pyrimidin-4-one

Molecular Formula- $C_{23}H_{27}FN_4O_2$

Molecular Weight - :410.493 g/mol

Storage condition: - store below 40^0c, protect from sunlight & heat.

Physical properties:-

Solubility-Soluble in methylene chloride; sparingly soluble in alcohol; practically insoluble in water, freely soluble in methylene chloride ,methanol . Melting point**:- 170^{0}c**

Dose: -orally 1 or 2 mg once or twice day ,maximum dose 4 or 8mg per day

Mechanism of action:

The ability of risperidone to inhibit the D2 dopaminergic receptors and 5-HT2A serotonergic receptors in the brain. Schizophrenia is thought to be caused by an excess of dopaminergic D2 and serotonergic 5-HT2A activity, resulting in over activity of central mesolimbic pathways and mesocortical pathways, respectively D2 dopaminergic receptors are transiently inhibited by risperidone, reducing dopaminergic neurotransmission, therefore decreasing positive symptoms of schizophrenia, such as delusions and hallucinations. Risperidone binds transiently and with loose affinity to the dopaminergic D2 receptor, with an ideal receptor occupancy of 60-70% for optimal effect · The high affinity binding of risperidone to 5-HT2A receptors leads to a decrease in serotonergic activity. In addition, 5-HT2A receptor blockade results in decreased risk of extrapyramidal symptoms, likely by increasing dopamine release from the frontal cortex, and not the nigrostriatal tract. Dopamine level is therefore not completely inhibited. Through the above mechanisms, both serotonergic and D2 blockade by risperidone are thought to synergistically work to decrease the risk of extrapyramidal symptoms .Risperidone has also been said to be an antagonist of alpha-1 (α1) alpha-2 (α2) receptors, and histamine (H1) receptors ·. Blockade of these receptors is thought to improve symptoms of schizophrenia, however the exact mechanism of action on these receptors is not fully understood at this time.

Pharmacokinetics:

Absorption

Well absorbed. The absolute oral bioavailability of risperidone is 70% (CV=25%). The relative oral bioavailability of risperidone from a tablet is 94% (CV=10%) when compared to a solution.

Distribution: - volume of distribution 1 to 2 L/Kg

Protein binding :- Risperidone, ~88% bound in human plasma; 9-hydroxyrisperidone, ~77% bound in human plasma

Metabolism

Extensively metabolized by hepatic cytochrome P450 2D6 isozyme to 9-hydroxyrisperidone, which has approximately the same receptor binding affinity as risperidone Hydroxylation is dependent on debrisoquine 4-hydroxylase and metabolism is sensitive to genetic polymorphisms in debrisoquine 4-hydroxylase]. Risperidone also undergoes N-dealkylation to a lesser extent

Route of Elimination

Risperidone is extensively metabolized in the liver. In healthy elderly subjects, renal clearance of both risperidone and 9-hydroxyrisperidone was decreased, and elimination half-lives are prolonged compared to young healthy subjects . Half life3 hours in extensive metabolizers [9] Up to 20 hours in poor metabolizers ·

Excipient profile:-

Magnesium Stearate:

Synonyms: Dibasic magnesium stearate; magnesium distearate; magnesium salt; magnesium octadecanoate.

Chemical Name: Octadecanoic acid magnesium salt

Chemical Formula: $C_{36}H_{70}MgO_4$ **Melting range**: 117–150ºC

Molecular Weight: 591.24 **Structural Formula:** $[CH_3(CH_2)_{16}COO]_2Mg$

Functional Category: Tablet and capsule lubricant.

Description: Magnesium stearate is a very fine, light white, precipitated or milled, impalpable powder of low bulk density, having a faint odour of stearic acid and a characteristic taste.

Solubility: Practically insoluble in ethanol, ethanol (95%), ether and water; slightly soluble in warm benzene and warm ethanol (95%).

Storage Conditions: Magnesium stearate should be stored in a well-closed container in a cool, dry place

Cross carmellose sodium

Structural formula:

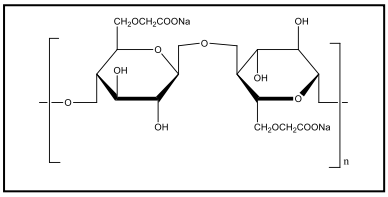


Fig 4.2: Structure of cross carmallose sodium.

Synonyms: Ac-Di-Sol; Cross linked carboxyl methyl cellulose sodium

Chemical Name: Cellulose, Carboxy methyl ether , Sodium salt.

Molecular Weight: 90000 to 700000 **Melting point:** more then 300°C

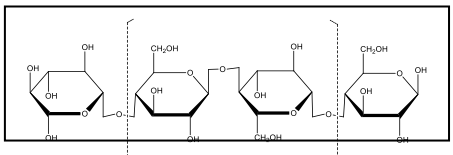
Category: Tablet and capsule disintegrate.

Description: An odorless white or grayish white powder.

Storage condition: Stored in well closed container in cool and dry place.

Incompatibilities: The efficacy may be slightly reduced in tablet formulations prepared by either wet granulation or direct compression process that containing hygroscopic Excipients such as sorbitol.

Micro crystalline cellulose



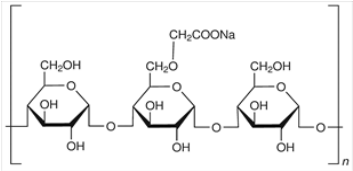
Structure of MCC

Synonym: Avicel PH 102 **Chemical name:** Cellulose **Molecular formula:** $(C_6H_{10}O_5)_n$
Functional category: Adsorbent, Suspending agent, tablet and capsule diluents, tablet disintegrant
Typical properties:
Angle of repose: 35° **Bulk density:** 0.37g/cm^3 **Tapped density:** 0.478g/cm **Melting point**: -260-270^{0}c
Moisture content- Typically less than 5% W/W. **Solubilit**y: Slightly soluble in 5% w/w sodium hydroxide solution

SODIUM STARCH GLYCOLATE-

Synonym: Carboxymethyl starch, sodium salt; carboxy methylamylum natricum, Explosol, Explotab, Glycolys, Primojel **Chemical Name**: Sodium carboxymethyl starch

Molecular Weight :500000-11000000



Category: -Tablet and capsule disintegrant Structural Formula **Melting point**: > 210^{0}c

Description: - Sodium starch glycolate is a white or almost white free flowing very hygroscopic powder. Under microscope it is seen to consist of granules, irregularly shaped, ovoid or pear shaped, 30-100µm in size. Very fine, white or off white, free flowing powder; odorless or almost odorless

Applications: Sodium starch glycolate is widely used in oral pharmaceuticals as a disintegrant in capsule and tablet formulations. It is commonly used in tablets.

Talc

Nonproprietary names: Purified talc (B.P.), Talc (J.P., U.S.P.), Talcum (PhEur). **Chemical name** : Talc

Synonyms: Altalc; E553b; hydrous magnesium calcium silicate; hydrous magnesium silicate; Luzenac Pharma; magnesium hydrogen metasilicate; Magsil Osmanthus; Magsil Star; powdered talc; purified French chalk; Purtalc; soapstone; steatite; Superiore.

Structural formula: Mg6(Si2O5)4(OH)4

Empirical formula and molecular weight: Talc is a purified, hydrated, magnesium silicate, approximating to the formula Mg6(Si2O5)4(OH)4. It may contain small, variable amounts of aluminum silicate and iron.

Functional category: It is an anticaking agent; glidant; tablet and capsule diluent; tablet and capsule lubricant.

Preformulation studies:

Preformulation testing is the first step in the rational development of dosage forms of all drugs . it can be defined as an investigation of physical and chemical properties of drug substance , alone and when combined with excipient . the overall objective of Preformulation testing is to generate information useful to the formulator in developing stable and bioavailable dosage form. Which can be produced at large scale . a thorough understanding of physicochemical properties may ultimately provide rationale for formulation design or support the need for molecular modification or merely confirm that There are no significant barriers to the compound's development.

Description: The sample was analyased for physical appearance ,Colour, and odour .

Melting point :the melting point of API was determined by digital melting point apparatus .the capillary filled with powder was powder was placed in melting point apparatus .separately containing liquid paraffin and the melting point of the drug powder were noted.

Drug excipient compatibility studies :

1 . Infrared absorption spectrum

The identification of risperidone was done by FTIR spectroscopy .FTIR spectrum recorded using FTIR -4000 spectrophotometer (jasco corporation , japan) .the wavelength range From 400 to 4000 cm^{-1} .

2. DSC analysis

Dsc analysis was performed using shimadzu DSC -60,shimadzu limed japan . drug and excipient was weighed into aluminum crucible . and sample was analyased by heating at a scanning rate of 20^0 c -300^{0}c under nitrogen environment.

3. analytical methods :

Preparation of standard stock solution:

a standard stock solution of risperidone was prepared by dissolving accurately weighted 100 mg of risperidone in PH 6.8 phosphate buffer in 100 ml volumetric flask and volume made up to 100 ml with PH 6.8 phosphate buffer , to obtain solution of 1 mg /ml(1000 ug/ml .)

Preparation of risperidone stock solution:

by taking 1 ml of above stock solution and diluting it with PH 6.8 phosphate buffer up to 100 ml 0.01 mg/ml (10ug/ml) . from this stock solution aliquots stock solution take 0.2 ml,0.4ml,0.6ml,0.8ml,1ml were pipette out into 10 ml volumetric flask and volume made up to mark with PH 6.8 phosphate buffer produced concentration 2,4,6,8,10 ug/ml respectively .the absorbance (abs) each concentration was measured with respective wavelength 278 nm.

Preparation of pH 6.8 phosphate buffer (0.2 M) : -

Dissolved 28.80 gm of disodium hydrogen orthophosphate ,& 11.45 gm potassium dihydrogen orthophosphate in sufficient quantity of distilled water to produced 1000ml with distilled water.

Process development

A. Formulation trial :

Trial batches of risperidone tablet were fabricated by direct compression technique . tablet containing 100 mg of risperidone fast dissolving tablet were prepared by direct compression technique . the drug was procured from Ajanta pharma Pvt ltd , Aurangabad ,and crosscarmellose sodium procured from market . talc, sodium starch glyoclate , magnesium stearate, microcrystalline cellouse was isolated in laboratory . the powder was compressed into a tablet using 8 mm punch set.Trial batches were performed by taking different humidity ,temperature ,compressibility condition.

Method & material s:

Method 1:

1. weight method : to all different humidity condition maintain by using prepared saturated salt solution & pour in to the desiccator . Maintain different temperature placed desiccator with solution placed in to oven. tablet formulation powdered are weight placed into desiccator containing different humidity condition by solution that desiccator placed in to oven that particular temperature for 1 hr. then evaluation precompression & post compression parameter of powder & tablet.
2. Room temp: placed tablet formulation powered in to room temperature environment. Then evaluation of precompression & post compression parameter of powder & tablet
3. dry moisture : placed tablet formulation powdered in to hot air oven at temp 45 0c for 1hr.then evaluation of precompression & post compression of powder& tablet.

Method 2 :

To compressibility study to select different compression knob or mode using compression knob moving different angle by rotation then study post compression parameter.

Fast dissolving tablet risperidone formula:

Preparation of co processed super disintegrates:

Co processed super disintegrates were prepared by using sodium starch glycollate and cross carmellose sodium. The super disintegrates were mixed in different concentrations and labeled as CP .The blend of super disintegrates was mixed thoroughly for a period of 15 min, collected and used for preparing formulations in different concentration .

ngredient	Mg
Ccs	**300**
Ssg	**100**

Cp =coprocessed Superdisintegrants

Formulation of Oro dispersible tablets of Risperidone:

Ingredients	**Quantity**
Risperidone	8 mg
Cp (ccs 300mg +ssg 100mg)	20mg
Magnesium stearate	2mg
Talc	2mg
Microcrystalline cellouse	68mg
Total	100mg

DIFFERENT HUMIDITY & TEMPETURE CONDITION

Sr no	**Humidity**	**Temperatures**	**Maintain condition**
F1	33%	25^0c	Magnesium chloride solution
F2	45%	50^0c	Magnesium nitrate solution
F3	53%	25^0c	Magnesium nitrate solution
F4	64%	25^0c	Sodium nitrate solution
F5	75%	40^0c	Sodium chloride solution
F6	84%	30^0c	Potassium chloride solution
F7	96%	40^0c	Potassium sulphate solution
F8	Room temperature	25^0c	Room environment
F9	Dry moisture	45^0c	By using hot air oven

Compressibility codes

Compression modes	**Rotation knob**
C1	Move by 30^0
C2	Move by 60^0
C3	Move by 90^0
C4	Move by 120^0
C5	Move by 150^0

Evaluation parameter:-

Appearance: the control of general appearance of a tablet involves the measurement of number of attributes such as a tablet size, shape, and Color.

Flow Properties

Angle of Repose: It is performed to determine the flow rate of powder done by the funnel method. The powder was poured into a funnel which is fixed from height of 2cm of the plane surface. Circumference was drawn with a pencil on the graph paper and the radius of base of a pile was measured at 5 different points and average was taken for calculating Angle of repose using following formula: Θ= tan-1 H/R Θ=angle of repose H=height of powder cone, R=radius of powder cone Angle of Repose less than 300 shows the free flowing property of the material.

Sr .no	θ^0	Type of flow
1	<20	Excellent
2	20-30	Good
3	30-40	Passable
4	>3	Very poor

Loose bulk Density (LBD):

Loose bulk density was obtained by dividing the mass of powder by the bulk volume in cm3. The sample of about 50 cm3 of powder, previously been passed through a standard sieve no. 20, was carefully introduced into a 100 ml graduated cylinder. The cylinder was dropped at 2 second intervals on to hard wood surface three times from a height of 1 inch. The bulk density of each formulation was then obtained by dividing the weight of sample in grams by the final volume in cm3 of the sample contained in the cylinder.

It was calculated by using equation given below:

Df = M /Vp Where, Df = bulk density M = weight of sample in grams Vp = final volume of powder in cm3

Tapped bulk density (TBD):

It is the ratio of total mass of the powder to the tapped volume of the powder. Volume was measured by tapping the powder for 750 times if the difference between these two volumes is less than 2%. If it is more than 2%, tapping was continued for 1250 times and tapped volume was noted. Tapping was continued until the difference between successive volumes is less than 2 % (in a bulk density apparatus). It is expressed in g/ml and is given by

Do = M /Vp Where, Do = Tapped density, M = weight of sample in grams Vp = final volume of powder after tapping in cm3

Carr's consolidation index: .

The Carr index is an indication of the compressibility of a powder. This is calculated by the formula C=100(1- ρb/ρt) Where, ρb is the bulk density , ρt is the tapped bulk density A Carr index greater than 25 is considered to be an indication of poor flowability, and below 15, of good flowability

Sr .no	% compressibility	Flowability
1	5-12	Excellent
2	12-16	Good
3	18-21	Fair passable
4	23-35	Poor
5	33-38	Very poor
6	<40	Very very poor

Hausner's ratio : The Hausner ratio is a number that is correlated to the flowability of a powder or granular material. The Hausner ratio is calculated by the formula H= ρb/ ρb Where, ρb is the bulk density ρb is the tapped bulk density Hausner ratio greater than 1.25 is considered to be an indication of poor flowabilityHausner's ratio = ρt\ ρb ρt - tapped density ρb - untapped bulk density**Post compression parameter :**

weight variation test :

the weight variation test was carried out as per the method described in the usp .twenty tablet were weighted and the average weight was calculated . the individual weight was compared with average weight . the tablet pass the test if not more than two tablet are outside the percentage limit . the following percentage deviation in weight variation is allowed according to usp.

Sr no	Weight variation	Deviation
1	130 mg or less	+10
2	More than 130 mg	+7.5
3	324 mg and above	+5

Uniformity of thickness:

Randomly 10 tablets were taken from formulation batch and their thickness (mm) was measured using a Vernier calipers

Hardness test:

The hardness of the tablets was determined using Monsanto hardness tester. It is expressed in Kg/cm2. Six tablets were randomly picked from each formulation.

Friability test:

It is the phenomenon whereby tablet surfaces are damaged and/or show evidence of lamination or breakage when subjected to mechanical shock or attrition. The friability of tablets was determined by using Roche friabilator (Lab India, FT 1020). It is expressed in percentage (%). Ten tablets were initially weighed [W(initial)] and transferred into friabilator. The friabilator was operated at 25 rpm for 4 min or run up to 100 revolutions. The tablets were weighed again [W(final)]. The percentage friability was then calculated by, F=[W initial −W(final)]/W(initial)X100

Drug Content estimation:

The content uniformity test is used to ensure that every tablet contains the amount of drug substance intended with little variation among tablets within a batch. Four tablets were weighed and crushed in the mortar. The powder equivalent to 1.25 mg of the drug were weighed and dissolved in 100ml phosphate buffer PH 6.8 to give a concentration of 12.5 µg/ml. 2ml of this solution was taken **and** diluted to 10ml to give a concentration of 2.5µg/ml. The absorbance of the prepared solution was measured at 278nm using UV Visible spectrophotometer

***In -vitro* dissolution studies**:

In-vitro release studies were carried out using a modified USP XXIII dissolution test apparatus (Lab India, DS-800). The dissolution fluid was 500ml of phosphate buffer pH 6.8 at a speed of 50rpm at a temperature of 370c were used in each test. Samples of dissolution medium (5ml) were withdrawn for every 2 min and assayed for Risperidone by measuring absorbance at 278 nm. For all the tests 5ml of the test medium were collected at specified time intervals and replaced with same volume of phosphate buffer PH 6.8

Bio relevant dissolution studies:

When dissolution testing used to forecast the in vivo performance of a drug. it is critical used to examine the solubility and dissolution characteristics of a drug to assist in predicting in vivo absorption behavior bio revelnt in vitro dissolution testing is useful for qualitative forecasting of formulation and food effect on the dissolution and availability of orally administered drug .The formulation and preparation of the bio relevant media are detailed below :

Fasted state simulated intestinal fluids (FaSSIF) pH 6.5

Ingredient	**Quantity taken**
Sodium taurocholate	3mM
Lecithin	0.75mM
NaOH pellets	0.174g
$NaH_2PO_4H_2O$	1.977g
NaCl	3.093g
Purified water q .s	500 mL

For dissolution studies in FaSSIF a volume of 500 mL is recommended .

Fed state simulated intestinal fluid (FeSSIF) PH 5

Ingredient	**Quantity taken**
Sodium taurocholate	15 Mm
Lecithin	3.75 Mm
NaoH pellets	4.04 g
Glacial acetic acid	8.65 g
Nacl	11.874g
Purified water q.s	1000ml

FT-IR :

The drug excipient interaction was studies using Fourier infrared spectrophotometer (FT-IR) . IR spectra for drug and powdered tablets were recorded in a Fourier transform infrared spectrophotometer. The spectra were scanned over the 4000 to 400 cm^{-1}range.

Differential scanning calorimetry :

Thermal behavior for risperidone and excipient was studied. The sample was scanned at the heating rate of 20-300^0 c .under nitrogen atmosphere and thermo gram recorded.

6. Result and discussion

Standardization of raw material

Table 12..Standardization of risperidone :

Test	**IP standard**	**Observation**
Colour	White	Complies
Odour	Odourless	Complies
Identification	FT-IR	Complies
Melting point	169^{0}c-170^{0}c	170^{0}c
Solubility	Soluble in methanol and phosphate buffe6.8,insoluble or sparingly soluble in water.	127.4 mg/ml in methanol,130.841 mg/ml in phosphate buffer 6.8,24.73 mg/ml in water

6.2 FT-IR analysis of drug

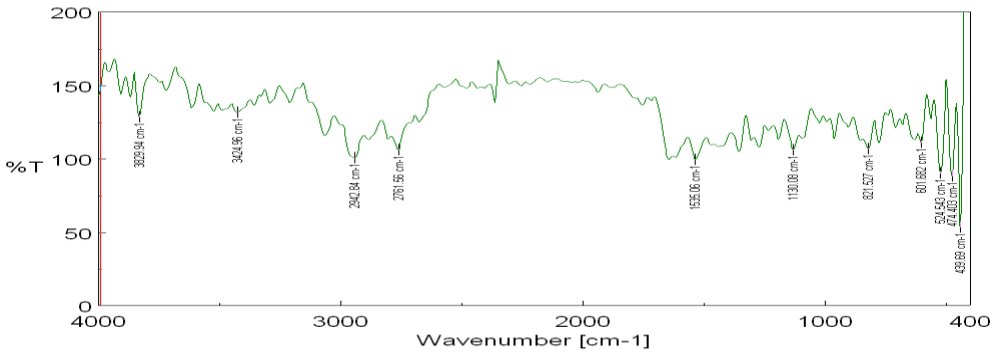


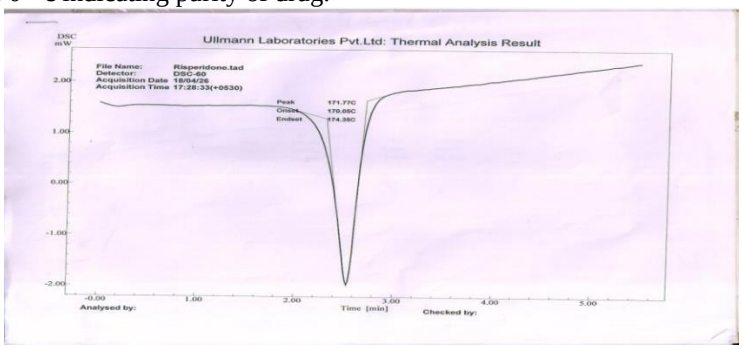
FIG 7. FT-IR SPECTRA OF RISPERIDONE

Table 14 interpretation of FT-IR SPECTRUM OF risperidone

Type of vibration	Observed frequencies (cm^{-1})	Reported frequencies (cm^{-1})
C-H bending(aromatic)	821.527	900-690
Aromatic	1536.99	1600,1475
C-F (fluoride)	11.30.08	1400-1000
C-H stretching (Alkanes)	2942.84, 2761.56	3000-2850
C-H stretching(aliphatic)	2942.84	2946.70
C=O (amide)	1643.41	1680-1640

FT-IR study was performed with the sample of risperidone. This FTIR spectrum was found concordant with FTIR of risperidone reported in official monograph and peak were matched with the standard peak of risperidone

6.3 DSC study: The thermal behavior of risperidone was examined by DSC. The DSC thremogram is shown in fig representing a sharp endothermic peak at 170 ^{0} c indicating purity of drug.



6.4 Cross carmallose sodium

Cross carmallose sodium was characterized for different tests like colour, odour and solubility

Table 14. standardization of cross carmellose sodium

Test	Standard	Observation
Color	White powder	Grayish White powder
Odor	Odorless	Odorless
Solubility	Water insoluble	Water insoluble

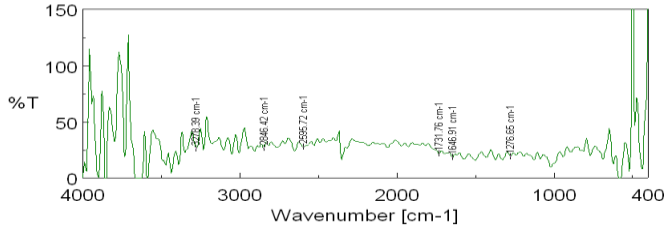


Fig .9.FTIR spectra of cross carmallose sodium

Table 15. spectral assignment of cross carmallose sodium

Wave number (cm^{-1})	Vibration mode

1646.9	C=O
1276	C-O-C
2600,2700,2850,3200	O-H
1731	O-Na

FT-IR of spectra show peak which are typical of an in consistent with cross carmellose sodium as reported In literature.

6. STANDRADIZATION OF SODIUM STARCH GLYCOLATE

Sodium starch glyclolate was characterized by colour, odour solubility

Table 18. Standardization of sodium starch glyclolate

Characteristics	Standard	Observed
Colour	White, off white powder	White
Odour	Odourless	Odorless
Solubility	Soluble in water	Soluble in water

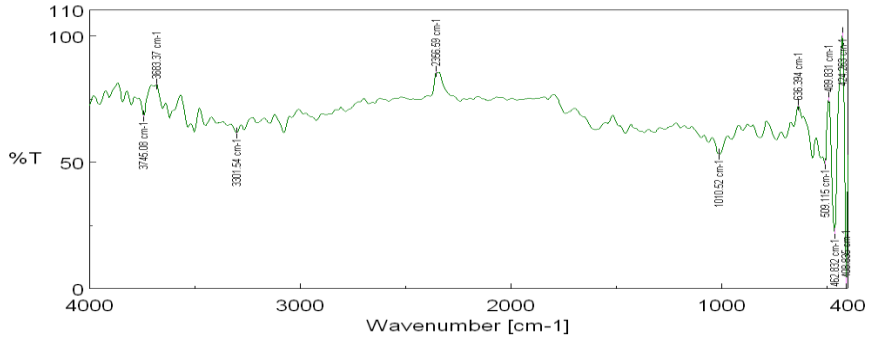


FIG 11. FT-IR of sodium starch glycolate

Table 19. IR SPECTRA OF SODIUM STARCH GLYCLOLATE

Wavenumber(cm^{-1})	Vibration Mode
1010	C-N
3301,636.53,	C-H stretch,CH_2 bend

FT-IR spectra as shown in above table show peak which are typical of and in consistence with sodium starch glyclolate as reported in literature.

6.7 FT-IR spectra cross carmellose sodium with risperidone

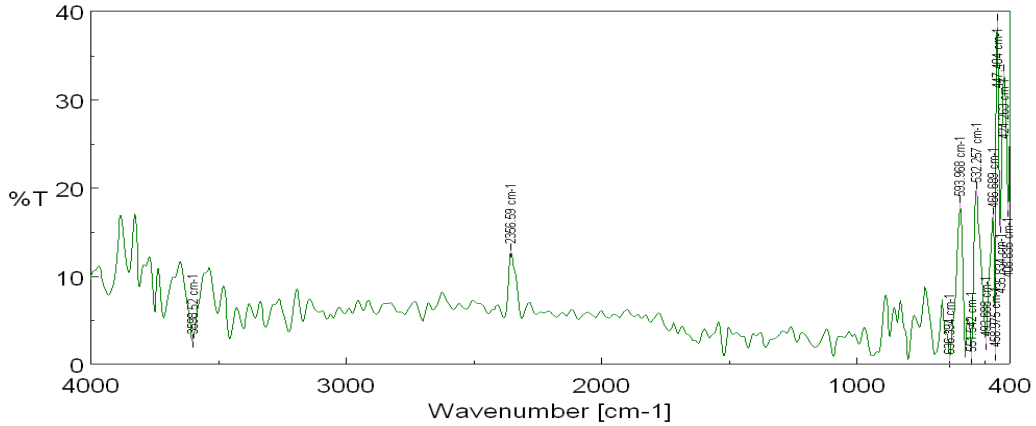


FIG .12 FT-IR spectra crosscarmellose with risperidone

Table 20. Interpretation of FT-IR of crosscarmellose sodium with risperidone

Wavenumber (cm^{-1})	Vibration mode
O-H,CN stretch	3598,2356
=C-H	636
C-H AROMAIC	798
C-O-C	1276

FT-IR spectra as shown in table show Peak which are typical of and in consistence with crosscarmellose sodium & risperidone as reported in literature. The FT-IR of pure risperidone & pure cross carmellose sodium was compared with pure FT-IR of the mixture was observed there is no functional peak obtain there indicating no chemical interaction.

6.8 FT-IR spectra of Risperidone with MCC

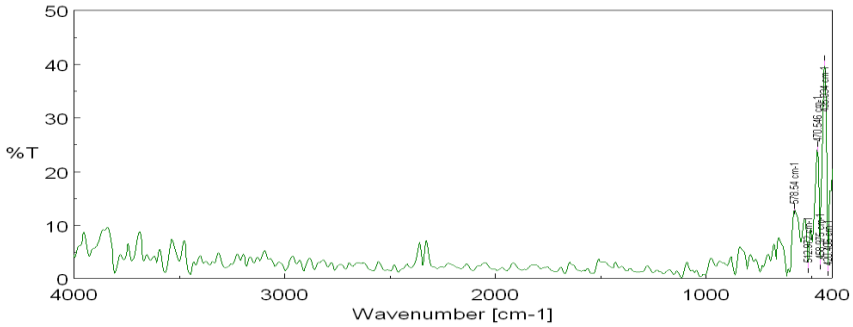


FIG .13. FT-IR Spectra of MCC with risperidone

FT-IR of pure risperidone & pure microcrystalline cellouse was compared with the pure FT-IR mixture was no functional peak observed there indicating no significant chemical interaction.

Table 21. FT-IR interpretation of MCC with risperidone

Wavenumber (cm^{-1})	**Vibration mode**
=C-H stretch	578.54
CN	1000
C-F,C=C	1080,1423

6.9 FT-IR spectra of SSG with risperidone

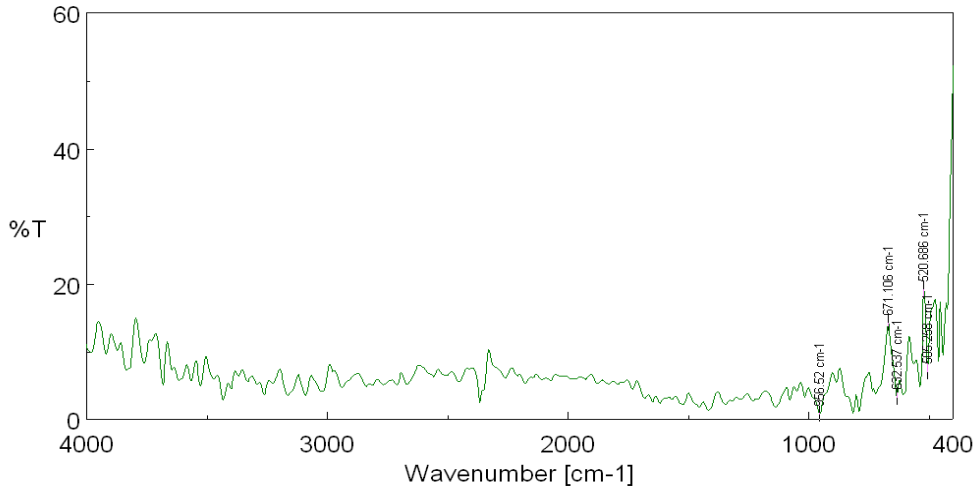


FIG .14. FT –IR of risperidone + SSG

FT-IR of pure risperidone & pure sodium starch glycloate was compared with pure mixture of FT-IR mixture was observed no functional peak that indicating no chemical interaction.

Table 23. FT-IR interpretation of SSG with risperidone

Wavenumber (cm^{-1})	**Vibration mode**
=C –H stretch	632.37
C-H stretch	3000
C-O	1000
C-N	996.52

6.9 FT-IR of tablet formulation optimized batch F 5 :

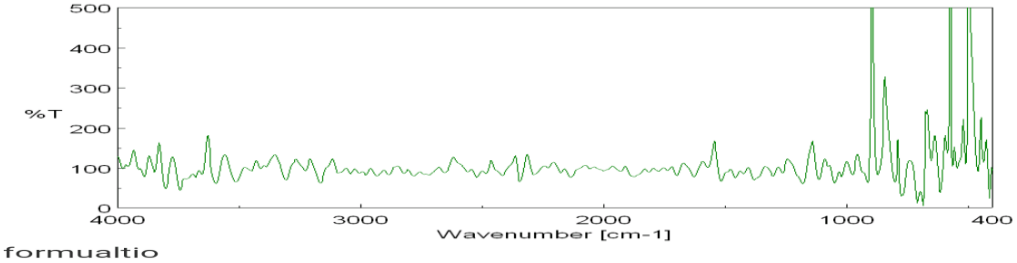


FIG.15 FT-IR spectra of formulation batch F5

Table 22. FT-IR tablet formulation batch F5 (75%)

Wavenumber(cm^{-1})	**Vibration mode**
3594,3745	C-H stretch ,N-H stretch
3166	=C-H stretch

1180	C-N stretch
1049	C-F stretch, C-O stretch

FT-IR of optimized formulation batch was done FT-IR spectra there 400-4000 cm^{-1} in the range in above spectra there is no found moisture absorption peak in the formulation.

6.12 . DSC study of optimized batch tablet :

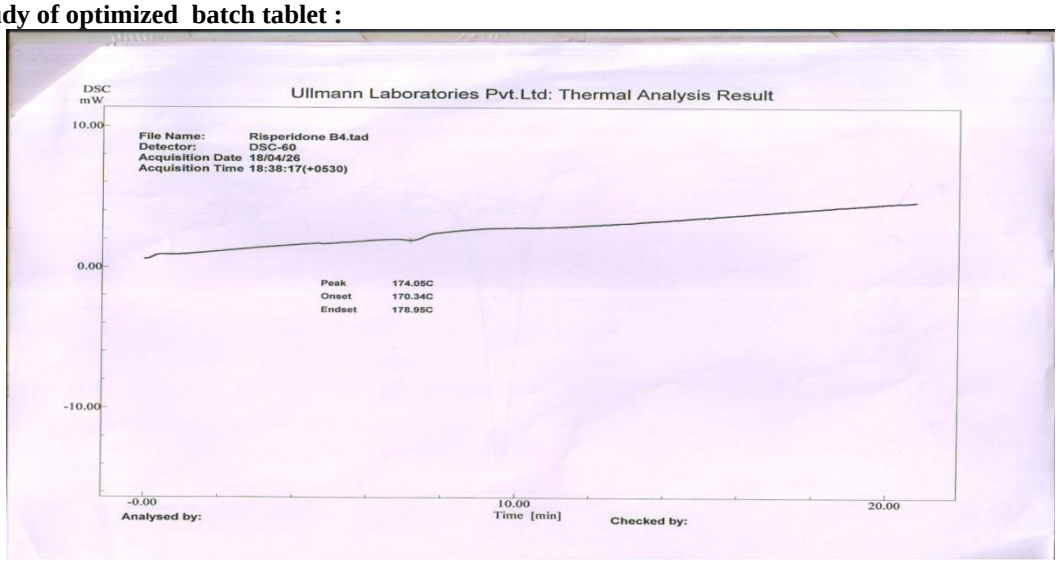


FIG.19. DSC of optimized batch F5

DSC thremogram of optimized tablet was also recorded as shown in fig Xix indicating endothermic peak at 174^0c.

6. METHOD OF DRUG ANALYSIS

6..15.1.UV spectroscopy of risperidone:

In uv spectroscopy study, the maximum wavelengths of risperidone in phosphate buffer were found to be 278 nm. The reported ⅄max of risperidone in phosphate buffer is 277 nm.

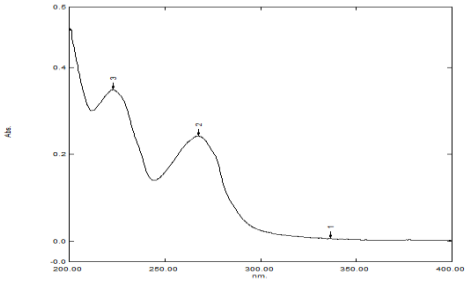


FIG .22.UV spectrum of risperidone in phosphate buffer pH 6.8

Table.26. Linearity data for risperidone in phosphate buffer pH 6.8

Sr.no	Concentration (ug/ml)	Absorbance at 277 nm
1	2	0.079
2	4	0.368
3	6	0.625
4	8	0.823
5	10	1.023

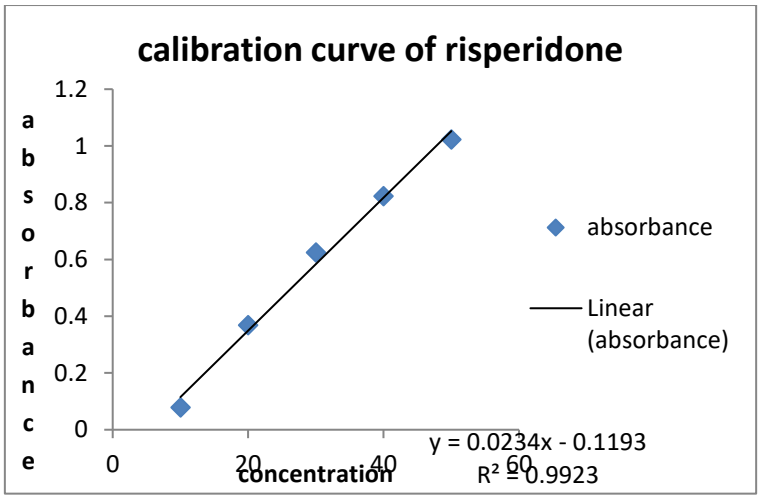


FIG .23.Calibration curve of risperidone in phosphate buffer pH6.8

6.16. EVALUTION OF PRELIMINARY TRIAL BATCHES :

Preliminary trial batches with different humidity, temperature condition was selected om the basis of different saturated salt solution. Experiment was analyased for release retardation and disintegration time, weight gain by moisture humidity condition. The tablet were evaluated for dissolution and other parameter. batches F1,F2,F3,F4,F6,F8 are gain more moisture absorption and weight gain, slow release in 20 minutes which is criteria for fast dissolving tablet .the batches F5 showed low moisture absorption (,negligible),more than 90% release in 2 minutes which acts as Superdisintegrants of cross carmellose, sodium starch glyoclate respectively. The tablet were formulated using F5 formula and evaluated for various parameters.

6.16.1.Evaluation of tablets parameter for different moisture & temperature batches : Preliminary trial batches with different combination of different moisture and temperature batches were formulated , was selected on the basis of preliminary screening . Experiment was analyazed by moisture effect on tablet formulation for release of disintegration time .the tablet were evaluated for dissolution and other parameter. In –vitro drug release of preliminary trial batches : I revealed that the batches FT1,FT2,FT3,FT4,FT5,FT6,FT7,FT8,FT9 are not given more than 80% drug release in 2 minutes which criteria for fast dissolving tablet .the batch of F5 showed more than 80% drug release in 2 minutes by using Superdisintegrants sodium starch glyoclate & crosscarmellose sodium with low moisture absorption of tablet formulation .the tablet were formulated and evaluated various parameter.

Table 27. Evaluation of tablet formulation of different moisture & temperature batches (precompression parameter)

Formulation codes	Wt gain by moisture(mg)	Angle of repose	Bulk density(gm/cm^2)
FT1	109mg	27.38^{0}c	0.40
FT2	122mg	24.70^{0}c	0.456
FT3	166mg	21.80^{0}c	0.5375
FT4	200mg	20.80^{0}c	0.562
FT5	08mg	18.26^{0}c	0.472
FT6	22 mg	17.27^{0}c	0.452
FT7	218mg	16.72^{0}c	0.51
FT8	112mg	16.17^{0}c	0.4511
FT9	13 mg	15.48^{0}c	0.49

6.16.2.weight gain by moisture -All prepared different moisture & temperature condition of tablet formulation powder were evaluated and result are in given table .all formulated powder in which F5 containing lowest moisture absorption.

6.16.3Angle of repose: All prepared different moisture & temperature condition of formulation tablet formulation powder were evaluated <20 ^{0} excellent type of powder flow .F5,F6,F7,F8,F9 batches excellent flow of powder. different moisture & temperature containing angle of repose in the range27.38^0 c-15.48 ^{0}c

Table 28.evalution of tablet formulation precompression:

Formulation codes	Tapped density(gm/cm^2)	Carr's index(%)	Hausner's ratio
FT1	**0.50**	**20%**	**0.8**
FT2	**0.48**	**6%**	**0.5**
FT3	**0.66**	**18.36%**	**0.18**
FT4	**0.75**	**25%**	**0.74**
FT5	**0.54**	**12%**	**0.12**
FT6	**0.51**	**13%**	**0.13**

FT7	**0.57**	**10.15%**	**0.10**
FT8	**0.62**	**19.3%**	**0.93**
FT9	**0.45**	**6%**	**0.06**

6.16.4 Tapped density ,bulk density:
All different moisture & temperature condition of tablet formulation powder evaluated and there result was in the range 0.45 to 0.75 gm/cm^2 tapped density,0.40 to 0.56 gm/cm^2 bulk density

6.16.5Carr's index ,hausner,s ratio :
All different moisture & temperature condition of tablet formulation powder evaluated and 5% -12% excellent flowability. carr's index in the range of 6%-20% .hausner's ratio in the range of 0.06-0.18

Table 29. Post compression parameter:

Formulation codes	Hardness(kg/cm$^{2)}$	Thickness(kg/cm$^{2)}$	Friability(%)
F1	**1.5±0.23**	**3.65±0.11**	**2.7±0.003**
F2	**2.5±0.56**	**3.62±0.20**	**2±0.10**
F3	**3.5±0.39**	**3.64±0.14**	**3±0.12**
F4	**1.5±0.81**	**3.64±0.28**	**1.9±0.08**
F5	**2.5±0.21**	**3.62±0.17**	**1±0.125**
F6	**3±0.36**	**3.63±0.23**	**2±0.18**
F7	**2±0.44**	**3.63±0.14**	**5±0.13**
F8	**3.5±0.19**	**3.63±0.18**	**2±0.18**
F9	**1.5±0.25**	**3.63±0.43**	**4±0.12**

6.16.6Hardness and friability : The hardness of the prepared fast dissolving tablet of risperidone was found to be in the range of 2.5 to 3 kg/cm^2 this ensure good handling characteristics of all batches. The friability of all the tablets was found to be less than 2% i.e. in the range of F5 are 1% ensuring tablets are resistant to abrasion.

Table .30.Evaluation of tablet formulation of different humidity& temperature batches post compression parameter

Formulation code	Weight variation	Disintegration time	Drug content
F1	**100±0.56**	**33sec**	**98.06%**
F2	**100±0.72**	**63sec**	**99.87%**
F3	**100±0.23**	**49sec**	**98.84%**
F4	**100±0.65**	**55sec**	**100.3%**
F5	**100±0.87**	**15sec**	**99.2%**
F6	**100±0.98**	**45sec**	**96.59%**
F7	**100±0.32**	**1min46sec**	**99.2%**
F8	**100±0.84**	**1min42 sec**	**96.22%**
F9	**100±0.98**	**50 sec**	**97.83%**

6..7weight variation :-the prepared fast dissolving tablet of different humidity ,temperature condition of tablet were evaluated for weight variation and the results are given in table. All formulated (F1 to F7) tablet passed .weight variation test as the % weight variation was within the pharmacopeial limits of +_ 5% of the weight and none deviate by more than 10% . the weight of all tablets was found to be uniform with low standard deviation valu$_e$.

6.8 uniformity of drug content :-the percentage of drug content for FT1 to FT7 was found to be in the range of 99.2% to 98.4% of risperidone given in the table it complies with official specifications.

In –vitro drug release of tablet formulation different moisture ,temperature condition F4,F5,F6

Sr no	Time (mintes)	FT4	FT5	FT6
1	2	0±0	2.68±0.90	0±0
2	4	38.17±1.256	99.90±0.50	4.28±0.66
3	6	41.50±0.4354		56.81±1.24
4	8	47.2±0.2918		99.37±0.875
5	10	80.23±0.3549		
6	12	99.37±1.15		

In –vitro drug release studies for batches F4, F5,F6 were carried out .F4,F5,F6 batches showed 99.37 %,99.90%,99.37% drug release respectively .out of these three batches F6 showned highest drug release of 99.90% 2 mintes.

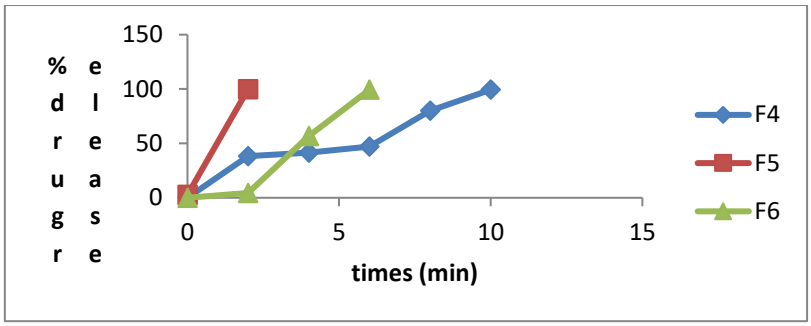


FIG. 23.DRUG RELEASE OF F4,F5,F6

The batch F5 shown highest drug release 99.70% with in time 2 min. hence it is evident that the selected release retardant of humidity condition played a vital role in the dissolution behaviour.

Table .34.In –Vitro drug release studies comparison of between bio revalant dissolution media and in-vitro drug release at pH 6.8 for optimized batch (F5)

Sr.no	Time(min)	% drug release (FaSSIF) pH5	% drug release (FeSSIF)pH6.5	% drug release pH 6.8
1	0	0.93	1.34	2.68±0.90
2	2	90.23	93.89	99.90±0.50
4	4		93.89	

In-vitro drug release studies were also performed using bio relevant dissolution medium (FaSSIF & FeSSIF) . bio relevant dissolution medium did not show any significant effect on the drug release as it is bcs class II drug which is f5 maintain condition of humidity & temperature. In bio relevant media the FaSSIF state having a pH 6.5 and that of FeSSIF has pH 5 . in the fasted state initially the drug release is more compare to the fed state which is due to the absence of food while in the fed state the drug release is more .at 4 mintues no significant change in the drug release as the drug risperidone ,which indicated that the drug release is independent of dissolution medium.Comparison of dissolution profiles at different PH was done . the pH for in-vitro drug release ,fasted state and fed state was 6.8,6.5 and 5 respectively .a different is drug release profile was observed. The drug release at ph 6.8,6.5 and 5 was found to be 99.70%,93.89%,90.23%

Table .35.Stability studies of formulation & evaluation:

Sr no	Formulation code	Thickness (kg/cm^2)	Friability	Hardness (kg/cm^2)
1	F3	3.00	3±0.89	4
2	F5	3.54	1±0.16	2.5
3	F8	3.23	2±0.63	3

All formulation code of different moisture & temperature condition of tablet formulation placed under stability condition of 1 month after study formulation no significant change in the f5 formulation of optimized batch.

Table 36. post compression tablet evaluation parameter

Sr no.	Formulation code	Wt variation	Disintegration time(sec)	Drug content (%)
1	F3	100±0.89	120	92.41
2	F5	100±0.12	17	99.23
3	F8	100±0.56	62	97.01

All above formulation of stability studies of different moisture level & temperature condition tablet formulation code F3,F5,F8 was studied and no significant variation in theF5 formulation.

Table 37.IN –VITRO DRUG RELEASE OF STABILITY STUDIES FORMULATION :

Sr no	Time (min)	F3	F5	F8
1	0	0±0	1.05±0.87	1..88±0.23
2	2	1.52±0.58	98.09±0.58	16.2±0.02
3	4	6.38±0.47		58±0.058
4	6	11.36±0.12		77±0.078
5	8	16.25±0.54		95.43±0.01
6	10	18.02±0.89		
7	12	27.09±0.74		
8	16	33.56±0.21		

9	18	68.47±0.33		
10	20	92.01±0.21		

In vitro drug release of above formulation in which F3 ,F5,F8 drug release of formulation code 92.01%,98.09%,95.43% respectively. Stability studies of formulation containing change in drug release profile of F3,F8 . no significant changes in the formulation code F5 .

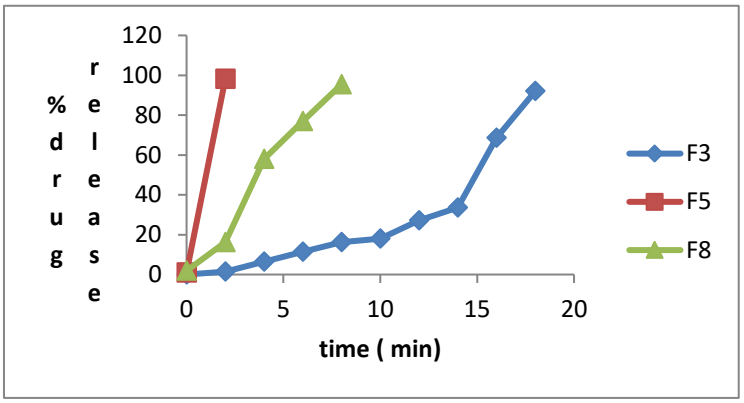


FIG .26.% DRUG RELEASE OF FORMULATION F3,F5,F8

6.17 EFFECT OF compression knob:

Table. 38.Evolution of tablet parameter :

Sr .no	Formulation code	Hardness (kg/cm^2)	Friability (%)	Disintegration Time (sec)
1	CT1	2	3	1min 46 sec
2	CT2	1.5	13	30 sec
3	CT3	2.5	1	20 sec
4	CT4	3	8	90 sec
5	CT5	4	1	3 min 8 sec

The hardness of the prepared fast dissolving tablet of risperidone of different compression mode or rotation knob was found to be in the range of 1.5 to 4 kg/cm^2. The friability of all the tablet was found to be less than 1 % in the range of 1 to 13% ensuring that the tablet are resistant to abrasion.

Table .39.of post compression parameter

Sr no	Formulation code	Weight variation	Drug content
1	CT1	100±0.47	93%
2	CT2	100±0.52	95%
3	CT3	100±0.23	98%
4	CT4	100±0.12	97%
5	CT	100±0.14	94%

All prepared fast dissolving tablet were evaluated for weight variation and drug content result are given in the table .all the formulated (CT1 –CT5) tablet passed weight variation test a the % weight variations was within test as the % pharmacopeial limits of ±5 of the weight and none Deviate by more than 10% . the weight of all tablet was found to be uniform with low standard deviation value.

6.17.1Uniformity of drug content:

The percentage of drug content for CT1 to CT 5 was found to be the range of 93% to 98% of risperidone given in table .it complies with official specification.

Table .41.In-vitro drug release of formulation code C3, C4, C5:

Sr no.	Time(min)	C3	C4	C5
1	0	1.43	4.10	0
2	2	100.26	28.53	6.24
3	4		36.22	19.77
4	6		39	31.02

In –vitro release studies of formulation batches C3,C4,C5 were carried out 100.26%,99.85%,97.04% drug release respectively. Out of these batches C3 batch showed highest release of 100.26%. different angle rotation of compression knob studies on formulation batches.

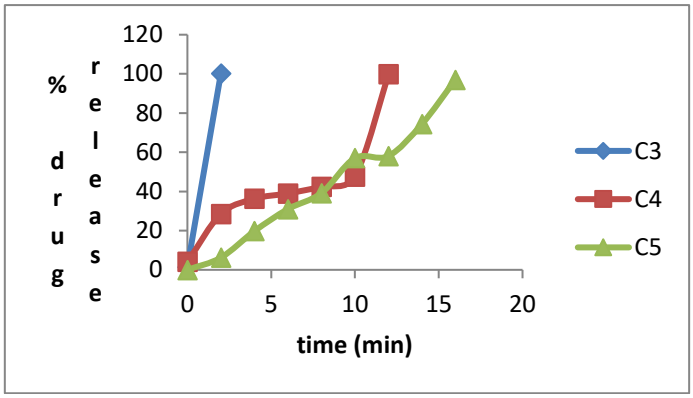


FIG .27.% DRUG RELEASE OF C3,C4,C5 BATCHES

From this study of compression knob effect on tablet were optimized C3 batch having more accurate result to formulation to conduct drug release of tablet.

SUMMARY AND CONCLUSION: -

The different moisture & temperature condition of different humidity condition of fast dissolving tablet formulation was formulated successfully by direct compression. was studied successfully. For the present work risperidone was chosen as a drug candidate. The present work led to be successfully formulation of different moisture & temperature condition of fast dissolving tablet of risperidone by using Superdisintegrants respectively which fast dissolving drug release in 2 minutes and give 99.90% release of F5 formulation. The drug excipient compatibility studies were carried out to determine interaction between drug & excipient. Moisture absorption of formulation were studies all formulation& lowest moisture absorption of F5 formulation.

DSC thremogram revealed that there was no interaction between the drug and excipient. Studies moisture absorption of F3, F5, and F8 formulation code that F5 contain suitable humidity (moisture & temperature condition).

The variation in the amount of release affected by different moisture & temperature condition spectrophotometric method was developed .studied drug, &drug content. A formulation batches design was used to investigate the effect the effect of drug release, moisture absorption by formulation, friability ,disintegration ,dissolution was taken as dependent on different moisture& temperature level.

Different moisture & temperature condition of release of dissolution.by using fast dissolving tablet Superdisintegrants .the compressed tablet were evaluated for thickness, hardness, friability, weight variation, disintegration time, drug content ,in vitro release and biorelevent studies.

Result for drug content shows percentage drug content for F5 as 99.90%.

Also the in-vitro drug release studies were carried out which show highest drug release 99.90%

Different moisture & temperature condition studies that with lowest level of moisture absorption in F5 and highest drug release in 2 min.

Hence F5 was selected as the optimizes batch .biorelevent dissolution studies that drug is hydrophilic ,the dissolution is independent of media used.

Deceased moisture absorption of formulation of increased release of drug dissolution.

Optimized moisture& temperature condition fast release fast dissolving tablet drug release for 2 minutes for F5 formulation .comparison of drug release at different $_{P}$H was done which revealed that the best release is at $_{P}$H 6.8 with 99.90% drug release.

Therefore it may be concluded that this different moisture & temperature condition was studied on formulation by precompression & post compression parameter. the optimized batch of F5 means 75% humidity40c is stable for formulation and drug .it may be industrially feasible .also there will be maintain stability longer less less effect on formulation

REFERENCE:-

1. Monika T, singh A, amit, effect of moisture content of excipient (microcrystalline cellulose) on direct compressible solid dosage forms , international journal pharmaceutical research, (2017),8(1)282-288.
2. Armin A. gerhardt ,moisture effects on solid dosage form formulation processing and processing ,journal of gpx compalience,2009,13(1),59-65.
3. Claes A , george z, the molecular basis of moisture effects on the physical and chemical stability of drugs in the solid state ,international journal of pharmaceutics, (1990), 62,87-95
4. Xiangji z,patricia h, moisture determination in hygroscopic drug substances by near infrared spectroscopy xiangji zhou, journal of pharmaceutical and biomedical analysis, (1998) ,17,219–225, 12.
5. S.malamatenis,p.govidas, moisture sorption and tensile strength of some tablet direct compression excipients, elsevier science biomedical division,1991,68,51-60. 11
6. Mira j,luigi g, an overview of the different excipients useful for the direct compression of tablet ,international journal of pharmaceutics (2014)473, 64-72

G. Sandhyarani, formulation and evaluation of Orodispersible tablets of risperidone, World health journal of pharmaceutical research , 2017,6(7),507-518.
8. Ehab m. elzayat ,studying the impact of formulation and processing parameters on the release characteristics from hydroxypropyl methylcellulose matrix tablets of diclofenac, Acta Poloniae Pharmaceutical Drug Research,2016, 73 (2),. 439-452.Mudhulkar M, Preethi S, orally disintegrating tablets: an overview, International Research Journal of Pharmaceutical and Applied Sciences , 2012, 2(5),124-132
9. Maja š, a compressibility and compatibility study of real tableting mixtures: the effect of granule particle size, acta pharm, , (2012),62, 325–340.
10. Kapil r. compression parameters involved in powder compression and manufacturing of tablet, 2011 ,7(5), 13
11. Sarsvatkumar p, compression physics in the formulation development of tablets, Critical Reviews TM in Therapeutic Drug Carrier Systems,2006,23(1):1.
12. Andries f. ,effect of compression force ,humidity& disintegrant on the disintegrant & dissolution of directly compressed furosemide tablets using crosscarmellose sodium as disintegrant ,tropical journal of pharmaceutical research ,2003,(1),125-135
13. Arijit G. ,mouth dissolving tablet ; a new venture in modern formulation technology, the pharma innovation,2012,1(8),14-31.
14. Ganesh D C ,kundan S P, me of some physical parameter and crrospovidone on directly
15. Compressed frusemide tablets, Asian journal of pharmaceutics,2008,(oct-dec),235-240.
16. Alsabbagh M ,assessment of the impact of formulation and packaging on the stability of cabrgoline tablet, international journal of pharmacy & pharmaceutical science,2012,4(5),511-518.
17. Preetanshu p, Dilibir S B, influence of process parameter on tablet bed microenvironment factors during pan coating ,2014,15(2),296-305.
18. Tesfai S, claes A ,the effect of moisture content on the compression and bond – formation of amorphous lactose particle, international journal of pharmaceutics ,1997,146(1),101-114.
19. Peck L C ,the effect of moisture content on compression properties of maltodextrins ,journal of pharmacy and pharmacology,1990,2042-7158.
20. Marc S G ,process consideration in reducing tablet friability and their effect on in vitro dissolution ,drug development and industrial pharmacy,1994,20,11-29.
21. Nursin G ,the consolidation & compressibility properties of some novel directly compressible filler –binder ,acta poloniac, 2000,57(4),311-317.
22. Yanixa LI, yeswant D,a study on moisture isotherm of formulation use of polynominal
23. Equitation to predict the moisture isotherm of tablet predicting ,AAps pharm sci-tech , 2003,4(4),59(1-8).
24. Ali N, an overview of effect of moisture on compaction &compression, pharmaceutical
25. Technology,2005,46-66.
26. Michael S, Arnold USA ,choosing method for measuring for material moisture content,2002,2,9.
27. John A, Omonyemen E ,effect of humidity on physical properties of aspirin tablets produced by melt granulation & slugging method, journal of pharmacy & biological science, 2013,7(5),20-25.
28. W chen ,D guo, effect of highly hygroscopic excipient on hydrolysis of simvastatin in tablet at high relative humidity, indian journal of pharmaceutical science, 2012,527-534.
29. Maja S, Ljja I, a compressibility & compatibility study of real of tableting mixture: the effect
30. Of granule particle size, acta pharm,2012,62,325-340.
31. priyanka N ,kusum S ,orally disintegrating tablet formulation, preparation technique & evaluation ,journal of applied pharmaceutical science,2011,1(4),35-45.
32. Emant b, saranjit S ,increase in the rate of moisture grain hygroscopic drug in the presence of non-hygroscopic water soluble substance :study of generalization of this hit hetero unknown
33. Phenomena ,explanation to this to it's once & implication in formulation development ,Asian journal of pharmaceutics,2007,2007,1(1),69-76.
34. lachman :the theory & practice of industrial pharmacy, Varghese publishing house ,third edition .
35. Marrtin a:physical pharmacy, B.I. waveray, sixth eidition,2011.
36. Harhata S ,burgio J ,effect of storage at specified temperature& humidity on properties of the The direct compressible tablet formulation ,journal of pharmaceutical science,2015,5(12),1749.
37. Gopinath R, naido ,international journal of pharmaceutical& biological archives,2013,4(6),1134-1154.
38. Nehal S, garima G, fast dissolving tablet preparation ,characterization & evaluation :on overview ,international journal pharmaceutical science review &research,2010,4(2),15.
39. Devala R, development & validation of TLC –densitometry method for the estimation of antipsychotic drugs in bulk& tablet formulation ,international journal of chemical tech research ,2010,2(4),2063-2069.
40. Rockville M, dissolution media & stimulating fasted & fed states, may 2004 .
41. Arnold W, Saburohase G ,relative humidity-temperature &relationship of some saturated Salt solution in the temperature range 0^0 to 50^0c,journal of research of national bureau of standard,1954,53(1),9-25.
42. Equilibrim relative humidity saturated salt solution-omega.
43. Venkatesh K ,formulation & evaluation of risperidone fast disintegrating tablet by using co-processed Superdisintegrants ,2016,3(2),334-342.

44. Shende M ,studies of moisture absorption & development of stable ranitidine hydrochloride Tablet ,journal of pharmacy research ,2009,2(9),1438-1443.
45. Ashraful S ,amirh study of moisture absorption by ranitidine hydrochloride effect of % RH, Excipient, dosage form & packaging material ,Dhaka university. pharm .science,2000,7(1),59-64.