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FORMULATION DEVELOPMENT AND EVALUATION OF RANITIDINE HYDROCHLORIDE TABLETS 150 MG

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ABSTRACTS

Ranitidine Hydrochloride is a antihistaminic drug and H_2 antagonists which is a competitive inhibitors of histamine at the parietal cell H_2 receptor. It suppress the normal secretion of acid by parietal cells and the meal-stimulated secretion of acid. The present research work involves the formulation development and evaluation of Ranitidine Hydrochloride Immediate Release tablets. The final optimized formulation contains microcrystalline cellulose (Avicel PH 112) as diluents, Croscarmellose sodium (Ac-di-sol-SD-711) as disintegrant in intragranular part and magnesium stearate, calcium stearate as lubricants in extragranular part in the optimized batch. Ranitidine Hydrochloride immediate release tablet disintegrate within 15 mins for the treatment of Peptic ulcer. As Ranitidine Hydrochloride is a moisture sensitive drug, direct compression method was selected for the formulation of Ranitidine Hydrochloride IR tablets. Among the 10 trials, trial 3 (0.75% magnesium stearate of Peter Greven, 1% Croscarmellose sodium) and trial 9 (1% Calcium stearate,1% Croscarmellose sodium) showed the very close DR profile and having higher f_2 values followed by magnesium stearate of Peter Greven vendor at 0.75% concentration showed better results in lower concentration than 1% Calcium stearate. All the trials produce tablets meeting all the product specifications like thickness, hardness, weight uniformity, appearance and the tablets compression challenges such as chipping, capping, sticking, picking, and lamination are no where observed.

KEYWORDS: Ranitidine Hydrochloride, Immediate release tablet, Crosscaramellose sodium, Avicel PH102.

INTRODUCTION

Tablets are solid dosage forms usually obtained by single or multiple compressions of powders or granules. In certain cases tablets may be obtained by moulding or extrusion techniques. They are uncoated or coated. Tablets contain one or more active ingredients. They may contain excipient such as gastrointestinal tract, colouring matter authorized by the appropriate national or regional authority, and flavouring substances.[1] When such excipient are used, it is necessary to ensure that they Immediate release oral dosage forms i.e., tablets and capsules, are most widely used drug delivery systems available. These products are designed to disintegrate in the stomach followed by their dissolution in the fluids of the gastrointestinal tract.

The release of drug from the conventional tablet dosage form and its absorption from the GIT depends upon two main processes. Firstly, the disintegration of tablet and dissolution of the particles followed by permeation through the GIT into the blood. Disintegration is the rate limiting step in case of highly soluble drugs whereas dissolution is the rate limiting step in case of drugs with low solubility.[3]

do not adversely affect the stability, dissolution rate, bioavailability, safety, or efficacy of the active ingredient(s); there must be no incompatibility between any of the components of the dosage form. Diluents, binders, disintegrating agents, glidants, lubricants and other excipient are capable of modifying the behaviour of the dosage forms.[2] Tablets are single-dose preparations intended for oral administration.

IMMEDIATE RELEASE TABLET

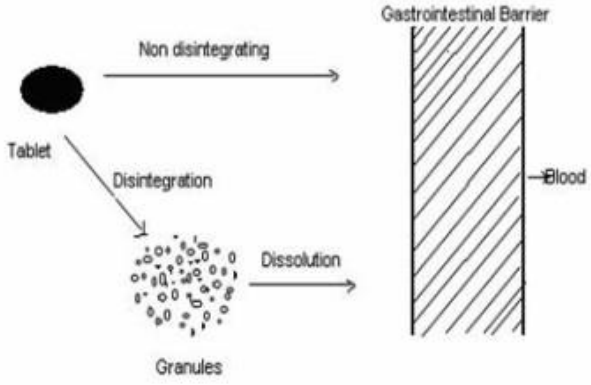

Fig no. 1: Rate limiting steps in the absorption of drug from the GIT.

The release of drug from an immediate release dosage form can be achieved by, Placing the drug in a layer or coating that is sufficiently thin to allow fast penetration by gastrointestinal fluid which then leaches the drug at a rapid rate.

- Incorporating the drug in a mixture that includes a supporting binder or other inert material that dissolves readily in gastrointestinal fluid, releasing the drug as the material dissolves.
- Using a supporting binder or other inert material that rapidly disintegrates into fine particles upon contact with gastrointestinal fluid, with both the binder particles and the drug quickly dispersing into the fluid.[4]

Advantages of Immediate Release Tablets

- Economical and cost effective.
- Quick onset of action.
- Suitable for industrial production.
- Improved stability and bioavailability.
- Provides some advantages of liquid dosage forms.
- Adaptable and amendable to existing processing and packaging machinery.
- Unique product differentiation.

Disadvantages of Immediate Release Tablets

- Rapid drug therapy intervention is not possible.
- Sometimes may require more frequency of administration.
- Dose dumping may occur.
- Reduced potential for accurate dose adjustment.

Desired Criteria For Immediate Release Drug Delivery System

Immediate release dosage form should have these following properties.

- In the case of solid dosage it should dissolve or disintegrate in the stomach within a short period.
- In the case of liquid dosage form it should be compatible with taste masking.
- Be portable without fragility concern.
- Have a pleasing mouth feel.
- It should not leave minimal or no residue in the mouth after oral administration.
- Exhibit low sensitivity to environmental condition as humidity and temperature.
- Be manufactured using conventional processing and packaging equipment at low cost.
- Rapid dissolution and absorption of drug, which may produce rapid onset of action.

Potential Candidate For Immediate Release Oral Dosage Form[5]

Analgesics and Anti-inflammatory Agents

Aloxiprin, Auranofin, Azapropazone, Benorylate, Diflunisal, Etodolac, Fenbufen, Sulindac, Fenoprofencalcim, Flurbiprofen, Ibuprofen, Indomethacin, Ketoprofen, Meclofenamic Acid, Mefenamicacid, Nabumetone,Naproxen, Oxyphenbutazone, Phenylbutazone, Piroxicam.

Gastro-intestinal Agents

Bisacodyl, Cimetidine, Cisapride, Diphenoxylatehcl, Domperidone, Famotidine, Loperamide, Mesalazine, Nizatidine, Omeprazole, Ondansetron HCl, Ranitidine HCl, Sulphasalazine.

Anthelmintics

Albendazole, Bephenium, Hydroxynaphthoate, Cambendazole, Dichlorophen, Ivermectin, Mebendazole, Oxamniquine, Oxfendazole, Oxantelembonate, Praziquantel, Pyrantelembonate, Thiabendazole.

Anti-Arrhythmic Agents

Amiodarone HCl, Disopyramide, Flecainideacetate, Quinidine sulphate.

Histamine H2-Receptor Antagonists

Acrivastine, Astemizole, Cinnarizine, Cyclizine, Cyproheptadinehcl, Dimenhydrinate, Loratadine Flunarizine HCl, Meclozine Hcl, Oxatomide, Terfenadine, Triprolidine.

Anti-Bacterial Agents

Benethamine Penicillin, Cinoxacin, Ciprofloxacin HCl, Clarithromycin, Clofazimine, Cloxacillin, Demeclocycline, Doxycycline, Erythromycin, Ethionamide, Imipenem, Nalidixicacid, Nitrofurantoin, Rifampicin, Spiramycin, Sulphabenzamide, Sulphadoxinesulphamerazine, Sulphacetamide, Sulphadiazine, Sulphafurazole, Sulphamethoxazole, Sulphapyridine, Tetracycline, Trimethoprim.

Anti-Coagulants

Dicoumarol, Dipyridamole, Nicoumalone, Phenindione.

Anti-Depressants

Amoxapine, Ciclazindol, Maprotiline HCl, Mianserin HCl, Nortriptyline HCl, Trazodone HCl, Trimipramine Maleate.

Anti-Diabetics

Acetohexamide, Chlorpropamide, Glibenclamide, Gliclazide, Glipizide, Tolazamide.

Anti-Epileptics

Beclamide, Carbamazepine, Clonazepam, Ethotoin, Methoin, Methsuximide, Methylphenobarbitone, Oxcarbazepine, Paramethadione, Phenacemide, Phenobarbitone, Phenytoin, Phensuximide, Primidone, Sulthiame, Valproic Acid.

Anti-Fungal Agents

Amphotericin, Butoconazolenitrate, Clotrimazole, Econazolenitrate, Fluconazole, Flucytosine, Griseofulvin, Itraconazole, Ketoconazole, Miconazole, Natamycin, Nystatin, Sulconazole nitrate, Terbinafinehcl, Terconazole, Tioconazole, Undecenoic Acid.

Tablet manufacturing processes

i) Granulation method.
a) Wet granulation.
b) Dry granulation.
ii) Direct compression method.

Compacted or compressed tablets are produced from granulations or powder mixtures made by the following general techniques.

- Direct compression (dry mixing and blending)
- Wet granulation (high shear, low shear) combined with tray drying or fluid-bed drying.
- Dry granulation by roller compaction or slugging.[6]

Introduction To Product Development

Product development usually begins when the active chemical entity has been shown to possess the necessary attributes for a commercial product. Generally product development activities can be sub divided into formulation development and process development.[7]

Formulation development

Formulation development provides the basic information on the active chemical, formula and the impact of raw materials or excipients on the product. A typical supportive data generated during these activities may include:

- Preformulation profile, providing all the basic physical and chemical information about the chemical entity.
- Formulation profile, consisting of physical and chemical characteristics required for the product, drug excipient compatibility studies, and effect of formulation on In-vitro dissolution.
- Effect of formulation variables on the bioavailability of the product.
- Specific test methods.
- Key product attributes and specifications.
- Optimum formulation.[8,9]

Formulation development is not considered complete until all the factors which significantly alter the formulation have been studied. Subsequent minor changes to the formulation, however, may be acceptable, provided they are thoroughly tested and shown to have no adverse effects on product characteristics. In case of drug development process, compound tested is only one.[10,11] A variety of studies must be performed for this single drug, each designed to characterize its efficacy, safety, or purity. Much of the data generation is driven by strict and extensive regulatory control and most of the studies are interdependent.[12,13]

AIM AND OBJECTIVES

Aim

The aim of present work is to determine the efficiency of lubricant with effective lubricant concentration among two selected lubricant (Magnesium Stearate and Calcium Stearate) and to sketch out the effect of lubricant concentration and disintegrant concentration in the formulation of Ranitidine HCl Immediate Release tablets 150 mg.

Objectives

The different objectives, which will be achieved during this work of Ranitidine HCl Immediate Release, are as follows.

- To study the challenges that may occur during the direct compression by changing the lubricant i.e Magnesium Stearate and Calcium Stearate and with different lubricant concentrations and disintegrant concentration.
- To study the effect of the selected lubricant,their respective lubricant concentration and disintegrant concentrations on various pre-compression parameters.
- To study changes that may occur in the post compression parameters and release pattern of drug by changing the lubricant and concentration of lubricant.
- To determine the drug release via dissolution with selecting an appropriate dissolution media and USP apparatus-II, which helps determination of the drug release into systematic circulation after ingestion.
- To optimise the method with the specified concentration of lubricant and disintegrant, so that the process meets its predetermined specification and quality attributes.
- To achieve the robustness of the process and dissolution methods by comparing with different trail samples.
- To determine the effective concentration of lubricant and disintegrant based on the similarity factor.
- To develop a stability indicating assay method for the developed drug formulation.
- To evaluate the prepared immediate release tablet dosage forms.
- To develop stable and efficacious immediate release tablet of an anti ulcer drug that is equivalent to the reference product i.e. to match the dissolution profile with that of the innovator.

DRUG PROFILE

RANITIDINE HYDROCHLORIDE

1. Microdetails of the drug molecule

i) Chemical name: **Ranitidine Hydrochloride**

ii) Chemical formula: N[2-[[[5-[(dimethylamino)]-2-furanyl}methyl]thio]ethyl]-N'-methyl-2-nitro-1,1- ethenediamine,HCl

iii) Empirical formula: $C_{13}H_{22}N_4O_3S.HCl$

iv) Molecular weight: 350.87

v) Chemical structure

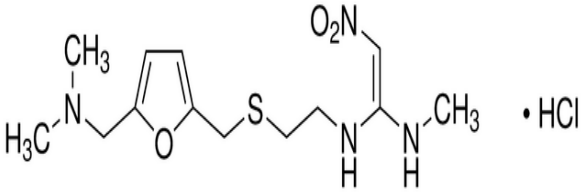

Fig no. 2: Structure of Ranitidine Hydrochloride.

Physical properties

Table no. 1: Physical properties of Ranitidine Hydrochloride.[14]

Physical properties	Description
Name and description	**Ranitidine**: Off-whice to pale yellow powder with a characteristic sulfur-like odor..
Solubility	Freely soluble in ethanol (95%),in chloroform, in ether and in water
Melting point	133 to 134 °C.
Polymorphism	Form II
pKa (strongest basic)	8.08
Hygroscopicity	Very hygroscopic
Bulk density	0.56 g/ml
Tapped density	0.70 g/ml
Hausner's Ratio	1.25
Compressibility Index	

3. Chemical properties

Table no. 2: Chemical properties of Ranitidine Hydrochloride.

Pka	**Ranitidine has a P^{ka} value of 8.2**
Photo sensitivity	Sensitive,Protection required
Purity/ Assay	97.5%-102.0% w/w
Partition coefficient	Log P : 1.03 ±0.11
UV Absorption	315 nm
Moisture sensitivity	Sensitive,Protection recommended.

4. Clinical Pharmacological properties

Table no. 3: Clinical Pharmacological properties of Ranitidine Hydrochloride[14,15]

Category	Anti-histaminic
Mechanism of action	The H2 antagonists are competitive inhibitors of histamine at the parietal cell H2 receptor. They suppress the normal secretion of acid by parietal cells and the meal-stimulated secretion of acid. They accomplish this by two mechanisms: histamine released by ECL cells in the stomach is blocked from binding on parietal cell H2 receptors which stimulate acid secretion, and other substances that promote acid secretion (such as gastrin and acetylcholine) have a reduced effect on parietal cells when the H2 receptors are blocked.[16,17]
Route of administration	Oral/IM/IV routes
Bioavailability	50%
Indications and Usage	The treatment of duodenal ulcer, benign gastric ulcer, reflux esophagitis, post-operative peptic ulcer, Zollinger-Ellison syndrome and other conditions where reduction of gastric secretion and acid output is desirable. These include treatment of NSAID-induced lesions (ulcers, erosions) and gastrointestinal symptoms and prevention of their recurrence, prophylaxis of gastrointestinal hemorrhage from stress ulceration in seriously ill patients.[18]

5. Pharmacokinetic / Pharmacodynamic Data

Table no. 4: Pharmacokinetic / Pharmacodynamic Data of Ranitidine Hydrochloride.

T max	2-3 hrs
C max	440- 545 mcg/mL
$T_{1/2}$	2.5- 3 hours
Bioavailability	50%
Site of absorption	50% absorbed after oral administration
Distribution	Volume of distribution 1.4 L/Kg
Serum protein binding	15%
Metabolism	Hepatic metabolism is the major pathway. Metabolism occurs by oxidation.
Metabolites	N-Oxide, S-Oxide and desmethyl ranitidine
Activity of Metabolites	Meta-O-dealkylated flecainide is one-fifth as potent as the drug[19,20]
Route of excretion	Feces, urine
Elimination half life	2.5 - 3 hours

EXPERIMENTAL WORK

Analytical Method For Ranitidine Hydrochloride

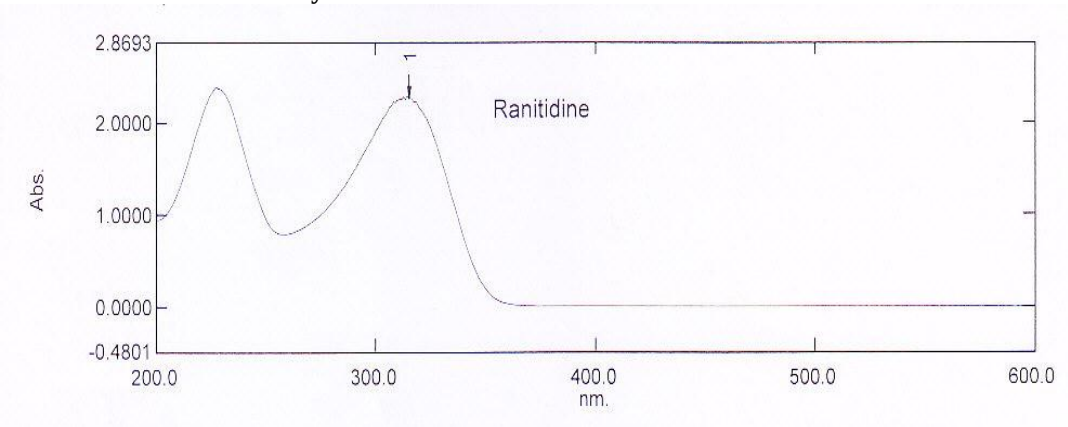

Fig no. 3: Full UV-Visible spectra of Ranitidine Hydrochloride.

Determination of λmax

Weighed an accurate amount 10mg of Ranitidine Hydrochloride was dissolved in 100ml of distilled water to obtain a 100µcg/ml concentration of Ranitidine Hydrochloride in solution. This solution was subjected to scanning between 200 – 400 nm and absorption maxima at 315 nm was determined.

Preparation of Standard Stock Solution

A stock solution containing 100 µcg/ml of pure drug was prepared by dissolving accurately weighed 10mg of Ranitidine Hydrochloride in distilled water and volume was adjusted to 100ml with the same in 100ml volumetric flask.

Preparation of working standard solution

Stock solution is used as working standard solution.

Construction of calibration curve

The aliquots working standard solution was diluted serially with distilled water to obtain the concentration range of 1 – 21 µcg/ml. Then 3, 6, 9, 12, 15,18,21 ppm solution are prepared and a calibration curve for Ranitidine Hydrochloride was obtained by measuring the absorbance at the λmax of 315 nm. These solutions were used for the construction of calibration curve. The linear regression analysis was carried on absorbance data points. A straight line equation (Y = mx + C) was generated to facilitate the calculation of amount of drug.

Absorbance = (Slope x concentration) + intercept

Statistical parameters like the slope, intercept, coefficient of correlation, standard deviation, relative standard deviation, and standard error were determined.

Table no. 4: Standard absorbance of Ranitidine Hydrochloride.

Conc. (µg/ml)	Absorbance
Blank	0.000
3	0.142
6	0.278
9	0.427
12	0.532
15	0.672
18	0.812
21	0.964

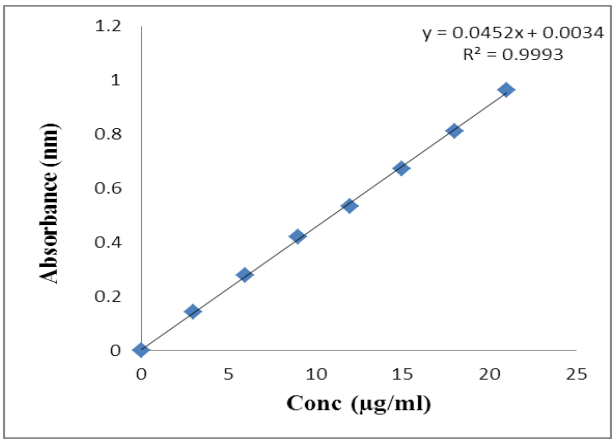

Fig. no 4: Standard calibration Graph of Ranitidine Hydrochloride.

PREFORMULATION STUDIES

Preformulation testing is the first step in the development of dosage forms of a drug substance. It can be defined as an investigation of physical and chemical properties of a drug substance alone and when combined with the excipients. It is the first step in the rationale development of dosage forms. The overall objective of preformulation studies is to generate information to the formulator in developing stable and bioavailable dosage forms, which can be mass-produce.

Preformulation studies on active pharmaceutical ingredients (API), Inactive ingredients (Excipients) and their combinations were carried out to serve following purposes.

A. Bulk active testing of Ranitidine Hydrochloride
B. Solubility data by saturated solubility method.
C. Drug and Excipients compatibility studies.
D. Characterization of Innovator Product.

Bulk active testing of ranitidine hydrochloride

Organoleptic evaluation

These are preliminary characteristics of any substance, which is useful in identification of specific material. Following physical properties of active pharmaceutical ingredient were studied.

Color- White to pale yellow, granular substance.

Taste- Bland in taste.

Odour -It is odorless or may have slight characteristics odor.

Loss on drying

0.5g of sample Ranitidine hydrochloride was accurately weighed and the powder was kept in a IR moisture analyzer apparatus for 5 min. At 105ºc and the moisture content was observed to 0.25% w/w.

Table no. 5: Physical parameters of Ranitidine Hydrochloroide API [Flow properties].

Sl. No	Parameter	Results
1	Bulk density	0.56 g/ml
2	Tap density	0.70 g/ml
3	Carr's index	20.00 %
4	Hausner's Ratio	1.25
5	Angle of repose	38˚

Ranitidine Hydrochloroide has a flow property between 16-20 that is fair.

Particle Size analysis

2-3 gm Ranitidine Hydrochloroide was weighed and transferred to the Malvern particle size analyzer (Mastersizer 2000 version 5.60). It is operated by the laser diffraction technique. It can be used for wet and dry type materials. It can analyse the particle with the range of 0.01µm to 3500µm.

Procedure

Placed about 0.5 g of sample in clean and dried sample tray. The particle size for two times for the same sample was measured. Average result was taken and reported.

B. solubility profile

Ranitidine Hydrochloride is freely soluble in acetic acid, water, moderately soluble in alcohol, very slightly soluble in dichloromethane, freely soluble in methyl alcohol, Sparingly soluble in dehydrated alcohol and in chloroform.

Table no 6: Data of solubility profile of drug in various solvents

Sl.No.	Solubility medium	Solubility of RHCl [mg/ml]
1	Water	Freely Soluble
2	Acetic acid	Freely Soluble
3	Alcohol	Moderately Soluble
4	Dichloromethane	Very Slightly Soluble
5	Methyl alcohol	Freely Soluble
6	Dehydrated alcohol	Sparingly Soluble
7	Chloroform	Sparingly Soluble

pH solubility analysis

A semi quantitative determination of solubility can be made by adding a solute in small incremental amounts to fixed volume of solvents. Solubility of Ranitidine Hydrochloride was studied over the pH range of 1.2 to 6.8 and it was inferred that Ranitide HCl is a freely soluble drug substance.

Table no. 7: pH Solubility profile of Ranitidine Hydrochloride.

Sl. No.	Media	Solubility [mg/ml]	Dose/Solubility Ratio
1	0.1 N HCl	162.27	0.92
2	pH 4.5 Acetate buffer	148.11	1.01
3	Purified Water	766.56	0.19
4	pH 6.8 Phosphate Buffer	747.82	0.20

DRUG-EXCIPIENT COMPATIBILITY STUDY

It is necessary to confirm that the drug does not react with the polymers and excipients under experimental conditions and affect the shelf life of product or any other unwanted effects on the formulation.

Different excipients are included in the dosage form along with the active ingredient.

The excipients for the compatibility study have been selected on the basis of following considerations.

- Excipients included in the innovator's product.
- The quantity of excipients used is in line with the IIG (Inactive ingredient guideline of USFDA).
- Well established usage of the excipients in terms of safety and efficacy.

Method: DSC measurements were carried out using a thermal analyser-60 WS, DSC-60 (Shimadzu, japan). All the samples were prepared by placing 10mg of the powder in an aluminium pan for analysis and each sample was heated from 30°C to 300°C at a rate of 10°C per minute in an atmosphere of nitrogen.

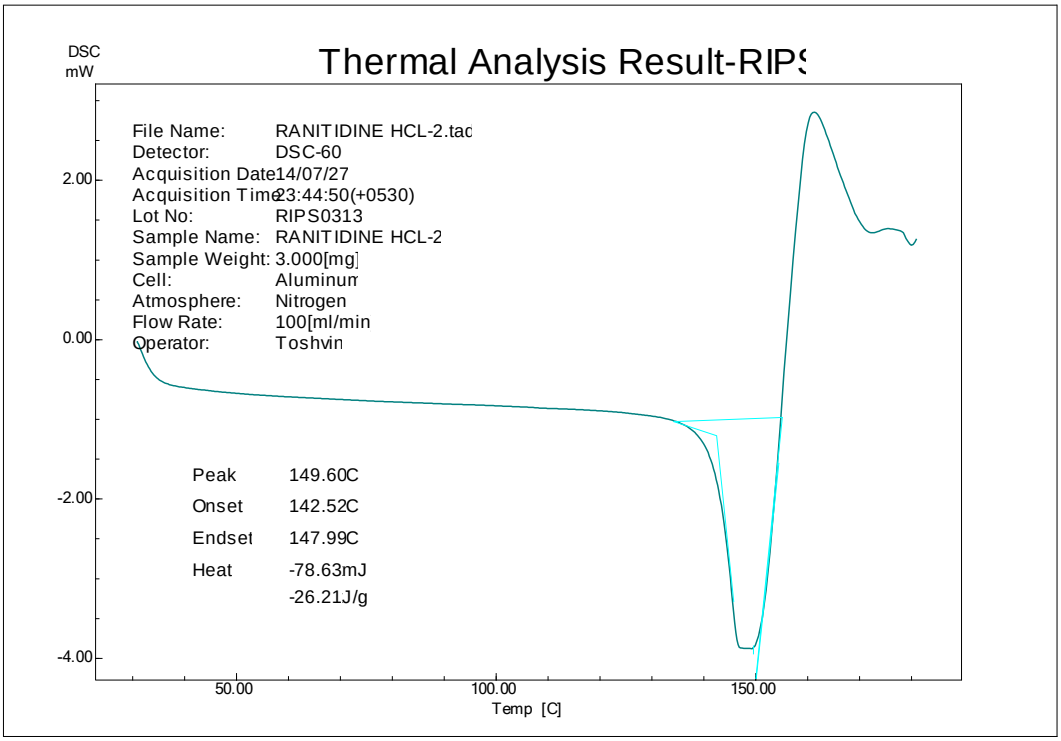

Fig no.5: Melting point of Ranitidine Hydrochloride API.

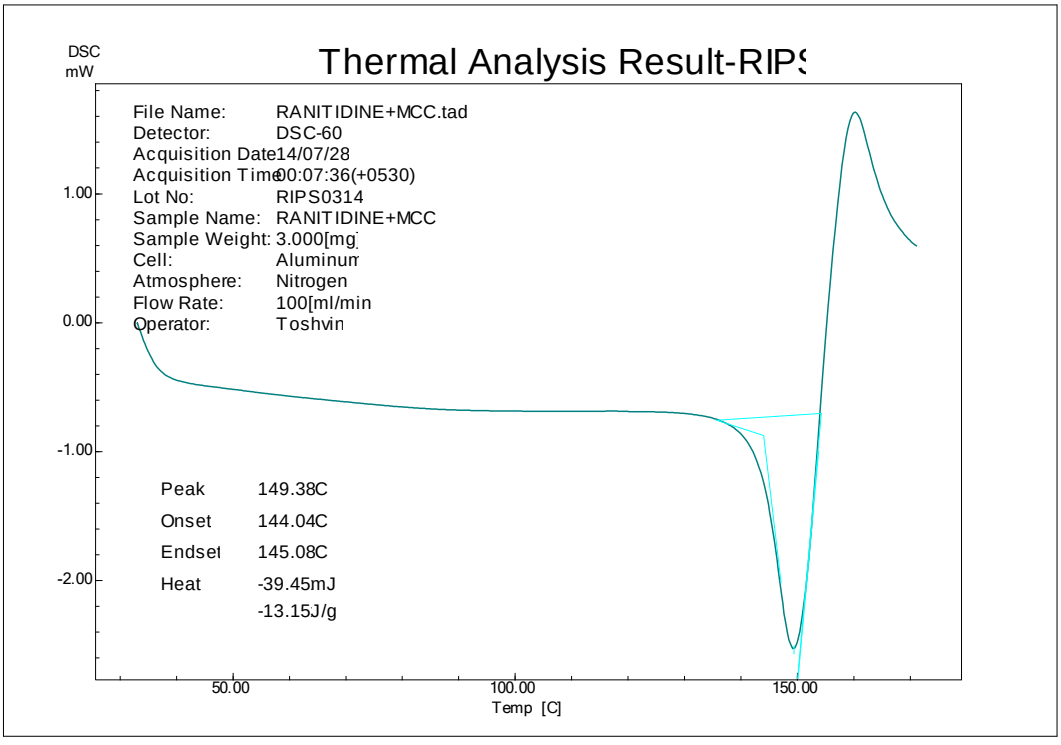

Fig no. 6: DSC of Ranitidine HCl + Microcrystalline Cellulose.

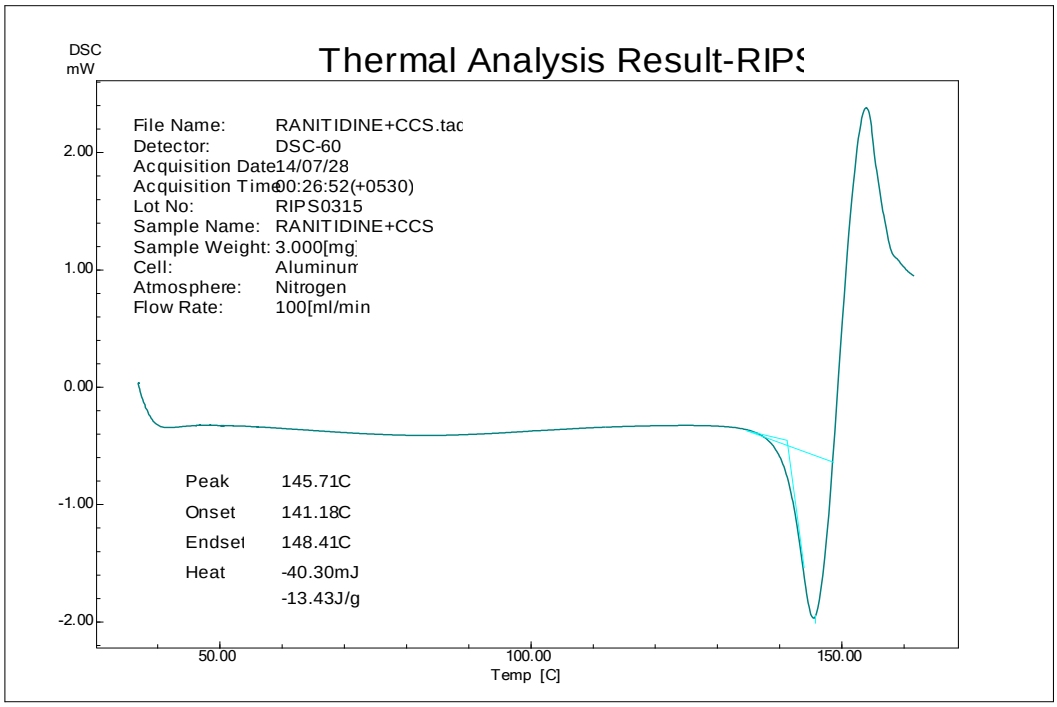

Fig no.7: DSC of Ranitidine HCl + Croscarmellose sodium.

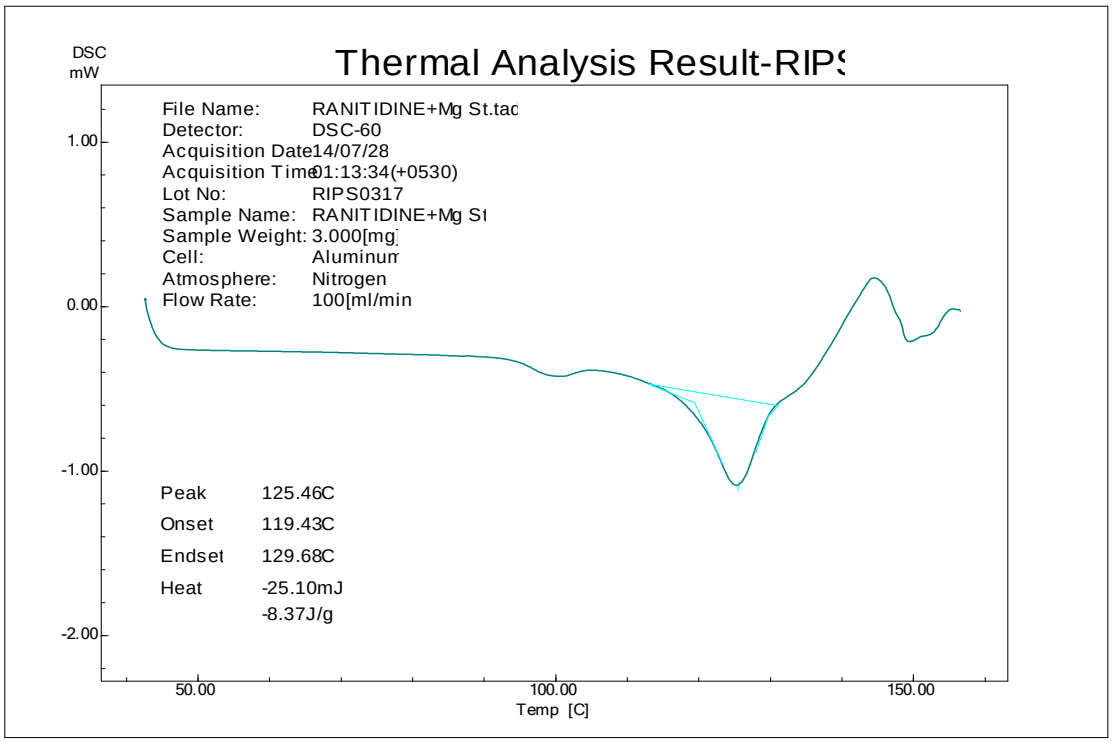

Fig no.: DSC of Ranitidine HCl + Magnesium stearate.

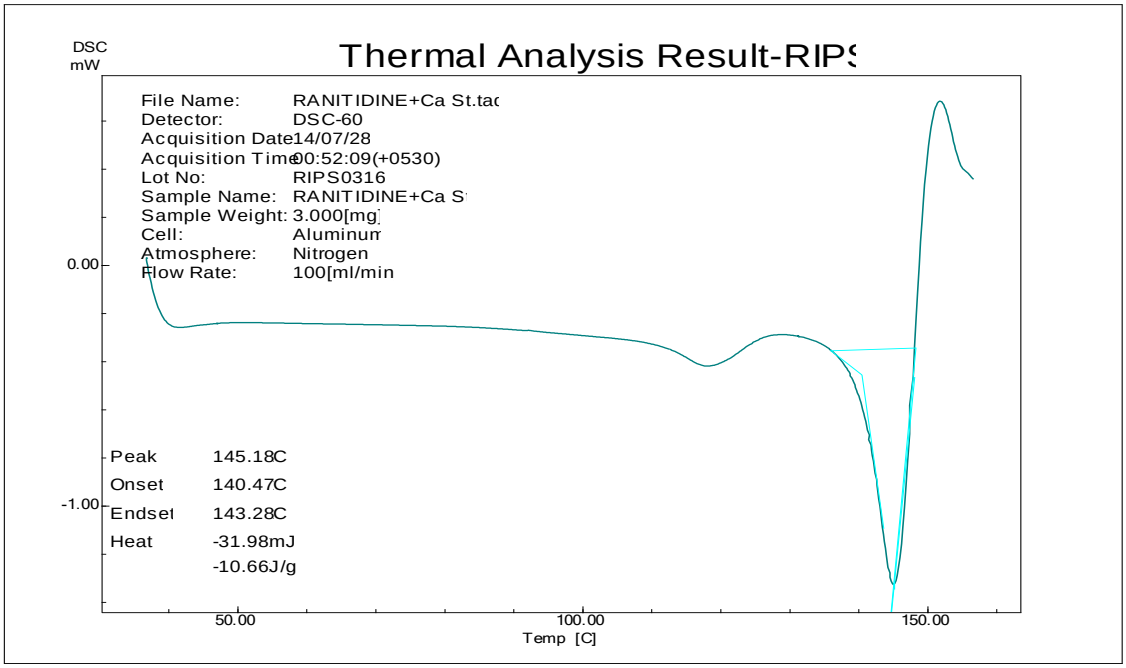

Fig no. 8: DSC of Calcium stearate based formulation.

Table no. 8: Schedule for analysis of Sample of compatibility study.

Parameters	**2-8° C 1M Closed**	**40° C/75%; 1M Closed**
Ranitidine Hydrochloride API		
Description	Off white	Off white
Assay	**99.89**	**99.85**
Related Substance		
Ranitidine Simple Nitroacetamide	0.00	0.00
Ranitide Oxime	0.00	0.00
Ranitidine amino alcohol	0.00	0.00
Ranitidine Related Compound A	0.00	0.00
Ranitidine S-Oxide	0.01	0.01
Ranitidine N-Oxide	0.00	0.00
Ranitidine Complex Nitroacetamide	0.00	0.00
Ranitidine formaldehyde adduct	0.01	0.03
Ranitidine Related compound B	0.07	0.07
Unknown impurity	0.00	0.00
Total Impurity	0.09	0.11
Ranitidine Hydrochloride API + Microcrystalline Cellulose (1:2)		
Description	Off white	Off white
Assay	**99.87**	**99.86**
Related Substance		
Ranitidine Simple Nitroacetamide	0.00	0.00
Ranitide Oxime	0.00	0.01
Ranitidine amino alcohol	0.00	0.00
Ranitidine Related Compound A	0.00	0.00
Ranitidine S-Oxide	0.01	0.01
Ranitidine N-Oxide	0.00	0.00
Ranitidine Complex Nitroacetamide	0.00	0.00
Ranitidine formaldehyde adduct	0.01	0.02
Ranitidine Related compound B	0.08	0.07
Unknown impurity	0.00	0.00
Total Impurity	0.10	0.11
Ranitidine Hydrochloride API + Croscarmellose Sodium (1:1)		

Description	Off white	Off white
Assay	**99.9**	**99.87**
Related Substance		
Ranitidine Simple Nitroacetamide	0.00	0.00
Ranitide Oxime	0.00	0.00
Ranitidine amino alcohol	0.00	0.00
Ranitidine Related Compound A	0.00	0.00
Ranitidine S-Oxide	0.00	0.00
Ranitidine N-Oxide	0.00	0.01
Ranitidine Complex Nitroacetamide	0.00	0.00
Ranitidine formaldehyde adduct	0.01	0.01
Ranitidine Related compound B	0.07	0.07
Unknown impurity	0	0.00
Total Impurity	0.08	0.09
Ranitidine Hydrochloride API + Magnesium Stearate (1:2)		
Description	Off white	Off white
Assay	**99.89**	**99.86**

No significant drop in assay and increase in related compounds indicative of an incompatibility was not observed for the selected excipients; hence the above studied excipents can be utilized for the further development studies.

UNIT FORMULA

Table no. 9: Unit formula for Ranitidine Hydrochloride tablets 150 mg.

Ingredients	Brand name	Function	Unit formula (in mg)
			For 150 mg
Ranitidine Hydrochloride	-	API	167.414
Microcrystalline cellulose PH112	Avicel PH112	Diluent	77.586
Croscarmellose sodium	Ac-di-sol	Disintegrant	2.500
Magnesium stearate	Ligamed MF-2-V	Lubricant	2.500
Total dry mix weight			250

Batch calculation

The batch size is calculated for 1200 tablets, the materials and their quantities are tabulated in the following table.

Table no. 10: Batch calculation for 1200 tablets from trial 1-5.

Ingredients	Unit formula (mg)	Trial (in Kg)				
		1	2	3	4	5
Ranitidine Hydrochloride	167.41	0.201	0.201	0.201	0.201	0.201
Microcrystalline cellulose PH112	77.58	0.094	0.091	0.093	0.091	0.093
Croscarmellose sodium	2.50	0.001	0.004	0.003	0.003	0.003
Magnesium stearate	2.50	0.003	0.003	0.002	0.003	0.002
Total weight	**250**	**0.300**	**0.300**	**0.300**	**0.300**	**0.300**

Table no. 11: Batch calculation for 1200 tablets from trial 6-10.

Ingredients	Unit formula (mg)	Trial (in Kg)				
		6	7	8	9	10
Ranitidine Hydrochloride	167.41	0.201	0.201	0.201	0.201	0.201
Microcrystalline cellulose PH112	77.58	0.092	0.092	0.093	0.092	0.091
Croscarmellose sodium	2.50	0.003	0.003	0.003	0.003	0.003
Magnesium stearate	2.50	0.003	0.003	0.002	0.003	0.002
Total weight	**250**	**0.3000**	**0.3000**	**0.3000**	**0.3000**	**0.3000**

Table no. 12: In-process parameters of 250 mg tablets from trials 1-10.

Trial	Average weight (mg)	Uniformity of weight (mg)	Thickness (mm)	Hardness (kg/cm^2)	Disintegration (Min)	Friability (% W/W)
1	250.8	248.0	4.37	5.0	8'.10"	0.3
2	253.1	250.5	4.40	3.9	7'.53"	0.3
3	250.8	249.2	4.39	4.7	7'.26"	0.2
4	250.4	248.4	4.38	4.2	9'.20"	0.3
5	251.2	249.9	4.39	4.9	7'.10"	0.3
6	250.8	247.2	4.41	4.3	7'.23"	0.3
7	251.4	248.8	4.43	4.0	9'.17''	0.9
8	251.4	249.8	4.39	4.2	8'.43''	0.4
9	251.4	249.3	4.45	4.5	8'.20''	0.3
10	251.3	249.1	4.40	4.0	11'.30''	0.4

Table no. 13: Dissolution data of 250 mg strength tablets.

Time (mins)	% Drug release for 150 mg tablet									
	TRIAL									
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
10	37	38	33	35	24	29	27	34	33	31
15	53	61	52	67	63	69	54	64	54	53
20	76	73	72	84	86	89	79	76	70	63
30	92	95	97	99	99	98	100	96	96	96
45	95	102	102	101	99	101	102	102	101	103

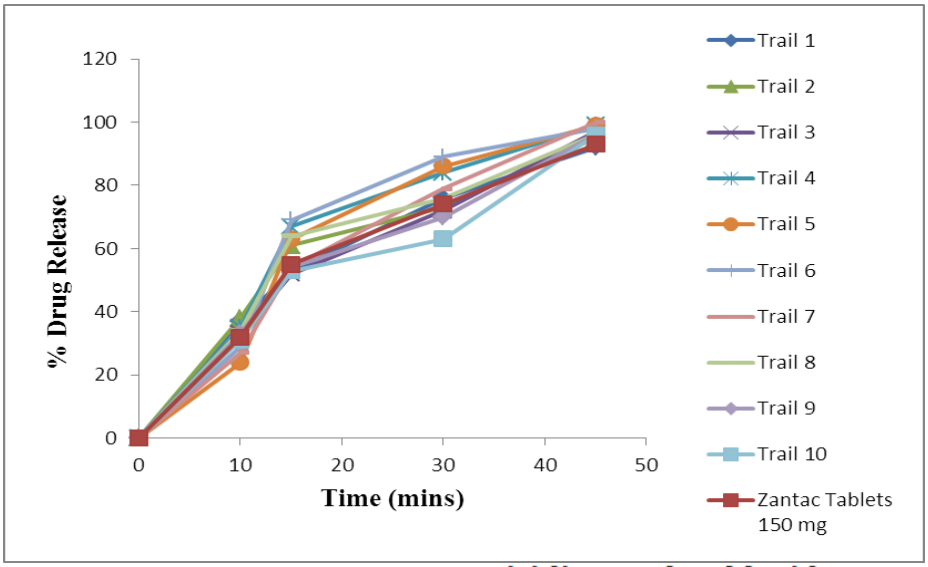

Fig no. 9: Dissolution profile of Ranitidine Hydrochloride.

Table no. 14: Dissolution parameters of Optimized Trails.

Formulation	MDT (min)	$Q_{15\ min}$	T_{50} (min)	Hixson Crowell's(r^2)
T_3	23.75	52	14	0.654
T_4	23.67	54	12	0.650

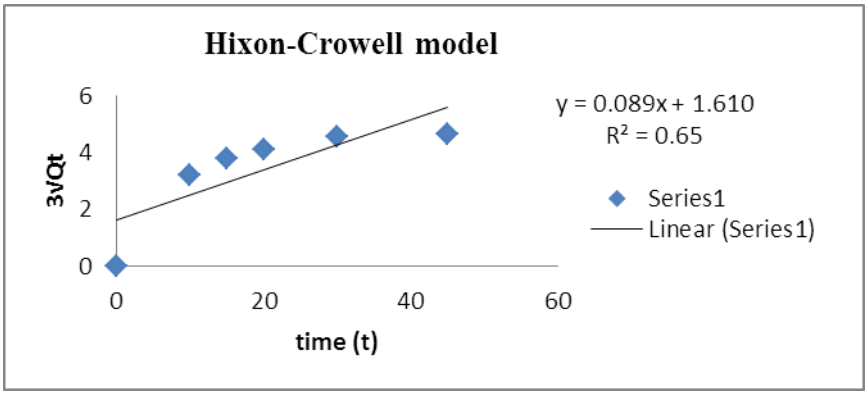

Fig no. 10: Plot showing Hixon-Crowell model for Trial 3.

CONCLUSION

From the above observations it is concluded that all the formulations produce the good tablets which are meeting all the product specifications without any tableting problems. Variation in concentration of lubricant showed the variation in disintegration time as well as dissolution of drug which has been concluded from trial 3 (0.75% magnesium stearate) and trial 4 (1.25% magnesium stearate) increase in lubricant concentration led to decrease in dissolution i.e. less drug release. The hydrophobic coating of Magnesium Stearate interferes with "wetting" thereby leading to increases in the time required for the tablet to disintegrate and/or the drug to become dissolved, among two different lubricants i.e. magnesium stearate and calcium stearate chosen to study their effect in the formulation showed not much difference but variation in drug release, where trial 4 with (1.25% magnesium stearate) has showed low dissolution i.e. less drug release when compared to trial 10 (1.25% calcium stearate) with same concentration.

From the above studies physic chemically, it is concluded that there is an effect of lubricant and disintegrants concentration on the drug release profile and certainly it had variation with different vendor and different lubricant though taken in same concentrations.

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