Formulation development and characterization of Powder for oral suspension containing H2 blocker drug to Combat GERD and Peptic ulcer

Megha Singhal*, Pankaj Bhatt, K. Nagarajan

Department pf Pharmaceutics, KIET Group of Institution (KIET School of Pharmacy), Ghaziabad, Utter Pradesh, India

ABSTRACT

In this modern era, the cases of GERD (Gastroesophageal reflux disease) and peptic ulcers are increasing rapidly, so there is an urgent need for a dosage form to target both the disorders effectively and safely. Considering this, dosage form called as POS (Powder for oral suspension) decided to formulate. Proton pump inhibitor-based drug used in this formulation has high aqueous solubility and dissolution rate in water, and it is very soluble at lower pH, i.e., increased gastric pH. Therefore, it is an ideal drug candidate in patients with peptic ulcers as gastric acid secretion is high in these patients, promoting the dissolution and bioavailability of the drug. The drugs showed compatibility with other excipients used to formulate the dosage form. The results of various trials related to this drug indicated its great therapeutic potential against the treatment of GERDand peptic ulcers. There are currently limited treatment options for the management of GERD and peptic ulcers as there is no adequate evidence to confirm this association is unavailable. In light of that, this dosage can overcome most significant gastrointestinal complications and improve overall response.

Key words: famotidine, suspension, Wet granulation, GRED, POS

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Introduction

The oral suspension, including those prepared by reconstitution, provide a convenient way to administer dosages to infants and children and to adult patients who prefer liquid preparations to solid ones[1]. Many drugs are unstable when maintained in solution for an appreciable length of time, and therefore, from a stability standpoint, insoluble forms of the drug substances in aqueous suspensions or as dry powder for reconstitution are attractive to manufacturers [2]. famotidine is the histamine type-2 receptor antagonists (H2RAs) have made a significant impact on the prevention and management of gastroesophageal reflux and ulcers. This class includes cimetidine, ranitidine, famotidine, and nizatidine. Famotidine is a competitive histamine H-receptor antagonist (H2RA) that binds to the H-receptors located on the basolateral membrane of the parietal cell in the stomach, effectively blocking histamine actions. Its pharmacologic activity results in the inhibition of gastric secretion by suppressing acid concentration and volume of gastric secretion. Famotidine inhibits both basal and nocturnal gastric acid secretion [3-5]. Per famotidine's package insert (11dose) it is available in intravenous (IV) solution, oral suspension, and tablet formulations (10 mg, 20 mg, and 40 mg). Infants who required treatment withfamotidine or other H2RAs for GERD or alternatively had a therapeutic need for acid suppression [6]. Famotidine decreases the production of stomach acid, and its pharmacologic activity is used in the treatment of acid-related gastrointestinal conditions. [7] [8] Famotidine is also FDA approved for over-the-counter treatment and prevention of heartburn due to gastroesophageal reflux in adults and pediatrics[4]. Famotidine is used off-label for reducing gastrointestinal risks of NSAIDs [9] It is also used off-label for the treatment of refractory urticarial, prevention of stress ulcer in critically-ill patients and symptomatic relief of gastritis. [10]

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MATERIAL AND METHODS

Material: Famotidine,Citric acid, Powder cellulose, Sucrose, Xanthan gum, Methyl paraben sodium, Propyl paraben sodium, Sodium benzoate, Sucralose, Aerosil, Isopropyl alcohol, Cherry flavor, Peppermint flavor, Banana Flavor. These are the material which is used in the formulation.

Method: Wet granulation: Wet granulation in the pharmaceutical industry is a frequent unit operation. A high-shear blender and fluidized bed processer is commonly used for the wet granulation. High-shear mixture is commonly used for blending and granulation in the pharmaceutical industry. The particles are moved by a puller revolving at a high speed in this sort equipment (approx. 50-100rpm). The equipment also includes a chopper rotating around (1500-4000rpm) each minute. The binder liquid is added by pouring from the top. After process get complete wet mass dried with the help of rapid dryer.

Procedure: 10% of sucrose shifted through 30# to form layer on butter paper. mixed API with equivalent quantity of sucrose and shifted through 30# mesh by adding 1 scoop of (API + sucrose) and 1 scoop of sucrose and collect in polybag.Mixed aerosol and powdered cellulose in a polybag with equivalent quantity of sucrose and pass through30# mash and collect in a separate polybagPass the material of step (iii) through quardro co-mill (co-milling on quardro performed at 1750rpm) by using 18R sieve and collect the material back-to-back milling the material of step (iv) using same 18R sieve Collect the material from step (v) and mix them thoroughly and load it in RMG bowl for dry mixing (10mins).

Binder solution preparation

Take 105.41g of sugar using for preparation of binder solution and take 396gm of purified water in a beaker and kept under mechanical stirrer then Add 105.41g of sugar in a purified water and stir till the sugar dissolved completely. After that take out 20ml sugar solution using 2× (10ml syringe) for rinsing aluminum foil for weighing the preservative. Weighing of methyl paraben sodium and sodium benzoate on analytical balance and added to sugar solution stir the solution till the preservative completely dissolved. Finally add 369gm of IPA to the above solution stirring done manually by using spatula.

RMG granulation

Unload the material from the rapid dryer bowl and pass the material through #30 sieve and collect the 30pass and 30 retain material.#30 pass = 55%, #30 retain = 45%. Pass the material through Quadro co-mill by using 32G sieve and collect the material and again pass through #30 mesh sieve (Quadro co-mill machine RMG). Collect the material in the polybag mix the material manually and check the LOD (loss on drying). LOD should be less than 0.50. Percentage Yield of collected dried granules is 96.5%

EVALUATION TEST

Pre-formulation studies

Melting point:is usually defined as the point at which material changes from a solid to a liquid. Melting point of Drug-X is determined by the capillary tube method using melting point apparatus.

Identification of drug by HPLC Method

HPLC is the form of liquid chromatography that is generally used in the pharmaceutical industry, as it can provide the precise results that are required. The results can be used to analysis finished product and their ingredient qualitatively and quantitatively during the manufacturing process. The purpose of High-Performance Liquid Chromatography analysis of drug is to confirm the identify of a drug X.

LOD (loss on drying)

LOD was calculated by using Halogen Moisture Balance apparatus. 1gm of pure drug was weighed accurately and was placed in Halogen Moisture Balance at temp of 105°C for 10 minutes.

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Solubility of Drug X

It is defined as the maximum quantity of solute dissolved in an equilibrium solvent. The drug solubility was evaluated by dissolving an excess quantity of the drug in 5ml of various solvents. Solubility of the Drug X given in the tabular form in the result section.

Bulk Characterization

BD and TD (Bulk Density and Tapped Density)

Density is a concept derived from the division of powder weight by powder thickness. The g/cm^3 is used. BD is measured in a graduated in a cylinder, according to the bulk volume and the dry powder weight. Bulk powder volume is the amount of the volume tapped plus the volume void. Vacuum is removed by tapping on a smooth, horizontal surface the graduated cylinder from constant height 10,500,1250 times by constant power. This volume gives the TD. The equations are as following:

$$\rho_B = W/V_B \quad \text{.....eq.1}$$

where, W is the weight of dry blend, V_T is the tapped volume.

Drug- Excipient's compatibility studies

Physical compatibility

Before formulation, it is critical to ensure that the drug and excipients are compatible in an experimental condition. Compatibility study was carried out at 25°C/60% RH, 40°C/75% RH (open condition), 40°C/75% RH (closed condition) for 4 weeks.

The selected drug and excipients mixture of 1:1 ratio was packed in open & closed vials respectively for weeks and any physical observation was noted. The selected drug and excipient mixture of 1:1 ratio was packed in open & closed vials respectively for 4 weeks and any physical observation was noted.

Analytical identification of drug

Assay of famotidine

Preparation of buffer (pH 3.50) for mobile phase: Weigh and transfer about 1.34g of potassium dihydrogen orthophosphate in a glass bottle containing 100ml of water and sonicate to dissolve it completely. Add 1ml of trimethylamine and mix well. Adjust the pH to 3.50 by diluted orthophosphate acid solution. Filter this solution through membrane filter.

Preparation of mobile phase A:

Prepare suitable quantity of mixture of buffer (pH 3.50) and acetonitrile in the ratio of 98:02(v/v) mix well at sonicate to degas.

Preparation of mobile phase B:

Prepare suitable quantity of mixture of buffer (pH 3.50) and acetonitrile in the ratio of 30:70 (v/v) mix well at sonicate to degas.

Preparation of 1N sodium hydroxide solution:

Weigh and transfer about 7g of sodium hydroxide in to a 200ml volumetric flask add 100ml of water and sonicate to dissolve it completely. Allow the solution to cool at room temperature, and make up the volume with water and mix well.

Preparation of buffer (pH 7.00) for diluent:

Weigh and transfer about 13.6g of sodium dihydrogen phosphate monohydrate in a glass bottle containing 900ml of water and sonicate to dissolve it. Adjust the pH to 7.00 by 1N sodium hydroxide and make up the volume up to 1000ml with water and mix.

Preparation of diluent-1:

Prepare a suitable quantity of mixture of buffer pH 7 and methanol in the ratio of 60:40 and mix well.

Preparation of diluent-2:

Prepare a suitable quantity of mixture of buffer pH 7 and acetonitrile in the ratio of 93:7 and mix well.

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Preparation of solution:

Transfer 5ml of diluent-1 to 50 ml volumetric flask. And make up the volume with diluent-2 and mix well.

Chromatographic conditions:

Table No.-1 Chromatographic condition for perform Assay of Drug

Column	X bridge C18 (150x4.6)mm
Column temperature	40°C
Autosampler temp.	25° C
Flow rate	1.50ml/min
Injection volume	15µm
Wavelength	268nm
Run time	20min
Needle wash solution	water: methanol
Needle wash mode	extended
Seal wash solution	water: methanol
Sampling rate	1.0 points/sec
Time constant	for detector 2487: (1sec)For detector 2489 (normal)

Gradient program:

Table No.- 2 Gradient program for perform Assay

Time (min)	Mobile phase A%	Mobile phase B%
0.0	100	0
10.0	100	0
12.0	20	80
14.0	20	80
15.0	100	0
20.0	100	0

Preparation of standard stock solution for drug X

Accurately weigh and transfer 40mg of drug X working/standard drug USPRS into a dried amber colored 50ml volumetric flask. Add 35ml of dilent-1 and sonicate for 5 min to dissolve it completely. Make up the volume to mark with diluent-1 and mix well

Preparation of standard solution

Transfer 5 ml of drug X standard stock solution in amber colored 50ml volumetric flask and make up the volume to the mark with diluent-2 and mix well.

Preparation of constituted sample

40ml volume of water required for the constitution of sample.

Preparation of constituted of sample solution

Add 40ml of water as mention on the label of bottle using measuring cylinder. Shake well about 10 sec homogenize it completely.

Preparation of sample solution for assay 40mg/5ml.

Accurately weigh and transfer the suspension equivalent to 4 dosage unit (160mg of drug X, taking into consideration the weight per ml of suspension) to a dried ambered colored 200ml volumetric flask. Add 140ml of diluent-1 and sonicate for 15min. allow attain room temperature. Make up to the vol. with dilent-1 and mix well. Keep in bench top for 10min at room temp. for settle down the suspended

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particle. Transfer 5ml of this solution into 50ml of volumetric flask, make up the vol. up to the mark with diluent-2 and mix well. Filter the solution through 0.45µm nylon membrane syringe filter.

Related substance by UPLC (H-Class)

Chemicals and reagents used:

Potassium dihydrogen orthophosphate
Sodium dihydrogen phosphate
Sodium hydroxide
Orthophosphoric acid
Acetonitrile
Methanol
Water

Preparation of diluted orthophosphoric acid solution:

Transfer 5ml of orthophosphoric acid (88%) in 100ml volumetric flask containing 50ml if water makeup the volume to the mark with water and mix well.

Preparation of buffer (pH 4.00) for mobile phase:

Weigh and transfer about 4.0g of potassium di hydrogen orthophosphate in a glass bottle containing 1000ml of water and sonicate it to dissolve it. Adjust the pH to 4.00±0.05 by diluted orthophosphoric acid solution. Filter this solution through 0.22µm Durapore PVDF membrane filter.

Preparation of mobile phase A:

Use buffer (pH 4.00) as mobile phase.

Preparation of mobile phase B:

Prepare a suitable quantity of mixture acetonitrile and methanol in the ratio of 70:30 (v/v). mix well and sonicate.

Preparation of 1N sodium hydroxide solution.

Weigh and transfer about 8g of sodium hydroxide pellets in to a 200ml volumetric flask. Add 100ml of water and sonicate to dissolve it completely. Allow the solution to cool at room temperature. Makeup the volume with water and mix well by shaking manually.

Preparation of 0.1N sodium hydroxide solution:

Transfer 5ml of 1N sodium hydroxide solution to a 50ml volumetric flask. Make up to volume with water and mix well.

Preparation of buffer (7.00) for diluent:

Weigh and transfer about 13.6g of sodium dihydrogen phosphate monohydrate in a glass bottle containing 900ml of water and sonicate to dissolve it. Adjust the pH to 7.00± 0.05 by 1N sodium hydroxide solution and make up the volume up to 1000ml with water and mix well by shaking.

Preparation of Diluent:

Prepare a suitable quantity of mixture of buffer (pH 7.00) and methanol in the ratio of 85.15 (v/v) and mix well.

Preparation of Blank solution:

Use diluent as blank.

Preparation of mixture Acetonitrile: water (80:20v/v)

Prepare a suitable quantity of mixture of acetonitrile and water in the ratio of 80:20 (v/v). mix well.

Chromatographic condition:

Table No.- 3 Chromatographic condition for perform Related Substance Evaluation

Column	Acquity BEH C18
Column temperature	30° C
Atmosphere temperature	10° C
Flow rate	0.2ml/min
Injection volume	2µL
Wavelength	268nm
Run time	90min
Sample manager purge	Water: methanol (10: 90)

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Sample manager wash	Water: methanol (10: 90)
Seal wash solution	Water: methanol (90:10)
Sampling rate	5 points
Filter time constant	Normal

Gradient program:

Table No.- 4 – Gradient Program for Related Substance

Time (mins)	Mobile phase A%	Mobile phase B%
0	100	0
22	97	3
40	85	15
50	83	17
60	50	50
65	45	55
75	45	55
77	100	0
90	100	0

Preparation of standard stock solution for drug X (concentration approx. 4ppm)

Accurately weigh and transfer about 40mg drug X working standard/drug X into a dried ambered colored 100ml volumetric flask. Add 70ml of diluent and sonicate for 5mins to dissolve it completely. Make up the volume to the mark with diluent and mix well.

Preparation of standard solution:

Transfer 5ml of drug x standard stock solution to a ambered colored 50ml volumetric flask and make up the volume to the mark with diluent and mix well. Further transfer 5ml of this solution to a amber colored 50ml volumetric flask and make up the volume to the mark with diluent and mix well.

Preparation of sensitivity solution:

Transfer 5ml of standard solution to a amber colored 100ml volumetric flask and make up the volume to the mark with diluent and mix well.

Preparation of impurity solution-1:

Accurately weigh and transfer about 2.4mg of drug x to a 20ml volumetric flask, add 5ml of mixture of acetonitrile and water 80:20 and sonicate for 10min to dissolve it completely make up the volume with diluent and mix well.

Preparation of impurity solution-2:

Accurately weigh and transfer about 2.4mg of impurity F to a 20ml volumetric flask, add 2ml o 0.1N NaOH and sonicate for 10min to dissolve it completely. Make up the volume with methanol and mix well.

Preparation of impurity solution-3:

Accurately weigh and transfer about 2.4mg of each Impurity A, Impurity B, Impurity C, Impurity D, Impurity E, Impurity G to a volumetric flask add 12ml of methanol and sonicate for 10 mins to dissolve it completely. Make up the volume with buffer pH 7.00 and mix well.

Preparation of constitution of sample solution:

Add 46ml of water as mentioned on the table of bottle using measuring cylinder. Shake vigorously for 10sec to homogenize it completely. Again shake the bottle for about 10sec immediately prior to preparation of sample solution.

Preparation of placebo solution (for strength – 40mg/5ml)

Accurately weigh and transfer the placebo suspension equivalent to 2 dosage unit to a dried amber colored 200ml volumetric flask. Add 120ml of diluent and sonicate for 20mins with intermittent shaking. Allow to attain

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room temp. make up the volume with diluent and mix well. Filter the solution through 0.22µm PVDF membrane syringe filter after discarding first 3ml of filtrate.

Preparation of sample solution (strength-40mg/5ml) (concentration approx. 400ppm)

Accurately weigh and transfer the suspension equivalent to 2 dosage unit (equivalent 80mg of drug X, taking into consideration the weight per ml of suspension) to a dried amber colored 200ml volumetric flask. Add 120ml of diluent and sonicate for 20mins with intermittent shaking. Allow to attain room temperature. Make up the volume with diluent and mix well. Filter the solution through 0.22µm PVDF membrane syringe filter.

Microbial enumeration test and test for specified microorganism.

The test describes the method to demonstrate antimicrobial efficacy for multidose parenteral, nasal, ophthalmic, oral and topical products made with aqueous bases or vehicles, the effectiveness or any added preservative, during the shelf lives of the preparation to ensure that the antimicrobial activity has not been impaired by storage by challenging with a prescribed inoculum of suitable micro-organism and storing the inoculated preparation at a prescribed temperature. Sample are withdrawn at specific intervals of time and counting of organism is carried out to determine the viable count.

pH of the formulation

pH of the phases of suspension also contributes also contribute to stability and characteristics of formulation. After reconstitution as directed in labelling the pH should be in between 6.5-7.5.

Viscosity

Viscosity of suspension is required in order to model two-phases flow correctly, in the same manner as the (molecular) viscosity of a fluid is needed to describe single-phase flows.

Formulation and preparation of different batches:

***In- vitro* drug release:**

Preparation of 0.1M phosphate buffer, pH 4.5 (OGD)

Weigh and transfer about 136g of potassium dihydrogen orthophosphate in 10L of demineralized water and mix well with glass rod in clockwise and anticlockwise direction to dissolve it completely. Adjust the pH to 4.5 with 1% v/v orthophosphate acid solution or 0.5% w/v sodium hydroxide solution.

Dissolution parameter:

Table No.- 5 – Dissolution Parameter for In-vitro Drug Release

Medium	As specified
Volume	900ml
Apparatus	USP-II
RPM	25rpm or 50rpm
Temperature	37°C
Time points	As specified

Preparation of 0.2M trisodium phosphate solution:

Weigh and transfer about 7.6g of trisodium phosphate in 100ml wide mouth volumetric flask. Add 70ml of water and sonicate to dissolve it completely. Make up the volume to the mark with water and mix well.

Preparation of buffer (pH 3.50) for mobile phase:

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Weigh and transfer about 1.36 g of potassium dihydrogen orthophosphate in a glass bottle containing 1000ml of water and sonicate to dissolve it completely. Add 1ml of trimethylamine and mix well. Adjust the pH to 3.50 by 10%v/v orthophosphate acid solution. Filter this solution through 0.45µm Durapore PVDF membrane filter.

Preparation of mobile phase A

Prepare a suitable quantity of mixture of buffer (pH 3.50) and acetonitrile in the ration of 98:02 (v/v) mix well.

Preparation of mobile phase B

Prepare a suitable quantity of mixture of buffer (pH 3.50) and acetonitrile in the ration of 30:70 (v/v) mix well

Preparation of blank solution:

Dissolution media used as blank

Preparation of blank solution for 0.1 N Hydrochloric acid media

Accurately transfer5ml of 0.1N HCl to 10ml volumetric flask and add 2ml of 0.2M trisodium phosphate solution and mix

Chromatographic conditions:

Table No.- 6 – Chromatographic Condition of in-vitro drug release

Column	X Bridge C18 (150X4.6) mm
Column temperature	40°C
Autosampler temperature	10°C
Flow rate	1.8ml/min
Injection volume	10µL
Wavelength	268nm
Run time	20min
Needle wash solution	Water: methanol
Needle wash mode	Extended
Seal wash solution	Water: methanol
Sampling rate	1.0 points/sec
Time constant	For detector 2487: (1sec)
	For detector 2489: (normal)

Gradient program:

Table No.- 7 – Gradient Program for In-vitro Drug release

Time (in mins)	Mobile phase A%	Mobile phase B%
0.0	100	0
11.0	100	0
13.0	20	80
15.0	20	80
16.0	100	0
20.0	100	0

Preparation of standard stock solution for drug X

Accurately weigh and transfer about 44mg of drug working standard into a dried amber colored 50ml volumetric flask. Add 35ml of methanol and sonicate for 5min to dissolve it

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completely. Make up the volume to the mark and mix well.

Preparation of standard solution for 0.1M phosphate buffer, and DM water

Transfer 5ml of famotidine standard stock solution in amber colored 100ml volumetric flask make up the volume to the mark with respective dissolution media and mix well.

Preparation of Standard solution for 0.1N hydrochloric acid media

Transfer 5ml of famotidine standard stock in amber colored 100ml volumetric flask and make up the volume to the mark with 0.1N HCL dissolution media and mix well. Immediately transfer 5ml of this solution to amber colored 10ml volumetric flask previously containing 2ml of 2.0M trisodium phosphate solution and mix well

Preparation of constituted sample:

Tap the closed bottle several times to loosen the powder. 46ml of water required for constitution of sample and claimed strength is 40mg/5ml.

Procedure for constitution of sample for determination of weight per ml of suspension:

Add water as mention above using measuring cylinder. Gently shake the bottle up and down and swirl or shake he bottle in left, right and round direction for about 1-2min. again slowly shake the bottle up and down and swirl or shake the bottle in left and round direction for about 1min before determining weight /ml of sample suspension

Take a 100ml volumetric flask containing 50ml of water. Add approximately 25g of well shaken suspension and gently swirl the contents to mix. Weigh the flask, from a burette, add water to bring the flask contents to volume, while gently swirling the contents of the flask.

Procedure for constitution of sample solution:

Add water as mentioned on the label of bottle using measuring cylinder. Shake vigorously for about 10 sec to homogenize it completely.

Preparation of sample solution for dissolution media at 0.1M phosphate buffer, pH4.5 (OGD); pH 6.8 phosphate buffer media; DM water media (40mg/5ml) (concentration approx. 44.4ppm)

Accurately weigh and transfer the suspension with the help of syringe to each of the six amber colored dissolution vessels and start the dissolution test as per the given parameter. Withdraw 10ml pf aliquot from each dissolution vessel at a specified interval. After withdrawing sample, replace the media with the same amount of respective dissolution media. Filter the sample solution through 0.45µm nylon membrane syringe filter after discarding first 3ml of filtrate.

Preparation of sample solution for dissolution media at 0.1N hydrochloric acid media (concentration approx. 31.7ppm)

Fill the syringe with constituted suspension equivalent to one dosage unit.Accurately weigh and transfer the suspension with the help of syringe to each of mixed amber colored dissolution vessel and start the dissolution test as per the given parameter mentioned above. Withdraw 10ml of aliquot from each dissolution vessel at the specified time interval. After withdrawing the sample, replace the media with the same amount of respective dissolution medium. Filter the solution through 0.45µm nylon membrane syringe filter after discarding first 2ml of filtrate.Immediate transfer 5ml of this solution to 10ml volumetric flask previously containing 2ml of 0.2M trisodium phosphate solution and mix well. After that put the samples in HPLC instrument and run.

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Result and Discussion:

Pre-formulation studies:

Appearance, Melting point, LOD (loss on drying), bulk Characterization areShown in Table No-8.

Table No- 8 Results of Appearance, Melting Point, LOD, Bulk Characterization

Sr No.	Famotidine Drug	Explanation and Values
1	Appearance	Off white crystalline powder
2	Melting Point	164°C
3	Loss on Drying	0.21 % at 105°C for 10min
4	Bulk Density	0.34
5	Tapped Density	0.59

Identification of drug X by HPLC method.

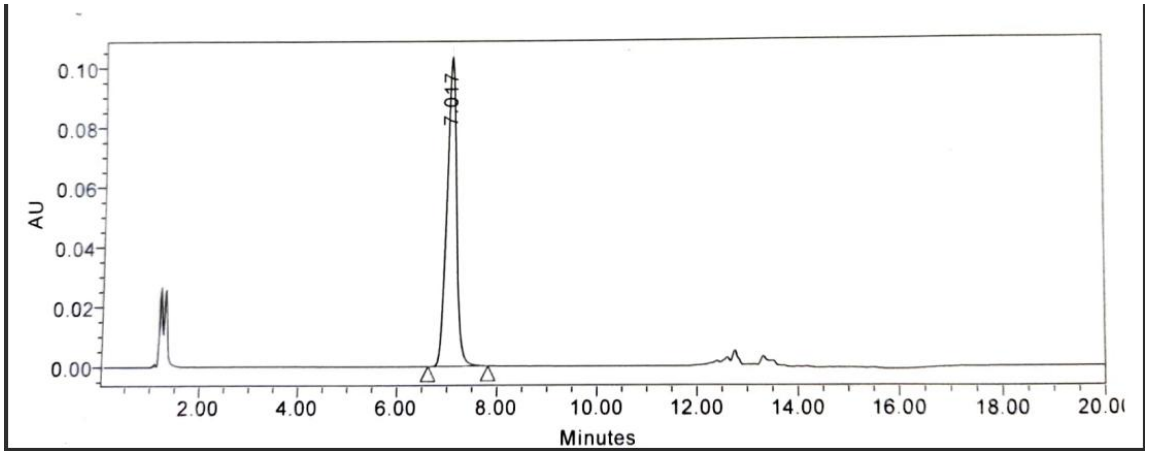

Fig-1: Standard chromatogram showing the famotidine peak for the identification.

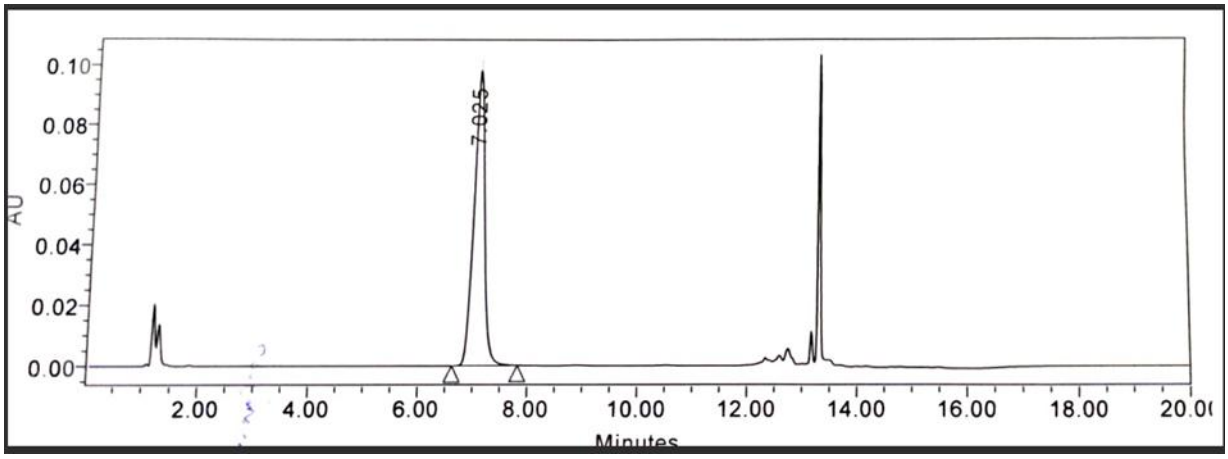

Fig-2: Sample chromatogram showing the famotidine peak in the sample for the identification

Inference: By comparing standard and test sample we can clearly conclude that the test sample shows the same results as standard.

Solubility of Drug X

Table No.- 9 Solubility Results

Solubility of Drug X	
Water	Very slightly soluble
Ethanol	Insoluble
Methanol	Slightly soluble
Glacial acetic acid	Freely soluble

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Drug Excipient's compatibility studies

Table: Drug excipient compatibility study, binary mixture, physical observation.

Binary mixture	Initial	Open 40°C/75% RH (1M)
API	Off-white granular powder	No change in colour with free- flowing powder
API + powdered cellulose	Off-white granular powder	No change in colour with free- flowing powder
API+ Sucrose	Off-white granular powder	No change in colour with free- flowing powder
API + sodium benzoate	Off-white granular powder	No change in colour with free- flowing powder
API + methyl paraben sodium	Off-white granular powder	No change in colour with free- flowing powder
API+ propylparaben sodium	Off-white granular powder	No change in colour with free- flowing powder
API+ citric acid	Off-white granular powder	No change in colour with free- flowing powder
API+ xanthan gum	Off-white granular powder	No change in colour with free- flowing powder
API+ sucralose	Off-white granular powder	No change in colour with free- flowing powder
API+ colloidal silicon dioxide	Off-white granular powder	No change in colour with free- flowing powder
API+ peppermint flavour	Off-white granular powder	No change in colour with free- flowing powder
API+ banana flavour	Off-white granular powder	No change in colour with free- flowing powder
API+ cherry flavour	Off-white granular powder	No change in colour with free- flowing powder
API+ Avicel	Off-white granular powder	No change in colour with free- flowing powder
API+ sodium citrate	Off-white granular powder	No change in colour with free- flowing powder
API+ HPC	Off-white granular powder	No change in colour with free- flowing powder

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Analytical identification of drug

Assay of Drug X

Chromatogram showing the peak of Drug X in the assay.

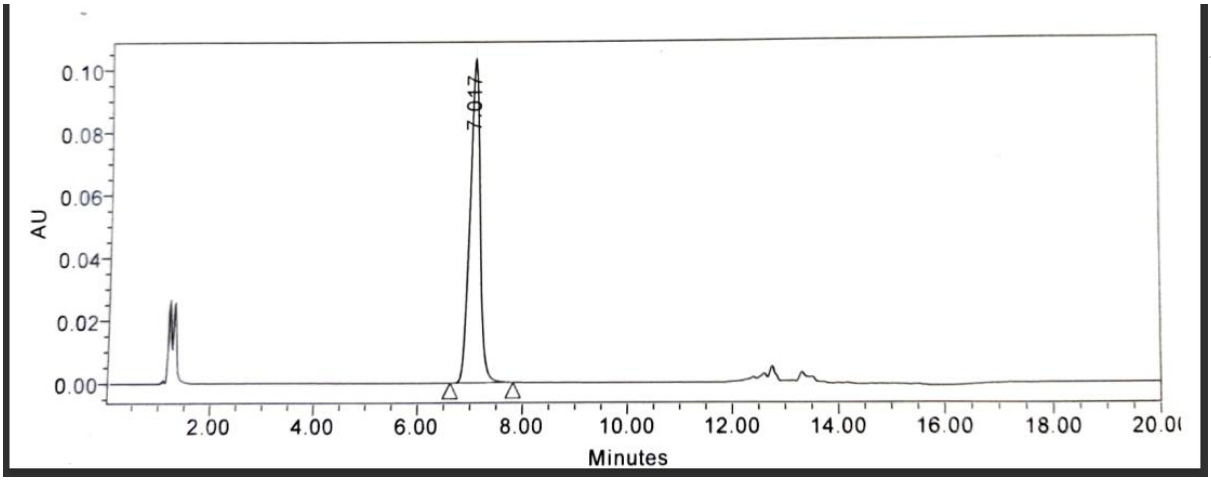

Fig-3: Standard chromatogram showing the Drug X peak for the determination of assay.

Fig-4: Sample chromatogram showing the Drug X peak in the sample for the determination of assay

Table No.- 10 Results of Assay

Batch no.	condition	Claim(mg/5ml)	Assay	
			(Mg/5ml)	%claim
Trial batch	initial	40	39.32	98.3
Trial batch	40°C/75%RH	40	38.65	99.1
Trial batch	25°C/60%RH	40	39.62	98.9

- **Related substance**

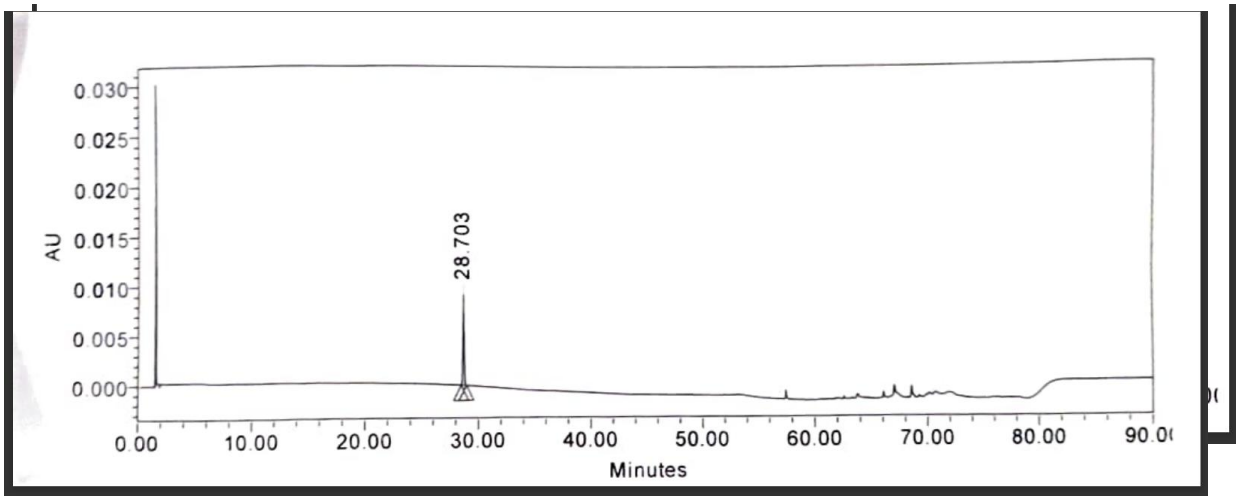

Fig-5: standard graph of related substance in the formulation

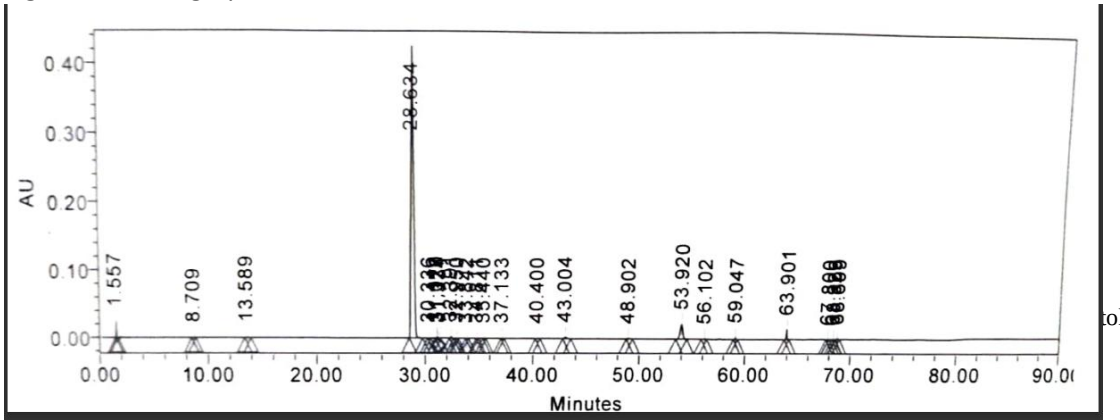

Fig-6: sample graph showing the impurities in the formulation when its stored in 40°C/75%RH

Table No.- 11 Results of Relates Substance

Name	vial	RT	%Area	USP plate count	USP tailing	RT ratio	USP resolution
Impurity1	1: A5	68.33	0.02	5384637	1.19	2.34	2.89
Impurity2	1: A5	67.70	0.12	7365	2.32	2.33	6.65
Impurity3	1: A5	2.76	0.49	75468	1.32	0,98	1.09
Impurity4	1: A5	8.71	0.03	543674	1.32	0.87	5.76
Impurity5	1: A5	13.67	0.09	63754	1.32	0.54	88.76
Impurity6	1: A5	28.98	92.23	36389	4.23	1.00	9,87
Impurity7	1: A5	30.34	0.02	464783	2.21	1.06	5.97

Table: peak results

Microbial enumeration test and test for specified microorganism

The test describes the method to demonstrate antimicrobial efficacy for multidose parenteral, nasal, ophthalmic, oral and topical products made with aqueous bases or vehicles, the effectiveness or any added preservative, during the shelf lives of the preparation to ensure that the antimicrobial activity has not been impaired by storage by challenging with a prescribed inoculum of suitable micro-organism and storing the inoculated preparation at a prescribed temperature.

Sample are withdrawn at specific intervals of time and counting of organism is carried out to determine the viable count.

Table No. – 12 Results of Microbial Enumeration

Batch no.	**TAMC**	**TYMC**	**E. coli (per ml)**	**salmonella**
Trail 1	<10	<10	absent	absent
Trail 2	<10	<10	absent	absent

pH of the formulation:

pH of the phases of suspension also contributes also contribute to stability and characteristics of formulation.

after reconstitution as directed in labelling the pH should be in between 6.5-7.5.

Table No.-13 Results of pH

Batch no.	**pH**
Trail 1	7.23
Trail 2	7.03

Viscosity

Viscosity of suspension is required in order to model two-phases flow correctly, in the same manner as the (molecular) viscosity of a fluid is needed to describe single-phase flows.

Table No.- 14 Results of Viscosity

Batch no.	Viscosity (mean)
Trail 1	223.95
Trail 2	213.95

Formulation and preparation of different batches:

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Table No.-15 Formulation Batches F1 to F14

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13	F14
API	40.1	40.1	40.1	40.1	40.1	40.1	40.1	40.1	40.1	40.1	40.1	40.1	40.1	40.1
Sucrose	902.5	902.5	902.5	902.5	902.5	902.5	902.5	902.5	902.5	902.5	902.5	902.5	902.5	902.5
Sodium benzoate				2.5	5									5
Methyl paraben sodium	2.5	5	5	2.5	5									5
Propyl paraben sodium	0.5	0.5	1	1	1									1
Citris acid						2	2.5	3						2.5
Aerosil	3.25	3.25	3.25	3.25	3.25	3.25	3.25	3.25	3.25	3.25	3.25	3.25	3.25	3.25
Xanthan gum (75)									7	9	11			9
xanthan gum (180)												7	9	
sucralose	3	3	3	3	3	3	3	3	3	3	3	3	3	3
water	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
cherry flavour	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
peppermint flavour	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
banana flavour	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
powdered cellulose	100	100	100	100	100	100	100	100	100	100	100	100	100	100
total weight	1090	1090	1090	1090	1090	1090	1090	1090	1090	1090	1090	1090	1090	1090

Final optimized formula:

Final formula composition for desired batches to be prepared

Table No.-16 API and Excipients Quantity

Manufacturing process and details	Wet granulation and blending	
Sr. no	Ingredients	Quantity (mg)
1.	API	40.11
2	Colloidal silicon di oxide	3.25
3	Sucrose	902.58
4	Powdered cellulose	100.00
5	Citric acid	2.30
6	Methyl paraben sodium	5.22
7	Sodium benzoate	5.05
8	water	8.90
9	Xanthan gum	12
10	Peppermint flavour	2.5
11	Cherry flavour	2.5
12	Banana flavour	2.5
13	Sucralose	3
Total weight		1100

In-vitro drug release:

In-vitro dissolution:

Table No.- 17 Trial Parameter

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Water / 900 ml / USP Apparatus II / 50 RPM			
Time (Min)		Drug X dissolved	
		Batch No.	
		Trails 1	Trial 2
0		0	0
10		98	96
15		98	99
20		98	98
30		99	98

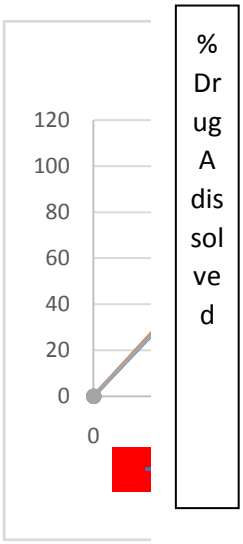

Fig-7 Calibration Curve of Drug

Conclusion

Nowadays, cases of GERD (Gastroesophageal reflux disease) and peptic ulcers are increasing rapidly. There is an intense need for a dosage that can effectively treat both disorders. From the performed work, it can be concluded that the used drug is an ideal candidate indicates its huge therapeutic potential against GERD (Gastroesophageal reflux disease) and peptic ulcers. The physicochemical characterization and percent drug release studies clearly showed that the prepared prototype was similar in all aspects to the reference product. Moreover, stability studies also indicated the stability of the prepared prototype at different conditions for upto several months which led to the conclusion that the product was similar and effective in comparison to the RLD product.

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