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Method Development Technology and Optimisation Studies in Famotidine Pellets: An In Vitro Release

Deevan Paul A[1*], Vivek Morris Prathap[2], Tabish Qidwai[2], Niranjan Podili[3], Kritika Pandey[2], Mandapati Lavanya[3]

[1]Chettinad School of Pharmaceutical Sciences, Chettinad Academy of Research and education, Chennai, Tamilnadu, India.
[2]Shri Ramswaroop Memorial University, Lucknow, Uttar Pradesh, India.
[3]Seven Hills College of Pharmacy, Tirupati, Andhra Pradesh, India.

Corresponding Author
Dr. A. Deevan Paul

Assistant Professor, Department of Pharmaceutics, Chettinad School of Pharmaceutical Sciences, Chettinad Academy of Research and Education, Tamilnadu, India.
Email: dr.deevanpaul@care.edu.in

Abstract

Oral medication administration has long been the most convenient and widely utilized technique of drug administration. Pellets are fine powders or granules of bulk pharmaceuticals and excipients agglomerated together. They are made up of tiny, free-flowing spherical or semi-spherical solid units that range in size from 0.5 to 1.5mm. These are normally meant to be taken by mouth. Thus, Famotidine has been chosen to prepare pellet formulations employing polymers such as HPMC, Eudragit, and HPC in this study. To analyze and estimate the drug in buffers and acid media, calibration curves were constructed using UV at 306 and 286nm respectively. The flow properties like the angle of repose, bulk density, tapped density; Carr's index, and h-ratio were found to be within the pharmacopeia's guidelines. 12 formulations ranging from F1-F12 were prepared with various concentrations and types of polymers. The drug loading in all the formulations was estimated using HPLC and was found to be satisfactory. The pellets had a smooth surface and uniform drug loading, according to SEM examination. *In vitro*, drug release tests were conducted, and the F13 and F14 formulations reported the best release based on previous results. The improved formulation was further subjected to release kinetics testing. Formulations are appropriate for releasing medicine into the upper intestine and stomach, according to the research. According to the findings of this investigation, the developed sustained drug delivery system might be used for a variety of water-insoluble pharmaceuticals.

Keywords: Famotidine, Pellets, Extended-release, HPMC, Eudragit

INTRODUCTION

Oral drug delivery has been the most convenient and universally used method of administering drugs [1]. Dosage forms can be designed to modify the release of the drug over a given time or after the dosage form reaches the required location. Drug release only occurs sometime after the administration or for a prolonged period or to a specific targeted site in the body [2]. Delayed-Release dosage forms are designed to provide spatial placement or temporal targeted delivery of a drug to the distal human gut. The primary aim of using delayed-release products is to protect the drug from gastric fluids. Delayed-Release products are typically enteric-coated or targeted to the colon [3]. Pellets are agglomerates of fine powders or granules of bulk drugs and excipients. They consist of small, free-flowing spherical or semi-spherical solid units

typically from about 0.5-1.5mm. These are intended usually for oral administration [4]. As the conventional granulation, the most thoroughly studied, most classified pelletization process, which involves a rotating drum, a pan, or a disc, has been divided into three consecutive regions: nucleation, transition, and ball growth. However, based on the experiments on the mechanism of pellet formation and growth, the following steps were proposed: nucleation, coalescence, layering, and abrasion transfer. The coating process for pellets is carried out primarily to modify the release of the drug from the pelletized drug delivery systems. So in this current work, Famotidine is selected to prepare the pellet formulations using polymers like HPMC, Eudragit, and HPC.

MATERIALS AND METHODS

Famotidine drug was gifted by MSN labs. Hyderabad, polymers like HPMC, Eudragit, and HPC were procured from Evonik, Germany and other chemicals were procured from various companies and are of analytical grade.

Construction of calibration curve

A calibration curve of Famotidine in 0.1N HCl solution was performed to quantify the samples. All the solutions were prepared fresh before use. A 10 µg/ml standard solution of Famotidine was scanned on a double beam spectrophotometer against the solution as the blank. An absorption maximum (λ_{max}) of 306 nm was obtained for the solution and was selected to prepare the standard curve. A 10 µg/ml standard solution of Famotidine was scanned on a double beam spectrophotometer against the solution as the blank. An absorption maximum (λ_{max}) of 286 nm was obtained for the solution and was selected to prepare the standard curve. pH 7.0 phosphate buffer solution. Pre-formulation studies like FTIR on active pharmaceutical ingredients (API), inactive ingredients (Excipients), and their combinations were carried out to identify if there are any compatibility problems and to characterize the reference product. Solubility studies and the melting point analysis were carried out as per standard procedures. Preformulation parameters like bulk density, tapped density, Compressibility index, and Hausner's ratio along with the angle of repose were determined using standard procedure.

Experimental methods

Preparation and optimization of drug mixture

The composition of the formulation was developed with two objectives. First, complete drug release from the coated pellets in buffer media second, appearance and yield of the product. For achieving these objectives various formulation development trails were selected based on the recommended ranges in the literature and were further optimized in the course of various lab trials conducted during formulation development. During the first stage of optimization of drug loading, various percentages of the disintegrant concentration were tested. Famotidine sesquihydrate, Heavy magnesium carbonate, sucrose (Milled), L-HPC 31 in Blender and blended for 5 Minutes. This blend was sifted through #30 and sifted blend blended in Blender for 5 minutes. HPC was dissolved in Isopropyl alcohol under continuous stirring to get a clear solution. Then add Methylene dichloride to the above solution and continue the stirring to get a clear solution. Filter the final dispersion through nylon mesh. Then Famotidine was added under the same stirred conditions until a clear solution is obtained. Weighed quantity of Sugar spheres (#25-30#) was loaded onto the coating pan and the drug solution was coated onto the sugar spheres. Pellets are dried in a tray dryer for 30 minutes with conditions of inlet temperature (35°C ± 5°C) to maintain the bed temperature at 30°C ± 5°C. Dried pellets are sifted through #18 and # 25. The sifted pellets (#18-#25) are collected into HDPE containers lined with double polyethylene bags [5].

The measured quantity of isopropyl alcohol is taken in an SS container. HPC(Klucel) is added to isopropyl alcohol under continuous stirring to get a clear solution. Then Methylene dichloride is added to the above solution and stirring is continued to get a clear solution. Then titanium dioxide and talc are added to the above solution and stirring is continued to get a uniform dispersion. The final dispersion is filtered through nylon mesh. Drug-loaded pellets were loaded into the FBP bowl and a barrier coating solution was coated onto drug-loaded pellets. After completion of the coating solution, the pellets were dried in FBP for about 10 minutes at the given bed temperature and then the pellets were unloaded into pre-

labeled HDPE containers lined with double polyethylene bags.

Preparation and optimization of Immediate Delayed-Release coating

The measured quantity of Isopropyl alcohol is taken in SS containers. HPMC phthalate-55 is added to the Isopropyl alcohol under continuous stirring. After getting clear solution triethyl citrate, titanium dioxide, and talc are added to the above solution and the stirring is continued for 10 minutes to get a uniform dispersion. The above dispersion is filtered through nylon mesh. The Barrier coated pellets are coated with an Immediate Delayed-Release coating solution in FBP. The coated pellets are dried for 10 min in FBP and unloaded into pre-labeled HDPE containers lined with double polyethylene bags [6].

Preparation and Optimization of Extended Delayed Release Coating

The measured quantity of Isopropyl alcohol is taken in SS containers. the measured quantity of Eudragit-RSPO and Eudragit- RLPO according to table 3.12 were added and stirred to get a clear solution triethyl citrate, titanium dioxide, and talc were added according to quantities specified in table 3.10 and stirred for 10 minutes to get a uniform dispersion. The dispersion is filtered through nylon mesh. The Barrier coated pellets are coated with an Extended Delayed-Release coating solution in FBP.

Loading of the Coated Pellets into capsules

Immediately delayed-release pellets and Extended delayed-release pellets are blended in a ratio of 25:75 in a Conta blender.

Table 1: Formulation design of Famotidine pellets (formulations F1-F7)

Ingredients	F1	F2	F3	F4	Ingredients	F5	F6	F7
Sugar spheres (25#30)	25	25	25	25	Famotidine	22.5	22.5	22.5
Famotidine	22.5	22.5	22.5	22.5	HPMC Phthalate-55	5	7	10
Magnesium carbonate heavy	5	5	5	5	Triethyl citrate	0.5	0.7	1
L-HPC – 31	0	5	7	10	Talc	1.5	2	3
Sucrose (milled)	29.5	24.5	22.5	19.5	Titanium dioxide	1	1	1
HPC (Klucel LF)	2	2	2	2	HPC (Klucel LF)	2	2	2
Isopropyl alcohol	QS							
Methylene chloride	QS							

Table 2: Formulation design of Famotidine pellets (formulations F8-F12)

Formulation code	F8	F9	F10	F11	F12
Eudragit RSPO	2.5	3.5	4.5	5	5.5
Eudragit RLPO	2.5	3.5	4.5	5	3.5
Tri ethyl citrate	0.5	0.7	0.9	1	0.9
Talc	2	3	3.8	4	3.8
Titanium dioxide	1	1	1	1	1
Isopropyl alcohol	QS				
Methylene chloride					

Table 3: Formulation design of Famotidine pellets (formulations F13-F14)

Formulation code	F13	F14
Ingredients	25% of immediate-release pellets of F7 formulation combined with 75% of extended-release pellets of F10 formulation	25% of immediate-release pellets of F7 formulation combined with 75% of extended-release pellets of F12 formulation
Total weight	100mg	100mg
Total fill weight	266.7mg	266.7mg

Evaluation of the pellets [7,8]

Weight variation test

Individual weights of 20 capsules were taken randomly and the average weight was calculated by using the following formula.

$$\text{Weight variation} = \frac{\text{(Weight of tablet-Average weight)}}{\text{the average weight of tablets}} \times 100$$

Acid resistance test

This test was performed in the dissolution test apparatus. After the test, the assay is conducted for the remaining pellets.

Assay by HPLC

Chromatographic system

Column : Zorbax Eclipse XRB C_{18}, 150 x 4.6 mm, 5 µm
Detector Wavelength : 285 nm
Injection volume : 10 µl
Run time : 10 minutes
Flow rate : 1.5mL/min
Column oven temperature : 30°C

Mobile phase preparation

Prepare a mixture of water, acetonitrile, and triethylamine in the ratio o 65:35:0.5 and adjust to pH 7.0 with phosphoric acid. Filter the resulting solution by using 0.45µ nylon filter paper and sonicate to degas.

Diluent preparation

Take 600ml of water add 10ml of triethylamine and adjust to pH 10.5 with phosphoric acid, add 400 ml of acetonitrile. Filter the resulting solution by using a 0.45µ nylon filter.

Standard preparation

Weigh and transfer 100mg of Famotidine into a 100ml volumetric flask, and add about 70 ml of diluents and sonicate to dissolve and make up to the volume diluent. Transfer 5ml of the resulting solution into a 50ml volumetric flask and makeup to the volume with diluent. Filter the resulting solution by using a 0.45µm nylon filter.

Assay preparation

Weigh the pellets equivalent to 100 mg of Famotidine into a100 ml volumetric flask, add about 70 ml of diluents and sonicate to dissolve and make up to the volume diluents and mix well. Transfer 5ml of the resulting solution into a 50ml volumetric flask and make up the volume with diluent. Filter the resulting solution by using a 0.45µm nylon filter.

System suitability

- The column efficiency as the number of theoretical plates for Famotidine peak should not be less than 2000.
- The peak symmetry as tailing factor for Famotidine peak should not be more than 2.0
- The relative standard deviation for five replicate injections of Famotidine peak should be not more than 2.0%

Procedure

Separately inject 10 µl of standard preparation five replicates and the assay preparation into the chromatograph. Measure the peak responses for all the peaks.

Calculate the content of Famotidine in % by using the following expression.

Calculation:

$$\frac{R_T}{R_S} \times \frac{W_S}{W_T} \times \frac{P}{100} \times \frac{2\text{ ml}}{100\text{ ml}} \times \frac{10\text{ ml}}{100} \times 0.9319$$

R_S 100 ml 100 % 10 ml W_t 2 ml LC

Where,

R_T = peak response obtained from the assay preparation

Rs=peak response obtained from the standard preparation

Ws= Weight of Famotidine working standard took in mg

Wt=Weight of Famotidine taken in mg.

P = Purity of the Famotidine used in % (as is basis)

L=Label claim.

SEM analysis

The morphology of the Delayed-release (DR) pellets was examined using a scanning electron microscope (SEM) model no S-3700N, Hitachi. The effect of coating on the morphology of the pellets was observed using SEM. The main objective of scanning electron microscopy is to study the different coating layers on sugar spheres.

Capsule lock length

The capsules size 2 were taken and body and cap measurements were done before filling. After filling pellets into the capsule. The lock length of the capsule was measured. The measurements were done using Vernier calipers.

***In-vitro* Dissolution study [9]**

Acidic stage

Weigh and transfer pellets equivalent to 60mg of Famotidine into each bowl containing 500 ml of dissolution medium and operate the dissolution apparatus for 120 minutes. Withdraw 25 ml from each bowl by using 10µm dissolution disposable filters and then proceed immediately as directed for the test solution in the buffer stage, leaving the remaining 475ml for use in the buffer stage. Determine the amount of Famotidine dissolved by employing UV absorption at the wavelength maximum absorbance at about 306nm, using acid stage media as blank.

Buffer stage

Add 425 ml of concentrate buffer solution into each bowl containing 475 ml of 0.1 N hydrochloric acid sample solution adjust PH 7.0 by using dilute orthophosphoric acid or dilute sodium hydroxide. Withdraw 25 ml from each bowl by using 10µm dissolution disposable filters. Transfer 10ml of filtrate into a 25 ml volumetric flask and makeup to volume with buffer. Determine % drug release of Famotidine by using UV spectrophotometer at the wavelength maximum absorbance at 286 nm using buffer as blank. The respective kinetics of the study based on the dissolution data was calculated using the standard procedures and formulae [10].

Calculation of the similarity factor and dissimilarity factor

The similarity factor (f2) was defined by CDER, FDA, and EMEA as the "logarithmic reciprocal square root transformation of one plus the mean squared difference in percent dissolved between the test and reference release profiles". Dissimilarity or difference factor (f1) describes the relative error between two dissolution profiles. It approximates the percent error between the curves. The percent error is zero when the test and reference release profiles are identical and increases proportionally with the dissimilarity between the two profiles. There are several methods for dissolution profile comparison. f2 is the simplest among those methods. Moore & Flanner proposed a model independent mathematical approach to compare the dissolution profile using two factors f1 & f2.

$$f1 = \{ [\sum_{t=1}^{n} | R_t - T_t |] / [\sum_{t=1}^{n} R_t] \} . 100$$

$$f2 = 50. \log \{ [1 + (1/n) \sum_{t=1}^{n} (R_t - T_t)^2]^{-0.5} . 100\}$$

Where 'R_t' and 'T_t' are the cumulative percentage dissolved at each of the selected n time points of the reference & test product respectively. The factor f1 is proportional to the average difference between the two profiles, whereas factor f2 is inversely proportional to the averaged squared difference between the two profiles, with emphasis on the larger difference among all the time points. The similarity factor f2 and its significance are shown in table 4.

Table 4: Similarity factor f2 and its significance

S. No.	Similarity factor (f2)	Significance
1.	<50	Test and reference profiles are dissimilar.

2.	50 -100	Test and reference profiles are similar.
3.	100	Test and reference profiles are identical.
4.	>100	The equation yields a negative value.

Determination of the residual methylene chloride and isopropyl alcohol by GC

The GC used was Shimadzu, Model – 20. The analyses were performed under the following chromatographic conditions: Column – DB-5%, 30x0.32x0.37 µm. The temperature of the FID was 180ºC, and the injector temperature was 280°C. The oven temperature was programmed to 40°C (for 2 min), followed by an increase of 5ºC/min until 200ºC. The carrier gas was nitrogen with a flow of 1.5 mL/min. The injection of the test and standard was performed utilizing a 10 µL Hamilton syringe. Optimized pellets were taken in a 1000 ml volumetric flask containing. Pellets in a volumetric flask were crushed and volume was made using methanol. The flask was shaken and kept aside to get clear supernatant. A fixed volume of supernatant was injected into the chromatographic system and the amount of Methylene chloride and isopropyl alcohol in the pellets was calculated.

Stability Test

For all the pharmaceutical dosage forms it is important to determine the stability of the dosage form. This will include storage at both normal and exaggerated temperature conditions, with the necessary extrapolations to ensure the product will, over its designed shelf life, provide medication for absorption at the same rate as when originally formulated. The design of the formal stability studies for the drug product should be based on the knowledge of the behavior and properties of the drug substance and formal stability studies on the drug substance. Specification which is a list of tests, reference to the analytical procedures, and proposed acceptance criteria, including the concept of different acceptance criteria for release and shelf-life specifications, is addressed in ICH guidelines.

RESULTS AND DISCUSSION

λ_{max} of Famotidine in 0.1NHCl

The analytical method development for Famotidine was performed for the determination of absorption maxima using 5µg/ml of standard solution on a double beam spectrophotometer against 0.1NHCl and pH 7.0 phosphate buffer as the blank. An absorption maximum (λmax) of 306 nm was obtained and was selected to prepare the standard curve. An absorption maximum (λmax) of 286 nm was obtained and was selected to prepare the standard curve.

Preparation of standard graph

Standard solutions in the range of 1-5 µg/ml were prepared and absorption values were recorded at 306 nm against 0.1NHCl as the blank.

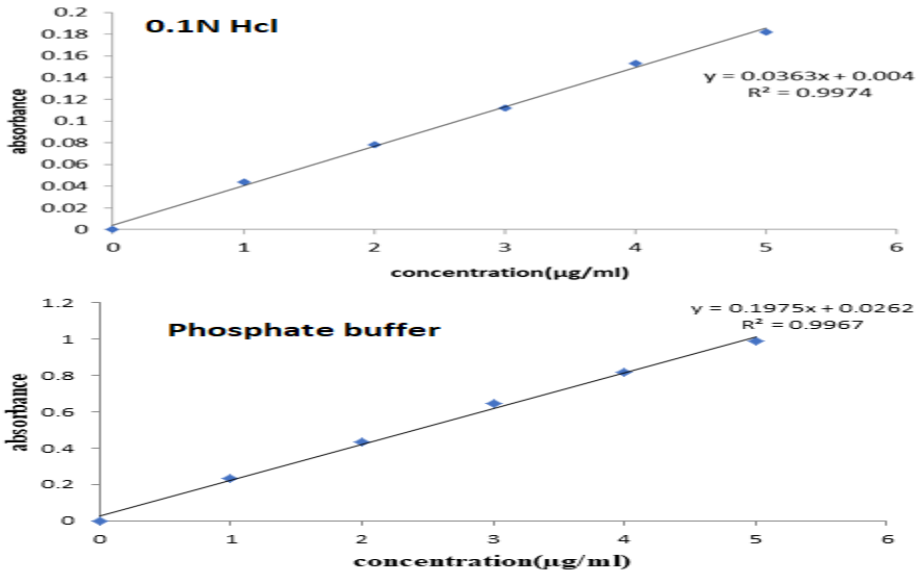

Figure 1: Standard graph of Famotidine in 0.1NHCl and Phosphate buffer

Standard solutions in the range of 1-5 µg/ml were prepared and absorption values were recorded at 286 nm against pH 7.0 phosphate buffer as the blank.

API characterization

a. Physical appearance of drug

The physical appearance was done by visual observation and Famotidine was a Dark brown color.

b. Solubility studies

Famotidine is freely soluble in Methylene chloride, soluble in methanol, slightly soluble in ethanol, ethyl acetate, dichloromethane, and insoluble in water and hexane.

c. Determination of melting point: 140°C

d. Determination of physical properties

Physical properties of Famotidine like bulk density, tapped density, compressibility index, and Hausner's ratio and angle of repose result are shown in table 5.

Table 5. Physical properties of Famotidine (API)

API Properties (Famotidine**)**				
B.D (gm/ml)	**T.D (gm/ml)**	**C.I (%)**	**H. R**	**Angle of repose**
1.04	1.13	7.9	1.08	25.44
1.04	1.19	12.6	1.14	26.96

Drug-excipient compatibility studies

Compatibility studies were carried out to study the possible interactions between Famotidine and other inactive ingredients

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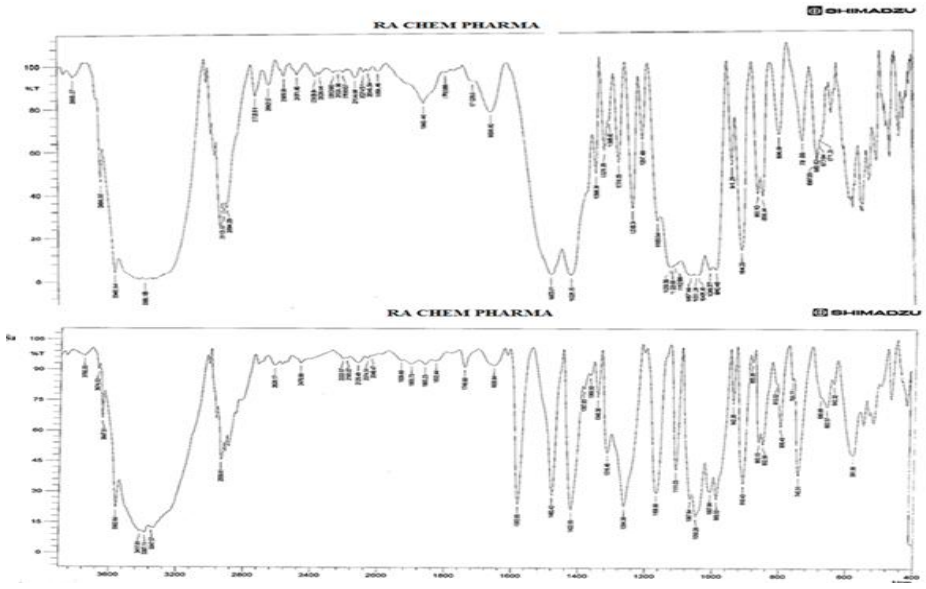

Figure 2: FTIR analysis of the API and formulations prepared

The IR spectroscopy was obtained by an FTIR spectrophotometer (Shimadzu, Japan) using KBR pellets and the scanning range was 4400 to 400 cm^{-1} at a scan period of 1 min. The FTIR spectra of pure drug, the drug with excipients, and only excipients are shown in table no 4.5, and fig no 4.5 and fig no 4.6, it was observed that the characteristic peaks at 3448 (N-H stretching), 1638.58 (C=N stretching), 1358.97 (S=O stretching), 1467 (C-H bending), 1244 (C-N vibrations)cm^{-1} are present in both the pure drug, the drug with excipients without any change in their positions, indicating no chemical interaction between drug and excipients, as confirmed by the FTIR studies.

Dissolution studies

Table 6: Dissolution profile of F1 –F4 (drug mixture optimization) with Comparison of the innovator product

TIME (mins)	**INNOVATOR**	**F1**	**F2**	**F3**	**F4**
Buffer stage (pH 7.0 phosphate buffer with SLS)					
0	0	0	0	0	0
10	24.6±0.07	7.9±0.35	11.4±0.35	31.2±0.28	8±0.56
20	26.3±0.14	14±0.14	26.4±0.49	50.1±0.26	18.8±0.42
40	28.3±1.14	25±0.42	33.6±1.41	58.2±0.77	23.8±0.56
50	34.2±2.26	32.9±0.35	39.4±0.42	66.1±0.29	28.7±0.28
60	47.5±2.57	38.4±0.24	46.7±2.68	74.3±0.38	35.5±0.58
75	65.6±3.13	45.6±0.56	59.9±0.56	89.2±0.42	45.7±0.49
105	92.7±2.82	56.7±0.02	65.7±0.28	94.1±0.56	50.3±0.47
120	97.6±1.26	61.5±0.65	74.2±0.81	99.2±0.82	57.6±0.41

From table 6 it was observed that in F1 formulation L-HPC-31 concentration is 0% i.e., no disintegrant and the drug release was incomplete after 120 min, so to improve the drug release L-HPC concentration was increased from 5 to 10%. In F2 formulation, L-HPC-31 concentration is 5% because the hydrophilic and swelling nature of the polymer-drug release improves from 61.5% to 74.2%. In the F3 formulation, L-HPC-31 concentration is 7% because of the hydrophilic and swelling nature of the polymer sudden and fast drug release occurred, and complete drug release occurred before gel-forming here. Hence no retardation occurs. Another reason for complete drug release is less particle size of the polymer. Here drug release at 120 min is 99.2%. In the F4 formulation, L-HPC-31 concentration is 10%, increase in L-HPC content also did not result in complete drug release. Further increase in L-HPC did not result in any significant increase. After dissolution studies, gel formation was observed in the basket and this could be the reason for the incomplete release. Here the drug release is 57.6% further increase in L-HPC-31 drug retardation occurs. Hence for drug loading optimization F3 formulation containing 7% of L-HPC-31 shows complete drug release. Formulation F3 was optimized. These pellets were subjected to barrier coating. Barrier coating of 5% HPC was optimized to proceed for further layer coating.

Table 7: Dissolution profile of F5 –F7

TIME (mins)	**INNOVATOR**	**F5**	**F6**	**F7**
Acid stage (0.1N HCL)				
120	3.8±1.23	24.7±0.38	15.5±0.51	3.2±0.36
Buffer stage (pH 7.0 phosphate buffer with SLS)				
130	24.6±0.07	65.3±0.84	48.2±0.46	39.8±0.35
140	26.3±0.14	78.2±0.35	63.7±0.42	56.8±0.19
160	28.3±1.14	79.1±0.37	70.3±0.21	82.3±0.14
170	34.2±2.26	84.3±0.28	81.2±0.56	85.4±0.28
180	47.5±2.57	91.1±0.07	89.4±0.48	93.5±0.42
195	65.6±3.13	94.2±0.42	92.8±0.49	99.4±0.35
225	92.7±2.82	98.3±0.77	96.3±0.20	-
240	97.6±1.26	99.1±0.98	98.2±0.21	-

From table 7, it was observed that for immediately delayed-release coating optimization F5-F7 formulations were formulated with HPMC phthalate -55 (5%-F5, 7%-F6, 10%-F7). In F5 formulation polymer concentration is 5% because of the less viscous nature of the polymer complete drug release occurs. But in the acid stage higher amount of drug release (24.75%) occurred. According to USP specifications, in the acid stage drug release is NMT 10%, and also release is not similar with innovator (3.8% in acid stage). In the F6 formulation polymer concentration is 7%, here also complete drug release occurred, but a higher amount of the drug release occurred in the acid stage (15.5%). And it crossed the limit. But in the F7 formulation, 10% of the polymer shows less amount of drug release in the acid stage (3.2%) and it is well below the USP limit. And also, sudden and fast release of the drug occurred, in the buffer stage and it can be called the immediate release of the drug generally it can occur 1-2 hrs. Here complete release of the drug occurs at 195min i.e., 99.4%. Hence, 10% of the HPMC phthalate-55 (F7) is optimized for immediately delayed-release coating.

Table 8: Dissolution profile of F8 –F12

TIME (mins)	INNOVATOR	F8	F9	F10	F11	F12
Acid stage (0.1N HCL)						
120	3.8±1.23	29.5±0.56	14.4±0.35	4.2±0.47	2.2±0.56	2.5±0.46
Buffer stage (pH 7.0 phosphate buffer with SLS)						
130	24.6±0.07	54.7±1.06	30.3±0.42	14.4±0.21	12.9±0.42	3.4±0.37
140	26.3±0.14	65.3±0.63	37.5±0.06	25.5±0.20	28.3±0.38	14.2±0.58
160	28.3±1.14	79.2±0.56	53.9±0.39	51.4±0.35	48.8±0.17	28.9±0.49
170	34.2±2.26	84.1±0.28	58.8±0.18	60.5±0.22	59.4±0.35	44.2±0.43
180	47.5±2.57	88.6±0.27	66.1±0.07	76.5±0.44	67.6±0.57	55.8±0.55
195	65.6±3.13	92.1±0.35	73.5±0.06	86.1±0.21	77.6±0.28	73.9±0.63
225	92.7±2.82	96.3±0.57	85.1±0.42	89.5±0.14	88.2±0.12	88.8±0.28
240	97.6±1.26	97.1±0.49	90.1±0.30	97.4±0.42	91.3±0.41	97.1±0.42

From table 8, it was observed that for extended delayed-release coating optimization F8-F12 formulations formulated with a combination of Eudragit-RSPO and Eudragit-RLPO in the ratio of 1:1 (5%-F8, 7%-F9, 9%-F10, 10%-F11). In the F8 formulation polymer concentration is 5%, In the buffer stage complete drug release occurs 97.1% at 240 min but in the acid stage higher amount of drug release (29.5%) occurs. According to USP specifications, in the acid stage drug release is NMT 10%, and also release is not similar with innovator (3.8% in acid stage). In the F9 formulation, polymer concentration is 7%, because of the hydrophobic nature of Eudragit RSPO the complete drug release does not occur in the buffer stage i.e., 90.1% at 240 mins, and also higher amount of the drug release occurred in the acid stage (14.4%). And it crosses the limit. But in the F10 formulation 9% of the polymer which shows less amount of drug release in the acid stage (4.2%) is well below the USP limit. And also, an extended-release of the drug occurs in the buffer stage and it can be called the extended-release of the drug generally it can occur 4-5 hrs. Here complete release of the drug occurs at 240 min i.e., 97.4%, but the drug release is not similar to innovator. In F11formulation, Polymer concentration is 10%, increase in polymer concentration also did not result in complete drug release i.e.,90.1% at 240 mins. Further increase in the polymer concentration did not result in any significant increase and drug retardation occurred. So, little modification in F10 formulation taken, it Formulated as F12 here 9% of polymer taken, here 5.5% of Eudragit RSPO and 3.5% of Eudragit RLPO formulated instead of 4.5% of Eudragit RSPO and 4.5% of EudragitRLPO. Because of the increase in the hydrophobic concentration of the polymer-drug retardation occurs up to 240 min and now it is called an extended delayed-release formulation. Here drug release in the acid stage is 2.5% and which is well below the USP limit also

extended-release of the drug occurs in the buffer stage at 97.1% at 240 min. Hence, 9% of the theEudragit-RSPO and Eudragit-RLPO (5.5% of Eudragit RSPO and 3.5% of Eudragit RLPO) (F12) was optimized for extended delayed-release coating.

Table 9: Dissolution profile of F13 and F14 with comparison of innovator

TIME (mins)	INNOVATOR	F13	F14
Acid stage (0.1N HCL)			
120	3.8±1.23	3.9±0.46	3.1±0.41
Buffer stage (pH 7.0 phosphate buffer with SLS)			
130	24.6±0.07	32.7±0.36	22.5±0.32
140	26.3±0.14	51.8±0.42	25.7±0.53
160	28.3±1.14	56.9±0.28	29.1±0.39
170	34.2±2.26	65.2±0.33	44.3±0.44
180	47.5±2.57	77.5±0.42	56.6±0.46
195	65.6±3.13	85.3±0.37	74.9±0.43
225	92.7±2.82	89.4±0.25	89.8±0.27
240	97.6±1.26	98.1±0.37	96.9±0.46
DISSIMILARITY FACTOR(f1)		32	5
SIMILARITY FACTOR (f2)		19	65

From table 9, it was observed that the F13 formulation contains 25% of the F7 formulation and 75% of the F10 formulation. Shows less acid drug release (3.9%) and also extended drug release in buffer stage (98.1% at 240 min) but the release is not similar to innovator. F14 formulation which contains 25% of F7 formulation and 75% of F 12 formulation. Shows less acid drug release (3.1%) which follows USP limit and also extended drug release in buffer stage (96.9% at 240 min) which is similar to innovator. Hence, the F14 formulation was optimized.

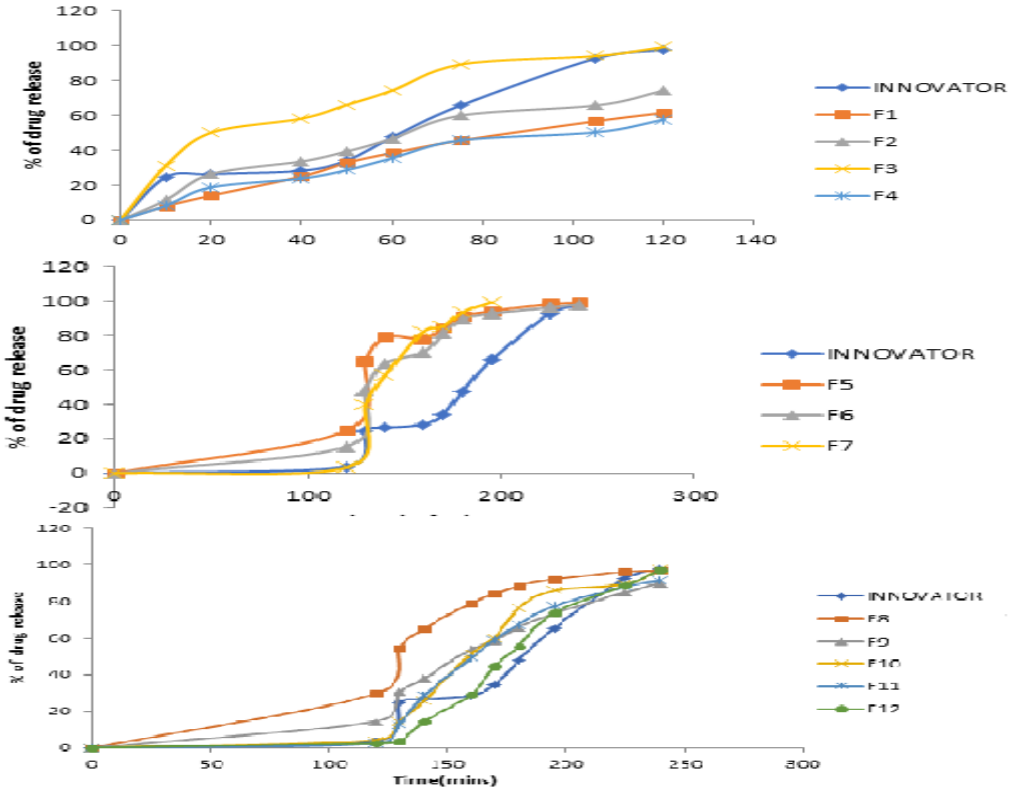

Figure 3: *In-vitro* Dissolution studies of formulations

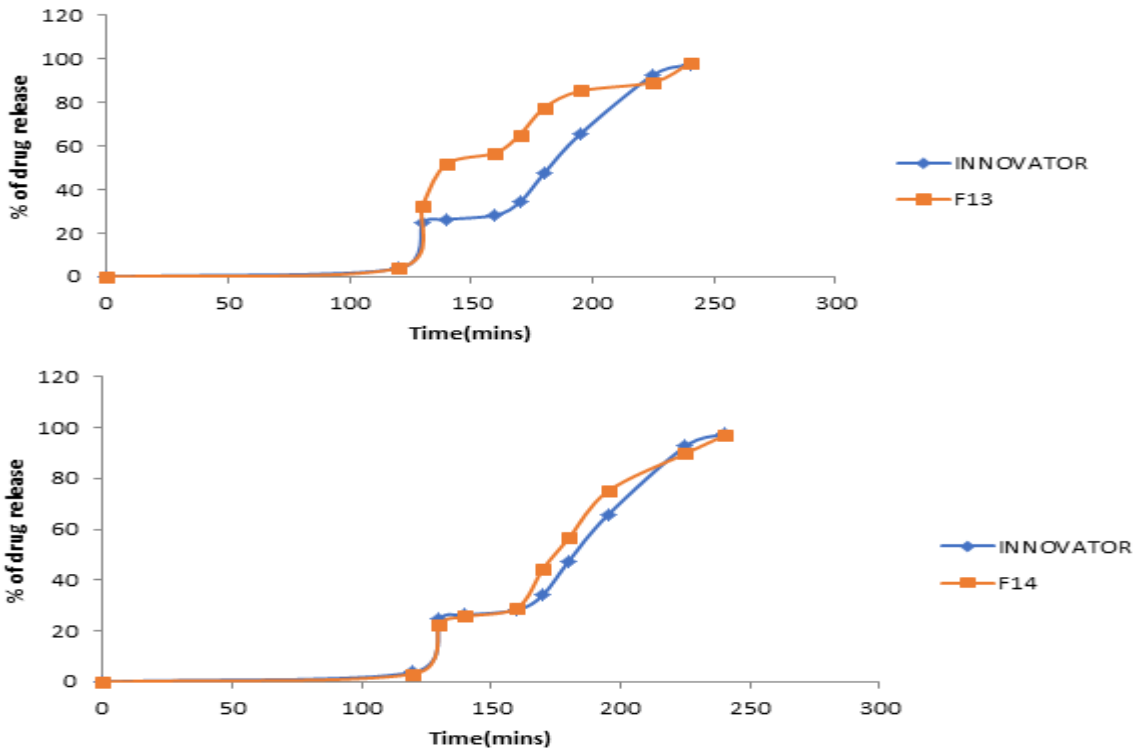

Figure 4: *In-vitro* dissolution studies of formulations F13-F14

Physical observation

0.5g of pellets was transferred into a dry Petri dish and the contents were observed visually. It was found that pellets were off-white to grey.

Sieve analysis

Famotidine pellets were tested for particle size by sieve analysis using different mesh numbers. All pellets passed #16mesh easily and retained on #22. For 100 gms of pellets taken 98gms passed and retained on #22. The size of the pellets was found to be within the range of standard sieves. It was observed that bulk densities of formulations of Famotidine pellets were found to be in the range of 0.66-0.74 gm/ml and tapped density was found to be in the range of 0.67-0.76gm/ml. It was observed that all the formulations were having values within the range of 1.01-1.03 and thus had a good flowing character. Hausner's ratio was determined by using bulk density and tapped density of the pellets. It was observed that all the formulations were having values within the range of 1.14-1.18%. It was determined by the KF Titration Method and the results of % moisture content of all were within the limits.

Table 10: Evaluation parameters of Famotidine pellets

Formulations	Bulk Density (gm/ml)	Tap Density (gm/ml)	Hausner's Ratio	% Moisture Content
F1	0.666± 0.03	0.675± 0.02	1.01± 0.02	1.14%
F2	0.694± 0.03	0.714 ± 0.03	1.02± 0.03	1.15%
F3	0.704± 0.04	0.724± 0.04	1.02± 0.02	1.15%
F4	0.714± 0.04	0.735 ± 0.03	1.02± 0.04	1.16%
F5	0.719 ± 0.03	0.740 ± 0.02	1.03± 0.03	1.17%
F6	0.724 ± 0.04	0.740 ± 0.03	1.02± 0.03	1.16%
F7	0.729 ± 0.03	0.751± 0.04	1.03± 0.02	1.14%
F8	0.733 ± 0.03	0.753 ± 0.03	1.02± 0.02	1.18%
F9	0.740± 0.02	0.753± 0.04	1.01± 0.04	1.16%
F10	0.740± 0.03	0.763± 0.03	1.03± 0.03	1.15%

F11	0.740± 0.05	0.763± 0.04	1.03± 0.02	1..18%
F12	0.740± 0.06	0.763± 0.06	1.03± 0.02	1.17%
F13	0.738± 0.05	0.760± 0.05	1.02± 0.03	1.18%
F14	0.738± 0.04	0.760± 0.04	1.02± 0.03	1.18%

Weight variation

From table no 4.11, it was observed that weight variation for enteric-coated formulations ranged from 2.665±0.08 to 4.92±0.05. For all the formulations the percent deviation was less than 10%.

Acid resistance test

From table no 4.11, it was observed that the acid resistance test for enteric-coated formulations ranged from 73.93±0.16 to 96.62±0.23. But F5, F6, F8, F9 formulations drug release is 73.93%, 83.2%, 69.14%, 83.71% and drug release less than 90%. Hence these formulations failed to pass the acid resistance test. F7, F10, F11, F12, F13, F14 formulations shows above 90% release. These formulations follow USP specifications.

Table 11: Evaluation tests for capsules containing pellets

Formulations	**weight variation test(mg±SD)**	**Assay (%)**	**Acid resistance test (%)**
F1	2.665±0.08	98.4±0.45	-
F2	2.786±0.07	97.86±0.57	-
F3	3.835±-0.06	97.6±0.90	-
F4	3.921±0.06	98.06±0.91	-
F5	4.062±0.07	98.14±0.22	73.93±0.16
F6	3.82±0.05	98.45±0.55	83.2±0.21
F7	3.86±0.06	99.13±0.56	95.95±0.31
F8	4.923±0.05	98.06±0.42	69.14±0.25
F9	3.912±0.05	97.8±0.51	83.71±0.43
F10	4.04±0.07	98.8±0.4	96.62±0.23
F11	3.98±0.06	98.96±0.6	94.80±0.54
F12	3.87±0.05	98.4±0.7	94.57±0.22
F13	3.92±0.02	98.1±0.2	95.65±0.34
F14	3.97±0.07	97.3±0.56	94.29±0.44

Assay by HPLC

From table no 4.12, it was observed that assay for enteric-coated formulations ranged from 97.3±0.90% to 99.13±0.56%. The prepared enteric-coated formulations have been compiled with the reference specification.

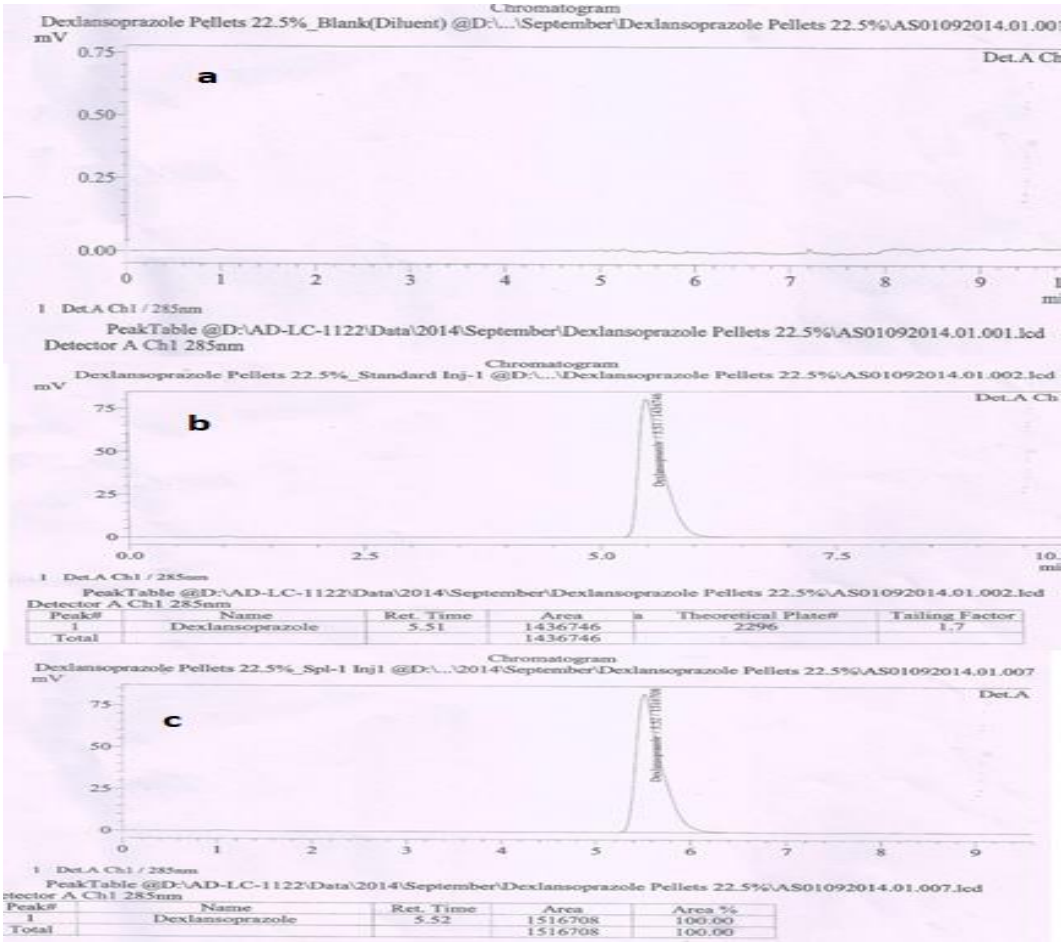

Figure 5: HPLC Chromatogram for a. blank; b. Standard and c. Optimized Formulation F14

From the above figure 5, the chromatogram % of dexlansoprazole can be calculated by comparing the peak area of the standard with the sample (optimized formulation F14). It was found to be 97.3%.

System suitability

- The column efficiency as several theoretical plates for Famotidine peak was found to be above 2000.
- the peak symmetry as tailing factor for Famotidine peak was found to be less than 2.0
- the relative standard deviation for five replicate injections of Famotidine peak should be not more than 2.0%

Capsule lock length

The capsule lock length was measured after filling the pellets into the capsules using vernier callipers. The lock length (mm) of F13 was found to be 18.10 mm and F14 was found to be 17.90 mm. The lock length of capsule size "2" should be 18 mm (0.3 deviations allowed). Lock length of F13 and F14 capsules are within the limits.

Table 12: Model dependent kinetic analysis for the dissolution profile of different formulation

Batch	Zero-order	First-order	Higuchi	Korsmeyer-Peppas
	R^2	R^2	R^2	R^2
INN0VATOR	0.748	0.899	0.496	0.708
F1	0.844	0.947	0.643	0.962
F2	0.804	0.959	0.584	0.925

F3	0.930	0.898	0.791	0.988
F4	0.826	0.955	0.618	0.943
F5	0.852	0.806	0.798	0.958
F6	0.851	0.847	0.728	0.940
F7	0.725	0.814	0.555	0.741
F8	0.900	0.824	0.822	0.964
F9	0.885	0.911	0.686	0.969
F10	0.776	0.817	0.547	0.738
F11	0.767	0.879	0.541	0.819
F12	0.812	0.810	0.632	0.806
F13	0.710	0.827	0.455	0.677
F14	0.769	0.874	0.518	0.674

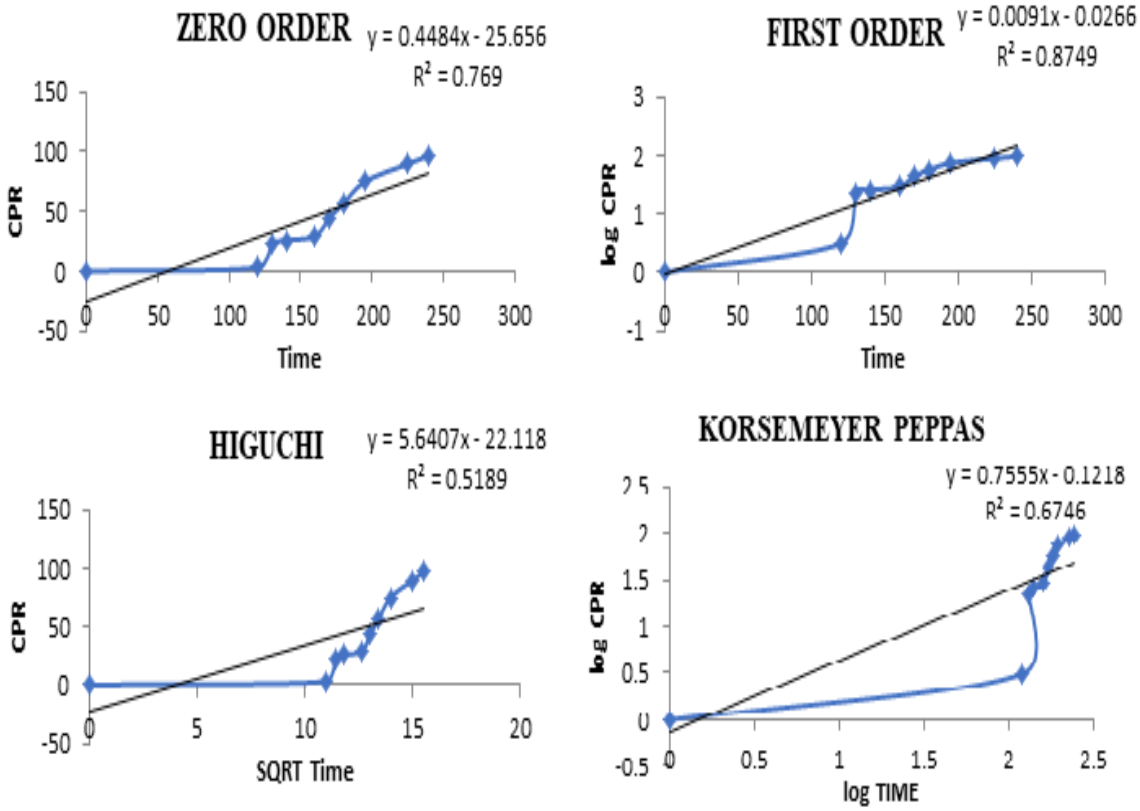

Figure 6: Model dependent kinetic analysis for the dissolution profile of optimized formulation

It was observed that the "n" value of 0.755 was obtained for the F14 formulation, and the drug release was found to follow Anomalous (non-Fickian) diffusion. This value indicates a coupling of the diffusion and erosion mechanism (Anomalous diffusion) and indicates that the drug release was controlled by more than one process. Based on the value

of "n" (n=0.745) for innovators' products, it was also found to follow the same release mechanism. Also, the drug release mechanism was best explained by the first-order equation, as the plots showed the highest linearity (r^2 = 0.874), followed by Higuchi's equation (r^2= 0.514). As the drug release was best fitted in first-order kinetics, it indicated that the rate of drug release is concentration-dependent. Even the innovator's product was found to follow the same pattern with the highest linearity (r^2 = 0.899) for a first-order equation. The "r" value for the Higuchi plot was found to be 0.514 indicating that drug release included diffusion as one of the release mechanisms.

Table 13: Dissolution profile comparison for F13 & F14 formulation

Time (mins)	INNOVATOR (R)	F13				F14			
		F13 (T)	(R-T)	$(R-T)^2$	f_2 value	F14 (T)	(R-T)	$(R-T)^2$	f_2 value
0	0	0	0	0		0	0	0	65
120	3.8	3.9	0.1	0.01		3.1	0.7	0.49	
130	24.6	32.7	8.1	65.61		22.5	2.1	4.41	
140	26.3	51.8	25.5	650.25		25.7	0.6	0.36	
160	28.3	56.9	28.6	1162.81	19	29.1	0.8	0.64	
170	34.2	65.2	31	1608.01		44.35	10.15	103.02	
180	47.5	77.5	30	1122.25		56.6	9.1	82.81	
195	65.6	85.3	19.7	580.81		74.95	9.35	87.42	
225	92.7	89.4	3.3	13.69		89.8	2.9	8.41	
240	97.6	98.1	0.5	0.25		96.9	0.7	0.49	
TOTAL	420.6			5203.69				288.05	

From the above table 13, it was observed that the f_2 value of formulation 13 is 19, which is not close to 100, the formulation F13 is said to be dissimilar to that of the reference product of Famotidine (Dexilant). It was observed that the f_2 value of formulation 14 is 65, which is very close to 100, the formulation is said to be more similar to that of the reference product of Famotidine (Dexilant).

SEM analysis

The optimized formulation F14 was subjected to SEM analysis.

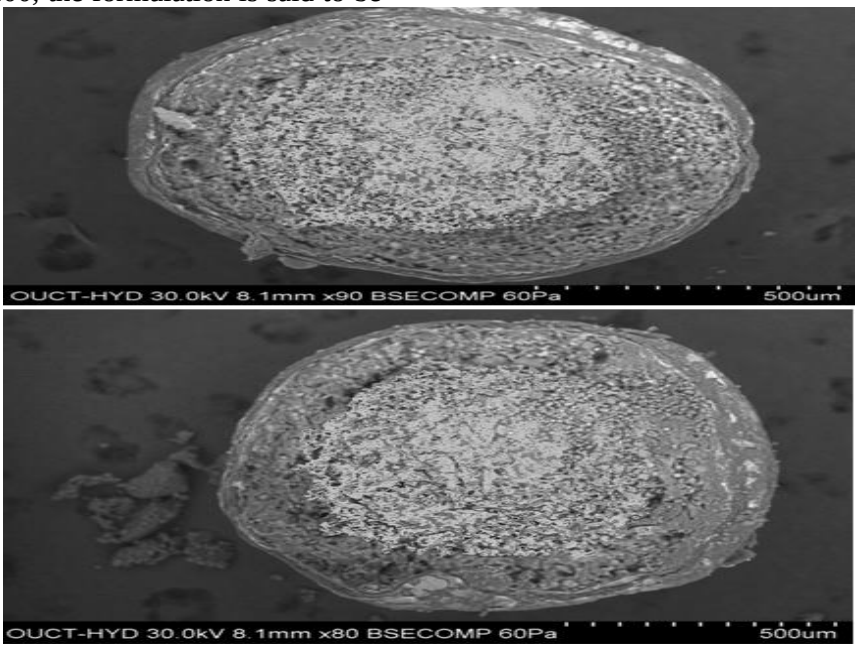

Figure 7: SEM analysis of a. immediate release pellets b. extended-release pellets

Following are SEM results for

- ✓ FormulationF7 (which contains immediate delayed-release coated pellets)
- ✓ Formulation F12 (which contains extended delayed-release coated pellets)
- ✓ It can be concluded that the coating is smooth and no cracking appears on the coating

Figure 7 shows a cross-section of pellets and it explains sugar spheres (white color), drug layering, barrier coating, and immediately delayed-release coating appear as different layers. The figure also shows a cross-section of pellets and it explains sugar spheres (white color), drug layering, barrier coating, and extended delayed-release coating appear as different layers.

Determination of residual methylene chloride and isopropyl alcohol

Gas chromatography was employed to estimate the number of residual solvents in the optimized pellets. The retention time of Methylene chloride was found to be 0.86. The retention time of isopropyl alcohol was found to be 1.43. Following are the chromatograms of i. Methylene chloride (STD m.wt -24mg); ii. Isopropyl alcohol (STD m.wt -200mg); iii. Optimized pellets 200mg (containing both methylene chloride and isopropyl alcohol).

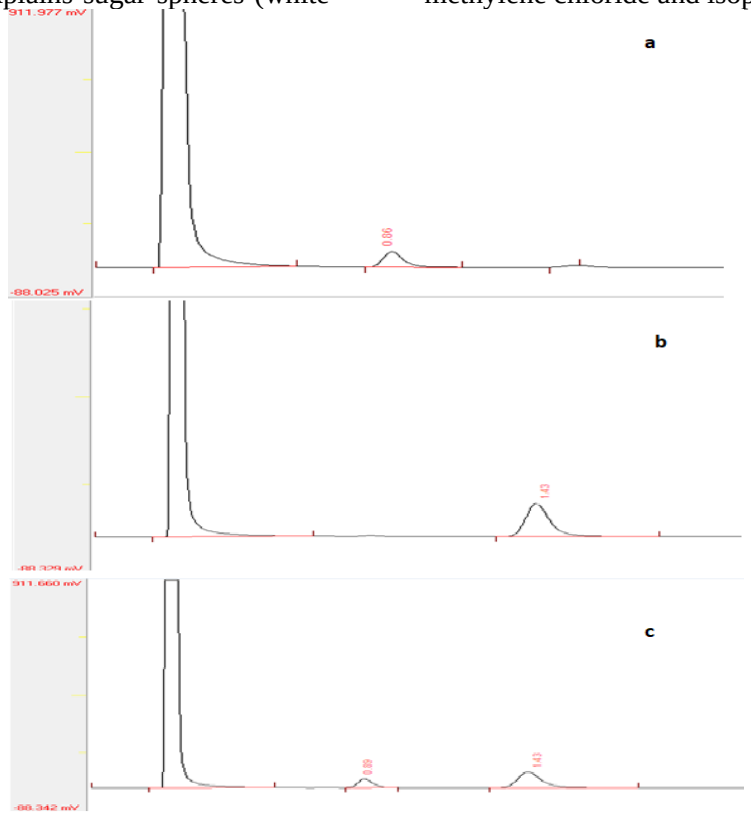

Figure 8: Chromatogram of a. Methylene Chloride; b. Isopropylene alcohol and c. optimized pellets

The amount of methylene chloride and isopropyl alcohol in the optimized formulation was calculated by using % of purity. And it was found to be 450ppmfor Methylene chloride and 1537ppm for isopropyl alcohol. Methylene chloride belongs to CLASS II by ICH and is in the range below 600 ppm, isopropyl alcohol is well below 5000 ppm. Based on the results of GC, Methylene chloride and isopropyl alcohol in optimized pellets were found to be well within the limits. Hence it can be concluded that the pellets prepared by solvents using Methylene chloride and isopropyl alcohol are safe and this solvent can be used for delayed-release pellets for dexlansoprazole.

Stability of the optimized formulation F14

It was observed that there is no significant change was observed in the dissolution profile of Famotidine capsules, after a storage period of 1,2,3 month at 40° C/75 % RH. There is no significant change was observed in the assay and acid resistance values of Famotidine

capsules, after a storage period of 1, 2, 3 months at 40°C/75 % RH. From the above data, it was evident that there was no significant change in the physical and chemical parameters of Famotidine during the stability studies conducted at 40°C &75% RH for 3 month period when compared with initial samples. So, it shows that formulation F14 was found to be a stable one.

Table 14: In vitro release profile comparison for Formulation Batch F14 with Reference at 40°C±2ºC/75% ± 5% RH

Time(mins)	Percentage of Drug release at 40°C±2ºC/75% ± 5% RH	
	INNOVATOR	F14
0	0	0
120	3.8±1.23	3.2±0.40
130	24.6±0.07	21.69±0.31
140	26.3±0.14	25.6±0.52
160	28.3±1.14	28.9±0.38
170	34.2±2.26	43.8±0.43
180	47.5±2.57	56.2±0.45
195	65.6±3.13	74.5±0.26
225	92.7±2.82	89.5±0.45
240	97.6±1.26	96.7±0.52

Table 15: Stability data for Optimized Formulation F14

Time	**Test (%)**	**40°C /75%RH**
1 month	Assay	97.2±0.31
	Acid Resistance	94.24±0.43
2 months	Assay	97.1±0.47
	Acid Resistance	94.21±0.36
3 months	Assay	97.0±0.30
	Acid Resistance	94.20±0.44

CONCLUSION

Famotidine pellets were made using a simple, quick, and cost-effective approach that did not need the use of hazardous solvents. Micromeritic characteristics, HR, and friability of the pellets were all within acceptable limits, indicating that the manufactured pellets had adequate flow potential. SEM photomicrographs and sphericity investigations revealed that drug-loaded pellets had a spherical shape with a homogeneous and smooth covering. According to the FTIR measurements, there was no chemical interaction between the drug and the polymers utilized, indicating that the drug was in a stable state. According to the findings, formulations are acceptable for delivering the medicine into the upper intestine and stomach. The created sustained drug delivery system may be employed for numerous water-

insoluble medicines, according to the findings of this study.

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