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Formulation Development & Optimization of Immediate Release Tablet of fexofenadine Hydrochloride

Jaimin Modi, Ravindra Kamble, Dr. Chetan Singh Chauhan, Nisarg Patel

Department of Industrial Pharmacy, Bhupal Noble's College of Pharmacy, Udaipur. India

ABSTRACT:

The investigation was concerned with design and characterization of oral immediate release tablets of Anti allergic drug, in order to improve efficacy and better patient compliance. The API is selective 2nd generation, non sedative, Histamine H1 receptor blocker. The API has become first line drug in the pharmacotherapy of allergic rhinitis. This is because the drug possesses tolerability and safety advantages over the Histamine H1 receptor blocker. The aim was to formulate various formulations of immediate release tablet of Anti allergic drug using different disintegrant and superdisintegrants (Sodium Starch Glycolate, Croscarmellose sodium) and by using different methods dry granulation and wet granulation. The drug-excipients interaction was investigated by FTIR showed no interaction of API with excipients. The granules and tablets of API were evaluated for various pre and post compression parameters like Angle of repose, Compressibility index, Hausner's ratio, Tablet hardness, Friability, Weight variation, Drug content and *invitro* dissolution. Their results were found satisfactory. The *invitro* dissolution studies show the release in the following order of superdisintegrants: Croscarmellose > Sodium Starch Glycolate. Maximum in vitro dissolution was found to be with Formulation F8 and it clearly shows due to optimum concentration ($4\%_{w/w}$) of Croscarmellose sodium and optimum concentration 2.5%w/w povidone. Based on linearity, the drug release data fit well to Higuchi equation plot ($r^2 = 0.915$) indicating the diffusion rate limited drug release from tablet formulation. Drug release mechanism in all media (pH1.2, pH4.0, pH6.8, water) was found as diffusion controlled (i.e., n value- 0.219 to 0.042).Higuchi square root law which indicates that the drug release follows diffusion release mechanism. Accelerated stability study was conducted as per ICH guidelines for 1 month. Developed formulation was stable for 1 month as compared to initial and innovator product from similarity factor f2 of *invitro* drug release study.

Keywords: Allergic rhinitis, Sodium Starch Glycolate, Croscarmellose sodium.

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For Correspondence:

Mr. ***Jaimin Modi***

Department of Industrial Pharmacy,

Bhupal Noble's College of Pharmacy,

Udaipur. India

Email: jaiminjmodi@gmail.com

(www.jpsbr.org)

INTRODUCTION:

Immediate Release Dosage Form [1,2]:

Pharmaceutical products designed for oral delivery and currently available on the prescription and over-the-counter markets are mostly the immediate release type, which are designed for immediate release of drug for rapid absorption.

The term "immediate release": Any formulation in which the rate of release of drug from the formulation and/or the absorption of drug, is neither appreciably, nor intentionally, retarded by galenic manipulations.

Advantages

- High drug loading
- Patient compliance
- Stability

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Disintegrating agents are substances routinely included in tablet formulations and in some hard shell capsule formulations to promote moisture penetration and dispersion of the matrix of the dosage form in dissolution fluids. Superdisintegrant improve disintegrant efficiency resulting in decreased use levels when compared to traditional disintegrants.

Componemts of Immediate release system:

1) Disintigrants and Superdisintigrants
2) Diluents
3) Lubricants
4) Flavours and Sweeteners

RATIONALE OF IR TABLETS:

- Provides effective release of the drug immediately after administration
- Hay fever, Seasonal Allergic Rhinitis and Urticaria requires immediate release of the drug to provide faster onset of action
- Improved stability of drug compare to liquid dosage forms.
- Simple manufacturing and patient compliance

RATIONALE OF DRUG SELECTION:

- Anti Histamines- 2nd Generation= Less Drowsiness
- Lacks CARDIO-TOXICITY
- Exhibits no anti-cholinergic, anti dopaminergic, alpha1-adrenergic or beta-adrenergic-receptor blocking effects
- Half life is **14.4 hr.**

MATERIALS AND METHODS:

Fexofenadine hydrochloride was from by Ind-Swift Laboratories Limited, Punjab, croscarmellosesodium, sodium starch glycolateand yellow and red ferric oxidereceived fromSignet chemical co.ltd, Mumbai, microcrystaline cellulose was received by FMC biopolymer, USA, pregelatinised Starch was received from Puredent, povidone was from EMD Chemicals,USAand all other chemicals and reagents were of analytical grade

Preparation of Fexofenadine hydrochloride tablets :

It was taken by followings methods

- **Dry Granulation Method[3,4,5]**
  - **Shifting and Lubrication:**

Preparation of Fexofenadine hydrochloride tablets :

It was taken by followings methods

- **Dry Granulation Method[3,4,5]**

  - **Shifting and Lubrication:**
    - Accurately weighed API passed through 20 ≠ and excipients through 30 ≠
    - API+Excipients blended for 5min,lubricated for 3 min
  - **Roller Compaction:**
    - Compacts with sufficient hardness were passed through different # in Quadro-co mill
    - Particles formed were passed through 60 ≠ to separate-out granules and fines.
    - Repeat cycle till sufficient granule: fine ratio obtained(65:35)
  - **Blending and Lubrication:**
    - Granules+fines blended with extra granular for 5 min
    - Above blend lubricated with Mg.stearate for 3 min.

- **Wet Granulation Method[4,6]**
  - **Shifting:**
    - API passed through 20#
    - Excipients Passed through 30#
  - **Granulation:**
    - Using Rapid Mixing Granulator(RMG), in 3 stages with sufficient binder concentration and Water quantity.
    - Dry mixing for 10 Min of 150 RPM Impellar Speed.
    - Binder addition for 2-2.5 Min of 150 RPM Impellar Speed.
    - Wet mixing for 5 Min of 150 RPM Impellar Speed.
    - Spherical granules with sufficient amount were obtained.
  - **Drying:**
    - Granules were dried in fluid bed dryer (FBD) at 60-65ºC till a LOD of dried granules obtained NMT 3.
  - **Sizing and lubrication:**
    - Dried granules were passed through 1.143# Quadro co mill and lubricated with mg. stearate for 3 min.

- **Drying [3,7]**

Drying is a mass transfer process resulting in the removal of water from a solid by evaporation.The fluidized bed drier is the most commonly used device for drying tablet granules. The solid is fluidized from below by a jet of hot air, and so each granule is separated from its neighbouring granules. The air provides an effective means of heat transfer, as well as of

removing water vapour. The speed of the drying process is governed by the distance that water molecules must diffuse before they arrive at the evaporative surface. Since the wet granules are present as individual units, the maximum distance over which diffusion occurs is equal to the radius of a granule. Hence, fluidized bed drying is a rapid process.

❖ **Compression** [4]

During compression the bulk volume of the material is reduced, resulting in the displacement of the gaseous phase (air). Further increasing the force leads to particle deformation and rearrangement. At this point, the three principal modes of deformation are as follows:

Elastic deformation: A spontaneously reversible deformation of the compact in which, upon removal of the load, the powder mass reverts back to its original form. Most materials undergo elastic deformation to some extent. Compression of rubber would be by elastic deformation.

Plastic deformation: After exceeding the elastic limit of the material (yield point), the deformation may become plastic, that is, the particles undergo viscous flow. This is the predominant mechanism when the shear strength between the particles is less than the tensile or breaking strength. Plastic deformation is a time-dependent process.

Brittle fracture: Upon exceeding the elastic limit of the material (yield point), the particles undergo brittle fracture if the shear strength between the particles is greater than the tensile or breaking strength. Under these conditions, the larger particles are sheared and broken into smaller particles

❖ **Tablet presses** [7]

Tablet presses, also called tableting machines, range from small, inexpensive bench-top models that make one tablet at a time (single-station presses), with only around a half-ton pressure, to large, computerized, industrial models (multi-station rotary presses) that can make hundreds of thousands to millions of tablets an hour with much greater pressure.

❖ **Film Coating**[8]

Tablets Coating was done in Neocota, Ganson. 2%w/w weight gain of uncoated tablets.

- In first step, HPMC was dissolved in Purified Water with the help of Mechanical Stirrer for 15 to 20 min until get clear solution.
- PEG was added in the above step and stirred for 10 min.
- TiO, yellow and red ferric oxide was dispersed in Purified water with the help of Mechanical Stirrer for 5 min then added in above step and mixed for 15 min.
- Finally coating solution was passed through the Colloidal Milling for 7 to 10 min.

Evalution of tablets:

Physical characterization[9]

- **Appearance:** The general appearance and elegance of tablet was identified visually, which include tablet size, shape, color, presence or absence of an odor, taste, surface texture avoid of sticking etc.

- **Hardness:** Tablets require certain amount of strength or hardness and resistance to friability, to with stand mechanical shocks of handling in manufacture, packaging, and shipping.

The most widely used apparatus to measure tablet hardness (crushing strength) is the Schleuniger hardness tester.

Method: Ten tablets were randomly selected and hardness was measured in Schleuniger hardness tester. The average was taken as hardness of the tablet.

- **Disintegration time:** Disintegration is evaluated to ensure that the drug substance is fully available for dissolution and absorption from the gastrointestinal tract. The disintegration test was measured using USP tablet disintegration test apparatus (ED2L, Electrolab, India).

Method: Six randomly selected tablets from each tablet batch were evaluated in purified water at 37±1^{o}C using disintegration apparatus. The time for each tablet to completely disintegrate and pass into solution was noted and the mean value was calculated.The tablet remain 2.5 cm from the bottom of media, a standard motor driven device move the basket containing tablet up and down through a distance of 5 to 6 cm at a 28 to 32 cycles per minute.

- **Thickness:** Ten Tablets were selected at random from individual formulations and thickness was measured by using verniercaliper scale, which permits accurate measurement.

- **Friability:** Friability is related to tablets ability to withstand both shocks and abrasion without crumbling during manufacturing, packing, transportation and consumer handling. Friability can be evaluated by means of friability test apparatus. Compressed tablets that loose less than 1.0% in weight are generally considered acceptable.

  Method: accurately weighed 6.5 gm of tablet and transfer into Friabilator and subjected to 100 revolutions in 4 minutes. Dedusted tablets were reweighed (final wt). Friability was calculated as below formula.

- **Weight variation:** Twenty tablets were taken randomly, weighed individually and average weight was determined. The individual tablet weight was compared with average tablet weight.

- **Content Uniformity:**Inject separately mobile phase, diluents, and standard and sample preparation into the chromatograph; record the chromatogram (The Japanese Pharmacopoeia, 2009).

Calculate the quantity in mg of API in One Tablet (mg) for all the sample preparations using the following formula.

Drug (mg) = Ws x (P/100) x (At/As) x (V/480)

Where,
A_t =Peak Area of the Drug X in the Sample preparation
A_s = Peak Area of the Drug X in the Standard preparation
W_s = Weight of the Drug X Reference Standard taken in mg
P = % Assay of Drug X Reference Standard

- **Bulk Density (BD):** Weigh accurately 25 g of drug (M), which was previously passed through 20 # and transferred in 100 ml graduated cylinder. Carefully level the powder without compacting, and read the unsettled apparent volume (V_0). Calculate the apparent bulk density in gm/cc by the following formula

- **Tapped bulk density (TD)**: Weigh accurately 25 g of drug, which was previously passed through 20 # and transfer in 100 ml graduated cylinder. Then mechanically tap the cylinder containing the sample by raising the cylinder and allowing it to drop under its own weight using mechanically tapped density tester that provides a fixed drop of 14± 2 mm at a nominal rate of 300 drops per minute. Calculate the tapped bulk density in gm/ml by the following formula.

- **Carr's Index:** It is one of the most important parameter to characteristic the nature of powders and granules. The Compressibility Index of the powder blend was determined by Carr's compressibility index. It is a simple test to evaluate the BD and TD of a powder and the rate at which it packed down. It can be calculated from the following formula:

Carr's Index= [(TD-BD)×100]/ TD

- **Hausner's Ratio:** The Hausner's ratio is a number that is correlated to the flow ability of a powder or granular material.

Hausner's Ratio = TD / BD

- **Angle of repose:** The angle of repose of API powder was determined by the funnel method. The accurately weight powder blend were taken in the funnel. The height of the funnel was adjusted in such a way the tip of the funnel just touched the apex of the powder blend. The powder blend was allowed to flow through the funnel freely on to the surface. The diameter of the powder cone was measured and angle of repose was calculated using the following equation.

$$\tan^{-1} \Theta = h / r$$

$$\Theta = \tan\text{-}1\ (h/r)$$

Where, 'Θ' is the angle of repose , 'h' is height of pile, 'r' is radius of the base of pile

Method for *invitro* dissolution study [10]

Media selection:
For the Products containing neutral or basic drugs, and coated products:
According to Guideline for Bioequivalence Studies of Generic Products
Agitation (RPM) 50 for pH1.2, pH3.0-5.0, pH6.8-7.5 and water
Agitation (RPM) 100 for pH1.2 OR pH3.0-5.0 OR pH6.8-7.5
Dissolution Parameters

Buffer phase : 900 ml, pH 1.2, pH 4.0, pH 6.8, Water.
RPM : 50 rpm
Apparatus : USP Type II (Paddle)
Time point : 5, 10, 15, 30, 45, 60, 120 min (for pH 6.8 and water 30 min)
Temperature : 37°C ± 0.5°C

Procedure: The release of API from the IR tablet was studied in 900 ml of respective dissolution media (pH 1.2, pH 4.0, pH 6.8, Water.) using a USP dissolution paddle apparatus at 50 rpm and 37 ± 0.5° C. An aliquot (5 ml) was withdrawn at specific time intervals, filtered and diluted to 100 ml with respective dissolution media and drug content was determined by HPLC at 220 nm. An equal volume of fresh dissolution media was replaced to maintain the sink condition. Dissolution studies were performed 3 times for a given time period and the mean value were taken.

Dissolution method
USP type I apparatus.
Media: 900ml of pH 1.2, pH 3, pH 6.8, Water.
Speed and time: 50 rpm.
Determine by liquid chromatography method.
Reference solution: 30mg of the API was taken in 5 ml of methanol shaked till it dissolved. Diluted above solution up to 100 ml with media.
Test solution: Pipette out 5 ml sample, filter through 0.45µ filter, diluted up to 10 ml with media.
Chromatographic system:
A stainless steel column 10 cm× 4.6 mm, packed with octadecylsilane bonded to porous silica (5µm)
Column temperature 35ºC
Mobile phase: A mixture of 30 volumes of buffer solution prepared by dissolving 1.0gm of monobasic sodium phosphate,0.5 gm of sodium perchlorate, and 3.0 ml of Ortho-phosphoric acid in 300 ml of water and 70 volumes of acetonitrile.
Flow rate: 1.0 ml per minute.
Spectrometer set at 220 nm.

Injection volume: 20µl.
Inject the reference solution. The test is not valid unless the relative standard deviation for replicate injections is not more than 2.0 percent.
Inject the test solution and reference solution.
Calculate the content of API.

RESULT AND DISCUSSION:

Immediate release tablet of Fexofenadine hydrochloride (API) was successfully prepared using dry and by wet granulation method using excipients like microcrystalline cellulose, cross carmellose sodium, Sodium starch glycolate, Pregelatinised starch, Povidone and Magnesium stearate, Aerosil.

Formulations batches F-01 to F-03 were prepared by dry granulation and batches F-04 to F-13 was prepared using wet granulation method(Table 2 to 4). The API having extremely bitter taste, so film coating of the prepared tablet was carried out to mask bitter taste of the drug.

The FTIR spectral analysis showed that there was no change in any characteristic peaks of pure drug API and excipients, which confirmed that the absence of chemical interaction between drug and excipients which is previously done.

The granules were prepared by dry granulation wet granulation method and evaluated for various physicochemical characteristics. Formulations were evaluated for pre and post compression parameters and also compared with marketed product for in-vitro dissolution.

The granules of Different formulations were evaluated for angle of repose, Bulk and Tapped density, Compressibility index, Hausner's ratio. It showed that the results of all formulations of the granules were within limits and thus it confirmed that the granules have good flow property except batches F-01 to F-03 (dry granulation) in Table 3 and Batches F-04 (wet granulation) containing different microcrystalline-cellulose have poor angle of repose and compressibility index due to insufficient granulation because of insufficient Povidone concentration.The post compression parameters such as hardness, thickness, friability, weight variation and drug content showed that the results of all formulations were within limits except F-01 to F-03(batches by dry granulation).

In formulations F-01 to F-03, by dry granulation method using microcrystalline cellulose avicel pH 101 and comprecel M 102 using povidone as a dry binder and mg.stearate and aerosol as a lubricant, That the physico-chemical parameter such as hardness of the tablet,disintegration time were not found satisfactory. So, Dissolution parameter for batch F-01 to F-03 was not carried out (table 3).

In formulations by wet granulation using povidone as a binder (batches F-04 to F-06) in proper concentration (table 2), so the physico-chemical parameters such as hardness and % friability of the tablet were improved with optimum concentration of povidone in F-05 having spherical, free flowing granules.

In Batches F-07 to F-09 the percentage drug release of formulations was improved to be due to increase the concentration of Superdisintegrant cross carmelose sodium due to added super-disintegrant in ratio of 1:2 (intragranularly: extragranularly) (table 2).The result of the percentage drug release was comparable than the marketed (Innovator) product.

In F-10 to F-12, sodium starch glycolate was used as a super-disintegrant and the effect on pre compression and post compression parameters were studied.

The *invitro* release was found to be the effect of Superdisintegrants such as Croscarmellose sodium, Sodium starch glycolate were studied. In this Croscarmellose sodium showed better percentage drug release than Sodium starch glycolate. From the release profile result Crosscarmellose sodium can release drug faster compare to Sodium Starch Glycolate (Croscarmellose Sodium > Sodium Starch Glycolate)

The similarity factor (f2) result in all media (pH 1.2, pH 4.0, pH 6.8 and water) showed that among the all formulations F8 was more similar to the marketed products (table 10) (Figure 1,2,3,4).

The results showed that the release of the drug was depended on different superdisintegrants used, in that Croscarmellose Sodium in lower concentration can release drug faster compare to Sodium starch glycolate. And the best formulation (F8) containing 4% Cross carmellose sodium showed minimum disintegration time and better drug release profile as compare to other formulations.

The prepared formulation batch F-08 (optimized batch)were placed in the stability chamber at 40˚C/75% RH for 1 month as per the ICH stability guideline Q1 (R2).the prepared batch F-08 was found to be stable.

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TABLES AND FIGURES:

Tables:

Table 1: Innovator Characterization

Parameter	Result	
Strength	60 mg	
Weight of the tablet	250 mg	
Manufactured by	Sanofi-aventis, Japan	
Label claim	Each film coated tablet contains 60 mg of API	
Description	Orange colored, oval shaped, biconvex, film coated tablet.	
Shape	Oval	
Diameter(mm)	12.2×5.6	
Hardness(kp)	15-16	
Thickness(mm)	3.8	
Disintegration time(sec)	50-80	
	CORE	**COATING**
Inactive Ingredients	Crystalline cellulose, Partially gelatinized starch, Crosscarmelose sodium, Magnesium stearate, Light anhydrous silica, Povidone,	Hypromellose, Titanium oxide. Macrogol 400 Iron sequioxide, Yellow sequioxide,

Table 2: Composition of Fexofenadine hydrochloride Tablets

Ingredients	**Quantity(mg/tab)**												
Batch No.	F-01	F-02	F-03	F-04	F-05	F-06	F-07	F-08	F-09	F-10	F-11	F-12	F-13
Intra-Granular													
API	61	61	61	60.5	60.5	60.5	60.48	60.48	60.48	60.48	60.48	60.48	60.48
MCC (Comprecel M102)	73	81	95	-	-	-	-	-	-	-	-	-	-
MCC (Avicel pH 101)	-	-	-	151	151	151	148.02	146.02	144.02	146.02	141	136.02	146.02
Pregelatinised starch	24	24	12	20	20	20	10	10	10	10	10	10	10
Cross Carmellose Sodium	4	4	6	12	12	12	4	5	6	-	-	-	5
Sodium Starch Glycolate	-	-	-	-	-	-	-	-	-	5	7.5	10	-
PVP k-30	3	5	5	**3.5 (1.5% w/w)**	**6.0 (2.5% w/w)**	**8.5 (3.5% w/w)**	6	6	6	6	6	6	6
Aerosil	-	-	0.5	-	-	-	-	-	-	-	-	-	-
Mg. Stearate	1.5	1.5	2	-	-	-	-	-	-	-	-	-	-
P.Water				Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S
Extra-Granular													
MCC (Comprecel M102)	74	64	56	-	-	-	-	-	-	-	-	-	-
Pregelatinised starch	-	-	-	-	-	-	10	10	10	10	10	10	10
Cross carmellose Sodium.	4	4	6	-	-		4	5	6	-	-	-	5
Sodium Starch Glycolate	-	-	-	-	-	-	-	-	-	5	7.5	10	-
Aerosil	-	-	0.5	-	-	-	-	-	-	-	-	-	-
Mg. Stearate	1.5	1.5	2	2	2	2	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Total	245	245	245	245	245	245	245	245	245	245	245	245	245

Table 3: Evaluation of Powder Blend

Powder blend	Angle of Repose (Q)	Loose Bulk Density	Tapped Bulk Density	Carr's Index(%) (gm/ml)	Hausner's Ratio (gm/ml)
F-01	29.89	0.36	0.48	25	1.33
F-02	27.46	0.48	0.59	18.6	1.22
F-03	26.58	0.53	0.64	17.18	1.21
F-04	25.58	0.62	0.77	19.84	1.25
F-05	25.08	0.69	0.78	11.48	1.13
F-06	25.47	0.64	0.76	15.42	1.18
F-07	22.68	0.75	0.85	12.11	1.14
F-08	22.77	0.76	0.85	10.55	1.12
F-09	22.49	0.77	0.86	11.19	1.13
F-10	23.72	0.75	0.84	11.45	1.13
F-11	23.4	0.77	0.87	11.84	1.13
F-12	23.29	0.78	0.89	11.99	1.14
F-13	22.54	0.77	0.86	10.51	1.12

Table 4: Evaluation of Uncoated Tablets

Batch No.	Avg. weight (mg)	Hardness (kp)	Thickness (mm)	Friability (%)	D.T (sec)
F-04	245.7	12.4	3.84	0.35	56
F-05	245.7	12.6	3.74	0.13	75
F-06	246.2	14.7	3.65	0.06	86
F-07	245.8	13.4	3.63	0.1	72
F-08	245.6	13.5	3.62	0.08	64
F-09	245.4	13.4	3.61	0.09	56
F-10	245.3	13.5	3.59	0.13	70
F-11	245.5	13.5	3.61	0.14	66
F-12	245.2	13.5	3.61	0.13	57
F-13	245.3	13.4	3.62	0.14	63

Table 5: Evaluation of Filmcoated Tablets

Batch	Avg. weight (mg)	Thickness (mm)	D.T (sec)	Assay (%)
F-04	---	---	---	---
F-05	250.5	3.84	90	---
F-06	251	3.75	101	---
F-07	250.6	3.73	87	99.48
F-08	250.4	3.72	79	99.31
F-09	250.2	3.71	71	99.32
F-10	250.1	3.69	85	99.54
F-11	250.3	3.71	81	99.49
F-12	250	3.71	72	99.24
F-13	250.2	3.72	78	99.57

Table 6: Comparative release profile with innovator of formulation (F-07 to F-13) at pH 1.2:

Comparative release profile of formulation (F-07 to F-13) at pH 1.2								
Time in minute	**Innovator**	**F7**	**F8**	**F9**	**F10**	**F11**	**F12**	**F13**
0	0	0	0	0	0	0	0	0
5	34.8	27.6	33.8	41.2	24.1	30.4	39.4	33.8
10	42	33.9	41.1	49.9	33.7	37.6	46.6	41.1
15	58.4	50.4	56.3	59.3	48.7	52.6	61.6	56.3
20	65.1	59.9	64.9	71.1	54.3	61.9	70.9	64.9
30	75.1	67.4	73.9	79.8	67.7	71.6	80.6	73.9
45	85.3	74.5	83.9	92.4	76.7	80.6	89.6	83.9
60	91.3	82.8	90.9	99.4	86.2	90.1	99.1	90.7
90	97.3	89.7	96.8		88.5	92.4	100.9	96.1
120	101.2	94.5	99.7		91.2	97.5		100.4
f_2 value		43.17	**82.29**	51.18	40.35	59.82	54.46	**85.03**

Table 7: Comparative release profile with innovator of formulation (F7 to F13) at pH 4.0

Comparative release profile of formulation (F7 to F13) at pH 4.0								
Time in minute	**Innovator**	**F7**	**F8**	**F9**	**F10**	**F11**	**F12**	**F13**
0	0	0	0	0	0	0	0	0
5	36.2	29.8	35.9	39.9	24.1	28.7	32.4	34.5
10	49.3	33.9	48.3	52.3	37.2	41.8	45.5	48.1
15	57.9	43.5	56	62.4	46.5	51.1	54.8	57.3
20	63.6	52.4	61.9	70.2	51.5	56.1	59.8	62.4
30	71.3	61.2	72.8	79.4	61.8	66.4	70.1	70.9
45	79.9	70.3	78.7	86.5	67.8	72.4	76.1	79.1
60	85.4	76.5	84.3	92.2	75.2	79.8	83.5	85.1
90	91.4	82.9	92.7	95.5	79.3	83.9	87.6	91.9
120	95.8	89.5	96.4	96.7	83.7	88.3	92.9	96.7
f_2 value		**36.93**	**80.82**	**51.44**	**34.89**	**45.78**	**62.11**	**85.81**

Table 8: Comparative release profile with innovator of formulation (F7 to F13) at pH 6.8

Comparative release profile of formulation (F7 to F13) at pH 6.8								
Time in minute	**Innovator**	**F7**	**F8**	**F9**	**F10**	**F11**	**F12**	**F13**
0	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**
5	**77.2**	**58.3**	**76.3**	**87.3**	**52.9**	**74.1**	**80.9**	**78.3**
10	**87.2**	**67.9**	**86.9**	**95.9**	**63.4**	**77.6**	**84.4**	**86.9**
15	**91.9**	**76.6**	**89.3**	**99.2**	**74.8**	**81.2**	**98.7**	**90.5**
20	**95.1**	**79.5**	**93.9**	**100.5**	**7.9**	**89.1**	**99.9**	**93.5**
30	**97.7**	**83.9**	**96.6**		**82.7**	**93.9**		**95.5**
f_2 value		**49.24**	**88.46**	**62.49**	**47.83**	**61.96**	**69.75**	**86.99**

Table 9: Comparative release profile with innovator of formulation (F7 to F13) at pH 6.8

Comparative release profile of formulation (F7 to F13) at Water								
Time in minute	**Innovator**	**F7**	**F8**	**F9**	**F10**	**F11**	**F12**	**F13**
0	0	0	0	0	0	0	0	0
5	83	68.6	82.6	89.7	58.3	79.4	86.5	83.4
10	92.6	78.3	91.3	96.4	66.1	89.9	89.9	92.0
15	96.6	82.6	94.1	98.9	73.4	94.3	95.5	95.7
20	98.8	91.5	99.5	100.1	85.3	95.6	99.8	99.2
30	100.5	92.7	100.3		90.6	97.6	102.8	99.8
f_2 value		**54.64**	**89.74**	**79.19**	**44.57**	**86.19**	**81.21**	**94.72**

Table 10: Comparative release profile of F-08 with INNOVATOR in pH 1.2

❖ **Comparative release profile of formulation F-08 with innovator in pH 1.2**

Comparative release profile of formulation F-08 with innovator in pH 1.2		
Time (min)	**Innovator**	**F-08**
0	0	0
5	34.8	33.8
10	42	41.1
15	58.4	56.3
20	65.1	64.9
30	75.1	73.9
45	85.3	83.9
60	91.3	90.9
90	97.3	96.8
120	101.2	99.7
f_2 value		**82.29**

❖ Comparative release profile of formulation F-08 with innovator in pH 4.0

Comparative release profile of formulation F-08 with innovator in pH 1.2		
Time (min)	**Innovator**	**F-08**
0	0	0
5	34.8	33.8
10	42	41.1
15	58.4	56.3
20	65.1	64.9
30	75.1	73.9
45	85.3	83.9
60	91.3	90.9
90	97.3	96.8
120	101.2	99.7

❖ Comparative release profile of formulation F-08 with innovator in pH 4.0

Comparative release profile of formulation F-08 with innovator in pH 4.0.		
Time (min)	**Innovator**	**F-08**
0	0	0
5	36.2	35.9
10	49.3	48.3
15	57.9	56
20	63.6	61.9
30	71.3	72.8
45	79.9	78.7
60	85.4	84.3
90	91.4	92.7
120	95.8	96.4
f_2 value		**80.82**

❖ Comparative release profile of formulation F-08 with innovator in pH 6.8

Comparative release profile of formulation F-08 with innovator in pH 6.8.		
Time (min)	**Innovator**	**F-08**
0	0	0
5	77.2	76.3
10	87.2	86.9
15	91.9	89.3
20	95.1	93.9
30	97.7	96.6
f_2 value		**88.46**

❖ Comparative release profile of formulation F-08 with innovator in Water.

Comparative release profile of formulation F-08 with innov in water.		
Time (min)	**Innovator**	**F-08**
0	0	0
5	83	82.6
10	92.6	91.3
15	96.6	94.1
20	98.8	99.5
30	100.5	100.3
f_2 **value**		**89.74**

Figures:

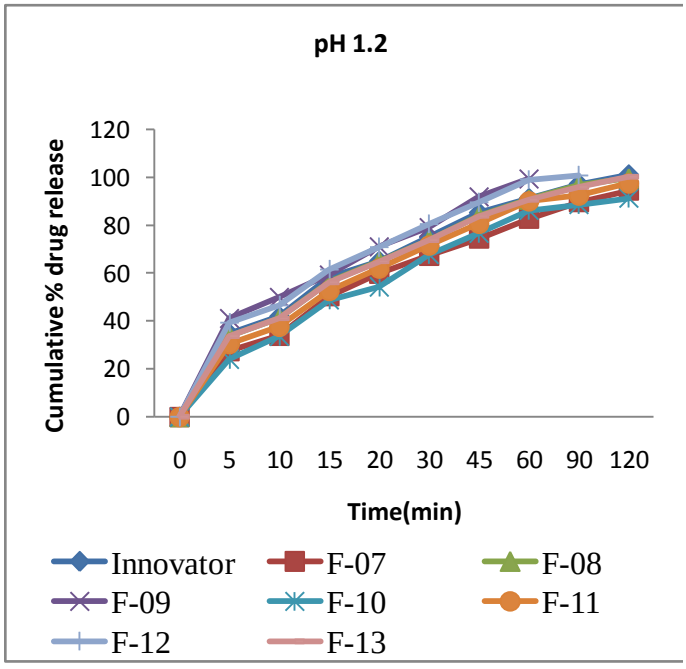

Figure 1: Comparative release profile with innovator of formulation (F-07toF-13) at pH 1.2

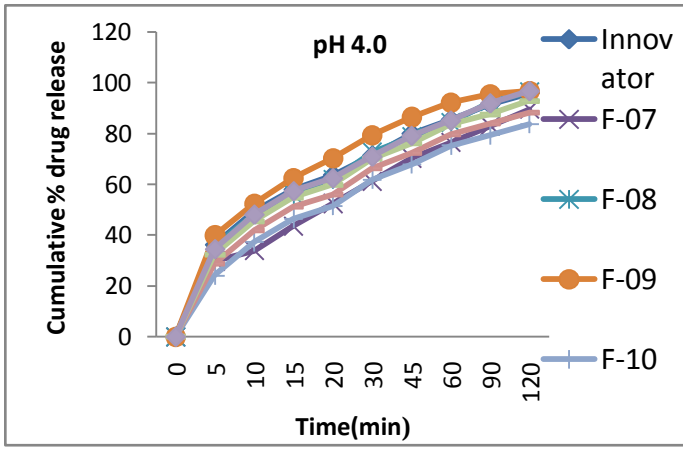

Figure 2: Comparative release profile with innovator of formulation (F7 to F13) at pH 4.0

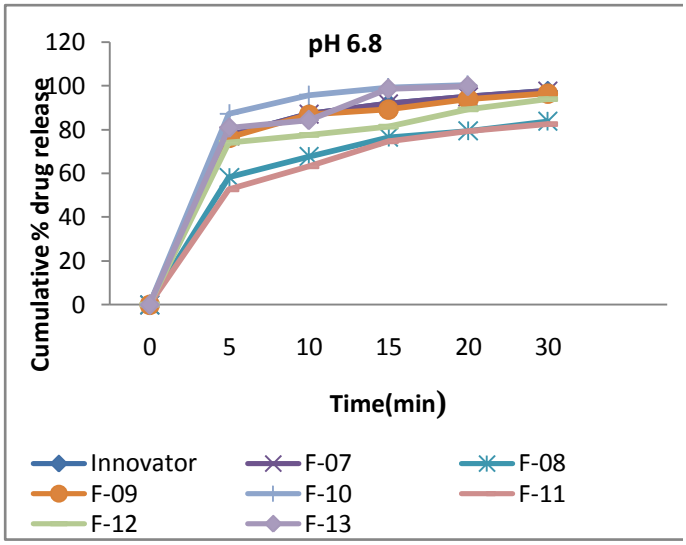

Figure 3: Comparative release profile with innovator of formulation (F7 to F13) at pH 6.8

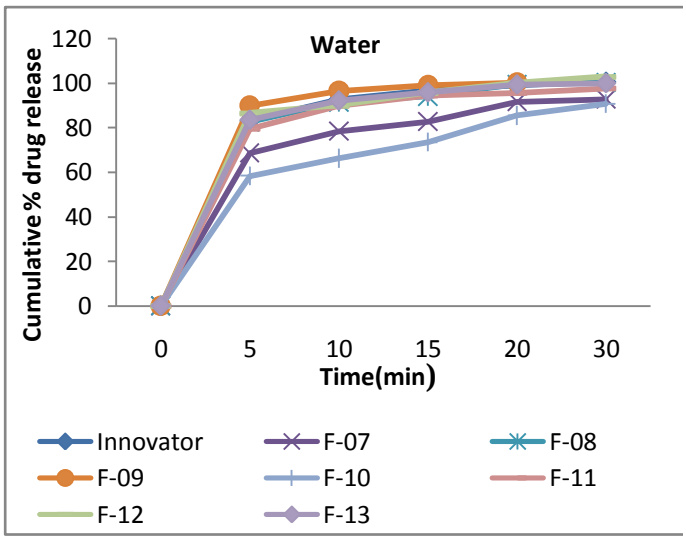

Figure 4: Comparative release profile with innovator of formulation (F7 to F13) at Water

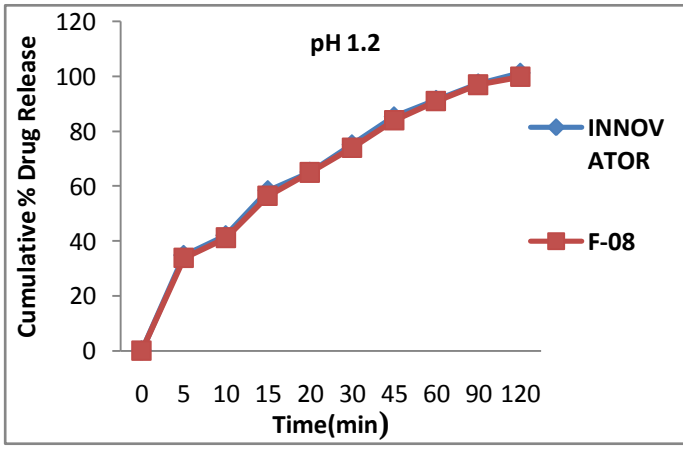

Figure 5: Comparative release profile of Batch F-08 with innovator in pH 1.2

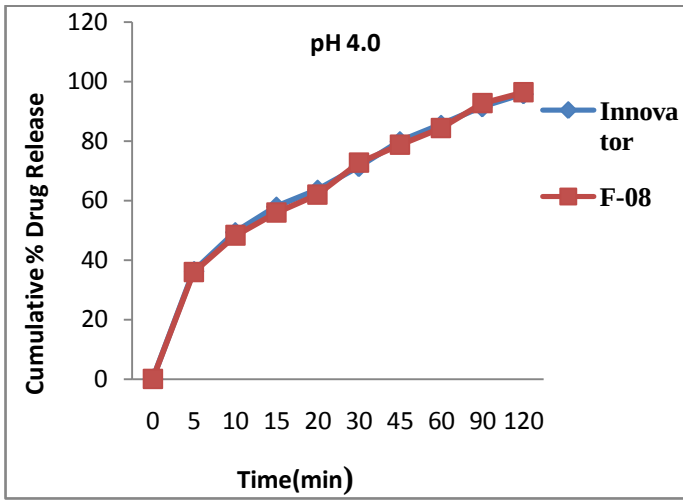

Figure 6: Comparative release profile of Batch F-08 with innovator in pH 4.0

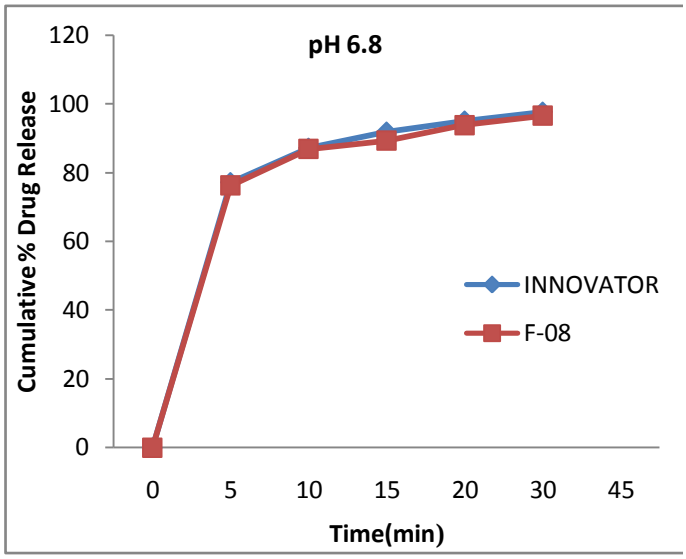

Figure 7: Comparative release profile of Batch F-08 with innovator in pH 6.8

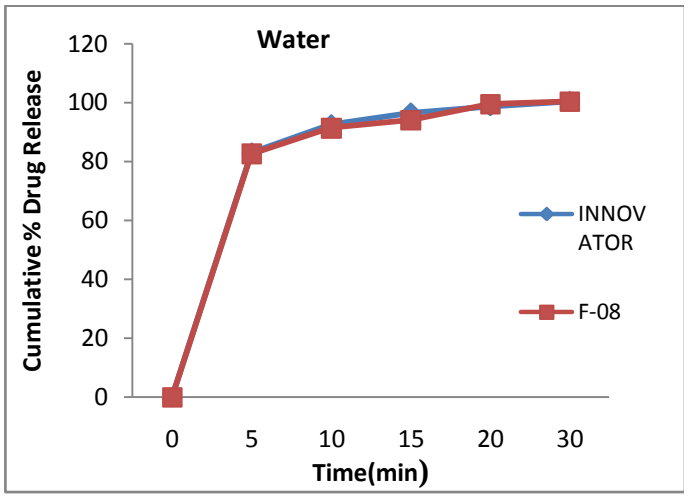

Figure 8: Comparative release profile of Batch F-08 with innovator in Water