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Research Article

FORMULATION AND EVALUATION OF CEFUROXIME AXETIL GRANULES FOR ORAL SUSPENSION

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ABSTRACT

Objectives: The aim of this study is formulation and evaluation of cefuroxime axetil (CA) granules for oral suspension and to compare its *in vitro* bioavailability with Innovator Product.

Methods: The granules of CA were prepared by wet granulation method. Six formulations of varying composition of ingredients were prepared. Preformulation studies were performed. The suspension was evaluated for its flow property, *in vitro* dissolution study, and assay.

Results: Preformulation parameters show that the flow property of powder is poor. The suspension was successfully prepared by wet granulation method. The flow property of granules varied form fair to excellent in different formulations. The f_2 value ranges from 25 to 77.

Conclusion: With a better release characteristic and excellent flow property, the formulation F6 is considered as the final formulation with an f_2 value of 77 and assay of 99.7%.

Keywords: Cefuroxime axetil, Granulation, Bioavailability, Dry suspension.

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INTRODUCTION

Cefuroxime axetil (CA) is associate organic compound prodrug of cefuroxime, a second-generation semi-synthetic cephalosporin antibiotic. Cefuroxime is stable to b-lactamase and demonstrates a broad-spectrum antibacterial drug activity against each Gram-positive and Gram-negative organism by inhibiting the synthesis of the bacterial cell walls. Cefuroxime is hardly absorbed once administrated orally, whereas with a 1-acetyloxyethyl ester modification, the prodrug CA displays anti-bacterial activity in oral delivery [1,2]. Succeeding oral administration, CA is absorbed, and then speedily hydrolyzed by the non-specific esterases that are distributed in the enteral membrane and portal blood, and ultimately transformed into the medical specialty active molecule cefuroxime [3]. The esterification has no impact on the antibacterial drug potency of cefuroxime. However, like different water-insoluble drugs, CA encompasses a restricted solubility associated dissolution rate within the gastrointestinal tract [4,5]. Furthermore, CA has an unpleasant style that is probably going to end in poor patient compliance, particularly in the case of youngsters and infants. Hence, taste masking and rising oral bioavailability are the key problems in the research work.

Among the various drug delivery systems, oral administration is preferred due to the advantages such as convenience and good patient compliance. However, oral administration is generally disadvantageous for non-tasting drugs. Bitter compounds have been reported to interact with taste buds and produce negative sensory response [6]. In addition to the classic addition of flavors and sweeteners, there are different approaches to solving this problem with different dosing platforms such as fast dissolving platform, physical barriers, chemical or soluble modification, granulation, and solid dispersion technology [6,7].

At present, available commercial formulations include tablets, capsules, dispersible tablets, and granules. In this work, we have developed a taste-masked dosage form of CA using a wet granulation process. Oral suspension is preferred by many patients due to its ease of swallowing and flexible administration. It is particularly beneficial for children, the elderly and infants, while the unpleasant taste of bitter medicinal substances can be eliminated by administering it in undissolved form particles. Dry suspension powders are more desirable for their stability and practicality [8].

Dry suspension of CA was well prepared with wet granulation method. The dry suspensions and its commercial formulation were evaluated for physical parameters, dissolution testing and assay.

MATERIALS AND METHODS

Materials

CA was purchased from Nectar Lifesciences Ltd., Punjab. Stearic acid was purchased from Stearinate Dubois, France. Sucrose was purchased from MB Sugars and Pharmaceuticals Ltd., Maharashtra. Aspartame was purchased from Sino Sweet Co. Ltd., China. Acesulfame potassium was purchased from Celanese, America. PVP K-30 was purchased from BOAI NKY Pharmaceuticals Ltd. Xanthan gum was purchased from CP Kelco Inc., USA. Tutti frutti was purchased from Firmenich, Switzerland.

Preformulation studies

It can be defined as an investigation of physical and chemical properties of a drug substance alone and when combined with excipients.

Organoleptic properties

CA's organoleptic characteristics, such as color, odor, and taste, were investigated.

Flow property

The powder's flow characteristic controls how it exits the hopper during manufacture. The bulk density, tapped density, compressibility index, and Hausner's ratio are used to quantify this [9,10].

Melting point

The melting point was determined by differential scanning calorimetry (DSC). DSC analysis was performed in a nitrogen atmosphere stream.

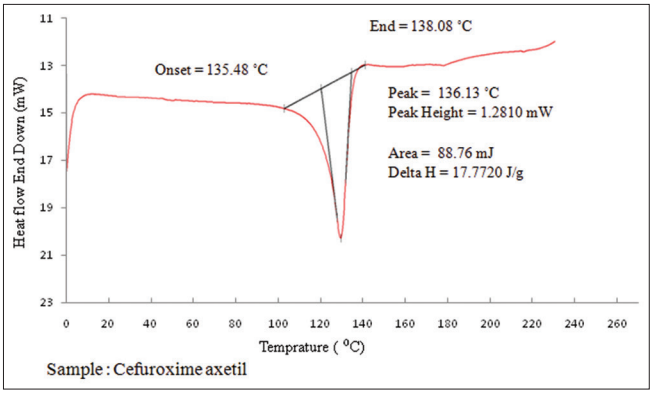

Fig. 1: Differential scanning calorimetry thermogram of cefuroxime axetil

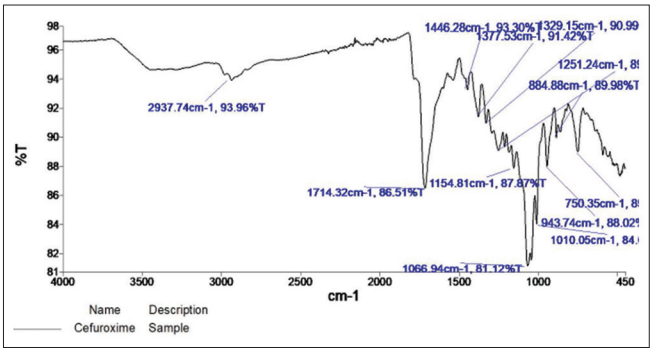

Fig. 2: Fourier transform infrared spectrum of cefuroxime axetil

An accurately weighed sample (10 mg) was heated in hard pressure plus perforated crucibles of aluminium pan. A heating rate of 10°C/min was used over a temperature range of 10–250°C. An empty tray was used as a reference standard [11].

Solubility

Solubility measurements of CA were performed by adding a known excess amount to 1 mL of various solvents such as water, acetone, methanol, ethyl acetate, ether, 0.1M HCl, acetate buffer pH 4.5, and pH 7.0 phosphate buffer. The samples were agitated with a mechanical stirrer at 50 rpm (37±0.5°C) for 24 h. Samples were centrifuged at 10,000 rpm for 5 min and the supernatant was filtered and then appropriately diluted for analysis with a UV spectrophotometer at 278 nm [12].

Identification of API by Fourier transform infrared (FTIR)

The FTIR spectrum of a compound or drug provides information about the groups present in that particular compound. FTIR spectroscopy was used to analyze the structure. 5–10 mg drug was introduced into the FTIR chamber. The infrared spectrum was recorded in the range of 4000–400 cm^{-1} [13].

Analytical method development

Determination of absorption maxima in methanol

A 1 mg/mL CA stock solution was prepared by dissolving 100 mg of CA in 100 mL of methanol buffer in a 100 mL volumetric flask. 1 mL of the above solution was further diluted to 10 mL with methanol to get 100 µg/mL. A UV scan was performed in 200–400 nm range using methanol as a blank. The wavelength of maximum absorption was observed.

Preparation of standard curve

From the stock solution 0.2, 0.4, 0.6, 0.8, 0.10, 0.12 mL, 0.16, and 0.2 mL were transferred to 10 mL volumetric flasks and were diluted with methanol, up to the mark to obtain concentration of 2, 4, 6, 8, 10, 12, 16, and 20 µg/mL, respectively. Absorbance of each solution was measured at 278 nm. The standard curve was obtained by plotting concentration (µg/mL) values in X-axis and the absorbance values in Y-axis [14].

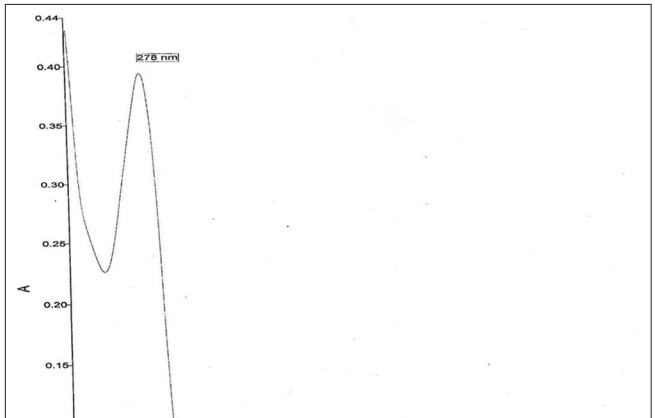

Fig. 3: Standard curve of cefuroxime axetil

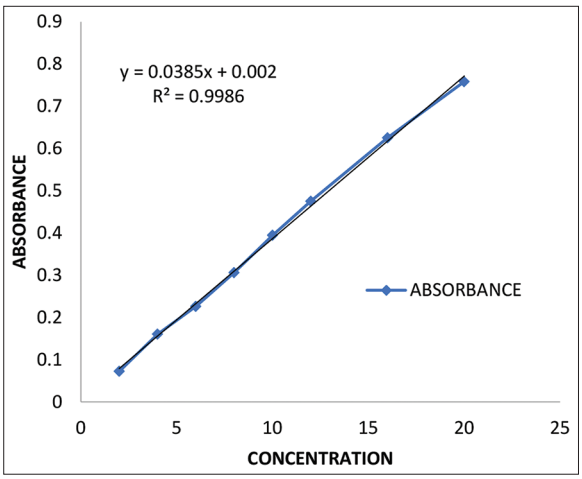

Fig. 4: Standard calibration curve of cefuroxime axetil

Drug-excipient compatibility

By physical method

Compatibility studies were performed by preparing blend of different excipients with drug and stored at 40°C/75% RH for 1 month. The blend was evaluated for every 15 days for changes such as caking, liquefaction, discoloration, and odor formation.

By FTIR

An FTIR spectrum of drug, excipients and drug-excipients mixture was recorded for the determination of drug interaction with excipients. Infrared spectrum was recorded in the 4000–400 cm^{-1} region [13].

Preparation of CA suspension by wet granulation method

Co-sift weighed API and weighed stearic acid (40% of the batch quantity) through #16 mesh. Transfer the above material in Rapid Mixer Granulator and dry mix the blend at 75 rpm of impeller speed for 10 min. Melt the remaining weighed quantity of stearic acid at 80–90°C on hot plate for 25–30 min and add this melted stearic acid to the

above blend material at slower speed of impeller (75 rpm) and chopper (1500 rpm) to get the blend into granular material and finally discharge the material into bowl. After granulation, granules were passed through #16 mesh. Now add 50% of the total quantity of sucrose in this and place the material in rapid mixer granulator. Weighed quantity of PVP K-30 is dissolved in water under stirring till a clear solution is obtained. Add the melted PVPK-30 in the above material slowly at low speed of impeller. After complete addition of binder, chopper was started to break the lumps and then discharge the materials into bowl. Wet granules were passed through #16 mesh. Dry the granules in fluidized bed dryer at inlet temp. 50±5°C for 30 min till the loss on drying is <1% at 105°C. Dried granules were passed through #40 mesh and collected in a polybag. Sift the remaining amount of 50% of batch quantity of sucrose, Tutti frutti, Aspartame, Acesulfame potassium, and Xanthan gum through #40 mesh and collected in polybag. Dried granules and the above ingredients are co-sifted through #40 mesh and collected in polybag. Load the above granules in suitable blender and mix for 10 min at 10 rpm. Fill the granules in amber colored glass bottle and submitted for analysis.

Six different formulations of CA suspension are prepared using the above described method and have different compositions, as shown in Table 1.

Evaluation of oral suspension

Flow property

This is measured in terms of bulk density, tapped density, compressibility index, and Hausner's ratio which have been described earlier.

Taste evaluation (sensory evaluation)

Sensory evaluation is defined as the scientific discipline of measuring, analyzing, and interpreting responses to those characteristic of materials as perceived by the senses of sight, smell, taste, touch, and hearing. Taste evaluation was done by taste panels. Ten volunteers were selected for this. The prepared suspension was coded and administered to volunteers. The intensity of bitterness was asked from volunteers.

In vitro dissolution studies

The *in vitro* dissolution studies of CA oral suspension are performed using USP type II dissolution apparatus (paddle type). Test 5 mL of reconstituted CA for oral suspension equivalent to 125 mg of cefuroxime. The dissolution medium consisted of 900 mL of 0.07 M phosphate buffer (pH=7.0) maintained at 37±0.2°C. The speed of paddle was set at 50 rpm. Test 5 mL of CA that has been reconstituted to make an oral suspension containing 125 mg of cefuroxime. Aliquots of samples (5 mL) were taken out at predetermined intervals of 10, 15, 30, 45, and 60 min [15].

$$\text{Calculation} = \frac{\text{Wt. of standard} \times \text{Sample absorbance} \times 900 \times \text{Sample dilution} \times \text{Potency of standard}}{\text{Standard dilution} \times \text{Standard absorbance} \times \text{Label claim}}$$

Multimedia dissolution study

A multimedia dissolution study of the reference product and the final formulation is conducted. All the dissolution specification is same as above except the media. In multimedia dissolution study, the media used are 0.1 N HCl, pH 4.5 acetate buffer, and pH 7.0 phosphate buffer.

Similarity factor (f_2)

The factor f_2 measures the closeness between the two profiles. According to FDA, the similarity factor (f_2) is a logarithmic reciprocal square root

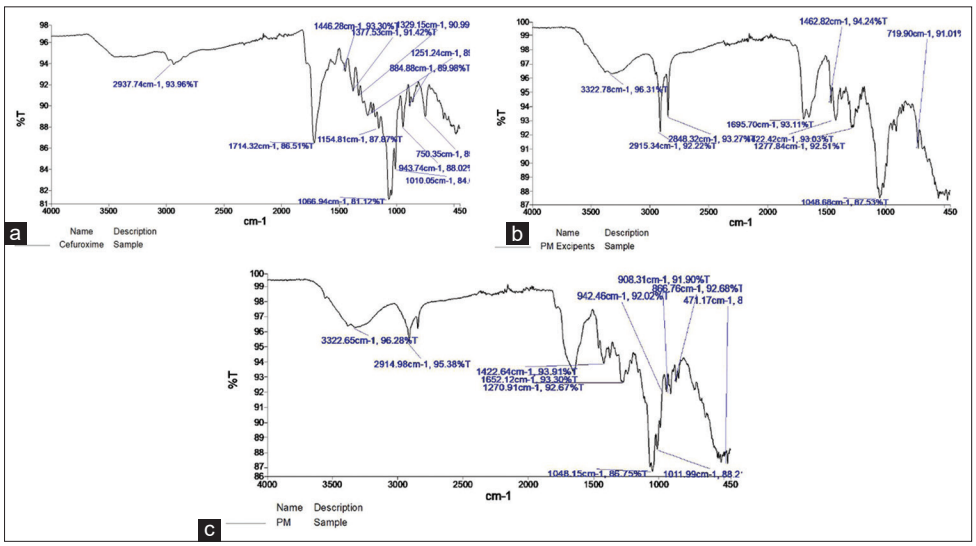

Fig. 5: (a) Fourier transform infrared (FTIR) spectrum of cefuroxime axetil. (b): FTIR spectrum of physical mixture of excipients. (c): FTIR spectrum of cefuroxime axetil and excipients

Table 1: Composition of different formulations

Ingredients	Quantity (mg/dose)					
	F1	F2	F3	F4	F5	F6
Cefuroxime axetil	153.31	153.31	153.31	153.31	153.31	153.31
Stearic acid	1533.10	1226.48	766.55	459.93	766.55	766.55
Sucrose	2347.59	2654.21	3114.14	3420.76	3121.14	3123.14
Povidone k-30	20	20	20	20	13	13
Aspartame	21	21	21	21	21	21
Acesulfame potassium	21	21	21	21	21	21
Xanthan gum	4	4	4	4	4	2
Tutti frutti	100	100	100	100	100	100

transformation of the sum of squared error and is a measurement of the similarity in the percent (%) dissolution between the two curves.

Where $f_2 = 50.\log\{[1+\frac{1}{n}\sum_{t=1}^{n} Wt(Rt-Tt)^2]^{-0.5}\times 100\}$,

→ n denotes number of dissolution intervals

→ Rt indicated percentage release results of the reference (before change) lot at time-point t

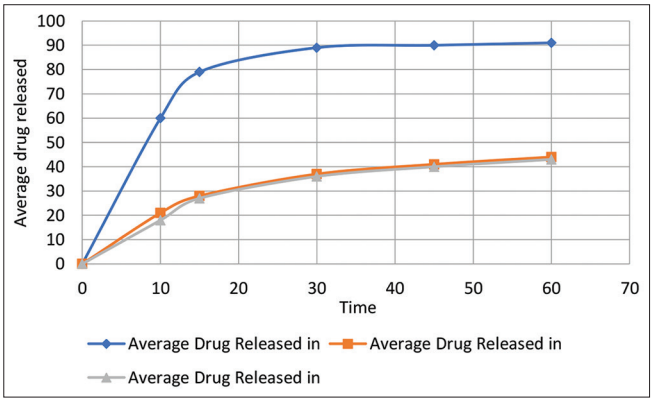

Fig. 6: Dissolution profile of innovator product in different media

Table 2: Observation of organoleptic properties

Test	Observation
Color	White to almost white powder
Odor	Nauseating
Taste	Very bitter

Table 3: Observation of flow property

Parameters	Results
Bulk density	0.18 g/mL
Tapped density	0.26 g/mL
Hausner's ratio	1.43
Carr's index	30.23%

Table 4: Standard curve data of cefuroxime axetil

Concentration (µg/mL)	Absorbance
2	0.072
4	0.160
6	0.226
8	0.306
10	0.394
12	0.475
16	0.625
20	0.758

→ Tt indicated percentage release results of the lot under evaluation (before change) lot at time t.

Assay by HPLC

Separately inject equal volumes of the standard preparation and the assay preparation into the chromatograph, record the chromatograms, and measure the responses. The chromatogram is recorded at 278 nm [15].

Detector: UV 278 nm
Column: 4.6-mm × 25-cm; 5-µm packing L13
Flow rate: 1.5 mL/min
Injection size: 10 µL

$$\text{Calculation} = \frac{\text{Test area}}{\text{Std. area}} \times \frac{\text{Std.conc.}}{\text{Test conc.}} \times \frac{P}{100} \times \text{Wt / mL} \times 5$$

RESULTS AND DISCUSSION

Preformulation parameters

Organoleptic properties

The following studies were performed for CA for its various physical parameters.

Flow property

From the above observations, the value of Hausner's ratio and Carr's index is 1.43 and 30.23% which signifies that the flow property of the CA amorphous powder is poor.

Melting point

The DSC thermogram was utilized to study the changeover structure of drug. The DSC of CA showed endothermic T_{max} of 136.13°C.

Solubility

Freely soluble in acetone, soluble in methanol and ethyl acetate, slightly soluble in 0.1M HCl, very slightly soluble in ph4.5 acetate buffer, and ph7.0 phosphate buffer and insoluble in ether and water.

Identification of API

The FTIR spectra of CA were shown in the above figure and table. The principal IR absorption peaks of CA at 2937.74 cm^{-1} (N-H amide), 1714.32 cm^{-1} (Carbonyl group), 1446.28 cm^{-1} (C-H bending), 1377.53 cm^{-1} (O-H bending), 1251.24 cm^{-1} (C-O stretching), 1066.94 cm^{-1} (C-N stretching), 1010.05 cm^{-1} (C-C stretching), 884.88 cm^{-1} (C-C bending), and 750.35 cm^{-1} (C-S bending) were all observed in the spectra of CA. These are the observed principal peaks. This observation confirmed the purity and authenticity of CA.

Determination of absorption maxima

The wavelength of absorption maximum was found to be 278 nm.

Preparation of standard curve

With the help of absorbance determined, a standard calibration curve of CA was plotted and the R^2 value was found to be 0.9986.

Table 5: Observation of drug excipient compatibility by physical method

Composition	Description		
	Initial	2 weeks	4 weeks
Cefuroxime Axetil	White to off white powder	No color change	No color change
Cefuroxime Axetil+stearic acid	White to off white powder	No color change	No color change
Cefuroxime Axetil+Aspartame	White to off white powder	No color change	No color change
Cefuroxime Axetil+Sucrose	White to off white powder	No color change	No color change
Cefuroxime Axetil+Povidone k30	White to off white powder	No color change	No color change
Cefuroxime Axetil+Tutti Frutti	White to off white powder	No color change	No color change
Cefuroxime Axetil+Xanthan gum	White to off white powder	No color change	No color change
Cefuroxime Axetil+Acesulfame potassium	White to off white powder	No color change	No color change

Drug-excipient compatibility

By physical method

From the above results, after 30 days of accelerated stability testing the drug-excipient mixture remains. Thus, it was concluded that the excipients selected for the formulation were compatible with drug.

By FTIR

- FTIR study of CAFTIR study of Physical mixture of drug and excipients

The FTIR spectra of CA, physical mixture of excipients, and CA + Excipients were shown in the above figures.The principal IR absorption peaks of CA at 2914.98 cm^{-1} (N-H amide), 1652.12 cm^{-1} (Carbonyl group), 1422.64 cm^{-1} (C-H bending), 1270.91 cm^{-1} (C-O stretching), 1048.15 cm^{-1} (C-N stretching), 1011.99 cm^{-1} (C-C stretching), 866.76 cm^{-1} (C-C bending), and 471.11 cm^{-1} (C-S bending) were all observed in the spectra of CA + Excipients. These are observed principal peaks. This observation confirmed the purity and authenticity of CA. It was observed that the drug shows characteristic peaks and there were no significant changes in the position of the characteristic peaks of drug when mixed with excipients indicate compatibility of drug with and excipients.

Evaluation of oral suspension

Innovator product

CA oral suspension 125 mg/5 mL is available in the market under the trade name Zinnat manufactured by Glaxo Smith Kline, UK Limited is considered as innovator product.

Blend evaluation

From the above results, the value of Hausner's ratio and Carr's index is 1.13% and 11.59% which signifies that the flow properties of granules are good. The taste of the formulation is pleasant initially and has a slight bitter after taste.

In vitro dissolution study

Multimedia dissolution study is performed on the Innovator Product to check its solubility in different media.

Table 6: Results of blend evaluation of innovator product

Parameters	Results
Bulk density	0.61 g/mL
Tapped density	0.69 g/mL
Hausner's ratio	1.13
Carr's index	11.59%

Table 7: *In vitro* drug release of innovator product at different time intervals in different media

Time (min.)	Average drug released in different media (in %)		
	pH 7.0 phosphate buffer	pH 4.5 acetate buffer	0.1 N HCl
10	60	21	18
15	79	28	27
30	89	37	36
45	90	41	40
60	91	44	43

Dissolution study of the innovator product was done using dissolution parameters in different media such as pH 7.0 phosphate buffer, pH 4.5 acetate buffer, and 0.1 N HCl. Figure shows the dissolution profiles of innovator product in different media. The drug is more soluble in pH 7.0 phosphate buffer, that is, 91% then the other two media.

Assay

The assay of this formulation was found to be 99.5%.

Formulation evaluation

Blend evaluation

All the formulation are evaluated for their flow properties. From the above results, in formulation 4 (F4), the value of Hausner's ratio and Carr's index is 1.18 and 15.94% which signifies that the flow properties of granules are fair and the taste of this formulation is bitter. The formulation 6 (F6) has an acceptable taste having the excellent flow properties with the value of Hausner's ratio and Carr's index –1.10 and 9.37%.

In vitro dissolution study

The *in vitro* dissolution study of different formulations is performed in release media, that is, pH 7.0 phosphate buffer.

Dissolution study of different formulations was done using dissolution parameters in release media, that is, pH 7.0 phosphate buffer. Figure 7 shows the dissolution profiles of Innovator Product in different media. The dissolution test was not performed on formulation 4 (F4) as the formulation was bitter in taste and the granules are not perfectly formed as they are soft. The f_2 is also calculated and the formulation 1 (F1) shows the lowest f_2 value of 25 whereas formulation 6 (F6) shows the highest f_2 value, that is, 77. The dissolution profile of Formulation 6 (F6) was found comparable with innovator product. Hence, it was decided to perform multimedia dissolution study in pH 4.5 acetate buffer and 0.1 N HCl.

In vitro dissolution study of formulation 6 (F6) in pH 4.5 acetate buffer

Dissolution study of formulation 6 (F6) was done using dissolution parameters in pH 4.5 acetate buffer media.

Comparison of In vitro drug release between innovator product and formulation 6 (F6) in pH 4.5 acetate buffer

The drug release of the formulation 6 (F6) was compared with that of the innovator product in pH 4.5 acetate buffer.

In vitro dissolution study in 0.1 N HCl

Dissolution study of formulation 6 (F6) was done using dissolution parameters in 0.1 N HCl.

Comparison of in vitro drug release between innovator product and formulation 6 (F6) in 0.1 N HCl

The drug release of the formulation 6 (F6) was compared with that of the innovator product in 0.1 N HCl.

Similarity factor

Table 14 shows the similarity factor of formulation 6 (F6) with the innovator product in different media

Table 8: Flow properties of different formulations

Parameters	F1	F2	F3	F4	F5	F6
Bulk density	0.63 g/mL	0.58 g/mL	0.63 g/mL	0.58 g/mL	0.66 g/mL	0.58 g/mL
Tapped density	0.74 g/mL	0.66 g/mL	0.71 g/mL	0.69 g/mL	0.76 g/mL	0.64 g/mL
Hausner's ratio	1.17	1.13	1.12	1.18	1.15	1.10
Carr's index	14.86%	12.12%	11.26%	15.94%	13.50%	9.37%

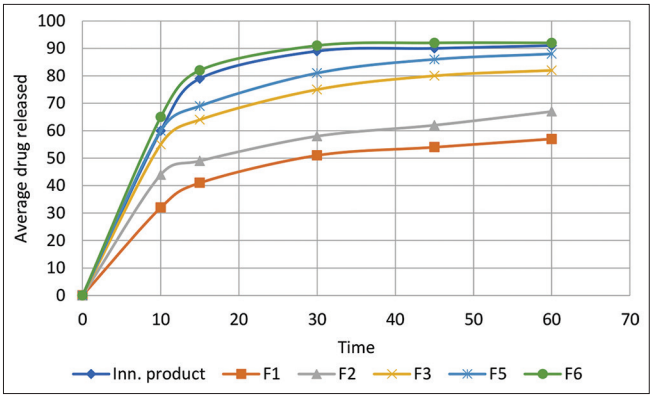

Fig. 7: Dissolution profile of innovator product and formulations in pH 7.0 phosphate buffer

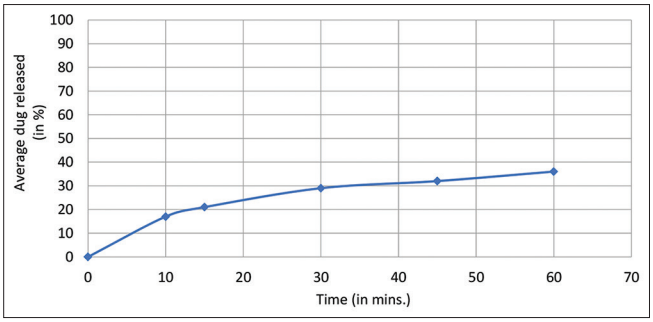

Fig. 8: Dissolution profile of formulation 6 (F6) in pH 4.5 acetate buffer

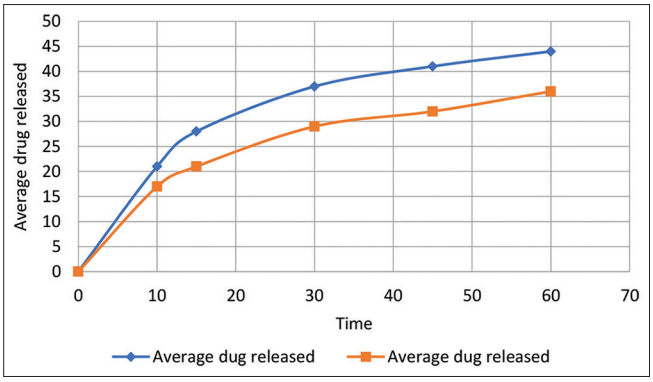

Fig. 9: Comparative dissolution profile of innovator product and formulation 6 (F6) in pH 4.5 acetate buffer

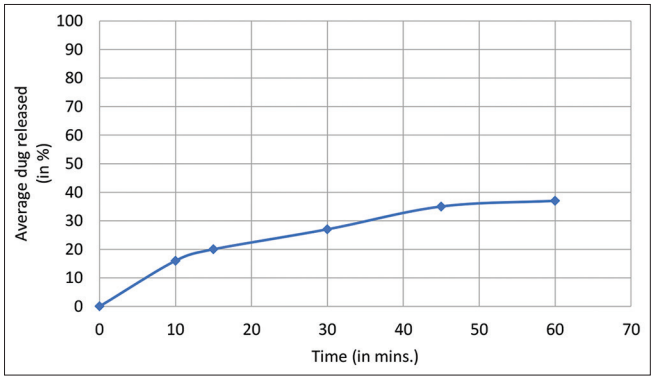

Fig. 10: Dissolution profile of formulation 6 (F6) in 0.1 N HCl

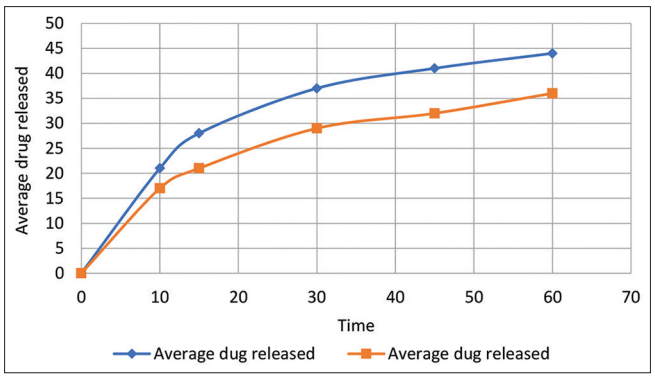

Fig. 11: Comparative dissolution profile of innovator product and formulation 6 (F6) in 0.1 N HCl

Table 9: *In vitro* drug release of innovator product and formulations at different time intervals

Time (min.)	Average drug released (in %)					
	Innovator	F1	F2	F3	F5	F6
10	60	32	44	55	60	65
15	79	41	49	64	69	82
30	89	51	58	75	81	91
45	90	54	62	80	86	92
60	91	57	67	82	88	92
f_2	-	25	31	49	62	77

Table 10: *In vitro* drug release of formulation 6 (F6) at different time intervals in pH 4.5 acetate buffer

Time (min.)	Individual units (% drug released) (n=6)						
	1	2	3	4	5	6	Average
10	18	17	17	18	17	17	17
15	20	20	22	22	21	21	21
30	28	29	30	29	30	29	29
45	32	32	32	31	31	31	32
60	38	36	38	37	35	34	36

Table 11: Comparative *in vitro* drug release of innovator product and formulation 6 (F6) in pH 4.5 acetate buffer

Time (min.)	Average dug released (in %)	
	Innovator	Test
0	0	0
10	21	17
15	28	21
30	37	29
45	41	32
60	44	36

Table 12: *In vitro* drug release of formulation 6 (F6) at different time intervals in 0.1 N HCl

Time (min.)	Individual units (% drug released) (n=6)						
	1	2	3	4	5	6	Average
10	15	16	17	16	16	17	16
15	20	21	20	21	20	20	20
30	27	27	27	27	29	28	27
45	34	34	34	34	36	35	35
60	37	36	37	38	38	38	37

Table 13: Comparative dissolution profile of innovator product and formulation 6 (F6) in 0.1 N HCl

Time (min.)	Average dug released (in %)	
	Innovator	Test
0	0	0
10	18	16
15	27	20
30	36	27
45	40	35
60	43	37

Table 14: f_2 of formulation 6 (F6) in different media

f_2	Media		
	0.1 N HCl	pH 4.5 acetate buffer	pH 7.0 Phosphate buffer
	66	58	77

Table 15: Assay of formulation 6 (F6)

Time	Results (%)
Initial	99.7
After 14 days	99.5

Assay

Table 15 shows the assay of the formulation 6 (F6). The assay is performed initially and after 14 days. The results of the assay of the formulation are in the limits.

CONCLUSION

Six different formulations of varying composition of ingredients are formulated using the wet granulation method. The taste masking of the drug is done by coating with stearic acid by granulation method. The suspensions were evaluated as per USP standards. It was concluded that the formulation 6 (F6) was satisfactory than other trial batches. The formulation 6 (F6) is considered as the final formulation with an excellent flow property and acceptable taste having f_2 value-77 with respect to the innovator product and assay of this formulation comes out to be 99.7%. Therefore, an attempt to formulate a suspension comparable to the innovator product has been made.

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AUTHORS' CONTRIBUTIONS

All the authors contributed to design and implementation of the research, to analysis of the results, and to writing of the manuscript.

CONFLICTS OF INTEREST

The author declares that there are no conflicts of interest to be declared.

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