RESEARCH ARTICLE

Formulation and Evaluation of Film-Coated Alalevonadifloxacin Mesylate Tablet using Opadry®

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ABSTRACT

Purpose: In this work, film-coated tablets of the antibiotic alalevonadifloxacin mesylate (AFM) were made using Opadry® yellow as the film coating material, and their different parameters, including *in-vitro* drug release, were assessed.

Method: Direct compression was used in the production of film-coated tablets of AFM. The film-coating substance was an aqueous coating dispersion that was opadry yellow. In 900 mL of 0.1N HCL solution, the film-coated tablets' rate of dissolution was assessed. *In-vitro* drug release was also evaluated. The generated film-coated tablets' stability was assessed in accordance with ICH recommendations.

Result: The coated tablets were subjected to gastrointestinal pH testing to ascertain the effectiveness of the film coating, and high-performance liquid chromatography was used to assess drug release. The coated tablets were in perfect condition. The AFM release satisfied the study's requirement of being at least after 30 minutes, 80% was dissolved in a 0.5% HCl solution.

Conclusion: According to these results, opadry yellow aqueous film coating is a simple, repeatable, and affordable method for creating stable AFM film-coated tablets without changing the properties of the medication release.

Keywords: Film-coated, Alalevonadifloxacin mesylate (AFM), Opadry®, *In-vitro* drug release.

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INTRODUCTION

Both levonadifloxacin and its prodrug alalevonadifloxacin are brand-new, broad-spectrum quinolone anti-MRSA medications designed for intravenous and oral administration, respectively.[1] AFM, (12S)-8-[4-[(2S)-2-aminopropanoyl]oxypiperidin-1-yl]-7-fluoro-12-methyl-4-oxo-1-azatricyclo[7.3.1.05,13]trideca-2,5,7,9(13)-tetraene-3-carboxylic acid; methanesulfonic acid, mesylate salt (Figure 1). These are broad-spectrum antibacterial medications designed to treat infections that are difficult to treat due to gram-negative bacteria, In addition to multidrug-resistant gram-positive bacteria, such as methicillin-resistant Staphylococcus aureus, rare bacteria, anaerobes, and biomedical pathogens are also present.[2] A well-defined mechanism of action of levonadioxacin includes a significant selectivity for both DNA gyrase and topoisomerase IV. AFM a highly water-soluble L-alanine ester mesylate salt, has an oral bioavailability of 89% and is being explored as the drug's oral prodrug formulation.[3-5]

Opadry® yellow, a shaded film-coating method that has been discovered to hide AFM from light action for a long time without changing AFM's release profile.[6] It is a prepared formulation, easy to prepare, takes little time to prepare and apply, and utilizes common coating equipment that is simple to clean.[7]

The uniformity of tablet coating within and between batches is essential in film coating operations to guarantee the

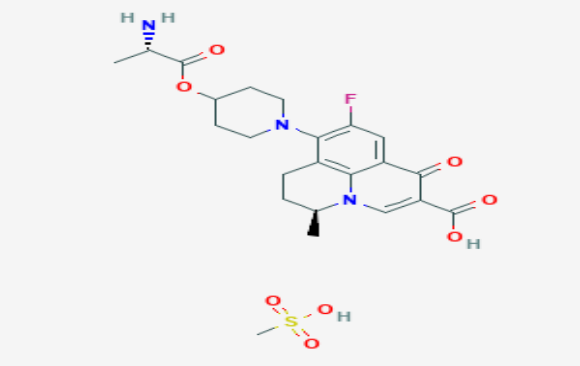

Figure 1: Chemical structure of AFM

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quality of the finished product. This is crucial for active film coatings because the coating layer contains an active medicinal component.[8] Moreover, modeling techniques are intensively researched to forecast how operation factors will affect the quality of finished goods and to maximize process variables for tablet film coating.[9,10]

MATERIALS AND METHODS

Materials

Alalevonadifloxacin mesylate (AFM) was obtained from Wockhardt Ltd. Aurangabad as a gift sample. Microcrystalline cellulose and cross carmellose sodium were purchased from DuPont Nutrition, polyvinylpyrrolidone was bought from veda oils, and opadry yellow was purchased from Colorcon Asia. All other solvents are of analytical grades.

Methods

Preformulation study

It is characterized as a study of the physical and chemical properties of an API both single and when mixed with other additives, and it is the first stage in the formulation of a drug's dosage form. Pre-formulation testing gives the formulator the information they need to make sustainable, effective dosage forms that adhere to all applicable dosage form regulations.[11,12]

Physical Properties

Melting point

The capillary tube method was employed to determine the melting point of a certain API. This method uses capillary tubes to hold the medication and a melting point device with a thermometer to estimate the temperature at which it melted.[13]

Solubility studies

Solubility testing was conducted to determine the best solvent solution to dissolve the medicine. By using an excessive quantity of the drug powder, a solubility drug was utilized to determine the dispersion conditions.[14]

Drug-excipients compatibility studies by FTIR

FTIR compatibility experiments were carried out to determine the drug's compatibility with various excipients. The sample's peaks were seen using the KBr FTIR method. In order to determine the compatibility between the medicine and the polymers that would be utilized in the formulation, the numerical values of the peaks found were given. Plastic film was used to calibrate the apparatus. A Shimadzu Model 8400 FTIR was used to scan the drug powder between wave numbers 4000-1cm and 400 cm^{-1} while utilizing air as a reference.[15]

Formulation of AFM Film-coated Tablet

Many batches were made in order to produce acceptable AFM core tablets with the necessary toughness, friability, volume, content uniformity, and appearance (Table 1). Wet granulation was the process employed in the creation of an AFM film-coated tablet. The required amount of raw materials was precisely weighed using a weighing balance. With a 16 # mesh, the MCC, AFM, and CCS were sorted.[16] PVPK-30 Polyvinyl pyrrolidone is dissolved and stirred to clear solution formation in adequate filtered water. The sifted materials were combined for 10 minutes in a quick mixer granulator. Finally, in 3–4 minutes, spray the prepared binder solution onto the dry, combined material with an atomizing pressure of 1.0 to 2.0 kg/cm^2. Talc, sodium stearyl fumarate, microcrystalline cellulose, and croscarmellose sodium were all used to lubricate the granules of the aforementioned dry sizes. This material is then blended for 10 minutes in a double-cone blender after being sorted through 40# mesh. Then, using D-type punch tooling and oval-shaped tablets, the lubricated blend was crushed to obtain an average weight of 908 mg and thickness of 6.9–7.0.[17,18]

Preparation of Opadry yellow Dispersion Solution

In a mixing tank, 1000 mL of filtered water and 140 mg of opadry yellow were blended for around 45 minutes. Before coating, the liquid suspension was then run through a 250 microns filter. Throughout the coating process, the dispersion was constantly agitated.[19]

Film Coating of AFM

The compressed tablets entered the coater for film coating, where they were coated with a dispersion solution coat up to the 3 to 3.5% weight gain that the compressed tablets achieved, which was set as the parameter in Table 2. [20]

Evaluation of Coated Tablet

In-vitro dissolution Studies

Using USP dissolution testing device 2, the release rates of AFM from tablets were calculated (paddle method). For the

Table 1: Composition of formulations F1 to F5 (in grams)

Sr. No.	*Name of Ingredient and supplier*	*F 1*	*F 2*	*F 3*	*F 4*	*F 5*
	Alalevonadifloxacin mesylate	720	720	720	720	720
	Microcrystalline cellulose	75	61	69	71	71.5
	Croscarmellose sodium	63	72	66	62	61.5
	PVPK-30 Polyvinylpyrrolidone	15	18	19	19.0	19.25
	Talc	15	16	17	17	17
	Sodium stearyl fumarate	20	21	17	19	18.75
	Opadry yellow	25	24	26	27	27
	Total	908.0 mg/ tab (uncoated tablets) 930.0–950.0 mg/tab (coated tablets)				

Table 2: Coating conditions

Specifications	*Film coating range*
Atomizing air pressure	0.1–0.6 mpa
Speed of pan	08–12 rpm
Distance of spray gun	5–6 mm
Diameter of spray nozzle	1.2 mm
Spray rate	1.5–2.0 mL/min.
Temperature of dry air	38 ± 5°C/ 30 min.
Temperature of bed	30 to 40oC

test, 900 mL of 0.1N HCL was used together with 50 rpm and 37°C ± 0.5°C for a predefined amount of time. In 5 mL of the samples were removed. The volume of the dissolving solution was expanded to 900 mL by replacing each 5 mL aliquot removed with 5 mL of 0.1N HCL pre-warmed at 50°C. Before being examined by HPLC at 290 nm, the materials were filtered using whatman filter paper and diluted with 0.1 N HCL.[21]

Disintegration Test

In the USP disintegration testing, single tablet was placed in each of the tubes of the apparatus. The device is run without discs for two hours at 37°C with simulated liquid (pH 1.2). The tablets are then taken out and must not exhibit any signs of eroding, cracking, or softening. Once the discs have been added, the equipment is used with simulated gastrointestinal liquid biological conditions.[22]

Assay

Using chromatographic conditions such as a stationary phase C-18 column and a mobile phase of buffer and acetonitrile in the ratio, this method verified the RP-HPLC chiral method (88:12). To make the mobile phase chiral, beta-cyclodextrin was combined with the buffer. The detection wavelength and flow rate were both held constant at 290 nm and 2 mL/minutes, respectively. The procedure can be used to separate and quantify AFM in bulk medications.[23]

Accelerated Stability Studies

Usually, it takes a lot of time to see how quickly a product deteriorates at typical room temperature. Following ICH recommendations, the accelerated stability study was performed. In a dark-colored container, the formulation was sealed and kept in storage at 40 ± 2°C and 75 ± 5% RH. At 1, 2, and 3 month intervals, *in-vitro* dissolution tests and content uniformity were performed on the specimens.[24]

RESULTS AND DISCUSSION

FTIR Spectral Analysis of Pure AFM

Pure AFM showed sharp characteristic peaks at 1649.4881, 1557.0240, 1540.0971, 1454.9155, 1349.0480, 1318.6372, 1221.9011 cm^{-1}. The FTIR spectrum of the physical mixes comprising AFM and other additives in the finished formula likewise shows strong evidence for these peaks. This suggests that neither physical observation nor FTIR research has shown any interactions between the medicine and excipients.

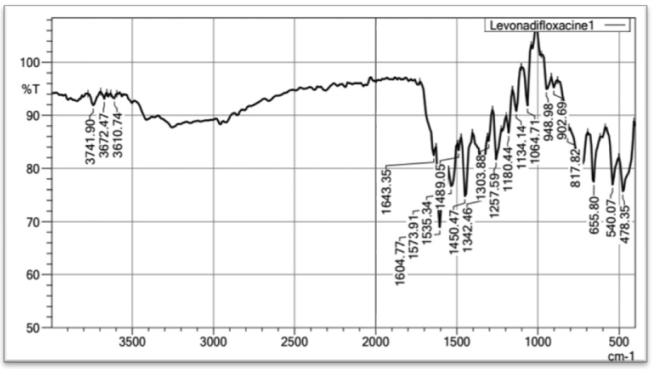

Figure 2: FTIR spectral analysis of pure AFM

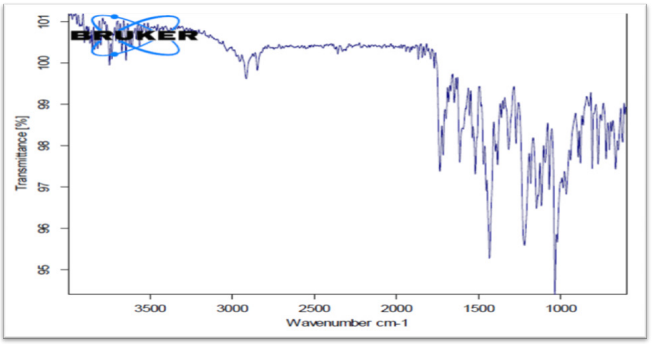

Figure 3: FTIR spectral analysis of AFM with excipients

Table 3: Evaluation Parameters of AFM-Coated Tablets

Batch	*Thickness of tablet (mm)*	*Variation in weight (mg)*	*Disintegration time (min)*	*Assay (%)*	*Release of drug (%)*
F3	7.36 ± 0.30 mm	951 mg ± 2.0%	(NMT 15 min) 13 min 25 sec	98.8% (Limit 95-105%)	86.36
F4	6.98 ± 0.45 mm	947 mg ± 4.0%	(NMT 15 min) 12 min 55 sec	98.2% (Limit 95-105%)	88.96
F5	7.05 ± 0.40 mm	940 mg ± 3.0%	(NMT 15 min) 12 min 48 sec	99.9% (Limit 95-105%)	98.89

The AFM tablet used in the aforementioned trial (F5) met all the criteria. The film coating process was used to coat it. The thickness of the coated tablets, the disintegration test, the weight variations, the assay, and the *in-vitro* studies were a few of the variables evaluated.

Study of Dissolution *In-vitro*

With the F3, F4, and F5 formulations, the percentage of drug release was calculated. Table 4 displays the typical cumulative percentage of drug released by formulations. Average overall medication release% from formulations.

It was determined through drug release trials whether the excipients ratio was adequate to maintain the drug's release for 120 minutes. As the proportion of MCC and croscarmellose sodium in the formulation grew, more drug release was seen, which was also the cause of the drug release and it also

Table 4: Average cumulative percentage of drug released by formulations

Time in min	*Cumulative %drug release*		
	F3	*F4*	*F5*
0	0	0	0
15	8.78	9.56	12
30	15.27	16.45	20.12
45	25.77	35.85	40.42
60	51.24	58.53	65.49
75	60.12	64.54	75.69
90	81.91	83.09	85.56
120	86.36	88.96	98.89

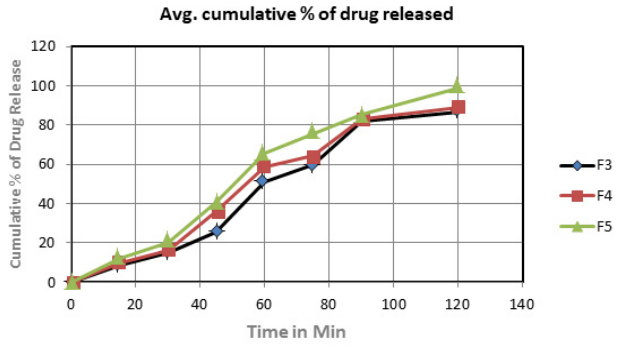

Figure 4: Cumulative% of drug release

Table 5: *In-vitro* drug release and assay

Formulation	*Storage condition 40 ± 2℃ /75 ± 5% RH*					
	In-vitro drug release (%)				*Assay (%)*	
	Initial	*1 month*	*2 month*	*3 month*	*Initial*	*After stability*
F5	98.89	98.71	97.96	97.99	99.9	100.1

sustained the drug release at 120 minutes. There is a first sudden bursting impact. However, the drug release in the F3 and F4 formulations is 86.36 and 88.96%, respectively. In formulation F5, the drug is delivered in 120 minutes at a rate of 98.89%. Consequently, F5 with the proportion of MCC & Croscarmellose sodium was the optimal formulation.

The order of medication release among formulations is F3 > F4 > F5, according to the findings of the comparison research of all formulations. As a result, F5 formulations are thought to be the ideal formulation for stability studies.

In-vitro Drug release and Assay

For the stability investigation, the F5 formulation of film-coated tablets was used. It was stored at 40, 2°C, and 75° RH for three months. The test and the percentage of drug release were calculated. Throughout stability studies, the data barely varies. The outcomes demonstrated the stability of the product.

CONCLUSION

The wet granulation process is being used to create film-coated tablets of the L-alanine ester prodrug of levonadifloxacin (ALM), which will be effectively made utilizing the amounts of the indicated excipients. Using the FTIR approach, preformulation tests were conducted to examine the composition of the API and its compliance with excipients. The findings demonstrated that the drug was compatible with the selected excipients and that API and any of the additives had no interaction. AFM film-coated tablets were coated using the film coating technique of opadry yellow. Formulation F5 demonstrated 98.89% drug release in 120 minutes among all batches. The medication release pattern is superior to the F3 and F4 batches; hence, it was decided that trial F5 was the best and most reliable formulation.

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