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DEVELOPMENT OF EXTENDED-RELEASE ANAGRELIDE TABLETS: A FORMULATION AND DISSOLUTION STUDY

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Abstract
Anagrelide immediate release is commonly used multiple times a day for patients with thrombocythemia. However, frequent dosing can lead to potential dose-related side effects. The purpose of this study was to formulate an extended-release of anagrelide by the matrix manufacturing method to be compressed into tablets and compare its release profile with the reference patented formulation. The wet granulation method was utilized to produce the extended-release tablet. Different formulations of anagrelide tablets containing HPMC, ethyl cellulose, and other excipients were prepared. Flow characteristics and quality control tests including Carr's index, Hausner's ratio, hardness, thickness, weight variation, content uniformity, as well as dissolution test were conducted using HPLC analysis. Finally, results were compared with the patent release profile as a reference. Through a series of pre-formulation studies and dissolution tests, it was determined that the F5 formulation, with an optimized balance of HPMC, ethyl cellulose, and other excipients, achieved a drug release profile similar to the reference patent formulation. The F5 formulation showed sustained release of anagrelide over the desired period, making it a promising candidate for further clinical evaluation. Further studies are needed to assess the pharmacokinetic profile and efficacy of the F5 formulation in patients with essential thrombocythemia.

Keywords: Anagrelide, thrombocythemia, extended-release, wet granulation

1. Introduction

Essential thrombocythemia (ET) is a long-term condition involving an excess of platelets in the blood, classified as a type of blood cancer known as a chronic myeloproliferative neoplasm (MPN) [1,2]. Around 50 to 60% of essential thrombocythemia (ET) cases have a mutation in the *JAK2* gene that is acquired during a person's lifetime. The most common mutation is the V617F mutation in exon 14, although other mutations in exon 12 of JAK2 can also be found, particularly in cases of polycythemia vera (PV) [2,3].

The primary objective of treating patients with ET is to reduce the risk of blood clots. Risk factors for thrombosis in individuals with ET include being over 60 years old, having a history of prior thrombotic events, having the JAK2 mutation, having cardiovascular risk factors, and having platelets count over 1500×10^9/L [4,5]. Anagrelide (ANA) is a well-known medication used to reduce the number of platelets in patients with ET or thrombocythemia related to MPN disorders who meet these risk criteria [6]. In Japan, ANA and hydroxycarbamide (HC) are considered the initial treatment options for

high-risk ET patients, as suggested by research comparing the two medications [7,8]. Anagrelide (Xagrid®) is licensed in Europe for patients with primary thrombocythemia who cannot tolerate hydroxycarbamide [9].

ANA was first created as an antiplatelet drug, but its ability to lower platelet count was only discovered during testing before it was approved for use [10]. Anagrelide was studied in 2 randomized clinical trials, showing response rates of around 80%, varying based on definitions and underlying conditions [8,11]. The predominant side effects of the medication were cardiovascular issues (such as palpitations, tachycardia, and dizziness), headache, diarrhea, nausea, fatigue, and anemia [12].

Immediate-release forms of anagrelide are effectively absorbed in the body, with about 75% of the drug's bioavailability. They are broken down in the liver by cytochrome P450 1A2 into either the active metabolite, 3-hydroxy-anagrelide, or inactive metabolites. The active metabolite is eliminated through either conversion to inactive forms or excretion via the kidneys [13]. Consuming food slows down the absorption of anagrelide and its active metabolite, resulting in lower peak concentrations but overall increased exposure to the drugs [14].

The decision to create an extended-release version of anagrelide was supported by a study that looked at the effects of two existing formulations. The formulation that had lower C_{max}, slower T_{max}, and a lower overall exposure (AUC) was linked to fewer side effects, although it maintained its effectiveness in managing platelet counts [15]. This unexpected result led to the development of the extended-release version. Therefore, this study aimed to develop and prepare the extended-release form of anagrelide by the matrix manufacturing method to be compressed into tablets and compare its release profile with the reference patented formulation (US9040483B2).

2. Material & Methods

2.1 Materials:

Anagrelide Hydrochloride (ANA) (J&K Chemical Company Shanghai, China); hydroxypropylmethylcellulose (HPMC, Methocel® E5, Colorcon, Orpington, UK); ethyl cellulose (Ethocel 10 cP, DOW, Midland, USA); microcrystalline cellulose PH 101 (Avicel® PH101, FMC Biopolymer, Ireland); magnesium stearate (Merck, Germany); lactose monohydrate (Pharmatoseâ, type 80M, DMV International, Veghel, Netherlands); HPLC grade acetonitrile (Fair Lawn, NJ).

2.2 Formulations of anagrelide matrix release

The formulation of anagrelide matrix tablets was prepared using the wet granulation method. By adjusting the excipients, their quantities, and the powder blending method, we developed different formulations to achieve the desired drug release profile based on the patent specifications (https://patents.google.com/patent/US9040483B2/en?oq=US9040483B2). The retarding agents used in our formulation were ethyl cellulose and HPMC. To prepare the adhesive, ethyl cellulose and HPMC were sieved through sieve #30 before being mixed and dissolved in a minimal amount of 96% ethanol. The ethanol was added drop by drop until a uniform thick glue was obtained. This adhesive was then added to a mixture of Avicel/lactose, and anagrelide. The contents were mixed until uniform, with occasional heating at 40-45°C if necessary. The resulting matrix was coated with ethyl cellulose and HPMC was allowed to reach 2% humidity at 65°C and passed through a sieve #18 to create coarse particles. Magnesium stearate was sieved through sieve #60 and added to the powder mixture. The powder was then weighed in 100-gram portions and pressed into tablets. These tablets were coated with Color con ready coating. Each tablet contained 2.44 mg of anagrelide as a sustained-release matrix formulation. The compositions for the different formulations are outlined in **Table 1**, and the same method was followed for each formulation.

Table 1. Composition of different excipients used for sustained release matrix tablets of anagrelide

Formulations	Components (mg/tablet)					
	Anagrelide	**Ethyl cellulose**	**HPMC**	**Avicel**	**Lactose**	**Magnesium stearate**
F1	2.44	18	18	56	3.56	2
F2	2.44	18	10	56	11.56	2
F3	2.44	3	10	56	26.56	2
F4	2.44	20	3.408	56	16.152	2
F5	2.44	26.152	3.408	56	10	2
F6	2.44	32	3.408	56	4.152	2
F7	2.44	26.152	3.408	40	26	2
F8	2.44	26.152	3.408	63	3	2
F9	2.44	26.152	3.408	56	7	5
F10	2.44	26.152	3.408	56	11.5	0.5

2.3 Pre-formulation studies and flow characteristic

2.3.1 Compressibility index (Carr's index) and Hausner's ratio

The flowability of powder was determined by examining the difference between its bulk density and tapped density, as well as how quickly it packs down. The compressibility index (Carr's index) of anagrelide sustained-release granules was calculated using the following formula

$$^{16}: Carr\ index\% = \frac{P_t(Tapped\ density) - P_b(Bulk\ density)}{P_t(Tapped\ density)}$$

Another approach to determine the flow properties of granules is by calculating the Hausner's ratio. This was done for all formulations of the prepared anagrelide sustained-release granules using the following formula [17,18]:

$$Hausner\ ratio\ \% = \frac{P_t(Tapped\ density)}{P_b(Bulk\ density)}$$

2.3.2 Powder flow time

To perform this test, we weighed 5 gr of anagrelide powder and put it in the funnel. This test is to calculate the time it takes for the powder in the funnel to be completely removed.

2.3.3 Moisture content

To determine the percentage of moisture in the granule samples, a portion of the powder was weighed and dried in an oven. The sample was weighed at regular intervals until the weight remained constant, indicating that all moisture had evaporated. The difference between the initial weight and the final weight was then calculated to determine the amount of moisture that was evaporated.

2.3.4 Visual characteristics

A sample of 20 tablets was chosen at random from various manufacturers to assess their appearance characteristics, including color, smell, and overall appearance. All the tablets needed to have a consistent appearance, with no cracks or delamination, a smooth surface, and no changes in color or smell. Any tablets found to have any of these issues were deemed to be rejected.

2.4 Quality control tests performed on Anagrelide extended-release tablets

These tests were performed on all tablet formulations made in the following order. If the formulation meets the necessary conditions to pass each test, the next test is performed on the formulation.

2.4.1 Drug Content Uniformity and Assay

To create the standard stock solution, 25 mg of anagrelide was transferred into a 100 ml flask. Acetonitrile was slowly added to fill the flask up to 80% capacity, then stirred the solution until the anagrelide was fully dissolved. The more diluting solution was gradually added to reach the desired

volume of the solution. In this case, acetonitrile was used as the diluting solution. Then, 4 ml of the stock solution was taken and diluted until the concentration of anagrelide hydrochloride reached 0.01 mg/ml. For the sample solution, 20 tablets were ground in a mortar until they were completely powdered. An amount of powder was taken equivalent to the mass of one tablet and transferred to a 100 ml flask. Diluting solution was added until the concentration reached 0.01 mg/ml. the solution was sonicated for 10 minutes, stirred for 15 minutes, and then centrifuged for 10 minutes. The volume was adjusted with acetonitrile before filtration through a 0.45-µm nylon membrane filter. 20 µL of filtrate was diluted to 1 mL with mobile phase before injection into the HPLC system. The HPLC method used was validated and slightly modified from the USP monograph on Agilent 1260, utilizing a mobile phase consisting of acetonitrile. An L11 column was employed, with a flow rate of 1.0 mL/min and UV detection at 254 nm. The amount of anagrelide was determined by comparing peak areas of test solutions to standard solutions. Content uniformity testing was performed on the first 10 tablets, and if the acceptance value exceeded 15%, an additional 20 tablets were tested. The final acceptance value for all tablets needed to be ≤25%, with individual values falling within 75–125% of the labeled strength [19]. The assay of the samples was calculated by averaging the anagrelide content in the tablets tested for content uniformity.\

2.4.2 Drug Weight Uniformity

Twenty tablets were weighed using an electronic balance (Infra Instruments Pvt. Ltd, Chennai; Model-IN 201 L EC) individually. The average weight and percentage deviations were then determined following United States Pharmacopeia (USP) guidelines [20]. If the average weight is 80 mg or less, the deviation limit is ± 10%. If the average weight is between 80 and 250 mg, the deviation limit is ±7.5%. If the average weight is 250 mg or more, the deviation limit is ±5%.

2.4.3 Thickness and Hardness

The thickness of 20 tablets from each series was measured by an electric caliper and the average was calculated. The thickness of the resulting tablets should be within ±5% of the standard. For hardness evaluation, 10 tablets were selected from a series and placed between two metal parts of the hardness tester, one of which is fixed and the other is movable. The amount of force used to break tablets is determined by Kp unit and the minimum acceptable value of Kp is 10-15 [21].

2.4.4 Friability test

This experiment was conducted to measure the durability and strength of tablets against mechanical pressure. Ten tablets (according to IP) were chosen from a batch, weighed, and put into a device where they were rotated for 4 minutes at 25 rpm and dropped from a height of 85 cm. Afterward, the tablets were taken out, cleaned, and weighed again to calculate the friability following the formula [22,23]. If a weight loss was no more than 1% w/w test was acceptable.

$$\%F = \left[1 - \frac{w_2\ (weight\ after\ test)}{w_1 (weight\ before\ test)}\right] \times 100$$

2.5 *In-vitro* drug Release Study (Dissolution test)

As per FDA regulations, the Paddle device (DT 706 HH, Erweka, Heusenstamm, Germany) was operated at a speed of 100 rpm for dissolution testing. The release medium used was HCL 0.1 N, and the volume of the test environment was 900 ml at the temperature of 37 °C. Sampling was done at 1, 2, 3, 4, 5, 6, 7, and 8-hour intervals, with 5 ml of the sample being withdrawn each time. After sampling, the withdrawn amount was replaced with fresh HCL 0.1 N solution at 37 °C. Each vessel in the device contained a tablet, and samples were collected using a graduated pipette at the specified time intervals. The dissolution profiles for each formulation were plotted, and compared with the standard release profile to calculate the similarity and difference factors for each formulation. HPLC analysis was conducted to analyze the results. This dissolution testing is crucial in identifying the optimal formulation for the product. The effect of the tablet compression on the release was assessed using the similarity (F2) and difference (F1) factors. These two factors show the degree of similarity

and difference between our formulation and the patent formulation. F2 shows the degree of similarity and F1 shows the degree of difference. If F2 is between 50 and 100% and F1 is less than 10%, our formulation is acceptable [24]. More F2 and less F1 is a more similar formulation to the Patent.

3. Results and Discussion

3.1 Pre-formulation studies and flow characteristic

The purpose of conducting this study was to develop a drug with a suitable release profile for individuals suffering from thrombocytopenia. The recommended dosage of anagrelide for these patients typically starts at 0.5 mg, 2 or 4 times daily, with the option to increase up to 10 mg daily based on the patient's response and tolerance levels [25]. By creating an extended-release tablet of this medication, patients can conveniently take it just once a day. This formulation allows for a more consistent blood concentration, resulting in improved therapeutic effects and fewer side effects, such as headaches and digestive issues [26]. Additionally, individuals with some conditions like Alzheimer's may find it challenging to adhere to complex medication schedules.

In this study, different formulations of anagrelide tablets were prepared and various investigations were performed on these formulations. All formulations were within the permissible limits in terms of appearance, weight, content uniformity, thickness, hardness, and friability rate, and after passing the tests, they were assessed for dissolution test. The average Carr's index of all formulations was determined to be 14.5%. Hausner's ratio ranged between 1 and 1.11. A low Hausner ratio means that the material flows more easily. However, if the ratio is between 1.25 and 1.5, the flowability of the powder can be enhanced by adding a suitable filler [27]. The flow characteristics of Carr's index and Hausner's ratio are represented in Table 2.

Table 2. Range of Carr's index and Hausner's ratio and flow character according to I.P

Hausner's ratio	Flow character	Carr's index
1.00-1.11	Excellent	10 <
1.12-1.18	good	11-15
1.19-1.25	Fair	16-20
1.26-1.34	Passable	21-25
1.35-1.45	Poor	26-31
1.46-1.59	Very poor	32-37

The moisture content of the granules was determined and kept around 2% for all formulations. As the moisture content increases, the bonding between particles also increases. In addition, the initial composition of the granules can impact the rate at which the content penetrates. When there is a higher moisture content, the particles tend to move more before reaching a pendular state. In this state, there is no uniform layer of water inside the granules, which prevents further migration [28]. Previous studies have discussed the impact of moisture content on tablet porosity [29,30]. The thickness of all resulting tablets was within ±5% of the standard range. Significantly higher acceptance value (AV) was also observed in the weight variation and content uniformity of the tablets. The friability percentage for each formulation was found to be less than 1%, which means that the friability was within the acceptable range according to official standards [31].

The most effective boundary lubricant is stearic acid or its salts, and magnesium stearate is the most commonly used lubricant due to its excellent lubrication properties. Stearic acid salts are typically used in low concentrations, usually less than 1% [32]. In the F10 formulation, the reduction in the percentage of magnesium stearate led to a decrease in the flowability of the granules. This resulted in adhesion on the surface of the matrix, ultimately leading to the rejection of this formulation in our study. The purpose of measuring the anagrelide powder flow time was to determine the flowability of the powder. This is important in pharmaceutical manufacturing as it can impact the consistency and quality of the final product. During the experiment, it was observed that the powder flowed out of the hopper in approximately 2-3 seconds. This indicates that the powder has good flowability, as it can flow smoothly and consistently. Measuring the flow time of the powder gives valuable

information that can help in optimizing production processes and ensuring the quality of the final product [33]. According to visual characteristics, all formulations found odorless white crystalline, and determining the drug content in all formulations showed that the permissible deviation was ± 10%, which was in the standard range.

3.2 Dissolution study

Various formulations have been proposed to develop an extended-release system for anagrelide, to achieve the best formulation in terms of physicochemical properties [15,34]. Our study focuses on obtaining a formulation that closely resembles the release profile outlined in the patent as a reference pattern. According to the patent, the drug release percentages have been determined at various time points (Figure 1), and our goal is to design different formulations to optimize the drug release percentage to match the patent reference. Before comparing the release profiles, the release diagram of the pharmaceutical component was plotted based on the patent specifications. All comparisons are made with this reference chart. The release rate of all study formulations in comparison to patent as well as the percentage of similarity and difference factors, is presented in Table 3 and Table 4 respectively.

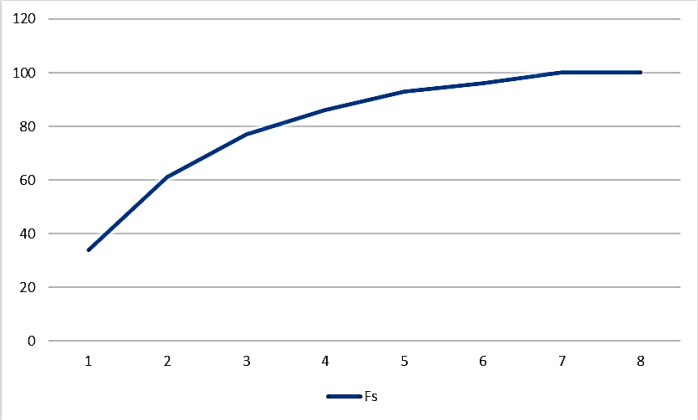

Fig 1. Anagrelide release curve in Patent at the different time intervals

Table 3. Dissolution rate of patent and formulations at different time intervals

	Dissolution (%)									
Time (h)	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**	**Patent**
1	30.17 %	32.10 %	37.50 %	36.20 %	**34.56**	29.89	35.56	33.44	35.21	34.12
2	48.30 %	55.12 %	73.09 %	63.77 %	**62.08**	46.98	63.66	59.87	62.98	61.34
3	57.32 %	64.90 %	80.11 %	79.03 %	**78.21**	55.76	79.12	70	78.64	77.56
4	68.12 %	78.56 %	89.33 %	88.55 %	**86.45**	68.43	87.6	80.87	87.12	86.23
5	88.56 %	90.05 %	95.90 %	95.34 %	**93.26**	88.79	95.9	89.99	94.56	93.46
6	90.04 %	93 %	99 %	98.11 %	**96.43**	94.54	97.32	95.08	97.10	96.31
7	93.65 %	94.43 %	104 %	101.67 %	**100.50**	98.21	102.33	97.43	102.1	100
8	95.44 %	98.76 %	104 %	102.05 %	**100.60**	100.34	103.09	98.55	102.34	100

Table 4. Similarity and difference factors in formulations (%)

	Formulations								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
Similarity factor (F2)	40	53	57	74	92	40	74	29	79
Difference factor (F1)	12	7	5	3	1	10	3	19	10

According to the results, it was observed that the release percentage of the F1 formulation was lower than what was specified in the patent (Figure 2a). By calculating the similarity and difference factors, it was determined that although the percentage of similarity was low, the degree of difference was high compared to other formulations. Furthermore, the release rate of the drug did not fall within the specified range outlined in the patent. On the other hand, in the F2 formulation, no changes were made to the manufacturing method, but the amount of HPMC, a key component in creating the tablet matrix [35], was reduced. Following the evaluation of the release percentage, it was noted that the release rate remained lower than that stated in the patent (Figure 2b), but it was closer to the patent specifications compared to the F1 formulation. HPMC is a commonly used polymer that is derived from cellulose and chemically modified. It is created through a reaction with methyl chloride and propylene oxide after alkali treatment of cellulose. HPMC forms hydrophilic matrices with a reversible thermal gelation property, allowing for diffusion-controlled drug release from the matrices [36].

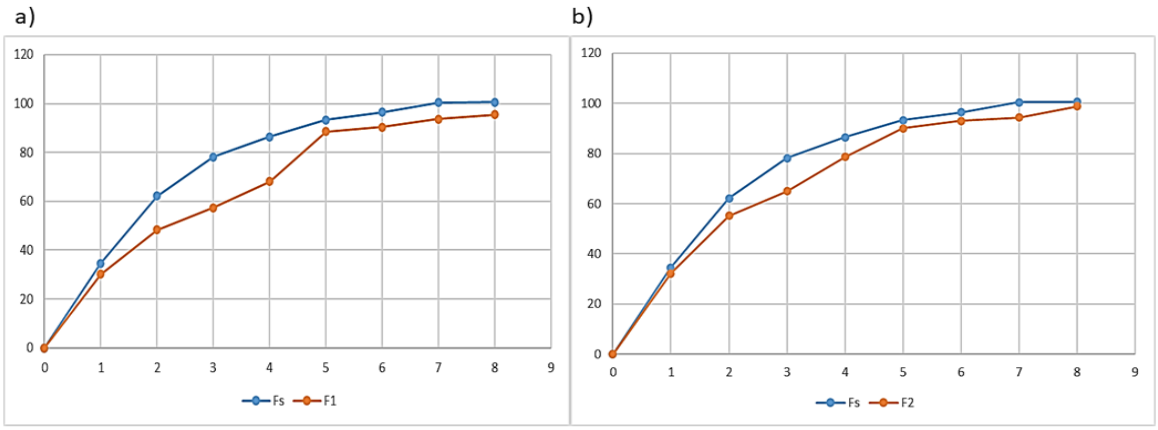

Fig 2. Anagrelide release rate (%) from a) F1 and b) F2 formulation. The blue curve (fs): patent release as standard pattern

In the F3 formulation (Figure 3a), the amount of ethyl cellulose was decreased. Despite this modification, the release profile of F3 was only slightly higher than the reference patent formulation. The similarity and difference factors for F3 were found to be almost identical to the previous formulation. Therefore, F3 was not selected as the optimal formulation for our study. For the F4 formulation (Figure 3b), we made adjustments by increasing the amount of ethyl cellulose and decreasing the amount of HPMC. Although these changes resulted in a decrease in the percentage of release, it was still higher than the patented formulation. By analyzing the similarity and difference factors, we found that the percentage of difference decreased and the percentage of similarity increased. However, the amount of release was still not very close to the patented formulation. Further refinement of the formulation was made to achieve a release profile similar to the patented formulation.

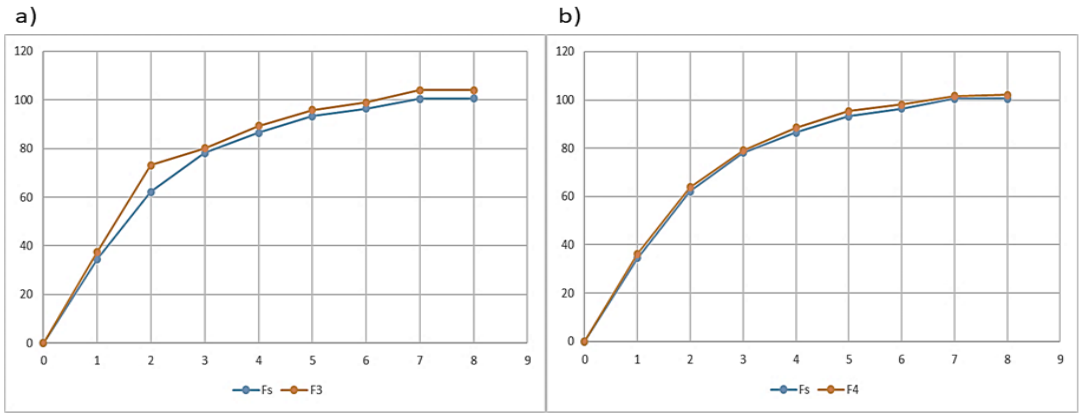

Fig 3. Anagrelide release rate (%) from a) F3 and b) F4 formulation. The blue curve (fs): patent release as standard pattern

F5 (Figure 4) formulation was developed and produced using the same method as the F4 formulation, with a slight increase in the amount of ethyl cellulose. It was noted that the use of HPMC polymer alone led to an initial burst release of the drug, as the drug is hydrophilic. This resulted in the majority of the drug being released within the first 8 to 10 hours [37]. Increasing the concentration of ethyl cellulose in the formulation can achieve a sustained release effect over a prolonged period. So, F5 formulation was found optimum at HPMC and ethyl cellulose polymer concentration. Following the dissolution test of the tablets, it was found that the release rate was within the acceptable range similar to the patent and with approximately 100% release by the end of the testing. Therefore, this formulation has been identified as the optimal formulation making this drug a suitable candidate for a controlled/sustained release. According to the studies related to the comparative external test and the values of similarity and difference factors, it was found that the release of this formulation follows the first-order kinetics, which is consistent with the patent sample.

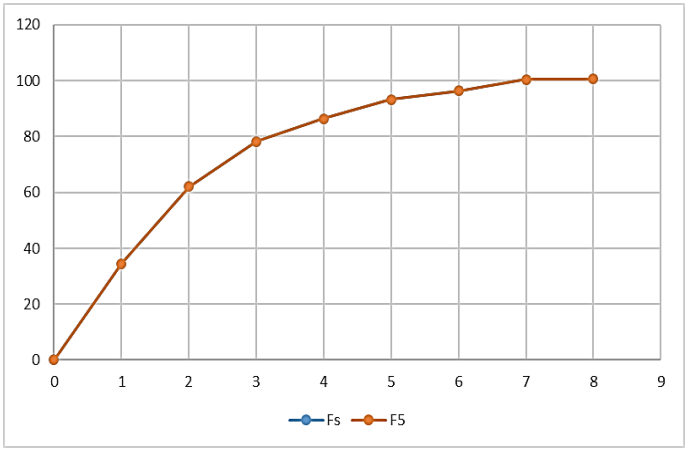

Fig 4. Anagrelide release rate (%) from F5 formulation. The blue curve (fs): patent release as the standard pattern

In the F6 formulation (Figure 5a), we increased the amount of ethyl cellulose, which acts as a retarding factor for drug release, to investigate the impact of this increase on drug release. Following the dissolution test, it was found that the drug release decreased, but still did not fall within the desired range. The results of the similarity and difference factors further supported these findings, as the difference factor increased and the similarity factor decreased, both of which were outside the acceptable limits. The reduced amount of Avicel in the F7 formulation (Figure 5b) resulted in a faster release profile compared to the patent formulation. So, Avicel optimization may help determine the desired release profile [38]. Therefore, In the F8 formulation (Figure 5c), we increased the amount of Avicel. However, the release was slower and different from the patent release. In the F9 formulation

(Figure 5d), the amount of magnesium stearate was increased to reach its optimum level. The release was slower and different from the patent release.

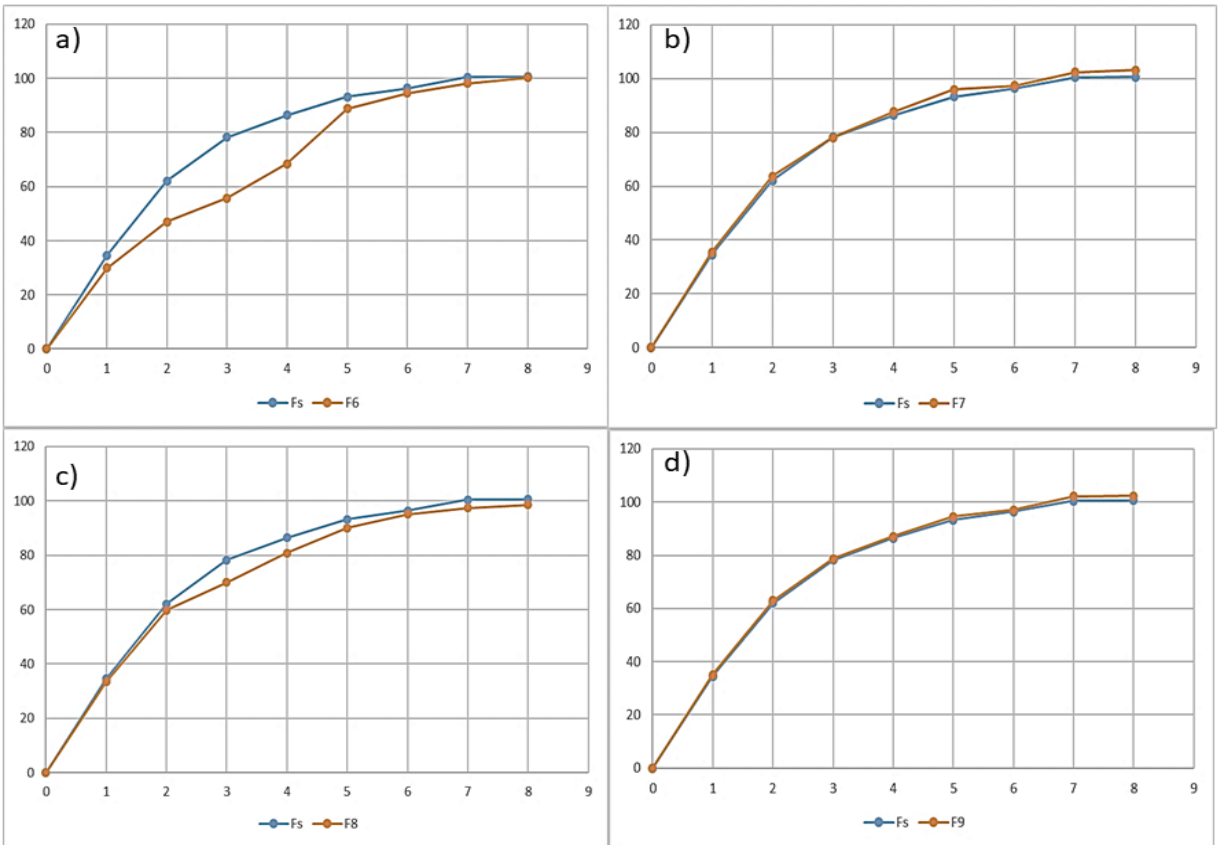

Fig 5. Anagrelide release rate (%) from a) F6; b) F7 formulation; c) F8 and d) F9. The blue curve (fs): patent release as standard pattern

4. Conclusion

In conclusion, the development of an extended-release formulation of anagrelide for the treatment of patients with essential thrombocythemia is a crucial step in optimizing therapeutic outcomes and enhancing patient adherence to treatment regimens. Through a series of pre-formulation studies and dissolution tests, it was determined that the F5 formulation, with an optimized balance of HPMC, ethyl cellulose, and other excipients, achieved a drug release profile similar to the reference patent formulation. This formulation showed sustained release of anagrelide over the desired period, making it a promising candidate for further clinical evaluation. Further studies are needed to assess the pharmacokinetic profile and efficacy of the F5 formulation in patients with essential thrombocythemia.

Conflicts of Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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