US2007/104782A1 and WO2007/016350A2 describe pH independent release tablet formulations with enhanced mechanical properties containing a methacrylic acid copolymer.

US2005/0249814A1 and US2005/0008704A1 disclose formulations comprising a compound with at least one carboxylic acid moiety having rapid dissolution upon contact with physiological solvents.

US2004/0028729A1 describes a pharmaceutical preparation for modified release comprising a plurality of irregularly shaped non-spherical cores. Anagrelide is disclosed in combination with other additives together with Eudragit.

It is an object of the present embodiments disclosed herein~~invention~~ to make available novel compositions of anagrelide with pH independent sustained release properties, which can be used for the prevention and treatment of symptoms related to chronic myeloproliferative disorders, such as essential thrombocythemia, but which lack some of the well known side effects of anagrelide treatment attributable to its main metabolite, 3-hydroxyanagrelide.

The object is achieved by the provision of the embodiments of the present application.

The ~~invention~~disclosure relates to novel formulations of anagrelide resulting in a non immediate release of the active ingredient of anagrelide.

In one aspect, there is provided a pharmaceutical composition free of gastric coating comprising anagrelide HCl, a non-pH dependent polymer and a pharmaceutically acceptable water soluble acid, wherein the non-pH dependent polymer is selected from the group of polyacrylacids, cellulose derivatives or polyacrylamids, preferably it is Carbopol™ and wherein the amount of the non pH dependent polymer is 1.5 to 2.5 fold of anagrelide (w/w).

It has been shown that a pharmaceutical composition free of gastric coating comprising anagrelide HCl, a non-pH dependent polymer and a pharmaceutically acceptable water soluble acid have sustained and continuous release characteristics when administered to a patient.

Specifically, the anagrelide HCl is in the form of particles wherein at least 90% of said particles are smaller than 10μm in diameter.

According to an embodiment of the ~~invention~~disclosure, anagrelide HCl in an amount between 0.5 and 5 mg, preferably between 1 and 3.5 mg , preferably between 2 and 3 mg, preferably in an amount of about 2.3 mg. Specifically, anagrelide can have a mean particle size of about 5 μm.

According to a further embodiment, the non pH dependent polymer can be contained about

1.5 to 2.5 fold of the pharmaceutically active agent (w/w).

In the composition, the non-pH dependent polymer can be for example selected from the group of polyacrylacids, cellulose derivatives or polyacrylamids, preferably it is Carbopol™.

The polyacrylacid within the inventive composition can be comprised in an amount between 1 and 10 mg, preferably between 2.5 and 5 mg, preferably between 3 and 4 mg.

The inventive pharmaceutical composition can further comprise pharmaceutically acceptable water soluble acid which can be selected from, but is not limited to, the group of adipic acid, ascorbic acid, citric acid, fumaric acid, malic acid, succinic acid, tartaric acid or a mixture thereof, which, according to a specific embodiment, can be present in an amount between 5 and 40 mg, preferably between 10 and 20 mg, preferably between 15 and 19 mg.

Additionally, the inventive composition can comprise microcristalline cellulose, specifically in an amount between 10 and 150 mg, preferably between 25 and 100 mg, preferably between 70 and 80 mg. Surprisingly, the composition was shown to have an in-vitro release of at least 45% after 8 hours without having any gastric coating.

In an alternative embodiment, a composition is provided containing anagrelide HCl, polyacrylacid, citric acid, microcristalline cellulose and magnesium stearate. Preferably, the composition according is in the form of a tablet.

According to a further embodiment of the ~~invention~~disclosure, the composition according can be used for the preparation of a medicament for the treatment of essential thrombocythemia.

In another aspect, there is provided the use of a pharmaceutical composition as defined above for the preparation of a medicament for the treatment of essential thrombocythemia.

Figures:

Figure 1: dissolution curve of anagrelide retard

Figure 2: typical plasma levels in comparison to immediate release formulation. Geometric means of plasma angrelide concentration – PAC (µg/L) versus time curves following a single oral 2mg dose of anagrelide in 28 subjects.

Figure 3: 3OH anagrelide immediate release versus sustained release formulation.

Figure 4: 2 Amino 5,6-dichloro-3,4-dihydrochinazolin immediate release versus sustained release formulation