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Non Aqueous Formulation Attempts of Carfilzomib Formulations and Evaluation

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ABSTRACT

Carfilzomib is commercially available in the market as a lyophilized dosage form in various geographies. Commercially, there is no availability of the solution form of Carfilzomib. Proteasome inhibitors are drugs that block the action of proteasomes, cellular complexes that break down proteins. They are being studied in the treatment of cancer; and three are approved for use in treating multiple myeloma. Literature suggested that the drug candidate is very unstable in the liquid dosage form. It undergoes hydrolytic degradation in the presence of water. Commercially, there is no availability of the drug candidate in the solution form. Literature suggested that the drug candidate is very unstable in the liquid dosage form. It undergoes hydrolytic degradation in the presence of water. The aqueous based formulation trials attempted gave significant levels of known and unknown impurities. Hence an attempt for developing simple nonaqueous based carfilzomib formulations was attempted and the data indicated that two results of the nonaqueous formulation found satisfactory and however, the stability of the same needs to be evaluated further.

INTRODUCTION:

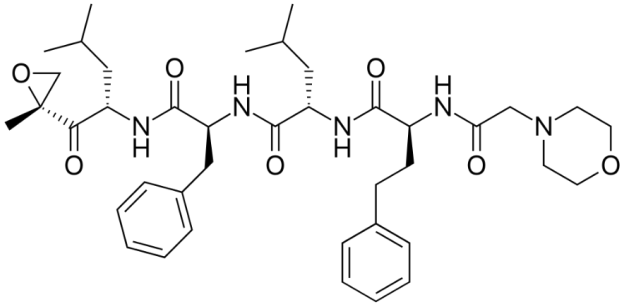
Cancer is a disease of uncontrolled cell division, invasion, and metastasis[1]. It is generally considered to be due to the clonal expansion of a single neoplastic cell. Cancers are classified in two ways[2]: Carfilzomib (marketed under the trade name Kyprolis in the US, developed by OnyxPharmaceuticals) is an anti-cancer drug acting as a selective proteasome inhibitor. Chemically, it is a tetrapeptide epoxy ketone and an analog of epoxomicin. Bortezomib (Velcade) was approved in 2003. This was the first proteasome inhibitor approved for use in the U.S. Its boron atom binds the catalytic site of the 26S proteasome[3]. Carfilzomib (Kyprolis) was approved by the FDA for relapsed and refractory multiple myeloma in 2012[4]. It irreversibly binds to and inhibits the chymotrypsin-like activity of the 20S proteasome. Ixazomib (Ninlaro) was approved by the FDA in 2015 for use in combination with lenalidomide and dexamethasone for the treatment of multiple myeloma after at least one prior therapy. It is the first orally-available proteasome inhibitor[5].

Carfilzomib is derived from epoxomicin, a natural product that was shown by the laboratory of Craig Crews at Yale University to inhibit the proteasome[6]. The Crews laboratory subsequently invented a more specific derivative of epoxomicin named YU101[7], which was licensed to Proteolix, Inc. Scientists at Proteolix invented a new, distinct compound that had potential use as a drug in humans, known as carfilzomib. Proteolix advanced carfilzomib to multiple Phase 1 and 2 clinical trials, including a pivotal phase 2 clinical trial designed to seek accelerated approval[8]. Clinical trials for carfilzomib continue under Onyx Pharmaceuticals, which acquired Proteolix in 2009[8].

Carfilzomib is an irreversible proteasome inhibitor. It selectively blocks the chymotrypsin-like activity of the 20S proteasome. With this, the degradation of unwanted proteins in the cell is blocked, leading to the buildup of polyubiquitinated proteins. This causes cell cycle arrest, apoptosis, and cell death, which is more in myeloma cells, as the protein production is enhanced in this cancer[9].

It differs from bortezomib in the following aspects: (1) its binding is more selective than bortezomib; (2) it is irreversible; and (3) because of 1 and 2, it is less prone to the development of resistance[9].

The chemical name for carfilzomib is (2S)-N-((S)-1-((S)-4-methyl-1-((R)-2-methyloxiran-2-yl)-1-oxopentan-2-ylcarbamoyl)-2-phenylethyl)-2-((S)-2-(2-morpholinoacetamido)-4-phenylbutanamido)-4-methylpentanamide. Carfilzomib has the following structure:



Carfilzomib is a crystalline substance with a molecular weight of 719.9. The molecular formula is $C_{40}H_{57}N_5O_7$. Carfilzomib is practically insoluble in water and very slightly soluble in acidic conditions.

Carfilzomib is approved by the DCGI for used in relapsed myeloma. DCGI has mandated that a Phase IV trial with this agent be conducted by the parent company. In India, the drug product is approved as the Lyophilized powder Injection 60 mg/vial. Lyophilization is a time consuming, tedious, and involves cumbersome procedures. Further, it involves expensive technology to develop a lyophilized product. Hence, an attempt to develop a non-lyophilized drug product such as liquid formulation which would offer convenience for practitioners by avoiding the reconstitution step when preparing the drug for administration.

As per the literature available, Carfilzomib's active substance is a non-polar ionizable weak base, is practically insoluble in water. The epoxide group of carfilzomib degrades over time in the aqueous solution therefore, dosage form development focused on the identification of compositions that could provide adequate stability of carfilzomib while enhancing the solubility necessary for the required therapeutic dose. Hence, an attempt is made to evaluate the simple aqueous based formulations of Carfilzomib.

MATERIALS AND METHODS:

Carfilzomib was procured from Laurus Pharma Labs, Ahmedabad. Ethanol was sourced from Hayman Labs, Mumbai. Citric Acid was received as a gift sample from Merck. PEG 400, Glycerin, Soyabean oil, and Polyoxy castor oil 40 were purchased from the commercial sources. All required chemicals used were of standard grade.

Preparation of Carfilzomib Formulations

A total of 3 formulations were prepared. The concentration was chosen of carfilzomib is 5 mg/mL based on the solubility. Initially, the drug substance was dissolved in Ethanol. Alter on one by one excipient was added per below composition table. Finally, the volume is made to 100% per below composition table. Citric acid is used as an acidifier in the formulation.

Table No. 1: Formulation of Carfilzomib Injection.

Sr. No.	Ingredients	NACF1	NACF2	NACF3
1	Carfilzomib	5 mg/mL	5 mg/mL	5 mg/mL
2	Ethanol	400 mg/mL	400 mg/mL	400 mg/mL
3	PEG 400	400 mg/mL	--	--
4	Propylene Glycol	--	400 mg/mL	
5	Glycerine	--	--	400 mg/mL
6	Citric Acid	0.2 mg/mL	0.2 mg/mL	0.2 mg/mL
7	Soyabean Oil	400 mg/mL		--
8	Polyoxyl 40 castor oil	q.s. to 1 mL	q.s. to 1 mL	q.s. to 1 mL

Evaluation of Carfilzomib Formulations

Physical evaluation

***Description*:** This is a physical observation made by an individual.

pH: pH was measured using a pH meter at about 25°C temperature by diluting the one part of the formulations with 10 mL of water.

Water Content: water content of all the formulations was measured using Karl-Fischer USP 921 <1a>.

Light Transmission: All the formulations were tested for light transmission at 650 nm using a UV spectrophotometer. The formulations were diluted in a 1:10 ratio with water and then measured.

Chemical Evaluation:

Assay: HPLC method was adopted to measure the active drug content from the 3 formulations. The active obtained is expressed as a percent of the labelled amount of Carfilzomib content. The obtained value of drug content is expected to be within limits of 90.0 % to 110.0 % (General compendia like USP & BP requirement).

Related Substances: % content of known and unknown impurities were determined by the HPLC method.

RESULTS AND DISCUSSION:

The results are compiled in Table No. 2. A clear colourless to light yellow colour solution was observed in all three formulations. The pH of all 3 formulations was observed in the range of 3.2 to 3.6due to the presence of citric acid in the formulation. It is also noted from the pH trend that all the three formulations indicated that formulation stability is towards the acidic nature. Light transmission measured for the three formulations found close to 100% indicating the clear transmission of the liquid formulation when each of the formulations was transmitted through a UV spectrophotometer at 650 nm. The water content results of all the three formulations were found satisfactory. With respect to the chemical analysis of all the three formulations, it was observed that all the three formulations have shown satisfactory assay levels indicating the correct input of % content of the carfilzomib vs label claim. It also indicates that the analytical method employed for estimating the % content of carfilzomib is correct. From the related substances analysis, it was observed that all the known impurities formed in the first two formulations are less when compared to the third formulation. Also, the content of the single highest unknown impurity is found satisfactory in all three formulations.

Table No. 2: Physical and Chemical Evaluation of Carfilzomib Formulations

Sr. No.	Formulation Codes	Description	pH	LT (in%)	Water Content	Assay (in %)	Related Substances
1	NACF1	@	3.58	99.5	0.48%	98.4%	Acid Impurity: 0.18% Chloro Impurity: 0.08% Diol Impurity: 0.22% N-Oxide Impurity: 0.11% Single Highest UNK Imp: 0.17% Total Imp: 0.82%
2	NACF2	@	3.41	98.6	0.51%	98.9%	Acid Impurity: 0.14% Chloro Impurity: 0.09% Diol Impurity: 0.17% N-Oxide Impurity: 0.12% Single Highest UNK Imp: 0.12% Total Imp: 0.71%
3	NACF3	@	3.62	99.7	0.45%	99.6%	Acid Impurity: 0.27% Chloro Impurity: 0.15% Diol Impurity: 0.26% N-Oxide Impurity: 0.14% Single Highest UNK Imp: 0.17% Total Imp: 1.04%

@: Description: A clear colorless to light yellow solution. LT is Light Transmission.

CONCLUSION:

The overall characterization of all the three formulations concluded that no physical description complications were observed. Analytical results of pH and light transmission test parameters were found satisfactory. The water content results of all the three formulations were found satisfactory. The presence of citric acid helped to maintain acidic pH which is helping for the better stability of the drug. Chemical evaluation such as assay test parameter result was observed satisfactory. However, with respect to impurities formation such as acid impurity, diol & N-Oxide impurity levels were found lower side for the first 2 sets of formulations. It is also to be noted that the % content of unknown impurities is a satisfactory level in all three formulations. However, overall control of Chloro impurity is observed in all the three formulations. From the above experiment, it can be concluded that carfilzomib can be formulated as nonaqueous formulations to arrest the degradation impurities in the formulation which were in significant levels in the aqueous based formulations. Compared to the three formulations, ACF2 has lesser impurity levels when compared to the other two formulations. The scope of attempting further trials of nonaqueous carfilzomib shall be attempted.

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