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RESEARCH ARTICLE

Preparation and Evaluation of Bendamustine Hydrochloride Non Aqueous Formulations

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ABSTRACT

B-cell chronic lymphocytic leukemia (B-CLL), also known as chronic lymphoid leukemia (CLL), is the most common type of leukemia. Leukemias are cancers of the white blood cells (leukocytes). CLL affects B cell lymphocytes. B cells originate in the bone marrow, develop in the lymph nodes, and normally fight infection by producing antibodies. Bendamustine (INN, trade names Ribomustin and Treanda; also known as SDX-105) is a nitrogen mustard used in the treatment of chronic lymphocytic leukemias (CLL) and lymphomas. It belongs to the family of drugs called alkylating agents. It is also being studied for the treatment of sarcoma[1]. Bendamustine Hydrochloride is commercially available in the market as lyophilizzed dosage form. Also enough literature is available that Bendamustine Hydrochloride is very unstable in the liquid dosage form. It undergoes hydrolytic degradation in the presence of water[2]. Hence an attempt for developing a simple, aqueous and non aqueous based Bendamustine Hydrochloride formulations have been attempted.

KEYWORDS

Bendamsutine Hydrochloride, Dimethylacetamide, Polyethylene glycol 300, Propylene glycol.

INTRODUCTION

Bendamustine was first synthesized in 1963 by Ozegowski and Krebs in East Germany (the former German Democratic Republic). It is a white, water soluble microcrystalline powder with amphoteric properties[3]. Until 1990 it was available only in East Germany. East German investigators found that it was useful for treating chronic lymphocytic leukemia, Hodgkin's disease, non-Hodgkin's lymphoma, multiple myeloma and lung cancer[4]. The IUPAC name of bendamustine Hydrochloride is lH-benzimidazole-2-butanoic acid, 5-[bis(2-chloroethyl)amino]-l methyl-, monohydrochloride. Its empirical molecular formula is $C_{16}H_{21}Cl_2N_3O_2$•HC1, and the molecular weight is 394.7. Bendamustine hydrochloride contains a mechlorethamine group and a benzimidazole heterocyclic ring with a butyric acid substituent, and has the following structural formula[5]

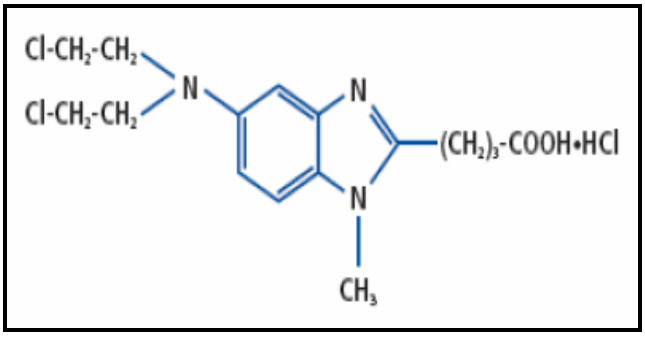

Figure 1: Structure of Bendamustine

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EXPERIMENTAL

Chemicals and Reagents

Bendamustine Hydrochloride was procured from Shilpa Medicare Limited, Raichur, Ethanol, Polyethylene glycol 300 and Propylene glycol were procured from Merck chemicals. All the other chemicals used were of standard grade.

Preparation of Aqueous Based Bendamustine Hydrochloride

A total of four non aqueous based formulations were prepared. The concentration chosen of Bendamustine Hydrochloride was 5 mg/mL based on the solubility trials. Non aqueous formulations were prepared by dissolving Bendamustine Hydrochloride in dimethylacetamide as the drug substance has the solubility in dimethylacetamide only. Rest others are used as co solvent. However the pH of non aqueous based formulations were not measured due to non availability of H+ and OH- ions. However, pH is measured by diluting the one part of the non aqueous formulations with ten parts of water for injection.

Evaluation of Non Aqueous based Bendamustine Hydrochloride Formulations

Physical evaluation

Description: This is a physical observation made by individual.

pH: pH of the each formulations were measured using Metrohm pH meter at about 25°C temperature by adding one part of non aqueous formulations to 10 parts of water for injection.

Chemical Evaluation

Assay: HPLC method was used to determine the active drug content from the 4 formulations. The recovered amount of active drug is the expressed as percent of labeled amount of Bendamustine Hydrochloride content. The obtained value of drug content should be within established limits of 90.0% to 110.0% (General compendia like USP & BP requirement)

Related Substances: HPLC method was used to determine % content of known and unknown impurities.

Figure 1: Formulation of Non Aqueous Bendamustine Hydrochloride Injection

Sl. No.	Ingredients	NAF1	NAF2	NAF3	NAF4
1	Benndamustine Hydrochloride	5 mg/mL	5 mg/mL	5 mg/mL	5 mg/mL
2	Dimethylacetamide	8 mg/mL	8 mg/mL	8 mg/mL	8 mg/mL
3	Propyleneglycol	Nil	Nil	0.4 mL/mL	0.6 mL/mL
4	Polyethyleneglycol 300	0.4mL/mL	0.6 mL/mL	Nil	Nil
5	Ethanol (anhydrous)	Qs to 1 mL	Qs to 1 mL	Qs to 1 mL	Qs to 1 mL

RESULTS AND DISCUSSION

The results are compiled in the table 2. A clear colorless solution from AF1 to AF4 were observed. pH of all 4 formulations were observed in the range of 2.5 to 3.0 indicating the pH of the formulations [when diluted with 10 parts of water for injection]. Also the pH trend observed from four formulations indicates that formulation stability towards the acidic nature as the drug substance is salt of weak acid and it contains butyric acid moiety. With respect to the chemical analysis of the four formulations, it was observed that all the four formulations has shown assay value in the range of 98.0 to 100.0% indicating the correct input of % content of Bendamustine Hydrochloride vs label claim. It also indicates that the analytical method employed for estimating the % content of Bendamsutine Hydrochloride is correct. From the related substances analysis, it was observed that monohydroxy Bendamustine (impurity A) was observed in all the four formulations in a less significant amount and other % impurities content are satisfactory.

Table 2: Physical and chemical evaluation of aqueous Bendamustine Hydrochloride Formulations.

Sl. No.	Formulation Codes	Description	pH	Assay	Related Substances
1	NAF1	#	2.62	99.42%	Imp A:1.12% Imp B: 0.04% Imp C: 0.09% Highest UNK Imp: 0.08% Total Imp: 1.35%
2	NAF2	#	2.68	100.12%	Imp A: 0.98% Imp B:0.05% Imp C: 0.09% Highest UNK Imp:0.08% Total Imp: 1.29%
3	NAF3	#	2.79	98.56%	Imp A:0.84% Imp B:0.06% Imp C:0.04% Highest UNK Imp:0.11% Total Imp: 1.02%
4	NAF4	#	2.92	99.23%	Imp A:0.71% Imp B:0.02% Imp C:0.08% Highest UNK Imp:0.09% Total Imp:0.91%

#: A clear colorless solution

Imp: Impurity, UNK: Unknown

CONCLUSION

Form the overall characterization of non aqueous based formulations of Bendamustine Hydrochloride, it can be concluded that no physical description complication were observed with aqueous based formulations. Also the assay test parameter result was observed satisfactory. But With respect to the results of related substances, the impurity A monohydroxy bendamustine was observed in the significant levels which is about 0.7% to 1.1% indicating the hydrolytic degradation nature of impurity A. however, the other known impurities and unknown impurities are well within the control. From the above experiment, it can be concluded that Bendamustine hydrochloride can be formulated with non aqueous based formulations but however, the impurity A which is a hydrolytic impurity is observed in the levels which is not in line with the requirements of ICH Q3 B R(2). Though the content of % impurity A in non aqueous based formulations of Bendamustine Hydrochloride is observed less when compared to aqueous based formulations but it requires further optimization to have less % of Impurity A in the non aqueous formulations of Bendamustine Hydrochloride.

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