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RESEARCH ARTICLE

Optimization of Tertiary Butyl Alcohol in the Bulk Formulations of Bendamustine Hydrochloride Injection

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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, Tertiary butyl alcohol, Hydroxypropyl beta cyclodextrin, Mannitol.

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.

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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]

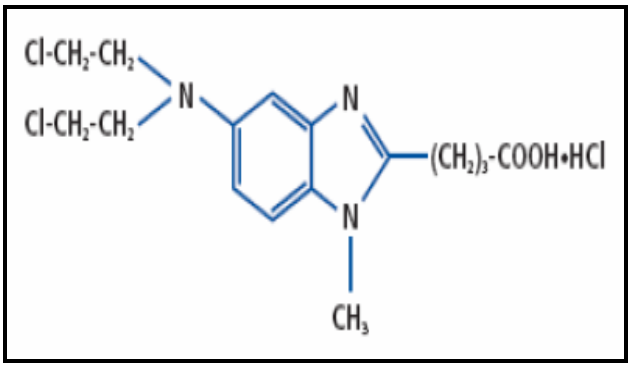

Figure 1: Structure of Bendamustine

The toxicity of TBA is low. According to the ICH Guidelines, solvents are divided into three different categories: class 1, class 2 and class 3 solvents, with class 1 indicating extremely high toxicity, and class 3 indicating a very low toxicity. Although not listed in the ICH Guidelines[6] for Residual Solvents, TBA is likely to fall in the category of a Class 3 solvent based on its similarity of LD50 toxicity data for other Class 3 solvents. As per ICH, Class 3 solvent is said to have PDEs of 50 mg or more per day. Assuming a TBA content of 0.5%w/w a patient may take up to 10 g of solid dispersion, since the maximally allowed dose for Class 3 solvents is 50 mg/day. Obviously, toxicity is not an issue[7]

EXPERIMENTAL

Chemicals and Reagents

Bendamustine Hydrochloride was procured from Shilpa Medicare Limited, Raichur, Tertiary butyl alcohol was procured from Finar Chemicals, Mumbai. All the other chemicals used were of standard grade.

Preparation of Aqueous Based Bendamustine Hydrochloride

A total of five bulk formulations containing tertiary butyl alcohol as co solvent apart from water for injection as a vehicle in the formulations. In order to understand the role of tertiary butyl alcohol as stabilizer for controlling the degradation, a bulk formulation without tertiary butyl alcohol was prepared.

The concentration chosen of Bendamustine Hydrochloride was 5 mg/mL based on its solubility. The above formulations containing water and tertiary butyl alcohol as a co solvent were prepared apart from containing Mannitol as an osmolality contributing agent. There were no pH adjusting agent used in the formulation as the injection formulation pH was observed in the range of 2.5 to 3.0 without adjusting the pH and this pH is favorable pH for the formulations containing Bendamustine Hydrochloride.

Evaluation of Aqueous based Bendamustine Hydrochloride Formulations containing different concentrations of Water: Tertiary Butyl Alcohol

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.

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.

Table 1: Formulation of Aqueous Bendamustine Hydrochloride Injection

Sl. No.	Ingredients	CSF1	CSF2	CSF3	CSF4	CSF5
1	Benndamustine Hydrochloride	5 mg/mL	5 mg/mL	5 mg/mL	5 mg/mL	5 mg/mL
2	Mannitol	20 mg/mL	20 mg/mL	20 mg/mL	20 mg/mL	20 mg/mL
3	Tertiary butyl alcohol	Nil	0.2mL/mL	0.3mL/mL	0.4mL/mL	0.5mL/mL
4	Water For Injection	Qs to 1mL	Qs to 1mL	Qs to 1mL	Qs to 1mL	Qs to 1mL

RESULTS AND DISCUSSION

Table 2: Physical and chemical evaluation of aqueous Bendamustine Hydrochloride Formulations containing different concentrations of Water: Tertiary Butyl Alcohol

Sl. No.	Formulation Codes	Description	pH	Assay	Related Substances
1	CSF1	#	2.72	88.42%	Imp A:9.82% Imp B:0.25% Imp C:0.12% Highest UNK Imp:0.08% Total Imp:11.26%
2	CSF1	#	2.84	99.62%	Imp A:2.45% Imp B:0.08% Imp C:0.12% Highest UNK Imp:0.08% Total Imp:2.86%
3	CSF1	#	2.79	98.56%	Imp A:1.95% Imp B:0.04% Imp C:0.16% Highest UNK Imp:0.12% Total Imp:2.34%
4	CSF1	#	2.94	98.56%	Imp A:1.38% Imp B:0.08% Imp C:0.12% Highest UNK Imp:0.11% Total Imp:1.61%
5	CSF5	#	2.85	97.58%	Imp A:0.89% Imp B:0.02% Imp C:0.14% Highest UNK Imp:0.04% Total Imp:1.04%

CONCLUSION

Form the overall characterization of 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 2.45% to 0.9% indicating the hydrolytic degradation nature of impurity A depending upon the concentration of Tertiary butyl alcohol: Water present in the formulations. Lower the amount of Tertiary butyl alcohol, the more the % content of Impurity A in the bulk formulations. Also about 10% of Impurity A was observed in the bulk formulations wherein, the formulation was Tertiary butyl alcohol free and was only water based formulation. From the above experiment, it can be concluded that Bendamustine hydrochloride can be formulated with co solvent approach for the better control of impurity A by optimized concentration of tertiary butyl alcohol in the bulk formulation and then lyophilize the bulk formulation for the improved and better stability.

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