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Formulation and Evaluation of Novel Antineoplastic Dosage Forms.

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Research Article

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ABSTRACT

This study examines the rationale for intellectual property protection in the development of products useful for pharmaceuticals. This study is developed to evaluate the Non-infringing (NI) lyophilized compositions of antineoplastic drug candidate to bypass the existing patents and provide patients drug at affordable price. Antineoplastic drug is Nitrogen mustard. Bendamustine Hydrochloride (further referred in this article as Bendamustine HCl) is marketed in India as Bendamustine HCl by two different manufacturers (M1 & M2) and supplied as a lyophilized product. The pharmaceutical formulations can be used for any disease that is sensitive to treatment with Bendamustine HCl, such as neoplastic diseases.

INTRODUCTION

Antineoplastic or Anticancer drugs are the drugs that prevent or inhibit the maturation and proliferation of neoplasm. Antineoplastic agents travel the body and destroy cancer cells.

Bendamustine HCl represents one of the earliest rationally designed anticancer drugs that incorporated three functional groups; a benzimidazole ring, a mechlorethamine group and a butanoic acid residue. These groups putatively endowed Bendamustine with both alkylator and anti-metabolite activities. Bendamustine HCl has been found to be especially effective in hematologic-related cancers including multiple myeloma, chronic lymphocytic leukemia (CLL) and indolent B-cell non-Hodgkin lymphoma (NHL) for which the FDA has approved its use, and multiple myeloma. Importantly, Bendamustine is highly effective in NHL patients who have failed conventional alkylator therapies [1, 3, 4, 8, 9, 12, 13].

Bendamustine was initially synthesized in 1963 in the German Democratic Republic (GDR) and was available from1971 to 1992 in that location under the name Cytostasan®. Since that time, it has been marketed in Germany under the tradename Ribomustin®. It has been widely used in Germany to treat chronic lymphocytic leukemia, Hodgkin's disease, non-Hodgkin's lymphoma, multiple myeloma, and breast cancer [5, 6, 7].

Bendamustine is a bifunctional alkylating agent with cytotoxic activity against human ovarian and breast cancers *in vitro.* It shows only partial *in vitro* cross-resistance with cyclophosphamide, melphalan, carmustine and cisplatin [12].

Bendamustine as monotherapy or as part of combination chemotherapy protocols for first-line or subsequent treatment produced objective response rates of 61 to 97% in patients with Hodgkin's disease or non-Hodgkin's lymphoma (NHL) [41 to 48% in high grade NHL] [10].

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Presently Cephalon the innovator owns composition and polymorph granted patents and have protection until 2031 and 2029, respectively [2].

In this article non-infringing compositions of Bendamustine HCl were prepared and tried to evaluate different excipients in combination with different bulking agents to arrive at a suitable composition.

EXPERIMENTAL

Chemicals and Reagents

Bendamustine Hydrochloride was procured from Cephalon Drugs Pvt Ltd, Hyderabad, all the other Excipients and chemicals used were of standard grade.

Preparation of Non-Infringing Compositions

Considering the innovator composition and patent protection few non-infringing lyophilized compositions are developed and evaluated.

Table1

Sl. No.	Ingredients	C1	C2	C3	C4
1.	Bendamustine Hydrochloride	10 mg/mL	10 mg/mL	10 mg/mL	10 mg/mL
2.	N,N-Dimethyl acetamide	20 mg/mL	-	-	20 mg/mL
3.	Acetone	-	20 mg/mL	20 mg/mL	-
4.	Sucrose	-	10 mg	-	25 mg
5.	Lactose	-	-	10 mg	-
6.	Water For Injection	Qs to 1mL	Qs to 1mL	Qs to 1mL	Qs to 1mL

Note: Each vial was filled with 10 mL of above bulk solution to obtain 100 mg/vial strength and the said compositions were lyophilized.

Evaluation of non-infringing lyophilized Bendamustine compositions

Physical evaluation

Description

This is a physical observation made by individual.

pH

pH of the each formulations were measured at about 25°C temperature using Calibrated pH meter.

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.

Water Content

Karl Fischer instrument was used to assess the water content.

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RESULTS AND DISCUSSION

Table 2: Physical and chemical evaluation non-infringing lyophilized Bendamustine compositions

Sl. No.	Formulation Codes	Description	pH	Assay	Related Substances
1	C1	#	2.88	96.99%	Imp A:4.62% Imp B:0.19% Imp C:0.14% Highest UNK Imp: 0.34% Total Imp: 5.39%
2	C2	#	2.98	99.02%	Imp A:1.73% Imp B:0.14% Imp C:0.09% Highest UNK Imp: 0.13% Total Imp: 2.19%
3	C3	#	2.97	98.21%	Imp A: 2.12% Imp B:0.16% Imp C:0.12% Highest UNK Imp: 0.18% Total Imp: 2.68%
4	C4	#	2.79	97.54%	Imp A: 3.21% Imp B:0.18% Imp C:0.10% Highest UNK Imp:0.24% Total Imp:3.80%

Imp: Impurity, UNK: Unknown

The results are compiled in the above table. Clear colorless solution NI compositions from C1 to C4 were observed. The pH of all 4 formulations were observed in the range of 2.7 to 3.0 indicating the pH of the formulations independent of drug substances though there is a quantitative change in the formulation. 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 as it contains butyric acid moiety. With respect to the assay of the four formulations, it was observed that all the four formulations has shown assay value about 97.0 % indicating the correct input of % content of Bendamustine Hydrochloride vs label claim. It also indicates that the analytical method employed for estimating the percent content of Bendamustine 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 significant amount and other two known % impurities content are satisfactory but single maximum unknown impurity is found high.

CONCLUSION

Considering the above NI lyophilized compositions of Bendamustine HCl, it can be concluded that no physical description complication were observed. Further the assay test results were found to be satisfactory. However with respect to related substances results, the impurity A monohydroxy bendamustine was observed in the significant levels which are about 4.62% indicating the hydrolytic degradation nature of impurity A. In this study the NI composition C2 having acetone and sucrose reduce the % content of Impurity A i.e., 1.73% which is the lowest of all four NI compositions. However, other two known impurities are well within the control. % content of unknown impurities is not satisfactory, hence comparing the above four NI compositions (Table 2) it can be concluded that the unknown impurities were above the specification limits, hence those compositions are ruled out. From the above experiment, it can be summarized and graded as C2> C3>C4>C1:

C2 is the most preferable, C3 is the next preferred, C4 is the subsequent preferred and C1 is the last preferred.

As an alternate, the scope of developing other NI compositions for liquid Bendamustine Hydrochloride Injection shall be attempted.

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