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Research Article

RECOVERY PROCESS OF SALICYLIC ACID FROM LAMIVUDINE AND REDUCING ITS IMPACTS ON ENVIRONMENT BY USING THE RECOVERY AND MANUFACTURING PROCESS

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ABSTRACT
Salicylic acid is used in the manufacturing process of Lamivudine, so far no literature available for recovery salicylic acid in Lamivudine manufacturing process. The present work relates to recovery of salicylic acid from Lamivudine manufacturing process. It was obtained as a byproduct, combination of Ethyl acetate and Triethyl amine containing salicylates. Recovery of Salicylic acid from Lamivudine is a new treatment for Ethyl acetate and Triethyl amine which contains salicylic acid, which is difficult to treat using biological effluent treatment processes. The brief description of proposed recovery of salicylic acid process is, by distillation of mass and eliminate the Ethyl acetate and Triethyl amine. After distillation the remaining mass is filtered in water and carbon media, which on further treatment with Hydrochloric acid, adjust the pH up to 1-2 and then filter the mass and dry it gives result of white crystalline salicylic acid recovery. This process offers particular advantages in term of swiftness, high efficiency, cost reduction and chemical waste reduction in Lamivudine manufacturing process. It is a recyclable and eco-friendly recovery process. The aim of the present study was recovery of the salicylic acid in Lamivudine manufacturing process and reducing its impacts on environment. Experiments were carried out at batch and tests in order to investigate equilibrium and dynamic condition of salicylic Acid recovery process.

Key words: Recovery process of salicylic acid, Environmental aspects, Eco -toxicological, Hydrochloric acid, Lamivudine.

INTRODUCTION

Lamivudine is an antiretroviral drug. In 1984, shortly after the human immunodeficiency virus (HIV) had been confirmed as the cause of AIDS, Racemic BCH-189 (the minus form is known as Lamivudine) was invented by Bernard Belleau while at work at McGill University and Nghe Nguyen-Ga at the Montreal-based IAF BioChem International, Inc. laboratories in 1989. Lamivudine is an analogue of cytidine and it can inhibit both types (1 and 2) of HIV reverse transcriptase and also the reverse transcriptase of hepatitis B. It is phosphorylated to active metabolites that compete for incorporation into viral DNA. They inhibit the HIV reverse transcriptase enzyme competitively and act as a chain terminator of DNA synthesis. Mainly change in amino acid sequence from YMDD to YIDD results in a 3.2 fold reduction in the error rate of the reverse transcriptase, which correlates with a significant growth disadvantage of the virus[1]. Lamivudine usage increasing every year in the world. Lamivudine making purpose Salicylic acid is used in the Lamivudine manufacturing process. Salicylic acid consumption increasing along with Lamivudine requirement in the world, Lamivudine and salicylic acid consumption showed in the table.

Every year 2761 tonnes of salicyclic acid is consumed in manufacturing process of Lamivudine. Salicylic acid usage is increasing with a pace of 20% per year, based on the Lamivudine requirement in the world To manufacture 1Kg of Lamivudine, 0.8 Kg's of salicylic acid required. Salicylic acid is a monohydroxybenzoic acid, and a type of phenolic acid and a beta hydroxy acid. Salicylic acid is usually produced from phenol[2]. Some applications this colorless crystalline organic acid is widely used in organic synthesis and functions as a plant hormone. For manufacturing of Lamivudine in pharmaceutical industries, thousands of tons of salicylic acid is consumed every year. Phenolic compounds are undesirable pollutants in the environment, specifically in aquatic media. Salicylic acid is a phenolic compound, which is its precursor; it is present in wastewaters from different industries.

Sodium salicylate is commercially prepared by treating sodium phenolate (the sodium salt of phenol) with carbon dioxide at high pressure (100 atm) and high temperature (390K) -a method known as the Kolbe-Schmitt reaction. Acidification of the product with sulfuric acid gives salicylic acid.

Pharmaceuticals are biologically active substances which have been recognized as a continuing threat to environmental stability. Chronic ecotoxicity data as well as information on the current distribution levels in different environmental compartments continue to be sparse and are focused on those therapeutic classes that are more frequently prescribed and consumed. Nevertheless, they indicate the negative impact that these chemical contaminants may have on living organisms, ecosystems and ultimately, public health. This article reviews the different contamination sources as well as fate and both acute and chronic effects on non-target organisms.

The presence of medicines in the environment has become a recent research topic. Initially, the problem was highlighted in the US back in the 1970s and almost a decade later in England. Yet, it was only in the mid 90s with advances in analytical techniques that important knowledge on environmental contamination by those compounds grew. In fact, tons of them are produced annually worldwide to be consumed by humans or animals. However, these same properties are paradoxically responsible either for bioaccumulation and toxic effects in aquatic and terrestrial ecosystems. In a different way from some conventional pollutants (such as pesticides, detergents, fuels, among others), medicines are continuously delivered at low levels which might give rise to toxicity even without high persistence rates .Wide dissemination at low concentrations

mainly in the aquatic environment is evident today. Such concentrations have been detected in aquatic compartments such as influents and effluents from sewage treatment plants (STPs), surface waters (rivers, lakes, streams, estuaries, among others), Seawater, groundwater and drinking water. The scientific community is in broad agreement with the possibility that adverse effect may arise from the presence of pharmaceuticals Not only for human health but also for aquatic organisms[3]. Lamivudine (INN)[4] or 3TC is a levorotatory pyrimidinone-1,3-oxathiolane derivative and has the molecular formula of $C_8H_{11}N_3O_3S$. They are conceived primarily to have particular physiological modes of action and frequently to resist to inactivation before exerting their intended therapeutic effect.

There has been a great concern for public health and environment over the last few decades. Methods like aeration, biological degradation, chemical oxidation, photo oxidation, solvent extraction and adsorption have been developed for the removal of organics from waste water. Of all these methods solvent extraction and adsorption are the most commonly used methods. It has been developed by the experiment given below. It helps to protect the environmental aspects and health. We focused on to recovery process of salicylic acid from Lamivudine and reducing its impacts on environment by using the recovery and manufacturing process.

METHODOLOGY

The brief description of the Lamivudine preparation

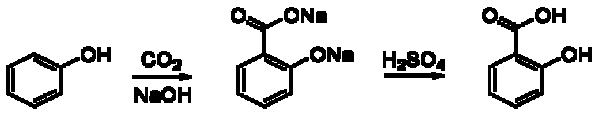
Reduction of 4-amino-2- oxo-pyrimidinyl-oxathiolane -2-carboxylicacid –isopropyl-metyl-cyclohexyl ester by sodium borohydride in ethanol and treatment with salicylic acid yields (2R-Cis)-4-amino-1-[2-(hydroxymethyl)-1,3-oxathiolan-5-yl]-2-(1H)-Pyrimidinone salicylate monohydrate.

(2R-Cis)-4-amino-1-[2-(hydroxymethyl)-1,3-oxathiolan-5-yl]-2-(1H)-Pyrimidinone salicylate monohydrate is desaltified with Triethyl amine in Ethyl acetate affords crude material of (2R-cis)-4-amino-1-[2-(hydroxymethyl)-1, 3-oxathiolan-5-yl]-2-(1H)-Pyrimidinone. And triethylamine salt in effluent it is having the salicylic acid, Triethyl amine and ethyl acetate, it is taken for recovery salicylic acid further process as follows.

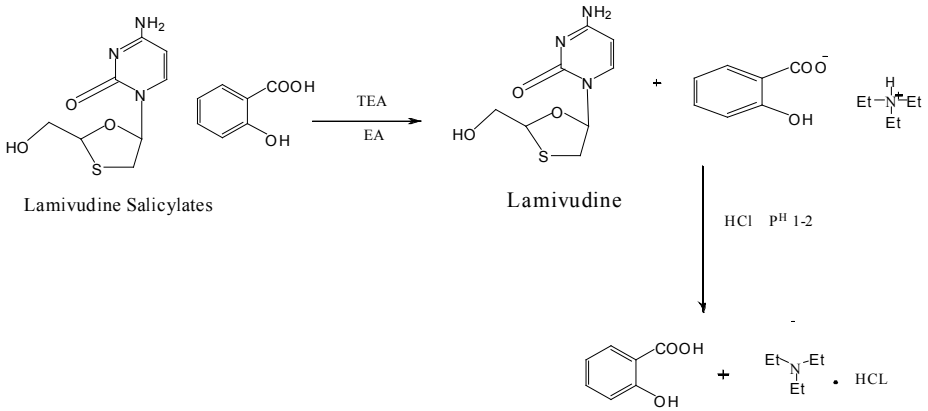
Salicylic acid recovery process

Mother liquor obtained from the Lamivudine manufacturing process is having the triethylamine and ethyl acetate it is called as triethylamine salicylates. Distillation eliminates the ethyl acetate and water, acidifying the mass with hydrochloric acid yields salicylic acid. The entire recovery process showed in below schemes.

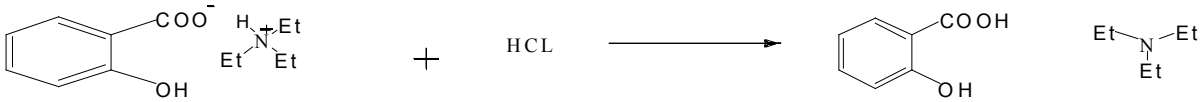
YEAR	% of Increasing Every year	Lamivudine consumption in (TONS)	Salicylic acid usage (TONS)
2007	20%	2000	1600



Scheme-I



Scheme-II



Reaction mass taken from the mother liquors generated in manufacturing process of Lamivudine. 70 g of Lamivudine mother liquor taken in to flask stir and raise the temperature, then distill the ethyl acetate completely under vacuum below 70°C.After completion of the distillation slowly add the water (30 ml) at 60-70°C and remaining residue, filter the mass in to water and carbon media at 80°C. Cool the filtrate, which on further treatment with hydrochloric acid and adjust the pH up to get pH range is 1-2. Allow the cooling up to stand the temperature 25-35°C and maintain the 2 hours at 25-35°C under stirring. Filter the solid and wet cake dried in to hot oven at 60-70°C. Samples were collected periodically and analyzed. In all experiments white crystalloid salicylic acid was spectrophotometrically determined at 295nm, by an UV-vis spectrophotometer Jasco (model 7800, Japan).

RESULTS AND DISCUSSION

An efficient and simple recovery process of salicylic acid is offers advantages swiftness and efficient way. The target quantity of salicylic acid gained from this process. Throughout the entire process recovery method performed

equal quality as that of fresh. Melting point is 159°C, Boiling point is 211°C, density is 1.443 g/cm3, Molecular mass is 138.12 g/cm-1, and purity 99.9% by GC. Above process is best Industrial process for the recovery of Salicylic acid and usage in Lamivudine production which reduces the environmental impacts. Today, the presence of pharmaceuticals in the environment is being reported worldwide. For example while the lipid regulator, clofibrate, will not be detected in the environment, its major metabolite clofibric acid appears in significant amounts in the environment. Clofibric acid can adversely affect cholesterol synthesis and consequently could influence endocrine regulation in aquatic species [5]. Drugs in the environment did not capture the attention of the scientific with some significant Overviews and reviews [6]. Furthermore, new data on the sources, fate and effects of pharmaceuticals in the environment, seems to indicate the possibility of a negative impact on different ecosystems and imply a threat to public health. Other substances of environmental relevance we concluded that this new route of recovery salicylic acid process from the Lamivudine manufacturing process is eco supportive process it helps to reduce the salicylic acid consumption in the pharmaceutical industries.

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