

Purification of Chlorzoxazone by Adsorption

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Abstract: Chlorzoxazone (C₇H₄ClNO₂) chemically 2-hydroxy chlorobenzoxazole, an aromatic organic compound of benzoxazole family which is having benzene fused oxazole ring structure, is a centrally water insoluble acting muscle relaxant used to treat muscle spasm and the resulting pain or discomfort. It is a white, odorless, crystalline powder mostly soluble in organic solvent. Chlorzoxazone is produced from the hydrolysis of 2-amino-chloro benzoxazole (C₆H₆ClNO). The undesirable brown color in downstream of reactor is removing by adsorption. This paper reviews selection of solvent and adsorbent for purification.

Keywords: Chlorzoxazone, Purification, Adsorption, Solvent, Adsorbent

I. INTRODUCTION

Chlorzoxazone, chemically 2 hydroxy chlorobenzoxazole and is a centrally active muscle relaxant for the treatment of painful muscles spasm associated with musculoskeletal disorders, such as fibrositis, bursitis, myositis, spondylitis, sprains, and muscle strains. Chlorzoxazone C₇H₄ClNO₂ is White, odorless, crystalline powder which is soluble in solutions of alkali hydroxides and ammonia; sparingly soluble in alcohol, in isopropyl alcohol, and in methanol.[1] The composition of the present compound comprises a benzoxazole compound selected from the group consisting of 2-hydroxy benzoxazoles having the structural formula shown in fig 1. [2]

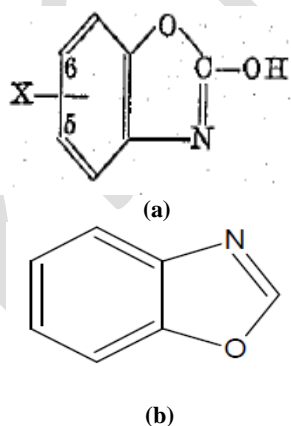


Figure 1 .Structural formula (a) 2-hydroxy benzoxazoles (b) Benzoxazole

Where X is selected from the group consisting of 5-chloro and 4-chloro which are known as pharmaceutical carrier. The compositions of the present compound have been found to produce relaxation of the skeletal muscles by a mechanism involving the depression of the polysynaptic, pathways of the central nervous system. [2] Benzoxazole is an aromatic organic compound having benzene fused oxazole ring structure with a molecular formula C₇H₅NO molar mass 119.12 g/mol, and an odor similar to pyridine with IUPAC name 1-Oxa-3-aza-1H-indene, Insoluble in water and melting point 27-30°C. Benzoxazoles can be considered as structural isosteres of the naturally occurring nucleic bases adenine and guanine, which allow them to interact easily with polymers of living systems [3]. Chlorzoxazone is having IUPAC name 5-Chloro-2-benzoxazolinone.its physical and chemical properties are shown in Table 1.

Name	Chlorzoxazone
Chemical name(IUPAC)	5-Chloro-2-benzoxazolinone
Molecular formula	C ₇ H ₄ ClNO
Chemical structure	
Molecular weight	169.565
Chemical family	Heterocyclic Benzoxazole
Phase	Crystalline solid
Color	White
Odor	Odorless
Melting point	191-192°C
Nature(pH)	Not applicable
Water solubility	Slightly soluble
Other solubility	Sparingly soluble in alcohol, isopropanol and methanol; soluble in ammonia and alkaline solutions
Basic Use	Muscle relaxant

Synonyms	C ₇ H-Cl-N-O ₂
	5-chloro-2-benzoxazolinone
	5-chlorobenzoxazolin-2-on
	6-chloro-2-benzoxazolinone
	5-chlorobenzoxazolidone
	5-chlorobenzoxazol-2-one
	5-chloro-3(H)-2-benzoxazolone
	5-chloro-
	2-hydroxybenzoxazole
	Biomioran
	Chloroxazone
	Flexazone
	Muscol
	Myoflexine
	Paraflex
	Parafon
Solaxin	
USAF MA-10	

Table 1 Properties of Chlorzoxazone [11]

II. MANUFACTURING PROCESS

2-hydroxy chlorobenzoxazole is prepared by hydrolysis of the corresponding 2-amino-5- or 4-chloro benzoxazole. Benzoxazole compound is also water insoluble in nature and an aromatic organic compound having benzene fused oxazole ring structure. So, during the production of this compound it is dissolve in organic solvent like methanol, ethanol, acetone, ethyl acetate and chloroform etc [1]. These organic solvents have been used for solubilization of poorly water-soluble drugs production. Drawbacks of organic solvents include high cost and error in analysis due to volatility [3].

2-hydroxy chlorobenzoxazole is produced by reaction between 2-amino-5- or 4-chloro benzoxazole, HCl and Urea at 115°C with constant pH of 4.5 – 5. In this reaction HCl is added to solubalise 2-hydroxy chlorobenzoxazole and neutralizes the ammonia released from reaction. Here acetic acid is added as buffer solution. Further solution is centrifuge for getting crude product which further purified by adsorption (decolorization) and finally crystallization occurs in presence of organic solvent like methanol. [11]



Undesirable brown color is present in downstream of reactor. So it is necessary to purify it according to USP standard. As chlorzoxazone is a pharmaceutical product it has to follow the USP standards and according to USP the chlorzoxazone should be white crystalline solids.

III. PURIFICATION OF CHLORZOAZONE

Chlorzoxazone is a solid substance so there is very limited choice for the purification operation. Another thing in selecting is efficiency & concentration of feed stream. As it is pharmaceutical product it requires very high degree of purification. The downstream of reactor contains around 95% of chlorzoxazone so it is required to remove 5% impurities. So for this reason conventional heat driven process can be proved costly. Thus for removing undesirable impurities adsorption is carried out by using activated charcoal [2].

IV. SOLVENT FOR ADSORPTION

Chlorzoxazone is water insoluble compound. It is having good solubility in organic solvents like chloroform, methanol, ethanol, ethyl acetate, acetone, etc. The solvent required for this operation should have higher volatility, less cost, uniform crystals, high dissolution rate etc. The study on different properties of solvent like volatility, dissolution rate, crystals are done by Talluri Chandrasekar and his co workers. His results are shown in following Table 1.

Table 1: Dissolution rate of chlorzoxane in different solvent by Talluri et al [1]

Time (min)	Dissolution			
	Percentage of drug release			
	Chloroform %	Ethanol/ Methanol %	Acetone %	Ethyl acetate %
10	62.1	60.5	43.2	42.3
20	70.2	67.5	58.5	51.5
30	78.3	73.8	63.9	62.1
40	86.4	81.9	76.5	70.2
50	91.8	90.9	84.6	80.1
60	98.1	97.4	92.7	87.3

For any pharmaceutical compound the dissolution rate is very important thing. Here in this Table 2 it can see that the highest dissolution rate is obtained with Chloroform, Methanol and Ethanol. Another important thing is the crystals formed from these solvents. This also uniform in case of all three. Here chloroform is toxic as compared to Ethanol and Methanol so it cannot be selected. [1]

Now considering economical factor like cost which is shown in table. It's high in case of ethanol as compared to methanol. Another thing related to ethanol is the legal restriction. Due to less cost, more volatility, less toxicity, and uniformity of product size methanol is selected as best solvent among of all.

Solvent	Vapour pressure (kPa) at 25 ^o c	Nature of crystals	Hardness of crystals	Disintegration time(min)	Cost (Rs/liter)
by Talluri et al [1]					
Chloroform	21.28	Uniform	4.12	98	399
Ethanol	5.95	Uniform	4.18	118	49.5
Acetone	31	Non uniform	4.40	129	90
Ethyl acetate	9.	Non uniform	4.63	145	72
Methanol	13.02	Uniform	4.22	116	22

Table no: 3 comparisons of different solvent properties

V. ADSORBENT FOR ADSORPTION OPERATION

In adsorption the adsorbent plays very important role. So selection of it is crucial parameter. At present the available adsorbent in India are Fly ash, Silica gel and Activated Charcoal. In India as the thermal power station use bituminous grade coal as fuel, it contains high amount of SiO₂ & Al₂O₃. This may affect the product characteristics. It also required costly pretreatment. [8] Another option is silica gel. The much research is not done on it for adsorption of solids. It is mostly used for adsorption of vapor from gas mixtures. The mechanism of adsorption for silica gel involves the making of hydrogen bond so, to adsorb anything on the silica gel it is necessary that it makes hydrogen bond and this thing cannot be predict in this case as the compound giving color is unknown.[10]

Activated carbon has wide range different desired properties are available. The study is also done on the behavior of different activated carbons so the performance can be easily predicted. Activated carbon contains very less amount of ash and heavy metal. So for these reasons activated carbon is gives good result then above tow adsorbent.

VI. CONCLUSIONS

This review paper concludes that for purification of chlorzoxazone methanol can be used as solvent as it gives product having good rate of dissolution, volatility, less cost and better crystals uniformity. Activated carbon silica gel and fly ash used as adsorbent.

REFERENCES

- [1]. Talluri chandrashekar, Bairy padma, Kantham Srinivas Kusuma praveen Kumar, (2110) Preparation and characteristics of polymer of chlorzoxazone, International Journal of Biopharmaceutics.
- [2]. U S Patent No: 2895877
- [3]. U S Patent No: 2890985
- [4]. U S Patent No: 2780633
- [5]. Priyanka Lokwani1, B.P. Nagori, Nikhil Batra, Anju Goyal, Stuti Gupta and Nisha Singh, (2011) Benzoxazole: The molecule of diverse biological activities.
- [6]. Rajesh Sharma, Pandurang Gaikwad, Rupali Joshi, (2010) A Novel Application of Hydrotropic Solubilization for Simultaneous Estimation and Validation of Acetaminophen, Chlorzoxazone, and Aceclofenac in Tablet Dosage Form.
- [7]. Preparation and characteristics of polymer of chlorzoxazones
- [8]. Anjan K. Chatterjee, Indian Fly Ashes, Their Characteristics, and Potential for Mechano-Chemical Activation for Enhanced Usability
- [9]. Mass-Transfer Operation by Robert E. Treybal, Third Edition.
- [10]. United State Pharmacopeia.