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Analysis of Antineoplastic Drugs: Clinical Pharmacology and Therapeutic Study

Chandrashekhar Kr. Roy[1] and R.P. S.Chauhan[1,*]
[1](*PG Department of Chemistry, Magadh University, Bodh Gaya, Bihar 824234)*

Abstract: *The current study depicts that it is observed the even the slight presence of easily oxidizable substance like thio-urea, ascorbic acid, hydrazine; alcohols etc. interfere in the estimation. In such case higher recovery is obtained because the compound reacts with the reagent. Therefore, the presence of such substances was avoided. Excipients like starch, calcium carbonate, sodium carbonate, cellulose, magnesium tri-silicate, tri-calcium phosphate and gum acacia if present in the pharmaceutical preparations do not interfere in the estimation.*

Background*: Antineoplastic agents are a group of specialized drugs used primarily to treat cancer (the term "neoplastic" refers to cancer cells). The first antineoplastic agents used in the 1940s, were made from either synthetic chemicals or natural plants. Antineoplastic agents are classified by origin and by how they work to destroy cancer cells. Antineoplastic agents can be administered to patients alone or in combination with other antineoplastic drugs. They can also be given before, during or after a patient receives surgery radiation therapy. Antineoplastic agents travel the body and destroy cancer cells.Side effects are expected to occur when treated with these agents, and can include nausea, mouth sores, hair loss, and lowering of the blood counts. Many of the side effects associated with antineoplastic agents occur because chemotherapy treatment destroys the body's normal cells in addition to cancerous cells.*

Materials and Methods*: An aliquot containing 5mg of the sample was taken in a l00mL stoppered conical flask and 5mL of 0.02NNCS reagent, prepared in hydrochloric acid and 5mL of 4N hydrochloric acid was added to it. The reaction mixture was shaken thoroughly and allowed to react for 15minutes at room temperature (25-300C). After the reaction is over 5mL of 5% potassium iodide was added to it. Contents were shaken thoroughly and allowed to react for a minute. The unconsumed NCS was determined iodometrically. A blank experiment was also run under identical conditions using all the reagents except the sample.*

Results*: Methotrexate is a complex compound having six membered heterocyclic ring attached to substituted benzene ring which has got a side chain at para position attached to –NH2 group. The most probable reaction may be chlorination of the benzene ring at ortho position to substituted nitrogen atom. On this basis following reaction product may be postulated.Cytarabine is a derived pyrimidine base nucleus. One of the nitrogen is substituted five membered heterocyclic ring which contain a side chain having a primary hydroxy group. Etoposide is another complex molecule containing two benzene ring along with two five membered rings. One of the ring is highly substituted at ortho and meta position. The other benzene ring has got two five membered substituted cyclic rings. It has also got a glucopyranose ring attached through live membered cyclic ring. It becomes difficult to predict the reaction of this compound with NCS. The central benzene ring has got two active positions at para positions. Therefore chlorination may happen on these available positions. Doxorubicin hydrochloride has got four cyclic rings of which the main molecule is anthraquinone derivative.*

Conclusion: *The current study depicts that it is observed the even the slight presence of easily oxidizable substance like thio-urea, ascorbic acid, hydrazine; alcohols etc. interfere in the estimation. In such case higher recovery is obtained because the compound reacts with the reagent. Therefore, the presence of such substances was avoided. Excipients like starch, calcium carbonate, sodium carbonate, cellulose, magnesium tri-silicate, tri-calcium phosphate and gum acacia if present in the pharmaceutical preparations do not interfere in the estimation.*

Key Word*: Antineoplastic Drugs, Clinical Pharmacology, Therapeutic Study*

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I. Introduction

Antineoplastic agents are a group of specialized drugs used primarily to treat cancer (the term "neoplastic" refers to cancer cells). The first antineoplastic agents used in the 1940s, were made from either synthetic chemicals or natural plants. Antineoplastic agents are classified by origin and by how they work to destroy cancer cells. Antineoplastic agents can be administered to patients alone or in combination with other

antineoplastic drugs. They can also be given before, during or after a patient receives surgery radiation therapy. Antineoplastic agents travel the body and destroy cancer cells.
Side effects are expected to occur when treated with these agents, and can include nausea, mouth sores, hair loss, and lowering of the blood counts. Many of the side effects associated with antineoplastic agents occur because chemotherapy treatment destroys the body's normal cells in addition to cancerous cells.

II. Material and Methods

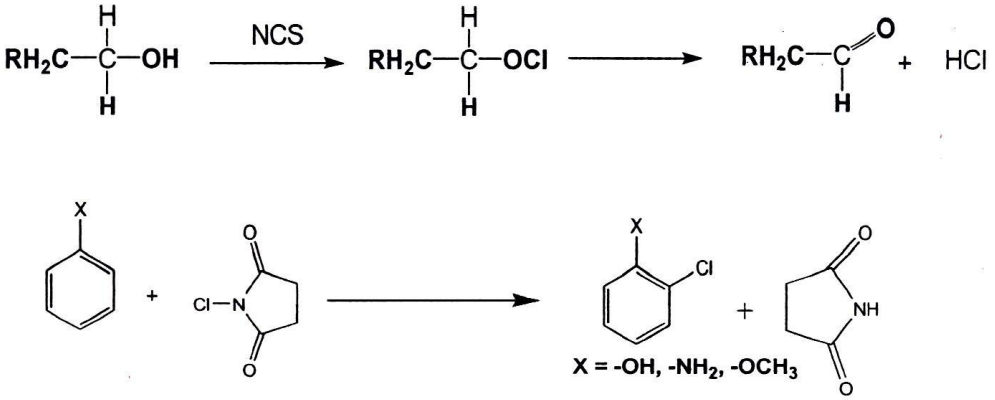
An aliquot containing 5mg of the sample was taken in a l00mL stoppered conical flask and 5mL of 0.02NNCS reagent, prepared in hydrochloric acid and 5mL of 4N hydrochloric acid was added to it. The reaction mixture was shaken thoroughly and allowed to react for 15minutes at room temperature (25-300C). After the reaction is over 5mL of 5% potassium iodide was added to it. Contents were shaken thoroughly and allowed to react for a minute. The unconsumed NCS was determined iodometrically. A blank experiment was also run under identical conditions using all the reagents except the sample. The amount of NCS consumed for the sample was calculated with the difference in the volumes of sodium thiosulphate solution for blank and the actual experiments. The recovery of the sample was calculated with the amount of NCS consumed for the sample. For every sample percentage error, standard deviation and relative standard deviation were calculated.To evaluate the authenticity of the method recovery experiments were also carried out by standard drug addition method. For such experiments a known amount of the pure drug taken and varying amounts of the pharmaceutical preparations of that compound are added and the total amount of the sample was finding out with titration and calculations.

III. Result and Discussion

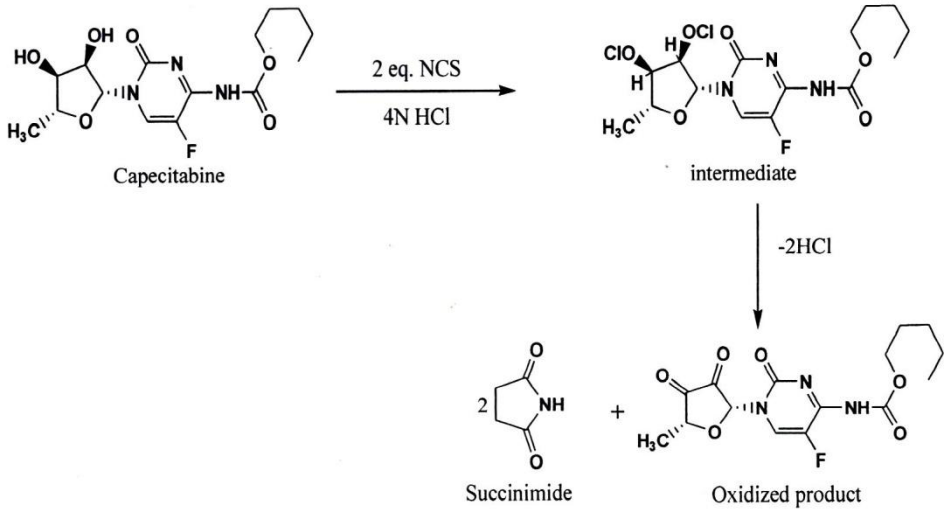
The stochiometric ratios between NCS reagent and antineoplastic drugs such as Capecitabine (1:2), Methotrexate (1:3), Cytarabine (1:3), Etoposide (1:2) and Doxorubicin hydrochloride (1:4) in pure form and in their pharmaceutical preparations has been mentioned. This ratio remains constant even under varying reaction conditions i.e., change in reaction time, concentration of reagent and reaction temperature etc. As described in the study of variation of the reaction time for concordant and accurate results, a particular reaction time was needed for completion of the reaction. It varies from one compound to another. At a reaction time lesser than the described, inaccurate results are obtained because of incomplete reaction. The increase in reaction time does not change percentage recovery of the sample because the reaction is completed at recommended time.

The use of hydrochloric acid as a proper reaction medium has also been studied. Hydrochloric acid gives quantitative and stochiometric results with capecitabine and methotrexate. The same results were obtained in the case of other samples. Reaction was also carried out in the absence of hydrochloric acid. In this case, it was found that the reaction is slow and the percentage error is very high. It is because of less ionization of the reagent. So it was observed that the recommended reaction medium is very necessary for accurate results. While studying variation in the concentration and volume of hydrochloric acid, it was observed that the use of 5mL of 4N hydrochloric acid was necessary for suitable reaction medium. NCS is the main active agent, which reacts with antineoplastic drugs. As indicated, that 5mL of 0.02NNCS was sufficient for all the samples for accurate results. Reaction was also carried out at lower and higher concentration at variable volumes of NCS. In this case, it was observed that the concentration and volume other than the prescribed under reaction conditions gives lesser recovery because of insufficient reagent. Higher concentration and volume do not give any improvement over the results. Therefore, prescribed concentration and volume of the NCS reagent was used. The effect of temperature 5-40^{0}C has also been studied. It was observed that results improve with increase in reaction time. The best recovery was obtained at room temperature (25-30^{0}C). An increase in the reaction temperature above 25-30^{0}C gives inaccurate results. It happens due to decomposition of the reagent at higher temperature. At a lower temperature it was observed that the reaction is very slow and needs more reaction time. It gives higher percentage error, because of less ionization of the reagent. At higher temperature the reagent starts decomposition.

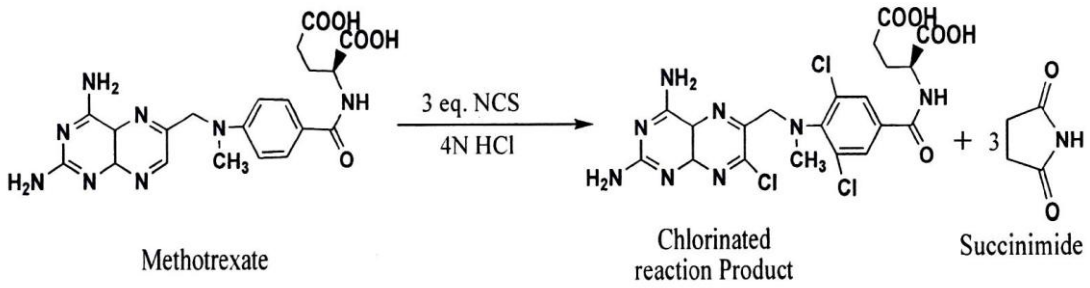
Possible course of reaction: On the basis of oxidation pattern of these compounds and literature availablefollowing course of reaction may be suggested for the reactions of NCS with each antineoplastic drug.As described, the oxidation of primary and secondary alcohols gives rise to carbonyl group. Similarly, if there is an activating group in benzene ring the chlorination takes place at proper position.



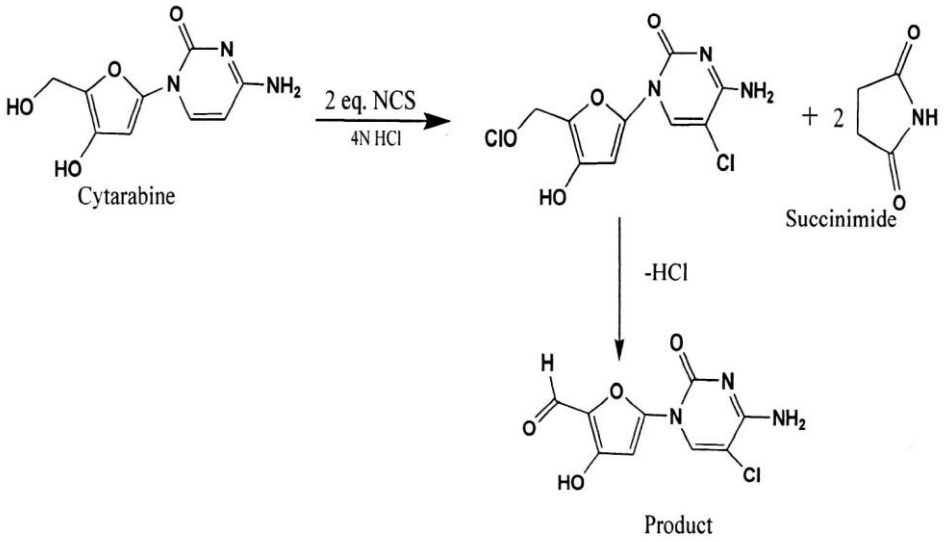
On the same basis it can be postulated that all antineoplastic drugs, depending on their structure get oxidized or and chlorinated to given corresponding product.The compound is firmly stable having two heterocyclic rings attached with each other. All the groups are quite stable and have no possibility of reaction with the reagent. The only possibility may be the oxidation of the two secondary hydroxyl groups attached at vicinity at furan ring. On this assumption the reaction may be written as below:



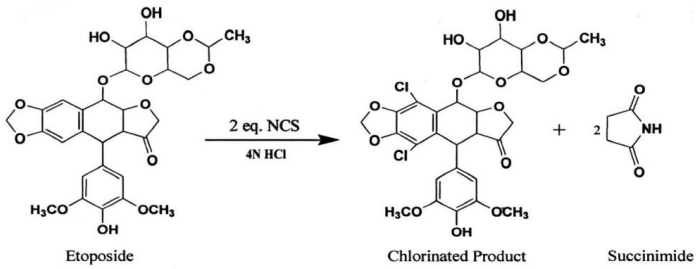
Methotrexate is a complex compound having six membered heterocyclic ring attached to substituted benzene ring which has got a side chain at para position attached to $–NH_2$ group. The most probable reaction may be chlorination of the benzene ring at ortho position to substtituted nitrogen atom. On this basis following reaction product may be postulated.

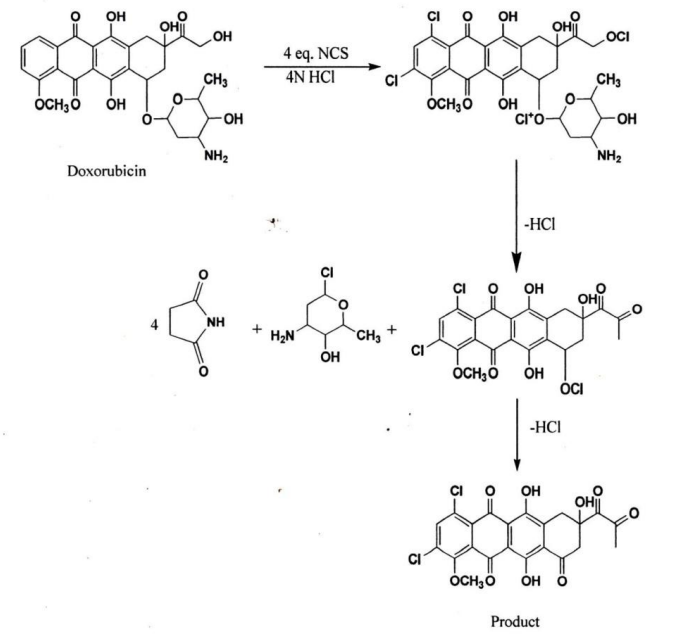


Cytarabine is a derived pyrimidine base nucleus. To one of the nitrogens is substituted five membered heterocyclic ring which contain a side chain having a primary hydroxy group. 1st, primary alcoholic group is oxidized in to a carbonyl group. On that basis the primary hydroxy group present in side chain may be oxidized to aldehyde group. One mole of NCS used as chlorinating agent and gives corresponding chloro-derivative. On the basis following reaction product may be postulated.



Etoposide is another complex molecule containing two benzene rings along with two five membered rings. One of the rings is highly substituted at ortho and meta position. The other benzene ring has got two five membered substituted cyclic rings. It has also got a glucopyranose ring attached through live membered cyclic ring. It becomes difficult to predict the reaction of this compound with NCS. The central benzene ring has got two active positions at para positions. Therefore, chlorination may happen on these available positions. Following product may be presumed:





Doxorubicin hydrochloride has got four cyclic rings of which the main molecule is anthraquinone derivative. To this is attached a carbocyclic ring to which at para position is another six membered carbocyclic ring having different substituent at three position. Taking into account several complications in the structure of the compound, it may be postulated as above that the compound gets halogenated at available position on the benzene ring.

In any one of the reaction products predicted for above compound no authentic proof could be produced. It has not become possible to isolate intermediate and the final reaction product. All the reactions were hypothetical based on stoichiometry and the nature of the reagent.

IV. Conclusion

The current study depicts that it is observed the even the slight presence of easily oxidizable substance like thio-urea, ascorbic acid, hydrazine; alcohols etc. interfere in the estimation. In such case higher recovery is obtained because the compound reacts with the reagent. Therefore, the presence of such substances was avoided. Excipients like starch, calcium carbonate, sodium carbonate, cellulose, magnesium tri-silicate, tri-calcium phosphate and gum acacia if present in the pharmaceutical preparations do not interfere in the estimation.

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