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The Chemical Contamination In Glucose Containing Sterile Fluids

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Dedication

**To my family
and
friends**





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Abstract

This work is to study the chemical contamination in medical glucose fluids, that are produced by the formation of glucose degradation products during the heat sterilization cycle.

Fourteen glucose fluids are subjected to this study, which include intravenous infusions, a peritoneal dialysis fluid, also it include the study of the various electrolytes that used in these fluids. A group of sample was sterilized by microbial filtration and used as control. Another samples were sterilized by one heat sterilization cycle. In some samples the heat sterilization cycle is repeated from two to six cycles. The study depend on measuring:

- 1- The main glucose degradation product, 5. hydroxy methyl furfural (5HMF). Which absorbed at 284 nm, and an intermediate degradation product (P_1) which absorbed at 228 nm.
- 2- pH value .
- 3- The optical rotation (α)
- 4- Color intensity
- 5- Toxicity testing by using a cell growth inhibition method.

The solutions that sterilized by microbial filtration found to contain 0.019 mM 5HMF in the 5% glucose solutions. The 5HMF increases by increasing glucose concentration to 0.19 mM in the 50% glucose solution. By the heat sterilization cycle, 5HMF increases in all glucose solutions studied and the highest amount was 48.45 mM which found in glucose 50% after six sterilization cycles. The absorbance due to the intermediate compound Ap_1 at 228 nm in the microbial filtered solution was ≤ 0.005 . By the heat sterilization cycle Ap_1 increases in all test solutions.

Ap_1 was very high in the heat sterilized glucose solutions that contain sodium acetate or sodium lactate. Also Ap_1 was high in the heat

sterilized solutions that contain $MgCl_2$. The pH value reduces by the heat sterilization cycle and the solutions become more acidic. The color is changed by the heat sterilization cycle. Although any solution that it is glucose concentration is $\leq 10\%$ and not contain sodium acetate or sodium lactate is considered as colorless solution even by repeating the sterilization cycle six times. While such solutions, glucose concentration $\geq 20\%$, or contain sodium acetate and sodium lactate, they obtain a high color intensity with the heat sterilization cycle and repetition of the cycle from yellow to dark brown. The optical rotation (α) was reduced by the heat sterilization cycle in all test solutions. The decrease in the optical rotation found to be very large in solutions that contain sodium acetate and sodium lactate. The sterile filtered solutions cause $\leq 2.6\%$ cell growth inhibition, except the concentrated glucose solutions 20%, 40% and glucose 50%. Which they cause 32%, 98.39% and 98.9% cell growth inhibition respectively. By the heat sterilization cycle the effect of cell growth inhibition increased in all test solutions. The cell growth inhibition increased by the heat sterilization cycle, glucose concentration and all electrolytes except HCl and NaCl. It is found that there is no relationship between the cell growth inhibition and 5HMF nor the pH value. The correlation coefficients $[r] = 0.33$ and 0.20 respectively. While there is a strong relationship between the cell growth inhibition and the intermediate degradation product p_1 , $[r] = 0.76$. a very strong relationship is found between the cell growth inhibition and glucose concentration, $[r] = 0.89$.

The preparation, sterilization and the chemical analysis of the fluids were done in Balsam pharmaceutical company. While the in vitro toxicity testing was done in the Animal Resources Research corporation.

ملخص الأطروحة

هذا البحث عبارة عن دراسة للتلوث الكيميائي للمحاليل الطبية المحتوية على الجلوكوز والذي ينتج عن تكون مركبات من التفكك الحراري للجلوكوز أثناء التعقيم الحراري . الدراسة شملت أربعة عشر نوعاً من المحاليل منها محاليل وريدية ومحلول غسيل كلوي كما شملت دراسة مفصلة للإلكتروليتات المستخدمة في هذه المحاليل عندما يتم تعقيمها حرارياً مع الجلوكوز . تم تعقيم عينات من المحاليل بواسطة الفلاتر الميكروبية لتصبح عينات Control كما تم تعقيم عينات بواسطة التعقيم الحراري. وعينات اخري تمت فيها اعادة التعقيم من مرتين إلي ست دورات تعقيم حراري . تعتمد الدراسة علي قياس .

- المركب الرئيسي الناتج عن التفكك الحراري للجلوكوز وهو الفيرفيورال (5-Hydroxy methyl furfural) 5HMF والذي يمتص عند 284 nm . ومركب وسيط (P₁) يمتص عند 228 nm .
 - قيمة الاس الهيدروجيني pH .
 - شدة اللون .
 - الدورانية الضوئية (α)
 - فحص السمية وذلك عن طريق فحص تثبيط النمو الخلوي .
- وجد أن المحاليل المعقمة بالفلتر الميكروبية تحتوي علي 0.019 mM من الفيرفيورال 5HMF وذلك في محاليل الجلوكوز 5% ويزيد الـ 5HMF مع زيادة تركيز الجلوكوز ويصل إلي 0.19 mM في محلول الجلوكوز 50% . مع التعقيم الحراري يزداد الـ 5HMF في كل المحاليل وكان اعلي تركيز هو 48.45 mM وذلك في محلول الجلوكوز 50% وبعد ست دورات تعقيم حراري . امتصاصية المركب الوسيط Ap₁ عند 228mM وجدت ≤ 0.005 في المحاليل المعقمة بالفلتر الميكروبية. مع التعقيم الحراري تزداد امتصاصية المركب الوسيط Ap₁ . وجد أن هناك ارتفاع كبير في Ap₁ عند التعقيم الحراري للجلوكوز مع اسيتات الصوديوم ولاكتات الصوديوم. كذلك هناك ارتفاع نسبي في Ap₁ عند التعقيم الحراري للجلوكوز مع كلوريد الماغنسيوم. قيمة الاس الهيدروجيني pH وجد انها تنقص مع التعقيم الحراري حيث تصبح المحاليل اكثر حامضية.

اللون ايضا وجد انه يتغير مع التعقيم الحراري. بالرغم من أن اي محلول تركيز الجلوكوز فيه $\leq 10\%$ ولا يحتوي علي اسيتات الصوديوم أو لاكتات الصوديوم اعتبر علي انه عديم اللون حتى بعد

اعادة دورة التعقيم ست مرات. اما المحاليل التي تركيز الجلوكوز فيها $\geq 20\%$ أو تحتوي علي اسيتات الصوديوم ولاكتات الصوديوم اظهرت مع التعقيم الحراري شدة لون تتراوح بين الاصفر الفاتح والبني الغامق.

الدورانية الضوية (α) وجد انها تنقص مع التعقيم الحراري في كل المحاليل. النقصان يكون كبيراً في وجود اسيتات الصوديوم أو لاكتات الصوديوم.

المحاليل المعقمة بالفلتره الميكروبية تسبب تثبيط نمو خلوي $\leq 2.6\%$ ما عدا محاليل الجلوكوز ذات التراكيز العالية 20% ، 40% و الجلوكوز 50% والتي تسبب تثبيط نمو خلوي 32% ، 98.39% و 98.9% علي التوالي. مع التعقيم الحراري يزداد تثبيط النمو الخلوي في كل المحاليل. التعقيم الحراري للجلوكوز مع اسيتات الصوديوم ولاكتات الصوديوم ينتج عنهما اعلي نسبة تثبيط نمو خلوي مقارنة بالالكتروليتات الأخرى. بينما ينتج عن Hcl ، Nacl النسبة الاقل من تثبيط النمو الخلوي عند التعقيم الحراري مع الجلوكوز. وجد انه لا توجد علاقة بين تثبيط النمو الخلوي وتركيز الفيرفيورال 5HMF ولا مع قيمة الأس الهيدروجيني pH وكانت قيم معامل الارتباط [r] هي 0.33 ، 0.2 علي التوالي. بينما وجدت علاقة قوية بين تثبيط النمو الخلوي وامتصاصية المركب الوسيط $Ap_1[r] = 0.76$. وعلاقة قوية جداً بين تثبيط النمو الخلوي وتركيز الجلوكوز $[r] = 0.89$.

تحضير المحاليل و تعقيمها و كذلك التحليل الكيميائي لها تم إجراؤها بشركة " بلسم للأدوية " . أما فحص تثبيط النمو الخلوي فتم إجراؤه بهيئة الأبحاث البيطرية.