Effect of Manufacturing Process on Stress Relaxation in Production of Cefuroxime Axetil Tablets

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ABSTRACT

The main objective of this study was to investigate the effects of compression forces applied during slugging on the dissolution rates of cefuroxime axetil, since the cefuroxime axetil is not stable during wet granulation and that aging affects the dissolution of core and film coated tablets where slugging was the method of choice in this study.

Dissolution was found to be dramatically affected by the compression force on tablets.

It has also been shown that interparticle bonding affects relaxation times, and that relaxation increases with decreased bonding.

The results obtained in this study confirmed that controlling both the compression force during slugging and film coating process of the core tablets will result in dissolution profiles within the acceptable USP limits. Furthermore, it has been demonstrated that any increase in compression force during slugging leads to dissolution rates outside the Pharmacopoeia limits, and therefore the undesired consequences of longer relaxation times.

Keywords: Stress relaxation, Cefuroxime axetil, Dissolution, Compression force, Manufacturing process.

1. INTRODUCTION

Cefuroxime axetil is a second-generation cephalosporin antibiotic with similar or less activity than first generation cephalosporin against Gram-positive cocci, but relatively resistant to beta-lactamases produced by Gram-negative bacteria such as *Haemophilus influenzae* and *Neisseria gonorrhoeae*. It is given orally as a Prodrug or by injection as a sodium salt. One gram of cefuroxime axetil is equivalent to 0.83069 gram of cefuroxime [(1)].

Upon contact with aqueous media cefuroxime axetil can form a gelatinous mass. This gelling effect is temperature dependent but does occur at temperatures of about 37° C. The gel formation leads to poor disintegration of the tablet core and hence to poor dissolution of cefuroxime axetil (US patent 2002/0119195 A1).

It is generally recognized that compression, moisture, heat and aging may create problems caused by chemical and physical changes in tablet (2).

Furthermore compression forces, moisture contents, aging and heat consequently producing high porous and weaker tablets and relate with relaxation of tablets. The breaking force and pellet hardness that indicated a very firm intrinsic binding force exists with Cefuroxime Axetil,

Study had investigated the decrease **in-vitro** dissolution is marked by the compact binding property of individual particles of Cefuroxime Axetil between the excipients due to the increase in compression force [(2,3)].

Tablets produced from materials with low interparticle attraction tend to suffer from more relaxation than tablets made from materials where interparticle

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Received on 1/2/2014 and Accepted for Publication on 22/6/2014.

attractions are large [4].

Lubricated tablets show however a much larger relaxation than the tablets without magnesium stearate due to the reduction of interparticle bonding by the lubricant, because a strong interparticle bonding counteracts tablet relaxation. Magnesium stearate affects interparticle bonding and that the latter has an effect on tablet relaxation immediately after compression, it can be assumed that magnesium stearate is a material that changes the relaxation properties of tablets [5,6].

Deformation properties of many materials, especially amorphous and partially crystalline polymers, are strongly dependent on environmental condition, at sufficiently low temperature; an amorphous material is the glassy state. A consequence of an increase in temperature of the material is that the rigidity of the material decreases and it is possible that the material yields without breakage. At the glass transition temperature, the resistance against deformation decreases dramatically and the amorphous material is then in the rubbery state [7,8].

Effect of pre-compression: Pre-compression provides an additional time for stress relaxation and effectively increase the tablet strength. It has a definite effect on porosity of the compact and the associated disintegration capacity[9]. Additionally, it was demonstrated that interaction between particles affects the relaxation behavior of tablets[10].

This paper discusses the effect of compression force during slugging, coating and time on bonding between particle in tablets containing cefuroxime axetil on the relaxation and dissolution of such product.

Materials and Methods

Materials used were Cefuroxime axetil (amorphous powder) USP supplied by (*Fako Ilaclari - Turkey*) is a mixture of the amorphous diastereoisomers of Cefuroxime axetil ($C_{20}H_{22}N_4O_{10}S$). It contains the equivalent of not less than 745 µg and not more than 875 µg of cefuroxime ($C_{16}H_{16}N_4O_8S$) per mg calculated on the anhydrous basis, microcrystalline cellulose (*FMC*®), Ac-disol (*FMC*®), Citric acid anhydrous (*Merck*-Germany), Sodium bicarbonate (*Merck*- Germany), Sodium Lauryl sulphate (*Henkel*-Germany), hydrogenated vegetable oil (Sterotex®) type I, (*Karlshamns- England*) , colloidal silicon dioxide (Degussa-Germany), magnesium stearate (*Mallinckrodt*-Ireland) and Opadry Y-1-7000 White (*Colorcon-England*). All other chemicals used were of analytical grade.

Table 1. Composition of Cefuroxime Axetil tablets

Ingredients	**Tablet Weight**
	Mg per tablet
Cefuroxime Axetil	617.28
Acdisol "Powder" (IN)	40.00
Microcrystalline Cellulose PH-102	146.72
Citric Acid Anhydrous	10.00
Sodium bicarbonate	13.00
Texapon K-12 (SLS)	9.00
Sterotex® type (I)	17.00
Acdisol (OUT)	40.00
Colloidal silicon dioxide (OUT)	2.50
Magnesium Stearate	4.50
Opadry Y-1-7000 White	36.00
Tablet Weight	**936.00**

Manufacturing process:

Two trials have the same ingredients and quantities per tablets and used for different compression forces, and manufactured first by dry granulation (slugging) followed by direct compression method. Different compression forces were applied in each batch.

Citric Acid (anhydrous), Sodium bicarbonate, Sodium Lauryl Sulphate and 50 percent of the Acdisol, were mixed and the premixed was passed through 0.8 mm sieve and mixed for 5 minutes.

Avicel pH 102, Sterotex® and Cefuroxime Axetil (Amorphous) were passed through sieve 0.8 mm and transferred to the mixer and mixed for 10 minutes.

Slug: Dry granules (slugs) prepared using Ronchi Tabletting machine at a controlled compression force of

250 Psi and hardness of 10-15 KP (thickness 5.2-6,5 mm) and at a compression force of a 1000 Psi and hardness of 20-30 Kp (thickness 4.5–6.0 mm) during trial 1 and trial 2 respectively using flat faced punches of 25 mm diameter. The slugs were then passed through a sieve of 2.5 and 0.8 mm respectively and mixed for 5 minutes. The other half of Acdisol and Aerosil - 200 of each trial were passed separately through sieve 0.8 mm then transfer to the mixtures (trials) and mix for 10 minutes.

Magnesium Stearate was passed through sieve 0.5 mm then transferred to the previous mixtures (trials 1 and 2) and mixed for 5 minutes. Final compression processes were then completed.

Main Tablets Compression*:*

All trials were compressed individually, to obtain predetermined hardness and processed as follows:

1000 tablets of each of Trials 1 and 2 were compressed by direct compression method separately, on Oval shaped punches of 19 X 11 mm diameter using Rotary Ronchi Tabletting machine at predetermined various compression force of 250 and 1000 Psi and hardness of 15-20 Kp using Erweka hardness testing machine, thickness of tablets were adjusted between 5.2-6.5 mm for trial 1 and 4.5-6.0 mm for trial 2, each tablet was made to contain cefuroxime axetil equivalent to 500 mg of cefuroxime.

The remaining quantities of trial tablets were separately aqueous film coated (Opadry Y-1-7000 White) using Accela Cota as coating machine. Disintegration and dissolution testing of the **coated** tablets were then conducted and results were compared with the Reference product, in order to check the effect of coating on the dissolution rate of coated tablets.

Scaling up to pilot batch of trial 1 was conducted as *Test Product* to be used for comparative dissolution testing against the *Reference Product*

Disintegration times of the tablets were tested in a 900 mL of purified water at 37°C + 0.5°C (Erweka disintegration tester) and disintegration times were recorded as mentioned in Table 2.

Table 2. Physical Properties of Slugs and Core Tablets of Trials 1-2

Trial No.	Compression force of slugs (PSI)	Compression force of final tablets (PSI)	Thickness of the final tablets (mm)	Average Hardness of the slugged tablets (Kp)	Average Hardness of the final tablets (Kp)	Disintegration time of the final tablets (min)
1	250	700	5.2-6.5	12	15	3
2	1000	700	4.5-6.0	25	18	15
Pilot	250	700	5.2-6.5	13	16	2

Dissolution Procedure:

Dissolution testing of the tablets were carried out using USP apparatus II Erweka dissolution tester, in 900 ml of hydrochloric acid 0.07 N in the vessel of the dissolution apparatus and assemble the apparatus at a temperature 37.0 ± 0.5°C, at the paddle speed 50 rpm. Vessel was covered for the duration of the test and temperature of the mixture was verified during the test every 15 minutes. Aliquots were collected and after suitable dilutions using dilution medium, then the amount of cefuroxime dissolved was determined using UV spectrophotometer (Du 7400i diode array Beckman, Germany) set at 278 nm, against the standard solution having a known concentration of cefuroxime axetil RS. Samples were analyzed at 15, 30, 45 and 60 minutes intervals respectively.

Tolerances- Not less than 60% (Q) of the labeled amount of cefuroxime is dissolved in 15 minutes, and not less than 75% (Q) is dissolved in 45 minutes, except where tablets are labeled to contain the equivalent of 500

mg of cefuroxime, not less than 50% (Q) of the labeled amount of cefuroxime is dissolved in 15 minutes and not less than 70% (Q) is dissolved in 45 minutes.

Results and Discussion

The slugged granules (core tablets) of Trial 2 were compressed on Oval shaped punches of 19 X 11 mm diameter at a compression force of 1000 Psi and hardness range between 15-20 KP, (thickness 4.5-6.0 mm).

Dissolution testing was carried out on twelve core tablets immediately after production at zero time (initial), 24 hours and 96 hours of production respectively to check the effect of aging on the dissolution of tablets and found that dissolution rate is increased significantly with time as shown in table 3 and Figure 1.

Table 3

Trial 2: Comparative Average Dissolution Profile of Core and Film Coated Tablets

Time\ minute	Core Tablets			Film Coated Tablets	
	Percent Drug Dissolved				
	Initial	24 hours	96 hours	Initial	24 hours
15	10	24	57	55	57
30	16	33	70	69	70
45	20	45	85	85	87
60	24	54	94	95	93

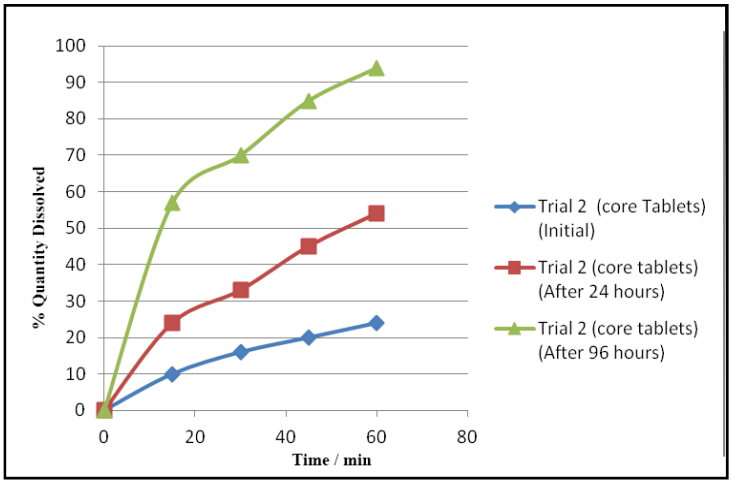

Figure 1: Comparative dissolution profile of Cefuroxime axetil core tablets at different time intervals, Initial, after 24 hours and 96 hours of manufacturing respectively

The above mentioned results shown in table 3 and figure 1, clearly indicate that the tablets tested initially (immediately after compression) shown not desired release within 45 minutes which was an average of 20% of the labeled amount of $C_{16}H_{10}N_4O_8S$ and furthermore it had an average of 45% of the labeled amount within 45 minutes after 24 hours which do not meet the dissolution requirements of the United States Pharmacopoeia.

The dissolution results of tablets of the same trial 2, after 96 hours of the compression significantly increased to about 85% in 45 minutes. This clearly indicates that there is an effect of compression force applied during

slugging on the stress relaxation of the interparticle bonds.

Second quantity of the same Trial 2 was immediately aqueous film coated using Opadry – Y-1- 7000, tested immediately for dissolution after coating. It was found that dissolution rate was significantly increased to 85%, and slightly increases to 87% after 24 hours of coating in 45 minutes as shown in figure 2 and 3.

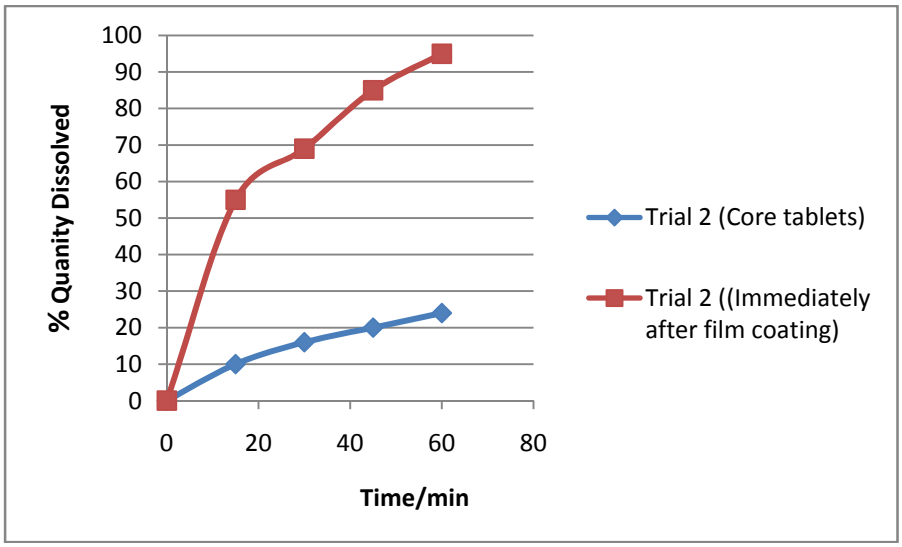

Figure 2: Comparative dissolution profile of Cefuroxime axetil core tablets, immediately after coating and after 24 hours of coating

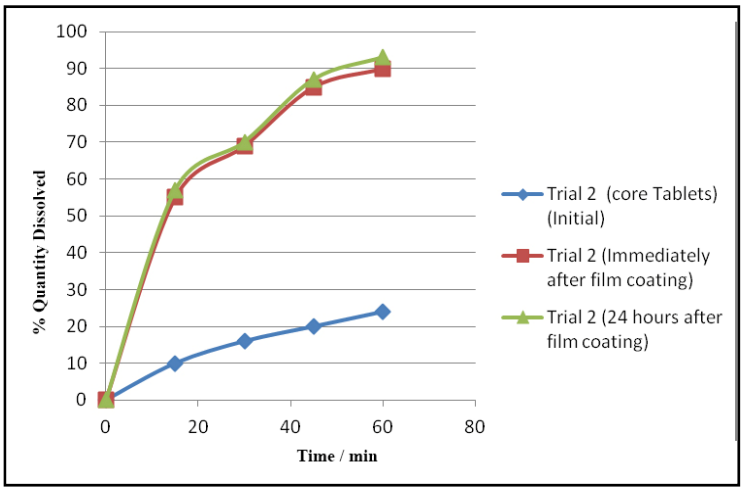

Figure 3: Comparative dissolution profile of Cefuroxime axetil core and film coated tablets

It is clear that tablets tested immediately after coating are complying with USP dissolution criteria, whereas 85% are dissolved in 45 minutes and not significantly increased to about 87% after 24 hours of coating in 45 minutes, which means that the bonds are almost completely relaxed during coating.

The slugged granules of Trial 1 were compressed on Oval shaped punches of 19 X 11 mm diameter at a compression force of 250 Psi and thickness between 5.2-6.5 mm. Tablets compressed at hardness range between

15-20 Kp, showed similar results between the samples tested before coating and after 24 hours of coating as shown in table 4 and figure 4.

Table 4

Trial 1: Comparative average dissolution profile of core and film coated tablets

Time\ minute	Core Tablets	Film Coated Tablets
	Percent Drug Dissolved	
	Initial	24 hours
15	58	60
30	80	76
45	95	80
60	97	91

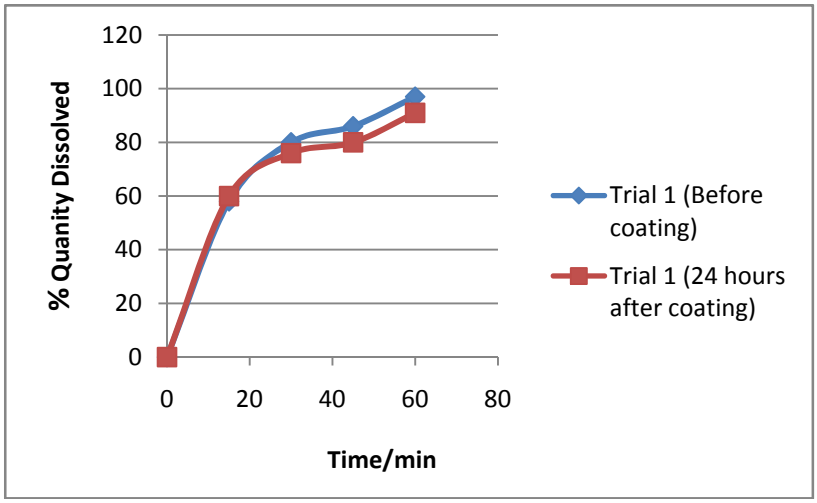

Figure 4: Comparative average dissolution profile of Cefuroxime axetil core tablets before coating and on the coated tablets after 24 hours after coating

As indicated in figure 5 the dissolution profiles of the core tablets of trial 1 are complying with USP dissolution criteria, while trial 2 is not complying whereas 20% are dissolved in 45 minutes of trial 2 and 85% of trial are dissolved respectively.

As demonstrated by table 3 and figure 2 the tablets tested initially meet the dissolution requirements of the United States Pharmacopoeia where an average quantity dissolved is 85% of the labeled amount of $C_{16}H_{10}N_4O_8S$ in 45 minutes and further insignificantly increased an average of 87% of the labeled amount after 24 hours of coating and this could be due to the lower compression force of the slugs where as much the compression force is decreased the stress relaxation is becoming negligible. This clearly indicates that there is an effect of low compression force applied during slugging on the stress relaxation of the interparticle bonds.

Scaling up of trial batch 1 to a pilot batch (*Test Product*) which is equivalent to 10 percent of production batch size was conducted using the same tabletting machine and dissolution testing was carried out on the tablets of the pilot batch versus the *Reference product.* Similar dissolution results were obtained as shown in table 5 and figure 6.

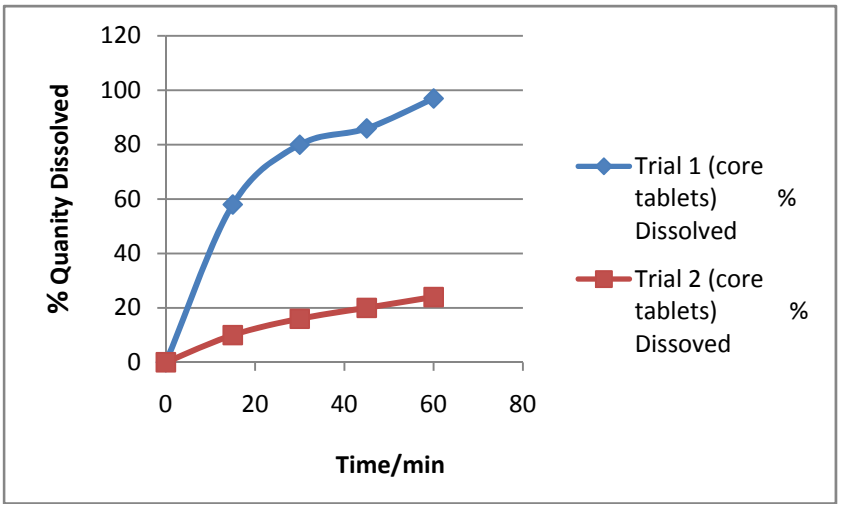

Figure 5: Comparative dissolution profile of Cefuroxime axetil core tablets of trials 1 and 2

Table 5: Comparative average dissolution profile of *Reference* and *Test Products*

Time\ minute	Reference Product	Test Product
	Percent Drug Dissolved	
15	55	58
30	69	80
45	84	90
60	97	94
Similarity factor $\mathbf{f_2}$ (50-100)	**58**	
Dissimilarity factor $\mathbf{f_1}$ (0-15)	**8**	

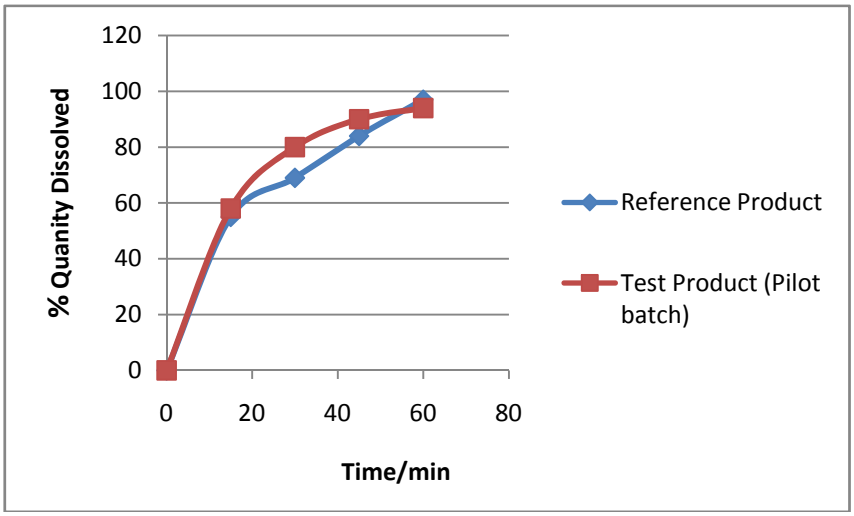

Figure 6: Comparative dissolution profile of the Test and Reference products

It is clear that *Test Product* and the *Reference product* meet the dissolution requirements of the United States Pharmacopoeia, where the average dissolution results of the Reference product was 55% and test product 58% in 15 minutes, and 84% versus Test Product, 90% of the labeled amount where dissolved in 45 minutes respectively, whereas all tablets tested were in compliance with USP requirements for dissolution, and this could be explained to the lower compression force applied of the slugs where compression force of the slugs has no effect on the stress relaxation of tablets and interparticle bonds.

The above mentioned dissolution results were statistically treated for similarity factors $\mathbf{f_2}$ was (58) and dissimilarity factor $\mathbf{f_1}$ was (8) and found that both products are similar as shown in table 5.

Conclusions

The observed increased dissolution rate of tablets containing cefuroxime axetil during this study may be attributed due to decreased interparticle bonds (relaxation of bonds) and increased porosity of the tablets resulting from elastic nature\ properties of the cefuroxime axetil.

From this study, it is concluded that the high compression forces of the slugs may significantly affect the dissolution rates, decreasing the compression force of the slugs which leads to a point where no effect is observed on the stress relaxation of tablets.

Dissolution is significantly increased after coating. This may be due to the heat involved in the coating process which affects the interparticle bonding and consequent production of highly porous and weaker tablets.

It can also be concluded that the compression force during slugging should be well controlled in order to achieve optimum dissolution. This will allow lower or no rejection of batches during production and lower waiting times for stress relaxation of tablets and therefore better compliance with USP criteria for dissolution.

The similarity and dissimilarity factors $\mathbf{f_2}$ and $\mathbf{f_1}$ values of drug release profiles of the test and reference products are considered to be comparable.

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تأثير طريقة التصنيع على الترييح أثناء إنتاج أقراص السيفيوروكسيم اكستيل

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ملخص

إن الهدف الرئيس من هذه الدراسة هو البحث في مدى تأثير قوة الضغط slugging على ذائبية الأقراص التي تحتوي على مادة السيفيوروكسيم اكستيل نظراً لأن هذه المادة غير ثابتة كيميائيا إذا تعرضت للتعجين بوجود الماء كما أن التقادم في التصنيع aging يؤثر على ذائبية الأقراص المغلفة والغير مغلفة حيث إن slugging هو الطريقة الوحيدة التي يمكن استعمالها أثناء تصنيع هذا النوع من الأقراص.

لقد تبين أن ذائبية هذه الأقراص تتأثر بشكل كبير بالضغط الموضوع على الأقراص، ناظراً لتأثر الروابط بين الحبيبات على stress relaxation، وتبين أنه كلما قلَّت قوة الروابط كلما زادت الذائبية لهذا النوع من الأقراص.

لقد أثبتت نتائج هذه الدراسة بأن ذائبية هذا النوع من الأقراص تكون مطابقة لمتطلبات دستور الأدوية الأمريكي إذا تم تحديد قوة الضغط أثناء عملية التصنيع وتغليف هذا النوع من الأدوية كما هو مبين في الدراسة. كما أثبتت الدراسة أيضاً أن أية زيادة في قوة الضغط خارج الحدود المبينة في الدراسة على الأقراص slugging ينتج عنها عدم مطابقة الدواء لمتطلبات دستور الأدوية الأمريكي من حيث الذائبية حيث تتطلب فترة طويلة للترييح stress relaxation وهذه ظاهرة غير مرغوب بها أثناء تصنيع الأدوية.

الكلمات الدالة: الترييح، السيفيوروكسيم، عملية، التصنيع.

تاريخ استلام البحث 2014/2/1 وتاريخ قبوله للنشر 2014/6/22.