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Research Article

IMPROVEMENT OF THE PHYSICOCHEMICAL PROPERTIES OF AMOXICILLIN TRIHYDRATE POWDER BY RECRYSTALLIZATION AT DIFFERENT pH VALUES

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ABSTRACT

The purpose of this research was to investigate and improve some physicochemical and solid-state properties of amoxicillin trihydrate. This raw material was obtained from different suppliers and differed in both particle size distribution and crystal shape.

The particle size and crystal shape were determined using eight sieves and a scanning fluorescence microscope, respectively. The drug was filled in hard gelatin capsules as a single dose of 250 mg. Drug dissolution was evaluated using dissolution tester. Samples were analyzed using U.V spectrophotometer at a wavelength 272nm.

The results indicated that the dissolution rates of amoxicillin trihydrate are affected by both the crystal shape and the particle size.

To improve the dissolution rate of amoxicillin trihydrate , it was recrystallized from aqueous solutions at different pH values (2, 4, 7, 9 and 11).

Amoxicillin trihydrate samples recrystallized from aqueous solutions at pH7 and pH9 appear to have superior physicochemical properties to the original amoxicillin trihydrate samples.

The pH of crystallization medium had a significant effect on the dissolution rate of amoxicillin trihydrate powder.

Samples recrystallized at pH 11 and pH9 showed higher dissolution rates compared to samples recrystallized at pH 2, pH4 , pH7 and the original amoxicillin trihydrate samples but the flowability of the powder recrystallized at pH 11 was very poor compared to other samples.

Keywords: Amoxicillin trihydrate, Dissolution rate, Particle size, Crystal shape, Recrystallization.

INTRODUCTION

Solid-state forms exhibit variable physicochemical properties that affect their processing and product performance.

The shape and the surface area of a particle affect the flow ability of a powder. The surface area per mass unit is an important characteristic of a powder when undertaking dissolution rate studies. According to the classic dissolution equation of Noyes and Whitney, the dissolution rate of a drug is directly proportional to its surface area available for dissolution[1]. This fact could be used to enhance the dissolution rate of slightly soluble drugs in water like amoxicillin trihydrate. Many substances that are chemically identical can have significant differences in their physicochemical properties like flow ability and dissolution profiles[2].

The crystallization technique can change the crystal form and the particle size. The nature and extent of these changes depend on the crystallization conditions such as the type of the crystallization medium and the pH of crystallization[3].

There are several reports of changing the crystal habit in the presence of impurities during crystallization[2,4&10]. The objective of this study was to achieve improved physicochemical properties of amoxicillin trihydrate powder through recrystallization from aqueous solutions at different pH values.

Amoxicillin is semisynthetic antibiotic (present as amoxicillin trihydrate and amoxicillin sodium). It is an analog of ampicillin, derived from the basic penicillin nucleus 6-aminopenicillanic acid[5,6&9]. The amoxicillin trihydrate molecular formula is $C_{16}H_{19}N_3O_5S\bullet 3H_2O$, and the molecular weight is 419.45. Chemically, amoxicillin trihydrate is (2S,5R,6R)-6-[(R)-(-)-2-Amino-2-(p-hydroxyphenyl)acetamido]-3,3 dimethyl7-oxo-4-thia-1-azabi-cyclo[3.2.0]heptane-2-carboxylic acid trihydrate and may be represented structurally as shown in figure 1.

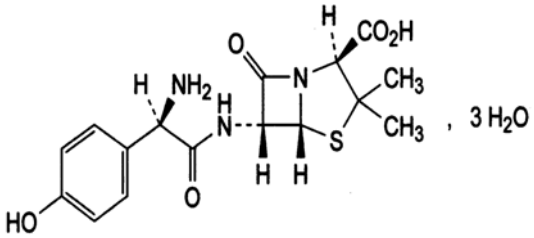


Fig. 1: Molecular structure of amoxicillin trihydrate

Also, various hydrated forms of amoxicillin, including monohydrate, dihydrate, and trihydrate, have been reported, among which, the trihydrate is the most stable hydrated form[7,8&15]. Amoxicillin trihydrate has a good oral bioavilability that is not affected by the concomitant ingestion of food. The effectiveness of amoxicillin is further enhanced by the addition of β-lactamase inhibitors such as clavulanic acid, this combination makes amoxicillin more resistant to enzymatic hydrolysis of the amid bond in the β-lactam ring and thus enhances amoxicillin bacterial activities against many β-lacatmase producing bacteria[16].

Amoxicillin is bactericidal in action and acts through the inhibition of biosynthesis of cell wall mucopeptide of susceptible organisms. Amoxicillin/Clavulanate has been shown to have a wide range of activity which includes β-lactamase-producing strains of both gram-positive and gram-negative aerobes, facultative anaerobes, and obligate anaerobes. Many strains of the following organisms, including β-lactamase producing strains, isolated from veterinary sources, were found to be susceptible to amoxicillin/clavulanate in vitro but the clinical significance of this activity has not been demonstrated for some of these organisms in animals[16].

Amoxicillin in trihydrate form is available in the market in various forms including capsules, tablets, suspensions and vials.

Amoxicillin trihydrate as a raw material was obtained from different suppliers. This material differed in both particle size and crystal shape[12,14].

Crystallization of amoxicillin trihydrate, like the other crystalline drugs, plays a critical role in controlling the crystal form, shape, size, and size distribution[11].

The objective of this study was to achieve improved physicochemical properties of amoxicillin trihydrate powder through recrystallization from aqueous solutions at different pH values[13].

In this study, scanning fluorescence microscope (SFM) was used to investigate the crystal shape of amoxicillin trihydrate obtained from different suppliers and from recrystallization at different pH values. The particle size distribution has been determined using sieves (particle size analyzer).

MATERIALS AND METHODS

MATERIALS

Amoxicillin trihydrate standard (U.S. Pharmacopeia, Catalog number: 1031503, RTECS Number: XH8310000), amoxicillin trihydrate as a raw material was obtained from (1- DSM anti-infectives Egypt S.A.E, batch. No: A449822, 2-Oman Chemicals, batch. No: 53-06090-0730A, 3-DSM Anti-Infectives India Limited, batch. No: M521414), Hard Capsules (size 4), electromagnetic sieve shaker equipped with eight sieves (1-1mm, SS-316, Serial. No: 0500083, 2-850µm, SS-316, Serial. No: 0500298, 3-600µm, SS-316, Serial. No: 0500107, 4-500µm, SS-316, Serial. No: 02020126, 5-250µm, SS-316, Serial. No:0201981, 6-125µm, SS-316, Serial. No:02019652, 7-63µm, SS-316, Serial. No:02010043, 8-45µm, SS-316, Serial. No:02107007), tapped density apparatus (Campbell Electronics, model:C-TDA2, Serial. No:CTD-30), pH meter (CRISON Instrument S.A Titromatric, Serial. No: 00404), A double-beam JASCO V-650 spectrophotometer (Serial. No:A025561150), Scanning fluorescence microscope (BRUNEL Microscope Ltd, model: SP-98-FL Inverted).

METHODS

Buffer preparation

Potassium chloride KCl and hydrochloric acid HCl were used for preparation of medium with pH = 2. Buffers pH =4 and pH=7 were prepared from potassium phosphate monohydrate K_2HPO_4 and sodium hydroxide NaOH. Buffers pH=9 and pH=11 were prepared from sodium hydroxide NaOH and sodium chloride NaCl.

Recrystallization procedure

Amoxicillin trihydrate samples were recrystallized from aqueous solutions at different pH values (2, 4, 7, 9 and 11). Saturated aqueous solutions of amoxicillin trihydrate with different pH values were prepared by dissolving 3 g of amoxicillin trihydrate in 90 mL of appropriate medium at 80 °C.

The saturated solutions were filtered through Milipore filter with pore size less than 0.45 mm and the filtrates were kept at 8 °C for a period of 48 hours. The precipitated crystals were filtered off and collected after 48 hours.

The crystals were spread out on a Petri dish, air-dried overnight and further dried in a vacuum oven, at room temperature (25 ± 2 °C) for 2 days. The crystals were stored at room temperature before use.

Flowability Test

Amoxicillin trihydrate samples obtained from different suppliers were subjected to this test by using a 250 ml volumetric cylinder on the tapped density apparatus with a test sample weight of 100 g.

The unsettled apparent volume (V_0) and the final tapped volume (V_{tap}) were measured, an average of three determinations was obtained.

Bulk density and tapped density were calculated as follows:

$$\text{Bulk Density [DB]} = \frac{M}{V_0} \qquad \text{Tapped Density [DTap]} = \frac{M}{V_{tap}}$$

The compressibility index and the Hausner ratio were calculated as described in the United States Pharmacopeia USP 30 monograph using measured values for bulk density and tapped density as follows:

$$\text{Compressibility Index (CI)} = \frac{[\text{Dtap}] - [\text{Db}]}{[\text{Dtap}]} \times 100$$

$$\text{Hausner Ratio} = \frac{[\text{Dtap}]}{[\text{Db}]}$$

Procedure for particle size distribution estimation

Amoxicillin trihydrate samples were sieved with eight sieves using electromagnetic sieve shaker for 10 minutes. Sieves were selected to cover the entire range of particle sizes present in the test samples (45 µm-1 mm).

The nest of sieves were assembled with the coarsest screen at the top and the finest at the bottom.

Electromagnetic sieve shaker was used to perform sieve analyses. The sieving analysis is complete when the weight of any of the test sieves does not change by more than 5% or 0.1 g of the previous weight as described in the USP 30 monograph. Sieve analysis was performed at controlled room temperature and at ambient relative humidity.

Preparation of hard gelatin capsules and dissolution testing

Amoxicillin trihydrate obtained from different suppliers and recrystallized amoxicillin trihydrate at different pH values were filled in hard gelatin capsules as a dose of 250mg.

A dissolution apparatus I of USP (baskets) was used. The capsules were placed into the baskets before the initiation of the dissolution testing, which was performed at 37^0 C and 100 rpm using 900 ml water as a dissolution medium.

Samples were collected at 5, 10, 20, 30, 40, 50, 60 and 90 minutes and analyzed immediately after sampling using U.V spectrophotometer at a wavelength 272nm on filtered portions of the test solution.

Each test was performed in triplicate and the relative standard deviation was found to be less than 3%

USP Tolerance: Not less than 80% of the indicated amount of amoxicillin trihydrate is dissolved in 60 minutes.

The in vitro release profiles of different amoxicillin trihydrate samples were compared using similarity factors, F2, as defined by the following equation[12]:

$$F2=50.\log\{[1+1/n\sum(Rt-Tt)^2]^{-0.5}.100\}$$

where n: is the number of time points at which percent of dissolved drug was determined, Rt: is the % dissolved from the sample at a given time point and Tt*:* is the % dissolved from the sample for comparison at the same time point. The similarity factor fits the result between 0 and 100. It is 100 when the test and reference profiles are identical and approaches 0 as the dissimilarity increases. An F2 above 50 indicates that the two profiles are similar.

pH measurement

The pH of a solution of 2 mg/mL amoxicillin trihydrate in distilled water (prepared using an ultrasonic bath) was measured using a pH meter.

The measured values using a calibrated pH meter could be reproduced to 0.02 pH units, as described in the USP30 monograph.

Crystal shape determination for amoxicillin trihydrate

Fluorescence microscope (BRUNEL Microscope Ltd) with a digital camera along with computer software were used to record the particle images. Optical images were performed by gently spreading the powder sample onto the glass stubs.

RESULTS AND DISCUSSION

Figure 2 shows the scanning fluorescence micrographs (SFM) of untreated (starting amoxicillin trihydrate obtained from different suppliers) and treated amoxicillin trihydrate crystals obtained by recrystallization at different pH values. It is clear from the figure that recrystallization of amoxicillin trihydrate at different pH values affected the size of amoxicillin trihydrate crystals. According to SFM, the length of amoxicillin trihydrated crystals changed in all recrystallized samples and had the values between 2.2µm and 26.4µm. The crystallization medium pH had no significant effect on the crystal shape.

Changes in the length of amoxicillin trihydrate crystals could be due to pH alteration or the presence of some additives in the medium[13]. The figures also show a clear difference in size of the treated crystals in comparison with untreated material. It can be concluded that crystallization of amoxicillin trihydrate from distilled water at pH7, pH9 and pH11 resulted in larger crystals than that of untreated samples.

The untreated samples of amoxicillin trihydrate which were obtained from three different suppliers, showed different lengths of amoxicillin trihydrate crystals.

Changes in the length of the original crystals could be due to pH variation of the preparation medium of amoxicillin trihydrate which differed from one supplier to another[9].

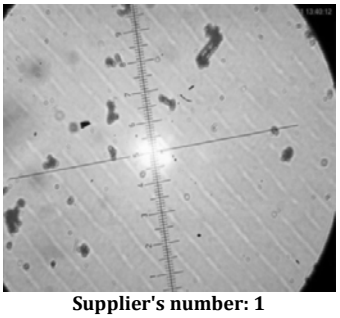
Solution pH is among the most important factor affecting amoxicillin trihydrate crystal form, which should be carefully monitored based on the United States Pharmacopeia (USP 30) specifications.

The relationship between the solution (2mg/ml) pH of amoxicillin trihydrate original samples and the length of the crystal was investigated.

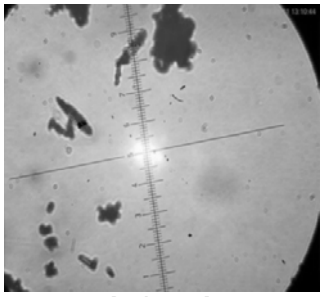
As in table 1, amoxicillin trihydrate powder subjected to the present study had a narrower pH range of 4.29 to 483. However, these powders showed a significant variation in physicochemical characteristics. Despite the fact that USP 30 monograph broadens the amoxicillin trihydrate solution (2mg/ml) pH range from 3.5 to 6.0, amoxicillin trihydrate powder subjected to the present study had a narrower pH range of 4.29 to 4.83. However, these powders showed a significant variation in the physicochemical characteristics.

Table 1: pH values of amoxicillin trihydrate solutions (2mg/ml) that have been obtained from different suppliers.

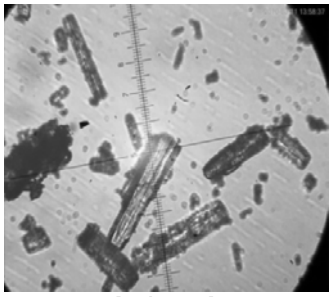
Supplier's number	pH value
1	4.29
2	4.43
3	4.83



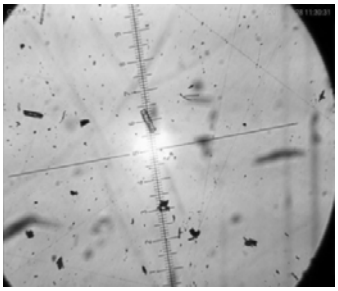
Supplier's number: 1
Solution pH value:4.29



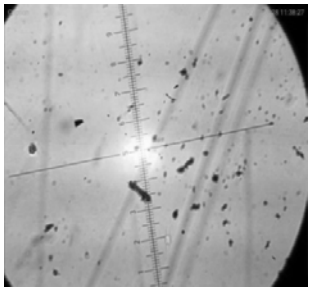
Supplier's number: 2
Solution pH value:4.33



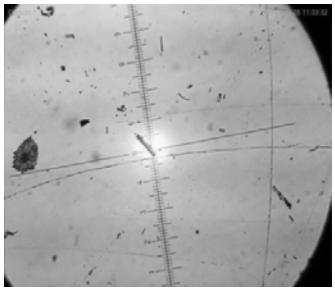
Supplier's number: 3
Solution pH value:4.83



Supplier's number: 1
Recrystallized at pH2



Supplier's number: 2
Recrystallized at pH2



Supplier's number: 3
Recrystallized at pH2

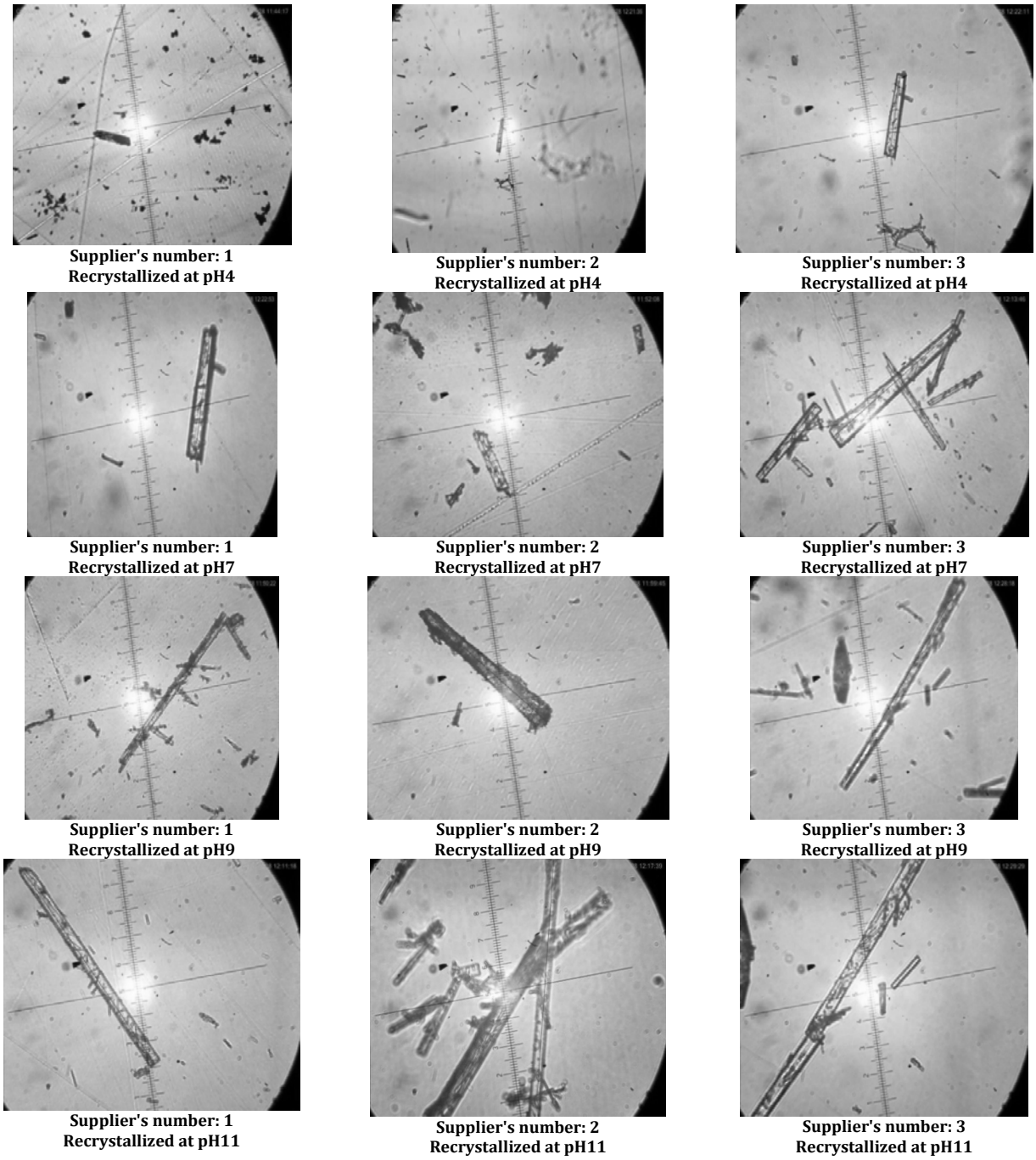


Fig. 2: Optical images of amoxicillin trihydrate crystals using scanning fluorescence microscope

Dissolution profiles of untreated and recrystallized amoxicillin trihydrate are shown in Figures 6, 7 and 8. It is clear from the figures that the highest dissolution rate was observed for the crystals recrystallized in media with pH 11 and the lowest dissolution rate was observed for the crystals recrystallized in media with pH 2 (f2<50). Dissolution rate of crystals recrystallized in media with pH 7 was higher than untreated amoxicillin trihydrate crystals as shown in Fig 3, 4 and 5.

Dissolution rate of materials could be affected by several factors, including morphology changes, particle size and adsorption of additives on the crystal surface[2].

Crystal formation and it's related properties, such as particle size, crystal length and hydrodynamic conditions during dissolution influence the dissolution profiles of crystals. The observed effects have been attributed to the different intrinsic dissolution rates of different crystals whose relative areas differ from habit to habit and also to their interaction with the solvent involved[3]. It is possible that the presence of some additives in the crystal growth medium may block the growth of the higher energy sites of crystal surface, making them less available for active dissolution[4].

These findings suggest that the preparation technique of amoxicillin trihydrate control the crystallization pH and the shape of the crystal as a result[13].

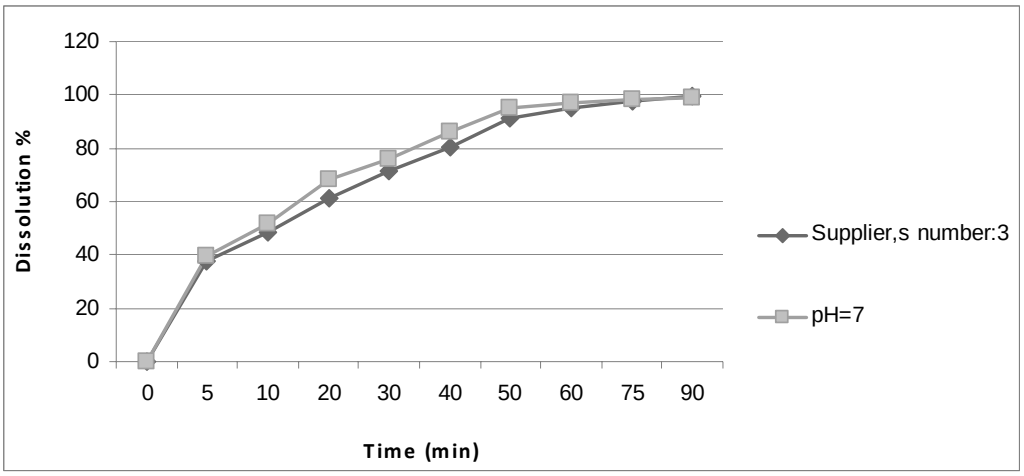


Fig. 3: Dissolution profiles of capsules prepared from untreated and recrystallized amoxicillin trihydrate at pH7 of supplier's number 3 F2=71.68.

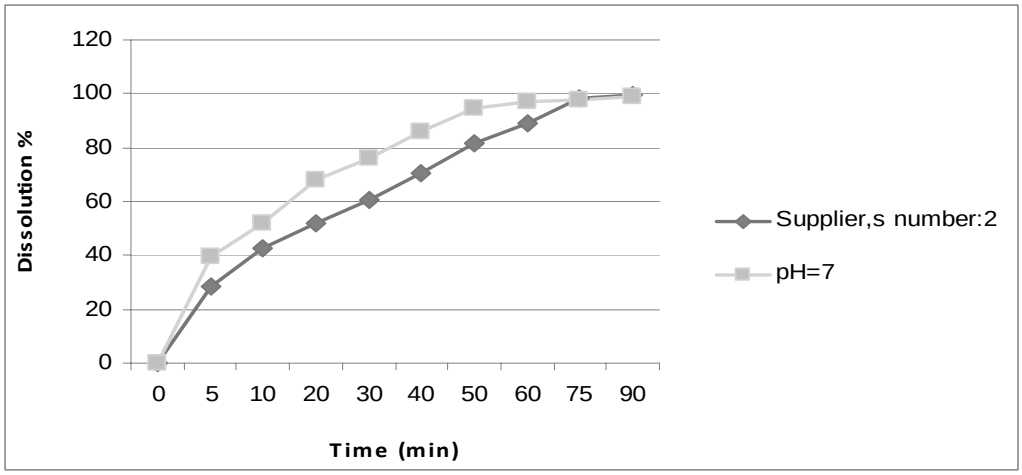


Fig. 4: Dissolution profiles of capsules prepared from untreated and recrystallized amoxicillin trihydrate at pH7 of supplier's number 2 F2=47.919.

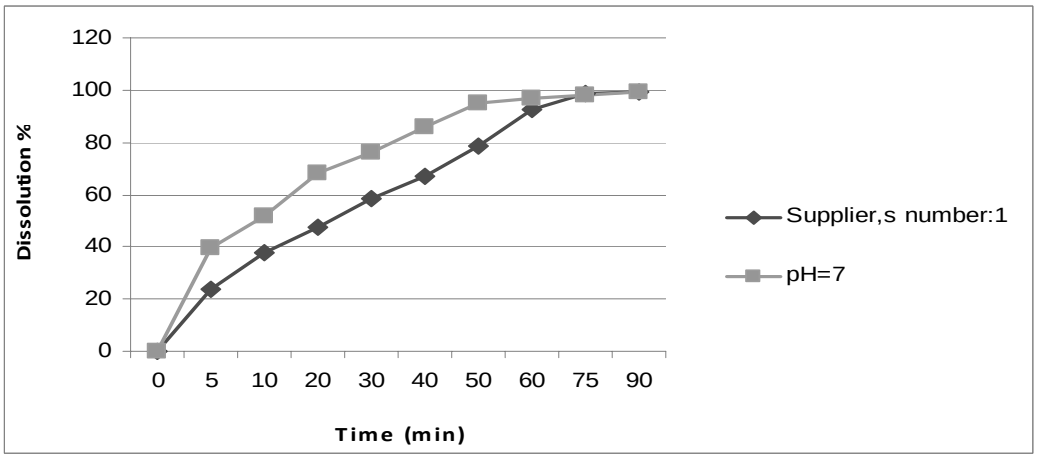


Fig. 5. Dissolution profiles of capsules prepared from untreated and recrystallized amoxicillin trihydrate at pH7 of supplier's number 1 F2=43.28.

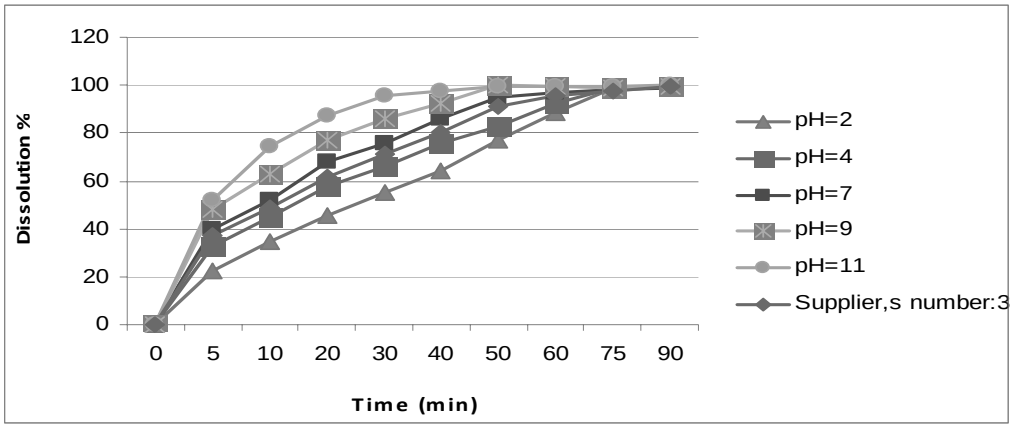


Fig. 6: Dissolution profiles of capsules prepared from untreated and recrystallized amoxicillin trihydrate at pH2, 4, 7,9 and 11 obtained from supplier's No3.

It is clear from the figures 3, 4 and 5 that the dissolution profiles of recrystallized amoxicillin trihydrate at pH7 of supplier's number 1 and 2 were dissimilar to the dissolution profiles of the original samples but the dissolution profile of recrystallized amoxicillin trihydrate at pH7 of supplier's number3 was similar to the dissolution profile of the original sample.

This can be explained by the presence of different solid forms of the same chemical compound which can exhibit different physical and chemical properties including solubility and dissolution profiles.It could be suggested that the physicochemical characteristics of amoxicillin trihydrate powder are significantly variable between different batches from different suppliers[12].

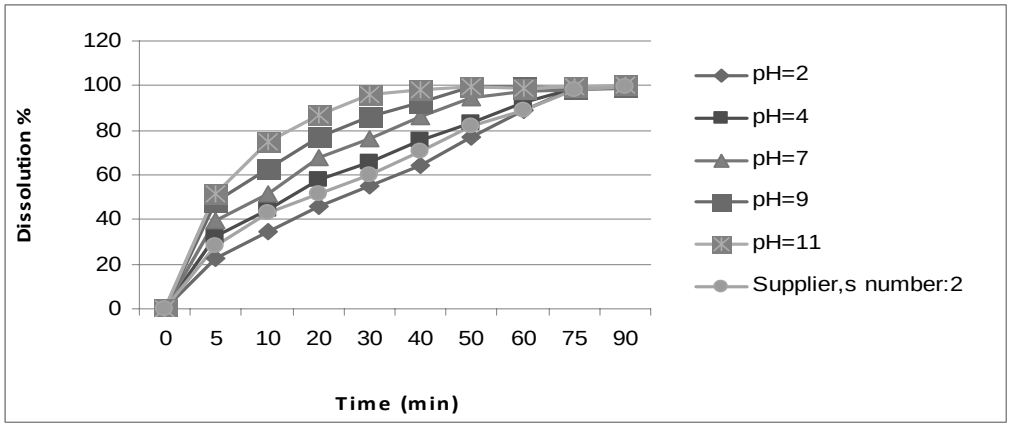


Fig. 7: Dissolution profiles of capsules prepared from untreated and recrystallized amoxicillin trihydrate at pH2, 4, 7,9 and 11 obtained from supplier's No2.

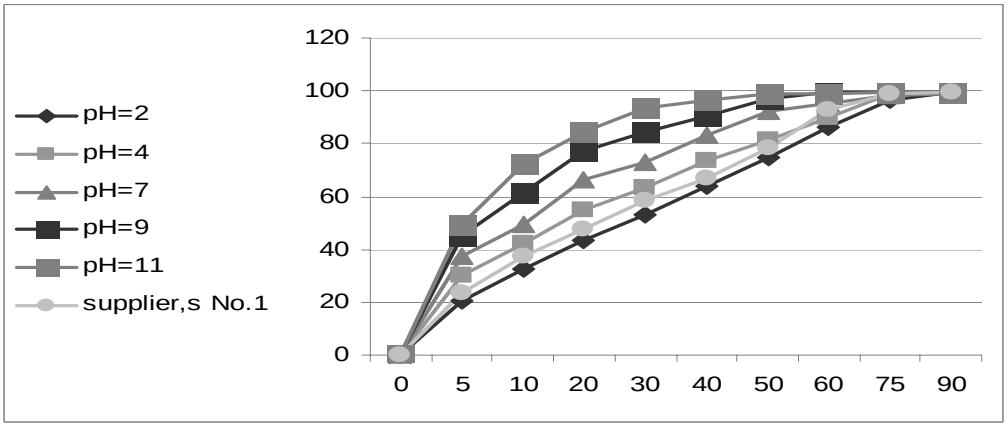


Fig. 8. Dissolution profiles of capsules prepared from untreated and recrystallized amoxicillin trihydrate at pH2, 4, 7,9 and 11 obtained from supplier's No1.

Untreated and recrystallized amoxicillin trihydrate samples were sieved by electromagnetic sieve shaker which contains eight sieves for 10 minutes. The results have shown that these samples differed in particle sizes from less than 45µm to more than 1 mm and the particle size distribution are different from one sample to another. The results are shown in figures 9, 10 and 11

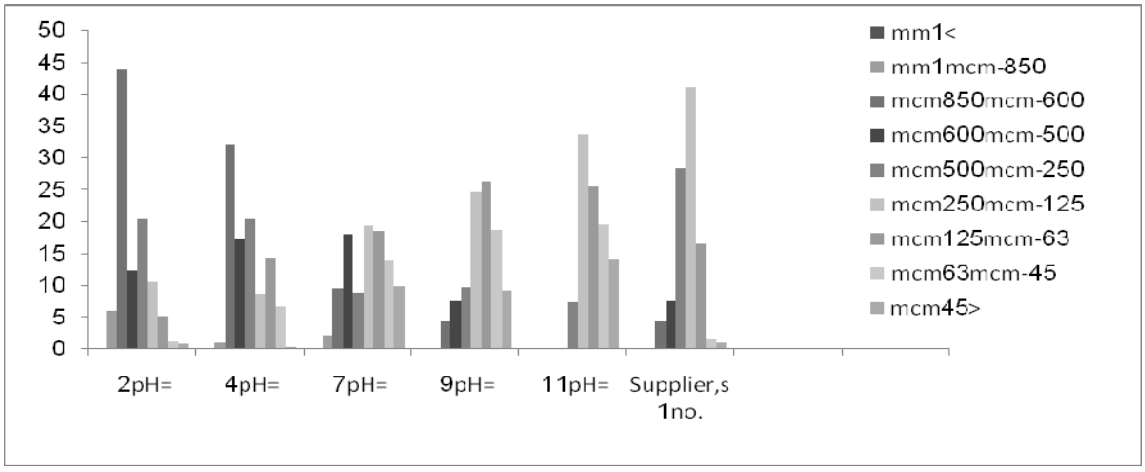


Fig. 9: Particle size distribution of untreated and recrystallized amoxicillin trihydrate obtained from supplier's number 1

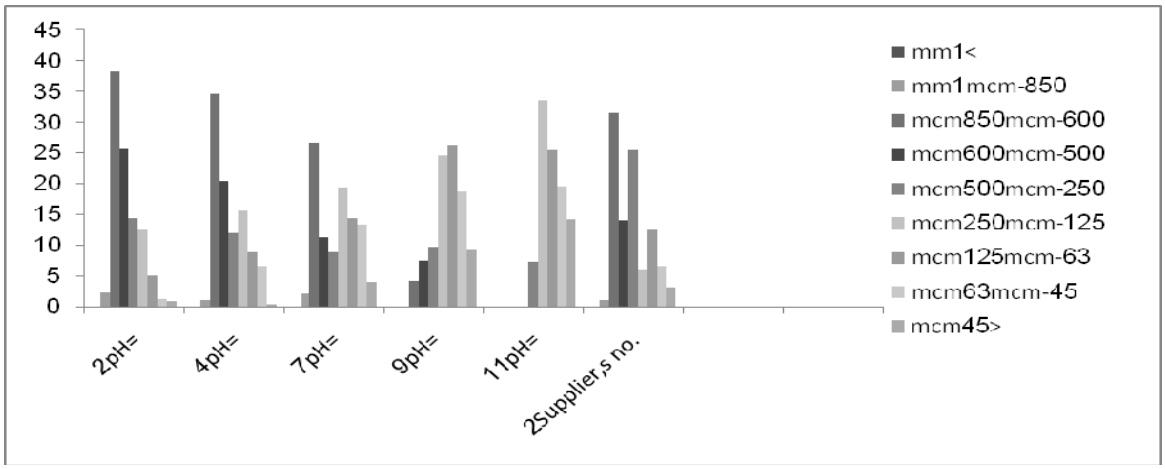


Fig. 10: Particle size distribution of untreated and recrystallized amoxicillin trihydrate obtained from supplier's number 2

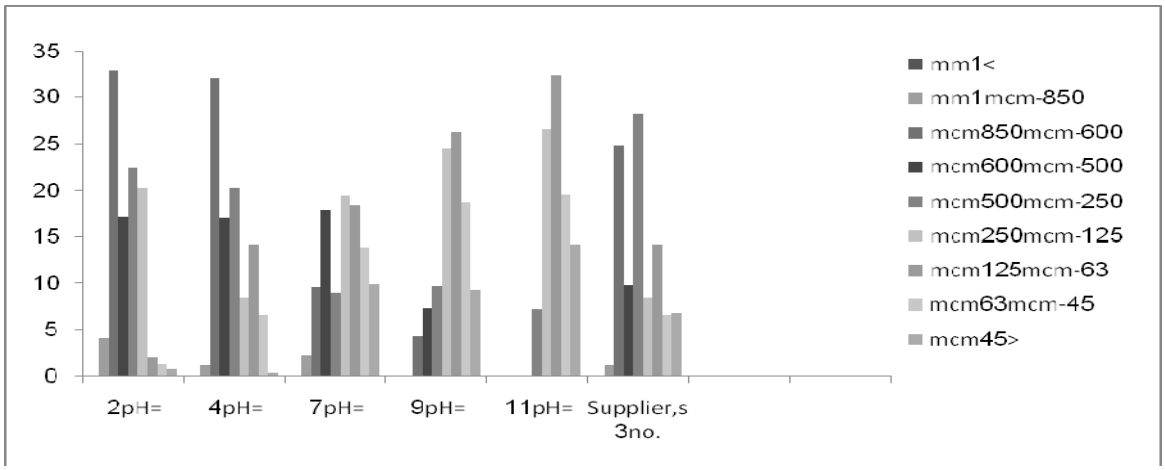


Fig. 11: Particle size distribution of untreated and recrystallized amoxicillin trihydrate obtained from supplier's number 3

Figures 9, 10 and 11 show that recrystallized amoxicillin trihydrate at pH 11 and 9 contain small particles more than amoxicillin trihydrate recrystallized at pH 2 and 4. Therefore, the flowability of these powders could be estimated to study the effect of different particle size distribution on the powder flow.

The Compressibility index has been proposed as indirect measure of bulk density, particle size and shape, surface area, moisture content and cohesiveness of materials because all of these can influence the observed Compressibility index. The Compressibility index and the Hausner ratio are determined by measuring both the bulk density and the tapped density of a powder.

For the Compressibility index and the Hausner ratio, the generally accepted scale of flowability as described in the USP30 monograph is given as follows:

Table 2: The accepted criteria for compressibility index and the Hausner ratio

Hausner ratio	Flow character	Compressibility index (CI)%
1.00-1.11	Excellent	<10
1.12-1.18	Good	11-15
1.19-1.25	Fair	16-20
1.26-1.34	Passable	21-25
1.35-1.45	Poor	26-31
1.46-1.59	Very poor	32-37
>1.60	Very, very poor	>38

Table 3: Compressibility index and Hausner ratio values of amoxicillin trihydrate samples

Amoxicillin trihydrate samples	Bulk density (mg/ml)	Tapped Density (mg/ml)	Compressibility index (CI)%	Hausner Ratio	Flow character
Supplier's N0.1	0.64	0.8	20	1.25	Fair
pH=2*	0.63	0.78	19.2	1.23	Fair
pH=4*	0.62	0.79	21.5	1.27	Passable
pH=7*	0.61	0.8	23.7	1.3	Passable
pH=9*	0.6	0.8	25	1.33	Passable
pH=11*	0.4	0.73	45.2	1.8	Very, very poor
Supplier's N0.2	0.65	0.81	19.7	1.2	Fair
pH=2**	0.63	0.79	20.25	1.25	Fair
pH=4**	0.62	0.8	22.5	1.29	Passable
pH=7**	0.63	0.79	20.25	1.25	Fair
pH=9**	0.6	0.79	24.05	1.31	Passable
pH=11**	0.39	0.72	45.8	1.84	Very, very poor
Supplier's N0.3	0.63	0.79	20.25	1.25	Fair
pH=2***	0.61	0.78	21.79	1.27	Passable
pH=4***	0.62	0.79	21.51	1.27	Passable
pH=7***	0.63	0.8	21.25	1.26	Passable
pH=9***	0.6	0.78	23.07	1.3	Passable
pH=11***	0.4	0.71	43.66	1.77	Very, very poor

*Amoxicillin trihydrate obtained from supplier's N0.1 and recrystallized at different pH values.
**Amoxicillin trihydrate obtained from supplier's NO.2 and recrystallized at different pH values.
***Amoxicillin trihydrate obtained from supplier's NO.3 and recrystallized at different pH values.

The flowability results in Table 3 showed that the recrystallized amoxicillin trihydrate at pH 11 was very poor in comparison to amoxicillin trihydrate recrystallized at pH 2, 4, 7, 9 and untreated amoxicillin trihydrate powder.

The flow properties of a material result from a number of forces. Solid particles attract one another and forces acting between particles when they are in contact are predominately surface forces. There are many types of forces that can act between solid particles: (i) frictional forces, (ii) surface tension forces, (iii) mechanical forces caused by interlocking of particles of irregular shape, (iv) electrostatic forces, (v) cohesive or van der Waals forces. All of these forces can affect the flow properties of a solid. In case of fine particles (≤ 125μm), the magnitude of frictional and van der Waals forces usually predominate. For larger particles (>125μm), frictional forces normally predominate over van der Waals forces[3]. Also, as particles increase in size, mechanical or physical properties of particles and their packing become important.

As evident from the Table 3, there were no significant differences in flow character between recrystallized materials in different pH media (2,4,7 and 9), but a different value was obtained at pH 11. It was mainly due to differences in the particle size distribution.

CONCLUSIONS

Amoxicillin Trihydrate samples recrystallized from aqueous solutions at pH7 and pH9 appear to have superior solubility and physicochemical properties compared to the original amoxicillin trihydrate samples. Amoxicillin Trihydrate recrystallized at pH11 showed higher dissolution rates and very, very poor flow character compared to samples recrystallized at pH 2, pH4 , pH7 and the original amoxicillin trihydrate samples.

This could be explained by the differences in the particle size distribution and the increase of small particles which are less than 125 μm and these can lead to poor flowability.

Recrystallization studies have been performed to investigate the possible effect of the crystallization pH on the powder's solution (2mg/ml) pH. The results showed that as the pH of the crystallization increased by adding NH_4OH, the pH of the resulting powder moved toward the upper limit of the specified pH range and the physiochemical properties of the resulting powder improved.

The possible explanation for this observation could be the increase of the solubility of impurities in water by increasing the pH. Therefore, increasing the crystallization pH resulted in the presence of more impurities in the ionic form and less impurities co-precipitating with the amoxicillin particles. This phenomenon could lead to more favorable crystallization conditions, and hence increasing the quality of the crystallized amoxicillin trihydrate. The possible mechanism behind this phenomenon is that the crystal faces are sometimes unable to discriminate between the host and impurity molecule.

This can lead to negative consequences as incorporated impurities can change the physical and chemical properties of the crystals to the worse.

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