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ORIGINAL RESEARCH

Development and *in-vitro* Evaluation of Reconstitutable Suspension of Flucloxacillin

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ABSTRACT

The objective of present study was to develop a stable reconstitutable suspension of Flucloxacillin magnesium using xanthan gum as suspending agent. The powder blend was evaluated for its flow properties and F3, F4 showed acceptable flow properties but remaining formulations were failed to show acceptable flow properties. There were no interactions between the drug and excipients used in the suspension which was confirmed from the compatibility studies. Reconstitutable suspension was evaluated for its color, taste, viscosity, pH, sedimentation volume, deliverable volume, density, resuspendability, drug content, drug release and stability. Formulation F3 showed maximum drug release of 97.03% in 45 min. in evaluating period of 14 days, there were no significant changes observed in viscosity, pH, drug content and rug release rate. From the obtained results, it could be concluded that the effective reconstitutable suspension of Flucloxacillin magnesium was achieved and successfully evaluated in the form of reconstitutable suspension.

Keywords: Antibiotic, FLOXAPEN, Flucloxacillin magnesium, Reconstitutable suspension, Xanthan gum.

1. INTRODUCTION

Flucloxacillin magnesium is an isoxazolylpenicillin containing ß-lactam group of antibiotic which shows a bactericidal effect upon many gram positive organisms including ß-lactamase producing staphylococci and streptococci (1). Flucloxacillin magnesium is stable in acidic medium and not inactivated by staphylococcal ß-lactamases. The mechanism of action is by interfering with bacterial cell wall synthesis by targeting Penicillin Binding Protein (PBP). Flucloxacillin is effective in the treatment of infections caused by penicillin-resistant staphylococci, which is the sole indication for its use because other penicillins like benzyl penicillin are not resistant to staphylococci producing penicillinase or β-lactamases. Flucloxacillin is not inactivated by staphylococci-producing penicillinases and it is used for the treatment to skin and soft tissue infections and respiratory tract infections (2). Improvement of bioavailability and patient compliance of the drug can be achieved by using the suspension dosage form of the drug (3). Oral pharmaceutical suspension is one of the most acceptable dosage forms for pediatric and geriatric patients because of the ease of swallowing and flexibility in administration of doses. Although it has a bitter taste, oral administration is the suitable route for administering Flucloxacillin magnesium. The drug is moisture sensitive that

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leads to chemical stability problems but it can be achieved by formulating the drug as in the form of reconstitutable oral suspension. Reconstitutable oral systems show adequate chemical stability of the drug during shelf life, avoids the physical stability problems related to solubility, pH, and incompatibilities with other ingredients and also reduces the weight of the final product because the aqueous vehicle is absent but requires the addition of water at the time of dispensing (4-5).

The main objective of this present study was to develop and formulate an effective, pleasant and stable Flucloxacillin magnesium reconstitutable oral suspension. This study used to find out the effect of different concentrations of suspending agent like xanthan gum as on the *in vitro* drug release profiles of the formulated suspensions and to overcome the chemical and physical stability problems associated with suspensions.

2. MATERIALS AND METHODS

2.1. Materials

Flucloxacillin Magnesium was obtained from Aurabindo Pharma, India and Xanthan gum (Xantural 75) from CP Kelco USA, Orange and Tutti Frutti flavours from Firmenich SA, India and remaining all obtained from Merck Chemicals, India.

2.2. Compatibility study

Flucloxacillin magnesium was mixed with excipients in different ratios using polybag manually. These mixtures were filled in glass vials and packed properly and exposed to 40°C/75% RH for a period of 4 weeks.

2.3. Development of Flucloxacillin magnesium reconstitutable oral suspension

Different formulations of Flucloxacillin magnesium as powder to be reconstituted were prepared by milling Flucloxacillin magnesium powder with selected suspending agent together with other ingredients mentioned in the table 1. The powder mixture was passed through 600 µm mesh (ASTM #30 sieve). Sucrose (60/200) was milled about two times through 0.5 mm screen using multimill (Neomachine, India) and Saccharin sodium dihydrate, sodium citrate dihydrate were added to the milled sucrose, again milled through 0.5 mm screen using multimill. The above material was divided into two equal parts (part I & part II) and passed through 600 µm mesh (ASTM #30 sieve). Flucloxacillin magnesium, xanthan gum, citric acid anhydrous, sodium benzoate, orange flavour, tutti frutti flavor, aerosil were sifted with part I material through 600 µm mesh (ASTM# 30 sieve). Part I and part II materials were loaded into shear blender (Octogonal Blender, India) and mixed for 30 min. Final blend of Flucloxacillin magnesium powder for oral suspension was filled into bottles.

Table 1. Composition of reconstitutable oral suspension

Ingredient	Quantity per dose (mg)				
	F1	F2	F3	F4	F5
Flucloxacillin magnesium	297.12	297.12	297.12	297.12	297.12
Sodium saccharin dihydrate	15	20	20	25	20
Xanthan gum	2.0	3.0	4.0	8.0	12
Citric acid anhydrous	1.0	1.5	2.0	1.0	3.0
Sodium citrate dihydrate	10	20	17	20	20
Sodium benzoate	25	25	25	25	25
Orange flavour	----	7.5	7.5	7.5	7.5
Tutti frutti flavour	----	----	2.5	5.0	10
Aerosil	----	----	8.0	5.0	10
Sucrose 60/200	3,149.88	3,125.88	3,116.88	3,106.38	3,095.38
Total weight	3, 500	3, 500	3, 500	3, 500	3, 500

2.4. Micromeritic studies

The formulated powder batches for oral suspension were evaluated for their bulk density, tapped density, Carr's index and Hausner's ratio according to the standard procedures (6-8).

2.4.1. Moisture content

The Moisture Content of the powder was determined gravimetrically using Moisture analyzer, A & D company Ltd., India. Approximately 5 gm of powder was uniformly placed onto the sample pan and then the heating cycle was started. The percentage of moisture content was calculated from the weight loss of the sample by heating (9).

2.4.2. Sieve analysis

A series of sieves were arranged in the order of decreasing pore diameter (increasing in sieve number) i.e. sieve numbers #30, #40, #60, #80, #100, #120 and #200. Fifty grams of powder blend was weighed accurately and transferred onto the sieve #30, which was kept on the top. The sieves were shaken for about 5-10 min. Then the drug retained on each sieve were taken, weighed separately and expressed in terms of percentage (10).

2.5. Evaluation of the suspension

The formulated suspension batches were evaluated for the description parameters (color, odor, taste) viscosity, effect of pH changes, sedimentation volume, resuspendability,

deliverable volume, drug content, dissolution rate and stability studies.

2.5.1. Description

The formulated suspensions were analyzed for color and taste.

2.5.2. Viscosity

Viscosity of Flucloxacillin reconstitutable oral suspension was measured by using Brookfield viscometer at 30 rpm using spindle-LV-I. The temperature of the substance being measured must be accurately controlled, since small changes may lead to marked changes in viscosity (11).

2.5.3. pH

It is another important parameter for the suspension stability. The pH determination study was carried out by using digital pH meter (Degisun electronics systems, India). The pH meter was calibrated and the electrode was dipped into the suspension sample, thereby the pH was measured at room temperature.

2.5.4. Sedimentation volume

Formulated suspensions were taken in 100 ml stoppered measuring cylinder individually and shaken vigorously to ensure uniformity, then left undisturbed and the sedimentation volume occurred under the influence of gravity was recorded at the time intervals of 2, 4, 6, 14th day (12). Sedimentation volume (F) was calculated by using the following formula

$$F = Hu/Ho$$

Where,

Hu = Ultimate settled height

Ho = Original height of the suspension

2.5.5. Deliverable volume

Contents of the container were emptied as completely as possible and the mass or volume of the contents was determined. The mass or volume should not be less than amount stated on the label (9).

2.5.6. Density

Density of the formulated suspension was determined by specific gravity bottle method. Specific gravity bottle was cleaned thoroughly, dried, weighed and denoted as W_1. Suspension was filled into the bottle, weighed and denoted as W_2. Then the density of suspension was calculated by mass $(W_2\text{-}W_1)$/volume (9).

2.5.7. Resuspendability

If a pharmaceutical suspension produces sediment on storage, it is essential that it should be readily dispersible on shaking, so that uniformity of dose is assured. Resuspendability of the sediment layer was checked by inversion of cylinder normally to 180^o and number of inversions required to redisperse the sediment layer into pourable suspension was noted (9).

2.5.8. Drug content

An HPLC (Shimadzu, India) method has been used for the quantitative measurement of Flucloxacillin. Mobile phase was composed of potassium dihydrogen orthophosphate and acetonitrile in the ratio of 75:25 v/v. Both the standard and sample solutions of Flucloxacillin were prepared. Sample was reconstituted as directed in label and from this sample equivalent to about 250 mg of Flucloxacillin was transferred into 250 ml volumetric flask. To this, 150 ml of diluent was added and sonicated at room temperature for about 5 min with intermittent shaking and volume was made upto the mark with diluent. Equal volumes (10µl) of standard preparation and sample preparation were injected at the flow rate of 1.5 ml/min into the chromatograph separately, chromatograms were recorded and peak areas were measured

The quantity of Flucloxacillin (mg/5 ml) in suspension was calculated by using the formula.

$$\text{Content of Flucloxacillin} = A_T/A_S \times D_S/D_T \times P/100 \times 453.9/475.9 \times W \times 5$$

Where,

A_T = Average area count of Flucloxacillin peak obtained in chromatogram of sample solution

A_S = Average area count of Flucloxacillin peak obtained in chromatogram of standard solution

D_S = Dilution factor of Flucloxacillin magnesium standard solution

D_T = Dilution factor of sample solution

P = Percent potency of Flucloxacillin magnesium working standard

W= Equivalent weight of the drug

2.5.9. In-vitro dissolution study

USP Paddle method (Electrolab dissolution apparatus, India) was used to study the release of drug for all prepared suspensions and reference suspension. 900 ml of acetate buffer (pH 4.5) was placed in dissolution vessel which was allowed to equilibrate at room temperature of 37±0.5 ^{o}C. A suspension sample equivalent to a typical dose (5 ml) was taken on weight basis using a suitable syringe-cannula system and quantitatively transferred into the dissolution vessel midway between the surface of dissolution medium and the top of the rotating blade. The specific gravity of each sample was determined to express the percentage of drug dissolved

in the sampled volume. 5 ml of sample was withdrawn at 10, 15, 20, 30, 45 min and 5 ml of fresh pH 4.5 acetate buffer was added immediately as replacement. Collected samples were filtered and assayed for percent drug release.

Amount of Flucloxacillin dissolved in dissolution medium was calculated by the formula

Amount of Flucloxacillin dissolved = $A_T/A_S \times D_S/D_T \times P/L \times 453.9/475.9 \times W \times 5$

A_T = Area count of Flucloxacillin peak obtained from sample solution

A_S = Average area count of five replicate injections for Flucloxacillin peak in the chromatograms of standard solutions, as obtained under system suitability.

D_S = Dilution factor of Flucloxacillin magnesium standard solution

D_T = Dilution factor of sample solution.

P = Percent potency of Flucloxacillin magnesium working standard

L = Label claim of Flucloxacillin per 5 ml of suspension in mg.

W = Weight per ml of suspension in grams.

2.5.10. Stability studies

Both dry mixture and reconstituted suspensions were subjected to stability studies according to the ICH guidelines by providing the desired conditions using programmable environmental chamber (REMI, India). Best formulation showing good dissolution profile was selected for stability studies at 25ºC/60%RH, 40ºC/75%RH for 6 months and evaluated for color, viscosity, pH, drug content, drug release at the time intervals of 1, 2, 3, 6 months. At the same time, the stability of the reconstituted suspension has been studied at 2-8ºC for a period of 14 days (13).

3. RESULTS AND DISCUSSION

3.1. Evaluation studies

The formulation development of Flucloxacillin magnesium reconstitutable oral suspension 250 mg/5 ml was done with different concentrations of xanthan gum as a suspending agent. Compatibility studies confirmed that there were no chemical interactions between the drug and excipients (Table 2). Powder blends have been checked for physical characteristics like flow properties (Bulk density, tapped density, compressibility index, Hausner's ratio), moisture content and particle size distribution (Table 3). Formulation F3 and F5 showed acceptable flow properties due to the presence of glidant aerosol in optimum concentration and remaining formulations showed poor flow properties. The moisture content of all five formulations was found to be in the range of 0.49-0.57%. The particle size distribution of five formulations was analyzed and all five formulations showed narrow and uniform particle size distribution. Formulations F3, F4, F5 masked the bitter taste of the drug due to the presence of tutti frutti flavor in addition to the orange flavor and were acceptable when compared to formulations F1 and F2. Formulations F4 and F5 exhibited high viscosity due to the presence of high concentration of xanthan gum. Formulation F3 containing 4 mg of xanthan gum as a suspending is sufficient to remain particles dispersed in the suspending medium for sufficient period of time and also sufficient to withdraw suspension from the container. The viscosity of all formulations ranged between 110-154 cps and formulation F5 showed more than the specified limit i.e. 100-150 cps. The pH of formulations F2, F3, F5 was found to be in the range of 5.18-5.76, which is desirable for the stability of the drug. Formulation F5 has shown maximum value (0.94 closest to 1 as compared to other formulations) of sedimentation volume followed by F4, F3, F2 and F1. Formulations F3, F4, F5 remained homogeneous after reconstitution and did not exhibit any signs of caking. Formulations F1, F2, F3 fulfilled the requirements of the desired deliverable volume. Results of resuspendability showed that F3, F4, F5 were readily redispersed without any signs of caking which might be due to the presence of aerosil. F1 and F2 required more number of inversions to redisperse the sediment layer into pourable suspension. The drug content was found to be in the range of 97-103% for all five formulations and it was present in the specified limit (i.e. ±10%) (Table 4). Different formulations were prepared i.e. F1, F2, F3, F4, F5 in order to study the effect of different concentrations of xanthan gum as a suspending agent on drug release. Among the five formulations, F3 having 4 mg of xanthan gum showed 97.43% of drug release within 45 min. The order of percent drug release at 45 min was F3>F2>F1>F4>F5 with values of 97.43%, 95.11%, 91.73%, 90.61%, 88.91% respectively and it was observed from the results that the amount of xanthan gum was directly proportional to the drug release rate upto 4 mg and beyond that concentration drug release was decreased (Table 5). The present study revealed that the dissolution rate was related to the viscosity of the suspension i.e. viscosity increased with increase in concentration of suspending agent, which in turn decreased the dissolution rate. Formulations F4 and F5 had shown decreased drug release because of formation of high viscosity regions, both in the tightly bound layer surrounding

the drug particles as well as in the bulk dissolution medium due to the hydrated polymer chains causing resistance in the diffusion process. Stability studies were accomplished at two levels, one for the reconstituted suspension for 14 days at 2-5°C (Table 6) and other for dried product for a period of 6 months at 25°C/60% RH and 40°C/75% RH (Table 7). The ageing and temperature are the two parameters, which affect the physical and chemical nature of the formulation. Stability studies carried out at 25°C/60% RH for 6 months, no significant changes in physical properties, drug content and dissolution rate of formulation F3 was observed. Stability studies carried out at 40°C/75% RH showed change of color to yellowish brown, antibiotic content decreased by approximately 5% and modification of the pH beyond the permitted limits which lead to conclusion that product cannot be stored at temperature higher than 25°C. Stability studies at 2-8°C, it was found that the reconstituted suspension will be stable for 14 days, if kept in the refrigerator.

Table 2. Compatibility studies of physical mixtures of Flucloxacillin magnesium

Drug + Excipient	Proportion	Observation		Conclusion
		Initial	4week	
Drug	NA	White	No change	Compatible
Drug + Saccharin sodium	1:10	White	No change	Compatible
Drug + Xanthan gum	1:10	White	No change	Compatible
Drug + Citric acid	1:10	White	No change	Compatible
Drug + Sodium citrate	1:10	White	No change	Compatible
Drug + Sodium benzoate	1:10	White	No change	Compatible
Drug + Orange flavour	1:10	White	No change	Compatible
Drug + Tutti frutti flavour	1:10	Yellowish white	No change	Compatible
Drug + Aerosil	1:10	White	No change	Compatible
Drug + Sucrose	1:10	White	No change	Compatible

Table 3. Evaluation of physical characteristics of powder blend

Formulation	Bulk density* (gm/cc)	Tapped density* (gm/cc)	Compressibility Index (%)*	Hausner's ratio*	*
F1	0.701±0.13	1.023±0.07	31.4±0.16	1.46±0.15	0.57±0.15
F2	0.709±0.05	1.030±0.08	31.1±0.11	1.45±0.36	0.54±0.13
F3	0.716±0.07	0.880±0.15	18.63±0.21	1.23±0.4	0.49±0.61
F4	0.743±0.09	1.032±0.09	28.52±0.31	1.39±0.26	0.52±0.38
F5	0.772±0.14	0.926±.16	16.63±0.18	1.19±0.36	0.54±0.56
			Particle size distribution*		
Sieve size	F1	F2	F3	F4	F5
#30 (600 µm)	1.49±0.43	1.42±0.09	1.53±0.57	1.58±0.18	1.61±0.69
#40 (425 µm)	4.65±0.19	4.96±0.14	4.63±0.59	4.75±0.63	4.32±0.63
#60 (250 µm)	67.12±0.56	66.82±0.36	67.52±0.55	68.24±0.43	69.72±0.73
#80 (180 µm)	84.8±0.5	87.31±0.51	85.13±0.63	85.7±0.47	84.89±0.49
#100 (150 µm)	87.81±0.61	89.14±0.43	88.37±0.43	88.87±0.61	89.32±0.43
#120 (125 µm)	90.82±0.16	94.32±0.31	92.16±0.48	92.04±0.64	91.38±0.56
#200 (75 µm)	95.72±0.37	96.79±0.36	96.57±0.50	96.48±0.69	95.42±0.63
Base	99.44±0.19	99.52±0.54	99.69±0.39	99.65±.58	99.78±0.73

*Results were expressed in mean±SD (n=3)

Table 4. Evaluation of formulated reconstitutable oral suspensions of Flucloxacillin magnesium

Formulation	Viscosity (cps)	pH	Deliverable volume (ml)	Density (mg/ml)	Resuspendability	Drug content (%)	Sedimentation volume (F) (Time in days)				
							0	2	4	6	14
F1	110	4.76	100	1.2072	18 inversions in 16 sec	98.87	1	0.87	0.76	0.69	0.55
F2	128	5.76	100	1.2098	14 inversions in 11 sec	99.12	1	0.89	0.80	0.75	0.66
F3	136	5.25	100	1.2127	10 inversions in 9 sec	103.75	1	0.91	0.82	0.78	0.69
F4	149	5.90	99	1.2860	8 inversions in 7 sec	101.5	1	0.96	0.95	0.93	0.91
F5	154	5.18	97	1.3102	5 inversions in 6 sec	100.4	1	0.97	0.97	0.96	0.94

Table 5. *In-vitro* drug release data of all the prepared suspensions

Formula code	At 10 min		At 15 min		At 20 min		At 30 min		At 45 min	
	Area	% Drug released	Area	% Drug released	Area	% Drug released	Area	% Drug released	Area	% Drug released
F1	3656.42	88.35	3669.39	88.66	3696.32	89.31	3759.04	90.81	3796.21	91.73
F2	3829.42	92.53	3841.03	92.81	3879.12	93.73	3924.38	94.82	3936.21	95.11
F3	3947.04	95.3	3950.14	95.45	3984.91	96.29	4021.26	97.15	4032.36	97.43
F4	3642.12	88.10	3652.33	88.26	3687.01	88.52	3739.08	89.70	3750.10	90.61
F5	3541.06	85.56	3549.12	85.76	3587.01	86.68	3639.12	87.92	3682.14	88.91

Table 6. Stability data of oral suspension stored at 2-8 °C

Parameter	Time in days	
	1st day	14th day
Description	Off white to pale yellow color	Off white to pale yellow color
Viscosity (cps)	136	142
pH	5.25	5.3
Drug content	103.35 %	101.76 %
Dissolution rate	97.4%	94.5%

Table 7. Stability data of dried product stored at 25°C/60% RH and 40°C/75% RH

Parameter	Time in months (stored at 25°C/60% RH)				
	Initial	1	2	3	6
Color	Complies	Complies	Complies	Complies	Complies
Drug content	103.75%	103%	102.75%	102.25%	101.5%
pH	5.25	5.22	5.38	5.28	5.32
Viscosity (cps)	136	136	136	135	135
Dissolution rate	97.4%	97.2%	96.8%	96.5%	96.1%
	Stored at 40°C/75% RH				
Color	Complies	Complies	Complies	Yellowish brown color lumps	Yellowish brown color lumps
Drug content	103.75%	101.5%	100.1%	99.7%	97.5%
pH	5.25	5.36	5.42	5.56	5.82
Viscosity (cps)	136	134	132	130	129
Dissolution	97.4%	96.9%	96.4%	95.8%	94.9%

3.2. Analysis of marketed product (Innovator)

The marketed product FLOXAPEN 250 mg/5ml manufactured by Beecham Pharmaceuticals was evaluated for the parameters like viscosity, pH, sedimentation volume, dissolution and drug content (Table 8). Dissolution profile of F3 was compared with the marketed product FLOXAPEN and experimental results are in very close agreement with the marketed product, hence there is a lot of scope for future *in-vivo* studies (Figure 1).

Table 8. Evaluation of marketed sample FLOXAPEN

Parameter	Observation
Viscosity	132 cps
pH	5.14
Sedimentation volume	0.79
Drug release	98%
Drug content	99.3%

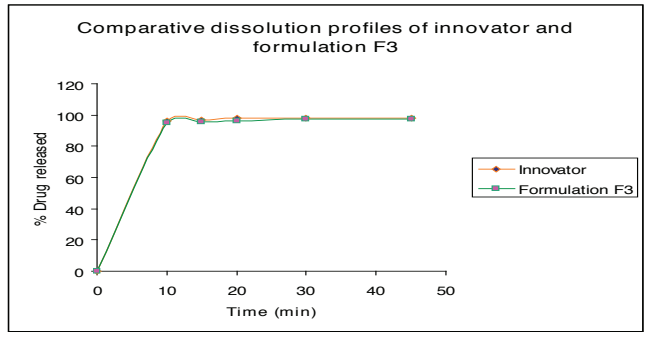

Figure 1. Comparison of dissolution profiles of FLOXAPEN and formulation F3

4. CONCLUSION

It could be concluded from the results that the viscosity of the suspension is proportional to the concentration of suspending agent which in turn decreases the dissolution rate. Formulation F3 containing 4 mg of xanthan gum showed a high dissolution rate with maximum drug release of 97.43% and formulation F5 containing 12 mg of xanthan gum retarded the drug release. Formulation F3 was confirmed as a better formulation as it masked the bitter taste of the drug and showed acceptable results in terms of viscosity, pH, sedimentation volume, resuspendability, drug content and dissolution. Formulation F3 is quite stable with regard to drug content, physical properties and dissolution rate when stored for 14 days at 2-8°C and 6 months at 25°C/60%RH and is comparable to the marketed product.

5. CONFLICT OF INTEREST

The authors report no conflict of interests. The author along are responsible for content and writing of paper.

Flukloksasilin'in yeniden-oluşturulabilen süspansiyonunun geliştirilmesi ve *in-vitro* değerlendirilmesi

ÖZ

Bu çalışmanın amacı süspansiyon ajanı olarak ksantan reçinesi kullanılarak flukloksasilin magnezyum'un stabil yeniden-oluşturulabilen süspansiyonlarını geliştirmektir. Toz karışımı akış özellikleri açısından değerlendirilmiştir ve F3, F4 kabul edilebilir akış özellikleri göstermişlerdir, fakat kalan formüller Kabul edilebilir akış özelliği gösterememişlerdir. İlaç ve yardımcı maddler arasında hiç bir etkileşme yoktur ve bu geçimlilik çalışmaları ile doğrulanmıştır. Yeniden-oluşturulabilen süspansyion renk, tat, viskozite, pH, çökme hacmi, dağıtılabilir hakim, yoğunluk, yeniden-oluşturulabilirlik, ilaç içeriği, ilaç serbestleşmesi ve stabilite açısından değerlendirilmiştir. Formülasyon F3 14 günlük değerlendirme sürecinde 45 dk. Içinde en yüksek serbestleşmeyi göstermiştir, viskozite, pH, ilaç içeriği ve serbesltleşme hızında anlamlı bir değişiklik yoktur. Elde edilen sonuçlardan flukloksasilin magnezyum'un en etkili yeniden-oluşturulabilen süspansiyonunun geliştirildiği sonucuna varılmıştır ve yeniden-oluşturulabilen süspansiyon şekli başarılı bir şekilde değerlendirilmiştir.

Anahtar kelimeler: Antibiyotik, FLOXAPEN, Flukloksasilin magnezyum, Yeniden-oluşturulabilen süspansiyon, Ksantan reçinesi.

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