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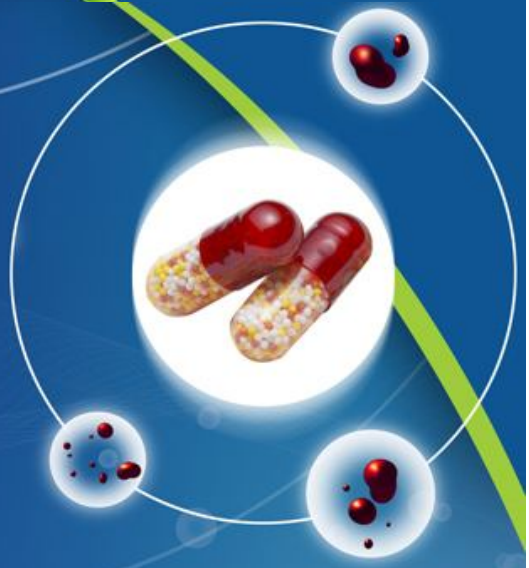

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Research Article

"FORMULATION AND EVALUATION OF ORO-DISPERSIBLE DOXYCYCLINE TABLETS"

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ABSTRACT

The aim for designing these dosage forms, convenient to be manufactured and administered, free of side effects, offering immediate release and enhanced bioavailability, so as to achieve better patient compliance. Though oral drug delivery systems, preferably, tablets are the most widely accepted dosage forms, for being compact, offering uniform dose and painless delivery. Oral drug delivery remains the most preferred route for administration of various therapeutic agents. Novel ODT technologies address many patient and pharmaceutical needs such as enhanced life cycle management to convenient dosing particularly for pediatric, geriatric and psychiatric patients who have difficulty in swallowing (Dysphagia) conventional tablet and capsules. Technologies used for manufacturing of ODTs are either conventional technologies or patented technologies.Orodispersible tablets (ODTs), also known as fastmelt, quick melts, fast disintegrating have theunique property of disintegrating in the mouth inseconds without chewing and the need of water.The present study demonstrated potentials forrapid absorption, improved bioavailability,effective therapy and patient compliance.

***KEYWORDS: ODTs** , Dosage forms,Dysphagia, Efficacy, Pharmaceutical needs.*

INTRODUCTION

An ideal dosage regimen in drug therapy of my disease is the one which immediately attains the desired therapeutic conclusions of drug in plasma and maintain it constant for entire duration of treatment.[1] the drug may be administered by variety of routes of dosage forms. The oral route of drug administration is most popular and has been successfully used for conventional delivery of drugs. It offers the advantage of convenience, ease of administration, greater flexibility in dosage forms design, ease of production and low cost. Hence it is adopted wherever possible. It is probable that at least 90 % of all drug is used to produce systemic effects are administered by oral route.

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The dosage forms available for oral administration are liquid like solution, suspension emulsion & solids like powders, tablets & capsules. The physical state of most of the drug being solid, they are administered in solid dosage forms.[1]

Among the drugs that are administered orally, solid dosage form represents the predefined class of product. They are versatile, flexible in dosage strength relatively stable, present lesser problem in formulation and packaging and it is convenient to manufacture, store handle and use. Solid dosage forms provides best protection to the drug against temperature, humidity, oxygen light and stress during transportation of two solid dosage forms i.e. tablets and capsules. The tablets are in wide use.[2]

Advantages of Oro-dispersible formulation:[7]

- Improved patient compliance is the primary benefit of this technology.

- Administration to patient who cannot swallow and patients who refuse to such as pediatric, geriatric and psychiatric patients.
- No need of water for swallowing the dosage forms. This is highly convenient release for the patients who are travelling or do not have immediate access to water.
- Added benefits of convenience and accurate dosing as compared to liquids.
- More rapid dry absorption through pre-gastric absorption from the mouth, pharynx and esophagus.
- Easily portable and suitable for transportation by patients.
- The fast dissolving dosage forms combines the benefit of liquid formulation with those of solid oral dosage forms.
- A wide range of drug can be considered as a candidate for this dosage forms.

Eg: Antipyretic, anti inflammatory agents, antibiotics, anti asthmatic agents, diuretics, anti arrythmatic, anti hypertensive.

Disadvantages of Oro-dispersible formulation:[7]

- Delayed absorbed at specific site cannot be given in these dosage forms.
- These tablets show high friability, less hardness than conventional tablets.

Basic approaches of designing ODT: [8]

To ensure the Tablet fast dissolving attribute. Water must quickly egress into the Tablet matrix to cause rapid disintegration and instantaneous dissolution of the Tablet. This can be achieved by,

- Maximizing porous structure of the Tablet matrix
- Incorporating the appropriate disintegrating agent.

LIST OF CHEMICALS USED

Sr.NO	Materials	Suppliers
1	Doxycycline Hyclate	Diamond Corporation
2	Dextrose	Diamond Corporation
3	Magnesium Hydroxide	Diamond Corporation
4	Aspartame	Diamond Corporation
5	Polyvinyl pyrolidone K30	Diamond Corporation
6	Sunset yellow	Diamond Corporation
7	Isopropyl alcohol	Yaksh pharma
8	Lactose monohydrate powder	K.P. Manish Global Ingredients
9	Sodium starch glycolate	Diamond Corporation
10	Aerosil	Siddhi Pharmachem
11	Crosprovidone(Poly plasdone XL)	Indo Chemicals Corporation
12	Sodium Lauryl sulphate	Diamond Corporation
13	Flavor strawberry	Diamond Corporation
14	Indion 234	Diamond Corporation
15	Magnesium stearate	Diamond Corporation

LIST OF INSTRUMENT USED

Sr. No	Instruments	Make and model
1.	Analytical balance	Shimadzu, Japan
2.	pH meter	Elico
3.	Dissolution apparatus	Electrolab, USP TDL-08L, India
4.	Disintegration tester	Electolab, Chennai
5.	Friability test apparatus	Electolab, Chennai
6.	Vernier callipers	Electolab, Chennai
7.	Hardness tester	Veego
9.	UV-Visible Spectrophotometer	Shimadzu -1601, Japan
10.	23 Station Rotary tablet compression machine	Cadmach, India
11.	FTIR Spectrophotometer	Shimadzu corporation
12.	Stability chamber	Osworld, Mumbai
13.	Differential Scanning Calorimetry	DSC 60, Japan

METHODS

METHODS

PREFORMULATION STUDIES

Organoleptic Properties

The drug (Doxycycline) powder was examined for its organoleptic properties like colour and odour.The sample of Doxycycline was identified from its organoleptic properties.This was shown in table 1.

IR Spectroscopy

The spectrum of the Doxycycline shows the following functional groups at their frequencies.The IR spectrum of pure drug was found to be similar to the standard spectrum of Doxycycline. The results was shown in Table 2 and figure 1& 2.

Solubility study

It is easily water soluble. The Procedure was- Sample of Doxocycline was taken and checked for its solubility as per the standards of Pharmacopoeia. The results was-

- Soluble in water.
- Soluble in solutions of alkali hydroxides and carbonates.
- Freely soluble in methanol.
- Slightly soluble in alcohol.
- Practically insoluble in chloroform and in ether.

Melting point determination

Melting point of the drug was determined by taking an appropriate amount of the Doxycycline Hyclate in a capillary tube closed at one end. It was placed in Thiele's melting point apparatus and the melting point was noted. Average of three readings was taken.[46]The melting point of Doxycycline Hyclate was found to be 201 ^{0}c, which meet Pharmacopoeial standards.

Partition Co-efficient

The results of partition coefficient determination carried out in n-octanol saturated with acidic buffer (pH 1.2) and n-octanol saturated with phosphate buffer (pH 7.4). The Log P values of prodrugs were found to be higher than the parent drug in both pH. The study showed that the major fraction of the prodrugs was partitioned towards the organic phase. High partition coefficient of synthesized prodrug as compared to the parent drug indicates the increase in lipophilicity of the compound. This may lead to the higher absorption of the compound through lipoidal cell membrane. The results of partition coefficient determination were 1.86.

UV Spectroscopy

Determination of λmax

A solution of 10 µg/ml Doxocycline was prepared in 6.8 pH Phosphate buffer and UV spectrum was taken using Shimadzu UV-1601 UV/Vis double beam spectrophotometer. The UV maxima of Doxocycline was found to be 276 nm in 6.8 pH Phosphate buffer. Spectrophotometric method based on the

measurement of absorbance at 276nm of UV region in water was used for the estimation of Doxycycline Hyclate.

Preparation of standard calibration curve of ACECLOFENAC

Preparation of stock solution No. I

Doxycycline Hyclate (50 mg) was dissolved in 50 mL of water. Then from this 1 mL solution was taken and diluted up to 10 mL with water. The concentration of this stock-I solution is 100 µg/ml.

Preparation of stock solution No. II

After preparation of stock I solution from this 1, 2, 3, and 4ml aliquots were withdrawn and diluted up to 10 ml with water to get subsequent concentrations of 5, 10, 20, 30 and 40µg/mlsolutions respectively. Wavelength scan of 20µg/ml Doxycycline Hyclate was carried out in the range of 200 to 400nm and sharp peak was obtained at 276 nm. This λ max 276 nm was used for measurement of further concentration of Doxycycline Hyclate against blank and average of three determinants was taken. The linear regression analysis was carried on absorbance data points. A straight line equation (Y = mx + C) was generated to facilitate the calculation of amount of drug.[39]

Absorbance = Slope × concentration + intercept

FORMULATION DESIGN

Preparation of Oro-dispersible tablets of Doxycycline Hyclate:

Wet granulation method was used for preparation of Oro-dispersible tablets of Doxycycline Hyclate. Formulation F1, F2, F3, F4, F5, F6, F7, F8 and F9 were prepared by accurately weighed quantities of divided in to 3 Parts.

Part-A:

- Doxycycline Hyclate, Dextrose, Magnesium hydroxide and Aspartame all these materials are mix and these materials were passed through sieve no. 40.
- Polyvinyl pyrrolidone and Isopropyl alcohol are mix.

Then mixture 1 and 2 are mixed and materials were dry for 15 minutes.

Part-B:

- Lactose monohydrate powder and sodium starch glycolate these materials are mix.
- Polyvinyl pyrrolidone, Sunset yellow and Isopropyl alcohol are mix.

Then mixture **1** and **2** are mix,and materials were dry for 15 minutes.

Then mixture **I** and **II** are mix and these materials were passed through sieve no. 20.

Part-C:

Aerosil, crospovidone, Sodium lauryl sulphate, Strawberry flavor and Indion 234 are mix and these materials passed through sieve no. 60.

Then again these mixture**III** and **IV** are mix Then these materials are bulk formation.

Before compression above 2 minutes add magnesium sterate in materials **(V)** and then these materials are mix properly and then after compressed. Tablets were compressed by using 23 Station Rotary tablet compression machine (Cadmach).

EVALUATION STUDIES

EVALUATION OF POWDER BLEND [47,49,50]

Angle of repose

The angle of repose of powder blend was determined by the funnel method. The accurately weight powder blend were taken in the funnel. The height of the funnel was adjusted in such a way the tip of the funnel just touched the apex of the powder blend. The powder blend was allowed to flow through the funnel freely on to the surface. The diameter of the powder cone was measured and angle of repose was calculated using the following equation.

$$\tan \theta = h/r$$

Where, h and r are the height & radius of the powder cone.The results were shown in the table 4.

Bulk and tapped density

Both loose bulk density (LBD) and tapped bulk density (TBD) was determined. A quantity of 10 gm of powder blend from each formula, previously shaken to break any agglomerates formed, was introduced in to 100 ml measuring cylinder. After that the initial volume was noted and the cylinder was allowed to fall under its own weight on to a hard surface from the height of 2.5 cm at

second intervals. Tapping was continued until no further change in volume was noted. LBD and TDB were calculated using the following equations.The results were shown in the table 4.

LBD= Weight of the powder blend/Untapped Volume of the packing

TBD=Weight of the powder blend/Tapped Volume of the packing

Compressibility Index

The Compressibility Index of the powder blend was determined by Carr's compressibility index. It is a simple test to evaluate the LBD and TBD of a powder and the rate at which it packed down. The formula for Carr's Index is as below:

Carr's Index (%)=[(TBD-LBD) x100]/TBD

The results were shown in the table 4.

EVALUATION OF TABLETS [13, 14, 15]

Weight variation test

To study weight variation twenty tablets of the formulation were weighed using a Sartorius electronic balance and the test was performed according to the official method.

Drug content

Drug content study of Oro-dispersible tablets were carried out by 5 tablets of formulations were weighed and powdered. A quantity of powder equivalent to 250 mg of Doxycycline Hyclate was taken. The amount of drug present in a 50 mg equivalent amount of powder was determined by dissolving the powder mixture in 100 mL of water, from that removed 5mL solution and UV absorbance was measured at 276 nm. Drug concentration was calculated from formula**.** Average three determinations were taken.

Hardness

The hardness of ten tablets was determined using the hardness tester and the average values were calculated.

Thicknesses and Diameter

The thickness and Diameter of the tables was determined by using vernier calipers. Five tablets were used, and average values were calculated.

Disintegration time

Six tablets from each batch were randomly selected and *in-vitro* disintegration time of tablets was determined by using tablet disintegration apparatus. *In-vitro* disintegration test was carried out at 37± 2°C in 900 ml distilled water.

Friability

The friability of tablets was measured by roche friabrator and average values were calculated.

Wetting time:[24]

A piece of tissue paper (12cmx10.75cm) folded twicewas placed in a Petri dish (10 cm diameter) containing 10 ml of water. Containing Eosin, a water soluble dye, was added to Petri dish. A tablet was carefully placed on the surface of the tissue paper and allowed to wet completely. The time required for water to reach upper surface of the tablet was noted as a wetting time.

These results was shown in table 5.

In Vitro dissolution studies [53]

The *in-vitro* dissolution study of oro-dispersible tablets of Doxycycline Hyclate were carried by using USP apparatus type II (Electrolab 8L). The study was perform in water 900mL volume of dissolution media, temperature was maintained at 37 ±0.1^{0}C.The paddles were rotated at 75 rpm, aliquots of sample 1mL were withdrawn at every 10 min time intervals for 30 min. Same volume of 1mL was replaced with drug free water maintain the sink condition. After suitable dilution dissolution of Doxycycline Hyclate was estimated by UV spectrophotometrically (Shimadzu) at λ max 277 nm against blank. Results shown in table 6 & 7.

RESULTAND DISCUSION

The oro-dispersible tablets of Doxycycline Hyclate were formulated and evaluated.The following results was found of Water dispersible tablets of Aceclofenac.

Table 1 API Characterization

Colour	Pale Yellow
Taste	Bitter
Smell	Aromatic smell
Touch	Hygroscopic

Table 2 FTIR interpretation of Doxycycline Hyclate

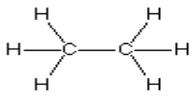
Found value	Functional group
1550.36	C=C Aromatic bond
1454.12	C-O bonding
1312.45	C-N bond
1223.04	- C-O
991.77	

Table 3 Standard calibration curve of ACECLOFENAC in 6.8 pHPhosphate buffer

Sr. No.	Conc. (µg/ml)	Absorbance*	Regression analysis
1	0	0	Slope = 0.058
2	5	0.079	Intercept =0.001
3	10	0.150	
4	20	0.310	Correlation coefficient = 0.998
5	30	0.460	
6	40	0.590	

Table 4 Formulation for the Oro-dispersible tablet

Ingredient	Formulation Codes								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
Part-A									
Doxycycline Hyclate	50	50	50	50	50	50	50	50	50
Dextrose	49.8	49.5	49.2	49.8	49.5	49.1	49.2	49.3	48.1
Magnesium Hydroxide	11.202	10.3	10.1	10.2	10.3	11	10.1	10.4	10.22
Aspartame	8	8.1	7.9	7.8	8.1	8	8.2	8	8.1
Polyvinyl pyrrolidone K30	4.5	3.8	3.95	4.2	3.8	4.1	3.95	3.655	4.4
Isopropyl alcohol	40	50	45	35	40	40	35	40	34
Part-B									
Lactose monohydrate powder	99.5	98.805	99.125	98.632	99.125	98.2	99.2	99.5	99.1
Sodium starch glycolate	13.5	13.1	13.603	13.25	13.603	13.5	13.8	13.4	13.6
Polyvinyl pyrrolidone K30	2.2	2.2	2.1	2.2	2.1	2.2	2.4	2.05	2.2
Sunset yellow	0.098	0.095	0.097	0.098	0.097	0.098	0.098	0.095	0.095
Isopropyl alcohol	20	20	18	22	20	20	18	20	18
Part-C									
Aerosil	9	7.9	7.95	7.97	9	7.9	9	7.8	7.98
Crosprovidone	13.5	18.8	18.795	18.55	15.67	18.202	15.152	18.5	18.8
Sodium Lauryl sulphate	6.8	6.4	6.03	6.05	6.8	6.5	6.8	6	6
Flavor strawberry	9.3	9.7	9.8	9.7	9.5	9.8	9.7	9.8	9.7
Indion 234	7.2	6.6	6.7	6.8	7.2	6.7	7.2	6.7	6.8
Magnesium stearate	5.2	4.7	4.65	4.75	5.2	4.7	5.2	4.8	4.9

Table 4Micromeritic properties of powder blend of Batches

Formulation code	Angle of repose*(^{0})	Bulk density* (gm/ml)	Tapped density* (gm/ml)	Carr's index (%)	Hausner's ratio
F1	31.16±0.55	0.326±0.004	0.392±0.04	16.88±1.21	1.21±0.02
F2	31.69±0.72	0.315±0.005	0.394±0.003	19.96±0.78	1.24±0.015
F3	31.98±0.91	0.339±0.014	0.396±0.016	14.03±0.48	1.17±0.005
F4	29.66±0.98	0.332±0.030	0.400±0.020	16.86±0.50	1.20±0.077
F5	31.27±1.06	0.342±0.009	0.413±0.010	17.93±1.69	1.20±0.015
F6	31.05±0.92	0.344±0.007	0.400±0.012	14.04±1.21	1.16±0.017
F7	31.19±.041	0.357±0.035	0.424±0.050	18.99±1.01	1.22±0.01
F8	33.28±1.11	0.363±0.016	0.443±0.028	14.01±0.87	1.21±0.115
F9	33.25±1.02	0.336±0.017	0.425±0.024	14.11±0.85	1.22±0.116

Table 5 Evaluation parameter of tablets

Batch	Weight variation test (%)	Thickness (mm)	Hardness (kg/cm^2)	Friability (%)	Diameter (mm)	D.T (sec)	Drug content (%)
F1	200±5%	8.80±0.03	3-4	0.75%	2.69±0.2	26	99.23
F2	200±5%	8.80±0.03	5-6	0.77%	2.79±0.2	29	94.91
F3	200±5%	8.80±0.03	3-4	0.78%	2.70±0.2	34	97.34
F4	200±5%	8.80±0.03	5-6	0.69%	2.80±0.2	37	100.23
F5	200±5%	8.80±0.03	3-4	0.81%	2.69±0.2	49	99.64
F6	200±5%	8.80±0.03	5-6	0.85%	2.78±0.2	48	98.26
F7	200±5%	8.80±0.03	5-6	0.68%	2.80±0.2	37	100.42
F8	200±5%	8.80±0.03	3-4	0.82%	2.68±0.2	49	98.64
F9	200±5%	8.80±0.03	4-5	0.84%	2.76±0.2	44	98.26

Table 6 Effect of polymer concentration on drug dissolution profile

S. NO	Time(min)	%CDR
1	0	0.00
2	2	15.58
3	4	28.15
4	6	31.83
5	8	53.86
6	10	72.88
7	12	85.82
8	15	89.96

Table 7 Effect of SLS concentration on dissolution ofDispersible Tablets

Time (min)	%CDR Batch-F2	%CDR Batch-F5	%CDR Batch-F7	%CDR Batch-F9
0	0.00	0.00	0.00	0.00
2	15.58	16.16	16.81	17.35
4	28.15	33.22	34.31	35.40
6	41.83	40.45	44.81	56.75
8	53.86	56.07	59.76	68.73
10	72.88	63.55	69.08	81.26
12	79.82	74.72	86.10	94.07
15	79.96	83.48	90.15	95.80

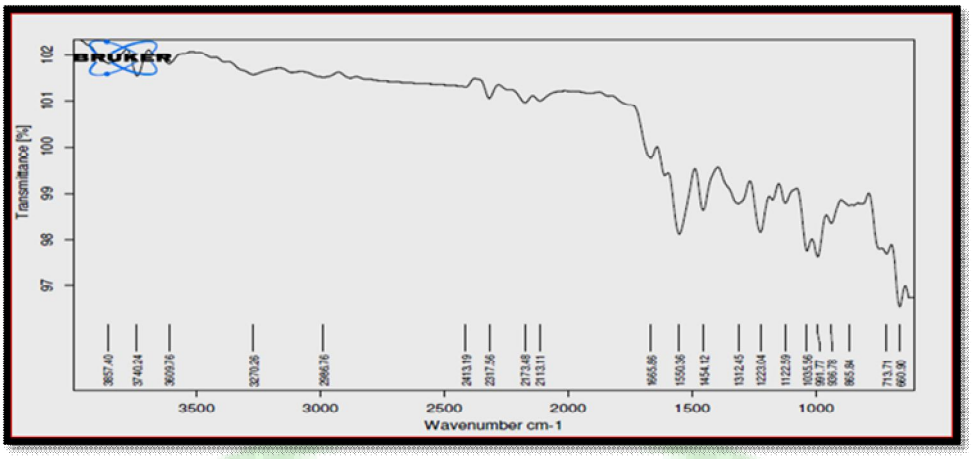


Figure 1 FTIR of Pure drug

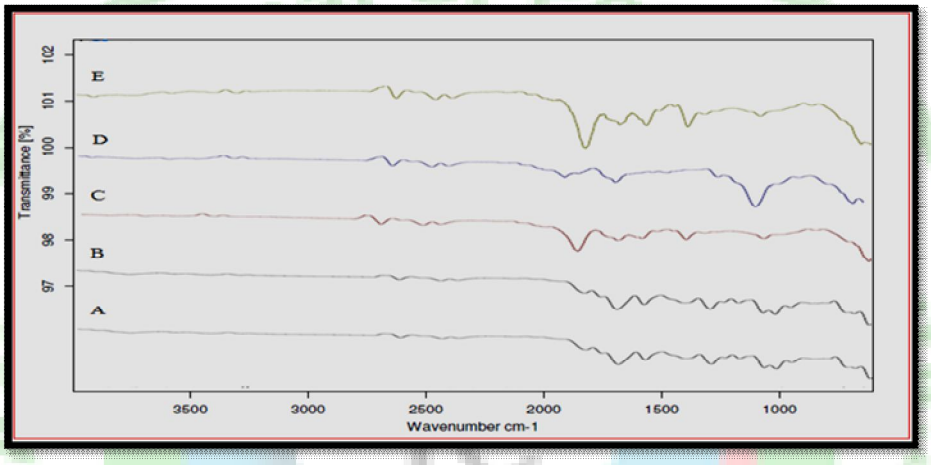


Figure 2 FTIR of drug with excipients

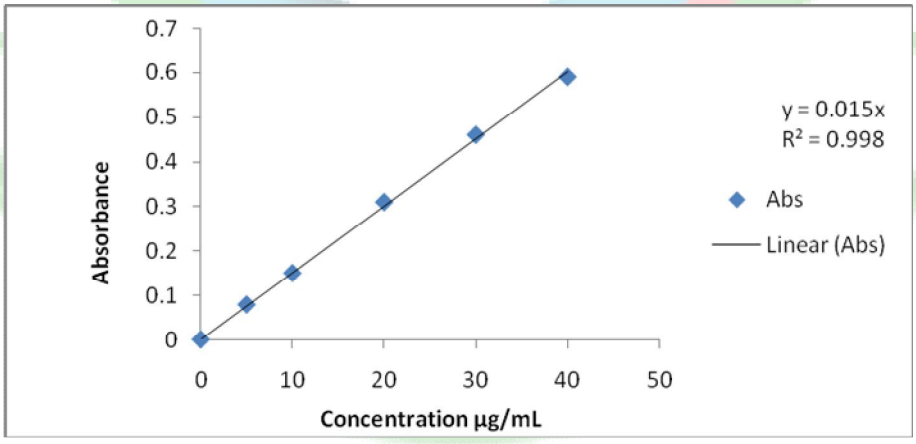


Figure 3 Standard Calibration curve of Doxycycline Hyclate

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