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Design and Evaluation of Doxofylline Immediate Release Tablets

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ABSTRACT

Doxofylline a bronchodilator and anti-tussive is used for chronic obstructive pulmonary disease (COPD) and asthma that acts as phosphor diesterase inhibitor with minimum cardiovascular side effects due to low affinity foradenosine receptors (both A1 and A2) unlike theophylline and other xanthine derivatives. Doxofylline is water soluble and comes under biopharmaceutical classification class III with high solubility and low permeability. In this study an attempt has been made in development and to evaluate the formulation of Doxofylline tablets of 400mg and these compressed tablets were tested for friability, thickness, disintegration time, hardness, weight variation and assay. The formulation trial F4 was optimized considering the drug release profile and the disintegration time of tablets as they were very close to the reference product values. From this study, it may be concluded that for Doxofylline tablets, F4 stands as a successful formulation and can be manufactured with reproducible characteristics from batch to batch to match the release profile with the reference product. The in-vitro release of Doxofylline tablets was studied in 900 ml of distilled water as dissolution medium using an I.P dissolution paddle assembly at 100rpm and 37±2°C for 45min.

Keywords: Doxofylline tablets, Micro crystalline cellulose, HPLC, Antiasthmatic

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INTRODUCTION

Administration of medications can be possible through numerous routes. Regardless, oral route of administration is most helpful route to administration of drugs for fundamental impact contrasted with different routes of administration. Oral medications are considered as the first investigated in the discovery and development of pharmaceutical active ingredients and pharmaceutical formulations, due to ease of administration, cost effective manufacturing, and patient acceptance. Bronchial asthma is a critical issue, particularly in developing nations. Over the most recent couple of decades, asthma has demonstrated an expanding commonness influencing kids and youngsters. It involves both inflammation and bronchoconstriction and hence the treatment of asthma aimed at reducing inflammation and bronchoconstriction. In India asthma is assessed to associate with 338% in youngsters and 212% among grownups, common stinkers. For the treatment of Asthma and COPD, Xanthine derivatives are utilized since an extensive period of time. Doxofylline is a xanthine subsidiary. It works byt here strain of phosphodiesterase and furthermore utilized for upkeep treatment in patients enduring with asthma and unending obstructive pneumonic ailment (COPD). Doxofylline is widely metabolized in liver by demethylation and oxidation to a degree of 80-90% and half plasma protein bound Elimination half-life(t½) is around 67 hour and day by day measure ments is 200-400mg a few times in multiday. Doxofylline goes underclass III of BCS arrangement and water dissolvable.

METHODS AND MATERIALS

Materials

Doxofylline (Biocon Ltd.,), Microcrystalline Cellulose (Viajy Enterprises), Lactose(Ramesh Trading Co.,),Sodium Starch Glycolate (Amishi Drugs & Chemicals Ltd.,), Colloidal Silicon dioxide (Cabot Sanmar Ltd.,), Isopropyl Alcohol (Nikitha Chemicals), Polyvinyl Pyrrolidone K-30 (Kollidone) (Ramesh Trading Co.,), Talc (GangotriIorganicsPvt Ltd.,), Magnesium Stearate (Global Medicines Ltd.,)

Methods

Construction of calibration curve

Doxofylline can be quantatively analyzed by various techniques. In the present study, doxofylline was estimated by U.V. spectrometric method.

Procedure:

An accurately weighed quantity of Doxofylline (100mg) was dissolved in 100ml of distilled water to generate stock solution having concentration of 1mg/ml. 1ml of stock solution was further diluted to 100ml to produce standard solution was further diluted to 100ml to produce standard solution having a concentration of 10mcg/ml. from this, 1, 2, 4, 6 and 8ml were taken and diluted to 10ml. it gives various concentrations of 1, 2, 4, 6 and 8mcg/ml respectively. The absorbances of the solutions were measured at 273nm against blank (distilled water) using U.V-Visible spectrometer.

PERFORMULATION STUDIES

Performulation testing is the first step in the rational development of the dosage forms. It can be defined as an investigation of physical and chemical properties of drug substance alone and combined properties of a drug substance alone and combined with excipients.

The objective of performulation testing is to generate information useful to the formulator in developing stable and bioavailable dosage forms that can be mass produced.

The use of performulation parameters minimizes the chances in formulating an acceptable, safe, efficacious and stable product and at the same time provides the basis for optimization of the drug product quality

The preformulation scientists must consider the following :

- Available pharmacokinetic data
- Anticipated dose
- Nature of the information of the formulator should have or would like to have.

Determination of the densities:

Apparent bulk density(bulk):

Bulk density is the ratio of the given mass of powder to its bulk volume. The bulk density, as a measure used to describe packing materials or granules, was determined transferring the accurately weighed amount of powder sample to the granulated cylinder with the aid of the funnel. The powder was leveled carefully without compacting and the unsettled apparent volume (V_0) was noted. The bulk density in g/ml was calculated by formula

$$\textbf{Bulk density} = M/V_0$$

Where M = weight of the sample taken

Tapped density:

After noting down the volume (V_0) in the bulk density testing, the graduated cylinder was tapped mechanically using a suitable tapped density tester density tester that provides a fixed tap of 14 ±

2nm at 300 drops per minute, for 500 times initially and tapped volume (V_a) was measured to the nearest graduated unit. The tapping was repeated for an additional 750 times and tapped volume was measured to the nearest graduated unit**.** The tapping was repeated of an additional 750 times and tapped volume (V_b) was measured to the nearest gratitude unit.If the difference between the two measurements is <2%, $V_b$is the final tapped volume (V_f). If the difference is >2%, the tapping was repeated at the increments of 1250 taps until the difference between the two successive measurements is <2%.The tapped density, in g/ml was calculated by the formula

$$\textbf{Tapped density} = M/V_f$$

Where M = weight of the sample taken for bulk density testing

Carr's Index (% compressibility):

The compressibility and hausner's ratio are the measures of the propensity of a powder to be compressed. As such, these are the measures of relative importance of inter particulate interaction. In a free flowing powder, such interactions are less significant and the bulk and tapped densities will be closer in value. For poor flowing materials, the bulk and tapped densities will be observed. These differences are reflected in the compressibility index and the Hausner's ratio. Based on the apparent bulk density and the tapped density, the percentage compressibility of the bulk drug was determined by using the following formula

$$\%\textbf{Compressibility} = \frac{Tapped\ density - Bulk\ density}{Tapped\ density} \times 100$$

Hausner's Ratio:

The ratio of tapped density to the bulk density of the powders is called the Hausner's Ratio

$$\textbf{Hausner's Ratio} = \frac{Tapped\ density}{Bulk\ desnity}$$

The following table shows the acceptance criteria for flow properties of the compound according to USP.

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

Formulation of tablets:

Table.1.Formulation trials:

S.no	Ingredients	Formulation (mg)				
		F1	F2	F3	F4	F5
1.	Doxofylline	400	400	400	400	400
2.	Micro crystalline cellulose	87	85	75	80	85
3.	Lactose	39	34	34	34	35
4.	Sodium starch glycolate	20	20	25	20	20
5.	Colloidal silicon dioxide	9	8	8	8	9
6.	Isopropyl alcohol	QS	QS	QS	QS	QS
7.	PVP K-30	12	25	25	25	18
8.	Sodioum starch glycolate	23	18	23	23	23
9.	Colloidal silicon dioxide	7.2	7.2	7.2	7.2	7.2
10.	Talc	20	20	20	20	20
11.	Magnesium stearate	3	3	3	3	3

Post Compression Parameters

Evaluation of tablets

The tablets were subjected to the following quality control tests

Physical appearance

As one of the quality control procedures, tablets should be inspected for smoothness, absence of chips and other undesirable characteristics. If they are colored, this would include examination of mottling and other evidence of non-uniform color distribution except where they are used intentionally.

Weight variation

Approximately 20 tablets were randomly selected from each formulation and their average weight was calculated using digital balance. Individual weight of each tablet was also calculated using the same and compared with average weight

Hardness

The hardness test is performed to measure the tablet strength. Tablet should be hard enough to withstand packing and shipping. Schluenzier hardness tester was used for the determination of hardness of tablets. Place the tablets between the jaws for each measurement; orient the tablet in the same way with respect to the direction of the application of the force . Carry out the measurement on 10 tablets, taking care that all fragments of the tablets have been removed before each determination

Thickness and diameter

The dimensional specifications like diameter and thickness can be accomplished by the use of vernier calipers. The thickness of the tablet is mostly related to the tablet hardness and can be used as an initial control parameter.

Friability

The friability test gives an indication of the ability of the tablets to resist chipping and abrasion on handling during packaging and shipping. Usually for conventional tablets, friability value of 1.0% or less desirable. The weight of 20 tablets was determined and then they were placed in the Roche friabilator, which makes 100 revolutions at 25rpm. The tablets were then removed, dedusted and reweighed. The friability is expressed as the loss of weight and it is calculated as a percentage of the initial weight.

$$\%\text{Friability} = (1\text{-}W/W_0) \times 100$$

Where, W = initial weight of 20 tablets, W_0 = weight of 20 tablets after 100 revolutions

For compressed tablets, the loss less than 1% in weight are generally considered acceptable.

Disintegration test

The disintegration time is considered to be one of the important criteria in selecting the best formulation. It is a measure of the time required for a group of tablets disintegrates into particles which will pass through a 10 mesh screen. Generally, the test is useful as a quality assurance tool for conventional dosage forms.

One tablet each was placed into 6 tubes of the basket rack assembly of disintegration tester water maintained at 37± 2^{oC} and the apparatus was operated for 30 sec. If one or two tablets fail to disintegrate, the teat is repeated using 12 tablets. The requirement is meant if not less than 16 of the total of 18 tablets tested disintegrate. For conventional tablets, the B.P. requires that the tablets disintegrate in 15min.

Dissolution test

The dissolution test measures the rate of release of the drug from the dosage form in-vitro; it is usually expressed as extent of dissolution occurring after a given time under specified conditions. For effective absorption of oral solid dosage form, simple disintegration of the dosage form is not adequate and the dissolution of the drug into surrounding medium plays the vital role. Though dissolution is not a predictor of the therapeutic efficacy it can be looked upon a tool.This can provide valuable information about biological availability of the drug and batch consistency. Dissolution is considered as one of the drug and batch to batch consistency. Dissolution is considered as one of the important quality control tests performed for pharmaceutical dosage form.

Standard preparation

An accurately weighed quantity of about 0.100gms of doxofylline working standard was transferred into a 100ml volumetric flask and 70ml of dissolution medium was added and sonicated to dissolve the content. The volume was made up to the mark with dissolution medium and mixed well. 1ml of this solution was diluted to 50ml with dissolution medium.

Method:

The absorbance of the standard preparation and sample were measured in a UV Visible spectrophotometer at 273nm using dissolution medium as a blank. The release of Doxofylline in the % with respect to label claim was calculated using the following expression-

Calculation: %per tablet

$$\frac{AT}{AS} \times \frac{WS}{100} \times \frac{1}{50} \times \frac{900}{1} \times \frac{100}{5} \times \frac{P}{100} \times \frac{100}{400} = \_\_\_\_\_\%$$

Where AS = absorbance of standard solution, AT = absorbance of sample solution

WS = weight of Doxofylline working standard (WS) taken for standard preparation in gms, P = %potency of Doxofylline WS on such basis

Assay/drug content (By HPLC)

Reagents:

HPLC grade acetonitrile, Milli Q water, Doxofylline working standard, Chromatographic conditions, **Mobile phase:** a filtered and degassed mixture of water, acetonitrile in the ratio of 85:15, **Column:** C8, 4.6mm×250, 5µ, **Wavelength:** 273nm, **Flow rate:** 1.3ml/min, **Load:** 10µL, **Run time:** 25min

Standard preparation 50mg of doxofylline WS was taken in 100ml of volumetric flask and made up to the volume with distilled water

Sample preparation

About 620mg of tablet powder (equivalent to 400mg) was weighed, placed in a 200ml volumetric flask, shaken well and made up to the volume with water. After 30min, the contents of the flask were centrifuged at 500rpm for 15min. then, 5ml of the supernatant was taken and diluted to 20ml with distilled water.

Procedure

Both the standard and the sample preparations were separately injected into the liquid chromatograph and the peak areas were recorded.

Calculation:

$$\frac{At}{As} \times \frac{Sw}{100} \times \frac{200}{Tw} \times \frac{20}{5} \times \frac{P}{100} \times \text{Avg wt}$$

Where ,

At = peak area due to doxofylline in sample preparation.

As = peak area due to doxofylline in sample preparation.

Sw = weight of doxofylline WS taken in mg.

Avgwt = average weight of tablet in mg

P = purity of doxofylline WS used.

Stability studies

The finalized formulations will be packed in suitable packaging like blisters and strips and the they will be kept at different temperatures, humidity conditions to check the stabilities as per ICH guidelines and the samples will be analyzed for their physical and chemical properties.

The selected trial (F4) tablets were packed in PVC/ Aluminum blisters pack and placed in stability chambers of 25^{oC}/ 60%RH, 40^{o}C /75% RH. The samples were withdrawn and analyzed as per stability protocol.

RESULTS AND DISCUSSION

Table.2.Calibration curve data of Doxofylline

S.no	concentration (mcg/ml)	Absorbance At 273nm
1.	0	0.00
2.	1	0.0374
3.	2	0.0743
4.	4	0.1484
5.	6	0.2232
6.	8	0.296

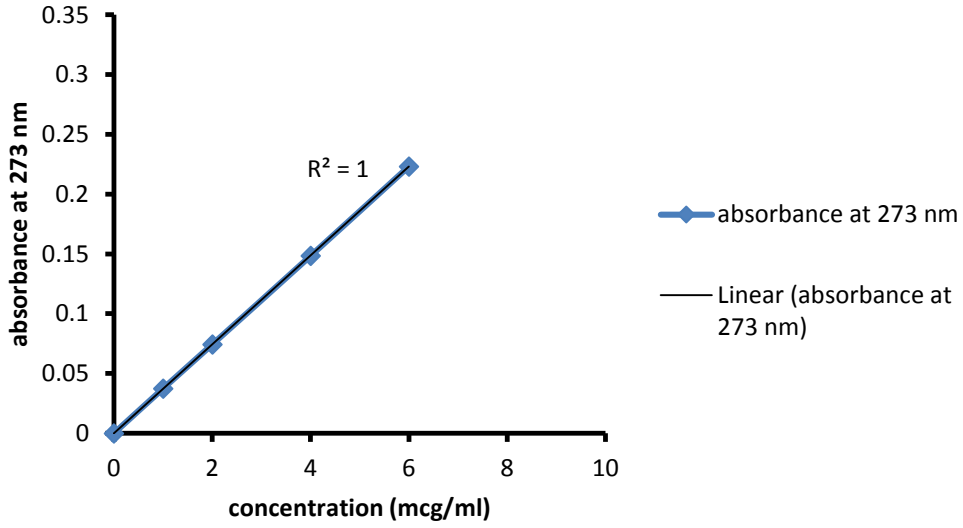
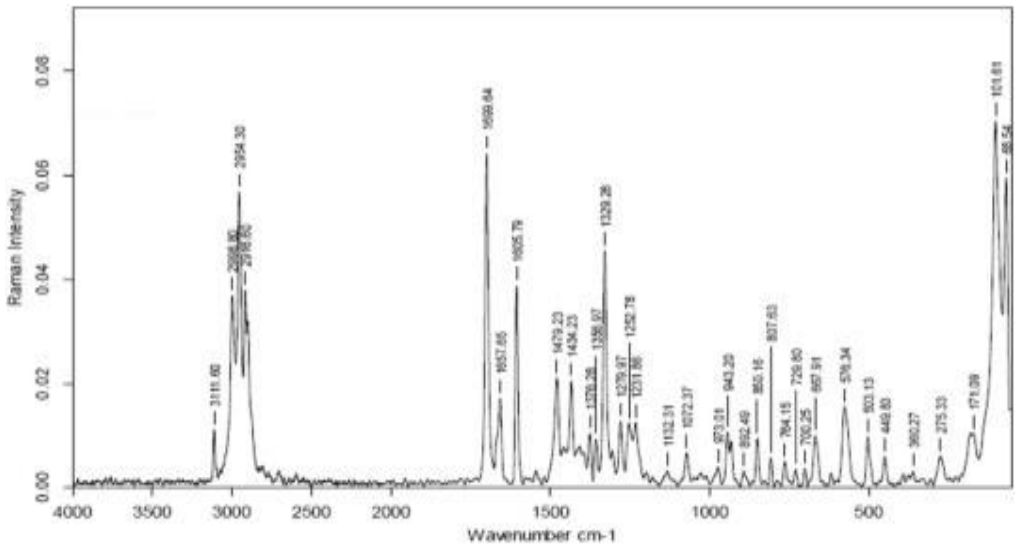


Figure 1:Calibration curve data of Doxofylline

Drug excipient compatibility study

Presence of any in compatibility between drug and excipients/polymers can be predicted by FTIR study. The spectra clearly showed the absence of any possible interactions between the drugs and excipients which was confirmed by the presence of characteristic peaks.



Pre-compression studies

The values of pre-compression parameters evaluated were found to be within the prescribed limits and indicated good free flowing property of the formulations.

Table.3. Pre-compression parameters of formulations

Formulation	Bulk Density (mg/ml)	Tapped Density (mg/ml)	Carr's Index (%)	Hausner's Ratio	Lod	Assay
F1	-	-	-	-	-	-
F2	0.587	0.786	25.31	1.339	1.9	99.46
F3	0.562	0.743	24.36	1.322	1.8	99.62
F4	0.5264	0.689	23.68	1.309	1.8	101.62
F5	0.59	0.733	19.51	1.242	1.8	99.22

Post compression studies

The data obtained for post compression parameters such as appearance, average weight, weight variation, thickness, hardness, diameter, friability, disintegration and assay.

In all the formulations, friability value was less than 1% indicating that the tablets formulated are mechanically stable. All the tablets passed the weight variation test as the percent weight variation was within specified limit.

The present investigation was undertaken to formulate Doxofylline tablets by wet granulation method for the treatment of bronchial asthma and chronic obstructive pulmonary disorder and compare their drug release patterns with the reference product. All the experimental formulation

batches have been subjected to various evaluations viz., average weight, height, thickness, friability, disintegration, dissolution and assay.

Table.4.Post compression parameters of F2-F5

S.No	Parameters	F2	F3	F4	F5
1.	Appearance	White, flat &round shaped tablets having one side scored	White, flat &round shaped tablets having one side scored	White, flat &round shaped tablets having one side scored	White, flat & round shaped tablets having one side scored
2.	Thickness (mm)	3.79	3.82	3.802	3.806
3.	Diameter (mm)	12.93	12.94	12.946	12.95
4.	Hardness (kg/cm^2)	5.5	5.0	4.5	4.5
5.	Friability (%)	0.18	0.39	0.76	0.93
6.	Average weight (mg)	622.2	620.7	619.66	621.0
7.	Weight variation	Complies	Complies	Complies	complies
8.	Disintegration time	9 min 25 sec	8 min 40 sec	3 min 29 sec	4 min 47sec
9.	Assay (%w/w)	99.12	98.87	100.04	99.52

Formulation F1 was made by using povidone K-30 (1.94%). But the binder was not sufficient enough to affect granulation. So, the granules were not formed. Hence, this formation was a failure.

Formulation F2 was made by using povidone K-30 (4.03%) and sodium starch glycolate (2.9%) in extra granulation. The hardness and disintegration time were found to be 5.5kg/cm2 and 9min 25sec respectively. The drug release being 70.98% in 45min was not satisfactory.

Formulation F3 was made by using povidone K-30 (4.03%) and sodium starch glycolate (4.03%) intra granulation. The hardness and disintegration time were found to be 5.0kg/cm2 and 8 min 40 sec respectively. The drug release was not satisfactory (75.12%).

Formulation F4 was made by using povidone K-30 (4.03%), avicel (12.9%) and sodium starch glycolate (3.23% in intra granulation and 3.71% in extra granulation). The hardness and disintegration time were found to be 4.5kg/cm2 and 3min 29 sec respectively. The drug release was 100.42% within 20min. These results were very much close to those of reference product.

Formulation F5 was made by using povidone K-30 (2.9%), avicel (13.7%) and sodium starch glycolate in the same concentrations as in F4. The hardness and disintegration time were found to be 4.5kg/cm2 and 4min 47 sec respectively. The drug release was 100.21% in 45min but only 89.12% in 20min as compared to the reference product.

As the formulation trial, F4 was similar to the reference product than the formulation trial F5; it was finalized as the optimized formulation

Table.4.Dissolution profiles of the trial formulations

S.no	Time (min)	Cumulative percentage of drug release				
		Reference	F2	F3	F4	F5

1.	5	71.78	21.02	24.99	76.14	65.26
2.	10	83.96	37.25	38.23	87.52	78.47
3.	20	98.94	52.11	54.36	100.42	89.12
4.	30	100.82	64.74	61.24	101.23	96.17
5.	45	101.12	70.98	75.12	101.06	100.21

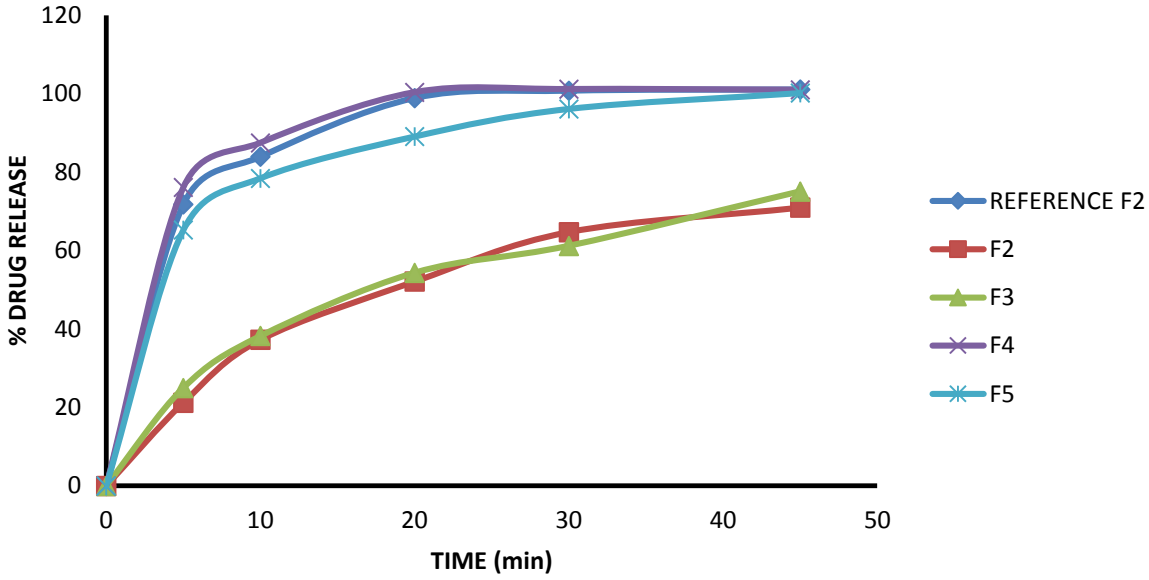


Figure 2: Dissolution profiles of formulations F2, F3, F4 and F5 compared to reference

SUMMARY AND CONCLUSION

In this study, an attempt has been made to develop a formulation for doxofylline tablets of 400mg. The linearity of doxofylline standard curve was checked in the dissolution medium i.e., distilled water. It was found to be linear in the range of 1 MCG/ml to 8MCG/ml. The dissolution profile of the reference product was evaluated in the dissolution medium. It was noticed that the product release more than 85% of the drug within 20min. Performulation studies were done initially and the results directed the further course of formulation. With the data from literature review, formulation trials (F1 to F5) were started using wet granulation method. Granules were evaluated for tests such as bulk density, tapped density, compressibility index and hausner's ratio before being punched into tablets. The compressed tablets were tested for weight variation, thickness, hardness, friability, disintegration time and assay. The dissolution profile of all the four trials were evaluated and compared with the reference product. Amongst all the four formulations, the release profile of the trial formulation F4 was found to be similar with the respect to the reference listed drug product and hence it was selected for the further study.

The stability study for the selected formulation (F4) was performed per ICH guidelines. The selected trial tablets (F4) were packed in PVC/aluminum blister lack and placed in the stability

chambers of 25ºC/60%RH and 40ºC/75%RH for 3months and analyzed at regular intervals. It was found that the product is stable in both the conditions as it showed a negligible change in drug content after storage in various condition for 3months. The formulation trial F4 was optimized considering the drug release profile and the disintegration time of the tablets as they were very close to the reference product values. From this study, it may be concluded that for Doxofylline tablets, F4 is a successful formulation and it can be manufactured with reproducible characteristics from batch to match the release profile with the reference product. The findings of the present study ensure the company to launch the product in the market in near future.

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