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Research Article

FORMULATION AND EVALUATION OF ORALLY DISINTIGRATING TABLET OF LAMOTRIGINE

Vinay Sharma*, Surya Pratap Singh, Nitin Nama, Khinchi M. P.

Department of pharmaceutics, Kota College of Pharmacy, Ranpur, Kota, Rajasthan, India

ABSTRACT

The objective of the present study was to develop orally disintegrating tablet of Lamotrigine, for treatment of epilepsy. It is also used in simple and complex partial seizures and secondary generalized tonic-clonic seizures. The results obtained revealed that solubility of the drug markably increased with both the polymers but as PVP K-30 itself act as a binder in tablet formulation, it increases the disintegration time so it was not suitable for the formulation of ODT. So for the preparation of solid dispersion β-CD was used in 1:1drug carrier ratio as revealed by phase solubility studies .The prepared tablets were evaluated for organoleptic characteristics like color, odor, taste and physical characteristics like diameter, thickness, hardness, friability, weight variation, disintegration time, and dissolution studies. Based on these parameters, concentration of SSG & crospovidone were selected for further studies. Results revealed that the concentration of SSG and Crosspovidone significantly affected the dependent variables (disintegration time, wetting time and %friability).Optimum formulation was suggested by the software.

Key words: *Orally disintegrating Tablet, SSG, Crosspovidon, Software*

INTRODUCTION

Convenience of administration and patient compliance are gaining significant importance in the design of dosage forms. Recently more stress is laid down on the development of organoleptically elegant and patient friendly drug delivery systems[1]. Since the development cost of a new drug molecule is very high, efforts are now being made by pharmaceutical companies to focus on the development of new drug dosage forms for existing drugs with improved safety and efficacy together with reduced dosing frequency, and the production of more cost-effective dosage forms[2].

Although various novel and advanced drug delivery systems have been introduced for therapeutic use, the popularity of oral dosage forms have not been eclipsed[3].

Corresponding author:
Vinay Sharma
Kota College of Pharmacy,
Kota,Pin-302005, Rajasthan,India
E mail: vnsharma451@gmail.com
Mob. - 9318016000

Tablets and capsules constitute a major portion of the drug delivery systems because of their convenience in terms of self-administration, compactness, pain avoidance and ease in manufacturing[4]. One important drawback of these dosage forms however is the difficulty to swallow[5].

Fast Disintegrating Tablets

US-FDA Definition: United States Food and Drug Administration (FDA) defined orally disintegrating tablets as "A solid dosage form containing medicinal substance or active ingredient which disintegrates rapidly usually within a matter of seconds when placed upon the tongue". The disintegration time for orally disintegrating tablets generally less than 30 sec.

Most benefits of FDT are for pediatric, geriatric, and bedridden or developmentally disabled patients. Patients with persistent nausea who are travelling or who have little or no access to water are also good

candidates for FDTs. In the near future, other patient populations will also be targeted. A novel application for FDTs is in veterinary medicine, for example, to overcome difficulties while administering pills to a cat. With fast-dissolving/disintegrating dosage forms increasingly available, it will be likely that prescribers will recommend such products for their noncompliant patients. The ease of administration of a fast-dissolving/disintegrating tablet, along with its pleasant taste, may encourage a patient to adhere to a daily medication regimen.

MATERIALS AND METHODS

MATERIALS:

The Chemicals which are used in the experimental studies were Lamotrigine, Sodium starch glycolate, Crospovidone, β-cyclodextrin, and other excipients which are used in preparation of orally disintegrating tablets.

A double-beam Shimadzu-1800 UV- Visible spectrophotometer, with spectral bandwidth of 2 nm, wavelength accuracy ± 0.5 nm and a pair of 1-cm matched quartz cells was used to measure absorbance, 10 station rotary tablet punching machine was used for compressing. For other evaluation test High Precision Water Bath, Infra Red Spectrophotometer, Hardness Tester was used.

METHODS

Kneading method was used to prepare solid dispersions of lamotrigine. Preliminary trial batches containing selected solid dispersion were prepared by direct compression method using single punch tablet machine to produce convex faced tablets weighing 150 mg each with a diameter of 7 mm. A minimum of 50 tablets were prepared for each batch. The formulations were developed by using different conventional technologies. The quality of tablet, once formulated by rule, is generally dictated by the quality of physicochemical properties of blends. There are many formulations and process variables involved in mixing step and all these can affect the characteristics of blend produced. The characterization of mixed blend was performed for the flow property of powders. Bulk density, tapped density, Hausner's ratio, Compressibility index, angle of repose has also been determined.

PREFORMULATION STUDIES

Physical Appearance: Physical appearance of drug was examined by various Organoleptic properties.

Melting Point: Melting point of the LAMO was determined by capillary fusion method; one sided closed capillary filled with drug and put into the Melting Point Apparatus. Temperature was noted at which solid drug changed into liquid. It was found to be 216-218^{0}C.

Infrared Spectral Assignment: The sample pellet was mounted in IR compartment and scanned at wavelength 4000 cm-1– 500 cm-1. On analysis of the IR spectra of the reference spectra given in Indian Pharmacopoeia (1996) and pure drug, no major differences were observed in the characteristic absorption peak.

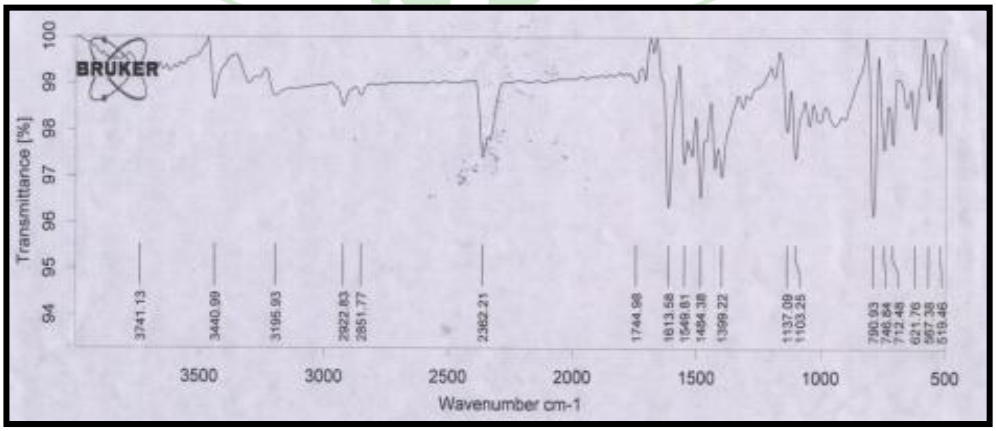

Figure 1 : IR of pure drug

Ultraviolet Absorption Maxima: Ultraviolet absorption in the rage 200 to 400 nm of a 20 g/ml solution in 0.1N HCl was measured. The absorption maxima (λmax) of lamotrigine (20µg/ml) in this solution were found to be 267.5 nm which is concordant with the Indian Pharmacopoeia (1996).

Solubility

The solubility of LAMO was determined in different solvent systems and buffers. An excess quantity of the drug was mixed with 10 ml of each solvent in screw capped glass tubes and shaken on constant water bath shaker for 24 hours at 25°. The solutions were examined physically for the absence or presence of drug particles and also by spectrophometrically for quantitative determination of drug in buffers.

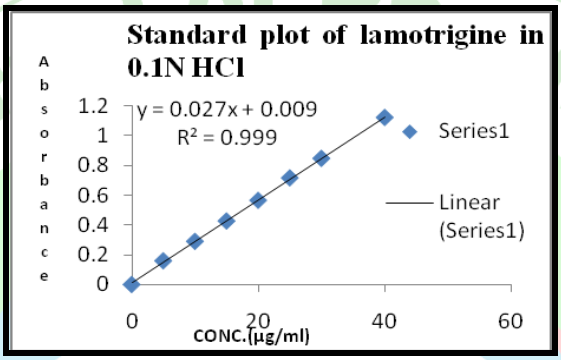

Figure 2: Standard curve of lamotrigine in 0.1N HCl

Drug Polymer Interaction Studies

While designing ODT it was imperative to give consideration to the compatibility of drug and polymer used within the system. It is therefore necessary to conform that drug is not interacting with the polymer under experimental conditions. The infrared absorption spectra of pure polymer and physical mixture of polymer and drug were performed for polymer drug interaction studies between 4000 cm^{-1}-500 cm^{-1} placed at 40 ± 5°C and 75 ± 5% RH for 4 weeks. The IR spectra of physical mixture of polymers and drug were shown in Figure Physical changes and absorption maxima were also evaluated.

Preparation of Solid Dispersions Of Lamotrigine

For the enhancement of solubility and dissolution profile of Lamotrigine solid dispersions and inclusion complexes are prepared using PVPK30 and β-cyclodextrin respectively.

Preparation of solid dispersion of lamotrigine by kneading method:

Kneading method was used to prepare solid dispersions of lamotrigine. Table depicts the composition for preparing solid dispersions of lamotrigine with Polyvinyl pyrrolidone K30 & β-CD in various ratios. Lamotrigine and polymers were weighed according to different weighed ratios. The physical mixtures was wetted with water-methanol(1:9) mixture and kneaded thoroughly for 30 min in a glass mortor. The paste formed was dried under vacuum for 24 hours. Dried powder was passed through seive no. 60 and stored in a dessicator until further evalution.[23]

Table 1 : Preparation of solid dispersion of lamotrigine

Formulation No.	Drug: carrier
LP1	1:1
LP2	1:2
LP3	1:3
LB1	1:1
LB2	1:2
LB3	1:3

Characterization of Solid Dispersions

The prepared solid dispersions were evaluated for percent drug content, solubility studies, Fourier transform infrared (FTIR), *in vitro* drug release and dissolution efficiency.

Determination of Drug Content

Drug content was calculated by dissolving physical mixtures and solid dispersions equivalent to 10 mg LAMO in 10 ml of methanol, filtered using Whatman filter paper (no. 41), suitably diluted with 0.1NHCL and analyzed by using UV spectrophotometer against 0.1N HCL as blank[104].

Determination of Solubility

Pure Lamotrigine and solid dispersions equivalent to 10 mg of Lamotrigine were added to 10 ml of 0.1N HCL in a 10 ml volumetric flask. The volumetric flasks were capped properly and shaken at 37^0C in a temperature controlled water bath (Shaking water bath) for 48 h. Resultant samples containing undissolved solid dispersions suspended in the volumetric flask were filtered through Whatman filter paper (no. 41), suitably diluted with 0.1N HCL and analyzed by UV spectrophotometer at 267.5 nm[3].

***In vitro* Drug Release**

Accurately weighed solid dispersions equivalent to 10 mg of Lamotrigine were added to 900 ml of dissolution medium i.e. 0.1N HCl in USP II Paddle type apparatus and stirred at a speed of 50 rpm at 37 ± 0.5^0 C.10 ml aliquots were withdrawn at 2, 4, 6, 8, 10, 15, 20, 25, 30 minutes and replaced by 10ml of fresh dissolution media. The collected samples were analyzed after filtration and dilution at 267.5nm using UV-visible spectrophotometer against the blank. Drug release studies were carried out in triplicate. The dissolution studies of pure Lamotrigine as performed similarly. The release profile data was analyzed for cumulative percent drug released at different time intervals and for dissolution efficiency at 6 and 10 minutes[23].

Fourier Transform Infrared (FTIR) Spectroscopy

Fourier Transform Infrared (FTIR) spectra of pure drug, β-CD and solid dispersion were recorded on samples prepared in potassium bromide (KBr) disks. Samples were prepared in KBr disks by means of a hydrostatic press. The scanning range was 400 to 4000 cm^{-1} and the resolution was 4 cm^{-1}.

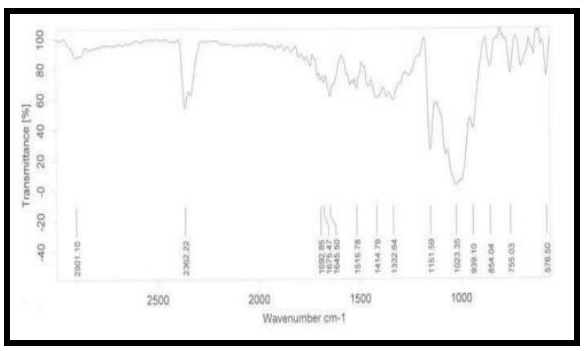

Figure 3: FTIR Drug + Crosspovidone

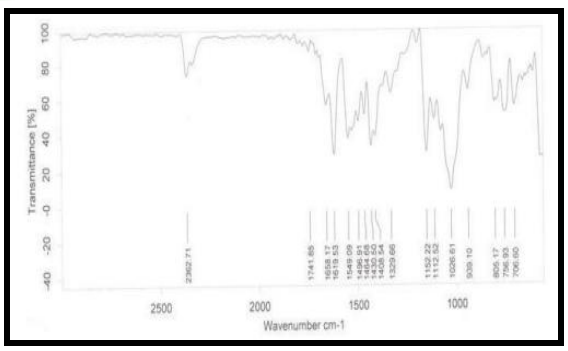

Figure 4: FTIR of Drug + βCD

Differential Scanning Calorimetry (DSC) Analysis

Differential Scanning Calorimetry analysis of pure drug, PVP K30, β-CD and solid dispersion were obtained by differential scanning calorimeter (DSC 60 Shimazdu, Japan). The samples were heated in an open aluminum pans at a rate of 10^0 per min^{-1} in a 30^0C to 300^0C temperature range under a nitrogen flow of 40 ml/min.

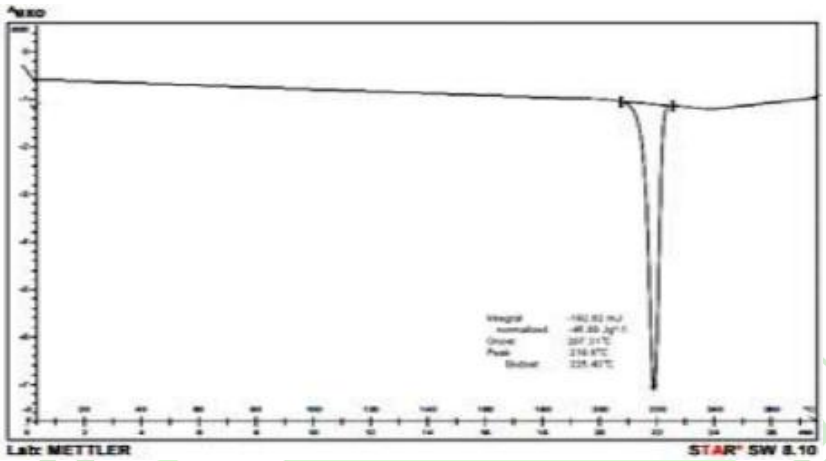

Figure. 5: DSC of pure Drug

Preparation of Preliminary Trial Batches

Preliminary trial batches containing selected solid dispersion were prepared by direct compression method using single punch tablet machine to produce convex faced tablets weighing 150 mg each with a diameter of 7 mm. A minimum of 50 tablets were prepared for each batch. The formulations were developed by using different conventional technologies.

By Addition of Super Disintegrants

The superdisintegrants (Sodium starch glycolate and Crospovidone) in varying concentration were used to develop the tablets. All the ingredients were shown in Table 5.5 were passed through sieve no.60 and were co-grounded in a glass pestle mortor for each formulation separately. These blends were evaluated for mass-volume relationship (Bulk Density, Tapped Density, Hausners Ratio, Compressibility Index) and flow properties (Angle of Repose). The mixed blend of excipients was compressed using a single punch tablet machine (Cadmach, Ahmedabad) to produce convex faced tablets weighing 150 mg each.

Table 2: Formulation of preliminary trial batches

Ingredient	F1	F2	F3	F4	F5	
LB1	50	50	50	50	50	50
SSG	1.5	3	4.5	-	-	-
Crospovidone	-	-	-	1.5	3	4.5
Mannitol	20	20	20	20	20	20
Avicel pH 102	73	71.5	70.5	73	71.5	70.5
Sodium saccharin	0.5	0.5	0.5	0.5	0.5	0.5
Magnesium Stearate	5	5	5	5	5	5

Characterization of Blends

The quality of tablet, once formulated by rule, is generally dictated by the quality of physicochemical properties of blends. There are many formulations and process variables involved in mixing step and all these can affect the characteristics of blend produced.

The characterization of mixed blend was performed for the flow property of powders. Bulk density, tapped density, Hausner's ratio, Compressibility index, angle of repose has also been determined.

Table 3: Characterization of blends

Parameters	Bulk Density	Tapped Density	Hausner's Ratio	Compressibility	Angle of repose
Formulation	(g/cc)	(g/cc)		Index (%)	(º)
F1	0.598±0.007	0.782±0.006	1.149±0.014	12.995±1.105	22±2.023
F2	0.590±0.010	0.672±0.006	1.138±0.027	12.107±2.119	24±1.564
F3	0.609±0.016	0.702±0.011	1.146±0.025	12.738±1.958	23±2.654
F4	0.669±0.024	0.757±0.025	1.131±0.015	11.599±1.213	25±1.589
F5	0.598±0.014	0.680±0.018	1.137±0.024	12.078±1.916	28±1.852
F6	0.668±0.031	0.754±0.010	1.129±0.038	11.362±2.985	26±1.324

Characterization of Orally Disintegrating Tablets

After compression of powder, the tablets were evaluated for organoleptic characteristics like color, odor, taste, diameter, thickness and physical characteristics like hardness, friability, disintegration time, wetting time, dispersion time and dissolution studies.

Table 4 : Characterization of orally disintegrating tablets

Parameters	Thickness	Weight	Friability	Hardness
Formulations	(mm)	(mg)	(%)	(kg/cm^2)
F1	3.175±0.014	151.8±3.551	0.52±0.043	3.1±0.152
F2	3.042±0.026	150.7±3.632	0.57±0.077	3.0±0.096
F3	3.143±0.034	149.2±4.427	0.62±0.022	2.9±0.126
F4	3.025±0.004	147.8±3.321	0.73±0.059	2.8±0.134
F5	3.094±0.037	151.1±2.731	0.71±0.053	2.8±0.157
F6	3.042±0.029	146.5±3.654	0.72±0.055	2.7±0.095

Table 5 : Characterization of orally disintegrating tablets

Parameters	Disintegration Time	Wetting Time	Dispersion Time
Formulations	(Seconds)	(Seconds)	(Seconds)
F1	75.03±1.52	79.66±4.50	98.66±5.85
F2	69.00±3.00	72.00±3.60	81.66±4.72
F3	62.00±0.64	69.33±2.51	65.00±4.58
F4	63.00±1.64	65.66±2.51	80.33±5.13
F5	51.43±2.08	54.66±1.52	61.33±3.05
F6	35.00±2.58	31.00±5.00	48.66±8.50

***In Vitro* Drug Release of Optimized Formulation and Comparison with Marketed Tablets**

Dissolution of orally disintegrating tablets *in vivo* is achieved in the mouth owing to the action of saliva, however amount of saliva in the mouth is limited and no tablet dissolution test was found in USP and IP to simulate *in vivo* conditions. A modified method was used to determine dissolution rate of the tablets. A cylindrical vessel was used in which 10 mesh screen was placed in such way that only 2 ml of disintegrating or dissolution medium

would be placed below the sieve (Figure 5.3). To determine disintegration, 6 ml of distilled water, was placed inside the vessel in such way that 4 ml of the media was below the sieve and 2 ml above the sieve temperature is maintained at 37±5°C. Tablet was placed on the sieve and the whole assembly was then placed on a shaker. Five milliliter aliquots were withdrawn at 0, 1, 2, 3, 4 and 5 min and an equal volume of fresh medium, prewarmed at 37°, was replaced into the dissolution media after each sampling to maintain the constant volume throughout the study. The collected samples were analyzed after filtration at 285 nm using UV-visible spectrophotometer against the blank[115]. The various kinetic treatments were applied to the dissolution data. The *in vitro* permeation data obtained were subjected to a zero order and first order kinetics to understand the release profile and release mechanism. When a graph of the cumulative percentage drug released from the tablet against time was plotted, zero order release was observed and the plot obtained was found to be linear, indicating that the release rate is independent of concentration. The rate of release of the drug can be described mathematically as follows:

Rate of release = (dCs/t) = k

Where, Cs = concentration of the drug present in the matrix,

K = rate constant,

t = timeand Cs is a constant.

The amount of drug released (X) can be described as, dx / dt = k

Integration of the equation yields

X = k t + constant

A plot of x versus t results in a straight line with the slope = k. The value of k indicated the amount of the drug released per unit of time and the intercept of the line at time zero is equal to the constant in the equation.

Table 6 : Cumulative % drug release data

Time (min)	Cumulative % Drug Released of Optimized Formulation	Cumulative % Drug Released of Marketed Formulation
0	0	0
1	79.54±0.51	45.31±0.59
2	85.32±0.56	47.43±1.17
3	87.45±0.18	54.53±1.73
4	89.31±0.84	60.41±1.60
5	91.23±0.56	65.72±1.08

Table 7 : Comparison with Marketed Tablets

Parameters	Optimized Formulations	Marketed Formulation
Weight (mg)	151±1.73	152±1.21
Hardness (kg/sq.cm.)	3.1±0.3	3.7±0.5
Friability (%)	0.54±0.013	0.91±0.051
Disintegration time (sec)	15±1.06	49.43±3.81
Drug content (%)	99.36	96.87

Table 8 : Fit of various kinetic models for ODT of lamotrigine

Formulation Code	Zero Order			First Order		
	Intercept	R^2	K(mg/min)	Intercept	R^2	K (min^{-1})
Optimized	37.29	0.537	13.92	1.701	0.743	0.176
Marketed	18.34	0.744	10.88	1.908	0.860	0.080

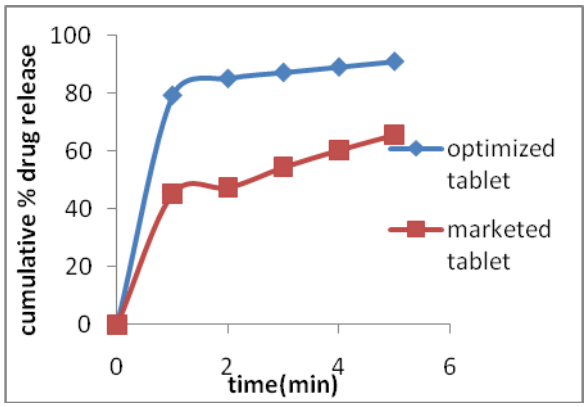

Figure 6: Drug release curve of lamotrigine optimized and marketed tablet

Temperature Dependent Stability Studies

The optimized orally disintegrating tablets of lamotrigine were packed in wide mouth air tight glass container and stored at (40 ± 1° and 75 ± 5% RH) for a period of 3 months. The tablets were withdrawn after a period of 15 days and analyzed for physical characterization and drug content spectrophotometrically at 267.5 nm.

The dissolution profile of optimized tablets was also compared. The dissolution similarity factor (*f2*) was also calculated to compare before and after storage dissolution profile.

In recent years, FDA has placed more emphasis on a dissolution profile comparison in the area of post-approval changes and biowaivers. Under appropriate test conditions, a dissolution profile can characterize the product more precisely than a single point dissolution test. A dissolution profile comparison between pre-change and post-change products for SUPAC related changes, or with different strengths, helps assure similarity in product performance and signals bioinequivalence.

Among several methods investigated for dissolution profile comparison, *f2* is the simplest.

$$f_2 = 50 \cdot \log\{[1+(1/n)\sum_{t=1}^{n}(R_t - T_t)^2]^{-0.5} \cdot 100\}$$

where R_t and T_t are the cumulative percentage dissolved at each of the selected n time points of the reference and test product respectively. When the two profiles are identical, *f2*=100. An average difference of 10% at all measured time point's results in a *f2* value of 50. FDA has set a public standard of *f2* value between 50 to 100 indicate similarity between two dissolution profiles[16,17].

The *f2* value of optimized tablet before and after storage condition was found to be 90.59 which were more than 50, indicating a close similarity between both the dissolution profiles.

Table 9 : Effect of storage conditions on optimized tablet

Days	Temperature				
	Weight	Hardness	Friability	Disintegration Time (s)	Drug Content
0	151	3.1	0.541	15	99.36
15	151	3.1	0.549	15	99.33
30	150.8	3.0	0.552	15	99.25
45	150.2	3.0	0.553	14	99.23
60	150	3.0	0.559	14	99.20
75	150	3.0	0.560	13	99.20
90	150	3.0	0.563	13	99.09

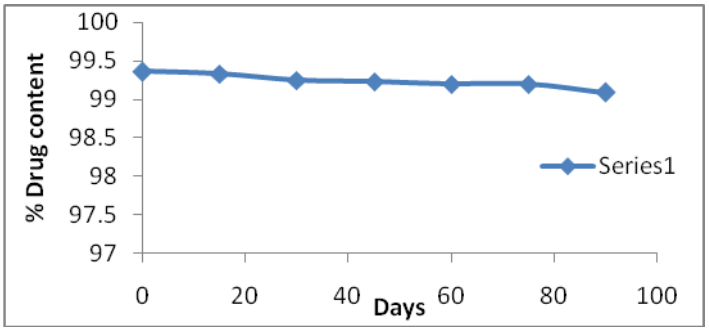

Figure 7: Graph of storage conditions on optimized tablet

RESULT & CONCLUSION

In the work undertaken an attempt was made to prepare Orally Disintegrating Tablet (ODT) of Lamotrigine an antiepileptic drug as it is used both in partial and generalized seizures and in that cases patient is not in the condition to take drug along with the water secondly it is easy for paediatric and geriatric patients to take ODT rather than conventional tablets.

Identification of drug and drug polymer interaction studies were successfully carried out. Formulation of ODT's of Lamotrigine was successfully prepared by direct compression technique using Sodium starch glycolate (SSG) and crospovidone superdisintegrants.

Optimum formulation was suggested by the software. The tablets were prepared using 2.44mg (-0.36%) SSG and 3.75mg (0.56%) crospovidone as suggested by the software design expert trial 8.7.0.1. The observed response values for disintegration time, wetting time, and friability were in close agreement with the predicted ones.

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