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Research Article

LAMOTRIGINE ORODISPERSIBLE TABLETS; IMPACT OF TOTAL WEIGHT OF THE TABLET-OPTIMISATION THROUGH TAGUCHI DESIGN

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A B S T R A C T

To study the impact of various diluents on evaluation parameters of orodispersible tablets of lamotrigine. Oro-dispersible tablets of lamotrigine were prepared by direct compression method using PVP K30 as binder, Lactose, Avicel 101, Avicel 102as diluents and superdisintegrantscroscarmellose sodium. A Taguchi L9 orthogonal array (3^3) design of experiment was applied to study the effect of independent variables i.e., different diluents (like Avicel 101, Avicel 102 and Lactose), total weight of the tablet (50mg, 75mg and 100mg) and percentage of superdisintegrant (1% ,2% and 3%) on disintegration time (DT) and percentage drug release as dependent parameter. One-way ANOVA was used in the analysis of Taguchi design of experiment to determine whether the factors are significantly related to the response. ODT formulations with Avicel 101, Avicel 102 & Lactose as diluents containing croscarmellose sodium were optimized. The formulations had weight variation (0.7-1.8%), hardness(2.3±0.5-2.6±0.56kg/cm2), friability (0.5±0.5-0.98±0.56 %), disintegration time (4.5±0.55-9.2±0.81sec), wetting time (4±0.32-13±0.77sec), water absorption ratio (70±0.32-192±1.16%) were found to have within USP limits. The formulations F2,F3,F5,F6,F8 and F9were optimized having less DT ranging from 4 sec to 10 seconds. There was no significant change in dissolution profile of the formulations. Tablets were stable for one-month. It can be concluded that total weight of the tablet, and type of diluents had influence on the dependent variables, but total weight of the tablet showed maximum impact on DT followed by use of different diluents.

INTRODUCTION

Currently, there is a high level of interest in the use of the oral cavity as a portal for drug entry to the systemic circulation (Lakshmi *et al*., 2011). Oral route is considered as widely accepted route because of its convenience but due to various drawbacks like difficulty in swallowing, especially pediatric and geriatric patients, but it also applies to people who are ill in bed and to those active working patients who are busy or traveling, especially those who have no access to water (Shirwaikar *et al*., 2004). United States Food and Drug Administration (FDA) outlined ODT as "A solid dosage form containing medicative substance or active ingredient that disintegrates quickly typically inside a matter of seconds once placed upon the tongue". The disintegration time for ODT's generally ranges from several seconds to about a minute. European pharmacopoeia described ODT's as uncoated tablets intended to be placed in the mouth where they disperse rapidly before being swallowed and as tablets which should disintegrate within 3 min (Evren *et al*., 2014). Recently, European Pharmacopoeia has used the term oral disintegration tablets for tablets that disperses readily and within 3 min in mouth before swallowing (Velmurugan *et al*., 2010).

Present study was done to study the effect of synthetic diluents on evaluation parameters of ODT. Lamotrigine was taken as model drug to formulate as ODT. It is used in the treatment of CNS disorders, particularly epilepsy, pain, edema, multiple sclerosis and psychiatric indications including bipolar disorder (Lakshmi *et al*., 2013). Lamotrigine belongs to BCS class II (Low solubility & High permeability) and it requires immediate action (Venkat *et al*., 2010).

The current pharmaceutical market for oral disintegrating tablets is on the rise due to availability of few technologies and patient demand. Hence, an attempt has been made in the development of a less laborious and economic method which could be industrially applicable for the delivery of lamotrigine for fast disintegration (Lakshmi *et al*., 2013). L9 orthogonal array Taguchi design was constructed to minimizes the experimental trials (Lakshmi *et al*., 2016).

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MATERIALS AND METHODS

Materials

Lamotrigine gift sample from Dr. Reddy's laboratory, lactose purchased from SD fine chemicals, Spray Dried Lactose purchased from SD fine chemicals, Avicel 101&102 purchased from Ankit pubs & boards pvt ltd., Ludiflash from Yarrow chem. Products, Crosspovidone from Corel pharma. Chem ltd, Croscarmellose from Mylan, PVP K30 from Yarrow chem. Products, magnesium stearate and talcum powder from SD fine chemicals ltd. All ingredients used were of analytical grade

Compatibility studies

Drug-excipients compatibility studies by FT-IR

Compatibility studies of pure drug and excipients were carried out using Fourier transformed infrared spectrophotometer (Shimadzu, Japan) in the range of 400 - 4000/cm by KBr disc method. A base-line correction was made using dried potassium bromide and then the spectrum of the pure Lamotrigine and Lamotrigine + Excipients were obtained (Kanagathara *et al*.,2011).

Preparation method for lamotrigine oral disintegrable tablets

All the required excipients (Table 2) were weighed and sieved then mixed properly, uniformly mixed blend was compressed into tablets containing 25 mg drug using 4.76 and 6mm punch on a Rimek-1 rotary punching machine by direct compression methodology. Total weight of tablet was kept at 50mg,75 mg and 100mg.

Precompression Parameters of the powder blend

The flow properties of the powder are vital for the performance of the tablet, so they must be evaluated before compression. The powder mixture was evaluated for angle of repose, bulk density, tapped density, compressibility index, Hausner's ratio (Indian pharmacopoeia,1996).

Bulk density

Apparent bulk density (*b) determined by running the mix into a measuring cylinder. The bulk volume (v*) and weight of the powder (M) determined. The bulk density was calculated using the formula (Martin *et al*.1983).

b=M/V

Tapped density

The graduated cylinder containing a known mass of mix was tapped for a set time (around 250). The minimum volume (Vt) occupied within the cylinder and therefore the weight (M) of the mix was measured. The tapped density (*t) was calculated using the formula (Lindberg *et al*. 2004).

*t=M/Vt

Compressibility index

The simplest manner for measure of free flow of powder is compressibility, a sign of the convenience with that blend may be induced to flow is given by compressibility index (C.I) which is calculated using the formula,

$$C.I\ (\%) = \frac{\text{Tapped density} - \text{Bulk density}}{\text{Tapped density}} \times 100$$

Hausner's ratio

Hausner's ratio is an index of easy powder flow. It was calculated by the using the formula, Where *t=tapped density *d=bulk density

Hausner's ratio=*t/*d

Angle of repose

100 g of the mix was accurately weighed and carefully poured through the funnel whose tip was secured at a height of 2.5 cm above the graph paper which is placed on a horizontal surface. The blend was poured until the apex of the conical pile just touches the tip of the funnel (Marshall *et al*, 1987). It is calculated by the following formula. Where Θ= angle of repose, r= radius of the pile, h= height of the pile,

$\Theta = Tan^{-1}(h/r)$

Optimization of ODT of lamotrigine using Taguchi OA L9 design experiment

Based on preliminary trials in the present study a 3^3 Taguchi OA experimental design was used to study the effect of independent variables i.e., total weight of the tablet, different diluent, and different concentration of superdisintegrant. These three factors were studied at all the three different levels. Disintegration time kept as response.An L9 orthogonal array was used for choosing the best and optimized formulation. The software used was Minitab-17English. Experimental runs formulae were given in Table 1,2.

Table 1 Taguchi L9 orthogonal array (3^3) design experimental trials

Trials	Factor A	Factor B (mg)	Factor C
1	Avicel101	50	Ccs (1%)
2	Avicel101	75	Ccs (2%)
3	Avicel101	100	Ccs (3%)
4	Avicel102	50	Ccs (2%)
5	Avicel102	75	Ccs (3%)
6	Avicel102	100	Ccs (1%)
7	Lactose	50	Ccs (3%)
8	Lactose	75	Ccs (1%)
9	Lactose	100	Ccs (2%)

Table 2 Formulation of lamotrigine oral disintegrating tablets using Taguchi design

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
Drug	25	25	25	25	25	25	25	25	
Avice101	23.5	47	70	-	-	-	-	-	-
Avicel102	-	-	-	23	46.25	72	-	-	-
Lactose	-	-	-	-	-	-	22.5	47.75	71
CCS	0.5	1.5	3	1	2.25	1	1.5	0.75	2
PVP	0.5	0.75	1	0.5	0.75	1	0.5	0.75	1
Mg stearate	0.25	0.375	0.5	0.25	0.375	0.5	0.25	0.375	0.5
Talc	0.25	0.375	0.5	0.25	0.375	0.5	0.25	0.375	0.5
Total wt	50	75	100	50	75	100	50	75	100

Note: All the quantities are in mg.

Statistical analysis of Taguchi Designs

One-way analysis of variance was utilized in the analysis of Taguchi design of experiment. It is used to determine whether the factors are significantly related to the response or not.

Post-compression parameters

Hardness

The strength of dosage form is expressed as tensile strength (Kg/cm2). The dosage form crushing load, that the force

needed destroy a pill into items by compression. It was measured employing a tablet hardness tester (Monsanto hardness tester). Three tablets from each formulation batch were tested randomly and the average reading noted (Swamy *et al*. 2007).

Friability

Friability of the tablet was determined using Roche Friabilator (Electro lab, India). This device consists of a plastic chamber which is set to revolve around twenty-five revolutions per minute for four minutes dropping the tablets at six inches with every revolution. Pre-weighed sample of twenty tablets was placed within the Friabilator and were subjected to a hundred revolutions. Tablets were dusted employing a soft fabric material and reweighed. The friability (F%) is given by the formula, Where, W0 is weight of the tablet before the test and W is the weight of the tablets after test

F%=(1-W0/W) x100

Weight variation

Twenty tablets were at random chosen, and average weight was determined. Then individual tablets were weight and percent deviation from the average was calculated.

In vitro dispersion time

Disintegration time was measured employing a modified disintegration methodology. For this purpose, a Petri dish was filled with 10 ml of water at 37˚C±0.5˚C. The tablet was carefully put in the center of the Petridish and the time for the tablet to completely disintegrate into fine particles was noted (Pankaj *et al*., 2010).

Wetting time

Five circular tissue papers of ten cm diameter were placed inside Petri dish with a ten cm diameter. 10 ml of water at 37˚C±0.5˚C containing eosin, a water-soluble dye, was added to the Petri dish. A tablet was slowly placed on the surface of tissue. The time needed for water to reach the upper portion of the tablets was noted as the wetting time. Six tablets from each formulation batch were tested randomly and the average reading noted (Raju *et al*., 2010).

Water absorption ratio

A piece of paper folded double was placed in a tiny Petri dish containing six milliliters of water. A tablet was placed on the paper and therefore the time needed for complete wetting was measured. The wetted tablet was then weighed (Akihikol *et al*., 1996).

Water absorption ratio R, was determined using following equation, Where Wa= weight of tablet after absorption, Wb= weight of tablet before absorption

R=Wa-Wb/Wb*100

Drug content determination

20 tablets were at random chosen, and average weight was calculated. Tablets were powdered in a glass mortar. Powder equivalent to 5 mg weighed and dissolved in 100 ml of 0.1N HCl filtered and drug content analyzed spectrophotometrically at 244 nm.

In-vitro release

In-vitro drug release of oral disintegrable tablets was determined using USP dissolution apparatus II (Paddle type) (Electrolab TDL-08L). The dissolution test was performed using 900 ml 0.1N HCl at 37˚C±0.5˚C. The speed of rotation of paddle was set at fifty revolutions per minute. 5 ml samples were withdrawn at time points of 1, 3, 5, 10, min and same volume was replaced with fresh media. Absorbance of solution was checked by UV spectrophotometer (ELICO-164 double beam spectrophotometer, Hyderabad, India) at a wave length of 244 nm and drug release was determined from standard curve (Kuchekar *et al*., 2001).

Stability Studies

The stability studies of prepared formulations were carried out at Room-Temperature as per ICH guidelines over a period of 1 month. The changes in their physical DT, wetting time and the drug content observed. If there are no significant changes in the physical as well as chemical characteristics of the formulations. Then, it can be concluded from the results that the developed tablets are stable.

RESULTS AND DISCUSSIONS

Drug-Excipients compatibility studies by FT-IR

Drug excipient interaction was checked by comparing the infrared spectroscopy (IR) spectra of the physical mixture of drug with the excipients used (Figure 1) with the IR spectrum of pure drug as shown in Lamotrigine (Figure 1) (Patil *et al*., 2011). All the reference peaks which are observed in the IR spectrum of Lamotrigine were also observed in the IR spectrum of physical mixture of drug and polymers. It was found that Lamotrigine was compatible with Superdisintegrants and excipients used in the formulation.

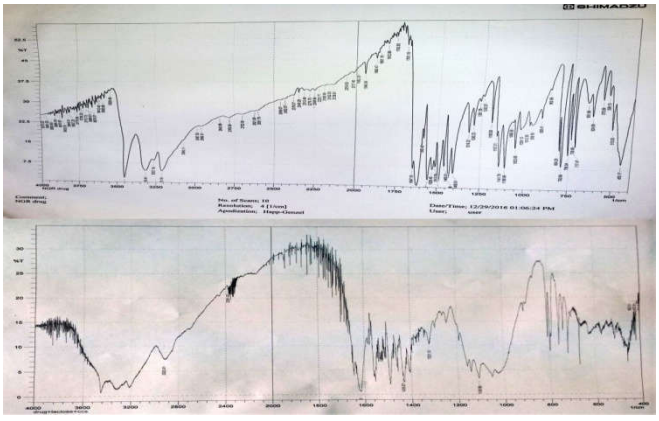

Figure 1 FTIR spectra of pure drug (lamotrigine) & FT-IR of optimized formulation

Pre-compression parameters of the powder blend

Bulk density (gm/cm3) ranges from 0.397±0.14 - 0.520±0.12, Tapped density (gm/cm3) ranges from 0.453±0.37 - 0.585±0.06, Hausner's ratio ranges from 1.12±0.38 - 1.17±0.58, Carr's index ranges from 11.11±0.21 - 14.87±0.57 and Angle of Repose (θ) was in range 30.4±0.14 - 34.5±0.65. The results of angle of repose, Carr's index, and Hausner's ratio indicated good flow ability of powders. Tablets produced were with acceptable weight variation due to uniform filling in the die.

Analysis of the results using Taguchi design

The obtained results (disintegration time) i.e., response was analyzed by Minitab 17 English software. Signal to noise ratio (S/N) for 'lower is the best' characteristic was chosen since the goal is to take the lower response that is lower disintegration time (Figure 2) (Shaikh *et al*., 2012). From Figure 2, it can be inferred that Factor B i.e.total weight of the tablet has greatest influence on the response. The other 2 Factors A and C i.e., type of diluent and percentage of CCS has less influence on the response (SachinSalunkhe *et al*., 2013). The ranks obtained for each factor will determine its effect on the response i.e, disintegration time.

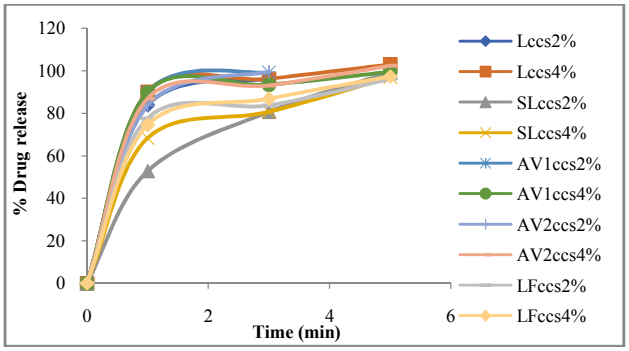

Figure 2 Dissolution profile of lamotrigine oral disintegrating tablets using Croscarmellose sodium

Statistical analysis of Taguchi Designs

It showed that the type of diluent has a significant effect on the disintegration time as the 'P' value is 0.492 at 95% confidence interval, that the concentration of diluent as a significant effect on the disintegration time as the 'P' value is 0.031 at 95% confidence interval and percentage of superdisintegrant as response is not significant as the P value is 0.850 at 95% confidence interval.

Post compression parameters

Tablet mean thickness was almost uniform in all the formulations. The prepared tablets in all the formulations possessed good mechanical strength with enough hardness in the range of 2.3±0.5-2.6±0.56kg/cm2,the friability was found to be between 0.5±0.5-0.98±0.56 %. All the formulated tablets were shown the % friability within the official limits (not more than 1%). The results of friability indicate that the tablets were mechanically stable and could handle the rigors of transportation and handling (Rajashree *et al*., 2016).

Prepared tablets were evaluated for weight variation and percentage deviation from the average weight of all tablet formulation (F1 – F9) and were found to be within (0.7-1.8%)the prescribed official limits. Superdisintegrant, Croscarmellose sodium was showed faster disintegration time, due to the rapid uptake of water from the medium, swelling and burst effect. As direct compression is a dry process, the high-water absorption ability of croscarmellose sodium serves to perform the disintegration process very quickly (Velmurugan S *et al*., 2010). In this study, effect of different diluents was studied on the disintegrating effect by changing different ratio, F5 formulation containing Avicel-101 with CCS 2% showed 3.5±0.76sec lowest disintegration time and F9 formulation containing Ludiflash 4% showed 10.0±0.12sec highest disintegration time. The mean of the disintegration times for all investigated tablets was less than 2 min, which fulfil the pharmacopoeial requirement. The disintegration time was found to be in the range of 3.5±0.32 - 11.0±0.51 sec. An anhydrous form of lactose shows fast disintegration time. Use of diluents as Avicel 101, Avicel 102, and Lactose in all formulations resulted disintegration time within 10 seconds as the diluents enhances the water penetration into the tablet (Adimoolam Senthil *et al*., 2011).

The wetting time of the all tablets was in the range of 4 to 13 seconds. Formulations containing lactose and Avicel 102 took more time for wetting compared to those containing Avicel 101 as the particle size of lactose and Avicel 102 influence the fastening of wetting time (Bharathi *et al*., 2014). It was observed that as the increase in total weight of the tablet increases water absorption ratio. Formulations containing Avicel 101 and Avicel 102 showed water absorption ratio 144% to 192% as they retain large amount of y*et al*lowing this stored water to be released easily (Adimoolam Senthil *et al*., 2011). The water absorption ratio was found to be in the range70±0.32 – 192±0.16 % (Table 3). The drug content of the ODT formulations were found to be in the range of 95.44±0.95 - 103.2±1.42.

Dissolution studies

Among the nine formulations (F1-F9) six formulations (F2, F3, F5, F6, F8, F9) were optimized using Taguchi design (Table 1,2). The maximum drug release was for the formulation F2, F3, F5 and F6 using different concentration of croscarmellose sodium and different concentration of three diluents, at the end of the 3 minutes were 96.21%, 94.29%,93.1%,90.42%. Dissolution profile of optimized formulations was compared with that of marketed formulation LAMICTAL (Figure 3) and the disintegration time taken was less with higher release than the branded.

Table 3 Comparative study of optimized formulations vs marketed ODT tablets

Formulation code	Weight variation (%)	Hard-ness (kg/cm^2)	Friability (%)	Disintegration time (sec)	Wetting time (sec)	Water Absorp-tionratio (%)	Assay (%)
F2	1.1	2.6±0.36	0.52±0.18	4.5±0.55	4±0.32	192±1.16	103.2±1.42
F3	0.7	2.5±0.5	0.5±0.26	7.1±0.21	10±0.5	166±1.22	101.65±1.06
F5	1.4	2.4±0.21	0.5±0.5	9.2±0.81	8±0.75	144±1.28	102.56±0.73
F6	0.9	2.6±0.56	0.85±0.09	9.2±0.36	13±0.62	152±1.92	99.56±0.75
F8	1.5	2.3±0.5	0.65±0.42	5.5±0.28	9±0.56	70±0.32	95.44±0.95
F9	1.8	2.5±0.5	0.98±0.56	7.3±0.62	13±0.77	92±0.44	97.12±0.93
Marketed	0.7	2.5±0.5	0.5±0.26	7±0.21	10±0.5	95±0.22	97.72±0.5

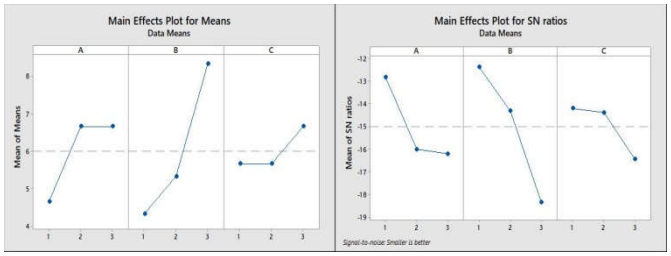

Figure 3 Main effect plot for Means & Main effects plot for signal to noise ratios

Stability studies

Optimized formulations were evaluated for stability studies which was stored at room temperature for 1 month and evaluated for their wetting time and in-vitro disintegration time at the end of initial and 4th week. Tablets were evaluated for hardness, disintegration time, wetting time, water absorption ration and Assay. No significant difference was found in the dissolution rate of the stored formulations when compared with freshly prepared formulation. Tablets have not shown any significant change during storage. Hence, it was concluded that the tablets have good stability during their shelf life.

CONCLUSION

In the present study, an attempt was made to study the effect of different diluents and change in the total weight of the tablet on ODT evaluation parameters. Preliminary studies have showed that there is no significant difference in disintegration time using various diluents. Taguchi orthogonal L9 design was used for optimization to study the impact of diluents lactose, Avicel 101 & Avicel 102, with varying quantity of total weight of the tablet using different diluents.

Quantity of diluent used in the formulation showed maximum impact on DT followed by use of different diluents. The formulations F2/F3/F5/F6/F8/F9 were optimized. There were no significant change in dissolution profile of optimized formulations. Tablets were stable for one month and its evaluation parameters were found to be within limits.

To conclude, total weight of the tablet using different diluents, and type of diluents had much influence on the dependent variable, i.e. disintegration time. Further study needs to be done with conventional and marketed co-processed diluents with different concentration of various super disintegrants to understand its impact on ODT evaluation parameters.

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