JOURNAL OF PHARMACEUTICAL SCIENCE AND BIOSCIENTIFIC RESEARCH (JPSBR)

(An International Peer Reviewed Pharmaceutical Journal that Encourages Innovation and Creativities)

Formulation and Optimization of Lamotrigin Fast Dissolving Tablet

Sachin S. Gupta[1], Hitesh Patel[2], B.G.Prajapati[2], Shreeraj Shah[1]

1. L.J.Institute of Pharmacy.Sanand Cross road, Sarkhej-Gandhinagar Highway, Ahmedabad.
2. Shree S K Patel College of Pharmaceuticaldcation &Research, Kherva Ganpat University.

ABSTRACT:

The objective of the present research was to prepare fast disintegrating tablet of lamotrigin because of its application in epilepsy and convulsion related problem. Fast on set of action and avoidance of abundant of water in oral route. Which is highly desirable in this type of disease condition. The effect of formulation and process variables such as hardness, disintegration time, and *in vitro* dissolution and physical characteristics of fast dissolving tablet were examined on optimized drug/super disintegrant ratio by 3^2 factorial designs. During the work tablets were prepared by direct compression using Kyron T-314 and sodium starch Glycolate as super disintegrant ,where MCC,Lactose monohydrate for direct compression, aspartame as sweetner.The different powder blends were evaluated for pre-formulation parameters such as bulk density, tapped density, angle of repose,carr's index,hausner's ratio. The tablets were evaluated for post-compression parameters such as weight variation, Tablet hardness and tablet friability. *In vitro* Disintegration test, tablet thickness, *in vitro* dissolution profile. All the physical characteristics of powder blend and fibrillated tablet were within acceptable limits. The result of Dissolution studies indicated that formulation F7 release 98.70% of drug at 25 min interval which give the most successful of study.F7 batch contain Lamotrigin(Drug),SSG(4%),kyron T-314(2%) and other excipients.F7 batch was the optimized batch since it showed of Disintegration time(17sec),friability(0.91%) and %Drug release (98.70%).

Key Words: Lamotrigin, Kyron T-314, Direct Compression, Sodium Starch Glycolate

Article history:
Received 08 Feb 2012
Accepted 23 March 2012
Available online 13 April 2012

For Correspondence:

Mr. Sachin S.Gupta

L.J.Institute of Pharmacy.Sanand Cross road, Sarkhej- Gandhinagar Highway, Ahmedabad.

Gujarat.

Email: sachin.gupta1228@gmail.com

INTRODUCTION[1-5]

The concept of Fast Dissolving Drug Delivery System emerged from the desire to provide patient with conventional mean of taking their medication. Difficulty in swallowing (Dysphasia) is a common problem of all age groups, especially elderly and pediatrics, because of physiological changes associated with these groups of patients. Recently fast dissolving formulation is popular as Novel Drug Delivery Systems because they are easy to administer and lead to Patient Compliance

Solid dosage forms that can be disintegrated, dissolved, or suspended by saliva in the mouth resulting in easy swallowing can provide significant benefits to the pediatric and geriatric populations.

FDT are prepared by various techniques, mainly direct compression,lyophilization & moulding.but most simplicity & cost effectiveness of the direct compression techniques. Usually superdisintegrants are added to dry formulation to facilitate the break up or disintegration of tablet into smaller particle than can dissolve more rapidly.

Lamotrigine [6- (2, 3-dichlorophenyl)-1, 2, 4-triazine-3, 5-diamine] is an antiepileptic agent shown to be effective in adjunctive treatment for refractory

Partial seizures and generalized seizures. It works by inhibiting voltage dependent sodium channels, resulting in decreased release of the excitatory neurotransmitters glutamate and aspartate2. It has an elimination half-life longer than 24 hr so once or twice daily dosing is possible in all patients. Lamotrigine is rapidly and completely absorbed after oral administration with negligible first-pass metabolism (absolute bioavailability is 98%). The bioavailability is not affected by food. Peak plasma concentrations occur anywhere from 1.4 to 4.8 h following drug administration (British National Formulary, 2009).Lamotrigine has a bitter taste. It is very slightly soluble in water (0.17 mg/ml at 25°C).

The object of this study was to formulate lamotrigine ODT using direct compression technique and to clarify the effect of different superdisintegrants like Kyron T-314, Sodium starch glycolate (SSG), on the disintegrating and dissolution properties of tablets.

MATERIALS AND METHODS

Lamotrigine was received as gift samples by Concern Pharma Ltd., Ahmedabad. Kyron T-314 was obtained as a gift sample from Corel Pharma Ltd., Ahmedabad. Microcrystalline Cellulose was obtained as a gift sample from Maple Biotech Pvt.Ltd, Pune.Sodium starch glycolate was obtained as a gift sample from DMV-Fonterra Excipients, Germany.Lactose Monohydrate IP- was obtained as a gift sample from Signet Chemical Corporation Pvt.Ltd. Mumbai. Sodium Steryl Fumarate & Aersoil were obtained as a gift sample from S.D Fine Chem. Ltd.Mumbai. . All other chemicals/solvents used were of analytical grade.

METHODS

Preparation of Fast Dissolving tablets of Lamotrigine[6]

The critical parameters to formulate a fast dissolving tablet are choice of super disintegrant and optimization of concentration of super disintegrant. The Main criteria for fast dissolving tablet is to dissolving tablet or disintegrate Rapidly in oral cavity in 15-60 seconds without need of water and should have pleasant mouth feel. The super disintegrant (Kyron T-314 & SSG) were used to formulate the tablets. All the ingredient as shown in table **1.**were Co-ground in a pestle & motor then Aerosil & SSF were added &mixed for 10 min.The mixed blend of drug-Excipient was compressed using single punch rotary tablet machine.

Full Factorial Design

A 3^2 randomized full factorial design was adopted to optimize the variables. In this design 2 factors were evaluated, each at 3 levels, and experimental trials were performed at all 9 possible combinations. The amounts of super Disintigrant agent Kyron T-314 (X_1) and the amount of SSG (X_2), were selected as independent variables. The disintegration time (DT) and percent friability (%F) were selected as dependent variables. Batches of factorial design are shown in **Table 2.**

EVALUATION OF OF LAMOTRIGINE FAST DISSOLVING TABLETS

Hardness[7]

The prepared tablets hardness was measured by using Monsanto hardness tester. The hardness was measured in terms of $kg/cm^{2.}$

Thickness and diameter[7]

Thickness and diameter of prepared tablets were tested by vernier callipers and the average was calculated.

Weight variation[7]

Twenty tablets were selected at random and weighed individually. The individual weights were compared with the average weight for determination of weight variation. The percentage deviation was calculated and then compared with USP specifications.

Friability[7]

Friability of tablets was measured by using Roche Friabilator (Electrolab, Mumbai, India). Friability was evaluated from the percentage weight loss of 20 tablets tumbled in a friabilator at 25 rpm for 4 min. The tablets were dedusted, and the loss in weight caused by fracture or abrasion was recorded as the percentage weight loss. Friability below 1% was considered acceptable.

% Friability = [(Initial weight – Final weight) / initial weight] * 100

Drug content[4]

Twenty tablets were powdered; powder equivalent to 50 mg of lamotrigine was accurately weighed and transferred into a 100 ml volumetric flask. Then, the volume was made up to 100 ml with 0.1N HCl. The filtrate was collected and diluted with sufficient amount of 0.1N HCl till the concentration of the drug lies within the standard plot range. The diluted solution was analyzed for the lamotrigine content by UV-spectrophotometer (UV-1700 Shimadzu Corporation, Japan) using 0.1N HCl as a blank at 254 nm.

Table 1. Composition of Lamotrigine FDT.

Batches	F1	F2	F3	F4	F5	F6	F7	F8	F9
Lamotrigine	5	5	5	5	5	5	5	5	5
Lactose	95.1	96.5	97.9	96.5	97.9	99.3	97.9	99.3	100.7
MCC	24.5	24.5	24.5	24.5	24.5	24.5	24.5	24.5	24.5
KyronT-314	5.6	5.6	5.6	4.2	4.2	4.2	2.8	2.8	2.8
SSG	5.6	4.2	2.8	5.6	4.2	2.8	5.6	4.2	2.8
Aspartame	1.4	1.4	1.4	1.4	1.4	1.4	1.4	1.4	1.4
Aerosil	1.4	1.4	1.4	1.4	1.4	1.4	1.4	1.4	1.4
SSF	1.4	1.4	1.4	1.4	1.4	1.4	1.4	1.4	1.4
Total	140	140	140	140	140	140	140	140	140

TABLE 2. Factorial Design Batches of Fast Dissolving Tablet

Batch code	X_1	X_2
F_1	-1	-1
F_2	-1	0
F_3	-1	1
F_4	0	-1
F_5	0	0
F_6	0	1
F_7	1	-1
F_8	1	0
F_9	1	1

X_1=Amount of Kyron T-314

X_2=Amount of Sodium Starch Glycolates

***In-vitro* disintegration time**[8]

Disintegration time was determined using USP tablet disintegration apparatus (ED2L Electrolab, India) using 900 ml distilled water without disk at 37°C±2°C temperature. A tablet was placed in each of the six tubes of the apparatus. The time taken for complete disintegration of the tablet with no palatable mass remaining in the apparatus was measured in seconds

In Vitro Dissolution studies[8]

The dissolution study was performed for all batches and marketed conventional tablet formulation by usingapparatus no. 2 or paddle apparatus (Electrolab, TDT 08L) (Indian Pharmacopoeia, 2007). The dissolution medium was 0.1 N HCl (pH 1.2, 900 ml, 37.0 ± 0.5°C). The rate of agitation of the paddle was 50 rpm. Aliquots of 10 ml were withdrawn at specific time interval at 1,3,5,10,15,20,30 min, filtered and absorbance was measured at 254 nm using Shimadzu by UV-1601 double spectrophotometer.

TABLE 3. Observation Table:

Batch No.	Hardness (Kg/cm^3)	Disintegration Time (Sec)	Friability (%w/w)
F_1	**3.9**	**20**	**0.84**
F_2	**4.2**	**17.9**	**0.87**
F_3	**3.8**	**18.3**	**0.89**
F_4	**3.9**	**22.5**	**0.89**
F_5	**3.5**	**18.9**	**0.94**
F_6	**3.5**	**18.1**	**0.95**
F_7	**3.4**	**17**	**0.84**
F_8	**3.6**	**17.5**	**0.96**
F_9	**3.2**	**17**	**1.21**

RESULTS AND DISCUSSION

Nine formulations of Lamotrigine were prepared with varying concentration of two superdisintegrants: Sodium starch glycolate & Kyron T-314 and microcrystalline cellulose, and Lactose Mono hydrate IP were used as diluents (Table 1). For each formulation, blend of drug and excipients were prepared and evaluated for various parameters as explained earlier. The powder blend was compressed using direct compression technique. Bulk density, was found in the range of 0.360-0.528 g/cm3 and the tapped density between 0.470-0.623 g/cm3. Using these two density data hausner's ratio and compressibility index was calculated. The powder blends of all formulations had hausner's ratio less than 1.25 indicates better flow property. The compressibility index was found between 13.5-19.7 which indicates a fairly good flowbility of the powder blend. The good flowability of the powder blend was also angle of repose (range of 24- 34) which is below 40 indicating good flowability. Tablets were prepared using direct

TABLE 4.*In Vitro* Dissolution Data Table

Time(Min)	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	**0**	0	0
5	21.10	21.40	20.20	22.30	21.40	23.40	**24.90**	19.10	17.20
10	36.00	33.00	38.10	38.01	36.12	34.90	**39.11**	29.90	30.13
15	62.35	61.44	63.10	63.01	60.75	62.11	**68.91**	58.64	57.01
20	82.31	80.11	81.34	83.04	79.77	80.11	**86.11**	71.33	70.29
25	90.00	9420	89.750	91.11	90.22	91.18	**98.70**	86.28	82.16

compression technique. Since the powder material was free flowing, tablets were obtained of uniform weight due of uniform die fill, with acceptable weight variations as per I.P. The hardness of tablet range b/w 3.25-4.3(Kg/cm$^{3)}$ was good mechanical resistance of the tablets shows in Table 3. The *invitro* disintegration time (DT) of the tablets was found to less than 30 sec which fulfilling the official requirements (< 3 min) for fast dissolving tablets (European Pharmacopoeia, 2001) & Friability also lass then 1% which fulfilling the official requirements for tablet as per I.P.(Table 3).

The cumulative percentage drug release of the tablets from the prepared batches tablet formulation is shown in Table 4. It was observed that nearly all the batches showed drug release close to 100% in 0.1 N HCl. In 0.1 N HCl, batch **F_7** gave better release profile of around 99% in 25 min as compared to other batches.

CONCLUSION:

The use of superdisintegrants for preparation of fast dissolving tablets is highly effective and commercially feasible. These superdisintegrants accelerate disintegration/dissolution of tablets by virtue of their ability to absorb a large amount of water when exposed to an aqueous environment. Kyron T-314 & Sodium Starch Glycolate used as a superdisintegrants agent increases the porosity of the tablets due to which the absorption of water takes place at high rate that results in breaking of tablets and therefore faster disintegration/dissolution From this research work, it can be concluded that among all the prepared batched from F1 to F9, batch F7 shows optimum characteristic with highest drug release and lowest disintegration time. So the batch prepared by the combination of two disintegrating agent Kyron T-314 (2%) and SSG (4%) was optimized batch.

REFERENCES

1. Lachman L, Lieberman HA, Kanig JL. The theory and practice of industrial pharmacy. Third Edition, Varghese Publication House, Bombay, India 1987: 296-300.

2. The Science and Practice of pharmacy, Remingtion part-I, 20th Edition-2000, Published by philladelphia college of pharmacy & Science.

3. .Prakash Goudanavar et al,. **"**Development and characterization of lamotrigine orodispersible tablets Inclusion complex with hydroxypropyl β cyclodextrin" International Journal of Pharmacy and Pharmaceutical Sciences 2011;3(3):208-214

4 P.S. Zade , P.S. Kawtikwar, D.M. Sakarkar "Formulation, Evaluation and Optimization of Fast dissolving tablet containing Tizanidine Hydrochloride**"** International Journal of PharmTech Research,2009 1 (1):34-42

5**.** Vineet Bhardwaj, Mayank Bansal and P.K. Sharma "Formulation and Evaluation of Fast Dissolving Tablets of Amlodipine Besylate Using Different Super Disintegrants and Camphor as Sublimating Agent" American-Eurasian Journal of Scientific Research 2010 5 (4): 264-269

6.C. Patil1 et al**., "**Effect of various superdisintegrants on the drug release profile and disintegration time of Lamotrigine orally disintegrating tablets" African Journal of Pharmacy and Pharmacology January 2011 5(1): 76-82,

7. Swamy PV,et al.,. "Or dispersible tablets of meloxicam using disintegrant blends for improved efficacy." Indian J Pharm Sci 2007; 69(6): 836-840.

8.Pankaj P. Amrutkar, Sanjay B. Patil, Abhijeet N. Todarwal, "Design and evaluation of taste masked chewable dispersible tablets lamotrigine by melt granulation" International Journal of Drug Delivery 2010 2 183-191

9.. Jain CP, Naruka PS. Formulation and evaluation of fast dissolving tablets of valsartan. Int J Pharm Pharm Sci 2009; 1(1): 219-226

10 Hand book of Pharmaceutical Excipients Fifth edition.edited By Raymond Rowe,PaulJ.Sheskey & sian c.owen.

11. http://www.drugbank.ca/drugs/DB00555