

Full Length Research Paper

Effect of various superdisintegrants on the drug release profile and disintegration time of Lamotrigine orally disintegrating tablets

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The demand for orally disintegrating tablets of lamotrigine has been growing during the last decade especially for the geriatric and pediatric patients. Lamotrigine is a recognized drug for epilepsy, so development of an ODT of lamotrigine and to evaluate the effect of various superdisintegrants on its disintegration time and release profile was the prime objective of this research work. Tablets were prepared by direct compression technique using 3 different superdisintegrants. Sodium starch glycolate, Croscarmellose sodium and Crosspovidone XL-10 were used as superdisintegrants in combinations to achieve optimum release profile, disintegration time and hardness. Direct compression process was selected for this formulation of ODT tablets, because porous nature is more in direct compression blend than wet granulation blend, so it will give faster disintegration. Microcrystalline cellulose was used as diluent and mannitol, mint flavor and sodium saccharin were used to enhance the organoleptic properties of tablets. The tablets were evaluated for weight variation, hardness, friability, *in-vitro* disintegration time and drug release characteristics. Hardness and friability data indicated good mechanical strength around 3 kg/cm² for all the batches. The results of *in-vitro* disintegration time indicated that the tablets dispersed rapidly in mouth within 8 s. Dissolution study revealed release rate of drug from the tablets was comparable with marketed tablet formulation of lamotrigine. It was concluded that superdisintegrants addition technique is a useful method for preparing orally disintegrating tablets by direct compression method.

Key words: Orally disintegrating tablets, superdisintegrants, Lamotrigine, direct compression.

INTRODUCTION

Most of the oral pharmaceutical dosage forms like conventional tablets and capsules are formulated to be swallowed or chewed. As a result children, bedridden patients and elderly patients have difficulty in swallowing these dosage forms (Avani et al., 2008). To overcome this drawback novel drug delivery systems like orally disintegrating tablets have been developed which disintegrate/dissolve/ disperse in saliva within few seconds without water.

United States of America Food and Drug Administration (USFDA) defines ODT as "A solid dosage form

containing medicinal substances or active ingredient which disintegrates rapidly usually within a matter of seconds when placed upon a tongue" (Rangasamy, 2009).

The major advantage of the ODT formulation is that it combines the advantages of both liquid and conventional tablet formulations. It provides the convenience of a tablet formulation, and also allowing the ease of swallowing provided by the liquid formulation (Rangasamy, 2009).

The various technologies used to prepare ODTs include direct compression, sublimation, tablet moulding, spray drying, and freeze drying and mass extrusion. Direct compression is the most cost effective and simplest technique of all.

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Advantages of orally disintegrating tablets (Kuchekar et al., 2003; Bradoo et al., 2001):

1. Improved patient compliance.
2. Rapid onset of action and may offer an improved bioavailability.
3. Useful for pediatric, geriatric and psychiatric patients.
4. Suitable during traveling where water is may not be available.
5. No specific packaging required, can be packaged in push through blisters.
6. Smooth mouth feel and pleasant taste.
7. Conventional manufacturing equipment.
8. Cost effective.
9. Good chemical stability as conventional oral solid dosage form.

The fast disintegration and dissolution effect of orally disintegrating tablets mainly depends on the type of superdisintegrants used in the tablet formulation. Most commonly used superdisintegrants include sodium starch glycolate, croscarmellose sodium (cross linked carboxymethylcellulose), crospovidone (cross linked povidone) (Mallikarjuna et al., 2008). Use of these superdisintegrants in combination mainly reduces the disintegration and dissolution time of ODT.

Lamotrigine is an antiepileptic for partial seizures and primary and secondarily generalized tonic-clonic seizures. Lamotrigine inhibits voltage-sensitive sodium channels, thereby stabilizing neuronal membranes and consequently modulating presynaptic transmitter release of excitatory amino acids (e.g., glutamate and aspartate). 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). The primary treatment objectives for patients with epilepsy are maintenance of adequate anti-epileptic drug levels and prevention of subsequent seizures. It becomes difficult to administer conventional tablet to patients who got seizure. But ODT does not require water to administer the tablet so the treatment becomes easier. Therefore, ODT of this drug was considered.

The objective of the present investigation was to prepare ODT's of lamotrigine and to evaluate the effect of three different superdisintegrants on their disintegration time because fast onset of action is desirable in epilepsy without the use of water.

MATERIALS AND METHODS

Materials

The materials used were: Lamotrigine (obtained as a gift from Yashica Pharmaceuticals Pvt. Ltd., Maharashtra, India), Sodium Starch Glycolate (SSG) (NB Laboratories Pvt. Ltd., Nagpur, India),

Croscarmellose sodium (CCS) (NB Laboratories Pvt. Ltd., Nagpur, India), Crospovidone XL-10 (CSP) (A. B. Enterprises, Maharashtra, India), Microcrystalline Cellulose (Avicel PH 102, Zeal Medichem, Mumbai), Mannitol (A. B. Enterprises, Maharashtra, India), Sodium saccharin (Prakash Chemicals Agencies Pvt Ltd., Vadodara, Gujarat), Mint flavour (Bharat Aromatics, Maharashtra), Aerosil (S.D. Fine chemicals, Mumbai), Magnesium Stearate (S.D. Fine chemicals, Mumbai).

Methods

Direct compression technique was used to prepare the tablets. It is the simplest and most economical method for the manufacturing of tablets because it requires less processing steps than other techniques such as wet granulation and roller compaction. Required quantity of mannitol, sodium starch glycolate, croscarmellose sodium, crospovidone XL-10 were passed through 60 # screen prior to mixing. Lamotrigine was mixed to this blend of powder. Thereafter, mint flavour, erosol, and magnesium stearate were added and mixed.

The powder blends prepared for different batches were compressed into concave tablets; 150 mg in weight and 8.00 mm in diameter, by using rotary tableting machine (Rimek minipress-II MT). The composition of powder blends of 9 different batches is presented in Table 1.

Evaluation of tablets

Uniformity of weight (weight variation)

I.P. procedure for uniformity of weight was followed. Twenty tablets were selected at a random and average weight was determined. Then individual tablets were weighed and the individual weight was compared with an average weight. None of the tablets deviated from the average weight by more than $\pm 5\%$.

$$\% \text{ weight variation} = \left[\frac{(\text{average weight} - \text{individual weight})}{\text{average weight}} \right] \times 100$$

Hardness

10 tablets were chosen randomly from composite samples and average value was determined. The tablet crushing load, which is the force required to break a tablet by compression in the radial direction, was determined using a Monsanto hardness tester (General trading corporation).

Friability

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.

$$\% \text{ friability} = \left[\frac{(\text{Initial weight} - \text{Final weight})}{\text{initial weight}} \right] \times 100$$

Assay of tablets

Twenty tablets were taken and powdered. Powder equivalent to 25 mg Lamotrigine was taken and was extracted with 0.1 N HCl (pH 1.2). After suitable dilution the drug content was analyzed by UV spectrophotometry at 267 nm (Perkin Elmer).

Table 1. Composition of Lamotrigine ODT.

| Ingredients | Amount (mg/tablet) | | | | | | | | |
|-------------------------|--------------------|-------|-------|-------|-------|-------|-------|-------|-------|
| | ODT 1 | ODT 2 | ODT 3 | ODT 4 | ODT 5 | ODT 6 | ODT 7 | ODT 8 | ODT 9 |
| Lamotrigine | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 |
| Sodium starch glycolate | 1 | ---- | 2 | 4 | ---- | 2 | ---- | 4 | ---- |
| Croscarmellose sodium | ---- | 1 | 2 | 2 | ---- | ---- | 2 | ---- | 4 |
| Crosspovidone XL-10 | ---- | ---- | ---- | ---- | 1 | 2 | 2 | 2 | 2 |
| Mannitol | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 |
| Avicel PH-102 | 91.5 | 91.5 | 88.5 | 86.5 | 91.5 | 88.5 | 88.5 | 86.5 | 86.5 |
| Sodium saccharin | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 |
| Mint flavour | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 |
| Aerosil | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 |
| Magnesium stearate | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 |

***In-vitro* disintegration time**

Disintegration time was determined using USP tablet disintegration apparatus (ED2L Electrolab, India) using 900 ml distilled water without disk at room 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.

Wetting time

Wetting time is closely related to the inner structure of the tablets and to the hydrophilicity of the excipient. It is obvious that pore sizes become smaller and wetting time increases with an increase in compression force or a decrease in porosity. A piece of tissue paper folded double was placed in a Petri plate containing 6 ml of water containing water soluble eosin dye. The tablet was placed on the paper and the time for complete wetting of the tablet was measured in seconds (Kuchekar et al., 2004; Mishra, 2006).

Wetting volume

The tablet was placed in the center of the petridish and with the help of 5 ml pipette; distilled water was added drop wise on the tablet. The volume required to completely disintegrate the tablet was noted as the wetting volume.

Dissolution studies

The dissolution study was performed for all batches and marketed conventional tablet formulation by using apparatus 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 5 ml were withdrawn at specific time interval of 5 to 30 min, filtered and absorbance was measured at 267 nm by UV spectrophotometer (Perkin Elmer).

FTIR studies

The powder blends (drug: superdisintegrants = 1: 1) were kept for one month after which they were physically evaluated and IR studies were carried out. The IR spectrum for pure lamotrigine and

overlay spectra between optimized batch ODT 4 and lamotrigine are shown in Figures 1 and 2 respectively.

RESULTS AND DISCUSSION

The results for evaluation of different batches of Lamotrigine ODT's prepared by direct compression method are shown in Table 2. The most important parameter that needs to be optimized in the development of orally dispersible tablets is the disintegration time of tablets. In the present study tablets in all the batches disintegrated in 30 s fulfilling the official requirements (< 3 min) for dispersible tablets (European Pharmacopoeia, 2001). Figure 3 depicts the disintegration behavior of the tablets in water. It was observed that the disintegration time for the batches (ODT 1, ODT 2, and ODT 5) containing a single superdisintegrant was nearly the same. In order to evaluate the effect of different combinations of superdisintegrants used in different ratios batches (ODT 3, ODT 4, ODT 6-ODT 9) were prepared. *In-vitro* disintegration time for different batches of ODT's was 8-22 s. The tablet formulations containing sodium starch glycolate, croscarmellose sodium and crosspovidone alone at low concentration (1 mg/tablet) showed higher values (20-22 s) for *in-vitro* disintegration time. The *in-vitro* disintegration time for tablet formulations containing low concentration of 1 mg/tablet for two superdisintegrants in combination was observed to be 8-18 s. similar results have been cited in reference (Avani et al., 2008). The tablet formulations containing each of 2 mg of sodium starch glycolate and croscarmellose sodium (ODT 3), each of 2 mg of sodium starch glycolate and crosspovidone (ODT 6), each of 2 mg of croscarmellose sodium and crosspovidone (ODT 7), showed 15, 16 and 18 s respectively. When the amount of sodium starch glycolate and croscarmellose sodium was increased to 4 mg in combination of other superdisintegrants in batch ODT 4, ODT 8, ODT 9 of the

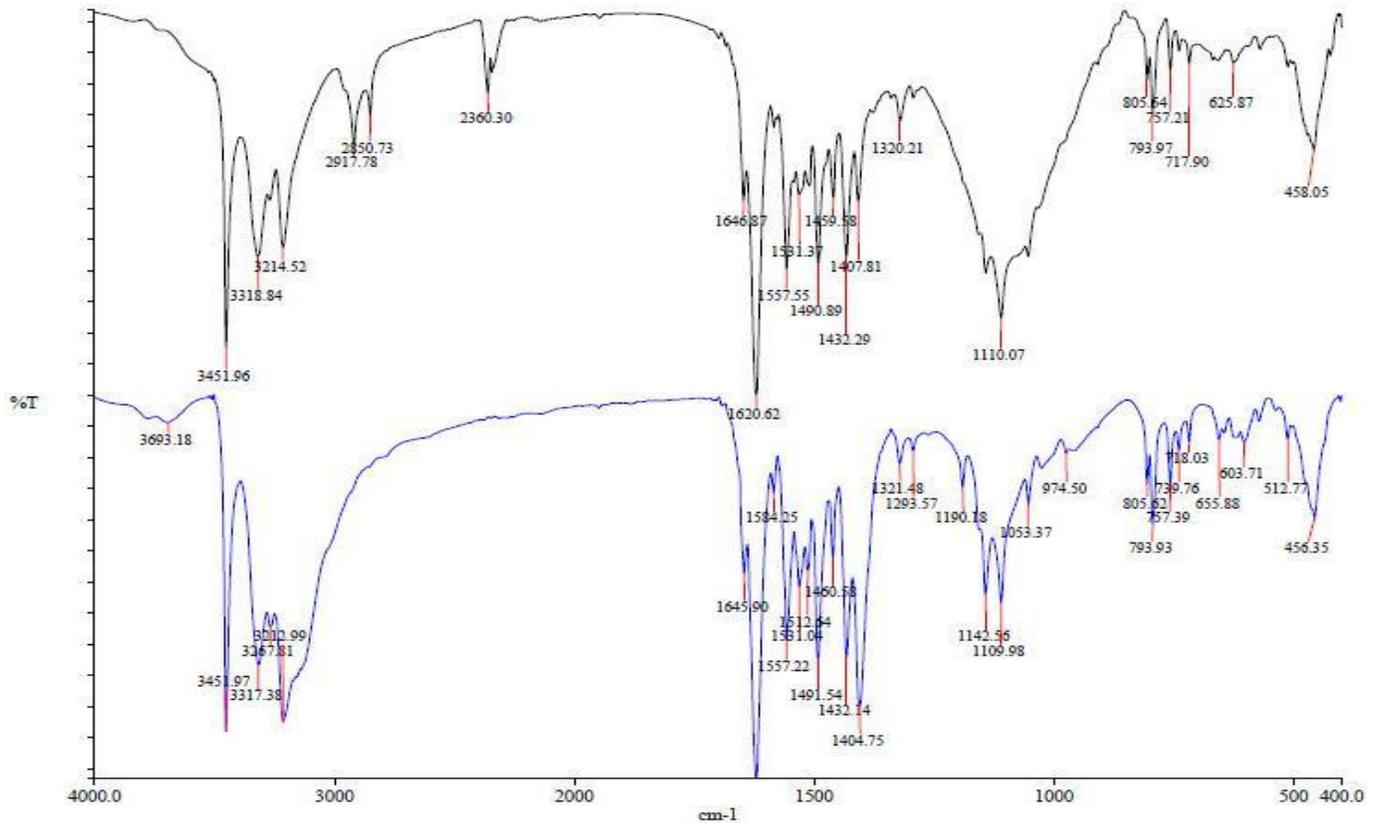


Figure 1. Overlay IR spectra between powder blend (a) and pure lamotrigine (b).

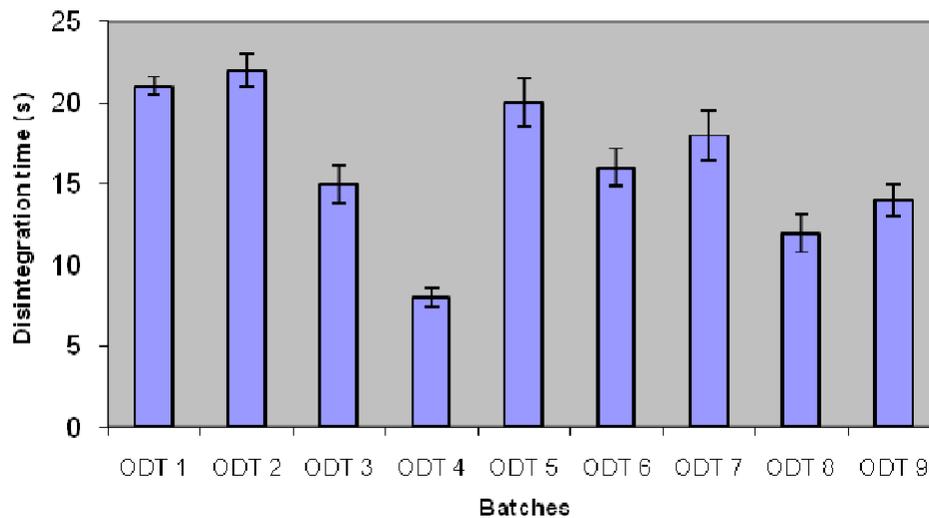


Figure 2. *In-vitro* disintegration time of all formulations in water.

respectively the *in-vitro* disintegration time was reduced to in between 8-14 s. This result of *in-vitro* disintegration time indicates that the batch ODT 4 containing croscarmellose sodium and sodium starch glycolate combination in the ratio of 1:2 showed minimum time of 8 s to disintegrate *in-vitro*.

The wetting volume is important to check minimum volume of water required for wetting of tablet. The wetting volume for batch ODT 4 was 0.45 ml which shows that very small amount of water is required for wetting of tablet. It has been reported that wetting is closely related to the inner structure of the tablets and the hydrophilicity

Table 2. Evaluation parameters of ODT's of Lamotrigine.

| Parameters | ODT 1 | ODT 2 | ODT 3 | ODT 4 | ODT 5 | ODT 6 | ODT 7 | ODT 8 | ODT9 |
|--------------------------------|------------|------------|------------|------------|------------|-------------|------------|------------|-------------|
| Weight variation (%) | 5.2±0.28 | 4.8±0.76 | 4.5±0.55 | 4.2±0.26 | 5.5±0.45 | 5.0±0.50 | 4.7±0.64 | 4.8±0.55 | 4.9±0.36 |
| Hardness (kg/cm ²) | 3.3±0.32 | 3.2±0.39 | 3.0±0.76 | 3.0±0.28 | 3.0±0.59 | 3.0±0.30 | 3.0±0.54 | 3.0±0.94 | 3.0±0.69 |
| Friability (%) | 0.7±0.13 | 0.62±0.16 | 0.67±0.12 | 0.63±0.15 | 0.58±0.14 | 0.7±0.12 | 0.65±0.11 | 0.64±0.13 | 0.61±0.15 |
| Assay | 95.44±0.95 | 94.13±0.93 | 107.2±1.42 | 99.15±0.55 | 94.43±1.34 | 104.65±1.06 | 95.69±0.68 | 92.05±0.59 | 102.56±0.73 |
| Disintegration time (s) | 21-23 | 22-24 | 15-17 | 8-10 | 20-22 | 16-18 | 18-20 | 12-14 | 14-16 |

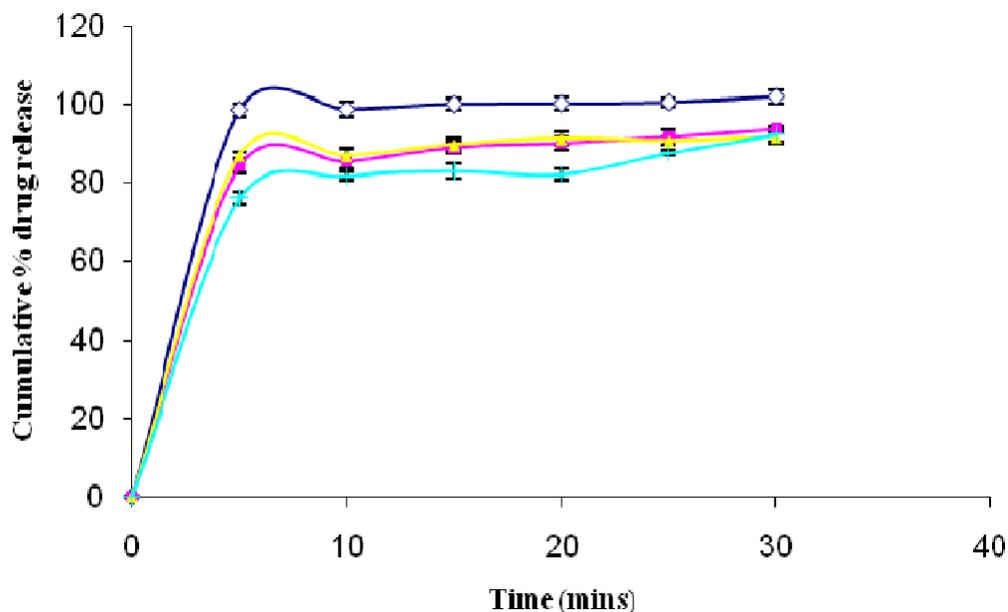


Figure 3. Comparison of drug release profile of batches containing single super disintegrant with marketed formulation in 0.1 N HCl, Mkted. Formulation (○), ODT 1 with Sodium starch glycolate (□), ODT 2 with Croscarmellose sodium (△), ODT 3 containing Crosspovidone XL-10 (+).

excipients. Sodium starch glycolate and croscarmellose sodium show its disintegrant effect by swelling. Thus the result indicates that these tablets would disintegrate almost instantaneously when they will come in contact with even slight

amount of saliva in the mouth. The cumulative percentage drug release of the tablets from the prepared batches along with the marketed tablet formulation is shown in Table 3. It was observed that nearly all the batches showed drug release

close to 100% in 0.1 N HCl. Therefore in order to differentiate between the release profile and to maintain the saliva pH, studies were carried out in pH 6.8 buffer also. In pH 6.8 almost 70% of the drug was released within 30 min for all the

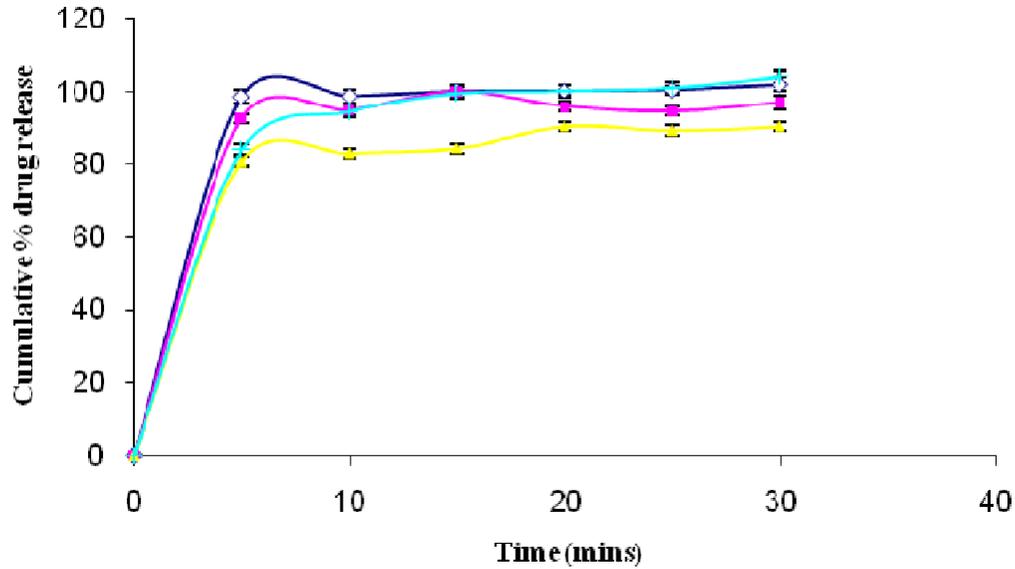


Figure 4. Comparison of drug release profile of batches containing blend of super disintegrants (1:1) with marketed formulation in 0.1 N HCl, Mkted. Formulation (), ODT 3 with Sodium starch glycolate and Croscarmellose sodium (), ODT 6 with Sodium starch glycolate and Crosspovidone XL-10, (), ODT 7 containing Croscarmellose sodium and Crosspovidone XL-10 (+).

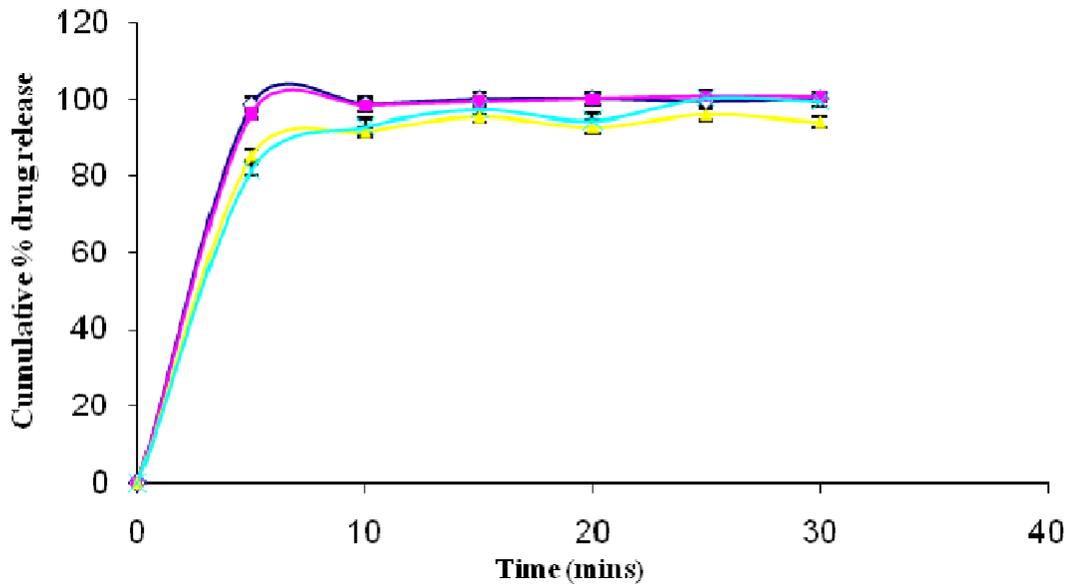


Figure 5. Comparison of drug release profile of batches containing blend of super disintegrants (2:1) with marketed formulation in 0.1 N HCl, Mkted. Formulation (), ODT 4 with Sodium starch glycolate and Croscarmellose sodium (), ODT 8 with Sodium starch glycolate and Crosspovidone XL-10 (), ODT 9 containing Croscarmellose sodium and Crosspovidone XL-10 (+)

batches. In 0.1 N HCl, batch ODT 4 gave better release profile of around 72% in 30 min as compared to other batches. Release profiles of batches containing a single superdisintegrant and a mixture of superdisintegrants in the ratio (1:1) and (1:2) compared with release profile of marketed formulation are shown in Figures 4 and 5

respectively. For the batch ODT 4, in first 10 min 98% of the drug was released which was comparable to the release profile of marketed tablet formulation as shown in Figure 5. Its disintegration time was also found to be within 8-10 s so this batch was selected as optimized batch. Thus the disintegration time was reduced and also

Table 3. Dissolution profiles of ODT's of Lamotrigine.

| Time (min) | Cumulative percentage drug release* | | | | | | | | | |
|------------|-------------------------------------|------------|------------|-------------|------------|------------|-------------|------------|-------------|-----------------|
| | ODT 1 | ODT 2 | ODT 3 | ODT 4 | ODT 5 | ODT 6 | ODT 7 | ODT 8 | ODT 9 | Marketed tablet |
| 5 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 10 | 84.31±1.73 | 87.12±0.82 | 92.57±1.29 | 96.24±1.20 | 76.2±1.77 | 80.75±1.22 | 83.89±1.55 | 85.28±1.47 | 81.55±1.29 | 98.57±1.78 |
| 15 | 85.52±1.57 | 86.99±1.67 | 94.74±1.76 | 98.33±1.52 | 81.85±0.96 | 82.97±1.39 | 94.47±1.42 | 91.66±1.23 | 93.01±1.94 | 98.72±1.85 |
| 20 | 89.11±1.62 | 89.86±1.59 | 99.97±1.52 | 99.24±1.47 | 83.19±1.79 | 84.29±1.40 | 99.52±1.75 | 95.53±1.57 | 97.4±1.79 | 100.07±1.59 |
| 25 | 90.15±1.79 | 91.32±1.66 | 95.85±1.39 | 100.06±1.53 | 82.31±1.59 | 90.28±1.45 | 100.13±1.49 | 92.89±1.79 | 94.56±1.66 | 100.21±1.64 |
| 30 | 91.68±1.82 | 90.76±0.89 | 94.47±1.44 | 100.74±1.34 | 87.78±0.82 | 89.09±1.48 | 101.07±1.68 | 96.08±1.65 | 100.32±1.73 | 100.5±0.96 |
| | 93.6±0.97 | 91.71±1.78 | 96.91±1.76 | 100.6±1.29 | 92.4±1.64 | 90.15±1.24 | 104.04±1.77 | 94.15±1.37 | 99.5±1.64 | 101.98±1.84 |

* The data are expressed as mean ± S.D. (n=3).

the release rate was improved by using two superdisintegrants (Croscarmellose sodium and Sodium starch glycolate in ratio of 1:2) in combination.

Further pharmacokinetic studies of the optimized batch were carried out to determine the release mechanism followed by the drug. It was found that the drug followed Korsmeyer model of drug release with a regression co-efficient (r^2) value of 0.975. The value of diffusional co-efficient (n) was found to be 0.0211 which was less than 0.45 which indicates that the drug follows Fickian diffusion mechanism.

CONCLUSION

Orally disintegrating tablets of lamotrigine were prepared by direct compression method using croscarmellose sodium and sodium starch glycolate as superdisintegrants in combination in the ratio of 1:2 (ODT4). The tablets had acceptable hardness of average 3 kg/cm² and approx. 0.67% friability. *In-vitro* disintegration time was reduced and *in-vitro* drug release was significantly improved. Hence it can be concluded

that using a combination of superdisintegrants viz., croscarmellose sodium and sodium starch glycolate in the ratio of 1:2 in formulation of orally disintegrating tablets of lamotrigine would be quite effective in providing fast onset of action without the need of water for swallowing.

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