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Formulation and evaluation of lacosamide fast dissolving tablets

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ABSTRACT

In spite of the fact that, the Oral administration of drug is the most popular route about 50-60% of total dosage forms are administered due to ease of ingestion, pain avoidance, versatility (to accommodate various types of drug candidates), and most importantly patient compliance. Solid oral delivery systems do not require sterile conditions and are therefore less expensive to manufacture. However the main aim of this study is to formulate Oral Disintegrating Tablets of Lacosamide to achieve rapid dissolution, absorption and further improving the bioavailability of the drug. Oral disintegrating Tablets and Films of Lacosamide were designed with a view to enhance the patient compliance and provide a quick onset of action.

Keywords: Fast dissolving tablets, Lacosamide, Oral disintegration and drug release profile.

INTRODUCTION

One important drawback of solid dosage forms is the difficulty in swallowing (dysphasia) or chewing in some patients particularly pediatric and geriatric patients [1, 2]. The problem of swallowing is common phenomenon in geriatric patient due to fear of choking, hand tremors, dysphasia and in children's due to underdeveloped muscular and nervous systems and in schizophrenic patients resulting in poor compliance with oral tablet drug therapy which leads to reduced overall therapy effectiveness. Difficulties in swallowing of tablet and capsule also occur when water is not available, in diarrhea, coughing during the common cold, allergic condition and bronchial infection.

Oral fast dissolving drug delivery system (OFDDS) is one such novel approach to increase consumer acceptance by virtue of rapid disintegration, self-administration without water or chewing [3]. Orally disintegrating tablets (ODT) are solid unit dosage forms like conventional tablets, but are composed of superdisintegrants, which help them to disintegrate the tablet rapidly in saliva without the need to take it water. Orally disintegrating tablets (ODT) are not only indicated for people who have swallowing difficulties, but also are ideal for active people.

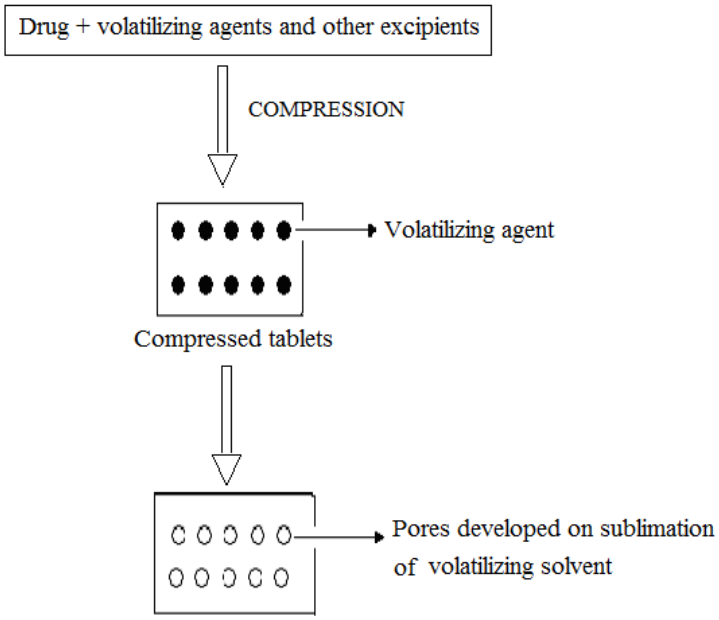

Figure 1: Steps involved in sublimation [7, 9]

MATERIALS & METHODS

Procedure for preparation of standard graph of Lacosamide

Accurately weighed amount of 100mg of Lacosamide is taken in a 100ml volumetric flask. The volume was made up to 100ml with distilled water, which constitutes the stock solution of 1mg/ml. by further diluting the stock solution suitably with distilled water solutions of 5, 10, 15, 20, 25 and 30µg/ml concentrations were prepared. These solutions were checked for their absorbance using UV – Visible spectrophotometer at λ_{max} 230 nm against distilled water as blank and a standard graph was potted [3-10].

Table 1: Calibration curve for the estimation of Lacosamide

S.NO.	Concentration(µg/ml)	UV Absorbance (n=5)
1	5	0.132
2	10	0.242
3	15	0.395
4	20	0.528
5	25	0.656
6	30	0.813

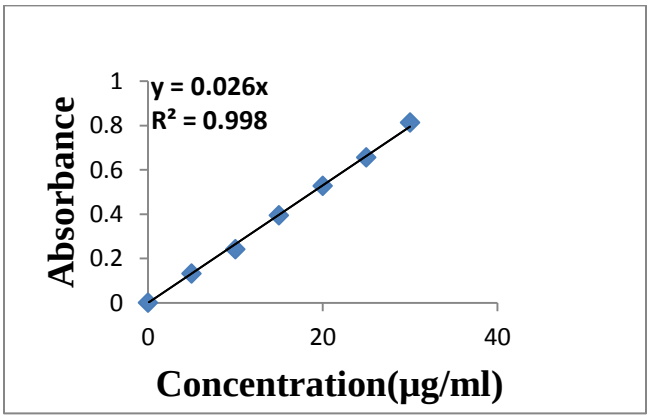

Figure 2: Calibration curve for the estimation of Lacosamide

The present analytical method obeyed Beer's law in the concentration range of 5 – 30 µg/ml and is suitable for the estimation of Lacosamide form different solutions. The correlation coefficient (r) value for the linear regression equation was found to be 0.998, indicating a positive correlation between the concentration of Lacosamide and its corresponding absorbance values [11-18].

Formulation design

Lacosamide ODTs were prepared using direct compression technique. Direct compression technique is a convenient method but the excipients used in this method are costlier when compared to the excipients used in the wet granulation technique [18-23].

RESULTS AND DISCUSSION

Dissolution test was carried out using USP rotating paddle method (apparatus 2). The stirring rate was 50 rpm. 6.8 pH phosphate buffer was used as dissolution medium (900ml) and was maintained at 37 ± 1^0C. Samples of 5ml were withdrawn at pre – determined intervals (2, 4, 6, 8, 10, 15, 20, 25, 30 min), filtered and replaced with 5ml of fresh dissolution medium. The collected samples were suitably dilutedwith dissolution fluid, where ever necessary and were analyzed for the Lacosamide at 230 nm by using UV spectrophotometer. Each dissolution study was performed for three times and mean values were taken [24-30].

Table 2: Preformulation characteristics of Lacosamide ODTs

Formulation	Bulk density (g/cc)	Tapped density (g/cc)	Hausner ratio	Compressibilty index (%)	Angle of repose (ɵ)
F1	0.435	0.522	1.20	16.66	32.67
F2	0.429	0.518	1.20	17.18	29.08
F3	0.430	0.524	1.21	17.93	31.78
F4	0.432	0.528	1.22	18.18	30.64
F5	0.428	0.518	1.21	17.37	30.36
F6	0.420	0.510	1.21	17.64	31.05
F7	0.416	0.509	1.22	18.27	32.54
F8	0.417	0.515	1.23	19.02	29.67
F9	0.425	0.515	1.21	17.47	31.85
F10	0.421	0.509	1.20	17.28	29.56
F11	0.419	0.515	1.22	18.64	30.17
F12	0.415	0.512	1.23	18.94	32.08

Table 3: Tabletting characteristics of Lacosamide ODTs

Formulation	Weight (mg)	Drug content (%)	Hardness (kg/cm^2)	Friability (%)	Thickness (mm)
F1	79.9±0.70	98.96±0.47	3.05±0.13	0.48	3.84±0.032
F2	79.52±0.85	99±0.65	3.10±0.15	0.53	3.85±0.028
F3	78.9±0.52	99.11±0.52	2.95±0.08	0.44	3.86±0.024
F4	80.2±1.17	99.15±0.60	2.95±0.10	0.57	3.86±0.051
F5	79.0±0.49	99.2±0.4	3.08±0.12	0.43	3.88±0.048
F6	78.8±0.58	98.85±0.58	3.11±0.14	0.56	3.90±0.052
F7	79.3±0.54	99.31±0.24	2.92±0.08	0.53	3.92±0.038
F8	80.4±1.0	98.96±0.28	3.0±0.09	0.45	3.91±0.042
F9	79.6±0.95	99.3±0.38	2.9±0.07	0.6	3.90±0.040
F10	79.2±0.97	99.36±0.29	3.05±0.08	0.49	3.89±0.042
F11	79.4±0.86	98.75±0.40	3.05±0.09	0.53	3.89±0.034
F12	78.5±0.42	99.21±0.38	2.93±0.08	0.58	3.87±0.031

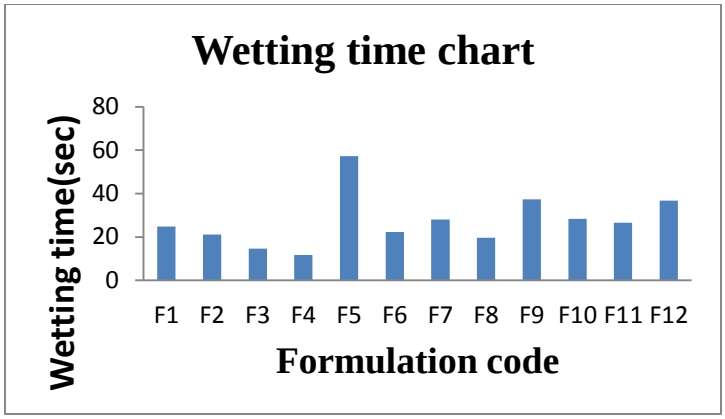

Figure 3: Graphical representation of wetting time of Lacosamide ODTs prepared by varying concentrations of superdisintegrants

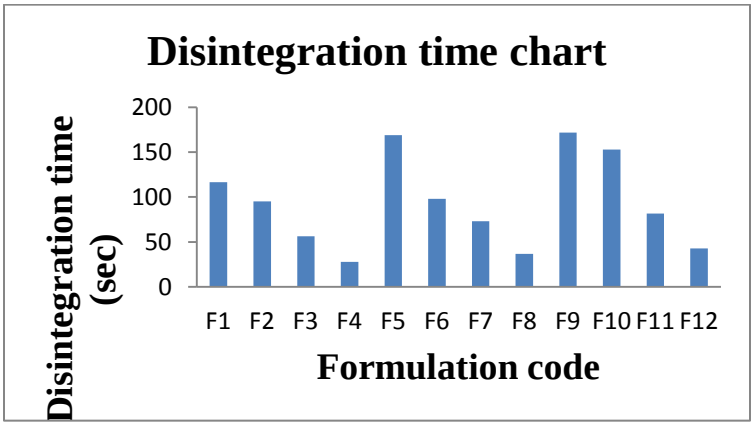

Figure 4: Graphical representation of disintegration times of Lacosamide ODTs prepared by varying concentrations of superdisintegrants

Table 4: Cumulative percent Lacosamide released from ODTs containing varying concentrations of different superdisintegrants

Cumulative percent (±S.D.) drug released						
Time (min)	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**
2	27.35±0.28	22.35±0.52	20.46±0.25	28.31±0.23	18.35±0.34	15.43±0.30
4	40.33±0.28	34.36±0.28	29.28±0.19	41.33±0.24	25.5±0.28	23.43±0.32
6	55.46±0.31	45.31±0.27	42.35±0.25	59.33±0.26	37.36±0.25	37.36±0.26
8	69.46±0.27	62.35±0.25	61.31±0.23	73.48±0.34	57.41±0.23	54.38±0.26
10	74.38±0.27	75.48±0.30	76.4±0.36	85.38±0.34	64.55±0.28	67.38±0.37
15	83.35±0.20	87.4±0.31	82.53±0.30	98.6±0.29	72.48±0.35	75.46±0.26
20	94.45±0.30	96.31±0.29	97.31±0.20	98.89±0.32	80.45±0.28	82.31±0.23
25	94.89±0.24	96.57±0.28	97.76±0.28	98.95±0.24	86.5±0.26	87.48±0.24
30	95.78±0.27	96.85±0.32	97.96±0.25	98.99±0.23	89.53±0.19	92.36±0.25

Table No 5: Cumulative percentage drug release

Cumulative percent (±S.D.) drug released						
Time (min)	**F7**	**F8**	**F9**	**F10**	**F11**	**F12**
2	22.33±0.25	14.38±0.31	19.33±0.20	23.43±0.16	18.48±0.33	19.4±0.32
4	33.36±0.31	22.1±0.59	28.36±0.32	35.31±0.27	27.18±0.18	27.41±0.26
6	45.46±0.26	36.43±0.30	36.45±0.25	47.36±0.29	34.43±0.23	35.28±0.29

8	62.43±0.23	55.46±0.30	49.43±0.26	53.5±0.34	45.61±0.17	52.43±0.26
10	70.28±0.20	62.46±0.25	55.48±0.26	64.45±0.30	52.41±0.36	65.41±0.33
15	78.41±0.26	75.58±0.27	68.46±0.32	72.6±0.27	61.25±0.55	78.45±0.35
20	86.28±0.24	80.4±0.26	74.58±0.27	78.41±0.14	70.46±0.21	84.51±0.24
25	90.28±0.17	83.48±0.30	78.43±0.27	83.45±0.28	75.41±0.24	88.36±0.18
30	94.46±0.25	95.43±0.19	85.4±0.22	88.45±0.18	90.4±0.33	92.38±0.19

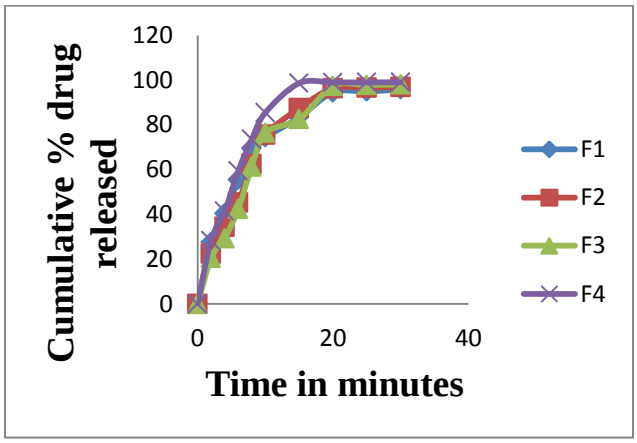

Figure 5: Graphical representation of Cumulative percent Lacosamide released from ODTs containing varying concentrations of crosspovidone

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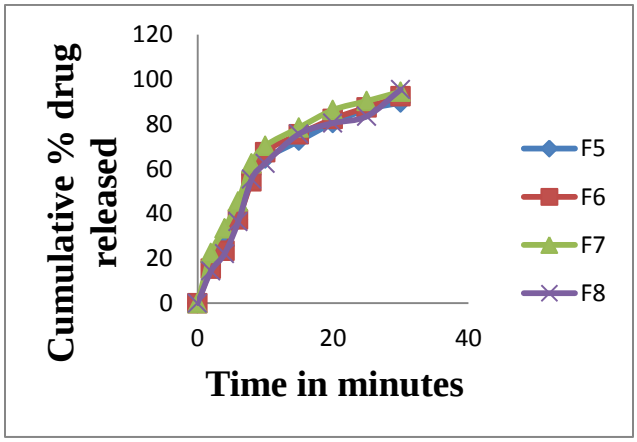

Figure 6: Graphical representation of Cumulative percent Lacosamide released from ODTs containing varying concentrations of croscarmellose sodium.

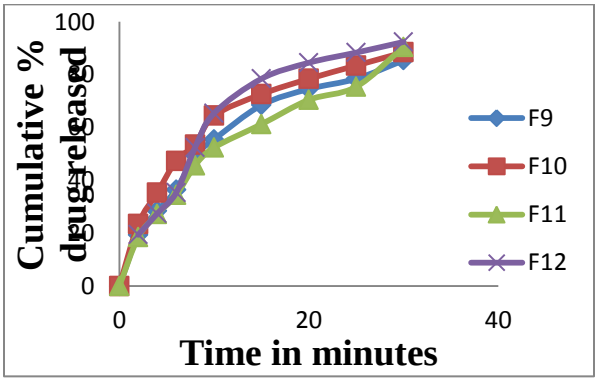

Figure 7: Graphical representation of Cumulative percent Lacosamide released from ODTs containing varying concentrations of sodium starch glycolate.

Table 6: Formulae of Lacosamide ODTs prepared with combination of superdisintegrants

Ingredients	CP + CCS				CP + SSG			
	6%	8%	10%	12%	6%	8%	10%	12%
Lacosamide	4	4	4	4	4	4	4	4
Superdisintegrants	4.8	6.4	8	9.6	4.8	6.4	8	9.6
Avicel PH 102	53.2	51.6	50	48.4	53.2	51.6	50	48.4
Pearlitol SD200	10	10	10	10	10	10	10	10
Sucralose	5	5	5	5	5	5	5	5
Orange flavor	2	2	2	2	2	2	2	2
Sodiumstearyl fumerate	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Colloidal silica	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Total weight (mg)	80	80	80	80	80	80	80	80

Note: CP – Crosspovidone, CCS – Croscarmellose Sodium, SSG – Sodium Starch Glycolate

Table 7: Preformulation characteristics of Lacosamide ODTs prepared with combination of superdisintegrants

Formulation	Bulk density (g/cc)	Tapped density (g/cc)	Hausner ratio	Compressibilty index (%)	Angle of repose (ɵ)
F13	0.420	0.520	1.23	19.23	29.67
F14	0.423	0.512	1.21	17.38	29.54
F15	0.435	0.520	1.20	16.34	31.76
F16	0.422	0.512	1.21	17.57	32.04
F17	0.425	0.523	1.23	18.73	30.56
F18	0.434	0.526	1.21	17.49	31.23
F19	0.426	0.512	1.20	16.79	29.52
F20	0.420	0.519	1.23	19.07	29.32

Table 8: Tabletting characteristics of Lacosamide ODTs prepared with combination of superdisintegrants

Formulation	Weight (mg)	Drug content (%)	Hardness (kg/cm^2)	Friability (%)	Thickness (mm)
F13	80.3±1.18	98.56±0.49	3.19±0.05	0.47	3.86±0.034
F14	79.3±0.53	98.61±0.60	3.16±0.04	0.52	3.86±0.023
F15	80.1±0.75	98.98±0.56	3.10±0.10	0.63	3.87±0.044
F16	80.3±0.86	99.03±0.58	3.05±0.09	0.58	3.89±0.051
F17	79.1±0.84	97.75±0.69	3.15±0.04	0.58	3.85±0.029
F18	78.8±0.56	98.76±0.56	2.92±0.08	0.53	3.88±0.046
F19	79.6±0.60	99.08±0.29	3.00±0.09	0.51	3.86±0.025
F20	80.0±0.75	98.86±0.39	3.12±0.12	0.55	3.84±0.034

Table 9: Other Parameters of the formulation

Formulation	Wetting time (sec)	*In vitro* dispersion time (sec)	Disintegration time (sec)	Water absorption ratio (%)
F13	19.33±0.51	91.66±1.21	82.5±1.04	59.49
F14	14.33±0.51	49.33±1.03	46±0.89	56.59
F15	**11.16±0.75**	**30.66±0.81**	**17.66±0.51**	**57.08**
F16	12.5±0.54	35.16±0.75	20.33±0.81	58.72
F17	19.1±0.75	96.83±0.40	86.16±0.75	57.95
F18	14.83±0.75	54.16±1.72	47.5±1.04	60
F19	11.5±0.54	46.66±0.81	23.66±0.51	61.50
F20	13±0.89	43.83±0.75	20.83±1.16	58.24

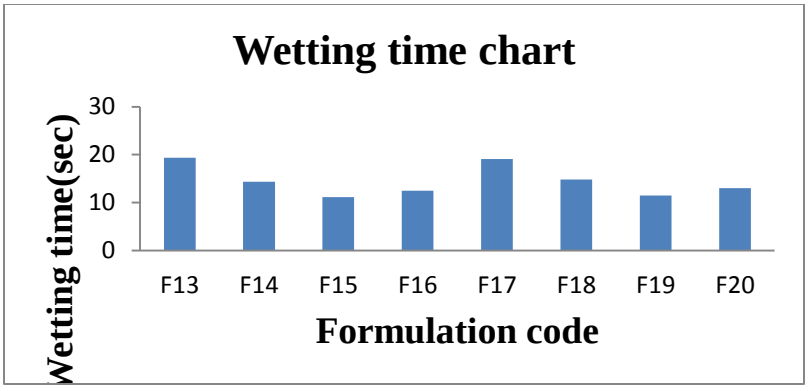

Figure 8: Graphical representation of witting time of Lacosamide ODTs prepared by varying concentrations of combination of superdisintegrants

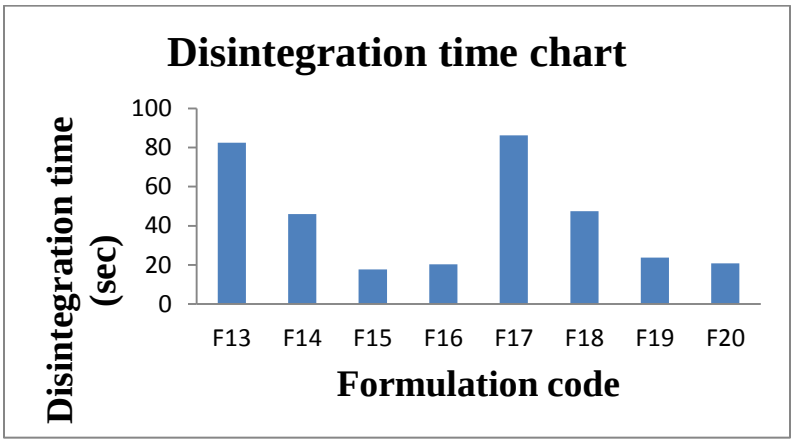

Figure 9: Graphical representation of disintegration times of Lacosamide ODTs prepared by varying concentrations of combination of superdisintegrants

Table 10: Cumulative percent Lacosamide released from ODTs prepared by varying concentrations of combination of superdisintegrants

Cumulative percent (±S.D.) drug released				
Time (min)	**F13**	**F14**	**F15**	**F16**
2	17.41±0.26	26.21±0.17	25.43±0.29	21.4±0.24
4	25.43±0.25	32.38±0.21	37.41±0.31	31.43±0.33
6	37.43±0.33	45.31±0.27	51.36±0.28	40.25±0.18
8	53.45±0.26	60.25±0.15	68.35±0.31	64.45±0.28
10	66.43±0.24	75.31±0.29	77.35±0.28	71.53±0.26
15	78.45±0.24	87.48±0.24	89.4±0.2	79.46±0.22
20	83.45±0.24	89.31±0.17	93.38±0.24	84.53±0.25
25	85.35±0.25	96.52±0.19	99.87±0.18	89.55±0.16
30	94.5±0.21	------	------	96.38±0.24

Table 11: Cumulative percentage drug release

Cumulative percent (±S.D.) drug released				
Time (min)	**F17**	**F18**	**F19**	**F20**
2	13.48±0.27	24.55±0.32	24.35±0.30	26.3±0.28
4	25.35±0.30	35.3±0.28	31.41±0.25	38.3±0.28
6	33.4±0.20	42.4±0.31	43.53±0.21	50.36±0.24
8	50.38±0.18	53.38±0.27	57.43±0.33	61.48±0.21
10	61.4±0.30	65.43±0.35	69.53±0.24	69.35±0.28

15	75.55±0.32	76.5±0.28	77.48±0.34	76.51±0.17
20	77.43±0.29	82.45±0.30	85.38±0.23	81.48±0.24
25	82.45±0.18	86.5±0.26	91.45±0.18	84.45±0.27
30	88.56±0.21	92.5±0.14	95.48±0.18	94.51±0.19

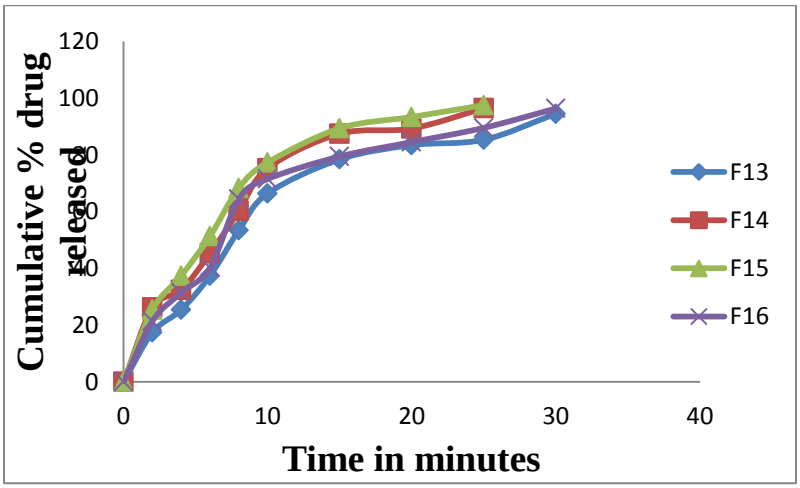

Figure 10: Graphical representation of Cumulative percent Lacosamide released from ODTs containing varying concentrations of CP + CCS

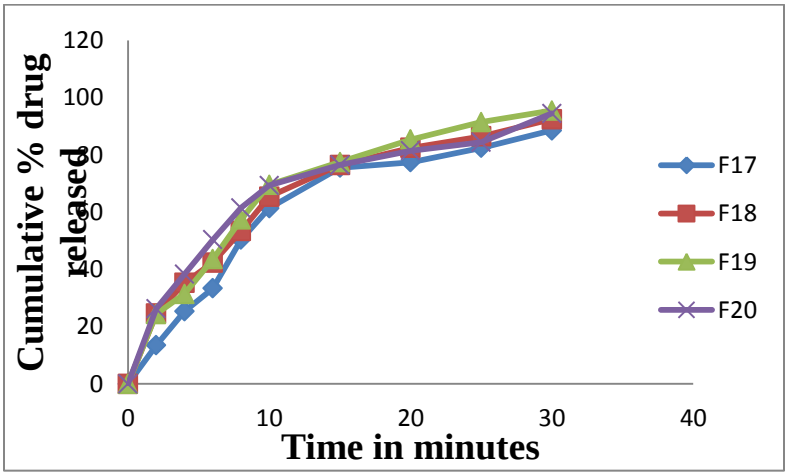

Figure 11: Graphical representation of Cumulative percent Lacosamide released from ODTs containing varying concentrations of CP + SSG

To achieve such a formulation, most of the excipients selected must be water soluble by nature. Pearlitol SD 200 is a directly compressible grade of mannitol with good flow properties and gives a refreshing or cooling effect in the mouth due to its negative heat of solution. This excipient was used a bulking agent to achieve the desired tablet weight. Avicel 102 was included in the formulation mainly as a disintegrant at the concentrations used and to some extent as diluents. This grade of microcrystalline cellulose is granular in nature and thus displays excellent flow. To impart pleasant taste and mouth feel sodium saccharin and orange were included as sweetening and flavoring agents respectively. Sodium stearyl fumerate was employed as a lubricant instead of magnesium stearate to overcome the metallic taste of the latter and also due to its water soluble nature.

Crosspovidone polymers are densely crosslinked homopolymers of N – vinyl 2 – pyrrolidones. Their porous particle morphology helps to rapidly wick liquids into the tablet by capillary action to generate the rapid volume expansion and hydrostatic pressures that cause tablet disintegration. In addition to its unique particle size and morphology, crosspovidone is non

ionic and its disintegration performance will neither be influenced by pH changes in the gastrointestinal tract nor will they complex with ionic drug actives. They can also be used as solubility enhancers resulting in a faster dissolution rate without forming gels.

Croscarmellose sodium is cross-linked carboxymethyl cellulose sodium which can be used at concentrations of upto 5% as a disintegrant. Its unique fibrous nature gives excellent water wicking capabilities and crosslinking makes it hydrophilic and highly absorbent material, resulting in its swelling properties. It rapidly swells upto 4 – 8 times its original volume on contact with water. Like crosspovidone, it is also used as a dissolution aid, hence the name Ac-Di-Sol (accelerates dissolution).

Sodium starch glycolate is a sodium salt of carboxymethyl ether of starch,usually employed at concentrations between 2 – 8% although an optimum concentration of 4% may sufficient in many cases. Disintegration occurs by rapid uptake of water followed by rapid and enormous swelling, which is its primary mechanism of action. It (explotab) swells upto 300 times its original volume in water.

In all formulations, tablet weight and thickness were within mean ±7.5% and mean ±5% respectively. The weight variation in all the twenty formulations was found to be 78.5 mg to 80.4 mg, which was in pharmacopoeial limits. The thickness varies between 3.84 to 3.92 mm. Friability values were less than 1% in all cases. Hardness of all the tablets was maintained at 2.9 to 3.19 kg for all the formulations as mentioned before. Assay was performed and percent drug content of all the tablets were found to be between 97.75% and 99.36% of Lacosamide, which was within the acceptable limits.

Wetting time was determined for all the formulations. The values lie between 11.16±0.75 to 57.33±0.81. The variability in wetting time for different formulations may be due to the changes in the compaction which cannot be controlled during tablet preparation and the type of the disintegrant affected the wetting of the tablets. On comparing the superdisintegrants the formulations containing crosspovidone + croscarmellose sodium and crosspovidone + sodium starch glycolate take less wetting time than the other formulatios containing single superdisintegrants.

Water absorption ratio ranged from 56.59 % – 67.54 %. Crosspovidone and croscarmellose sodium perform their disintegrating action by wicking through capillary action and fibrous structure, respectively with minimum gelling. The relative ability of the various disintegrants to wick water into the tablets was studied. After contact with water the tablets containing sodium starch glycolate swelled, the outer edge appeared gel like. Tablets containing crosspovidone quickly wicks water and were hydrated, but were soft as compared with tablets prepared with crosscarmellose sodium and sodium starch glycolate. The center of the tablets with sodium starch glycolate and croscarmellose sodium remained dry and hard.

Disintegration time is considered to be important criteria in selecting the best ODT formulation. The *in vitro* disintegration time for all the twenty formulations varied from 17.66±0.51 to 171.83±1.16 seconds. The rapid disintegration was seen in the formulations containing crosspovidone and formulations containing combination of superdisintegrants (CP + CCS, CP + SSG). This is due to rapid uptake of the water from the medium, swelling and burst effect. It is also noticed that as the disintegrant concentration was increased from 9 to 12% the time taken for disintegration was reduced. The disintegration time of formulation (F15) containing 5% CP + 5% CCS was found to be lower (17.66±0.51) and was selected as the best ODT formulation among all the 20 formulations.

In *vitro* dispersion is a special parameter in which the time taken by the tablet for complete dispersion is measured. The time for all the twenty formulations varied between 30.66±0.81 and 259.83±1.47 sec.

The development of dissolution method for ODTs is almost similar to the approach taken for conventional tablets until they utilize the taste masking. The taste masking aspect greatly influences dissolution method development, specifications, and testing. Several factors like varied thickness and pH dependent solubility of drug particle coating influence dissolution profiles of ODTs containing taste masked actives. Since Lacosamide is not bitter in taste, the metallic taste of drug was masked by using sweeteners and flavors. It has been reported that USP type II apparatus with a paddle speed of 50 rpm is commonly used for ODT formulations. Slower

paddle speeds are utilized to obtain good profiles as these formulations disintegrate rapidly.

In *vitro* dissolution studies of the prepared ODTs was performed in pH 6.8 phosphate buffer using USP dissolution apparatus type 2. The dissolution rate was found to increase linearly with increasing concentration of superdisintegrant. Formulations F1, F2, F3 and F4 which contained increasing concentrations of crosspovidone have recorded drug release 95.78%, 96.85%, 97.96 and 98.99% respectively within 20 to 30 min. Formulations F5, F6, F7 and F8 which contained increasing concentrations of croscarmellose sodium have recorded drug release 89.53%, 92.36%, 94.46% and 95.43% respectively, at the end of 30 min. Formulations F9, F10, F11 and F12 which contained increasing concentrations of sodium starch glycolate have recorded drug release 85.4%, 88.45%, 90.4% and 92.38% respectively, at the end of 30 min.

Formulations F13, F14, 15 and F16 which contained increasing concentrations of combination of CP + CCS have recorded drug release 94.5%, 96.52%, 99.87% and 96.38% respectively, at the end of 25 to 30 min. Formulations F17, F18, F19 and F20 which contained increasing concentrations of combination of CP + SSG have recorded drug release 88.56%, 92.5%, 95.48% and 94.51respectivel, at the end of 30 min.

CONCLUSION

In our current research, the Oral Disintegrating Tablets of Lacosamide were formulated with an aim to improve the versatility, patient compliance and accurate dosing. The formulation contained combination of CP with CCS showed better performance in terms of disintegration time when compared to other formulations. The formulation F15 was found to be the best among the all twenty Lacosamide ODT formulations because it has exhibited faster disintegration time (17.66 sec) when compared to the other formulations and it showed 99.87±0.18%drug release at the end of 25 min. Based on disintegration and dissolution results it was concluded that the formulation F15 contained CP 5% with CCS 5% was the best formulation among the all other formulations. The metallic taste of the drug was masked by Sodium saccharin and Orange flavor as well.

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