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FORMULATION DEVELOPMENT AND CHARACTERIZATION OF FAST DISSOLVING TABLETS OF OXCARBAZEPINE

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ABSTRACT:
The objective of this study was formulation, development and evaluation of Oxcarbazepine Fast Dissolving Tablets (FDTs) prepared by using novel co-processed super-disintegrants. FDTs were prepared by direct compression method using co-processed super-disintegrants crosscarmellose sodium and sodium starch glycolate in different ratios (1:1, 1:2, and 1:3). The prepared FDTs were evaluated for weight variation, thickness, drug content, friability, hardness, wetting time, water absorption ratio, in-vitro dispersion time, invitro disintegration time and invitro dissolution time. The optimized batch (F9) was subjected to stability testing for 3 months at temperatures 40^0C and 75% relative humidity and at room temperature and at 60% relative humidity. All the prepared formulae complied with Pharmacopoeial requirements of drug contents. FDT formula F9 has shown no appreciable changes with respect to physical characters, Drug content, in vitro dispersion and dissolution profiles when stored at prescribed temperature and relative humidity.

Keywords: Fast Dissolving Tablets (FDT), Co-processed superdisintegrants, Oxcarbazepine, Crosscarmellosesodium, sodium starch glycolate.

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INTRODUCTION

Oral drug delivery system[1, 2, 3, 4]

Oral drug delivery has been known for decades as the most widely utilized route of administration among all the routes that have been explored for the systemic delivery of drugs via various pharmaceutical products of different dosage forms. Drinking water plays an important role in the swallowing of oral dosage forms. Often people experience inconvenience in swallowing conventional tablets and capsules when water is not available, in case of motion sickness (kinetosis) and sudden episodes of coughing during the common cold, allergic conditions and bronchitis. For these reasons, tablets which can rapidly dissolve or disintegrate in the oral cavity have attracted a great deal of attention. Tablets are the most widely used dosage form existing today because of its convenience in terms of self-administration, compactness and ease of manufacturing. However, geriatric, pediatric and mentally ill patients experience difficulty in swallowing conventional tablets, which leads to poor patient compliance. To overcome these problems, scientists have developed innovative drug delivery system known as mouth dissolving/ disintegrating tablets (MDTs) or fast dissolving tablets. These are novel types of tablets that dissolve/ disintegrate/ disperse in saliva within few seconds without water.

Drug selection criteria for FDTs[5, 6]

The ideal characteristics of a drug for Fast dissolving tablet include

- At least partially non-ionized at the oral cavity pH.
- Provide pleasant feeling in the mouth.
- No water requirement for swallowing purpose, but it should dissolve or disintegrate in the mouth usually within fraction of minute.
- Be compatible with taste masking and other excipients.
- Low dose drugs preferably less than 50mg.
- Leave minimal or no residue in the mouth after oral administration.
- Exhibit low sensitivity to altered environmental conditions such as humidity and temperature.
- Drug should have good stability in saliva and water.

- Short half life and frequent dosing drugs are unsuitable for FDT.

Co-processed Excipients[7]

Co-processing is based on the novel concept of two or more excipients interacting at the subparticle level, the objective of which is to provide a synergy of functionality improvement as well as masking the undesirable properties of individual. Co-processing excipients results in granules with superior properties, compared with physical mixtures of components or individual components, like improved flow properties, improved compressibility, better dilution potential, fill weight uniformity, and reduced lubricant sensitivity. The combination of excipients chosen should complement each other to mask the undesirable properties of individual excipients and, at the same time, retain or improve the desired properties of excipients.

MATERIALS AND METHODS

Materials

Materials used in this experiment is given in table 0.1

Table 0.1: Materials and equipments used in this experiment

Drug / Excipients	Source	Equipment's	Source
Oxcarbazepine	Gift Sample From VergoPharma research Laboratories pvt. Ltd	Electronic Weighing Balance	Contech instruments Ltd
Microcrystalline Cellulose	Prima Ltd, Ahmadabad, Gujarat	Compression machine	Cadmach machine, Ahmedabad
Crosscarmellose sodium, Sodium Starch Glycolate , Aspartate	Maxwell Life Sciences, Tarapur.	Dissolution Apparatus (U.S.P.)	Electrolab, Mumbai
		FT-IR Spectrometer	Perkin Elmer
		Mechanical stirrer	Remi
Crospovidone , L-HPC	Fine Lab	Hardness tester	Monsanto
		Stability Chamber	Quality instruments and equip
Menthol , Magnesium Stearate, Methanol ,Ethanol & Camphor	Lobachem.	U.V. spectrophotometer	Systronics UV 2201
		Friability tester	Dolphin VFT-1D

METHOD FOR PREPARATION[8]

Direct compression method:

Nine batches of Fast dissolving tablets of Oxcarbazepine were prepared by direct compression as per composition shown in table No1.All ingredients (except avicel pH102 and co-processed superdisintegrants) were passed through # 60-mesh separately. Then the ingredients were weighed and mixed in geometrical order for 15 to 20 min. and compressed into tablets of 500mg using 8mm punch on 16-station rotary tablet punching machine (cadmach, Ahmedabad)

Table 1.Composition of Oxcarbazepine FDTs prepared by Direct Compression method.

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
Avicel pH 102	192	178	178	172	172	172	172	172	172
Crosscarmellose sodium (CCS)	-	14	-	-	-	-	-	-	-
Sodium Starch Glycolate (SSG)	-	-	14	-	-	-	-	-	-
CCS + SSG	-	-	-	20	20	20	20	20	20
Total	500	500	500	500	500	500	500	500	500

Oxcarbazepine (300mg) ,Magnesium Stearate(3mg)& Aspartate (5mg) for all 9 batches. * All values are in mg

F-1 Control formulation (without superdisintegrants),

F2 and F3- Formulation containing single Superdisintegrants crosscarmellose sodium and sodium starch glycolate respectively.

PM- Physical mixture of crosscarmellose sodium and sodium starch glycolate in different ratios 1:1(F4), 1:2(F5), 1:3(F6), CP-Co-processed Superdisintegrants of crosscarmellose sodium and sodium starch glycolate in different ratios1:1(F7), 1:2(F8), 1:3(F9),

Preparation of Novel Co-Processed Superdisintegrants:

The co-processed superdisintegrants were prepared by solvent evaporation method. A blend of crosscarmellose sodium and sodium starch glycolate (1:1, 1:2, 1:3) was added to 10ml of ethanol. The content of beaker (250ml capacity) was mixed thoroughly and stirring was continued till most of ethanol evaporated. The wet coherent mass was passed through # 40-mesh sieve. The wet granules were dried in a hot air oven at 60^0cfor 20 minutes. The dried granules were sifted through # 60-mesh sieve and stored in airtight container till further use.

3. RESULTS&DISCUSSION [9]

MICROMERITIC PROPERTIES:

The results of angle of repose, Bulk density and Tapped density, Carr's index, Hausner's ratio, Void Volume & % Porosity are shown in Table No.3

Table 3 Results of pre-compression properties by direct compression method

Sr. no	Formulation code	Bulk density (g/cc)* ±SD	Tap Density (g/cc)* ±SD	Angle of Repose (degree)* ±SD	Carr's index (%)* ±SD	Hausner's ratio* ±SD	Void volume* ±SD	Porosity (%)* ±SD
1	F-1	0.60±0.03	0.37±0.040	30.51±0.42	10.76±3.9	1.11±0.05	0.55±0.18	9.94±2.77
2	F-2	0.52±0.01	0.33±0.015	30.30±1.20	10.50±3.13	1.13±0.023	0.66±0.25	9.57±3.49
3	F-3	0.72±0.011	0.38±0.02	31.63±0.63	9.27±1.72	1.09±0.023	0.5±0.17	17.01±0.68
4	F-4	0.61±0.012	0.38±0.015	30.52 ±1.31	18.95±1.02	1.23±0.02	1.1±0.00	8.82±0.86
5	F-5	0.54±0.01	0.29±0.015	30.88±1.25	8.93±1.56	1.09±0.02	0.63±0.057	13.47±1.94
6	F-6	0.74±0.023	0.44±0.01	33.32±0.92	14.40±1.43	1.16±0.015	0.7±0.1	6.64±1.93
7	F-7	0.61±0.03	0.35±0.02	24.10±0.29	7.57±1.33	1.07±0.015	0.4±0.1	4.76±1.53
8	F-8	0.54±0.041	0.38±0.01	23.11±1.07	4.01±1.08	1.04±0.023	0.3±0.1	4.25±1.12
9	F-9	0.58±0.014	0.31±0.02	23.34±0.88	5.25±1.75	1.05±0.017	0.33±0.057	4.35±1.05

* All values are expressed as mean ± SD (n=3) (±SD - Standard Deviation

CHARACTERIZATION OF PREPARED TABLETS [10, 11]

Friability

Friability is related to tablet ability to withstand both shock and abrasion without physical damage during the handling of manufacturing, packaging, shipment and consumer use.Friability of formulations of FDT prepared by direct compression method were found in between 0.5352- 0.7006. (Table no 4)

Hardness

The tablet hardness was found to be in the range of 6.3-7.16 kg /cm^2 formulations prepared by direct compression method. (Table no 4)

Thickness

The thickness was found to be in between 5.6 mm to 6.1mm for formulations prepared direct compression method. (Table no 4)

Weight Variation

Weight variation test revealed that the tablets of all formulations were within the range of Pharmacopeial specifications. All the formulations pass weight variation test. (Table no 4)

***In-Vitro* Dispersion Time**

European Pharmacopoeia has used term or dispersible tablets for tablets that disperse within 3 min. in mouth before swallowing. In vitro dispersion time of prepared tablets were done by dropping the tablet in 10ml measuring cylinder containing 6ml of simulated salivary pH 6.8. It was clearly observed from the result that all formulations disperse within 3 min. in simulated artificial saliva pH 6.8 except control formulation F-1 (Table no.4)

Wetting time

Wetting is closely related to inner structure of tablets and the hydrophilicity of excipients. The record of wetting time for formulation prepared by direct compression method is shown in table No.4.The wetting time in all the formulations was very fast except in case of control formulation F-1.This is due to absence of superdisintegrants. From this we could conclude that superdisintegrants shows phenomenon of wetting by different methods like swelling & wicking. Formulation containing co-processed superdisintegrants shows faster wetting time than formulation containing simple physical mixtures.

Water absorption ratio:

The water absorption ratio results for formulations prepared by direct compression method are tabulated in table No.5

In vitro disintegration time:

The internal structure of tablets that is pore size distribution, water penetration into tablets and swelling of disintegration substance are suggested to be the mechanism of disintegration. The results for formulation prepared by direct compression are tabulated in table No.5 Formulation containing co-processed superdisintegrants shows faster disintegration time when compared with formulation containing simple physical mixtures of superdisintegrants.

Drug content uniformity:

The content uniformity was performed for all the 15 formulations prepared by the method direct compression. Three trials from formulation were analyzed spectrophotometrically at 276nm. The mean value and standard deviations of all formulations were calculated. The % drug content the tablets were found between (96.66% to 99.66%) of Oxcarbazepine. The % drug content data estimated for the prepared tablets No.5

Table 4: Post compression parameters of Oxcarbazepine tablets prepared by direct compression Method

Formulation	Weight Variation (mg)*± SD	Thickness (mm)*± SD	Friability (%)	Hardness (Kg/cm^2)	In vitro Dispersion time*±SD (sec)	Wetting time (sec)*± SD
F-1	498.35±0.193	5.6±0.115	0.5352	7.16±0.288	547±2.0	455±2.51
F-2	497.78±1.25	5.8±0.1	0.2930	7.3±0.288	92±1.0	82±2.08
F-3	497.2±0.656	6.1±0.05	0.8853	6.8±0.288	87±2.5	72±1.52
F4	499.3±0.726	5.8±0.115	0.7565	6.6±0.288	79±2.51	87±2.08
F5	498.75±2.00	5.7±0.173	0.8394	7.1±0.288	85±2.0	63±1.52
F6	500.3±0.733	5.6±0.05	0.4991	6.3±0.288	57±3.0	87±2.0
F7	499.61±1.99	5.7±0.116	0.6033	6.16±0.288	42±2.51	70±2.51
F8	502.21±0.75	6.2±0.115	0.5526	7.1±0.288	76±1.52	53±1.52
F9	496.2±1.47	5.6±0.05	0.7006	7.1±0.288	30±2.0	60±2.0

* All values are expressed as mean ± SD (n=3) (±SD- Standard Deviation)

Table 5: Post compression parameters of Oxcarbazepine FDT prepared by direct compression Method

Formulation	Water absorption ratio (%) ± SD	*In vitro* disintegration time*(sec) ± SD	Drug Content* (%)± SD
F-1	67.85±2.08	432±2.51	96.96±0.5
F-2	88.84±3.65	63±1.52	96.82±0.2
F-3	71.58±2.54	71±1.52	96.97±0.51
F4	83.90±2.65	80±2.08	99.46±0.28
F5	56.25±2.54	70±1.52	96.66±0.33
F6	85.57±4.00	74±2.00	98.83±0.20
F7	98.36±3.13	36±1.52	98.13±0.28
F8	89.89±2.54	65±1.52	97.73±0.24
F9	84.03±1.70	34±1.00	97.09±0.33

In vitro dissolution studies: According to ICH guidelines Q6A, an immediate release solid oral drug product is considered rapidly dissolving when not less than 80% of the labeled amount of drug substance dissolves within 15 minutes in each of the following media: (1) pH 1.2, (2) pH 4.0, and (3) pH 6.8.

All the Nine formulations were subjected for the in vitro dissolution studies using tablet dissolution tester (USP)

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TDT-08L, Electro lab. The samples were withdrawn at different time intervals and analyzed at 276 nm. Cumulative drug release, cumulative % drug release and cumulative loss were calculated on the basis of mean amount of Oxcarbazepine present in the respective tablet. The dissolution profiles of Oxcarbazepine prepared by direct compression are shown in table No. 6 to 7. All formulations show results which are in acceptable range. Dissolution profile of prepared tablets was compared with the control formulation F-1 (without superdisintegrant). *In vitro* drug release for all formulations was taken for 20 min. Control formulation F-1 showed 68.22% cumulative % drug release at the end of 20 min. Other batches F-1, F-2, F3, F4, and F5 showed 91.81%, 90.77%, 93.16%, 97.31% and 94.25% cumulative % drug release at 20 min. respectively. F6 and F7 showed 94.25% and 98.53% drug release at 16 min. F9 showed 99.31% drug release at 14 min.

Dissolution results of tablets prepared by direct compression method showed that dissolution rate depends on the ratio of Superdisintegrants & type of superdisintegrants used. Formulation containing single superdisintegrants i.e. crosscarmellose sodium and sodium starch glycolate shows lower dissolution rate than that of formulation containing combination of two superdisintegrants. Also formulation containing simple physical mixtures of superdisintegrants shows lower dissolution rate than that of formulation containing co-processed superdisintegrants. Ratio of superdisintegrants used also affect the dissolution profile. Formulation containing 1:3 ratio of co-processed superdisintegrants shows highest dissolution rate than other formulations. Hence order of increasing dissolution rate of prepared formulations were as, F9>F8>F7>F6>F5>F4>F3>F2>F1.

Comparative cumulative % drug releases of all batches are given in fig. No. 1 to 3.

Table 6: In vitro dissolution of Oxcarbazepine from FDT in phosphate buffer pH 6.8

Time (Min)	F1 Cumulative amount of drug released* %	F2 Cumulative amount of drug released* %	F3 Cumulative amount of drug released* %	F4 Cumulative amount of drug released*%	F5 Cumulative amount of drug released*%
0	0.000	0.000	0.000	0.000	0.000
2	32.44±0.50	30.16±0.35	30.28±0.79	32.43±0.35	35.26±0.43
4	40.17±0.57	37.35±0.36	36.91±0.52	45.37±0.36	47.99±0.44
6	41.83±0.44	48.55±0.36	47.69±0.44	52.01±0.36	53.75±0.50
8	46.28±0.51	53. 88±0.28	54.14±0.65	59.37±0.28	61.39±0.30
10	50.08±0.40	61.48±0.52	62.39±0.50	69.38±0.52	71.82±0.52
12	55.90±0.20	71.03±0.43	70.35±0.51	78.60±0.43	86.09±0.65
14	58.20±0.74	80.66±0.78	81.17±1.09	83.38±0.78	87.46±0.35
16	59.62±0.51	83.76±0.50	82.64±0.57	85.55±0.51	89.40±0.36
18	64.87±0.65	85.08±0.43	87.21±0.52	88.73±0.43	92.71±0.72
20	68.22±0.43	91.81±0.59	90.77±0.52	93.16±0.59	97.31±0.79

Table 7 In- Vitrodissolution profile of Oxcarbazepine from FDT in phosphate buffer pH 6.8

Time (Min)	F6 Cumulative amount of drug released*%	F7 Cumulative amount of drug released* %	F8 Cumulative amount of drug released* %	F9 Cumulative amount of drug released*%
0	0.000	0.000	0.000	0.000
2	34.54±0.43	44.45±0.58	46.27±0.44	56.79±0.58
4	48.74±0.65	52.07±0.52	49.81±0.44	61.88±0.36
6	60.64±0.50	67.08±0.43	67.87±0.72	75.69±0.44
8	62.75±0.51	73.19±0.87	72.98±0.58	78.20±0.29
10	74.61±0.93	76.65±0.76	76.87±0.51	86.32±0.36
12	84.33±0.72	86.15±0.59	83.28±0.87	94.51±0.36
14	86.96±0.43	92.01±0.44	93.53±0.66	99.31±0.36
16	88.74±0.36	98.53±0.51	100.2±0.72	-
18	91.41±0.43	-	-	-
20	94.25±0.73	-	-	-

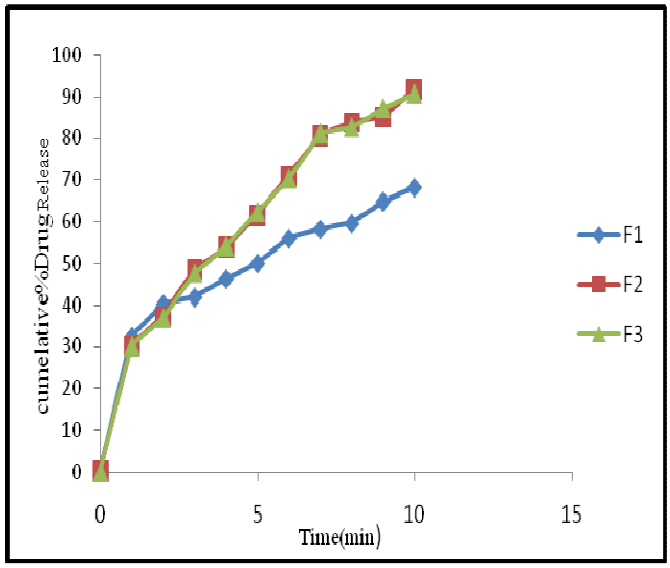

Fig 1 In- Vitro dissolution profile of from FDT in phosphate buffer pH 6.8

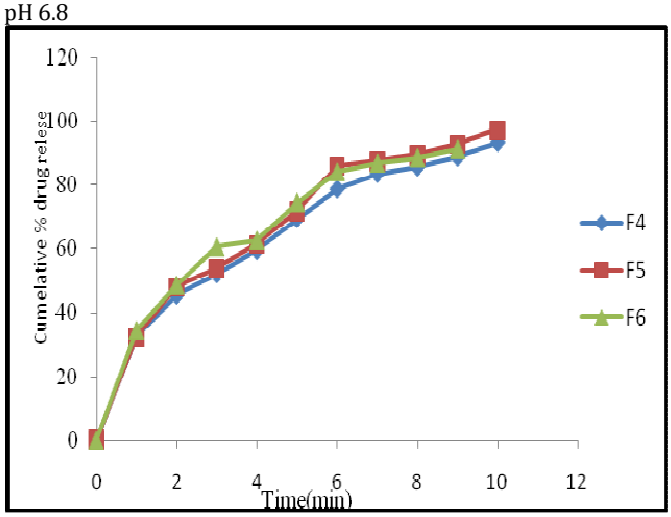

Fig 2. In- Vitro dissolution profile of Oxcarbazepine from FDT in phosphate buffer pH 6.8

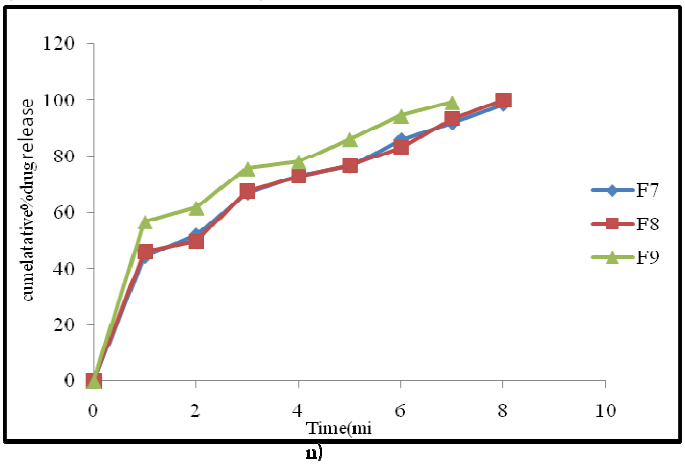

Fig 3 In- Vitro dissolution profile of Oxcarbazepine from FDT in phosphate buffer pH 6.8

Stability studies:

Optimized batch was selected for the stability studies. Optimization was done on the basis of results of cumulative % drug release, in vitro dispersion time, in vitro disintegration time and wetting time. By considering all above parameters F9 batch considered as optimized batch and kept for stability at prescribed temperatures. The results of stability studies revealed that there was no remarkable difference in the tested parameters of promising formulation after storage for 3 months at 40^0c ± 2^0c/ 75% ± 5%RH and at room temperature/ 65% ± 5%RH as compared to initial results (Table No.8 to No. 9). The results of stability study demonstrated that the selected formulation was found to be stable.

Table 8: Stability Parameters at 40^0 c ± 2^0c and 75% ± 5% Relative Humidity

Sr.No	Days	Physical Appearance	Hardness	Dispersion Time	Wetting Time	Drug Content (%)
1	0	White flat circular.	3.1±0.288	11±1.0	20±2.0.	97.09±0.33
2	15	No Change	3.1±0.288	12±1.52	22±1.52.	96.82±0.24
3	30	No Change	3.1±0.288	11±2.51	21±3.05	96.74±0.36
4	45	No Change	3.1±0.288	12±2.51	24±1.0	96.61±0.20
5	60	No Change	3.1±0.288	10±1.57	24±1.52.	96.58±0.36
6	75	No Change	3.1±0.288	11±2.08	23±2.08.	96.42±0.36
7	90	No Change	2.9±0.288	11±2.08	21±1.52.	96.13±0.33

Table 9: Stability Parameters at Room Temperature and 65% ± 5% Relative Humidity

Sr.No	Days	Physical Appearance	Hardness	Dispersion Time	Wetting Time	Drug Content (%)
1	0	White flat circular.	3.1±0.288	11±1.0	20±2.0.	97.09±0.33
2	15	No Change	3.1±0.288	12±1.52	19±2	96.77±0.28
3	30	No Change	3.1±0.288	11±1.52	18±3.6	95.84±0.24
4	45	No Change	3.1±0.288	12±1.0	17±2.0	95.44±0.24
5	60	No Change	3.1±0.288	12±2.64	17±1.52	95.38±0.24
6	75	No Change	2.9±0.288	10±1.52	18±1.52	95.28±0.32
7	90	No Change	2.9±0.288	11±2.64	18±1.52	95.14±0.16

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