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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 sublimation technique where different sublimating agents like camphor and menthol were used with L-HPC and crospovidone as a superdisintegrants. Oxcarbazepine is an anticonvulsant drug used in the treatment of epilepsy and bipolar disorder. Each sublimating agent was used in concentration of 10-20 mg per tablet. Tablets were first prepared and then kept in hot air oven for sublimation. The prepared FDTs were evaluated for weight variation, thickness, drug content, friability, hardness, wetting time, water absorption ratio, in-vitro dispersion time, in-vitro disintegration time and in-vitro dissolution time. All formulations showed disintegration time ranging from 8 to 332sec. Optimized batch (SA6) was selected for the stability studies. 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 All the prepared formulae complied with Pharmacopoeia requirements of drug contents.

Introduction

Oral drug delivery system

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. The reason that the oral route achieved such popularity may be in part attributed to its ease of administration as well as the traditional belief that by oral administration the drug is as well absorbed as the food stuffs that are ingested daily. In fact, the development of pharmaceutical products for oral delivery, irrespective of physical form involves varying extents of optimization of dosage form characteristics within the inherent constraints of gastrointestinal physiology. 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. Oxcarbazepine is chemically 10,11-Dihydro-10-oxo-5 H – dibenz (b,f) azepine -5-carboxamide. Oxcarbazepine is an anticonvulsant drug used in the treatment of epilepsy and bipolar disorder. To have the same mechanism as carbamazepine - sodium channel inhibition - and is generally used to treat the same conditions. Oxcarbazepine has recently been found associated with a greater enhancement in mood and reduction in anxiety symptoms than other drugs employed to treat epilepsy[1-5].

Drug selection criteria for FDTs

The ideal characteristics of a drug for Fast dissolving tablet include

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- 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[6-7].

Advantages of Fast Dissolving Tablets

- As FDTs are unit solid dosage forms, they provide good stability, accurate dosing, easy manufacturing, small packaging size, and easy to handle by patients.
- Administered without water, anywhere, any time.
- The rapid disintegration of the tablet results a quick dissolution of the drug and fast absorption that provide rapid onset of action.
- Convenience of administration and accurate dosing as compared to liquid formulation.
- Beneficial in cases such as motion sickness, pain or coughing, where an ultra rapid onset of action required.
- FDTs have opened new business opportunity like product differentiation, product promotion, patent extension and life cycle management.
- Provide advantages of liquid medication in form of solid preparation.
- Good mouth feels property[8].

Limitation of Fast Dissolving Tablets

- FDTsare hygroscopic in nature so must be keep in dry place.
- Tablets usually have insufficient mechanical strength. Hence, careful handling is required.
- Tablets may leave unpleasant taste and/or grittiness in mouth if not formulated properly.

FDTs require special packaging for proper stabilization and safety of stable product[4].

Materials and methods

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
Aspartate	Maxwell Life Sciences, Tarapur.	Dissolution Apparatus (U.S.P.)	Electrolab, Mumbai
Crospovidone , L-HPC	Fine Lab	FT-IR Spectrometer	Perkin Elmer
		Mechanical stirrer	Remi
		Hardness tester	Monsanto
		Friability	Dolphin VFT-1D
Menthol , Magnesium Stearate, Methanol ,Ethanol & Camphor	Lobachem.	Stability Chamber	Quality instruments and equip

Method for preparation

Preparation of fast dissolving tablets by sublimation method

Six batches of Oxcarbazepine fast dissolving tablets were prepared by sublimation as per composition shown in formulation table No.1. All ingredients were passed through #60 mesh before use (except avicel pH 102). Then the ingredients were weighed and mixed geometrically for 15 to 20min. and mixed components were compressed into 500mg tablet using 8mm punch

on 16-station rotary tablet punching machine (Cadmach, Ahmadabad). Oxcarbazepine tablets were then placed in an oven at 40^0C till a constant weight is obtained[9-10].

Table 1: Composition of Oxcarbazepine FDTs prepared by sublimating method

Ingredients	SA1	SA2	SA3	SA4	SA5	SA6
Oxcarbazepine	300	300	300	300	300	300
Avicel pH 102	174	164	164	164	164	164
Crospovidone	--	10	--	10	--	10
L-HPC	--	--	10	--	--	--
Camphor	20	20	20	--	--	--
Menthol	--	--	--	20	20	20
Magnessium stearate	3	3	3	3	3	3
Aspartate	3	3	3	3	3	3
Total	500	500	500	500	500	500

* All values are in mg

Results &discussion

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. 2[11-12]

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Table 2: Results of pre-compression properties

Pre-compression parameters of FDT prepared by sublimation 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	SA-1	0.363±0.023	0.440±0.016	30.96±0.22	18.6±1.68	1.20±0.037	0.96±0.11	17.55±1.81
2	SA-2	0.327±0.028	0.384±0.004	30.46±0.39	13.7±0.75	1.15±0.011	0.83±0.05	13.65±0.75
3	SA-3	0.338±0.005	0.397±0.004	31.54±0.98	15.89±0.76	1.17±0.01	0.86±0.05	14.68±0.78
4	SA-4	0.322±0.005	0.374±0.004	35.11±1.33	14.05±0.69	1.16±0.01	0.86±0.05	13.96±0.75
5	SA-5	0.332±0.005	0.384±0.007	31.95±0.64	13.43±0.01	1.15±0.00	0.8±0.00	13.33±0.24
6	SA-6	0.317±0.002	0.374±0.004	34.56±1.51	15.38±0.70	1.17±0.005	0.96±0.05	15.33±0.72

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

Characterization of prepared tablets

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 for formulation containing sublimating agents values lies between the prescribed limits (0.1-0.9%). (Table No 3.)

Hardness

The tablet hardness was found to be in the range of 6.3- 7.16 kg /cm^2 formulations prepared for formulations containing sublimating agents hardness was taken before and after sublimation, because there was decrease in hardness after sublimation. Hardness of tablet before sublimation lies between 4.1-6.1 kg/cm^2 and after sublimation lies between 2.8- 4.2 kg/cm^2. (Table No 3.)

Thickness

The thickness was found to be in between 5.6 mm to 6.1mm for formulations prepared by formulation containing sublimating agent's methods. (Table No 3.)

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 3.)[13-14]

Table 3: Post compression parameters of Oxcarbazepine tablets prepared by Sublimation Method

Formulation code	Friability (%)	*In vitro* Dispersion time* ± SD (sec)	Hardness ± SD* (Kg/cm^2)		Thickness (mm)* ± SD	Weight variation (mg)* ± SD	
			Before sublimation	After sublimation			
SA-1	0.7978	96±2.51	5.1±0.27	3.8±0.28	6.1±0.02	501.16±0.74	482.81±0.68
SA-2	0.8523	85±2.51	5.3±0.29	3.4±0.25	5.8±0.22	497.46±0.80	481.85±0.80
SA-3	0.7534	60±2.08	4.1±0.24	4.2±0.28	5.8±0.15	490.95±0.76	481.95±0.87
SA-4	0.6982	50±2.51	6.1±0.26	3.0±0.27	6.0±0.13	499.96±.86	462.05±2.15
SA-5	0.7997	87±2.0	6.1±0.24	3.1±0.25	6.1±0.10	500.53±0.93	482.45±0.95
SA-6	0.6455	43±2.08	4.3±0.26	3.3±0.28	5.9±0.05	500.1±1.45	463.05±0.33

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

***In-Vitro* Dispersion Time**

European Pharmacopoeia has used term orodispersible 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. Rapid dispersion within seconds observed in all the formulations. Formulation containing sublimating agent shows in-vitro dispersion time in between 43-96sec. (Table No 3.)

Wetting time

Wetting is closely related to inner structure of tablets and the hydrophilicity of excipients. Formulation containing co-processed superdisintegrants shows faster wetting time than formulation containing simple physical mixtures. For formulations containing sublimating agents results of wetting time are tabulated in (Table No 4.)In case of formulation containing sublimating agent wetting time is very fast. The tablets containing sublimating agent due to high porosity absorbs water rapidly when come in contact with water and shows rapid wetting of tablets. Formulation containing highest concentration of sublimating agent (20%) shows faster wetting time (SA-3 and SA-6).

***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 containing sublimating agents were tabulated in table No.4. While in case of tablets prepared by sublimating method disintegration time is lowest for formulation containing menthol (20%) and crosspovidone.

Drug content uniformity

The content uniformity was performed for all the 6 formulations prepared by Sublimation method 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 (98.00% to 100.24%) of Oxcarbazepine. The % drug content data estimated for the prepared tablets No 4 were in the prescribed limits.

***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 6 formulations were subjected for the in vitro dissolution studies using tablet dissolution tester (USP) 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 profile of Oxcarbazepine prepared by sublimation technique is shown in table No.5 All formulation shows acceptable results. Cumulative % drug release for formulation batches SA-1, SA-2, SA-3, SA-4, SA-5, and SA-6, were 93.37%, 94.93%, 95.16%, 95.75%, 94.29%, and98.66% respectively. Among these batches formulation containing 20% menthol and crospovidone shows higher % drug release 98.66% at 20 min.

In case of formulation containing sublimating agents, dissolution results showed that dissolution rate of prepared tablets depends on sublimating agent used along with its concentration and superdisintegrants used. The main factor for dissolution of formulation prepared by sublimating method was porosity formed in tablet due to sublimation. As porosity of tablet increases dissolution rate increases. When dissolution profile of formulation containing camphor (10%) with crospovidone and L-HPC compared (SA2 and SA3), it was found that formulation with camphor (10%) and crospovidone shows better dissolution profile than that of camphor (10%) and L-HPC. So next increasing concentration of camphor i.e. 20% was tried with crospovidone (SA4) and it gives highest dissolution profile than other formulation containing camphor as sublimating agent. Similar consideration was applied for formulation containing menthol and it was found that formulation containing menthol (20%) and crospovidone (SA6) shows highest dissolution rate amongst all the formulation containing sublimating agents. An order of

increasing dissolution rate were as, SA6>SA4>SA3>SA2>SA5>SA1.

Comparative cumulative % drug releases of all batches are given in fig. No. 1 to 2.

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

Formulation code	*In vitro* Disintegration time* ± SD (sec)	Wetting time* ±SD (sec)±	Drug Content* (%) SD
SA-1	61±1.41	105±0.57	100.24±0.24
SA-2	54±1.52	92±1.52	98.00±0.16
SA-3	41±1.15	72±1.00	98.81±0.20
SA-4	32±1.52	62±1.15	99.01±0.20
SA-5	57±1.0	96±1.52	98.64±0.28
SA-6	25±1.0	53±1.00	99.30±0.28

Table 5: *In- Vitro* dissolution profile of Oxcarbazepine from FDT in phosphate buffer pH 6.8

Time (Min)	SA1	SA2	SA3	SA4	SA5	SA6
	Cumulative amount of drug released* %	Cumulative amount of drug released* %	Cumulative amount of drug released* %	Cumulative amount of drug released* %	Cumulative amount of drug released* %	Cumulative amount of drug released* %
0	0.000	0.000	0.000	0.000	0.000	0.000
2	29.16±0.72	34.67±0.51	36.00±0.43	41.30±0.51	31.97±0.44	33.25±0.44
4	49.72±0.43	53.55±0.43	45.96±0.74	47.06±0.44	44.18±0.29	37.94±0.52
6	57.82±0.65	60.57±0.58	57.58±0.49	59.97±0.36	52.68±0.44	49.62±0.59
8	60.89±0.57	66.04±0.65	62.71±0.29	65.69±0.36	62.31±0.50	59.92±0.22
10	69.47±0.71	74.61±0.36	71.51±0.43	73.47±0.57	73.90±0.22	74.66±0.44
12	78.77±0.44	76.65±0.30	76.71±0.44	77.94±0.26	82.18±0.29	84.32±0.83
14	86.63±0.58	82.97±0.46	82.37±0.43	82.73±0.29	85.99±0.38	84.59±0.58
16	89.82±0.43	87.22±0.14	89.23±0.44	90.01±0.43	89.00±0.52	92.37±0.44
18	90.46±0.28	91.34±0.52	91.03±0.41	91.95±0.72	91.03±0.43	94.91±0.44
20	93.37±0.52	94.93±0.38	95.16±0.36	95.75±0.79	94.29±0.58	96.16±0.58

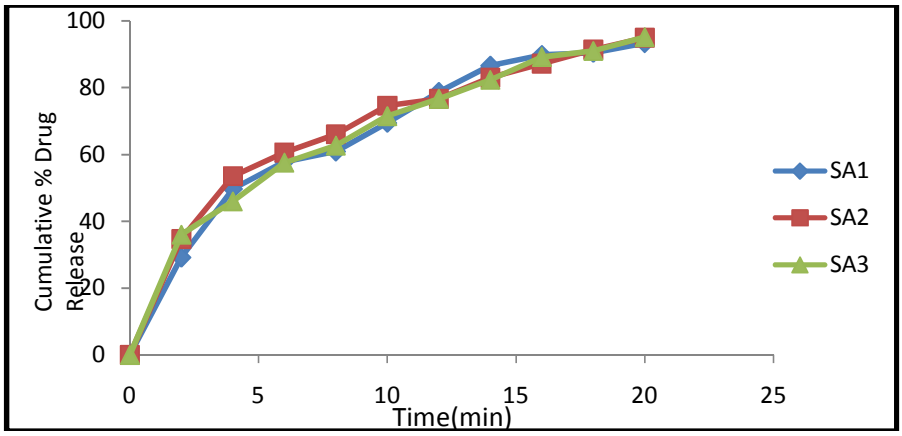

Fig 1: *In- Vitro* dissolution profile of Oxcarbazepine from FDT in phosphate buffer pH 6.8

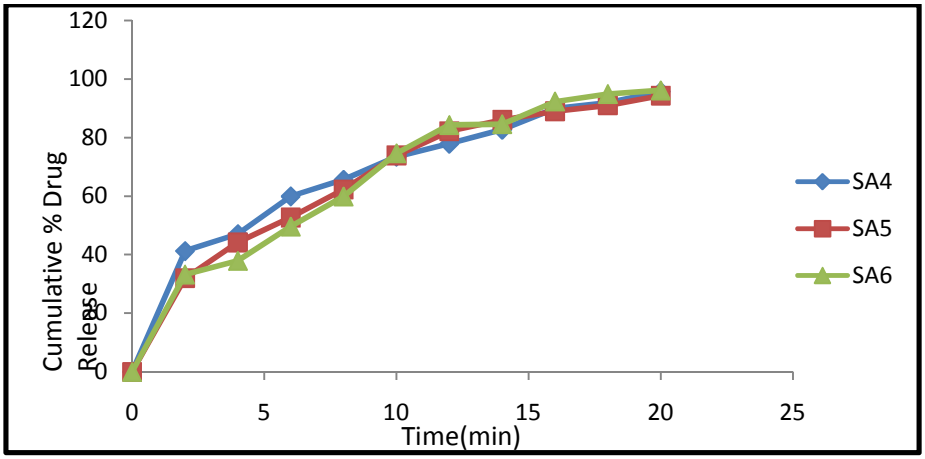

Fig 2: *In- Vitro* dissolution profile of Oxcarbazepine from FDT in phosphate buffer pH 6.8

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.7 to No. 8). The results of stability study demonstrated that the selected formulation was found to be stable.

Table 7: Stability Parameters at $40^0{}_C \pm 2^0{}_C$ 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

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

Table 8: 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

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

Conflict of interest statement

We declare that we have no conflict of interest.

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