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FORMULATION, OPTIMIZATION AND EVALUATION OF ESLICARBAZEPINE ACETATE

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Abstract:

The present study aims at developing an Eslicarbazepine fast dissolving tablet formulation for the effctive treatment of Epilepsy. To provide the patient with the most convenient mode of administration, FDT's will dissolve quickly. A Eslicarbazepine is absorbed to atleast 90% from the gut, independently of food intake. It is quickly metabolized to esclicarbazepine. So the present work was aimed at formulating fast dissolving tablet for Eslicarbazepine, total 6 formulations were developed by using synthetic superdisintigrants like cross caramellose sodium, Crosspovidone, sodium starch glycolate as superdisintigrants, in a different concentration and prepared by direct compression method and prepared tablets were evaluated for pre-compression and post-compression parameters after conducting pre-formulation studies. All the parameters were within the pharmacopoeial limits and drug disintigrations time was 30sec and wetting time was 38sec and the invitro dissolution showed that the drug release was about 100.62 within 15mins in formulation (F5) containing sodium starch glycolate as superdisintigrant, based on these parameters F5 was selected as best formulation.

Key words: ***Epilepsy, Crosspovidone, Sodium Starch Glycolate, Crosscaramellose Sodium, Direct Compression Method.***

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INTRODUCTION:

These are novel types of tablets that dissolve/ disintegrate/ disperse in saliva within few seconds without water. According to European pharmacopoeia, these FDTs should dissolve/disintegrate in less than three minutes. The formulation is more useful for the bed-ridden and patients who have the swallowing problem. The benefits of FDTs is to improve patients compliance, rapid onset of action, increased bioavailability and good stability which make these tablets popular as a dosage form of choice in the current market. Mouth dissolving tablets are also called as oral dispersible tablets, fast disintegrating tablets, orally disintegrating tablets, quick disintegrating tablets, fast dissolving tablets, rapid dissolving tablets, porous tablets, quick melt tablets and rapid melt tablets. However, of all the above terms United States Pharmacopoeia (USP) approved these dosage forms as ODTs [1-6].

MECHANISM OF SUPERDISINTEGRANTS

There are four major mechanisms for tablets disintegration as follows

1. Swelling

Perhaps the most widely accepted general mechanism of action for tablet disintegration is Swelling. Tablets with high porosity show poor disintegration due to lack of adequate swelling force. On the other hand, sufficient swelling force is exerted in the tablet with low porosity. It is Worthwhile to note that if the packing fraction is very high, fluid is unable to penetrate in the tablet and disintegration is again slows down [7-9].

2. Porosity and capillary action (Wicking)

Disintegration by capillary action is always the first step. When we put the tablet into suitable aqueous medium, the medium penetrates into the tablet and replaces the air adsorbed on the particles, which weakens the intermolecular bond and breaks the tablet into fine particles. Water uptake by tablet depends upon hydrophilicity of the drug /excipient and on tableting conditions. For these types of disintegrants maintenance of porous structure and low interfacial tension towards aqueous fluid is necessary which helps in disintegration by creating a hydrophilic network around the drug particles.

i. WICKING SWELLING

Water is pulled by disintegrant Particles swell and breaks up and reduced the physical the matrix form within bonding force between particles.

3. *Due to disintegrating particle/particle repulsive forces*

Another mechanism of disintegration attempts to explain the swelling of tablet made with ‘non swellable’disintegrates. Guyot-Hermann has proposed a particle repulsion theory based on the observation that nonswelling particle also cause disintegration of tablets. The electric repulsive forces between particles are the mechanism of disintegration and water is required for it. Researchers found that repulsion is secondary to wicking [10-14].

4. Due to deformation

During tablet compression, disintegrated particles get deformed and these deformed particles get into their normal structure when they come in contact with aqueous media or water. Occasionally, the swelling capacity of starch was improved when granules were extensively deformed during compression. This increase in size of the deformed particles produces a breakup of the tablet. This may be a mechanism of starch and has only recently begun to be studied.

i. DEFORMATION REPULSION

Particles swell to precompression Water is drawn into pores and Size and break up matrix particles repel each other because of Resulting electrical force.

ADVANTAGES

- Ease of administration to the patients who could not swallow such as the elderly, strokes victims and bedridden patients. Patients who should not swallow such as renal failure patients and also who refuse to swallow, such as pediatrics, geriatric and psychiatric patients.
- Patient’s compliance for the disabled bedridden patients and for travelling and busy people, who do not have the ready access to water. Good mouth feel property of Mouth Dissolving Drug Delivery System (MDDDS) helps to change the basic view of medication as "bitter pill" and particularly for pediatric patients due to improve taste of bitter drugs.
- Convenience of the administration and accurate dosing as compared to the liquid Formulations.
- Benefits of liquid medication in the form of solid preparation.
- More rapid drug absorption through the pre-gastric area i.e. mouth, pharynx and oesophagus which may produces rapid onset of action.
- Pre-gastric absorption could result in the improved bioavailability, reduced dose and improved clinical performance by reducing the side effects.
- New business opportunities like product differentiation, line extension and lifecycle

management, exclusivity of product promotion and patent life extension [6].

DISADVANTAGES

- The tablets usually have insufficient mechanical strength. Hence, careful handling is essential.
- The tablets may leave disagreeable taste or grittiness in mouth if not formulated properly
- Drugs with larger doses are hard to formulate into FDT e.g. rifampicin (600 mg), ethambutol (1000mg) etc [7].

MATERIALS AND METHOD:

MATERIALS

Super disintegrants, sugar based excipients, fillers or diluents, colours, flavours, sweetners, lubricants, glidants, preservatives, sublimating agents.

METHOD

DIRECT COMPRESSION

Direct compression normally requires careful selection of raw materials to achieve a free-flowing, non segregating, compressible mixture. Effervescent tablets were prepared by direct compression technique using varying concentrations of different grades of disintigrants with like crosscaramellose sodium, crospovidone, sodium starch glycolate. All the ingredients were accurately weighed and passed through different mesh sieves accordingly. Then, except Magnesium stearate all other ingredients were blended uniformly in glass mortar. After sufficient mixing of drug as well as other components, Magnesium stearate was added, as post lubricant, and further mixed for additional 2-3 minutes. The tablets were compressed using rotary tablet machine. The weights of the tablets were kept constant for all formulation.

Table 1: formulation of eslicarbazepine fast dissolving tablets

Parameters	F1	F2	F3	F4	F5	F6
Drug	300mg	400mg	300mg	400mg	300mg	400mg
Crospovidone	100mg	150mg	----	----	----	----
Crosscaramellose	----	----	100	150	----	----
Sodium starch glycolate	----	----	----	----	100	150
Lactose	50	50	50	50	50	50
Mannitol	46	46	46	46	46	46
Magnesium Stearate	2	2	2	2	2	2
Talc	2	2	2	2	2	2

PREFORMULATION EVALUATION:

It includes different tests like Bulk density, tapped density, Carr's index, Hausner's ratio, Angle of repose.

Evaluation Of Esli Carbazepine Acetate Fast Dissolving Tablets:

Weight variation:

20 tablets were selected randomly from the lot and weighted individually to check for weight variation. Weight variation specification as per I.P.

Weight Variation Specification as per IP

Table 2: weight variation

Average Weight of Tablet	% Deviation
80 mg or less	<10
More than 80 mg but less than 250 mg	<7.5
250 mg or more	<5

Hardness

The limit of hardness for the FDT is usually kept in a lower range to facilitate early disintegration in the mouth. The hardness of the tablet may be measured using conventional hardness testers (Monsanto tablet hardness tester). It is expressed in kg/cm2 or pound.

Friability

Friability of the tablet determined using Roche friabilator. This device subjects the tablet to the combined effect of abrasion and shock in a plastic chamber revolving at 25 rpm and dropping a tablet at I height of 6 inches in each revolution. Pre weighted sample of tablets was placed in the friabilator and were subjected to the 100 revolutions. Tablets were dusted using a soft muslin cloth and reweighed. The friability (F) is given by the formula.

$$F = \frac{W_{initial} - W_{final}}{W_{initial}} \times 100$$

Disintegration Time

Tablets were added to 10ml of buffer solution at 37±0.5^{0}C. Time required for complete dispersion of a tablet was measured. The results were tabulated.

Dissolution test

The dissolution methods for FDT are practically identical to conventional tablet when FDT does not utilize taste masking. Commonly the drugs may have dissolution conditions as in USP monograph. 0.1NHCl, pH 4.5 and pH 6.8 buffers should be used for evaluation of FDT in the same way as their ordinary table counter parts. USP 2 paddle apparatus is most suitable and common choice for dissolution test of FDT tablets as compared to USP1 (basket)apparatus due to specific physical properties of tablets. In paddle apparatus the paddle speed of 25-75 rpm is commonly used. Since the dissolution of FDT's is very fast when using USP monograph conditions hence slower paddle speeds may be utilized to obtain a comparative profile. Large tablets (≥1gram) may produce a mound in the dissolution vessel which can be prevented by using higher paddle speeds.

Wetting time

Wetting time is closely related to the inner structure of the tablets and to the hydrophilicity of the excipients. To measure wetting time, five circular tissue papers of 10 cm diameter are placed in a petridish with a 10 cm diameter. Ten millimeters of water-containing Eosin, a water-soluble dye, is added to petridish. A tablet is carefully placed on the surface of the tissue paper. The time required for water to reach upper surface of the tablet is noted as a wetting time. It is obvious that pores size becomes smaller and wetting time increases with an increase in compression force or a decrease in porosity. A linear relationship exists between wetting time and disintegration time. Thus wetting is the important step for disintegration process to take place.

Table 3: Standard Graph

S.NO	CONCENTRATION	ABSORBANCE
1	0	0
2	1	0.102
3	2	0.200
4	3	0.290
5	4	0.380
6	5	0.480

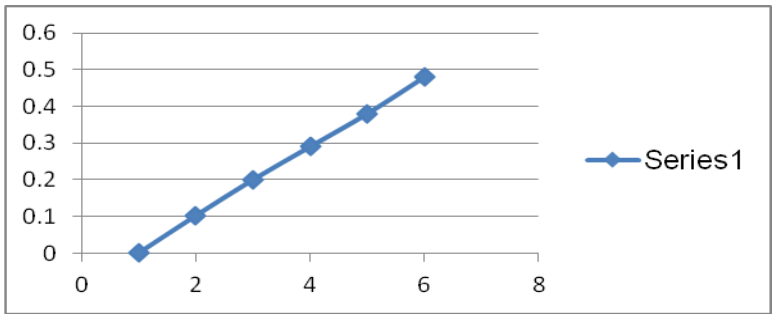

Fig. 1: Standard Graph

PRE EVALUATION PARAMETERS

Table 4: PRE EVALUATION PARAMETERS

Parameters	F1	F2	F3	F4	F5	F6
Bulk density (g/ml)	0.62	0.52	0.58	0.51	0.61	0.58
Tapped density(g/ml)	0.62	0.62	0.61	0.63	0.62	0.58
Hausner's ratio	0.60	0.46	0.48	0.49	0.45	0.50
Carr's Index	100	125.5	120	105	125	125.5

POST EVALUATION PARAMETERS

Table 5: POST EVALUATION PARAMETERS

Parameters	F1	F2	F3	F4	F5	F6
%Weight Variation	1.7	2.1	2.0	2.1	1.5	2.1
Thickness(mm)	3.76	3.60	3.66	3.77	3.70	3.81
Friability%	0.94	0.66	0.78	0.77	0.72	0.85
Disintegration time(Sec)	74	67	72	43	30	47
Hardness(Kg/cm^2)	4.0	4.6	4.60	4.40	4.21	4.30
Wetting time(sec)	50	55	42	46	38	39

DISSOLUTION PROFILE:

Table 6: % Drug release of esclicarbazepine acetate

TIME(Min)	F1	F2	F3	F4	F5	F6
0	0	0	0	0	0	0
1	16.1	17.82	16.41	21.32	36.72	31.72
2	38.09	23.3	28.71	38.14	39.02	34.02
3	46.76	48.47	37.23	46.35	47.69	41.69
5	54.63	57.5	54.35	57.73	65.56	59.99
10	89.02	88.9	80.56	88.30	95.7	90.45
15	90.21	93.6	91.4	95.7	100.62	99.45

DISCUSSION:

Hardness and friability

The hardness of the tablet formulations was found to be in the range of 4.0 to 4.30 kg/cm^2 the friability and thickness values were found to be in the range of 0.66 to 0.94% and 0.98 to 1.10% respectively, which was found to be according to the I.P limits and thus ensuring good mechanical strength to all the formulations.

Uniformity of weight:

All the prepared fast dissolving tablets of eslicarbazepine acetate were evaluated for weight variation. The weight of all the tablets was found to be uniform with low values of standard deviation and within the prescribed IP limits.

Disintegration time and Wetting time

Among the tablets prepared F5 formulation was found to be promising and has shown a disintegration time of 30 sec, wetting time of 58 sec which was found to be within the IP limits.

***In vitro* dissolution study:**

Invitro dissolution studies were performed in 0.1 Hcl buffer maintained at a temperature of 37+2^0 c at an RPM of 75 in a USP II apparatus the absorbance were noted at 215nm. The dissolution results showed gradient increase with the increase in the concentration of the superdisintegrants. Among all the formulation F5 was found to show best results with 100.62% release within mins.

CONCLUSION:

Fast disintegrating tablets of eslicarbazepine prepared using various of superdisintegrants like Crosspovidone, crosscaramellose, sodium starch glycolate by direct compression method. The prepared formulations were evaluated for the pre-compression parameters & the values were within prescribed limits and which indicates good free flowing properties. The physical parameters were found satisfactory & within the limits. This method was showed good results for disintegration time, wetting time & in vitro drug release studies because disintegrating of tablets to increase the porosity of the tablets. The tablets prepared with Crosspovidone, sodium starch glycolate and cross caramellose sodium as superdisintegrants and F5 by direct compression method was found to be best formulation as it exhibited satisfactory physical parameters, least disintegration time (30 sec.), wetting time (58 sec.) & highest % drug release 100.62 (%) in 15 min.

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