DESIGN & INVITRO EVALUATION OF ORO DISPERSIBLE TABLETS OF GABAPENTIN

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ABSTRACT

The objective of the work was to formulate and evaluate anti-epileptic tablets of Gabapentin using various super disintegrants in different ratios. Tablets were prepared by direct compression method using Mannitol, Menthol, Sodium saccharin, Magnesium stearate and talc. The drug-polymer incompatibility was ruled out by FTIR studies. Evaluation studies like drug content, *in-vitro* drug release, disintegration time, hardness, friability, wetting time and weight variation for formulations were performed. From the FTIR studies, the drug-polymer compatibility was confirmed, that, the polymer did not interfere with the drug used. In-vitro drug released varied from 95-99.64 %. The disintegration time was found to be in range of to 2.1-2.8 min. The hardness and friability was found to be in range 3.2-3.8 kg/cm^2 & 0.32-0.69% respectively. The formulation F12 since it showed good *In vitro* drug release of 99.64 % release at the end of 30 min. From this study it could be concluded that the formulated Gabapentin tablets by using various super disintegrates showed good and effective release with maximum concentration of polymer.

Keywords: Gabapentin; super disintegrate; FTIR; disintegration time; *In vitro* drug release, hardness; friability.

INTRODUCTION:

Orally disintegrating tablets (ODTs) is uncoated tablets intended to be placed in the mouth where they disintegrate within 3 min and disperse rapidly before being swallowed.6161 The benefits of ODTs is to improve patients compliance, rapid onset of action, good stability and increased bioavailability which make these tablets popular as a dosage form of choice in the current market.6161

The basic approach in development of FDT is the use of superdisintegrants like MCC, SSG, CP and CC etc, which provide instantaneous disintegration of tablet after putting on tongue, their by release the drug in saliva[1].

Gabapentin interacts with cortical neurons at auxillary subunits of voltage-sensitive calcium channels. Gabapentin increases the synaptic concentration of GABA, enhances GABA responses at non-synaptic sites in neuronal tissues, and reduces the release of mono-amine neurotransmitters. One of the mechanisms implicated in this effect of gabapentin is the reduction of the axon excitability measured as an amplitude change of the presynaptic fibre volley (FV) in the CA1 area of the hippocampus. This is mediated through its binding to presynaptic NMDA receptors. Other studies have shown that the antihyperalgesic and antiallodynic effects of gabapentin are mediated by the descending noradrenergic system, resulting in the activation of spinal alpha2-adrenergic receptors. Gabapentin has also been shown to bind and activate the adenosine A1 receptor[2].

MATERIALS AND METHODS:

FORMULATION AND EVALUATION OF GABAPENTIN TABLETS:

Formulation of Gabapentin tablets:

For the preparation of the Gabapentin as tablet, various super disintegrants were used such as MCC, SSG, CP, CC and other excipients such as menthol as flavoring agent, sodium saccharine, methyl paraben and mannitol. The composition of tablet formulation containing Gabapentin is given in table 1 and 2.

Direct Compression

Tablets of Gabapentin were prepared by direct compression method as per formula given in Table 1. Specified quantities of all materials were weighed and then active ingredients and excipients were mixed by mortar pestle. The granules were passed through a #40 number sieve to prepare the granules. After completion of dry screening the granules were mixed with magnesium stearate and talc which act as lubricants which prevent the adhesion of the tablet formulation to the punches and die during compression. After blending with the polymers the granules were subjected to the compression using 16 station tablet punching machine[3, 4].

Table 1: Tablet composition of different formulations of Gabapentin tablets F1-F6:

Ingredients	F1	F2	F3	F4	F5	F6
Gabapentin	300	300	300	300	300	300
Menthol	0.4	0.4	0.4	0.4	0.4	0.4
Crospovidone	10	20	30			
Micro crystalline cellulose	--	--	--	10	20	30
Sodium starch glycolate	--	--	--	--	--	--
Croscarmallose	--	--	--	--	--	--
Sodium Sacharin	0.04	0.04	0.04	0.04	0.04	0.04
Mannitol Qs	400	400	400	400	400	400
Talc	4	4	4	4	4	4
Magnesium stearate	5	5	5	5	5	5

Table 2 : Tablet composition of different formulations of Gabapentin tablets F7-F12:

Ingredients	F7	F8	F9	F10	F11	F12
Gabapentin	300	300	300	300	300	300
Menthol	0.4	0.4	0.4	0.4	0.4	0.4
Crospovidone	--	--	--	--	--	--
Micro crystalline cellulose	--	--	--	--	--	--
Sodium starch glycolate	10	20	30	--	--	--
Croscarmallose				10	20	30
Sodium Sacharin	0.04	0.04	0.04	0.04	0.04	0.04
Mannitol	400	400	400	400	400	400

Talc	4	4	4	4	4	4
Magnesium stearate	5	5	5	5	5	5

EVALUATION OF GRANULES:

1. Bulk density: bulk density was determined by taking a known weight of dried granules in measuring cylinder. The bulk volume is noted and the bulk density was calculated from the following equation

$$\text{Bulk density} = \frac{\text{Weight of granules}}{\text{Bulk volume of granules}}$$

2. Tapped density: it is the ratio of powder to the volume occupied by the same mass of the powder after a standard tapping a measure i.e. tapped volume

$$\text{Tapped density} = \frac{\text{Weight of granules}}{\text{Tapped volume}}$$

3. Hausner's ratio: Hausner's ratio is used for the predicting powder flow characteristics

$$\text{Hausner's ratio} = \frac{\text{Tapped density}}{\text{Bulk density}}$$

Values of Hausner's ratio: <1.25 good flow**,** >1.25 poor flow

If Hausner's ratio is between 1.25-1.5 flow can be improved by adding glidants.

4. Compressibility index: Compressibility index of the granules was determined by using bulk density and tapped density of granules

$$\text{Compressibility index} = \frac{\text{tapped density-bulk density}}{\text{Tapped density}} \times 100$$

Compressibility Index (%)	Flow Character	Hausner Ratio

Table 2: Relation between Carr's index and Hausner's ratio of powder and its flow characteristics:

1-10	Excellent	1.00-1.11
11-15	Good	1.12-1.18
16-20	Fair	1.19-1.25
21-25	Passable	1.26-1.34
26-31	Poor	1.35-1.45
32-37	Very poor	1.46-1.59
>38	Very, very poor	>1.60

5. Angle of repose: The powders-mix was tested by the fixed funnel Method. The accurately weighed powders were taken in a funnel with orifice 8 mm in diameter. The powders were allowed to flow through the funnel orifice freely on a powder paper to form a cone like heap. The diameter (base) and height of the powder cone were measured with the help of a ruler and

Angle of Repose	**Flow Character**
<25	Excellent
25-30	Good
31-35	Fair
35-40	Passable
>40	Poor

the angle of repose was calculated using the following equation:

$\theta = \tan^{-1}(h/r)$ Where,

θ = angle of repose, h = height of pile, r = radius of the base of the pile.

Table 3: Comparison between angle of repose and flow property:

EVALUATION OF TABLETS:

a) Hardness: the Monsanto hardness tester was used to determine the tablet hardness. The tablet was held between a fixed and moving jaw. Scale was adjusted to zero; load was gradually increased until the tablet fractured. The value of the load at that point gives a measure of hardness of the tablet. Hardness was expressed in kg/cm^2.

b) Friability: Pre-weighed tablets (W1) were rotated at 25 rpm for 4 minutes in the chamber of friability testing apparatus. Then the tablets were de-dusted well with the help of a blower and

re-weighed the same tablets (W2) to determine their loss in weight. Percent Friability (F %) was thus calculated according to the following formula

$$\% \text{ friability} = \frac{W1 - W2}{W1} \times 100$$

c) Weight Variation: Twenty tablets were accurately weighed individually in milligrams (mg) using an analytical balance. Average weight is calculated and comparing the individual weights to the average. The tablet meet the USP test if not more than 2tablets are outside the %limits and if no tablets differs by more than 2 times the %limits.

d) Drug content: 5tablets of various formulations were weighed individually and powdered. The powder equivalent to average weight of tablets was weighed and drug was extracted in phosphate buffer pH 6.8. The drug content was determined measuring the absorbance at 364nm after suitable dilution using UV-Visible spectrophotometer.

e) Wetting time: Wetting time is closely related to the inner structure of the tablets and to the hydrophilicity of the excipients. A piece of tissue paper folded double was placed in a petri plate containing 6ml of water. The tablet was placed on the paper and the time for complete wetting of the tablet was measured in seconds.

f) Disintegration time: One tablet from each batch was taken in disintegration assembly and time taken for the tablets to pass through the mesh was observed.

g) *In Vitro* Release Study: The in vitro release studies were conducted using USP type II apparatus; the dissolution media is comprised of phosphate buffer pH 6.8 (900 mL) kept at 37.0±0.5°C and 100 rpm. An aliquot of 5 ml was withdrawn and replaced with another 5 mL of fresh dissolution medium at various time intervals. The contents of Gabapentin in sample were determined by measuring absorbance at 161 nm in a UV-Visible spectrophotometer after suitable dilutions. The release study was performed in triplicates[5].

RESULTS AND DISCUSSION:

The results of the physical properties of the tablets are shown in the tables 5.6. The hardness of the tablets was found to be in the range of 3.2 – 3.8. The friability of all the prepared tablets was found to be in the range of 0.32 - 0.69. Weight variation test helps to check whether the tablet contain proper quantity of drug. From each of the formulations 10 tablets were randomly selected and weighed. The results are given in the tables 5.6. The average weights of the tablets were found to be within the prescribed official limits. Drug content for each of the formulation were estimated. The disintegration time was found be in the range of 2.1-2.8 min. The wetting time was found to be in the range of 10-49 sec. The drug content for all the formulations were found to be in the range of 92 – 99.80%. The results are given in the table 5.6.

In-vitro release studies were carried out using USP- 2(paddle method) apparatus in phosphate buffer pH 6.8. The results are given in the table 5.7 and 5.8. The results were estimated for up to 30 min. The formulations F1-F12 showed 99.16, 97.82, 99, 97.20, 100.08, 99.13, 98.80, 98.26, 99.09, 98.42, 99.48, 99.64% release respectively over a period of 30 min.

The formulation F12 showed drug release up to 99.64%. All The formulation parameters like Angle of repose, cars index, hausners ratio, hardness, wetting time, friability, drug content, weight variation, cumulative drug release for this formulation was within the range.

Table 5.5: EVALUATION OF GRANULES:

Formulation Code	Bulk Density (gm/ml)	Tapped Density (gm/ml)	Compressibility index (%)	Hausner's ratio	Angle of repose (Degrees)
F-1	0.45	0.52	13.46	1.15	35.8
F-2	0.42	0.48	12.5	1.14	36.86
F-3	0.39	0.43	9.30	1.10	37.23
F-4	0.40	0.45	11.1	1.125	34
F-5	0.39	0.45	13.1	1.15	34.90
F-6	0.41	0.46	10.86	1.121	33.8
F-7	0.39	0.43	9.3	1.10	35.57
F-8	0.460	0.522	12.06	1.134	36.12
F-9	0.45	0.5	11.7	1.11	35.45
F-10	0.41	0.6	13.5	1.4	31.38
F-11	0.46	0.54	14.81	1.17	25.64
F-12	0.40	0.45	14.7	1.12	29.24

Table 5.6 Table 4: EVALUATION OF GRANULES:

Formulation Code	Hardness (kg/cm^2)	Friability (%)	Weight variation (mg)	Drug Content	Disintegration time (mins)	Wetting Time

				(%)		(secs)
F-1	3.5±0.3	0.32± 0.2	400±3	96.2±0.58	2.83±0.65	45±0.65
F-2	3.5±0.1	0.43±0.61	400±2	97.63±0.24	2.79±0.24	37±0.24
F-3	3.3±0.2	0.51±0.12	400±3	98.43±0.5	2.3±0.16	42±0.37
F-4	3.8±0.2	0.47±0.15	400±1	96.8±0.61	2.7±0.47	13±0.65
F-5	3.8±0.23	0.33±0.9	400±1	98.2±1.72	2.67±0.34	39±2.7
F-6	3.2±0.5	0.69±0.12	400±2	99±01	2.46±0.69	36±2.11
F-7	3.3±0.15	0.493±0.5	400±2	97.2±0.58	2.9±0.11	45±0.19
F-8	3.3±0.2	0.45±0.3	400±3	97.34±0.26	2.50±0.17	44±0.22
F-9	3.3±0.11	0.43±0.2	400±1	96.45±0.62	2.86±0.28	45±0.14
F-10	3.2±0.5	0.32±0.6	400±1	98±32	2.3±0.71	10±0.11
F-11	3.2±0.13	0.34±0.2	400±2	97±0.73	2.2±0.39	25±0.54
F-12	3.2±0.35	0.46±0.9	400±2	99.04±0.3	2.1±0.44	22±0.37

*** Mean (x ± s.d) (n = 3)**

Table 5.7: Percentage *in-vitro* drug release of formulations (F1-F6):

Time (mins)	**F-1(%)**	**F-2(%)**	**F-3(%)**	**F-4(%)**	**F-5(%)**	**F-6(%)**
5	12.3±0.1	14.4±0.02	15.3±0.38	9±0.2	10.5±0.32	11.7±0.26
10	24.9±0.24	20.48±0.18	24.08±0.11	22.25±0.25	23.15±0.28	27.96±0.38
15	48.20±0.15	45.49±0.39	60.21±0.21	41.87±0.11	43.28±0.16	49.41±0.11
20	56.75±0.39	63.14±0.17	75.25±0.09	72.40±0.13	82.02±0.12	85.39±0.15
25	76.49±0.18	78.79±0.25	97.86±0.61	83.80±0.9	92.07±0.15	95.16±0.12
30	99.16±0.11	97.82±0.34	99±0.26	97.20±0.25	100.08±0.1	99.13±0.14

*** Mean Percent of Released (□x ± s.d) (n = 3)**

Table 5.8: Percentage *in-vitro* drug release of formulations (F7-F12):

Time	**F-7(%)**	**F-8(%)**	**F-9(%)**	**F-10(%)**		

(mins)					**F-11(%)**	**F-12(%)**
5	17.4±0.2	8.7±0.3	14.4±0.62	10.2±0.03	12±0.31	17.7±0.12
10	34.29±0.13	21.64±0.26	36.98±0.87	27.65±0.82	27.96±0.65	40.59±0.52
15	56.68±0.12	48.16±0.13	56.38±0.91	55.11±0.25	38.92±0.72	51.3±0.61
20	85.5±0.23	76.03±0.09	89.69±0.43	85.11±0.96	79.63±0.45	82.20±0.37
25	97.6±0.19	92.05±0.13	92.28±0.96	95.58±0.87	93.86±1.02	94.35±0.32
30	98.20±0.26	98.26±0.26	99.09±0.43	98.42±0.26	99.48±0.35	99.64±0.12

*** Mean Percent of Released (□x ± s.d) (n = 3)**

***In-vitro* Dissolution Profile of F1-F6 Formulations**

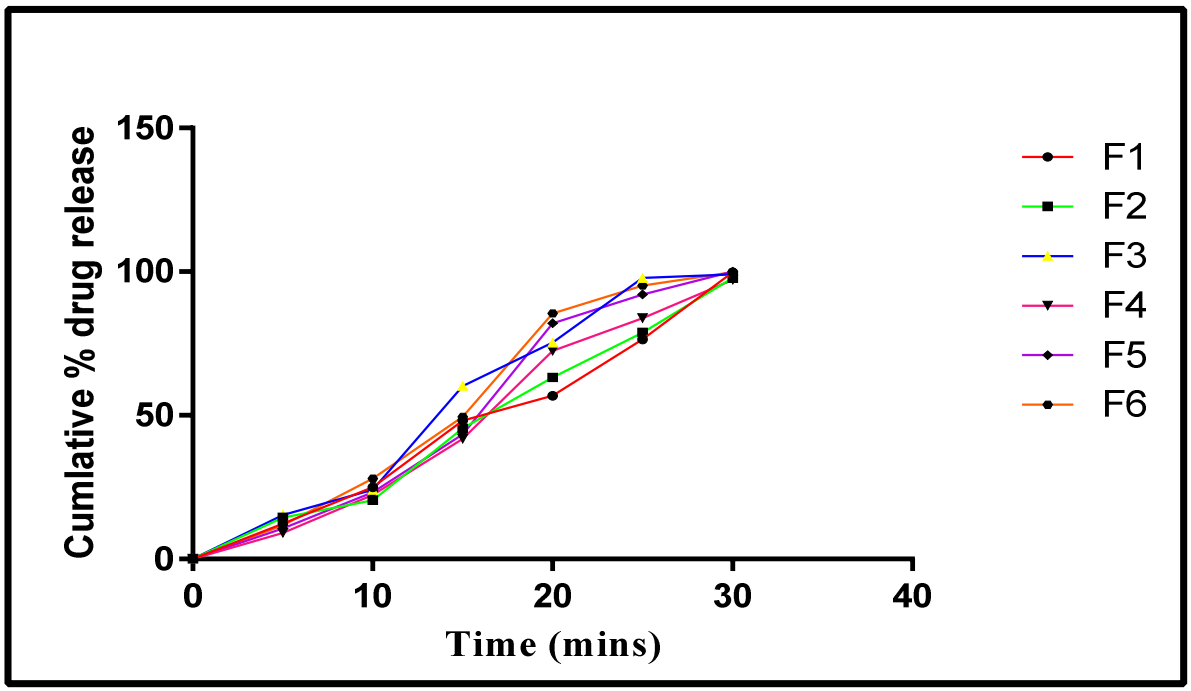

Figure 5.14: *In-vitro* Dissolution Profile of F1-F6 Formulations

***In-vitro* Dissolution Profile of F7-F12 Formulations**

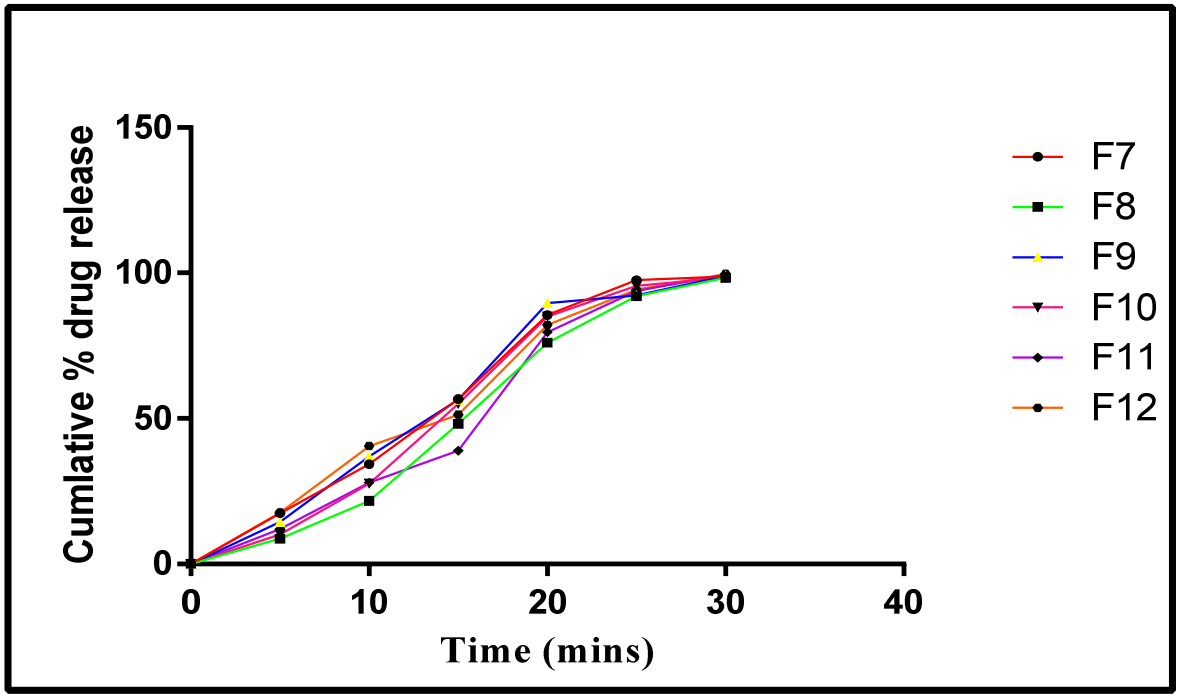

Figure 5.15: *In-vitro* Dissolution Profile of F7-F12 Formulations

CONCLUSION:

Overall, the results suggest that suitably formulated orodispersible tablets of gabapentin containing 30mg of Cross povidone as a super disintegrant used to improve flowability of powder mixture and as disintegrant by direct compression method. The optimum selected formula (F12) has satisfactory physical resistance, fast high dissolution rate and good stability.

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