FORMULATION DEVELOPMENT AND EVALUATION OF GABAPENTIN IMMEDIATE RELEASE TABLETS

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ABSTRACT

Immediate release tablets of Gabapentin were successfully formulated by employing direct compression method. Preformulation studies of drug were performed; the infrared spectral analysis revealed that there is no chemical interaction with excipients used was compatible with drugs. Based on Weight variation, Hardness, friability, and Drug Content it was found that all the formulation were satisfied mention criteria as per Pharmacopoeial Standards. Disintegration time in F13 formulation found 17 sec and dispersion time found 15 sec. The in vitro drug release was 99 %. Overall, in the formulations prepared by direct compression method, F13 which contain 4 % CCS as Super disintegrants releases 99 % drug in 2 minutes was found the best formulation. Stability study of F13 batch was found stable for 1 month.

Key Words: Gabapentin, Weight variation, Disintegration time ,Immediate release tablets.

- **INTRODUCTION**

Immediate release tablets are invented to disintegrate and release their dosage form with no special rate controlling features, such as special coatings and other techniques. Immediate release tablets are those which disintegrate swiftly and get dissolved to release the medicaments.

The oral bioavailability of drug dependent on disintegration, dissolution and various physiological factors. An immediate release dosage form helps a manufacturer to diversify market and simultaneously offering patients a convenient dosage form or dosage regimen. Immediate-release tablets disintegration is an essential requirement for dissolution and disintegration performance has a direct impact on the therapeutic effect of the medication and must be assessed and ideally quantified, using specifically designed disintegration tests. The disintegration process is an integral step in ensuring, and indeed maximizing, the bioavailability of the API from the majority of solid dosage forms.

Some examples of super disintegrants mentioned in above table. Superdisintegrants are generally used at low levels in solid dosage forms, typically 1-10 % of mass relative to the total mass of the dosage unit. The choice of superdisintegrant for a tablet formulation depends largely on the nature of the drug being used. For example, the rate and mechanism of tablet disintegration could be affected by the solubility of the

drug component. Water-soluble materials tend to dissolve rather than disintegrate, while insoluble materials generally tend to disintegrate if an appropriate amount of disintegrant is incorporated in the formulation.

Advantages of Immediate Release Drug Delivery System[3]

→ Improved compliance /added convenience, solubility, stability, bioavailability.

→ Allows high drug loading, cost-effective.

→ Ability to provide advantages of liquid medication in the form of solid preparation.

→ Adaptable and amenable to existing processing and packaging machinery.

→ Decreased dissolution and disintegration times for immediate release oral dosage forms.

Disadvantage[3]

→ Frequent dosing is necessary for a drug with a short half-life.

→ Drug release at a time may produce high plasma concentration which may produce toxicity.

- **Direct Compression** In which tablets formulations are directly compressed from a powder blend of suitable excipients and API is called a direct compression method. Pre-treatment of blended powder by dry or wet granulation procedure is not necessary. Its provide merits mostly in terms of speedy production, as it requires less machinery, reduced number of personnel, fewer unit operations and significantly less processing time along with improved product stability.

Preformulation Study

The flow property, and compressibility of pure Drug were determined during the preformulation studies. Moreover, the drug excipient compatibility was ensured using Fourier transform infrared (FTIR) spectrophotometry.

- **Organoleptic Properties**

This includes recording of color, odor and taste of the new drug using descriptive terminology. Record of color of early batches is very useful in establishing appropriate specifications for later production. Drugs generally have a characteristic odors and tastes. Unpleasant ones are masked later during formulation.

- **Melting Point Determination**

Melting point of Drug was determined by melting point apparatus using open capillary method. A small amount of drug sample was transferred in to capillary tube. Then capillary was placed in melting point test apparatus and noted down the temperature at which the drug started melting and was completely melted.

- **Calibration curves of Gabapentin**

A solution of Gabapentin was prepared in pH 1.2 0.1 N HCl. UV spectrum was taken using Shimadzu-1601, kroyoto, Japan. The UV maximum of Gabapentinwas found to be 217 nm in pH 1.2 0.1 N HCl.

- **Preparation of standard calibration curve of Gabapentin**

Gabapentin (10 mg) was dissolved in 10 ml of in pH 1.2 0.1 N HCl and volume was made up to 100 ml in 100 ml volumetric flask. This solution (100 mcg / ml) was further diluted with in pH 1.2 0.1 N HCl to obtain solution of 1.5 to 7.5 µg/ml using 1.5, 3.0, 4.5, 6.0 and 7.5 ml of stock solution. Absorbance of each solution was measured at 217 nm using Shimadzu-1601 UV-Visible spectrophotometer in pH 1.2 0.1 N HCl as reference standard. The standard curve was generated for the entire range from 1.5 to 7.5 µg/ml.

- **Drug-Excipients compatibility study by FTIR**

The Fourier transform infrared spectrum of moisture free powdered sample of drug and final formulation was recorded on IR spectrophotometer by potassium bromide (KBr) pellet method. The range of spectra was found to be 400 to 4000 cm^{-1}.The characteristics peaks of different functional group were compared with reported standard peak.

Compatibility Study by FTIR

The FTIR spectra of pure drug and Formulation are shown in below figure;

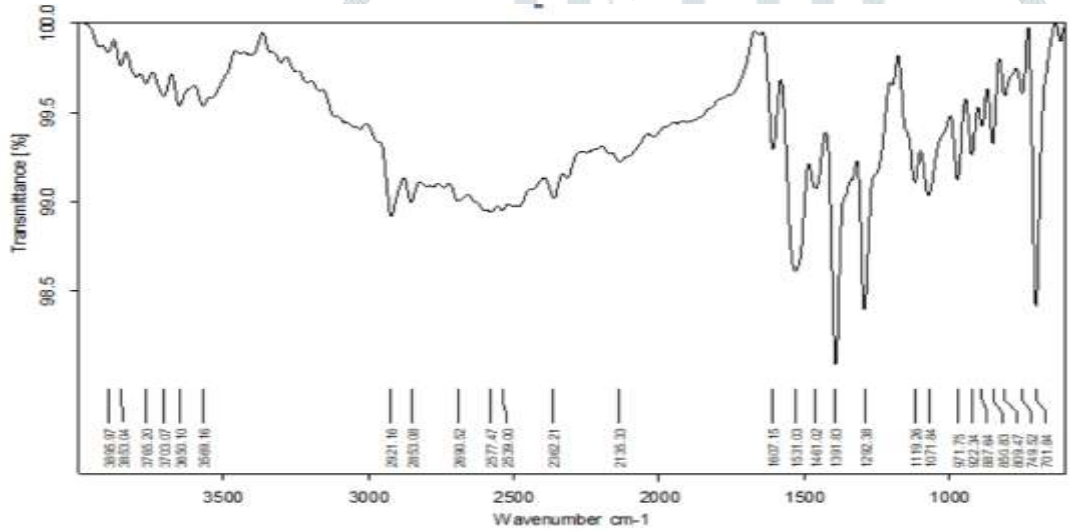
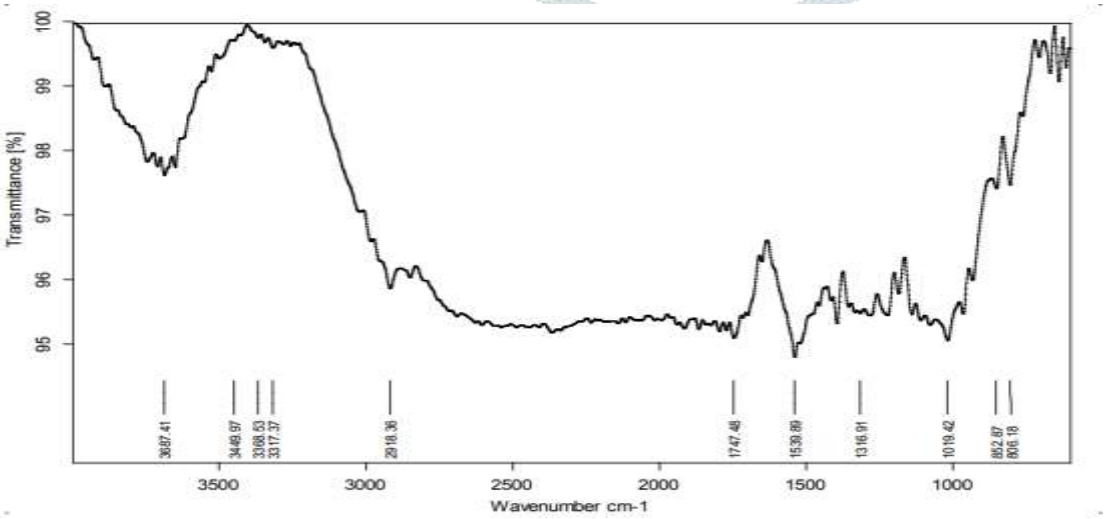


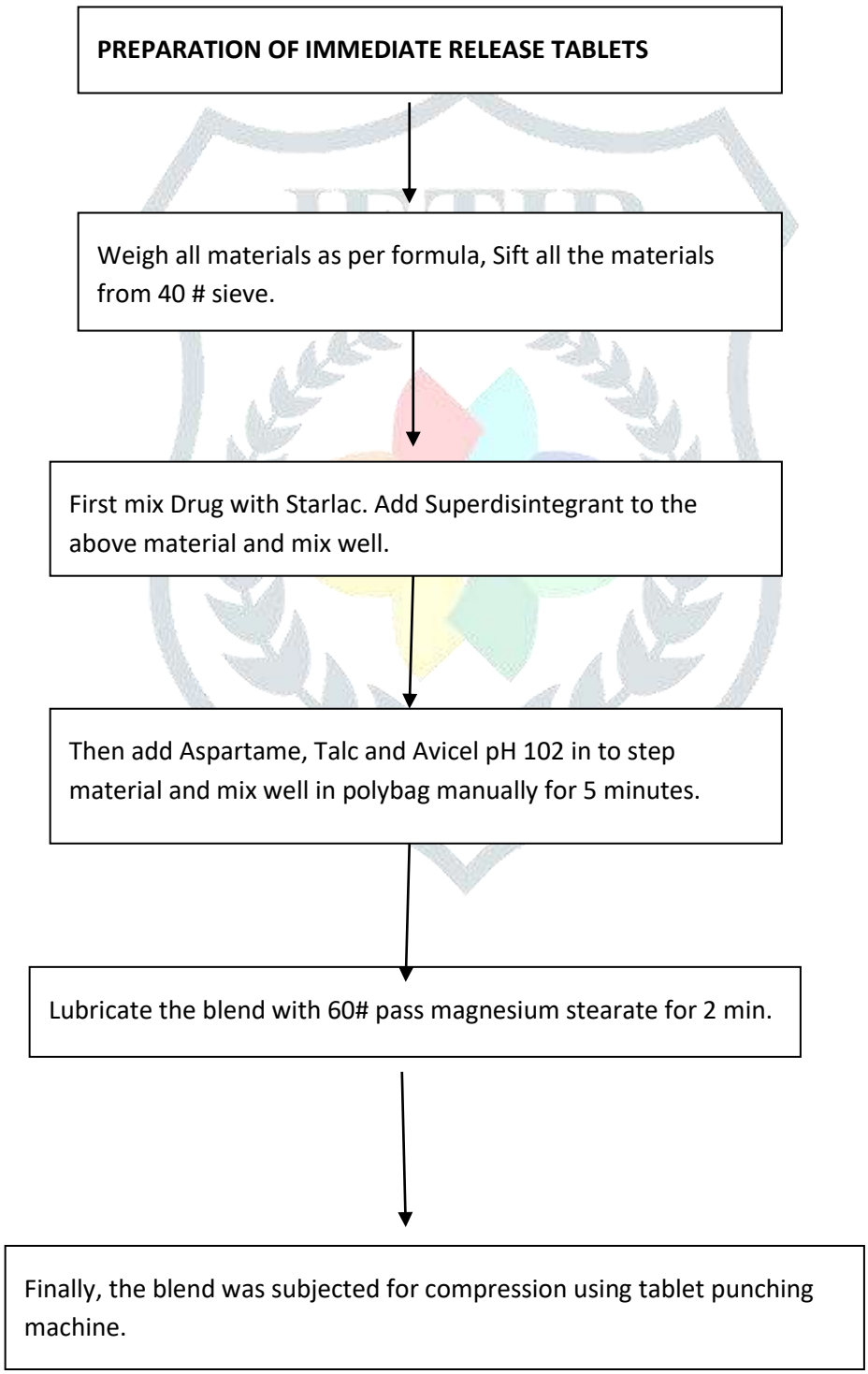
Figure FTIR spectra of pure drug Gabapentin



FTIR Interpretation

Functional group	Observed frequency in Pure Drug (Cm^{-1})	Observed frequency in Formulation (Cm^{-1})	Conclusion
C-H	2921.16	2918.21	***No Interaction***
C-O	1391.83	1316.91	

- **Direct compression method**



Formulation table of immediate release tablets

Sr. No.	Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13	F14	F15
1.	Gabapentin	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100
2.	Sodium Starch Glycolate	4	8	12	16	20	-	-	-	-	-	-	-	-	-	-
3.	Crospovidone	-	-	-	-	-	4	8	12	16	20	-	-	-	-	-
4.	Croscarmellose Sodium	-	-	-	-	-	-	-	-	-	-	4	8	12	16	20
5.	Aspartame	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
6.	Starlac	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20
7.	Talc	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4
8.	Magnesium Stearate	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
9.	Avicel pH 102	65	61	57	53	49	65	61	57	53	49	65	61	57	53	49
10.	Total weight of tablet	**200**	**200**	**200**	**200**	**200**	**200**	**200**	**200**	**200**	**200**	**200**	**200**	**200**	**200**	**200**

- **Evaluation Parameters of immediate release tablets**

Weight variation test

The 20 tablets were selected randomly from each formulation and weighed independently to check for weight variation. The U.S Pharmacopoeia allows a little difference in the weight of a tablet. The mean SD values were calculated.

Thickness

Thickness was measure by Vernier calliper, and results will be recorded.

Hardness

The hardness of the tablets was determined using Monsanto Hardness tester. It is expressed in Kg/cm^2. Three tablets were haphazardly picked from each formulation and the mean and standard deviation values were calculated.

Friability

It is the occurrence whereby tablet surfaces are damaged and/or show evidence of lamination or breakage when subjected to mechanical shock or attrition. The friability of tablets was determined by using Roche Friabilator. It is expressed in percentage (%). 6.5-gram weight equivalent tablets were initially weighed and transferred into friabilator. The friabilator was operated at 25 rpm for 4 minutes or run up to 100 revolutions. The tablets were weighed again. The percentage friability was then calculated by,

$$\% \text{ Friability} = \frac{\text{Initial weight - Final weight}}{\text{Initial weight}} \times 100 \quad \text{----- (d)}$$

% Friability of tablets less than 1% is considered acceptable.

Drug Content

Ten tablets were randomly selected, accurately weighed and average weight per tablet calculated. The tablets were ground individually to fine powder. Accurately weighed tablet powder transferred to 100 ml volumetric flask. Add 0.1 N HCl up to the spot. After few minutes the solution was filtered; rejecting first few ml of the filtrate. 1 ml of filtrate was taken in a 10 ml volumetric flask and diluted up to the mark with 0.1 N HCl and analysed spectrophotometrically at 217 nm.

Wetting time

Apiece of tissue paper (12×10.75 cm) folded twice was placed in a Petri dish (internal diameter=9 cm) containing 10 ml of phosphate buffer solution, pH 6.8. A tablet was placed on the paper and the time taken for complete wetting was noted. Three tablets from each formulation were randomly selected and the average wetting was recorded.

In vitro dispersion time

It is determined by placing one tablet in a beaker containing 10 ml of pH 0.1 N HCl at 37±0.5º and the time required for complete dispersion was determined.

In vitro disintegration time

The in vitro disintegration time of a tablet was determined using disintegration apparatus. Place one tablet in each of the 6 tubes of the basket. Add a disc to each tube and run the apparatus using 6.8 phosphate buffer maintained at 25±2°C.

In vitro dissolution studies

In vitro release studies were carried out using tablet USP type II dissolution test apparatus. Paddle speed was maintained at 75 rpm and 900 ml of 0.1 N HCl was used as the dissolution medium. Samples (2 ml) were collected at predetermined time intervals and replaced with equal volume of fresh medium, filtered through what man filter paper, and analysed with a UV—visible spectrophotometer at 217 nm.

- **Stability Studies**

The selected batches were subjected for stability study. All the immediate release tablets were suitably packed in aluminum foil. The tablets will be stored at 40º C/75% RH condition. At the end of 1 month, the sealed tabletswill be opened and evaluated for different parameters.

- **Pre Compression Parameters**

Formulations	Bulk Density (gm/ml) (n=3)	Tapped Density (gm/ml) (n=3)	Compressibility % (n=3)	Angle of Repose (θ)
F1	0.520 ± 0.04	0.655 ± 0.06	13.5 ± 0.2	26°56’
F2	0.525 ± 0.03	0.675 ± 0.07	15.0 ± 0.3	27°72’
F3	0.518 ± 0.02	0.671 ± 0.05	15.3 ± 0.3	25°60’
F4	0.530 ± 0.05	0.666 ± 0.08	18.9 ± 0.7	28°10’
F5	0.525 ± 0.07	0.675 ± 0.07	13.2 ± 0.5	29°38’
F6	0.515 ± 0.05	0.655 ± 0.06	14.0 ± 0.6	27°48’
F7	0.523 ± 0.04	0.653 ± 0.05	19.1 ± 0.8	25°89’
F8	0.535 ± 0.03	0.630 ± 0.04	12.5 ± 0.4	26°32’
F9	0.552 ± 0.02	0.663 ± 0.06	14.1 ± 0.3	30°12’
F10	0.531 ± 0.01	0.645 ± 0.05	11.4 ± 0.4	24°75’
F11	0.543 ± 0.05	0.652 ± 0.04	10.9 ± 0.5	22°45’
F12	0.535 ± 0.05	0.651 ± 0.06	11.6 ± 0.2	21°48’
F13	0.529 ± 0.04	0.668 ± 0.05	13.9 ± 0.1	25°11’
F14	0.541 ± 0.04	0.668 ± 0.06	12.7 ± 0.3	22°69’
F15	0.545 ± 0.06	0.653 ± 0.04	10.8 ± 0.4	23°28’

- **Post-Compression Parameters**

The tablets ready by direct compression technique were subjected to preliminary The evaluated parameters were within acceptable range for all the F1-F15 formulations. The values are indicated in below table.

Formulation Code	Weight Variation (mg) (n=3)	Thickness (mm) (n=3)	Hardness (kg/cm^2) (n=3)	Friability %
F1	200.6±2.36	3.07±0.02	3.40±0.36	0.50
F2	200.4±2.36	3.04±0.03	3.76±0.32	0.40
F3	200.5±2.05	3.04±0.02	3.86±0.25	0.35
F4	200.2±2.78	3.20±0.06	3.67±0.14	0.50
F5	200.0±2.72	3.06±0.08	3.96±0.12	0.60
F6	200.3±2.46	3.06±0.03	3.84±0.20	0.20
F7	200.7±2.30	3.04±0.03	3.77±0.35	0.40
F8	200.2±2.10	3.07±0.01	3.54±0.30	0.55
F9	200.8±2.01	3.02±0.05	3.88±0.22	0.45
F10	200.1±2.56	3.43±0.03	3.53±0.37	0.35
F11	200.7±2.20	3.51±0.02	3.90±0.10	0.40
F12	200.1±2.31	3.52±0.03	3.79±0.43	0.30
F13	**200.6±2.42**	**3.45±0.02**	**3.39±0.29**	**0.40**
F14	200.0±2.52	3.46±0.02	3.46±0.31	0.30
F15	200.4±2.32	3.43±0.01	3.81±0.25	0.40

Post compression parameters of formulation F1-F15

Formulation code	Wetting Time (Seconds) (n=3)	In vitro Dispersion Time (Seconds)(n=3)	In vitro Disintegration time (Seconds)(n=3)	% Drug Content (n=3)
F1	420 ±20	388±15	378±18	99.9 ± 0.1
F2	303±15	249±13	311±21	99.7 ± 0.2
F3	142±2	109±10	239±17	99.8 ± 0.4
F4	86±5	64±6	99±8	99.9 ± 0.2
F5	47±2	37±6	89±8	99.7 ± 0.6
F6	45±6	42±8	80±10	99.8 ± 0.2
F7	51±10	38±5	108±13	99.4 ± 0.3
F8	59±6	48±12	52±16	99.7 ± 0.2
F9	75±2	59±4	65±8	99.5 ± 0.2
F10	27±1	24±2	29±7	99.6 ± 0.1
F11	23±2	21±1	12±3	99.7 ± 0.3
F12	19±4	18±1	13±4	99.8 ± 0.2
F13	19±2	17±2	15±2	99.7 ± 0.3
F14	21±3	20±1	18±7	99.5 ± 0.5
F15	23±1	21±3	19±4	99.4 ± 0.8

- **In vitro dissolution studies**
- **In vitro dissolution studies**

The data obtained in the *in vitro* release for formulations prepared by direct compression technique.

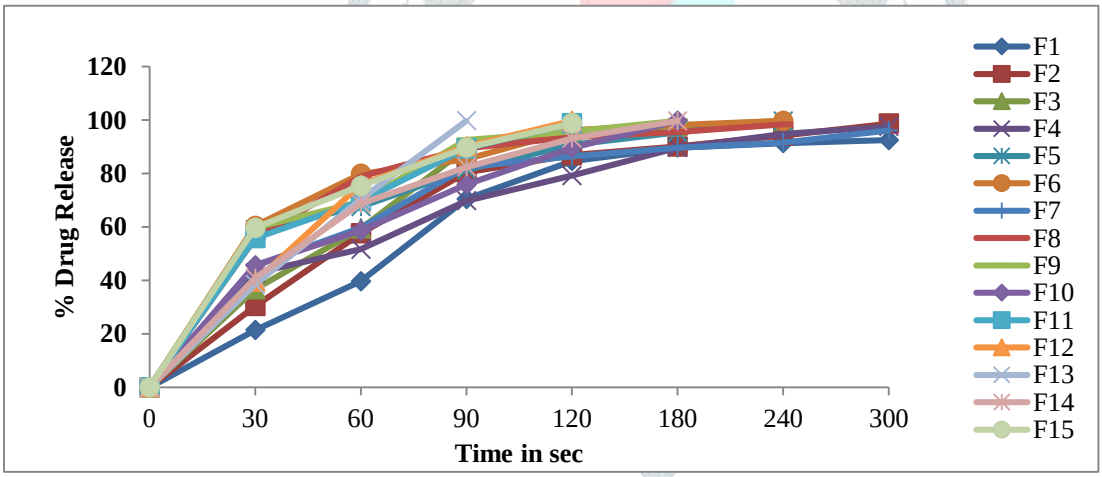
All the formulations showed rapid % drug release. But the rapid drug dissolution was noticed in F10 to F15 formulations compared to other formulations which release more than 95 % drug in 2 min because of croscarmellose sodium used as disintegrates in F11-F15 formulation. Because of fast disintegration and so rapid absorption gives high drug release.

Formulation F13 shows extreme faster dissolution than other formulation. It releases 99.6 % of drug within 90 sec.

From the above data it concluded that croscarmellose sodium as disintegrating agent in formulation help to drug release faster than the other agent used in formulation

% Drug Release of Formulation F1-F15

Formulation code	% Drug Release in seconds							
	0	30	60	90	120	180	240	300
F1	0	21.3±0.26	39.8±0.10	70.6±0.32	84.5±0.11	89.4±0.25	91.5±0.10	92.4±0.30
F2	0	30.4±0.30	57.7±0.15	80.4±0.05	86.6±0.30	90.2±0.15	94.3±0.23	98.4±0.15
F3	0	36.5±0.20	59.6±0.30	89.4±0.15	95.6±0.15	97.5±0.30	99.4±0.20	-
F4	0	42.3±0.40	51.7±0.10	69.6±0.26	79.3±0.20	89.5±0.20	94.4±0.32	97.4±0.20
F5	0	58.6±0.26	67.4±0.11	81.4±0.15	90.6±0.20	95.4±0.40	99.5±0.28	-
F6	0	60.5±0.10	79.7±0.20	85.5±0.15	96.5±0.20	98.4±0.20	99.5±0.20	-
F7	0	45.3±0.32	59.8±0.10	82.5±0.10	86.3±0.15	89.5±0.32	91.4±0.21	96.5±0.26
F8	0	55.8±0.10	78.8±0.26	89.5±0.28	93.4±0.11	95.5±0.20	98.3±0.10	-
F9	0	59.4±0.25	69.6±0.20	92.5±0.05	95.6±0.20	99.6±0.26	-	-
F10	0	45.6±0.23	57.8±0.98	75.5±0.32	89.5±0.20	99.5±0.20	-	-
F11	0	55.7±0.15	69.6±0.20	89.6±0.25	98.5±0.25	-	-	-
F12	0	39.3±0.32	75.8±0.10	90.4±0.20	99.5±0.15	-	-	-
F13	0	38.5±0.10	70.5±0.15	99.6±0.15	-	-	-	-
F14	0	40.8±0.20	68.7±0.15	82.5±0.20	93.4±0.25	99.6±0.11	-	-
F15	0	59.7±0.15	75.6±0.23	89.7±0.20	98.6±0.15	-	-	-



% Drug Release of Formulation F1-F15

- **Stability Study**

Optimized batch F13 was taken for 1 month stability study at 40°C and 75% RH. Initial results and after 1 month results were compared for any loss or change during stability. The batch was found stable and results were found satisfactory. The comparative results of initial and after 1 month were recorded in below table.

Table Stability study results

Parameter	Initial	After 1 Month
Appearance	White Colour round tablet	White Colour round tablet
Disintegration time(sec)	15 ± 2	17 ± 1
% Drug Content	99.7 ± 0.3	99.1 ± 0.7
% Drug release after 5 min	99.6 ± 0.1	99.8 ± 0.9

- **CONCLUSION**

Immediate release tablets of Gabapentin were successfully formulated by employing direct compression method. Preformulation studies of drug were performed; the infrared spectral analysis revealed that there is no chemical interaction with excipients used was compatible with drugs. Based on Weight variation, Hardness, friability, and Drug Content it was found that all the formulation were satisfied mention criteria as per Pharmacopoeial Standards. Disintegration time in F13 formulation found 17 sec and dispersion time found 15 sec. The in vitro drug release was 99 %. Overall, in the formulations prepared by direct compression method, F13 which contain 4 % CCS as Super disintegrants releases 99 % drug in 2 minutes was found the best formulation. Stability study of F13 batch was found stable for 1 month.

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