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FORMULATION DEVELOPMENT AND EVALUATION OF IMMEDIATE RELEASE TABLET DOSAGE FORM OF AMANTADINE

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Abstract:

The objective of this study was to develop and evaluate an immediate-release (IR) tablet dosage form of amantadine, an antiviral drug primarily used in the treatment of influenza and Parkinson's disease. Amantadine is known for its rapid absorption and onset of action, making it suitable for an IR formulation. Various excipients were selected based on their ability to enhance drug solubility and bioavailability. The tablets were prepared using direct compression and evaluated for physical characteristics, including hardness, friability, weight variation, and disintegration time. In vitro dissolution studies were conducted to assess the release profile of amantadine, ensuring it met the required pharmacokinetic parameters for rapid onset. The results indicated that the formulation provided efficient and rapid drug release, with acceptable pharmacotechnical properties.

Keywords: *Amantadine, Croscarmellose sodium, Sodium starch Glycolate and Crospovidone*

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1. INTRODUCTION:

The Oral route is one of the most sought after route for the systemic effect due to its ease of ingestion, simple, safest, convenient, non-invasive, versatility and most importantly, patient compliance. Solid oral delivery systems are cheaply manufactured because they don't require sterile conditions [1] . Although, increased focus and interest generated in the area of controlled release and targeted drug delivery system in recent years, tablet dosage forms that are intended to be swallowed whole, disintegrate, and release their medicaments fast and furiously in the gastrointestinal tract [2]An ideal dosage regimen of drug therapy is the one, which immediately nab the desired therapeutic concentration of drug in plasma (or at the site of action) and maintains it constantly for the entire duration treatment [3] . Of late, the scientists have focused their attention on the formulation immediately released tablet. The effort of developing a rapidly disintegrating tablet is accomplished by using suitable diluents and super disintegrants [4]

Definition: Immediate Release Tablets: 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. [5] The oral bioavailability of drug dependent on disintegration, dissolution and various physiological factors. [6] An immediate release dosage form helps a manufacturer to diversify market and simultaneously offering patients a convenient dosage form or dosage regimen. [7] The development of enhanced oral protein delivery technology by immediate release tablets which may release the drugs at an enhanced rate are very promising for the delivery of poorly soluble drugs high molecular weight protein and peptide. The oral route remains the perfect route for the administration of therapeutic agents because the low cost of therapy, manufacturing and ease of administration lead to high levels of patient compliance, [8]. Many patients require quick onset of action in particular therapeutic condition and consequently immediate release of medicament is required. It is estimated that50% of the population is affected by this problem, which results in a high incidence of ineffective therapy.

CRITERIA FOR IMMEDIATE RELEASE DRUG DELIVERY SYSTEM

Immediate release dosage form should in the case of solid dosage it should dissolve or disintegrate in the stomach within a short period.

- In the case of liquid dosage form it should be compatible with taste masking.
- Be portable without fragility concern.
- Have a pleasing mouth feel.
- It should not leave minimal or no residue in the mouth after oral administration.
- Exhibit low sensivity to environmental condition as humidity and temperature.
- Be manufactured using conventional processing and packaging equipment at low cost.
- Rapid dissolution and absorption of drug, which may produce rapid onset of action.[10]

Tablet Molding Technique: In this technology, water-soluble ingredients are incorporated to disintegrate and dissolve the tablet more swiftly. The hydroalcoholic solvents are used to moistened powder blend and then apply compression pressure that is lower than the conventional tablets compression to mold the tablet. The solvent is then removed by air-drying. Dissolution is enhanced by a porous structure of molded tablets .[11]

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.[12]

Granulation Technique: It is a process of size enlargement in which small particles convert into larger agglomerates and make it physically stronger. It is beneficial to avoid segregation of the product's constituent, refine powder flow and handling and minimize the dustiness.

It is ideally spherical, the smaller particle size is efficiently filling the void spaces between granules. This method can also be classified as two types.[13]

METHODOLOGY:

Buffer Preparation:

Preparation of 0.2M Potassium dihydrogen orthophosphate solution: Accurately weighed 27.218 gm of monobasic potassium dihydrogen orthophosphate was dissolved in 1000mL of distilled water and mixed.

Preparation of 0.2M sodium hydroxide solution: Accurately weighed 8 gm sodium hydroxide pellets were mixed in 1000ml of distilled water.

Preparation of pH 6.8 Phosphate buffer: Accurately measured 250ml of 0.2M potassium Dihydrogen ortho phosphate and 112.5 ml 0.2M NaOH was taken into the 1000ml volumetric flask. Volume was made up to 1000ml with distilled water.

Analytical method development for Amantadine:

a) Determination of absorption maxima

A spectrum of the working standards was obtained by scanning from 200-400nm against the reagent blank to fix absorption maxima. The λ_{max} was found to be 257 nm. Hence all further investigation was carried out at the same wavelength.

Table 7.1: Formulation of Immediate Release tablets

INGREDIENTS	FORMULATION CODE								
	A1	A2	A3	A4	A5	A6	A7	A8	A9
Amantadine	100	100	100	100	100	100	100	100	100
Croscarmellose sodium	25	50	75	-	-	-	-	-	-
Sodium starch Glycolate	-	-	-	25	50	75	-	-	-
Crospovidone	-	-	-	-	-	-	25	50	75
Povidone K-30	20	20	20	20	20	20	20	20	20
Aspartane	15	15	15	15	15	15	15	15	15
Magnesium stearate	10	10	10	10	10	10	10	10	10
Talc	10	10	10	10	10	10	10	10	10
Mannitol	120	95	70	120	95	70	120	95	70
Total weight	300	300	300	300	300	300	300	300	300

b) Preparation of Standard graph in pH 6.8 phosphate buffer

100 mg of Amantadine was dissolved in 100ml of Phosphate buffer of pH 6.8., from the primary stock 10ml was transferred to another volumetric flask made up to 100ml with Phosphate buffer of pH 6.8, from this secondary stock was taken separately and made up to 10 ml with Phosphate buffer of pH 6.8, to produce 5, 10, 15, 20 and 25µg/ml respectively. The absorbance was measured at 257 nm by using a UV spectrophotometer.

Formulation Development:

Drug and different concentrations for super Disintegrates and required ingredients were accurately weighed and passed through a 40-mesh screen to get uniform size particles and mixed in a glass mortar for 15 minutes. The obtained blend was lubricated with Magnesium stearate and glidant (Talc) was added and mixing was continued for a further 5 minutes. The resultant mixture was directly compressed into tablets by using a punch of a rotary tablet compression machine. Compression force was kept constant for all formulations.

Total weight of tablets = 300 mg

Pre formulation Studies

Pre-compression parameters:

Measurement of Micromeritic Properties of Powders

1. Angle of repose

The angle of repose of API powder is determined by the funnel method. The accurately weight powder blend are taken in the funnel. The height of the funnel is adjusted in way that, the tip of the funnel just touched the apex of the powder blend. The powder blend is allowed to flow through the funnel freely on the surface. The diameter of the powder cone is measured and angle of repose is calculated using the following equation.

$$\tan \theta = h/r \quad \text{.....(1)}$$

where, h and r are the height and redius of the powder cone.

Table 7.2: Flow Properties and Corresponding Angle of Repose

Flow Property	Angle of Repose (^{0})
Excellent	25-30
Good	31-35
Fair- aid not needed	36-40
Passable-may hang up	41-45
Poor-must agitate, Vibrate	46-55
Very Poor	56-65
Very, very Poor	>66

2. Bulk density

The powder sample under test is screened through sieve No.18 and the sample equivalent to 25 gm is weighed and filled in a 100 ml graduated cylinder and the power is leveled and the unsettled volume, V_o is noted. The bulk density is calculated in g/cm^3 by the formula.

Bulk density = M/V_0 …… (2)

M= Powder mass

V_0= apparent unstirred volume

3. Tapped density

The powder sample under test is screened through sieve No.18 and the weight of the sample equivalent to 25 gm filled in 100 ml granulated cylinder. The mechanical tapping of cylinder is carried out using tapped density tester at a nominal rate for 500 times initially and the tapped volume V_0 is noted. Tappings are preceded further for an additional tapping 750 times and tapped volume, V_b is noted. The difference between two tapping volume is less than 2%, V_b is considered as a tapped volume V_f . the tapped density is calculated in g/cm^3 by the formula.

Tapped density=M/V_f ……..(3)

M= weight of sample power taken

V_f= tapped volume

4. Compressibility Index

The Compressibility Index of the power blend is determined by Carr's compressibility index to know the flow character of a powder. The formula for Carr's Index is a below:

Carr's Index (%)=[(TD-BD)/TD]x100 ……..(4)

5. Hauser's ratio

The Hauser's ratio is a number that is correlated to the flowability of a powder or granular material. The ratio of tapped density to bulk density of the powders is called the Hauser's ratio. It is calculated by the following equation.

H=ρT / ρB ……..(5)

Where ρT= tapped density, ρB = bulk density

Table 9.3: Scale of Flowability

Compressibility index (%)	Flow character	Hausner Ratio
≤ 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

Post-compression parameters:

a) Thickness

The thickness of tablets was determined by using a Digital micrometer. Ten individual tablets from each batch were used and the results were averaged.

b) Weight variation

Twenty tablets were randomly selected from each batch and individually. Weighed the average weight and the standard deviation of three batches were calculated. It passes the test weight variation test if not more than two of the individual tablets' weights deviate from the average weight by more than the allowed percentage deviation and more deviate by more than twice the percentage shown. It was calculated on an electronic weighing balance.

c) Friability

The friability values of the tablets were determined using a Roche-type friabilator. Accurately weighed six tablets were placed in Roche friabilator and rotated at 25rpm for 4 min.

Percentage friability was calculated using the following equation.

Friability = ([w_0-w] / w_0) x 100

d) Assay

The content of drug was carried out by five randomly selected tablets of each formulation. The five tablets were grinded in mortar to get powder; this powder was dissolved in pH 6.8 phosphate buffer by sonication for 30 min and filtered through filter paper. The drug content was analyzed spectrophotometrically at 257 nm using UV spectrophotometer. Each measurement was carried out in triplicate and the average drug content was calculated.

e) Disintegration test

Six tablets were taken randomly from each batch and placed in USP disintegration apparatus baskets. Apparatus was run for 10 minutes and the basket was lift from the fluid, observe whether all of the tablets have disintegrated.

f) Dissolution test of Amantadine tablets

Drug release from Amantadine tablets was determined by using dissolution test United States Pharmacopoeia (USP) 24 type II (paddle). The parameters used for performing the dissolution were pH 6.8 phosphate buffer as the dissolution medium of quantity 500ml. the whole study is being carried out at a temperature of 37^{0}C and at speed of 50 rpm.

Drug-Excipients compatibility studies:

Drug excipients compatibility studies were carried out by mixing the drug with various excipients in different proportions (in 1:1 ratio were prepared to have maximum likelihood interaction between them) was placed in a vial, and closed with rubber stopper and sealed properly.

8. RESULTS AND DISCUSSION:

Determination of λ_{max} :

The prepared stock solution was scanned between 200-400 nm to determine the absorption maxima. It was found to be 257nm.

Calibration curve of Ertugliflozin:

The standard curve of Amantadine was obtained and a good correlation was obtained with an R^2 value of 0.999, the medium selected was pH 6.8 phosphate buffer.

Table 8.1: Standard graph values of Amantadine at 257 nm in pH 6.8 phosphate buffer

Concentrations (µg/ml)	Absorbance
0	0
5	0.126
10	0.241
15	0.362
20	0.477
25	0.597

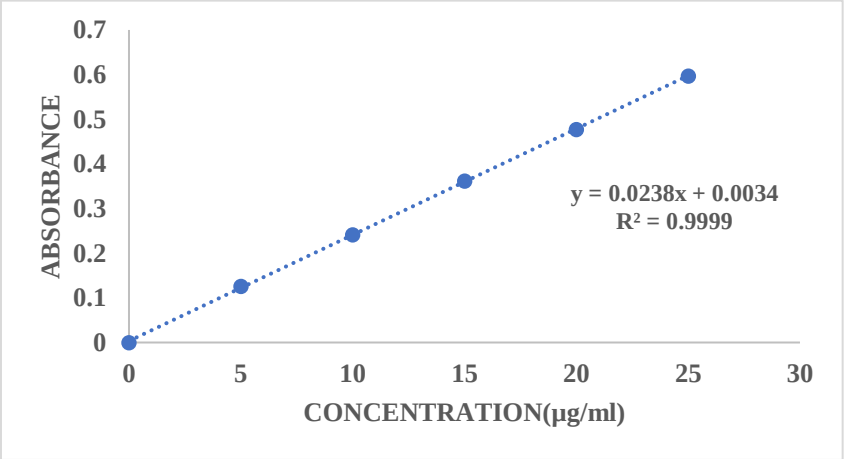

Fig 8.1: Standard curve of Amantadine

Evaluation:

Characterization of precompression blend:

Tablet powder blend was subjected to various pre-compression parameters. The angle of repose values was showed from 23.24±0.23 to 30.62±0.78; it indicates that the powder blend has good flow properties. The bulk density of all the formulations was found to be in the range of 0.479±0.06 to 0.523±0.30 (gm/cm^3) showing that the powder has good flow properties. The tapped density of all the formulations was found to be in the range of 0.66±0.42 to 0.712±0.26 showing the powder has good flow properties. The compressibility index of all the formulations was found to be ranging from 14.72±0.46 to 18.34±0.23 which showed that the powder has good flow properties. All the formulations showed the hausner ratio ranging from 1.21±0.23 to 1.30±0.32 indicating the powder has good flow properties.

Table 8.2: Physical properties of precompression blend

Formulation code	Angle of repose (Θ)	Bulk density (gm/cm^3	Tapped density(gm/cm^3)	Carr's index (%)	Hausner's ratio
A1	28.56±0.27	0.479±0.06	0.658±0.54	17.29±0.36	1.22±0.35
A2	26.76±0.42	0.515±0.24	0.680±0.23	18.34±0.23	1.24±0.44
A3	29.17±0.56	0.502±0.23	0.674±0.42	15.06±0.75	1.21±0.23
A4	23.96±0.88	0.485±0.74	0.712±0.26	15.15±0.34	1.22±0.37
A5	30.62±0.78	0.494±0.30	0.697±0.35	14.72±0.46	1.29±0.42
A6	26.07±0.60	0.481±0.64	0.652±0.60	17.87±0.84	1.25±0.45
A7	30.45±0.42	0.478±0.34	0.549±0.20	18.25±0.54	1.23±0.06
A8	27.20±0.75	0.491±0.92	0.657±0.60	15.84±0.76	1.26±0.72
A9	23.24±0.23	0.523±0.30	0.66±0.42	16.80±0.98	1.30±0.32

All the values represent n=3

Evaluation of tablets:

Physical evaluation of Amantadine immediate release tablets:

The results of the weight variation, hardness, thickness, friability and drug content of tablets are given in table 8.3. All the tablets of different batches complied with the official requirement of weight variation as their weight variation passes the limit. The hardness of the tablets ranged from 1.91– 2.12 kg/cm^2 and the friability values were < than 0.68 % indicating that the tablets were compact and hard. The thickness of the tablets ranged from 2.47 - 2.85mm. All the formulations satisfied the content of the drug as they contained 97.27-101.17% of Amantadine good uniformity in drug content was observed. Thus all physical attributes of the prepared tablets were found to be practically within control limits.

Table 8 .3: Physical evaluation of Ertugliflozin

Formulation code	Weight variation (mg)	Thickness (cm)	Hardness (Kg/cm^2)	Friability (%)	Content Uniformity (%)	Disintegration Time (Sec)
A1	298.12	2.85	1.91	0.26	98.38	51
A2	304.35	2.55	2.12	0.33	99.49	43
A3	300.48	2.47	1.89	0.12	99.83	35
A4	299.08	2.63	1.95	0.41	97.27	62
A5	297.22	2.71	2.05	0.29	98.65	48
A6	298.37	2.83	1.93	0.38	101.17	57
A7	301.75	2.59	1.97	0.25	99.83	39
A8	299.88	2.67	2.04	0.39	98.51	44
A9	298.29	2.81	1.98	0.22	97.34	54

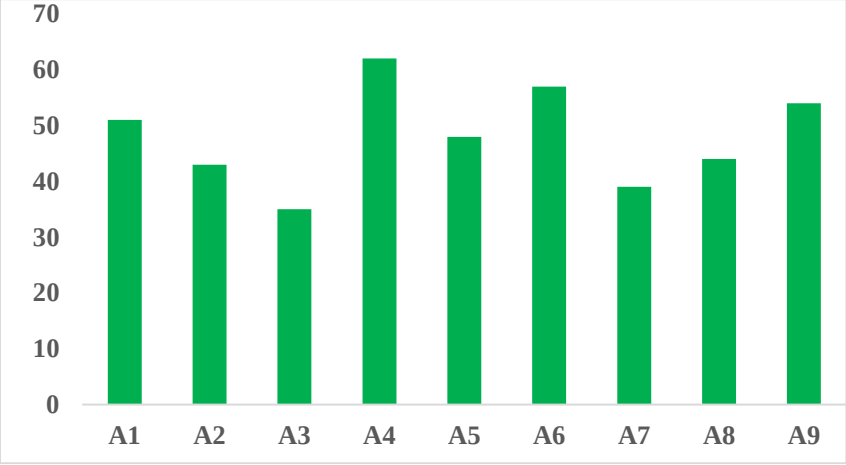

Figure 8.2: Disintegration Test (Sec)

***In vitro* release studies:**

The drug release rate from tablets was studied using the USP type II dissolution test apparatus. The dissolution medium was 500 ml of pH 6.8 phosphate buffer at 50 rpm at a temperature of 37±0.5 ˚C. Samples of 5 ml were collected at different time intervals up to 1 hr and has analyzed after appropriate dilution by using UV spectrophotometer at 257 nm.

Table 10.4: *In vitro* dissolution data for formulation A1-A9

TIME (MIN)	% OF DRUG RELEASE								
	A1	**A2**	**A3**	**A4**	**A5**	**A6**	**A7**	**A8**	**A9**
0	0	0	0	0	0	0	0	0	0
5	38.61	49.91	53.13	37.01	43.11	53.51	33.83	41.98	51.44
10	46.46	58.44	67.51	51.89	55.13	61.89	44.22	51.19	63.59
15	53.23	67.27	77.19	68.34	77.82	82.65	57.02	62.45	72.38
20	71.19	78.71	89.74	73.65	84.91	88.41	69.24	66.36	77.92
25	75.92	85.24	92.48	87.21	89.11	92.72	75.08	79.05	83.06

30	88.27	91.61	95.61	92.97	95.74	94.66	84.98	86.41	91.41
45	93.11	95.45	99.77	96.64	98.03	97.41	92.51	95.17	96.37

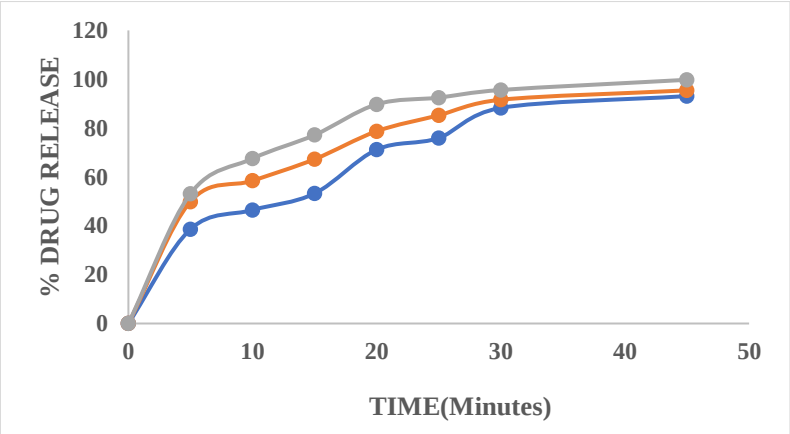

Fig 8.3: *In vitro* dissolution data for formulation A1-A3

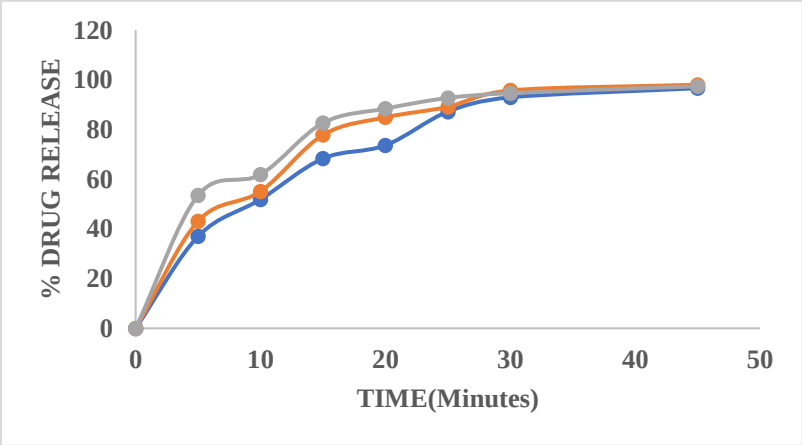

Fig 8.4: *In vitro* dissolution data for formulations A4-A6

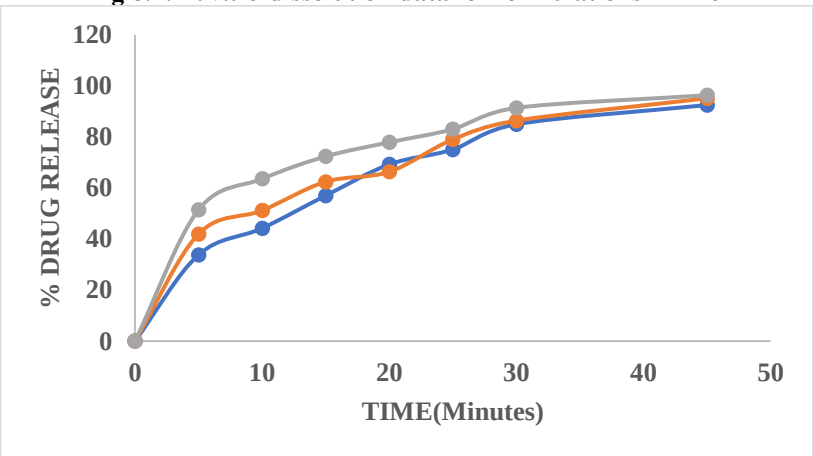

Fig 8.5: *In vitro* dissolution data for formulations A7-A9

From the table, it was evident that the formulation prepared with Croscarmellose sodium were showed good drug release i.e., A3 formulation (99.77%) in a higher concentration of blend i.e. 75 mg. Formulations prepared with Sodium starch Glycolate showed good drug release i.e., 98.03% (A5 formulation) in 50 mg concentration. Formulations prepared with Crospovidone showed maximum drug release i.e.,96.37% (A9 formulation) at 45 min in 75 mg of blend.

Among all formulations, A3 was considered as an optimized formulation which showed maximum drug release at 45 min i.e., (99.77 %. Croscarmellose Sodium showed good release when compared to Sodium starch Glycolate showed and Crospovidone. Finally concluded that the A3 formulation contains Cros carmellose sodium was optimized formulation.

Drug-Excipient compatibility studies by FTIR studies:

Amantadinewas mixed with various proportions of excipients showed no colour change at the end of two months, providing no drug –excipient interactions.

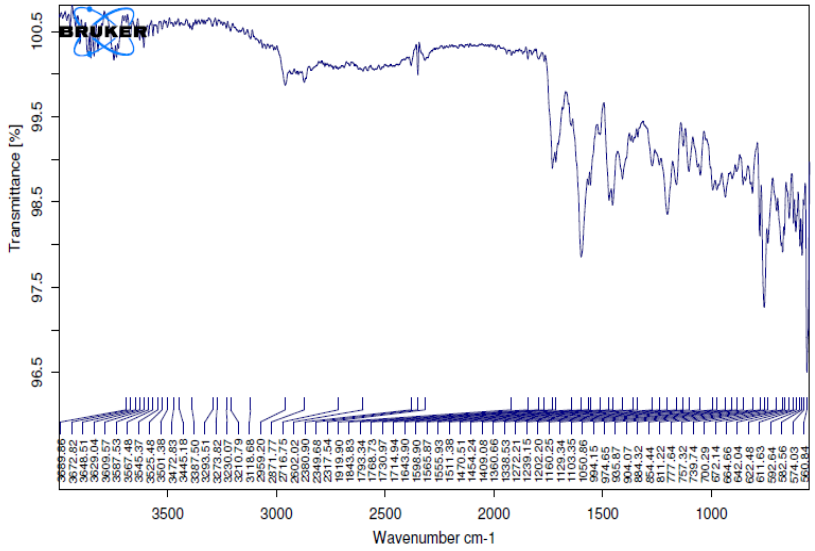

Fig 8.6: FTIR spectra of pure drug

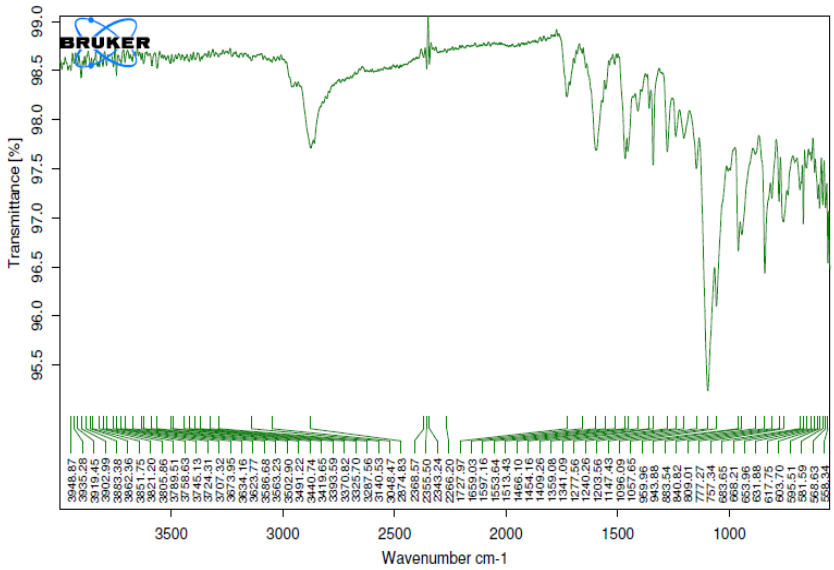

Fig 8.7: FTIR spectra of optimized formulation

From the above studies, it was found that there was no shifting in the major peaks which indicated that there were no significant interactions occurring between the amantadine and excipients used in the preparation of different Amantadine Immediate Release formulations. Therefore the drug and excipients are compatible to form stable.

Formulations under study, The FTIR spectra of Amantadine and physical mixture used for optimized formulation were obtained and these are depicted in the above figures. From the FTIR data, it was evident that the drug and excipients did not have any interactions. Hence they were compatible.

9. CONCLUSION:

In conclusion, the formulation development and evaluation of the immediate-release tablet dosage form of amantadine, utilizing polymers such as Croscarmellose sodium, Sodium starch Glycolate, and Crospovidone, highlighted the successful enhancement of drug release. Among the various formulations tested, the A3 formulation exhibited excellent drug release, with a remarkable 99.77% of amantadine released within 45 minutes. This rapid and efficient release profile demonstrates the potential of these polymers, particularly in optimizing the disintegration and dissolution characteristics of the tablet. The A3 formulation's performance suggests it could offer a reliable and effective therapeutic option, ensuring timely and complete drug absorption.

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